THE $S_{RN}1$ REACTIVITY OF HALOBENZENESULFONAMIDES AND RELATED COMPOUNDS

by

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(Abstract)

An investigation of the application of nucleophilic aromatic substitution by the $S_{RN}1$ mechanism of halobenzenesulfonamides and related compounds towards the synthesis of 1,2-benzothiazine 1,1-dioxides is reported. 3-Substituted and 3,4-disubstituted 2*H*-1,2-benzothiazine 1,1-dioxides were prepared in moderate to good yields via the photostimulated reaction of 2-halobenzenesulfonamides with ketone enolates. It was observed that with certain ketone enolates reduction to yield benzenesulfonamide competed with the substitution reaction. The presence of β-hydrogen atoms was a common structural feature of ketones used in reactions in which reduction competed with substitution. It was also observed that the amount of reduction product isolated increased as a function of the number of β-hydrogen atoms present on the ketone enolate. It was found that 2-bromo and 2-iodobenzenesulfonamide exhibit comparable reactivity with ketone enolates that do not possess β-hydrogen atoms. However, a marked decrease in the reactivity of 2-bromobenzenesulfonamide was observed when β-hydrogen atoms were present on the ketone enolate. Yet, the rate of consumption of 2-iodobenzenesulfonamide

was found to be independent of the presence of β-hydrogen atoms. A labeling study involving 2,4-dimethyl-3-pentanone-d_{14} demonstrated that intermolecular β-hydrogen atom transfer was the major pathway of reduction. An inhibition study indicated the radical chain nature of the reduction mechanism when 2-iodobenzenesulfonamide is treated with enolate anions possessing β-hydrogen atoms.

It was found that intramolecular hydrogen atom transfer from the *N*-methyl carbon to the intermediate aryl radical derived from *N*-methyl-2-iodobenzenesulfonamide precluded intermolecular aromatic nucleophilic substitution of that substrate. Similarly, an intramolecular $S_{RN}1$ cyclization reaction to yield 6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxides preempted efforts to effect intermolecular substitution of *N*-aryl-2-iodobenzenesulfonamides with ketone enolates. *N*-*t*-Butyl and *N*-acyl-2-iodobenzenesulfonamides were found to be participating substrates in the $S_{RN}1$ reaction with both ketone and ester derived enolates. The synthetic potential of the ester enolate substitution reactions of the *N*-acyl-2-ioidobenzenesulfonamide was demonstrated by methanolysis of the *N*-acyl function to yield the primary sulfonamide.

The potassium dianion obtained upon treatment of *N*-acetyl-2-halobenzenesulfonamides with excess KNH_2 in liquid ammonia, was found to undergo an intramolecular cyclization reaction to give 3,4-dihydro-1,2-benzothiazin-3(2*H*)-one 1,1-dioxide in satisfactory yields. An attempt to extend the dianion cyclization reaction to produce the 4-substituted analogs met with little success. Reduction and amination to yield the coresponding *N*-acylbenzenesulfonamides and *N*-acyl-2-aminobenzenesulfonamides respectively, were found to be the major reaction pathways. It is proposed that the amination reaction involves the interception of an intermediate aryl radical by amide ion. It was concluded that steric effects associated with substituted lateral dianion prevent intramolecular trapping of the aryl radical.

The air sensitivity and oxidative elaboration of some 3-substituted and 3,4-disubstituted-2*H*-1,2-benzothiazine 1,1-dioxides is discussed.

To Mary and Steven

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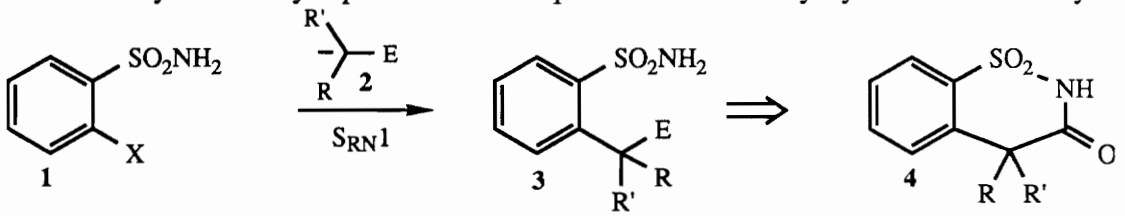
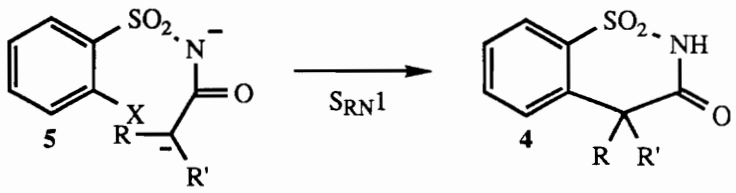
1. INTRODUCTION

Historically, two areas of interest of the Wolfe research group have been heterocyclic synthesis via $S_{RN}1$ reactions and the preparation of compounds with potential central nervous system (CNS) activity. A report by Sianesi of the CNS activity of certain 2-alkyl-1,2-benzothiazin-3(2*H*)-one 1,1-dioxides stimulated our interest in the preparation of these heterocycles.[1] A review of the literature revealed that a surprisingly limited variety of 1,2-benzothiazines exist. The preparation and biological activity of 1,2-benzothiazines have been reviewed thoroughly by Lombardino and Kuhla.[2,3] The two largest classes of 1,2-benzothiazines are the 3- and 4-ones. The limited number of other 1,2-benzothiazines include examples of 2-substituted and 2,3- and 2,4-disubstituted analogs. The preparations of these 1,2-benzothiazines are reviewed in the Historical Section of this dissertation.

Sianesi's report and Lombardino's review lead us to investigate the development of new synthetic routes to 1,2-benzothiazine 1,1-dioxides utilizing $S_{RN}1$ chemistry. In particular we sought to develop a convenient, general synthesis of 4-substituted and 4,4-disubstituted-1,2-benzothiazin-3(2*H*)-one 1,1 dioxides. Two routes involving $S_{RN}1$ type reactions were envisaged.[4] First, based on methodology pioneered by Beugelmans, it was thought that an intermolecular substitution on a 2-halobenzenesulfonamide **1** by an ester enolate or a synthetically equivalent nucleophile **2** followed by cyclization would yield

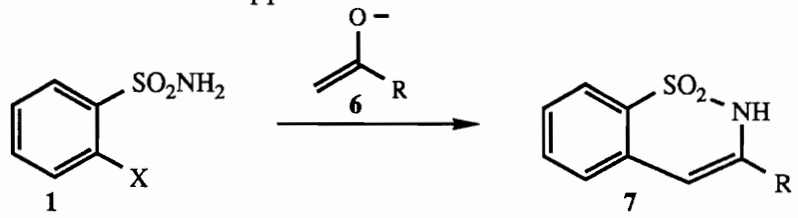


the desired 1,2 benzothiazin-3(2*H*)-one 1,1-dioxides **4**.[5] The second approach was based on methodology developed earlier by our group.[6] Thus, it was anticipated that the dianion, **5**, derived from *N*-acyl-2-halobenzenesulfonamide would undergo an intramolecular $S_{RN}1$



reaction to yield **4**. Examples of such heterocyclic annulation reactions involving the aromatic $S_{RN}1$ mechanism are summarized in the Historical Section.

Earlier attempts in our laboratories to implement the intermolecular $S_{RN}1$ approach failed to yield the desired 1,2-benzothiazin-3-ones.[7] However, the intramolecular $S_{RN}1$ approach was found by Campbell to be a viable synthetic route to the unsubstituted parent substrate **4** (R = R' = H).[8] In related work, several preliminary results revealed that 2-halobenzenesulfonamides **1** appeared to be useful substrates for the preparation



of 3-substituted-2*H*-1,2-benzothiazine 1,1-dioxides **7** upon photostimulated reaction with ketone enolates.[9,10] These results provided a starting point for the present research. The expansion of those early results in both synthetic and mechanistic terms is the subject of this dissertation.

The initial goal of this research was to optimize the synthetic utility of nucleophilic aromatic substitution reactions of 2-iodobenzenesulfonamide (**1a**) (X = I) and its *N*-substituted derivatives. However the substitution reactions proved to be more complicated than anticipated in that major competing side reactions were observed. Consequently a major portion of this dissertation involved studies to develop an understanding of the mechanism of such side reactions.

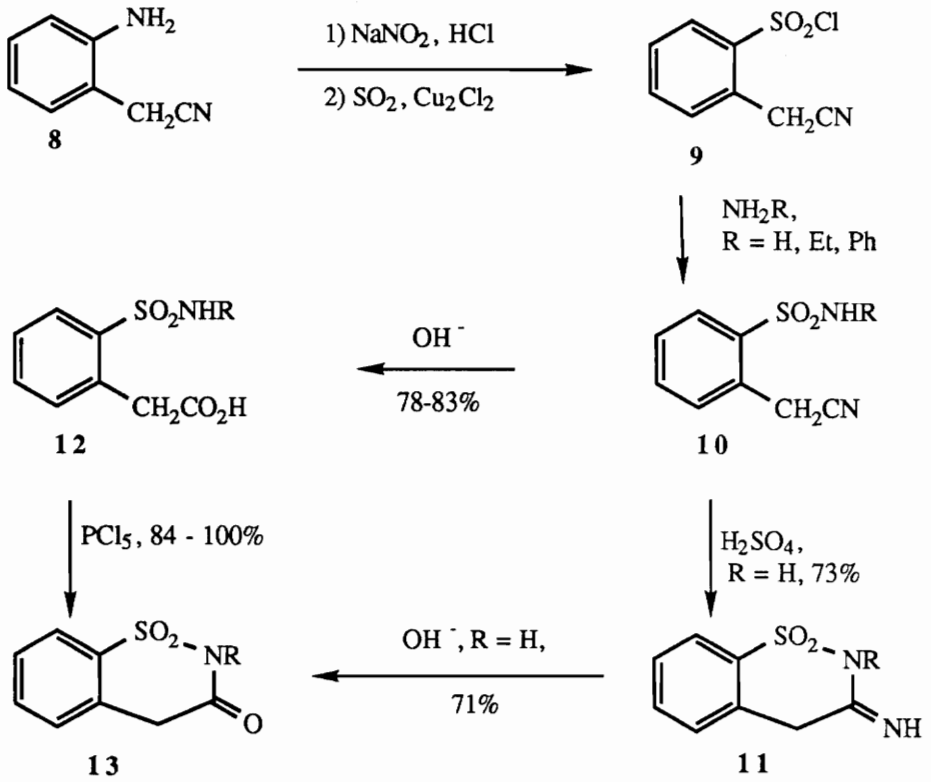
II. HISTORICAL

1. PREPARATION OF 1,2-BENZOTHIAZINES

1.1 1,2-Benzothiazin-3-ones

The first report of a preparation of a 1,2-benzothiazin-3-one was published by Sianesi and coworkers in 1970.[11] Sianesi reports the synthesis of phenylacetic acid **12** from 2-aminophenylacetonitrile (**8**) obtained in four steps from 2-nitrotoluene.[12] Diazotization of **8** followed by treatment with SO_2/Cu_2Cl_2 produced sulfonyl chloride **9**. Amination of **9** with ammonia or an appropriate primary amine gave 2-cyanomethylbenzenesulfonamides **10**. Acid hydrolysis of **10a** (R = H) resulted in formation of amidine **11**. Treatment of **11** with aqueous base produced 1,2-benzothiazin-3(2*H*)-one 1,1-dioxides **13**. Alternatively, sulfonamides **10** underwent base hydrolysis to yield phenylacetic acid **12**, which upon treatment with PCl_5 produced 1,2-benzothiazin-3(2*H*)-one 1,1-dioxides **13** (Scheme I). In a later report, Sianasi and coworkers applied

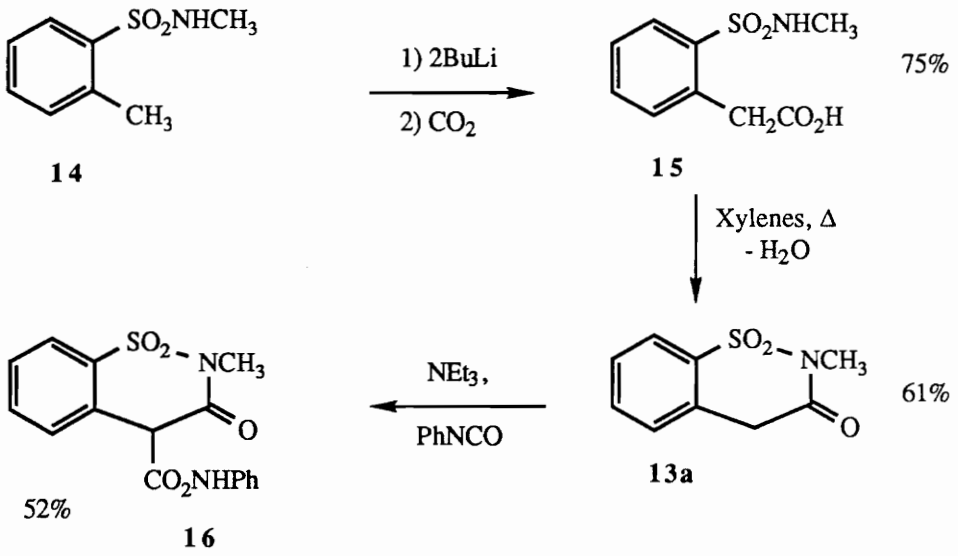
Scheme I



this synthetic route to the preparation of a series of 2-substituted-1,2-benzothiazin-3(2*H*)-one 1,1-dioxides with sedative hypnotic activity.[1]

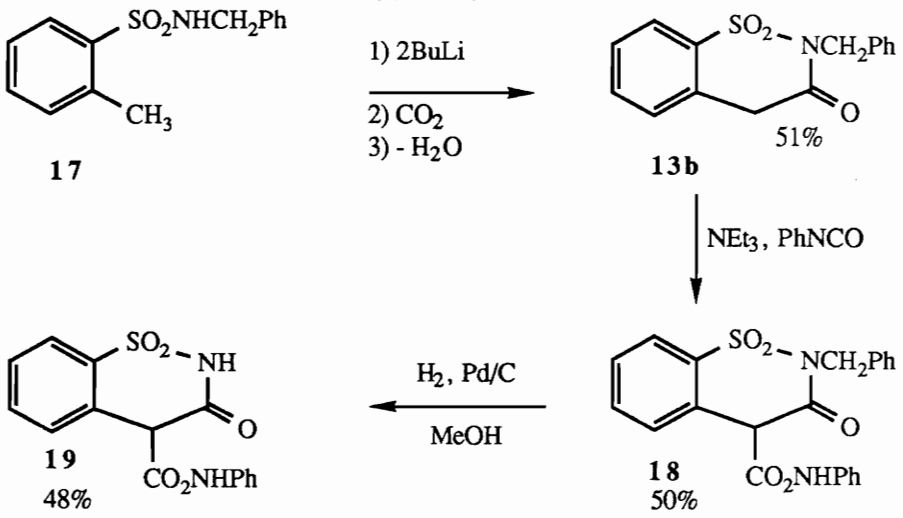
A second synthetic approach to 1,2-benzothiazin-3-ones was reported in 1971 by Lombardino and Wiseman.[13] These workers report the preparation of a series of 3,4-dihydro-2-methyl-3-oxo-1,2-benzothiazine-4-carboxamide 1,1-dioxides with antiinflammatory activity from readily available *N*-methyl-*o*-toluenesulfonamide (**14**). Thus treatment of **14** with two equivalents of *n*-butyllithium gave a dianion intermediate. Reaction of the dianion with CO_2, gave *o*-sulfamoylphenylacetic acid (**15**), which upon cyclodehydration in refluxing xylenes yielded 3,4-dihydro-2-methyl-benzothiazin- 3(2*H*)-one 1,1-dioxide (**13a**). Treatment of **13a** with phenylisocyanate in the presence of triethylamine resulted in formation of carboxamide **16** (Scheme II). Preparation of the analog of **16** without a 2-substituent could be realized through the use of *N*-benzyl-*o*-tol-

Scheme II



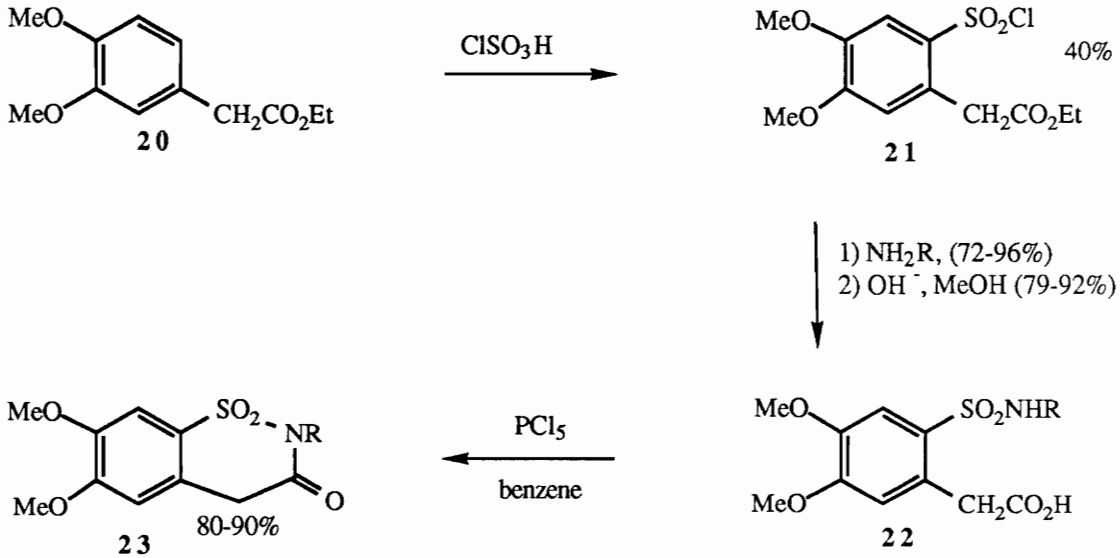
uenesulfonamide (**17**) in place of the *N*-methylated starting sulfonamide. Reductive cleavage with palladium of 2-benzyl-3,4-dihydro-3-oxo-2*H*-1,2-benzothiazine-4-carboxamide (**18**) yielded 3,4-dihydro-3-oxo-1,2-benzothiazin-4- carboxamide 1,1-dioxide (**19**) (Scheme III).

Scheme III



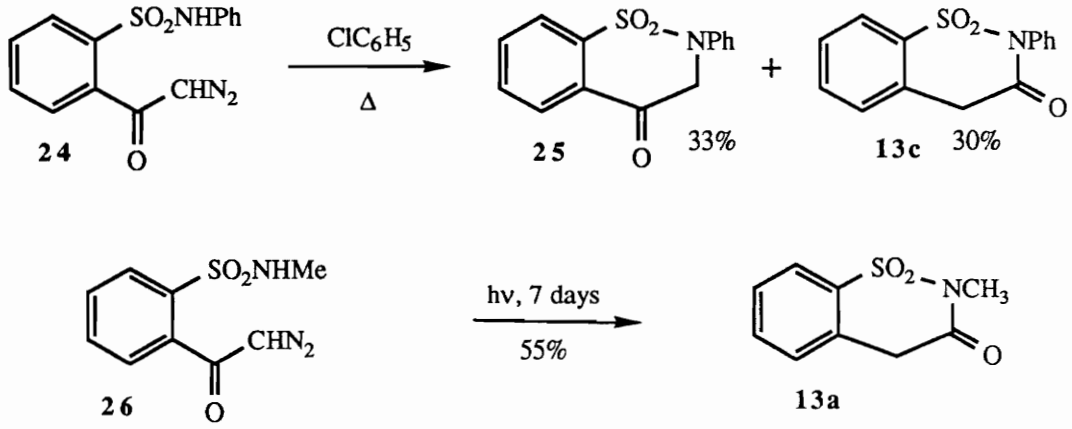
A third approach to 1,2-benzothiazin-3(2*H*)-one 1,1-dioxides has been described by Catsoulacos.[14] Chlorosulfonation of ethyl 3,4-dimethoxyphenylacetate (**20**) with chlorosulfonic acid gave 4,5-dimethoxy-2-carboethoxymethylbenzenesulfonyl chloride (**21**). Amination of **21** followed by basic hydrolysis of the ester yielded 2-sulfamoyl-4,5-dimethoxyphenylacetic acids **22**. Treatment of acids **22** with PCl_5 in benzene resulted in cyclization to afford 6,7-dimethoxy-1,2-benzothiazin-3(2*H*)-one 1,1-dioxides **23** (Scheme IV).

Scheme IV



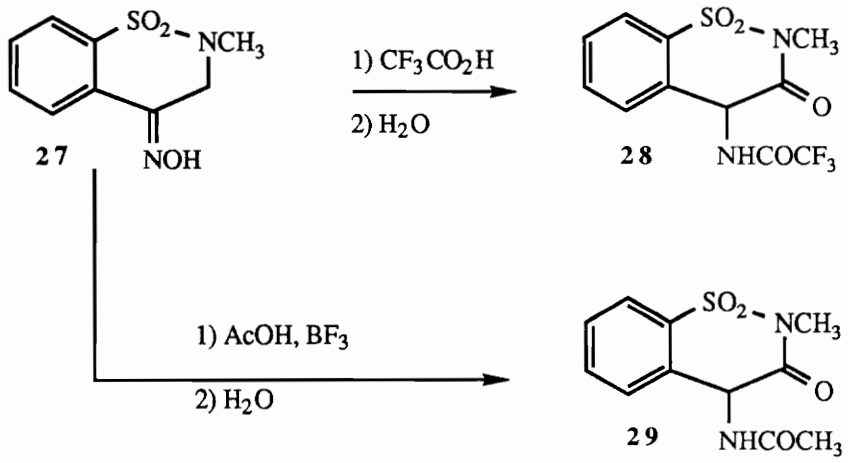
1,2-Benzothiazin-3-ones have been prepared using several other approaches. Holt, Heyes and Lewis isolated 2-substituted-3,4-dihydro-1,2-benzothiazin-3(2*H*)-one 1,1-dioxides from *N*-phenyl- and *N*-methyl-*o*-diazoacetylbenzenesulfonamides via a novel cyclization reaction.[15] Thermolysis of diazoketone **24** in chlorobenzene gave a mixture of 2-phenyl-2*H*-1,2-benzothiazin-4-one (**25**) and 2-phenyl-1,2-benzothiazin-3(2*H*)-one (**13c**). Similarly, photolysis of diazoketone **26** over a period of seven days gave 3,4-dihydro-2-methyl-1,2-benzothiazin-3(2*H*)-one 1,1-dioxide (**13a**) (Scheme V). Zinnes

Scheme V



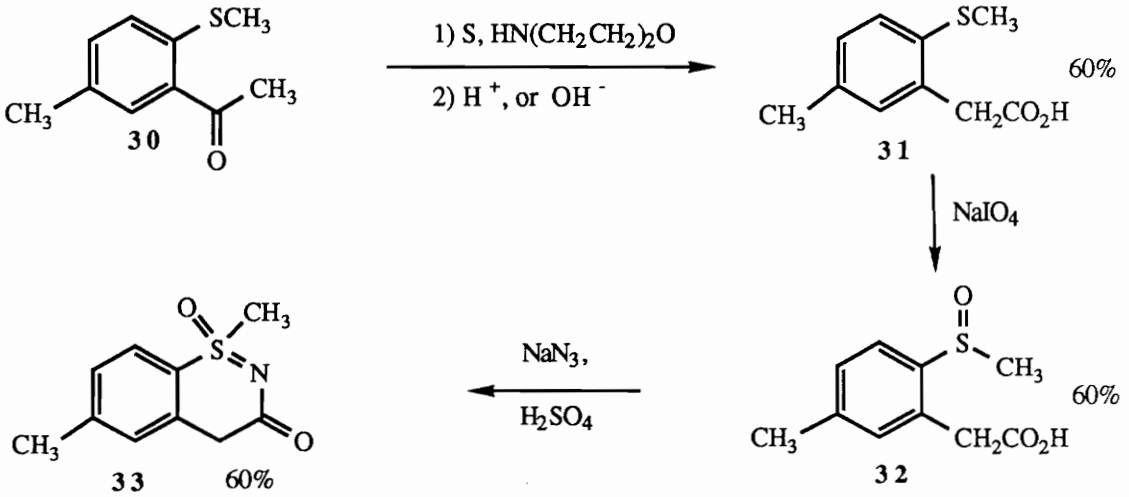
and coworkers report that *N*-acyl derivatives **28** and **29** of 4-amino-2-methyl-1,2-benzothiazin-3(2*H*)-one 1,1-dioxide result from a novel Semmler-Wolff transformation of oxime **27** (Scheme VI).[16]

Scheme VI

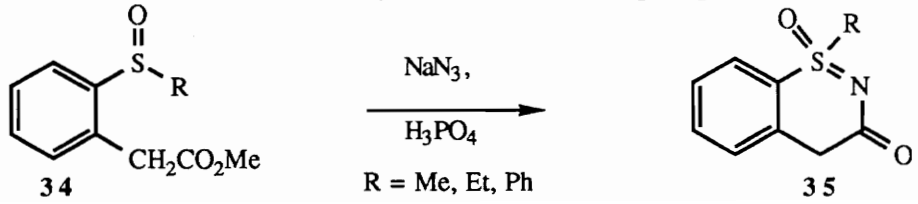


The preparation of structurally interesting benzothiazine **33** has been reported by Cram and Williams.[17] Thus, **33** was prepared in three steps from 2-methylthio-5-methylacetophenone (**30**). Compound **30** was transformed into 2-thiomethyl-5-methylphenylacetic acid (**31**) which in turn was oxidized to sufoxide **32**. Cyclization of **32** to sufoximide **33** was accomplished by treatment with sodium azide in sulfuric acid

Scheme VII

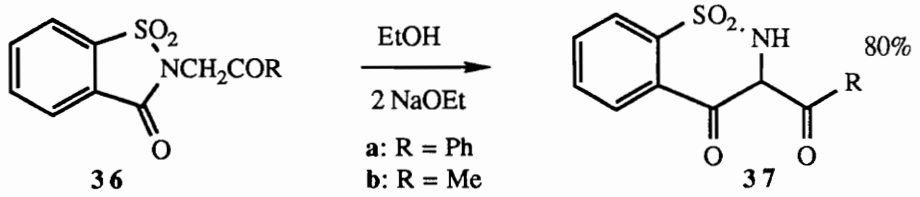


(Scheme VII). Stoss and Satzinger describe a similar preparation of sulfoximide **35** via sodium azide treatment of 2-alkylsulfinylacetic esters **34** in phosphoric acid.[18]



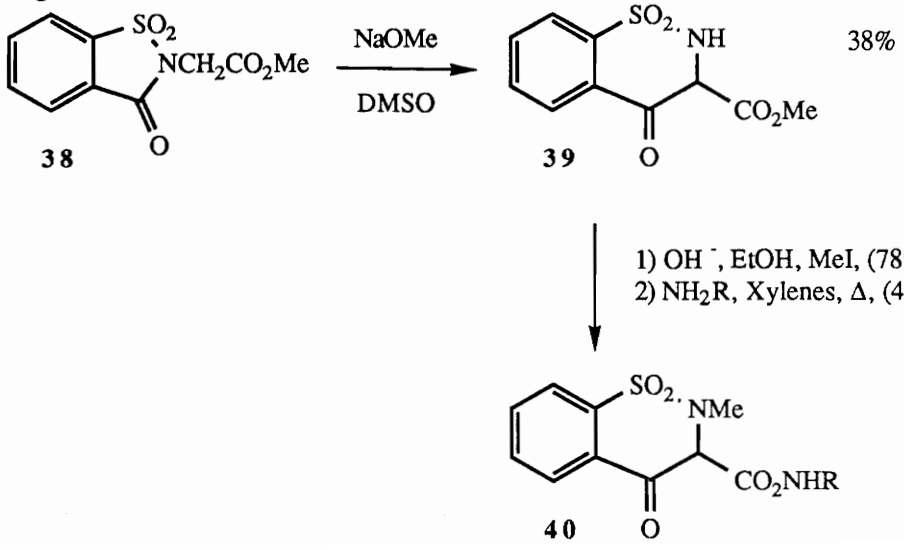
1.2 1,2-Benzothiazin-4-ones.

1,2-Benzothiazine-4-ones represent the most frequently encountered class of 1,2-benzothiazines. This can be easily attributed to the fact that these substrates are conveniently prepared from readily available sodium saccharin. In addition, the 4-one-3-carboxamides make up the bulk of the important class of non-steroidal antiinflammatory agents, the oxicams.[2,19] The most important of which is piroxicam, also known as Feldene® (**37**, R = NH-2-pyridyl).[20] The preparation of the 4-ones from sodium saccharin was originally developed by Abe et al.[2,20] Abe reported the rearrangement of *N*-phenacylsaccharin (**36a**) to give 3-benzoyl-2*H*-1,2-benzothiazin-4-(3*H*)-one 1,1-dioxide (**37a**)[21] Zinnes expanded Abe's method to include the 3-acetyl



36 **37**

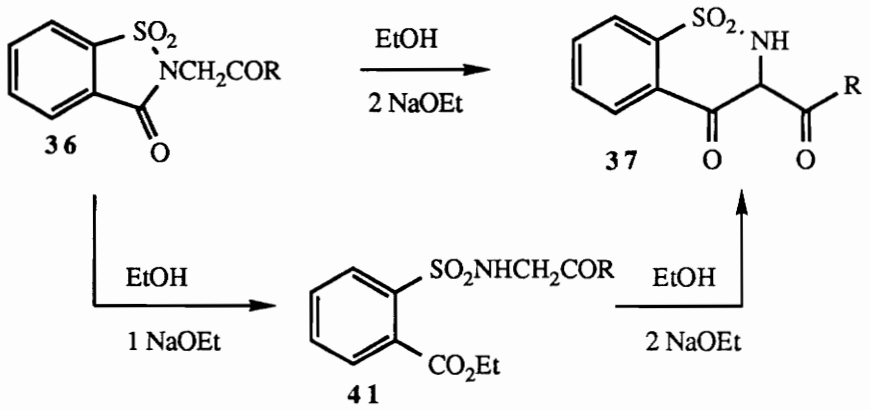
analog **37b**.[22] Diones **37** were *N*-methylated by treatment with excess NaH and methyl iodide. Lombardino applied the method of Abe to the preparation of the 4-one-3-carboxamides by treatment of 3-oxo-1,2-benzisothiazoline-2-acetic acid methyl ester (**38**) with NaOMe in DMSO to give rearrangement product **39**. *N*-Alkylation of **39** and amination gave the desired carboxamides.[23]



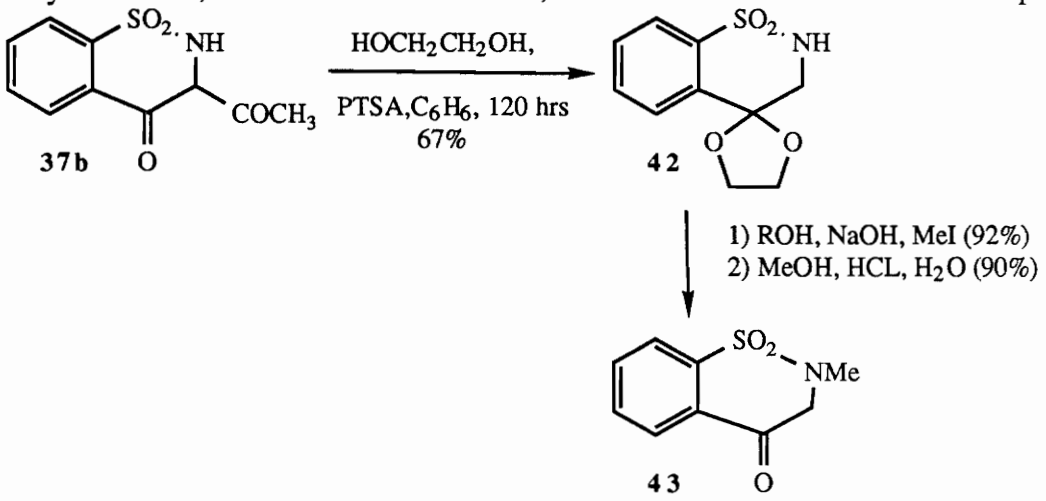
38 **39** **40**

Zinnes has proposed that the ring enlargement reaction occurs via a two-step mechanism. The first step involves alcoholysis of the carboxamide linkage to yielded the ring opened ester **41**. Dieckman cyclization yields the 1,2-benzothiazin-4-one heterocycle. In support of this mechanism, Zinnes reported that treatment of **36** with two equivalents of NaOEt yields **37**. However, treatment with only one equivalent of base results in the isolation of **41**. Furthermore, treatment of **41** with two equivalents of NaOEt results in formation of **37** (Scheme VIII) [22]

Scheme VIII

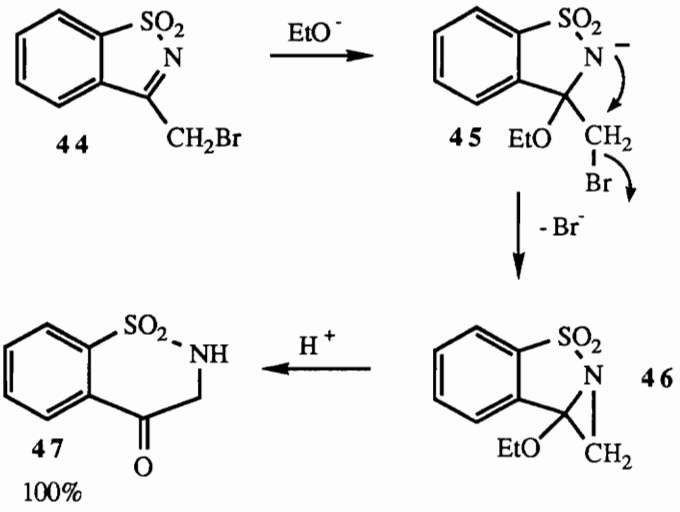


Zinnes reported the surprising result that treatment of **37b** with ethylene glycol in benzene in the presence of *p*-toluenesulfonic acid (PTSA) resulted in the formation of the deacetylated cyclic ketal **42**.[24] Alcoholic NaOH treatment of ketal **42** in the presence of methyl iodide followed by acid hydrolysis of the isolable intermediate ketal, gave 2-methyl-3,4-dihydro-2*H*-1,2-benzothiazin-4-one 1,1-dioxide **43**. Recall that the 2-phenyl



analog, **25**, of **43** was formed in 33% yield from diazoketone **24** (Section II.1.1 Scheme V) The 2-unsubstituted analog **47** is obtained from acid hydrolysis of ketal **42.** Abramovitch has described a more convenient preparation of **47** from 3-bromomethyl-1,2-

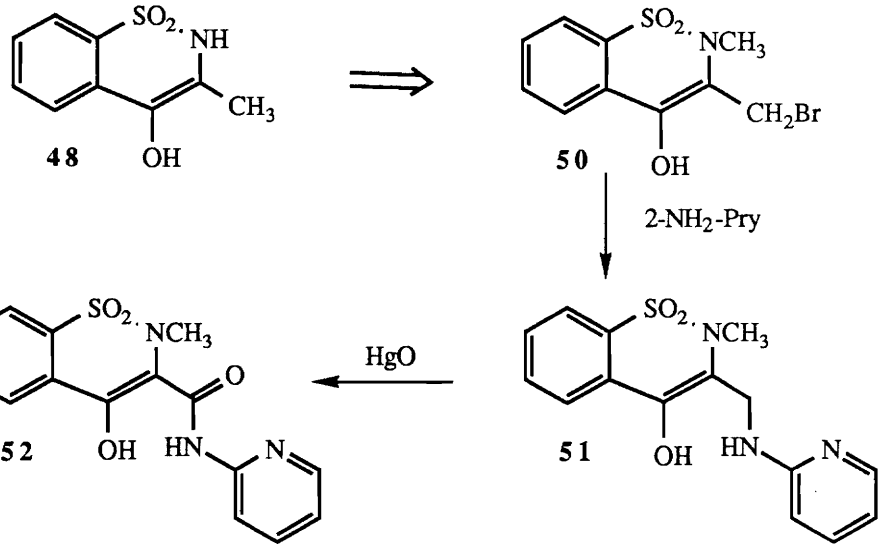
Scheme IX



benzisothiazole **44.**[25] The mechanism of this transformation has been proposed to involve the tricyclic intermediate **46** (Scheme IX). Similarly produced were 3-methyl and 3-ethyl-3-methyl derivatives **48** and **49**. The preparation of piroxicam **52** from enol **50** of 3-

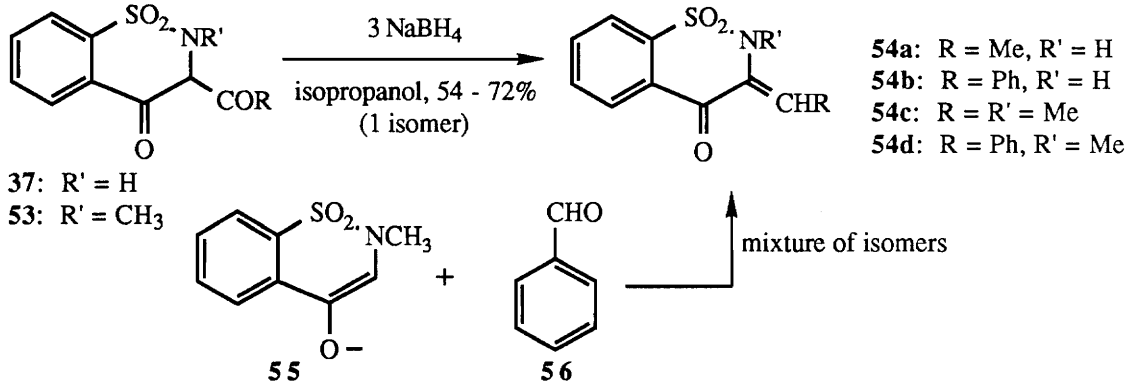
methyl-4-one **48** has been described by Rosell et al.[26] The synthesis involves amination of bromide **50** and HgO oxidation of allylic amine **51** to yield piroxicam **52** (Scheme X).

Scheme X



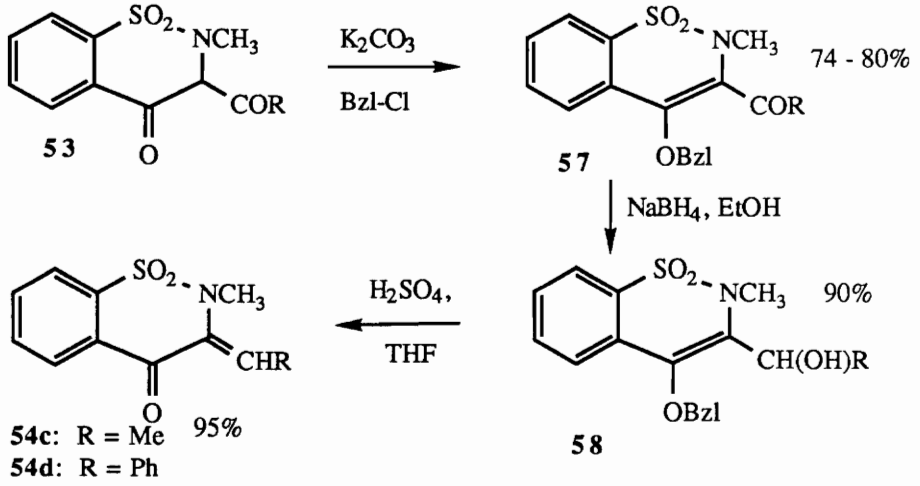
Several 3-substituted benzothiazin-4-ones have been prepared from diones **37** as well as 4-one **43**. Zinnes reported the preparation of 3-ethylidene and 3-benzylidene derivatives **54** via the sodium borohydride reduction of **37** and of 2-methyl derivatives **53** (Scheme XI).[22] Zinnes also described the preparation of 3-benzylidine derivative **54d** via

Scheme XI



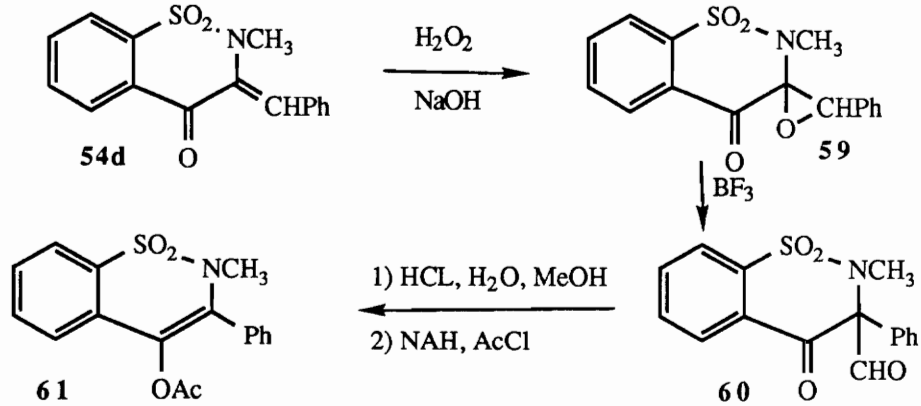
NaH treatment of **43** and condensation of the resulting enolate **55** with benzaldehyde.[22] Dalla Croce et al report that in their hands the sodium borohydride reduction of **53** did not yield **54**. Alternatively, these workers prepared the benzylated intermediate **57**, which upon $NaBH_4$ reduction and dehydration gave the 2-methyl derivatives **54c** and **54d** (Scheme XII).[27] Enone **54d** is an interesting intermediate in that Zinnes reported that

Scheme XII

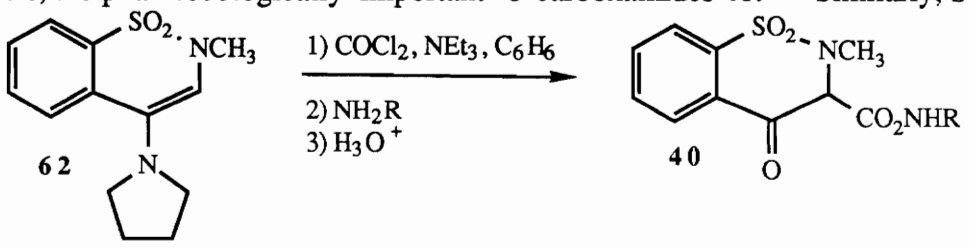


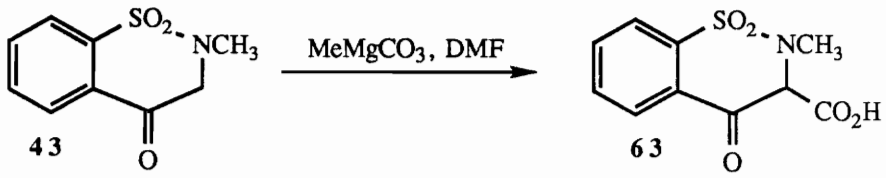
oxidation yields epoxide **59**, which upon treatment with BF_3 afforded rearrangement product **60**.[28] Decarbonylation of **60** and acetylation gives 3-phenyl derivative **61** (Scheme XIII). A synthetically useful reaction of **43** is the preparation of enamine **62**.

Scheme XIII



Treatment of the enamine with phosgene followed by an appropriate amine gives, upon hydrolysis, the pharmocologically important 3-carboxamides **40**.[29] Similarly, Suh and

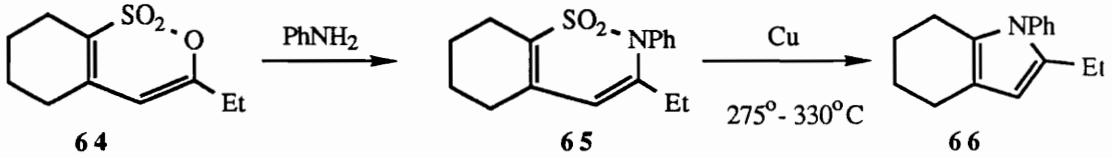




Hah report that treatment of the 1-2-benzothiazin-4-one **43** with methyl magnesium carbonate in dimethyl formamide gave the 3-carboxylic acid **63**.[30]

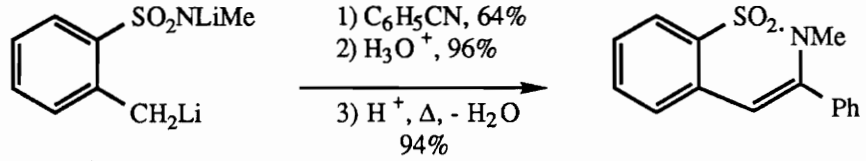
1.3 Other 1,2-Benzothiazines

Among the first reports of a 2*H*-1-2-benzothiazine 1,1-dioxide is that of Helferich and Klebert.[31] In 1962 these researchers described the preparation of 3-ethyl-5,6,7,8-tetrahydro-2-phenyl-2*H*-1,2-benzothiazine 1,1-dioxide (**65**) from aniline and sultone **64**.



64 **65** **66**

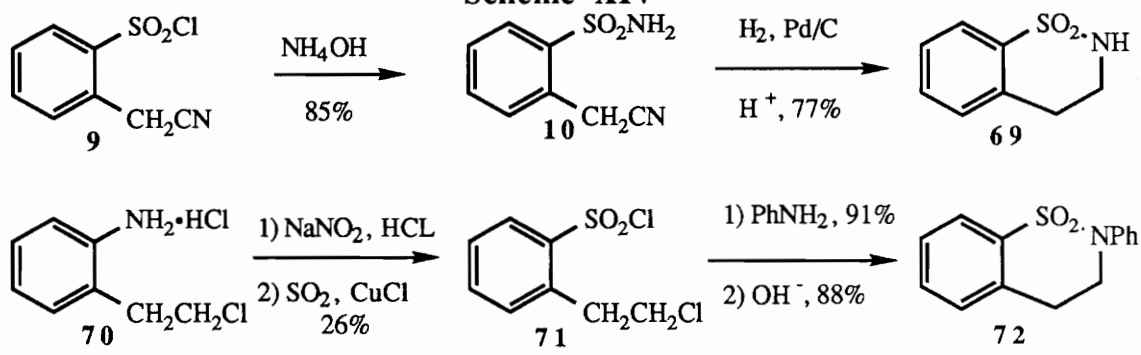
Pyrolysis of sultam **65** on Cu gave pyrrole **66**. Hauser reported that trapping of dilithiosulfonamide intermediate **67** with benzonitrile gave, upon cyclodehydration, 2-



67 **68**

methyl-3-phenyl-2*H*-1,2-benzothiazine 1,1-dioxide (**68**).[32] Siannesi reported the preparation of 3,4-dihydro-2*H*-1,2-benzothiazine 1,1-dioxide (**69**) from sulfonyl chloride

Scheme XIV



9 **10** **69**

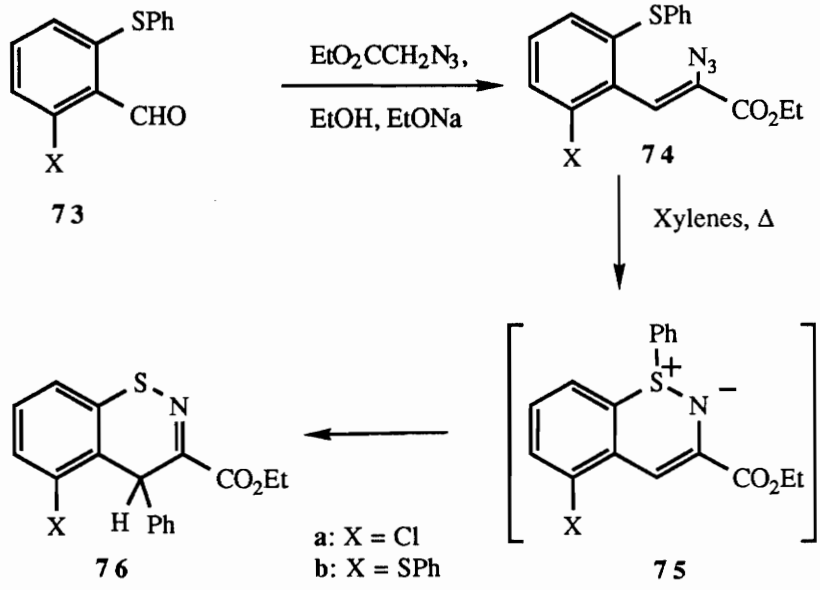
70 **71** **72**

9 (Scheme XIV).[33] Amination of **9** with ammonia and reductive cyclization gave the 3,4-dihydro derivative **69**. The 2-phenyl analog was prepared from *o*-(2-chloroethyl)aniline (**70**). Diazotization of aniline **70** and treatment with SO_2 and CuCl gave sulfonyl chloride **71**. Amination with aniline and base-promoted cyclization gave 3,4-dihydro-2-phenyl-2*H*-1,2- benzothiazine 1,1-dioxide (**72**).

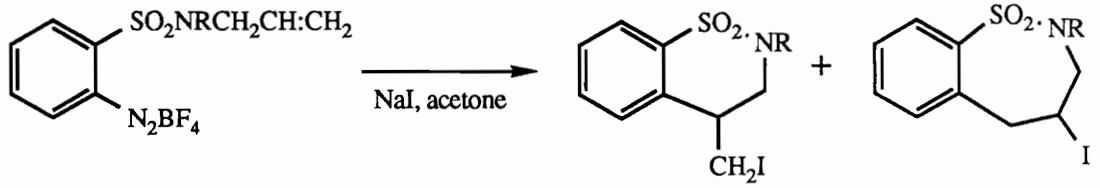
More recently, Grant et al. reported the formation of 3,4,5-trisubstituted-4*H*-1,2-benzothiazine **76** from diaryl sulfide **73**.[34] Condensation of 2,6-bis(phenylthio)-

benzaldehyde with ethylazidoacetate gave α-azidoenoate **74**. Thermolysis in refluxing xylenes gave 4*H*-1,2-benzothiazine **76** via proposed ylide intermediate **75** (Scheme XV). Curiously, when X = Cl the yield was 65%; yet when X = SPh the yield

Scheme XV



was only 13%. In another recent publication, Beckwith and Meijs report the formation of 3,4-dihydro-4-substituted benzothiazine iodides **81**.[35] The transformation of diazonium salts **77** to form benzothiazines **81** and benzothiazepines **83** was proposed to occur via an



77

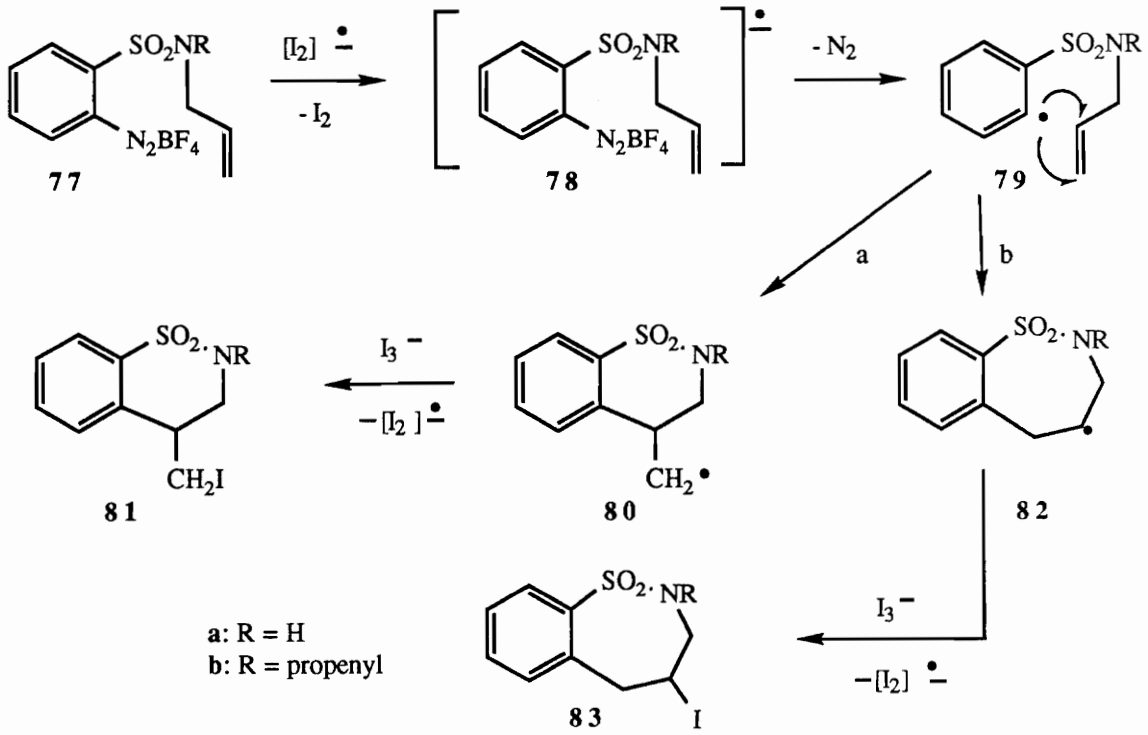
a: R = H
b: R = propenyl

81a 23%
81b 20%

83a 50%
83b 57%

$S_{RN}1$ related mechanism (Scheme XVI).[36] Reduction of the diazonium salt **77** by iodine radical-anion and fragmentation yields aryl radical **79**. Addition of the radical to the alkene

Scheme XVI



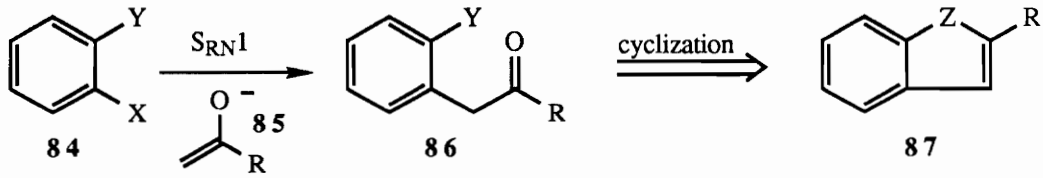
occurs either exo (path a) or endo (path b). Abstraction of an iodine atom from I_3^- by intermediate alkyl radicals **80** and **82** results in the formation of 4-(iodomethyl)-1,2-benzothiazin (**81**) and 4-iodo-1,2-benzothiazepine (**83**) respectively. The reaction also regenerates the iodine radical-anion initiator.

2 AROMATIC HETEROANNULATIONS INVOLVING THE $S_{RN}1$ MECHANISM.

2.1 Intermolecular Heteroannulations

Since the pioneering report by Bunnett and Kim, aromatic substitution via the $S_{RN}1$ mechanism has received much attention in the literature.[37] The several reviews and the landmark monograph by Rossi and Rossi have encouraged others to continue to extend the synthetic utility of aromatic $S_{RN}1$ reaction.[4] A particularly useful application of the $S_{RN}1$ reaction is the substitution-cyclization methodology of heterocyclic synthesis pioneered by Buegelmans.[5] This methodology is described in general terms by Scheme XVII.

Scheme XVII



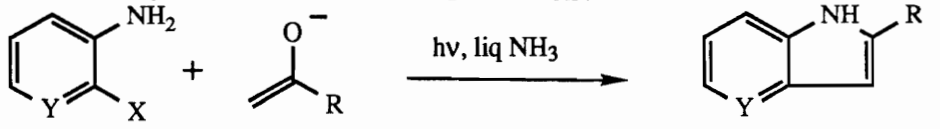
84 X = Cl, Br, I

86 Y = NH_2, OR', CH_2NH_2, CO_2H, $CONH_2$

87 Z = NH, O, CH_2NH, CO_2, CONH

Aromatic nucleophilic substitution on *ortho*-functionalized aryl halide **84** by enolate **85** results in arylated intermediate **86**. Cyclization via condensation of the *ortho*-nucleophile with the carbonyl function originating from the enolate yields the benzoheterocycle **87**. In some examples the substitution-cyclization sequence occurs in one pot. In other examples unleashing of the *ortho*-nucleophile is required.

The one-pot preparation of indoles and 4-aza-indoles has been reported independently by Beugelmans and by Bunnett.[5l,5m,37] The photoinitiated reactions proceed cleanly and efficiently for methyl ketone enolates yielding the 2-substituted indoles **89b-d** in excellent yields. In a rare example of $S_{RN}1$ participation of the enolate anion



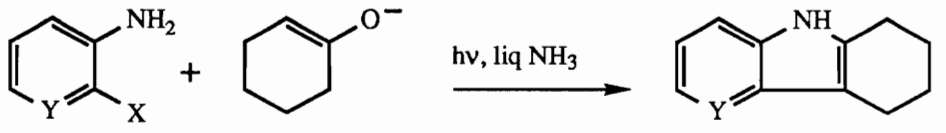
88: Y = CH
90: Y = N

85

a: R = H
b: R = Me
c: R = *i*-propyl
d: R = *t*-butyl

89: Y = CH, 80 - 100%
91: Y = N, 23-100%

derived from acetaldehyde, Beugelmans reported the preparation of indole (**89a**) by the action of acetaldehyde enolate (**85a**) on 2-iodooaniline (**88**; X = I).[5m] The analogous reactions of 3-amino-2-chloropyridine (**90**; X = Cl) with ketone enolates **85b-d** yields the 2-substitued-4-azaindoles **91b-c** in moderate yields.[51,38] In addition to the photopromoted $S_{RN}1$ preparation of indoles, Beugelmans has reported an electrochemically initiated preparation.[5i] Indole and 2-alkylindoles **89a-c** were prepared in yields of 75-93% by the electrochemical reduction of 2-iodoaniline in liquid NH_3 in the presence of the corresponding enolate. More recently Bunnett has demonstrated that 2-methylindole (**89b**) can be prepared in 51% yield by an $FeSO_4$ catalyzed $S_{RN}1$ reaction in liquid NH_3 of 2-chloroaniline with acetone enolate.[39] Carbazole derivative **93** and 6-aza-carbazole



88: Y = CH
90: Y = N

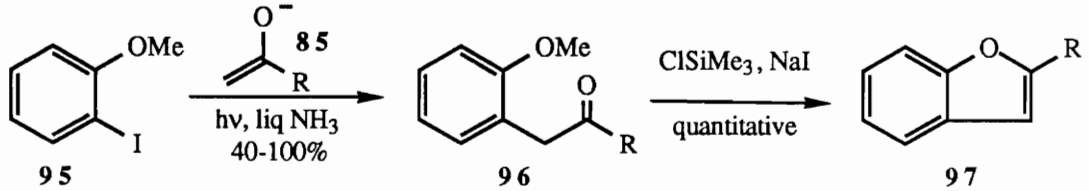
92

93: Y = CH, 14% (X = Br) 40% (X = I)
94: Y = N, 22%(X = Cl)

derivative **94** have been prepared by the photostimulated reaction of cyclohexanone enolate (**92**) with 2-haloanilines **88** and 3-amino-2-chloropyridine (**90**; X = Cl) respectively. The yield reported for 1,2,3,4-tetrahydrocarbazole **93** is significantly higher when 2-iodoaniline[5m] is employed than when 2-bromoaniline is used.[37]

Benzo[*b*]furans, furo[3,2-*b*]pyridines and furo[3,2-*h*]quinolines have been prepared via the $S_{RN}1$ substitution-cyclization methodology.[5a,k] Beugelmans reported the preparation of 2-substituted benzofurans **97** by the two step reaction sequence outlined in Scheme XVIII. Good to excellent yields of the substitution reaction combine with the

Scheme XVIII



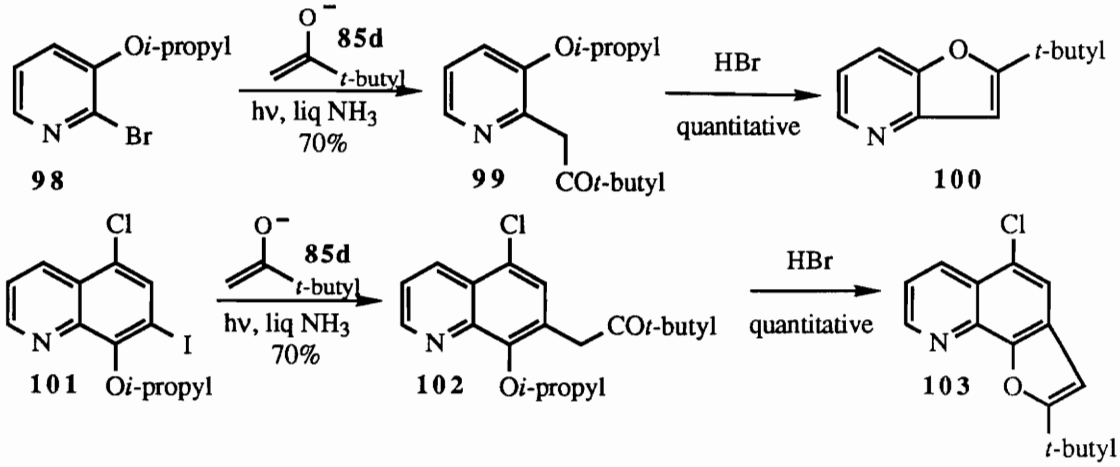
95

96
a: R = H
b: R = Me
c: R = *i*-propyl
d: R = *t*-butyl

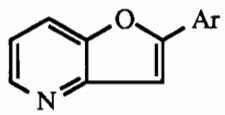
97

quantitative yields of the deprotection-cyclization reaction of the resulting *ortho*-substituted anisoles **96**, to make the method preparatively useful.[5k] In more recent work, Beugelmans has reported the preparation of furo[3,2-*b*]pyridine (**100**) and furo[3,2-*h*]-

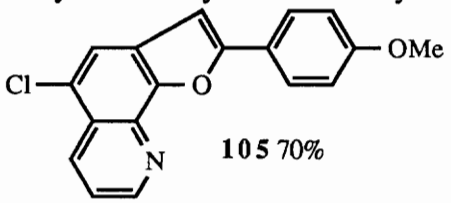
Scheme XIX



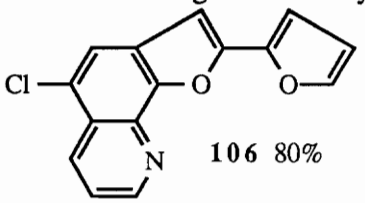
quinoline (**103**) via a similar reaction sequence (Scheme XIX). In addition to the reactions with pinacolone enolate (**85d**), Beugelmans extended the study to include enolates derived from methyl aryl and methyl heteroaryl ketones to yield the interesting heterobiaryl



104a: Ar = C_6H_5 70% (in DMSO)
104b: Ar = 4-MeO-C_6H_4 98% (in DMSO) 30% (in liq. NH_3)



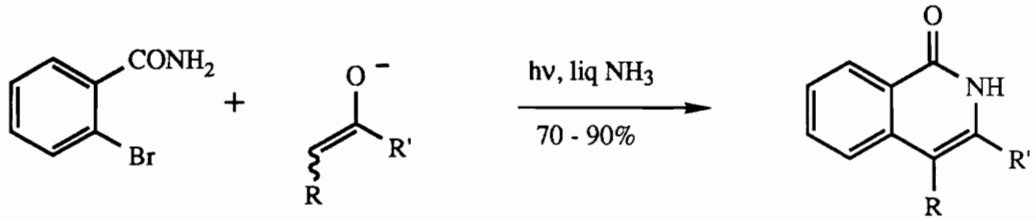
105 70%



106 80%

compounds **104-106**. The synthesis of furopyridines **104a** and **104b** required substitution in DMSO to obtain preparative yields. However, furoquinolines **105** and **106** were conveniently prepared in liquid NH_3.[5a]

The one-pot preparation of isocarbostyrils **109a-d** from 2-bromobenzamide **107** and the appropriate ketone enolate **85b-d** and **108a** was reported by Beugelmans.[5j] In general the reactions yield the isocarbostyriles in excellent yields. However, the reaction

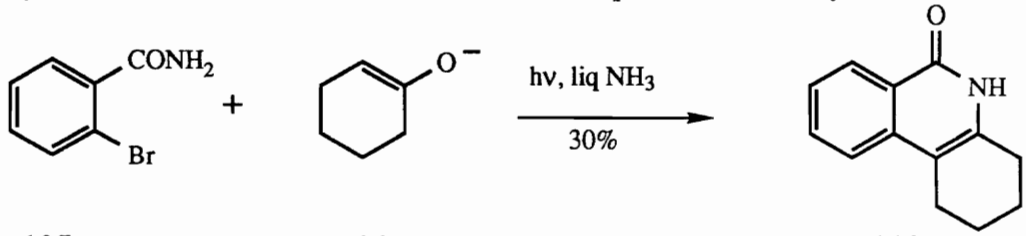


107

85b: R = H, R' =Me
85c: R = H, R' = *i*-propyl
85d: R = H, R' = *t*-butyl
108a: R = Me, R' = Et

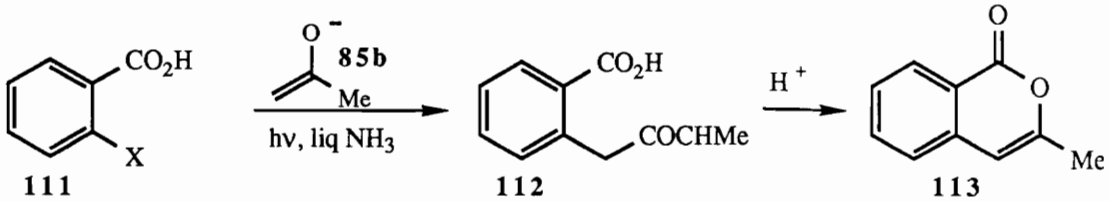
109a: R = H, R' = Me
109b: R = H, R' = *i*-propyl
109c: R = H, R' = *t*-butyl
109d: R = Me, R' = Et

involving the enolate **108a** derived from 3-pentanone gave a 20% yield of the reduction product benzamide. Similarly, the reaction of enolate **92** derived from cyclohexanone gave a 60% yield of benzamide in addition to the anticipated isocarbostyril derivative **110.**



107 **92** **110**

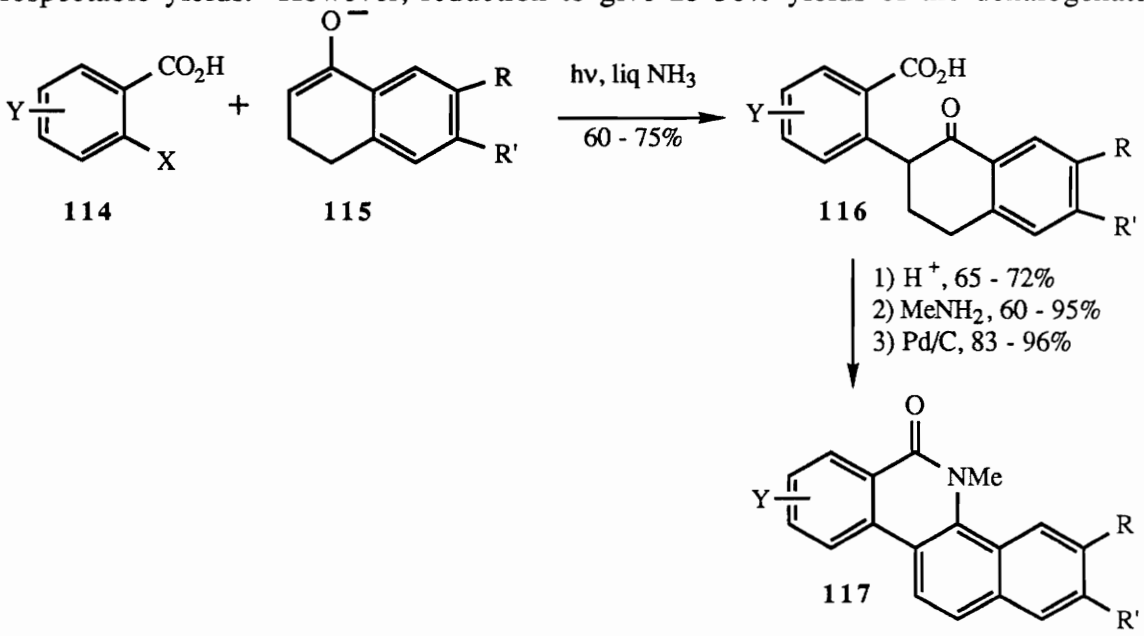
Interestingly, the reactions involving enolates **108a** and **92** required long reaction periods, five and three hours respectively. Yet the reactions involving enolates **85b-d** were complete within 30 minutes. This point is discussed within the Results and Discussion Section (Section III.1.3). Beugelmans also reported that the *N*-alkyl analogs of benzamide **107** gave poor yields of the 2-substituted isocarbostyrils when treated with acetone enolate under analogous conditions. Reduction via an unknown mechanism resulted in sluggish dehalogenation of the starting benzamide. The 2-substituted isocarbostyrils were alternatively prepared by *N*-alkylation of isocarbostyrils **109** or by the amination of isocoumarin **113**. Isocoumarin **113** was also prepared via the $S_{RN}1$ reaction.[5h] Similar to the reaction of 2-bromobenzamide, 2-bromo and 2-iodobenzoic acids **111**



111 **112** **113**

have been shown to participate in a substitution reaction with enolate **85b**. Acid treatment of the substitution product **112** gave 3-methylisocoumarin (**113**) in good overall yields.[5h] In a related report, Beugelmans describes the synthesis of benzo[*c*]phenanthridones in four

steps from 2-iodobenzoic acids **114** and the enolates **115** derived from substituted tetralones.[5d] The substitution reaction proceeds to give the α-arylated tertralones **116** in respectable yields. However, reduction to give 25-30% yields of the dehalogenated

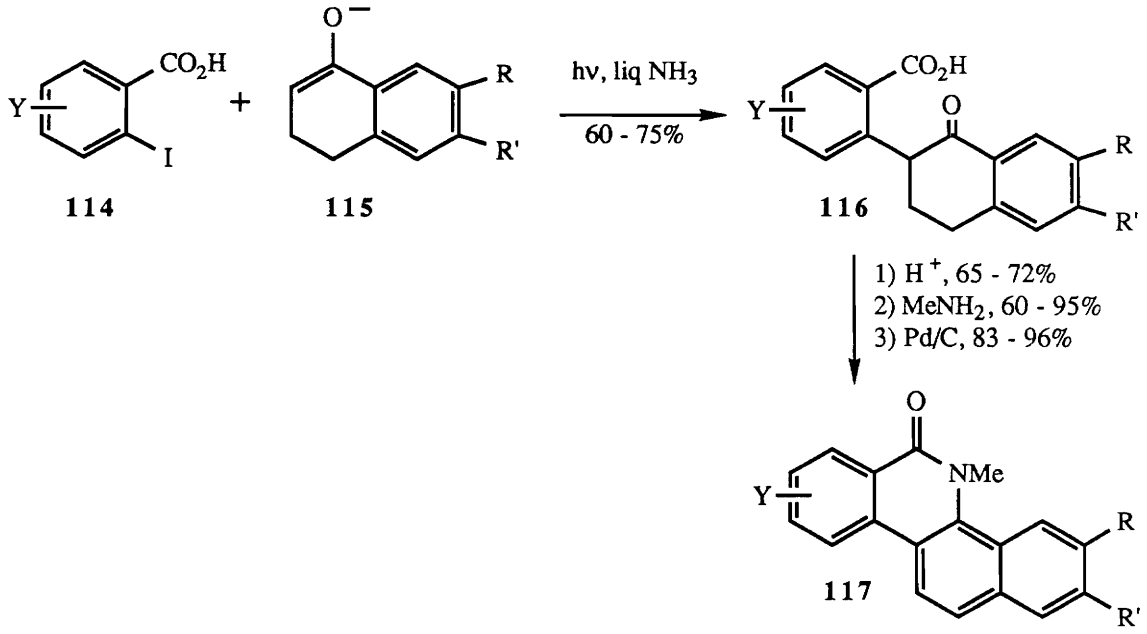


114 **115** **116** **117**

benzoic acids was also observed. Acid-promoted cyclodehydration, amination and finally oxidation by Pd/C, of the substitution product gave the desired benzo[*c*]phenanthridones **117**. Attempts at an alternate strategy starting with the analogous 2-iodobenzamides resulted in production of only dehalogenated benzamides. The reduction reaction required five hours to completely consume the starting amide. Beugelmans suggested that the mechanism of reduction involves a non-chain two electron reduction of the aryl halide with sequential protonation by NH_3.[5d]

In another report, Beugelmans described the application of the $S_{RN}1$ reactions of 2-halophenylacetic acids with ketone enolates in the synthesis of 3-benzoxepines and 3-benzazepines.[5c] 2-Bromo- and 2-iodo-4,5-dimethoxyphenylacetic acids **118** react with enolates **85b-d** to yield the corresponding arylated ketones **119** in good yields (Scheme XX). Once again, reduction to yield 10-40% of the dehalogenated starting material, was observed. The synthesis of the 3-benzoxepines **120** was accomplished by $NaBH_4$ reduc-

Scheme XX

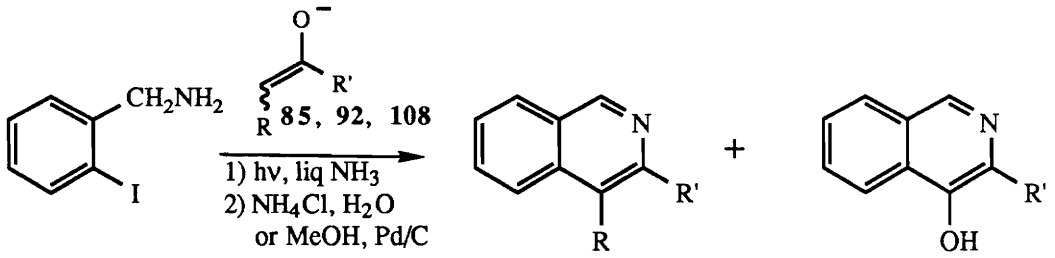


114 **115** **116** **117**

tion in methanol of the ketone and then cyclodehydration to yield the benzolactone. The synthesis of the 3-benzazepines was accomplished by treatment of the substitution product **119** with ammonium acetate in glacial acetic acid.

Isoquinoline derivatives have been prepared from 2-iodobenzyl amine with ketone and aldehyde enolates via the aromatic $S_{RN}1$ reaction.[5e,g] Beugelmans reported that isoquinoline **123** and its 3-alkyl (**124**) and 4-alkyl (**126b**) derivatives are formed in the one-pot reaction of 2-iodobenzylamine (**122**) with enolates **85a-d** and **108a** (Scheme

Scheme XXI



122

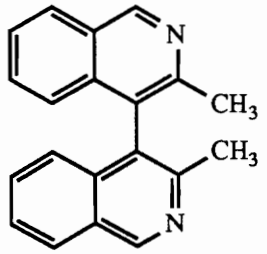
85a: R = H, R' = H
85b: R = H, R' = Me
85c: R = H, R' = *i*-propyl
85d: R = H, R' = *t*-butyl
92: R-R' = -$(CH_2)_2$-
108a: R= Me, R' = Et

123: R = H, R' = H
124a: R = H, R' = Me
124b: R = H, R' = *i*-propyl
124c: R = H, R' = *t*-butyl
125: R-R' = -$(CH_2)_2$-
126a: R= Me, R' = Et

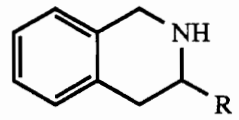
127a: R = H, R' = Me
127b: R = H, R' = *i*-propyl
127c: R = H, R' = *t*-butyl

XXI). The formation of 4-hydroxy-isoquinolines **127a-c** from the reactions of ketone enolates **85b-d** suppressed the yields of the anticipated 3-alkylisoquinolines. Beugelmans,

reported that an anaerobic work up with MeOH and Pd/C precludes the formation of **127** and gives preparatively useful yields of the 3-alkylisoquinolines. Employing the Pd/C work up, the synthetic methodology was extended to include the preparation of 3-ethyl-4-methylisoquinoline **126a** and tetrahydrophenanthradine **125**. In an attempt to optimize the yields of the 4-hydroxy substrates **127a**, air was bubbled through the NH_3 solution upon quenching of the reaction of enolate **85b** and 2-iodobenzylamine (**122**). This aerobic oxidative workup resulted in the formation of bisisoquinoline **128**. Likewise oxidation with MnO_2, resulted in the formation of bisisoquinoline **128** as well. The

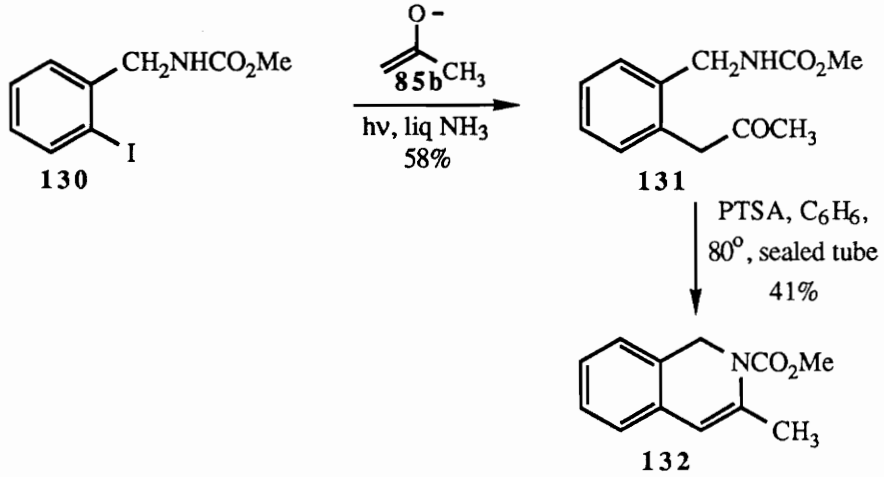


128

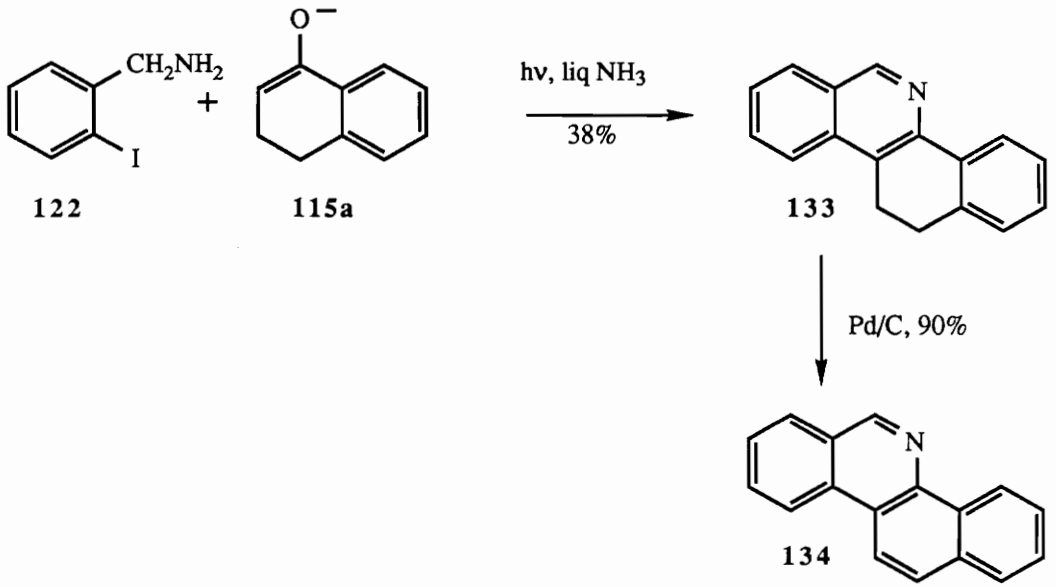


129a: R = Me
129b: R = *i*-propyl

preparation of tetrahydroisoquinolines **129a** and **129b** was accomplished by $NaBH_4$ in methanol treatment of the crude mixture from the substitution reaction. 2-Methoxycarbonyl-1,2-dihydro-3-methylisoquinoline (**132**) could be obtained from enolate **85b** and carbamate **130**. The aromatic $S_{RN}1$ reaction of **130** and **85b** resulted in formation of ketone **131**, acid catalyzed cyclodehydration gave the desired 2-protected 1,2-



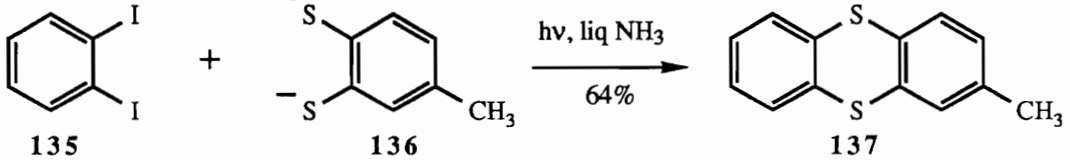
dihydroisoquinoline **132**. A similar approach using 2-iodobenzylacetamide gave the *N*-acetyl analog of *N*-methoxycarbonyl ketone **131**. However, attempts at acid catalyzed cyclodehydration of the *N*-acylated substitution product resulted in formation of a mixture of **124a** and **127a**. As an extension of this methodology Beugelmans employed 2-



122 115a 133 134

iodobenzylamine and a variety of its derivatives in the synthesis of 16 different benzo[*c*]phenanthridines in overall yields ranging from 30-70%.[5d] The reaction of 2-iodobenzylamine with enolate **115a** is representative. The aromatic $S_{RN}1$ reaction and acidic work up gave the dihydro species **133**. Treatment of **133** with Pd/C resulted in the fully aromatic polycyclic heterocycle **134**.

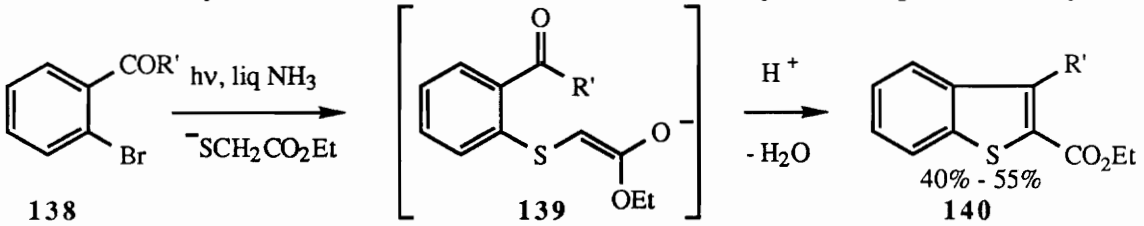
Another approach to heterocyclic synthesis via the intermolecular $S_{RN}1$ reaction involves substrates with two electrophilic sites. The electrophilic sites can be the C-1 and C-2 carbons of an *ortho*-dihaloaromatic substrate or the sites can be the halogenated ring carbon and the benzylic carbon of an *ortho*-functionalized aryl halide. At a point during the reaction sequence, substitution by a heteroatom of the nucleophile occurs. The hetero-substitution reaction can be either the $S_{RN}1$ reaction or a subsequent step involving the *ortho*-electrophile. An example of the first strategy is provided by reaction of dithiolate nucleophiles with a variety of *ortho*-dihaloaromatic substrates to yield several



135 136 137

1,4-dithianes.[39] The reaction of *o*-diiodoobenzene (**135**) with 3,4-toluenedithiolate ion (**136**) to yield 2-methylthianthrene **137** is representative. The reaction was found to yield the cyclization product in 55% yield along with recovered starting aryl halide in 29% yield. Two examples of the second approach have appeared in the literature. The first report

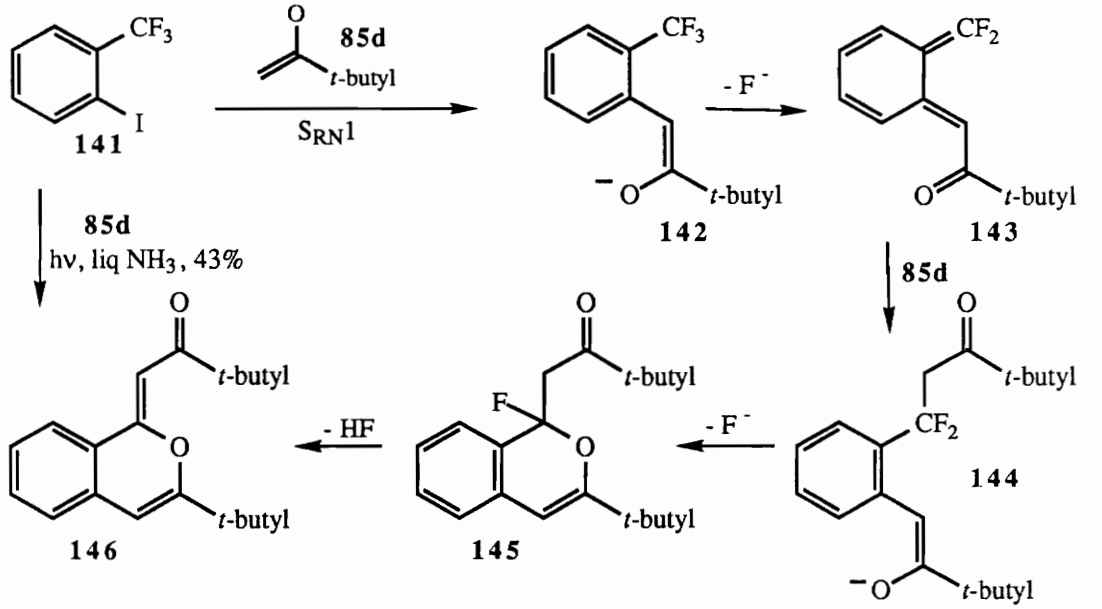
describes the substitution-cyclization reactions of 2-bromoacetophenone (**138a**) and 2-bromobenzaldehyde (**138b**) with the anion derived from ethyl 2-mercaptoacetate to yield



a: R' = Me
b: R' = H

benzothiophenes **140**. The $S_{RN}1$ reaction involves ring substitution by the thiolate nucleophile. The cyclization reaction results from ionization α to the ester and intramolecular aldol condensation. The yields are low due to cleavage of the sulfur-carbon bond of the ester to yield thiophenoxides. Bunnett in the second report, described the peculiar behavior of the triflouromethyl substituent in the $S_{RN}1$ reaction. Bunnett reported that when α,α,α-triflouro-*o*-iodotoluene (**141**) is treated with enolate **85d** derived from pinacolone, 1*H*-benzo[*c*]-pyran-1-ylidene **146** results (Scheme XXII).[41] The mechanism

Scheme XXII

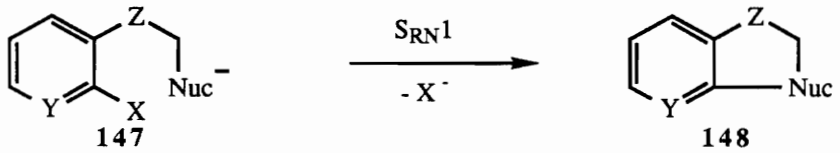


involves the $S_{RN}1$ substitution of **141** by **85d**, ionization of the resulting ketone and elimination of F^-. Conjugate addition of excess enolate yields **144**, which undergoes an intramolecular nucleophilic displacement of F^- by the oxygen of the enolate to yield benzopyran **145**. Elimination of HF yields the final product **146**.

2.2 Intramolecular Heteroannulations

Only a limited number of intramolecular $S_{RN}1$ reactions are known, and of those, only six feature the construction of a heterocycle during the cyclization step. These six examples include the preparation of benzoazipines, oxindoles, azaoxindoles, isoquinolinones, indoles and benzothiazoles. The heteroannulation strategy is outlined in

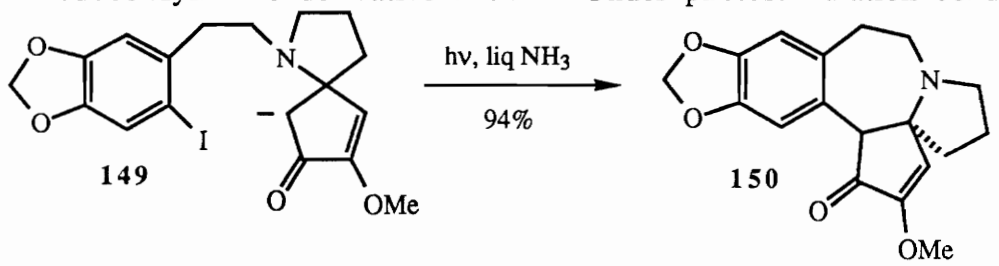
Scheme XXIII



Y = CH, N; X = Cl, Br, I; Z = $(CH_2)_nN$ (n = 0,1, 2)

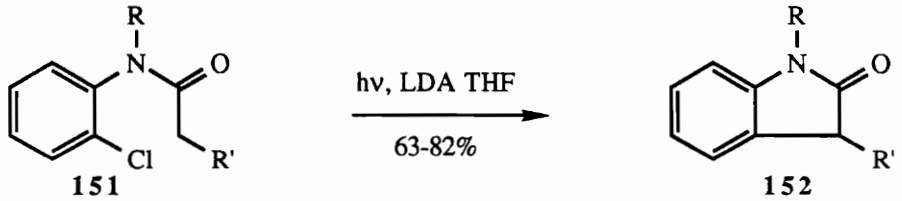
Scheme XXIII. Characteristic of the substrate **147** is a nucleophile (Nuc^-) tethered *ortho*- to an aryl halide via a heteroatom linkage. Electron transfer initiated cyclization results in the creation of the heterocycle **148.**

Heteroannulation via the intramolecular $S_{RN}1$ reaction was first reported by Semmelhack, who prepared cephalotaxine precursor cephalotaxinone (**150**) via cyclization of the 2-iodobenzylamine derivative **149.**[42] Under photostimulation conditions



the reaction gave a 94% yield of pentacyclic product **150.** By comparison, a relatively poor yield (45%) was obtained when the reaction was initiated via dissolving sodium metal. The preparation of cephalotaxinone (**150**) and its subsequent transformation into cephalotaxaine represents the first report of natural product total synthesis with a key step involving the $S_{RN}1$ mechanism.[42b]

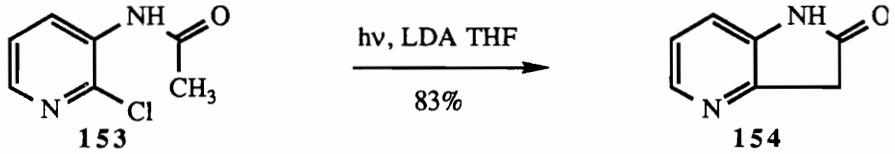
Wolfe et al. extended the intramolecular $S_{RN}1$ reaction to include the preparation of oxindoles, azaoxindoles and isoquinolinones.[6] Wolfe reported that *N*-acyl-*o*-chloro-anilines and *N*-alkyl-*N*-acyl-*o*-chloro-anilines **151a-f** undergo cyclization upon treatment



151 152

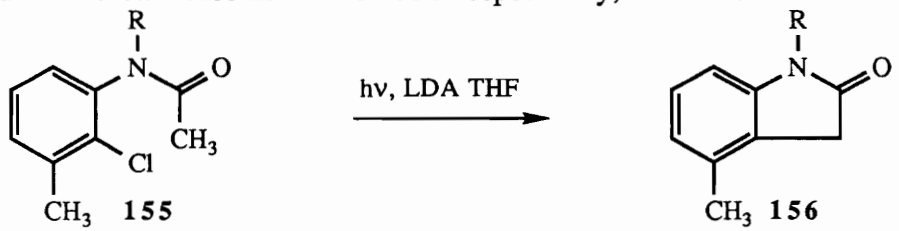
a: R = H, R' = H
b: R = H, R' = CH_3
c: R = H, R' = C_6H_5
d: R = CH_3, R' = H
e: R = CH_3, R' = *n*- C_4H_9
f: R = CH_3, R' = C_6H_5

with excess lithium diisopropyl amide (LDA) in THF-hexane followed by near-UV irradiation. The resulting oxindoles **152a-f** are obtained in good yields. In addition, Wolfe reported that similar treatment of 2-chloro-3-(*N*-methylacetamido)pyridine **153**



153 154

results in azaoxindole **154**. The isolation of oxindoles **156a** and **156b** from 3-substituted-2-chloroanilines **155a** and **155b** respectively, indicates that the reaction does

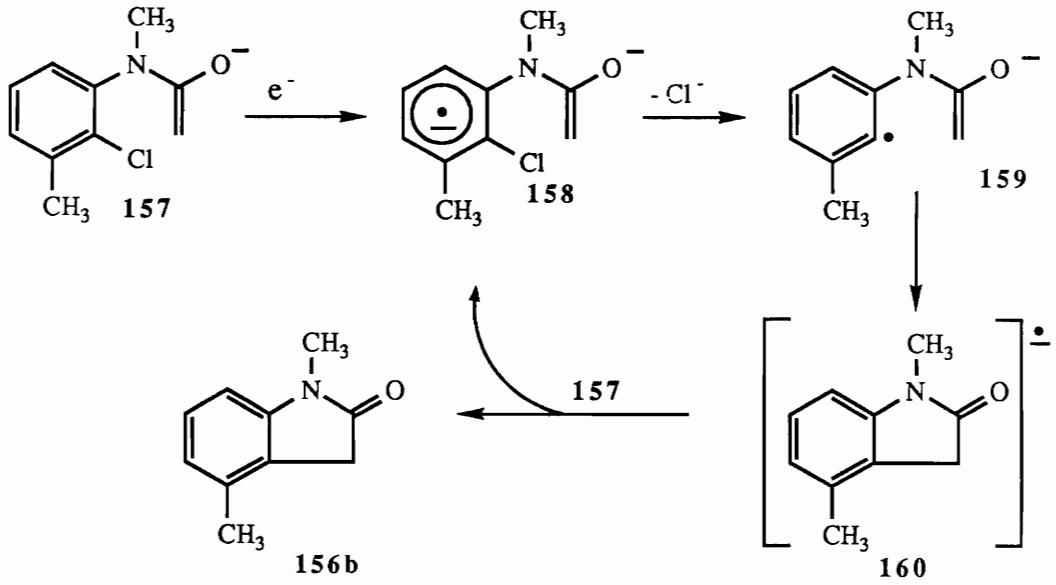


155 156

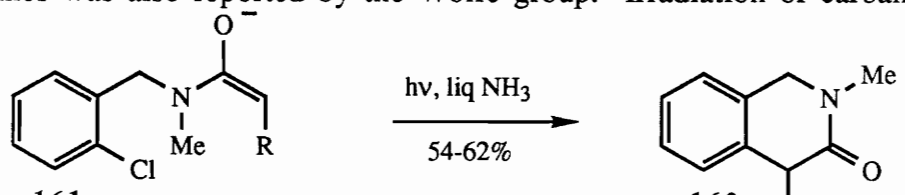
a: R = H, 76%
b: R = CH_3, 87%

not occur via an aryne type intermediate. The reaction characteristics of the cyclization of **151a** included the requirement of borosilicate glass-filtered light and the inhibitory action of di-*tert*-butyl nitroxide (DTBN). Based on these results it was concluded that the reaction mechanism involved the sequence outlined in Scheme XXIV.[6b] This mechanism

Scheme XXIV

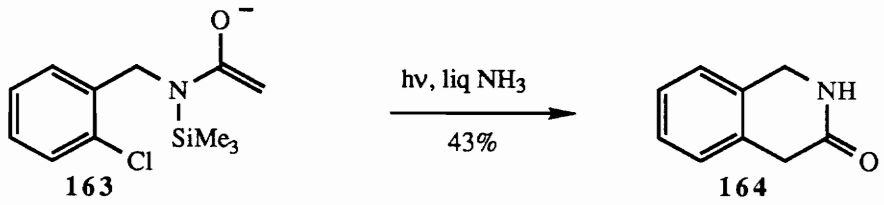


features an external electron transfer to acetamido enolate anion **157** to yield aryl radical anion **158**. Fragmentation of **158** results in aryl radical **159**. Intramolecular trapping of the aryl radical by the tethered enolate nucleophile results in oxindole radical anion **160**. Transfer of an electron from **160** to the starting anion **157** yields the oxindole **156b** and propagates a radical chain sequence. Similar behavior of *N*-acyl-*N*-methyl-*o*--chloro-benzylamines was also reported by the Wolfe group. Irradiation of carbanions **161**



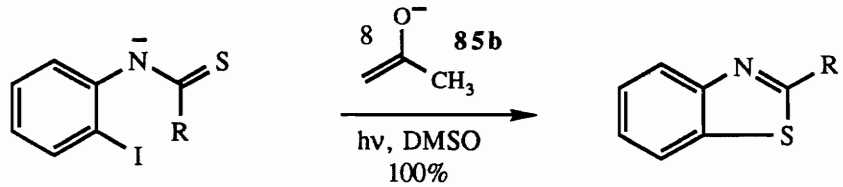
a: R = H **b**: R = Me **c**: R = Et

derived from *N*-acyl-*N*-methyl-*o*-chlorobenzylamines in liquid NH_3 gave 1,4-dihydro-3-(2*H*)-isoquinolinones **162** in yields of 54-62%. Attempts to effect the photocyclization reaction of **161** using LDA in THF returned starting material. The unsubstituted 1,4-dihydro-3-(2*H*)-isoquinolinones **164** could be obtained in moderate yields by photocyclization of *N*-(trimethylsilyl)amide **163**.



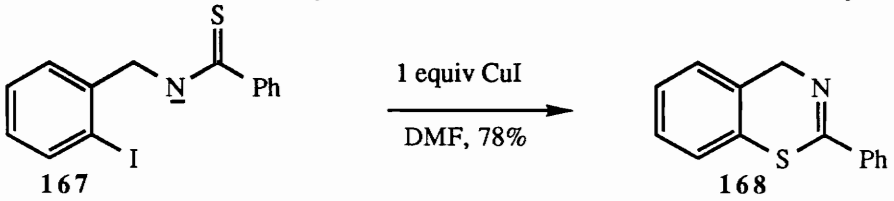
163 164

Bowman reported that benzothiazoles **166** resulted from an intramolecular photocyclization of thioamide anion **165** in DMSO. An entraining agent, enolate **85b** derived from acetone, was required for the cyclization to take place.[43] Bowman reported that the entrainment was inefficient when 0.2 equivalents of **85b** was used; the cycliza-

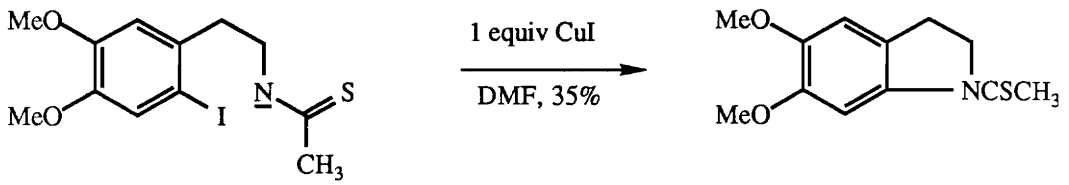


165 a: R = Me b: R = Ph 166

tion was sluggish yielding only 13% of **166** after 5.5 hours of photostimulation. Eight equivalents of **86b**, was needed to obtain high yields of the cyclization products. When **165** was treated with eight equivalents of **85d** in the presence of radical scavengers, the photocyclization reaction did not occur. When the *o*-chloro- and *o*-bromo- analogs of **165** were treated with eight equivalents of the entraining agent, the cyclization reaction resulted in formation of **166** in yields of only 5% and 22%, respectively. These results are in good agreement with the mechanism proposed by Wolfe (see Scheme XXIV) for the intramolecular $S_{RN}1$ cyclization of *N*-acyl-2-chloroanilides. The minor departure from the Wolfe mechanism is the source of the initial electron. For Bowman's study that source is clearly enolate **85b**, hence the term entraining agent. Bowman also reported that cyclization of thioamides **165a**, **165b** and the bromo and chloro analogs of **165b** gave quantitative yields of **166a** and **166b**, respectively, upon treated with base and a catalytic quantity of CuI in DMF. Similarly, 1,3-benzothiazine **168** and *N*-thioacetyl indole **170**

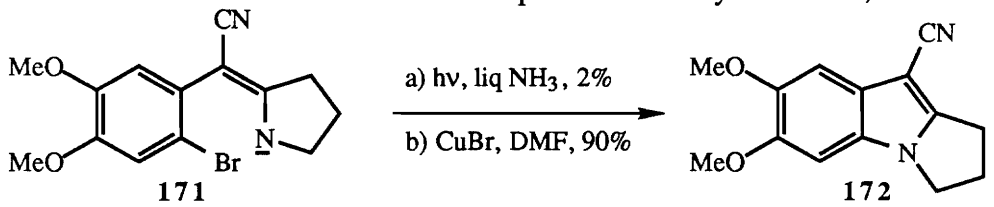


167 168



169 **170**

resulted from the CuI catalyzed cyclization of anions **167** and **169**, respectively. Bowman indicated that the CuI catalized cyclizations are not inhibited by radical scavengers.[43b] Similar results to that of Bowman's had been reported earlier by Kametani, who found that

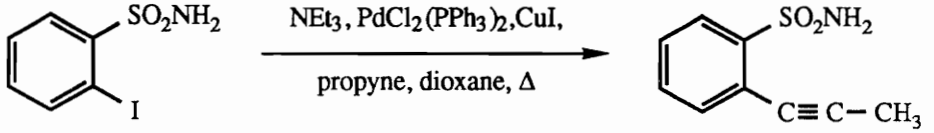


171 **172**

pyrroloindole **172** was formed in 2% yield upon photocyclization of anion **171** in liquid NH_3.[44] The yield of **172** increased to 90% when nitrile **171** was treated with catalytic quantities of CuBr in DMF.

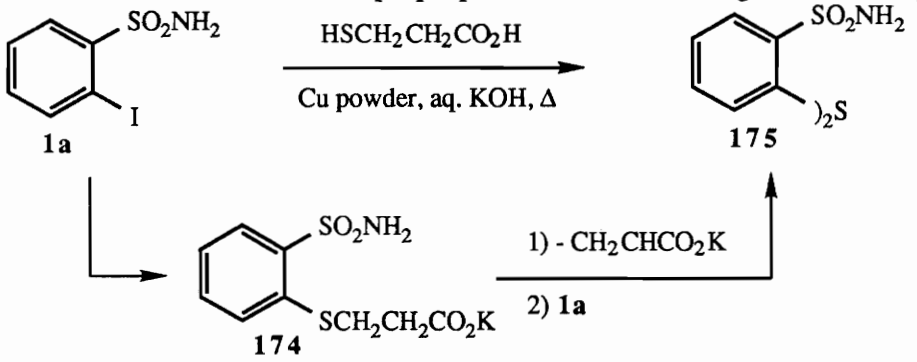
3 AROMATIC SUBSTITUTION REACTIONS OF 2-IODOBENZENESULFONAMIDE.

Two reports of aromatic substitution involving replacement of iodide from 2-iodobenzenesulfonamide (**1a**) have appeared in the literature in the recent past. The first report appears in a European patent application of Schurter, Foery and Meyer.[45] These workers describe the propynylation of sulfonamide **1a** via treatment with $PdCl_2(PPh_3)_2$,



1a **173** 73%

CuI, NEt_3 and propyne. This reaction gave **173** in 80% yield. The second report is that of Rabai, which described the preparation of a series of symmetrical diary sulfides from 2-iodobenzenesulfonamides and 3-mercaptopropionic acid.[46] Among the sulfides prepared



1a **175** **174**

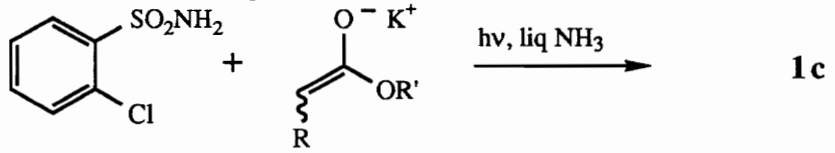
was **175**. The reaction requires Cu powder and refluxing 5-10 M KOH. The mechanism was proposed to involve substitution by thiolate to yield sulfide **174**. Elimination of acrylate and nucleophilic substitution by the resulting thiophenoxide on a second equivalent of 2-iodobenzenesulfonamide **1a** yields the symmetrical arylsulfide.

III. RESULTS AND DISCUSSION

1. INTERMOLECULAR REACTIONS OF 2-HALOBENZENE-SULFONAMIDES WITH ENOLATE NUCLEOPHILES

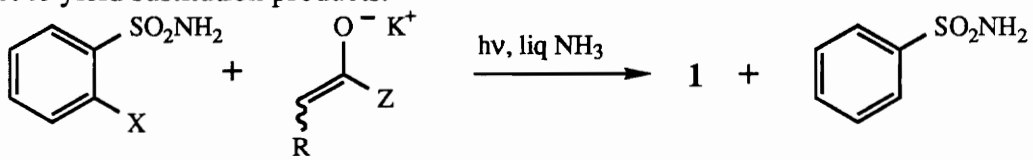
1.1 Reactions of 2-Iodobenzenesulfonamide with Ester Enolate Ions and Ester Enolate Equivalents.

Previous attempts in our laboratories to prepare 1,2-benzothiazin-3(2*H*)-one 1,1-dioxides with potential CNS-activity via nucleophilic aromatic sustitution of 2-chlorobenzenesulfonamide (**1c**) with ester enolates were unsuccessful. For example, Herman reported that only recovered starting material was obtained when **1c** was treated under irradiation with 350 nm light with the enolate anions **176a** and **176b**, obtained upon



1c **176a**: R = H, R' = *t*-butyl
176b: R = Ph, R' = Et

treatment with KNH_2 in liquid NH_3 of *t*-butyl acetate and ethyl phenylacetate, respectively.[7] In a subsequent attempt to improve the reactivity of the sulfonamide substrate, Nwokogu carried out the analogous reactions with 2-iodo- and 2-bromobenzenesulfonamides, **1a** and **1b**, respectively.[8] Nwokogu's efforts produced only recovered starting material contaminated with the reduction product, benzenesulfonamide (**179**). Next, Nwokogu investigated nucleophiles that are synthetically equivalent to ester enolates. However, as with the ester enolates, only recovered starting material and reduction products resulted. Nwokogu found that the potassium anion, **177**, derived from *N,N*-dimethylacetamide and the lithium dianion **178** derived from phenyl acetic acid failed to react to yield sustitution products.

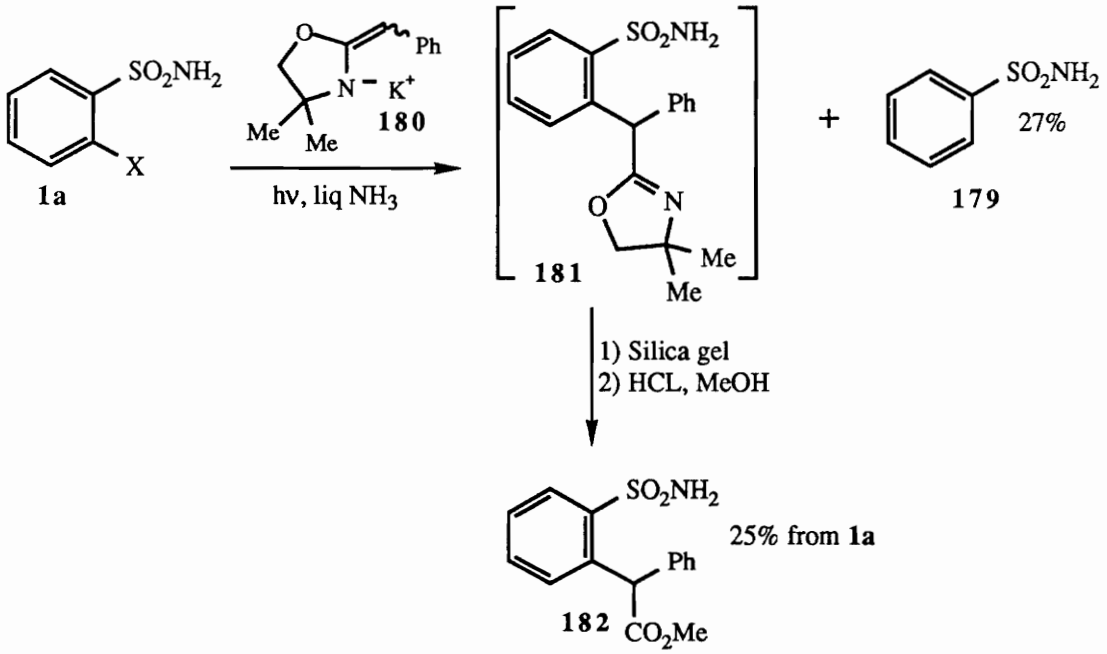


1a: X = I **177**: R = H, M = K, Z = $N(Me)_2$ **179**
1b: X = Br **178**: R = Ph, M = Li, Z = OLi

The failure of sulfonamides **1a-c** to participate in a substitution reaction with the nucleophiles investigated might be attributed to the poor solubility of the sulfonamides in the presence of those nucleophiles. Evidence for this supposition came to light as the present study unfolded. The first evidence that lead to that conclusion appeared in the reaction of 2-iodobenzenesulfonamide (**1a**) with the anion derived from 2-benzyl-4,4-dimethyl-2-oxazoline and KNH_2 in liquid NH_3.

Earlier, Wong had reported that the anion, **180**, derived from 2-benzyl-4,4-dimethyl-2-oxazoline reacts with iodobenzene via the $S_{RN}1$ mechanism to yield the corresponding α-phenylated product.[46] In the present study it was found that 2-iodobenzenesulfonamide (**1a**) undergoes photoassisted nucleophilic aromatic sustitution when treated with the oxazoline-derived anion **180** (Scheme XXV). However, the antic-

Scheme XXV



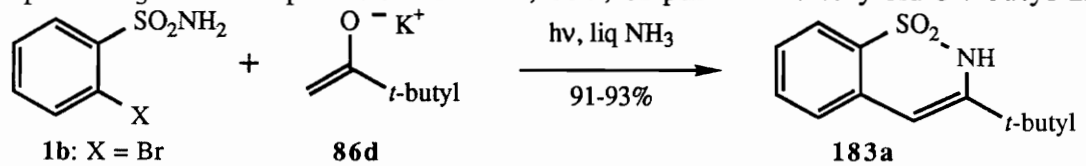
ipated α-arylated product **181** could not be isolated. Apparently, **181** is subject to opening of the oxazoline ring either under the conditions of the $S_{RN}1$ reaction or upon work up. Chromatography of the reaction mixture resulted in isolation of unreacted oxazoline and the reduction product, benzenesulfonamide (**179**). However, the products arising from the sustitution reaction co-eluted and were therefore characterized by conversion to ester **182** by refluxing the mixture in methanolic HCl. The poor yield of

182 is attributed to the tedious isolation procedure. The actual yield of sustitution product is estimated to approach 50%, based on the mass of the uncharacterized mixture of ring open products.

An interesting characteristic of the reaction of **1a** with the oxazoline derived nucleophile is the increased solubility of the substrate. Although the reaction mixture is still heterogenous, from a visual inspection it was noted that less of the substrate was out of solution in the presence of that nucleophile than in the presence of all other nucleophiles previously and yet to be mentioned. It is believed that because of this increased solubility, consumption of the starting material is facilitated. The nature of the solubility imparted by the oxazoline derived nucleophile is discussed in Section III.1.10. For now it is simply concluded that the lack of favorable reactivity of **1a** toward ester enolates, is in part due to the unavailability of the substrate in solution.

1.2 Reactions of 2-Iodobenzenesulfonamide with Enolates Derived from Acyclic Ketones.

At the outset of this work some preliminary results had already been obtained by earlier workers in our laboratories. These investigators had found that 2-bromo- and 2-chlorobenzenesulfonamide **1b** and **1c** react cleanly and efficiently under photostimulation in liquid NH_3 with the potassium enolate, **85d**, of pinacolone to yield 3-*t*-butyl-2*H*-



1b: X = Br
1c: X = Cl

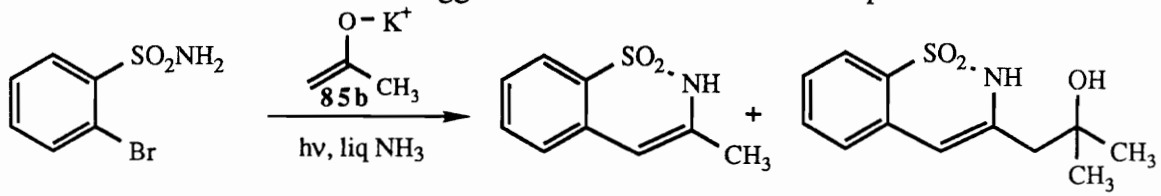
86d

183a

1,2-benzothiazine 1,1-dioxide (**183a**).[9] In view of this we wished to determine if enolates of other acyclic ketones would react in an analogous manner to yield other 3-substituted and 3,4-disubstituted 2*H*-1,2-benzothiazine 1,1-dioxides **183** and **184**, respectively. The results of that investigation are presented in Table I.

Upon inspection of Table I, two trends become immediately apparent. First, the substitution-cyclization reaction provides good yields with enolates derived from methyl ketones. Second, reduction to yield benzenesulfonamide (**179**) increases as the number of β-hydrogen atoms present on the starting ketone increases.

Entries 1 and 2 of Table I demonstrate that the reactivity of 2-bromo- and 2-iodobenzenesulfonamides towards pinacolone enolate (**85d**) are comparable in terms of yield and rate of reaction. It is important to point out that entry 3 shows that only 3-methyl-2*H*-1,2-benzothiazine 1,1-dioxide (**183b**) results when acetone enolate is employed. Interestingly, in earlier studies the yield of **183b** was decreased by formation of alcohol **185**.[10] Formation of **185** was suggested to have arisen from sequential ionization of

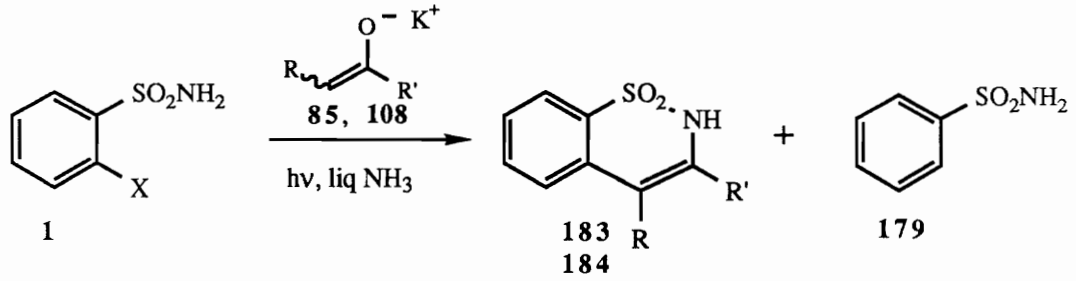


1b

183b, 50%

185, 20%

Table I. Photostimulated Reactions of 2-Halobenzensulfonamides with Potassium Enolates of Acyclic Ketones

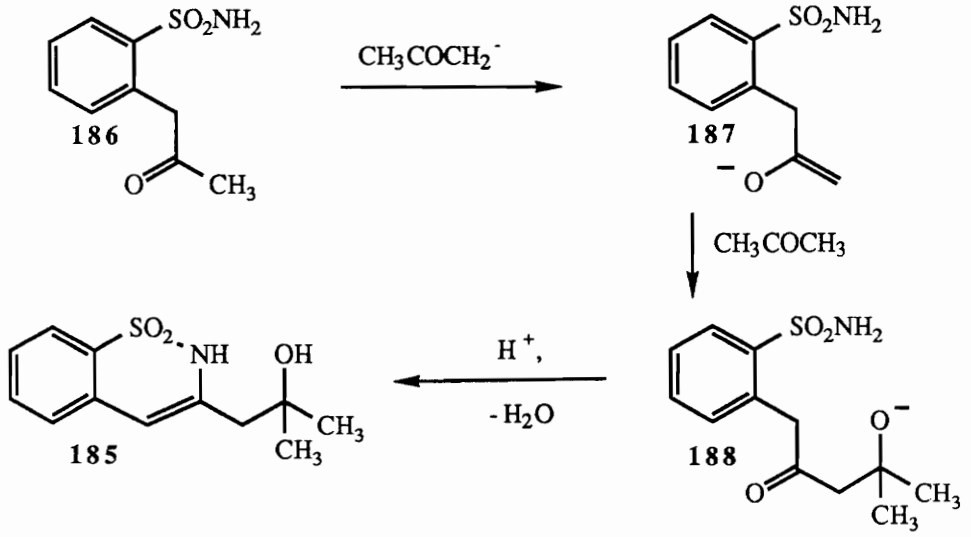


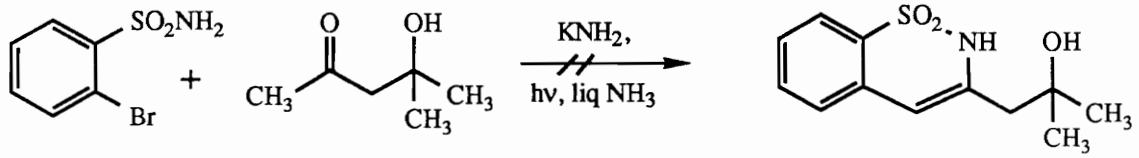
entry	X	**1**	R	R'	product, enolate	**179** (yield, %[a])	yield, %
1	Br	**1b**	H	*t*-butyl	**85d**	**183a** (80)	--
2	I	**1a**	H	*t*-butyl	**85d**	**183a** (80)	--
3	I	**1a**	H	Me	**85b**	**183b** (90)	--
4	I	**1a**	H	Et	**85e**	**183c** (27)	9
5	I	**1a**	H	*i*-propyl	**85c**	**183d** (67)	6
6[b,c]	I	**1a**	Me	Et	**108a**	**184a** (20)	42
7[b,d]	I	**1a**	Me	*i*-propyl	**108b**	**184b** (9)	58

[a]Yields given for products after chromatogaphy and recrystallization. [b]Product distribution given for anaerobic work-up. [c]Reaction also produced cyclohexenone **196** (10%) as well as alcohol **194** (trace). [d]Reaction also yielded pyridine **197** (2-4%) and alcohol **195** (2%).

186 to give enolate **187** and nucleophilic attack of **187** on acetone to yield alkoxide **188**. Cyclodehydration of **188** results in benzothiazine **185** (Scheme XXV). Failure of β-hydroxy ketone **189** to react with 2-bromobenzenesulfonamide **1b** was taken as evidence for the proposed mechanism.[10] Apparently the shortened reaction time employed in the present study does not allow for formation of **187**, and in turn suppresses formation of **185**.

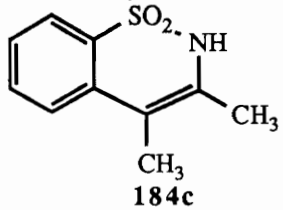
Scheme XXV





1b **189** **185**

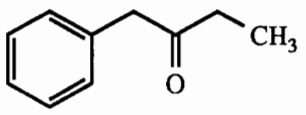
Entries 4 and 5 of Table I demonstrate the significant difference in regiochemical control associated with enolate formation from butanone and 3-methyl-2-butanone. Product **183c** arises from ionization at the C-1 carbon of butanone and the yield for that product is reported in Table I. 3,4-Dimethyl-2*H*-1,2-benzothiazine 1,1 dioxide (**184c**)



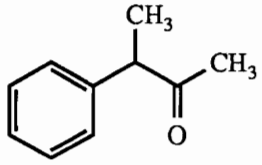
184c

was anticipated to form from the ketone enolate resulting from ionization at the C-3 carbon of butanone. The ^{1}HNMR spectrum and GC-MS analysis of the partially purified product mixture obtained from the reaction of **1a** and the butanone enolate indicated the presence of

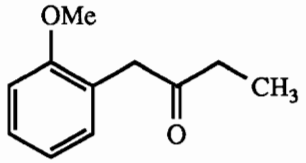
184c. However, **184c** could not be isolated. Similar regiochemical complications associated with employing methyl ethyl ketone as an enolate source are documented in the literature.[4e,5k,48] Rossi and Bunnett report formation of ketones **190** and **191** in the ratio of roughly 1.8 (**190**:**191**) from the reaction of butanone enolate with iodobenzene.[48]



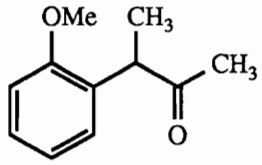
190



191



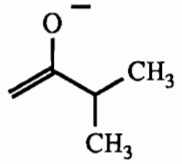
192



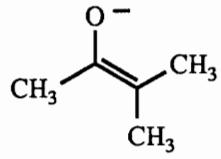
193

In similar work, Beugelmans reported a 60:40 ratio of ketones **192** and **193**, respectively, when butanone enolate is reacted under $S_{RN}1$ conditions with 2-iodoanisole.[5k]

The relatively high yield of product **183d** can be attributed to greater regiochemical control associated with enolate formation from 3-methyl-2-butanone. Qualitatively, the equilibrium mixture of enolates **85c** and **108d** has been estimated to be 98:2.[4e,49] It is



85c

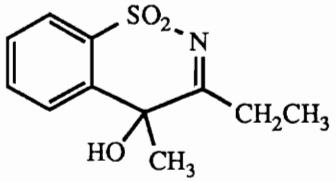


108d

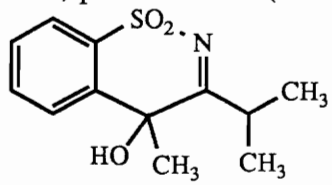
important to point out that products arising from substitution of **1a** by enolate **108d** were not observed. However, the reduction product **179** may very well arise from hydrogen atom transfer from the β-carbons of **108d**.[50,51,52] Hydrogen atom transfer is discussed in greater detail in the next section.

Entries 6 and 7 of Table I indicate that reduction competes significantly with substitution when ethyl ketone enolates are employed. Two factors combined to cause the

yields of products **184a** and **184b** to be disappointingly low. First, reduction of **1a** to form **179** was the major course of the reaction. Second, products **194** (trace) and **195**

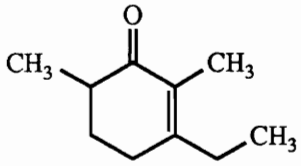


194



195

(2%) were also isolated. The formation of these alcohols is discussed in Section III.3.1. Interestingly, ketone byproducts **196** and **197** were also isolated from the crude product mixture obtained with 3-pentanone and 2-methyl-3-pentanone, respectively. It is docu-



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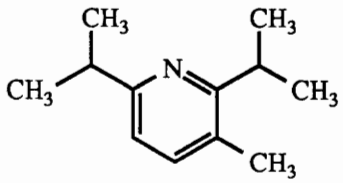

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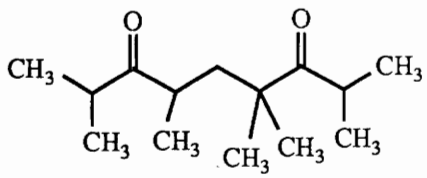


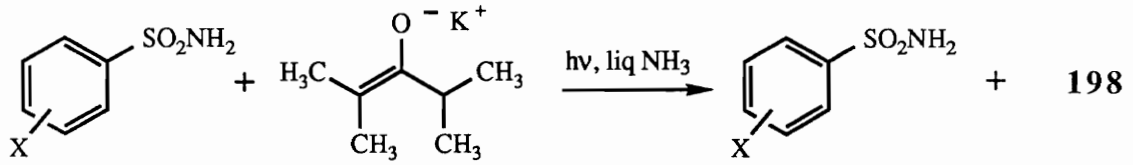
198

mented in the literature that the enolate derived from 2,4-dimethyl-3-pentanone when reacted with aryl halides under $S_{RN}1$ conditions yields unsymmetrical ketone dimer **198**.[51] This is the first time cyclohexenone **196** and pyridine **197** have been observed. The mechanism of formation of **196** and **197** is discussed in Section III.1.4.

Table II presents the results of an investigation of the affect that the nature and position of the halide have on the reactivity of halobenzenesulfonamides towards enolate **199** prepared from 2,4-dimethyl-3-pentanone and KNH_2 in liquid NH_3. Entries 1 and 2 indicate that unlike pinacolone enolate **85d**, diisopropyl ketone enolate (**199**) does not have comparable reactivity towards 2-iodo- and 2-bromobenzenesulfonamide, **1a** and **1b** respectively. 2-Iodobenzenesulfonamide was completely reduced to **179** in a rapid reaction with this enolate. The reaction also produced dione **198** in a yield essentially equivalent to that of **179**. On the other hand, 2-bromobenzenesulfonamide was slowly reduced to **179**. The reduction failed to consume all of the starting sulfonamide even after a reaction period 15 times that required to completely reduce 2-iodobenzenesulfonamide. Entries 3 and 4 indicate that *p*-iodo- and *p*-bromobenzensulfonamides **200a** and **200b** respectively, react sluggishly over a period of 120 minutes to yield substitution product **200c** and reduction product **179** as well as the starting sulfonamide.

Table III summarizes published results of photostimulated reactions in liquid NH_3 of related aryl halides with enolate ions derived from acyclic ketones. It

Table II. Photostimulated Reactions of 2- and 4-Halobenzenesulfonamides with Diisopropyl Ketone Enolate



1: 2-X
200: 4-X

199

1: 2-X
179: X = H
200: 4-X

entry	sulfonamide	rxn time	product	yield, %
1	**1a**, X = 2-I	8 min	**179**, X = H	90
			198	86
2	**1b**, X = 2-Br	120 min	**1b**, X = 2-Br	44
			179, X = H	37
			198	35
3	**200a**, X = 4-I	120 min	**200b**, X = I	28
			179, X = H	36
			200c, X = 4-$C(CH_3)_2COCH(CH_3)_2$	15
			198	28
4	**200b**, X = 4-Br	120 min	**200a**, X = Br	27
			179, X = H	23
			200c, X = 4-$C(CH_3)_2COCH(CH_3)_2$	29
			198	39

Table III. Photostimulated Reactions of Aryl Halides with Enolate Ions of Acyclic Ketones

entry	aryl halide	ketone	irradiation time, min	product, yield %	ref
1	PhBr	3-pentanone	70	$PhCH(CH_3)COCH_2CH_3$, 80% C_6H_6, trace	50
2	PhBr	2,4-dimethyl-3-pentanone	90	$PhC(CH_3)_2COCH(CH_3)_2$, 6% C_6H_6, 8% PhBr, 85% **198**[b]	50[a]
3	PhI	2,4-dimethyl-3-pentanone	180	$PhC(CH_3)_2COCH(CH_3)_2$, 32% C_6H_6, 19% PhI, 48% **198**, 20%	50[a] 51
4	MesBr	3-Pentanone	130	$MesCH(CH_3)COCH_2CH_3$, 14% *s*-$C_6H_3(CH_3)_3$, 20% MesBr, 58%	50
5	MesI	3-Pentanone	130	$MesCH(CH_3)COCH_2CH_3$, 24% *s*-$C_6H_3(CH_3)_3$, 25% MesI, 50%	50
6	2-Bromo-benzamide	3-Pentanone	300	**109d**, 70% $C_6H_5CONH_2$, 20%	5j
7	2-Bromo-benzamide	3-Methyl-2-butanone	30	**109b**, 90%	5j

[a]The structure of **198** was incorrectly reported in ref. 50, and correctly assigned in ref. 51. [b]Yield not reported.

has been reported that enolate **199** reacts sluggishly under photostimulation in liquid NH_3 with bromo and iodobenzene to yield a mixture of starting phenyl halide, arylated ketone (the substitution product), benzene (the reduction product) and the unsymmetrical ketone dimer **198**.[50,51] Entries 2 and 3 of Table III indicate the comparable reactivity of bromo and iodobenzene towards diisopropyl ketone enolate **199**. Likewise entries 3 and 4 demonstrate that the reactivity of mesityl bromide and mesityl iodide towards the enolate, **108a**, derived from 3-pentanone are comparable. Both mesityl halides gave low yields of substitution and reduction products as well as significant quantities of recovered starting material. The comparable reactivity of *para*-substituted sulfonamides **200a** and **200b** is in good agreement with this apparent trend. However, the very dissimilar reactivity of *ortho*-substituted sulfonamides **1b** and **1c** stands in stark contrast to the results just cited.

A comparison of entries 1, 4 and 6 of Table III and entry 6 of Table I can be interpreted to indicate that competition between reduction and substitution is a function of the steric requirement of the aryl halide. For example, bromobenzene when treated with the enolate **108a** derived from 3-pentanone, gave only a trace of reduction product. Yet, when mesityl bromide,[50] 2-bromobenzamide,[5j] and 2-iodobenzenesulfonamide (this study) were treated with the same enolate, significant yields of the corresponding reduction products were obtained. A similar trend was observed throughout this research for the reactions of ester enolates and enolate equivalents with 2-iodobenzenesulfonamide **1a** and its *N*-substituted derivatives (see Section III.1.10). Likewise, reduction was observed to compete with substitution as the steric requirements of the cyclization reactions of the potassium dianions of *N*-acyl-2-iodobenzenesulfonamide became more severe (see Sections III.2.1 and III.2.2) It is interesting to compare the large difference in the amount of reduction observed for the reaction of sulfonamide **1a** with 3-pentanone enolate **108a** (entry 6 of Table I) and that reported by Beugelmans for the reaction of that enolate with 2-bromobenzamide (entry 6 Table III; see p. 20 for the structure of **109d**). This difference may very well reflect the difference in steric demand associated with an *ortho*-sulfonamide and an *ortho*-carboxamide.

It is instructive to point out another trend in Table III. Thus extended reaction periods are required for reactions which yield significant quantities of reduction products. For example, reaction of bromobenzene, with the enolate ion of 3-pentanone, required 70 minutes of irradiation for complete consumption of the starting material (entry 1). Similarly, 2-bromobenzamide required 30 minutes of irradiation with the enolate to be

completely consumed (entry 7). However, the other reactions cited in the Table III required much longer irradiation periods and still, most gave back significant quantities of starting material. The great difference in reactivity of 2-bromobenzenesulfonamide (**1b**) towards the enolate ions of pinacolone and diisopropyl ketone is in keeping with this trend. However, the very similar reactivity of 2-iodobenzenesulfonamide towards the same two enolates is without precedent. Speculation as to the nature of the efficiency of the reduction of 2-iodobenzenesulfonamide **1a** is presented in the next section.

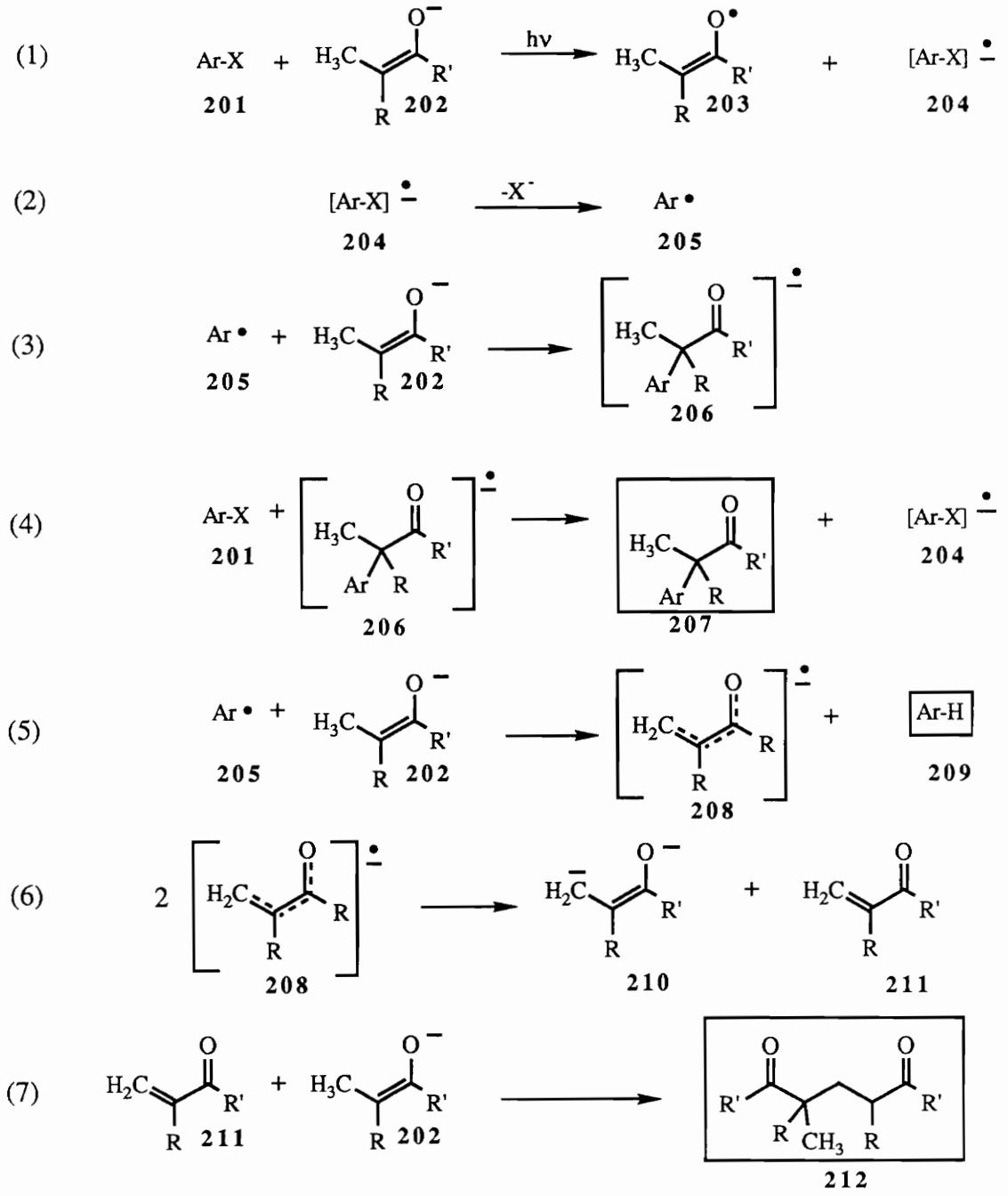
To summarize, 2-iodobenzenesulfonamide (**1a**) reacts cleanly and efficiently with enolates derived from methyl ketones to form 3-substituted-2*H*-1,2-benzothiazine 1,1-dioxides in good yields. However, reduction competes with substitution when β-hydrogen atoms are present on the ketone enolate. The yield of reduction product increases with increasing number of β-hydrogen atoms. Sulfonamide **1a** reacts with the enolate **199** derived from 2,4-dimethyl-3-pentanone under irradiation to yield benzensulfonamide and unsymmetrical ketone dimer **198** in equivalent yields. The rate of the reduction of sulfonamide **1a** by enolate **199** is without precedent and warrants further investigation.

1.3 Investigation of the Reduction of 2-Halobenzenesulfonamides by Diisopropyl Ketone Enolate

In the preceding section, results presented in Table I demonstrated the problem associated with employing enolate nucleophiles that posses β-hydrogen atoms in $S_{RN}1$-type reactions involving aryl halides. That problem is reduction. Table I and II contain results that demonstrate that the efficiency of reduction relative to substitution is a function of the number of β-hydrogens present on the nucleophile as well as the steric requirements of the aryl halide. The results and trends reported in Tables I and II are for the most part, consistent with results published in the literature for the reactions of acyclic ketone enolates with related aryl halides (Table III).[5j,50,51] However, as pointed out in the previous section, the rapid reduction of 2-iodobenzenesufonamide (**1a**) with diisopropyl ketone enolate (**199**) is unprecedented and was therefore investigated. Many of the mechanistic details of the reduction of aryl halides under $S_{RN}1$ conditions by nucleophiles possessing β-hydrogen atoms have been established.[51,52] A very recent report by Kornblum of a similar reaction stimulated our interest in taking a closer look at the mechanistic aspects of the reduction of **1a** by diisopropyl ketone enolate.[53]

In the preceding section attention was drawn to the fact that for all but one substrate the rate of consumption of the starting aryl halide was decreased significantly when reduction is involved in the reaction manifold. Assuming a radical chain reaction mechanism, this result could suggest that reduction is a chain termination step. This explanation was jointly suggested by Wolfe and Bunnett to account for the sluggish reaction of iodobenzene with diisopropyl ketone enolate.[51] The proposed mechanism is outlined in Scheme XXVI. The first step involves photostimulated electron transfer to the

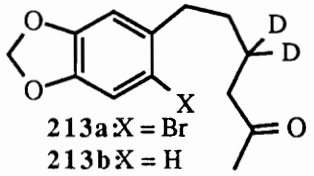
Scheme XXVI



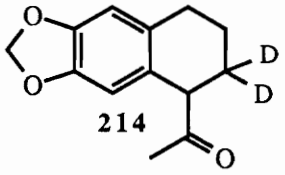
aryl halide **201** generating radical anion **204** (eq. 1). Expulsion of halide from **204** results in radical **205** (eq. 2). Radical intermediate **205** can then undergo nucleophilic attack by nucleophile **202** to yield radical anion **206** (eq. 3) Electron transfer from **206** to a second equivalent of **201** would yield substitution product **207** as well as **204** and thus

propagate the chain (eq. 4). Alternatively **205** can abstract a β-hydrogen atom from enolate **202** resulting in reduction product **209** and delocalized radical anion **208** (eq. 5). In a chain terminating step, **208** disproportionates to give dianion **210** and enone **211** (eq. 6). Protonation of **210** by NH_3 would result in **202.** Michael addition of **202** to **211** yields unsymmetrical ketone dimer **212** and thereby accounts for the formation of dimer **198** (eq.7).

Semmelhack and Barger reported that the deuterium labeled ketone **213a** gives products **213b-215** when treated with base in liquid NH_3 under photostimulation.[52] Formation of **215** strongly suggests that β-hydrogen atom transfer resulting in ring



213a X = Br
213b X = H



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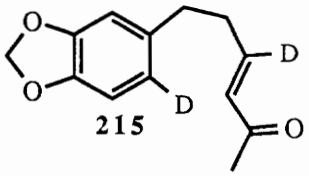

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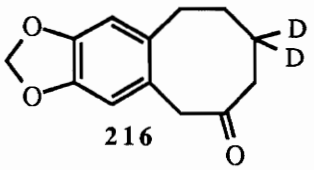

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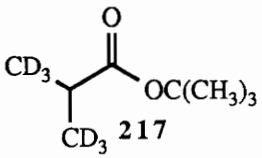
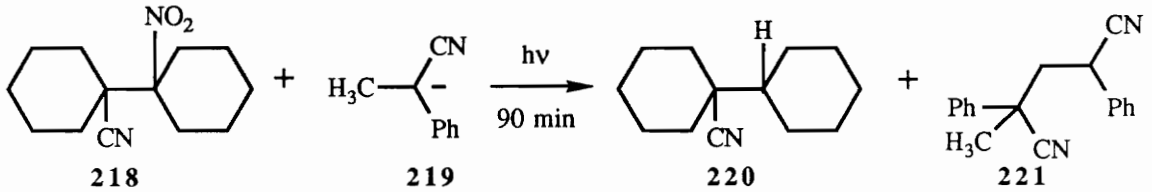


217

reduction and subsequent oxidation of the side chain enolate to form an α,β-unsaturated ketone can occur via an intramolecular reaction. These investigators also reported that when *p*-bromoanisole was reacted under photostimulation with the lithium enolate derived from labeled ester **217** and LDA in liquid NH_3 formed anisole in 54% yield. The anisole produced contained 65% d_0 and 35% d_1. Thus the role of β hydrogens in intramolecular reductions was confirmed. The question as to whether the diispropylamine generated upon ionization of **217** could act as a hydrogen atom source was not addressed.

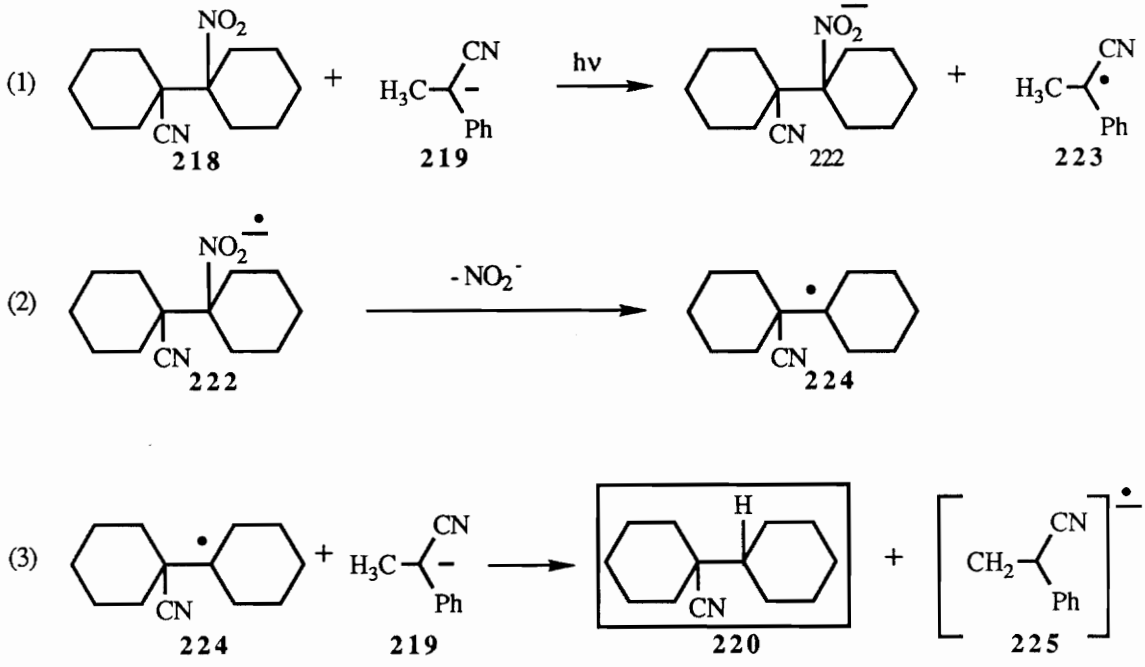
A recent report of related chemistry that appeared to have relevance to this study was published by Kornblum and coworkers. These investigators reported that β-nitronitrile **218** reacts with α-methylbenzyl cyanide anion (**219**) in DMSO under photostimulation to yield reduction product **220** and unsymmetrical dimer **221** in nearly



218 **219** **220** **221**

equivalent yields.[53] To account for this transformation Kornblum proposed the mechanism outlined in Scheme XXVII. Thus, photostimulated electron transfer from nitrile stabilized carbanion **219** to **218** generates nitosyl radical **222** (eq 1). Fragmentation releases an equivalent of nitrite and results in tertiary radical **224** (eq 2). Hydrogen atom transfer from carbanion **219** to **224** yields reduction product **220** and delocalized radical anion **225** (eq 3). In the next step, an electron is transferred from **225** to a second equivalent of **218** to form **222**; thereby propagating a chain as well as generating α-cyanostyrene **226** (eq 4). In the final step Michael addition of nucleophile **219** to **226** yields unsymmetrical dimer **221** (eq 5). The fact that the reaction is inhibited by the presence of 20 mole% of di-*tert*-butyl nitroxide (DTBN) is consistent with the proposed radical chain mechanism.

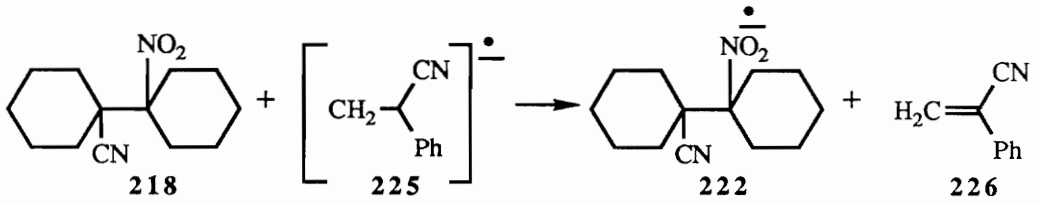
Scheme XXVII

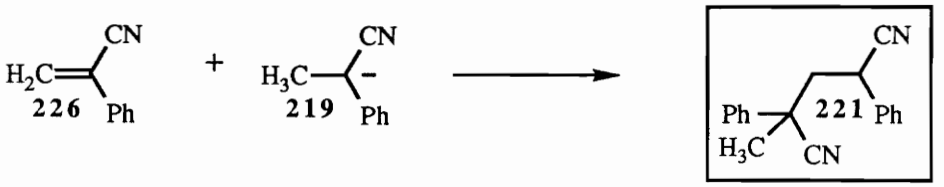


218 **219** **222** **223**

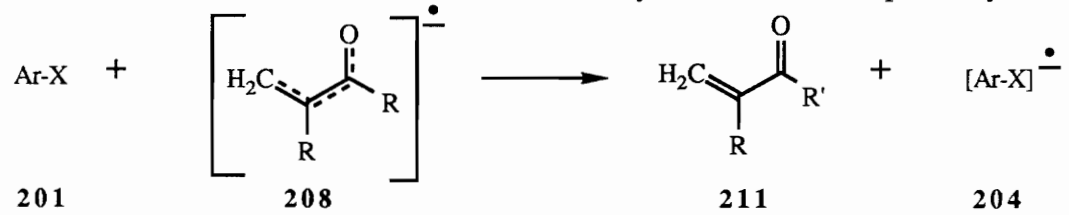
222 **224**

224 **219** **220** **225**

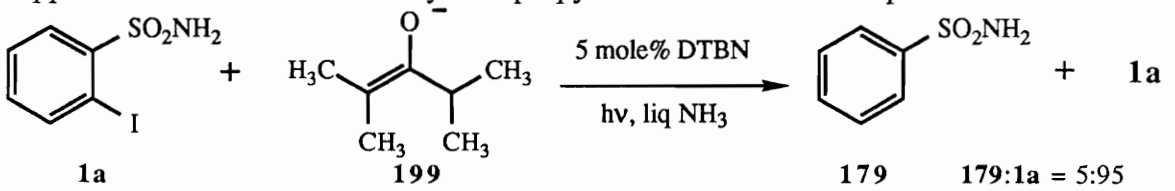
(4) 

(5) 

A chain transfer step similar to eq 4 of Scheme XXVII had been considered possible by Wolfe and Bunnett for the reduction of aryl halides by diisopropyl ketone enolate **199**.[51] However, they argued that because of the apparent sluggishness of the reaction, transfer of an electron from **208** to **201** to yield **211** and **204** probably did not



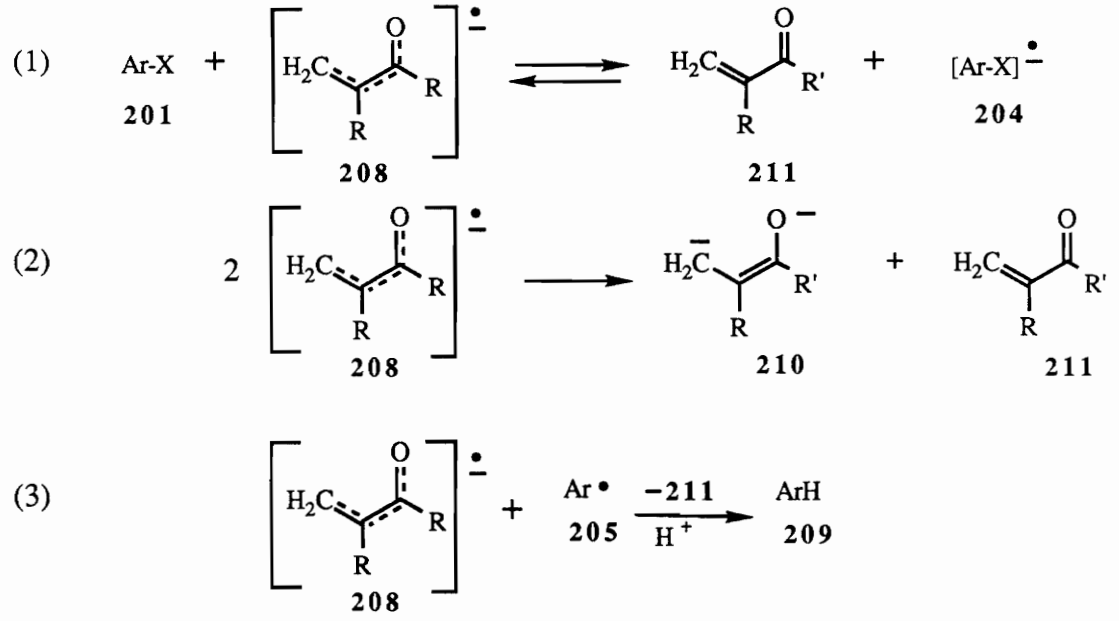
occur to any great extent. Citing similar arguments previously employed to rationalize the reduced reactivity of the enolate derived from acetophenone, these authors argued that **208**, a radical anion of an α,β-unsaturated ketone, is probably too stable to transfer an electron rapidly to iodobenzene. In contrast, the rapid reduction of 2-iodobenzenesulfonamide by enolate **199** (Table II) may be accounted for by a chain mechanism with the key step featuring electron transfer from **208** to the sulfonamide. Evidence for such chain character was obtained by reacting **1a** with diisopropyl ketone enolate (**199**) in the presence of a radical scavenger. Thus, it was found that the presence of 5 mole% of DTBN significantly suppressed the reduction of **1a** by diisopropyl ketone enolate. The question remains as to



why reduction via hydrogen atom transfer of the 2-bromo and 4-iodo analogs of sulfonamide **1a**, as well as all other examples of aryl halides heretofore reported in the literature, are non chain in character.

Common to the reactions of the 2-halobenzenesulfonamides with pinacolone enolate **85d** and diisopropyl ketone enolate (**199**), is an aryl radical intermediate analogous to **205** of Scheme XXVI. Because of the chain nature of the reaction, the reaction rate will be a function of all steps leading to the formation of the aryl radical intermediate. Chain terminating steps would result in a decreased rate of consumption of the starting halide. It is proposed that the sluggish reduction of 2-bromobenzenesulfonamide by enolate **199** is more a function of the reversibility of electron transfer from radical anion **208** to **201**

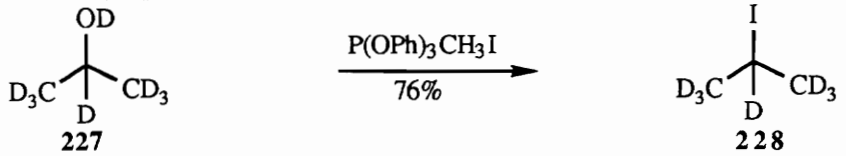
Scheme XXVIII



(ArX = 2-$BrC_6H_4SO_2NH^-$) than it is a result of such an electron transfer not occuring at all. This reversibility could allow for chain terminating steps such as those presented in equations 2 and 3 to occur, and thereby decrease the rate of reduction (Scheme XXVIII). Electron transfer from **208** to the 2-iodobenzensulfonamide analog of **201** (Ar = 2-$IC_6H_4SO_2NH^-$) is irreversible. This irreversibility could arise from stereoelectronic effects similar to that observed for 2-iodonitrobenzene. Bunnet and Galli encountered a similar enhanced reactivity of 2-iodonitrobenzene.[4g] They report that unlike all other halonitrobenzenes, only the 2-iodo substrate participates in the aromatic $S_{RN}1$ reaction. These authors suggest that the steric requirements of the iodide forces the π-system of the

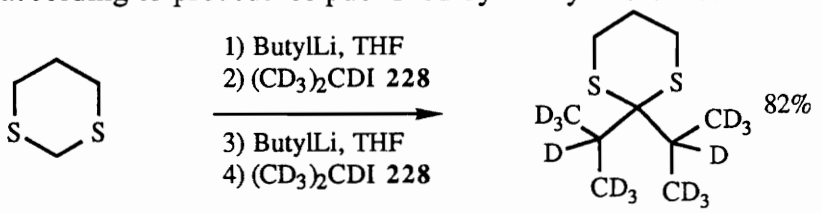
nitro group out of the plane of the aromatic ring. This results in reduced stabilization of the π* MO and in population of the σ* MO of the C-I bond. To account for the rapid reaction of 2-bromobenzenesulfonamide with pinacolone, it is argued that a reaction involving an enolate derived from a methyl ketone cannot form an α,β-unsaturated radical anion analogous to **208.** Therefore, the chain terminating steps as outlined above can not take place.

A labeling experiment modeled after Semmelhack's and Barger's earlier study, demonstrated that β-hydrogen atoms present on enolate **199** play a significant role in the reduction of 2-iodobenzenesulfonamide (**1a**). Thus, diisopropyl ketone-d_{14} (95%, 98 atom% D) **231** was prepared. The preparation of **231** was as follows. 2-Iodopropane-d_7



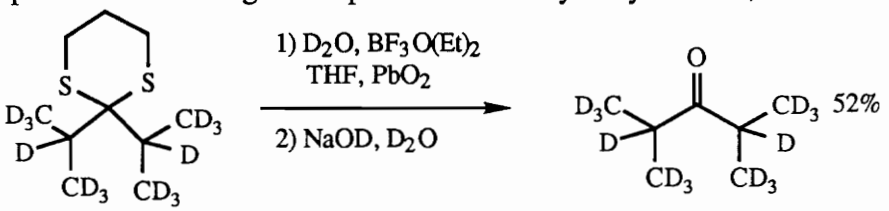
227 **228**

228 was prepared from 2-propanol-d_8 **227** (Aldrich) and triphenyl phosphite-methiodide complex according to the procedure described by Landauer and Rydon for the unlabeled alkyliodide.[54,55] Labeled 1,3-dithiane derivative **230** was prepared from **228** and 1,3-dithiane **229** according to procedures published by Corey and Seebach for the unlabeled



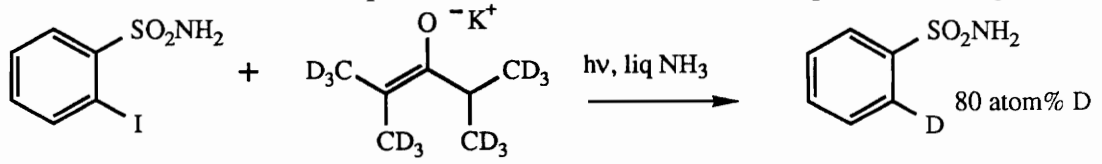
229 **230**

derivative.[56] Transformation of thioketal **230** to labeled ketone **231** was effected by a method adapted from Ghiringhelli's procedure for hydrolysis of 1,3-dithianes to yield



230 **231**

ketones.[57] Reaction of **231** with potassium amide in liquid NH_3 generated enolate **232** which was irradiated in the presence of **1a**. The reaction produced ring labeled

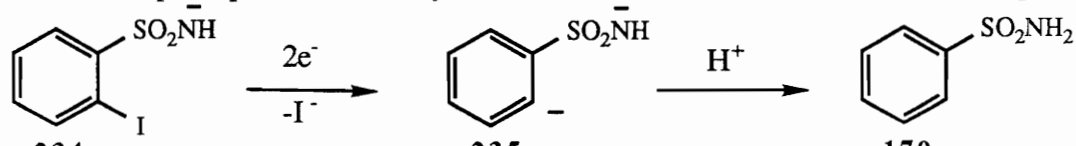


1a **232** **233**

benzenesulfonamide **233** in 55%. The benzenesulfonamide produced was found by mass spectral analysis to be 80% d_1 and 20% d_0. The location of the incorporated deuterium was shown by ^{13}CNMR and ^{2}HNMR to be exclusively *ortho* to the sulfonamide function.

The labeling study employing enolate **232** derived from diisopropyl ketone-d_{14} (**231**) demonstrates that intermolecular β-hydrogen atom transfer is the major mode of reduction of 2-iodobenzenesulfonamide (**1a**) by that enolate. However, this study like Semmelhack's seems to indicate that reduction by another mechanism can occur. A mechanism involving a two electron reduction of aryl halides with subsequent protonation of the resulting anion by the solvent has been proposed in the literature.[50] Likewise, reduction of aryl radicals via mechanisms involving hydrogen atom transfer from sources other than β-carbons such as solvents, have been discussed in the context of the aromatic $S_{RN}1$ reaction.[4e] Experimental evidence for reduction pathways involving hydrogen atom transfer to aryl radicals from a variety of sources have been documented. Quintard and coworkers report that deuterium atoms from 2,2,5,5-tetradeuterotetrahydrofuran were incorporated into mesitylene via the radical generated by the action of tributylstannyllithium on bromomesitylene.[58] Similarly, Saveant demonstrated that the aryl radical generated electrochemically from 4-bromobenzophenone was reduced via deuterium atom transfer from dimethylsufoxide-d_6 or acetonitrile-d_3.[59]

A sequential two electron transfer to ionized sulfonamide **234** to yield aryl anion **235** and subsequent protonation to yield benzensulfonamide **179** was deemed a possible

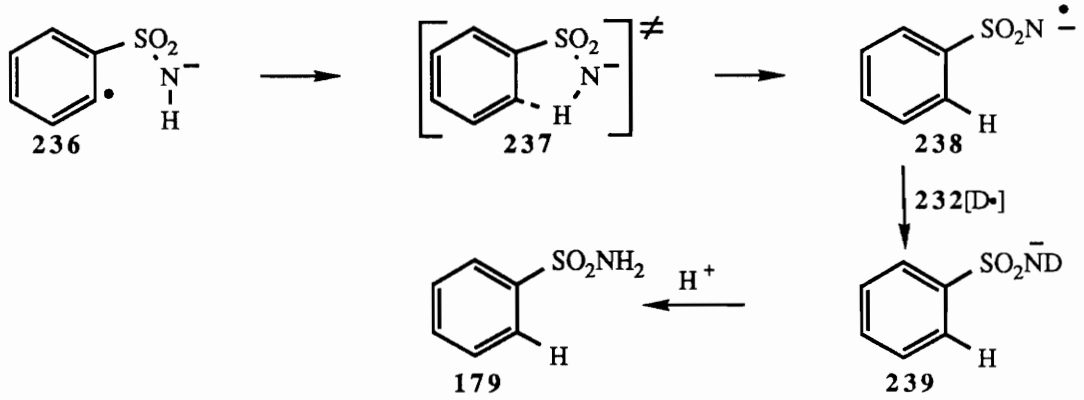


234 **235** **179**

reduction pathway. Likewise, hydrogen atom transfer from a source other than the β-carbons of the labeled enolate was considered to be a viable mode of reduction. Inspection of the possible chemical species present in the reaction of the labeled diisopropyl ketone

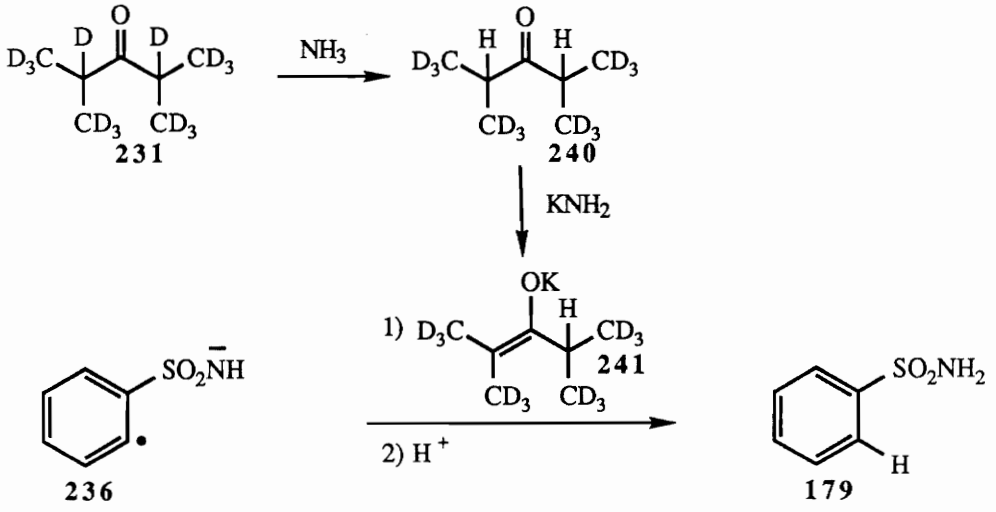
with 2-iodobenzenesulfonamide leads to speculation as to the existence of labile hydrogen atoms. A somewhat complex mechanism outlined in Scheme XXIX involving the hydrogen atom present on the ionized sulfonamide was considered. It was proposed that

Scheme XXIX



intramolecular hydrogen atom transfer via the five membered cyclic activated complex **237** could lead to reduction of the intermediate aryl radical **236** and in turn give rise to sulfonamide radical anion **238**. Deuterium atom transfer to **238** from enolate **232** would generate *N*-deuterio- benzenesulfonamide anion **239**. Clearly the deuterium label would be lost upon work up to yield benzenesulfonamide **179**. Also considered, was a reduction mechanism involving hydrogen atom transfer from the unionized α-carbon of enolate **241**

Scheme XXX



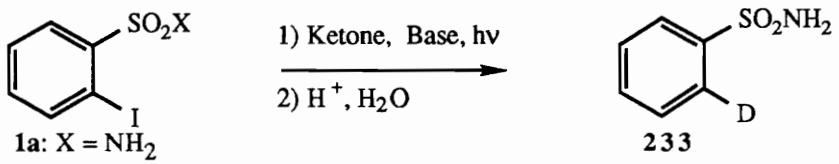
to the aryl radical intermediate **236** (Scheme XXX). Enolate **241** might arise from proton exchange with NH_3 present in a large excess prior to ionization of ketone **231** by KNH_2.

To test the hypotheses involving reduction via mechanisms other than β-hydrogen atom transfer, further labeling experiments were conducted (Table IV).

The results of the additional labeling studies are summarized in Table IV along with the initial labeling study. In brief, the further studies did not lend support to the alternate reduction pathways considered. The reaction of the starting sulfonamide **1a** with unlabeled enolate **199** in liquid ND_3 incorporated only a small amount of deuterium (entry 2). That result might indicate that reduction via a mechanism other than hydrogen atom transfer from enolate **199** had occured. However, the small amount of deuterium incorporated indicates that if a two electron reduction mechanism does occur, it does not occur to the anticipated extent of 20% based on the initial labeling study. Because of the possibility of acid base exchange with ND_3 of the sulfonamide protons as well as the α-protons of the ketone prior to ionization, the experiment can neither exclude nor support the mechanisms featuring hydrogen atom transfer from those sources. It can be argued that an incomplete proton deuterium exchange would result in hydrogen atom transfer via the mechanisms outlined above in Schemes XXIX and XXX.

Therefore two more labeling experiments were conducted. Reaction of *N*-d_2-2-iodobenzenesulfonamide (generated *in situ* from 2-iodobenzenesulfonyl chloride and ND_3) with the unlabeled enolate in liquid ND_3 did not provide evidence for an intramolecular hydrogen atom transfer from the sulfonamide nitrogen of aryl radical **236** (entry 3). Reaction of *N*-d_2-2-iodobenzenesulfonamide with 2,4-dideuterio-2,4-dimethyl-3-pentanone in liquid ND_3 did not yield evidence in support of hydrogen atom transfer from the nonionized α-carbon of enolate **241** to arylradical **236** (entry 4). A small amount of deuterium was incorporated in the three experiments performed in ND_3. It is noted in Table IV that deuterium is incorporated at a position other than the *ortho* site when the starting material is the sulfonyl chloride. A possible explanation of this nonregiospecific incorporation of ring deuterium, is a rapid deprotonation-deuteration involving the aromatic

Table IV. Isotopic Labeling Study of the Photostimulated Reduction of 2-Iodobenzenesulfonamide by 2,4-Dimethyl-3-pentanone.

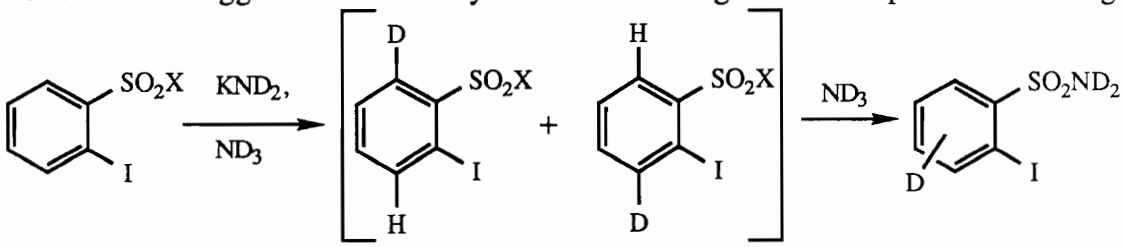


1a: X = NH_2
242: X = Cl
233

Entry	Aryl halide	Ketone	Solvent	% d_1[a]
1	**1a**	$(CD_3)_2CDCOCD(CD_3)_2$	NH_3	80
2	**1a**	$(CH_3)_2CHCOCH(CH_3)_2$	ND_3	5
3	**242**	$(CH_3)_2CHCOCH(CH_3)_2$	ND_3	5[b]
4	**242**	$(CH_3)_2CDCOCD(CH_3)_2$	ND_3	6[b]

[a]Based on ratio of $C_6H_5^{\bullet+}$ to $C_6H_4D^{\bullet+}$ (as determined from the mass spectrum) after correction for ^{13}C natural abundance. [b]^{2}HNMR analysis showed deuterium was not incorporated exclusively at the *ortho*-position.

hydrogens of the starting material prior to amination and or ionization. Sulfonamide **1a** and sulfonyl chloride **242** might undergo acid-base exchange of their C-6 hydrogens with deuterium. It is suggested that sulfonyl chloride **242** might be susceptible to exchange

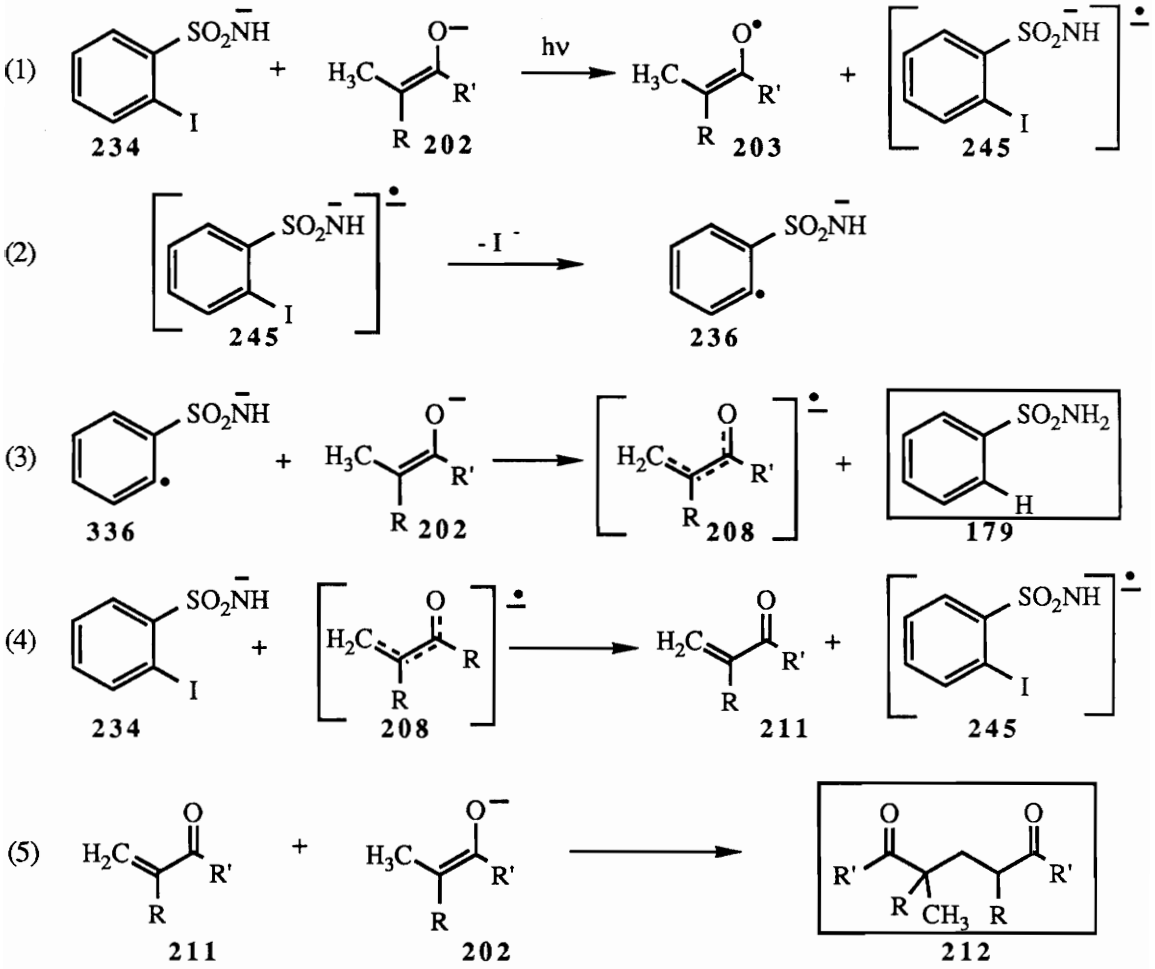


1a: X = NH_2 **243a**: X = ND_2 **243b**: X = ND_2 **243**
242: X = Cl **244a**: X = Cl **244b**: X = Cl

of its C-3 hydrogen. The additional labeling studies did not reveal a major source of reduction, if any. The occurrence of the small amounts of d_1-benzenesulfonamide observed may quite simply be due to an acid-base exchange and not the result of a reduction reaction. At this point it is believed that trace impurities with labile hydrogen atoms account for the 20% of benzenesulfonamide in which deuterium was not incorporated in the initial labeling experiment.

In summary, 2-iodobenzenesulfonamide reacts rapidly with enolate **199** under photostimulation in liquid NH_3 to give equivalent yields of benzenesulfonamide **179** and unsymmetrical ketone dimer **198**. The reaction is significantly inhibited by the addition of fractional quantities of DTBN. Labeling studies indicate that β-hydrogen atoms from the enolate are transfered to the C-2 of sulfonamide **1a**. Based on these findings the generalized mechanism outlined in Scheme XXXI is proposed. The mechanism is similar to the mechanism proposed by Wolfe and Bunnet for reduction of iodobenzene by ketone enolates with β-hydrogen atoms.[51] The first step of the mechanism presumably involves electron transfer from enolate **202** to sulfonamide anion **234** to produce radical dianion **245**. In the next step **245** fragments to liberate iodide and generate the localized radical anion **236**. Hydrogen atom transfer from the β carbon of enolate **202** yields on protonation benzenesulfonamide **179** (after protonation) and radical anion **208**. In the fourth step, α,β-unsaturated ketone radical anion **208** irreversibly transfers an electron to the ionized starting sulfonamide **245** in a propagation step that produces aryl radical dianion **245** and α,β-unsaturated ketone **211**. Michael addition of enolate **202** to enone **211** results in unsymmetrical dimer **212**.

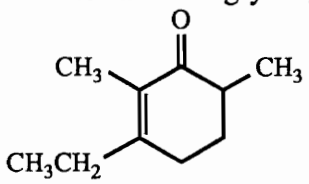
Scheme XXXI


(1)
234
202
hν
203
245
(2)
245
- I -
236
(3)
336
202
208
179
(4)
234
208
211
245
(5)
211
202
212

1.4 On The Mechanism of the Formation of (±)-3-Ethyl-1,6-dimethyl-2-cyclohexen-1-one and 2,6-(1-Methylethyl)-3-methylpyridine.

Recall that in section 1.2 of this chapter the formation of ketone derived products (±)-3-ethyl-1,6-dimethyl-2-cyclohexen-1-one (**196**) and 2,6-(1-methylethyl)-3-methyl-pyridine (**197**) were reported. Cyclohexenone **196** appeared in the product mixture from the photostimulated reaction in liquid NH_3 of 2-iodobenzenesulfonamide (**1a**) and enolate **108a** derived from 3-pentanone and KNH_2. Pyridine **197** was isolated from the analogous reaction of sulfonamide **1a** and enolate **108b** derived from 2-methyl-3-pentanone. This is the first report of the isolation of these products from the reaction of an aryl halide with the corresponding enolate under $S_{RN}1$ conditions. Structural assignments of these products were made in accord with IR, ^{1}HNMR, ^{13}CNMR, and GC-MS spectral data.

The IR spectrum of cyclohexenone **196** exhibited an absorption at 1670 cm^{-1} indicative of the enone function. Three distinctly different methyl resonances of the ^{1}HNMR spectrum of the isolated material strongly suggest structure **196**. The first

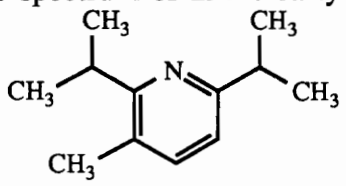


196

signal, a triplet centered at δ 1.04 (t, J = 7.6 Hz, 3 H) allowed the assignment of the ethyl group attached to the C-3 carbon. The second signal, a doublet centered at δ 1.10 (d J = 6.8 Hz, 3 H) indicates the presence of the methy unit attached to the methine C-6 carbon. The third resonance at δ 1.74 (t, J = 1.5 Hz, 3 H) suggests the allylic methyl unit attached to olefinic C-2 carbon. In support of the assigned structure **196** the proton-decoupled ^{13}CNMR spectrum consists of ten resonances. Four resonances were particularly diagnostic for structure **196.** The weak signal at 202.0 ppm was assigned to the carbonyl carbon. The weak signal at 159.9 ppm was attributed to the quaternary olefinic β-carbon (C-3). The weak signal at 129.6 ppm was assigned to the α olefinic carbon (C-2). And the fourth resonance, the signal at 40.8 ppm was assigned to the methine α carbon (C-6).

GC-MS analysis gave *m/z* 152 ($C_{10}H_{16}O$)M^+, 137 ($C_9H_{13}O$), 123 ($C_8H_{11}O$) and base peak 110 ($C_7H_{10}O$).

The IR spectrum of pyridine **197** exhibited absorptions at 1465, 1485, 1585 and 1605 cm^{-1} characteristic of heteroaromatic C⋯C and C⋯N ring stretching. The absorption at 825 cm^{-1} indicates C-H out of plane bending by two adjacent pyridine hydrogens. The ^{1}HNMR spectrum of the isolated material provides strong evidence for the structural assignment. The spectrum of **197** clearly indicates the existence of two

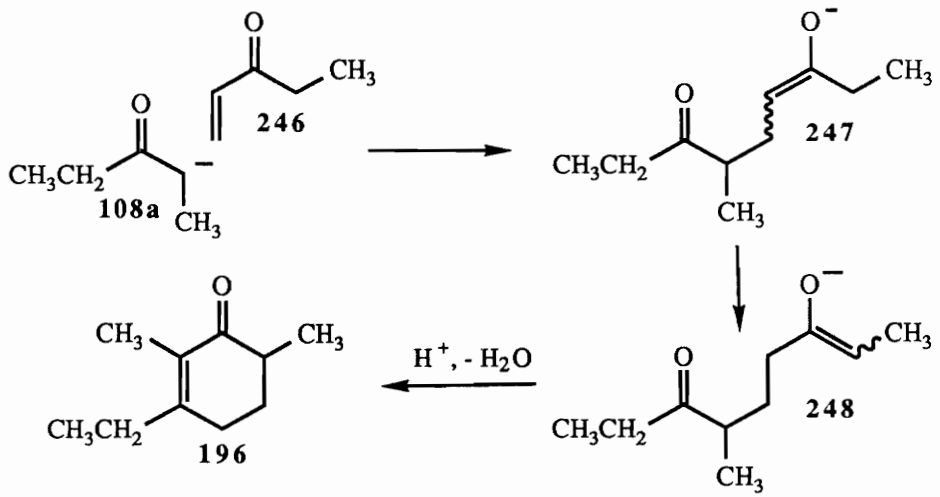


197

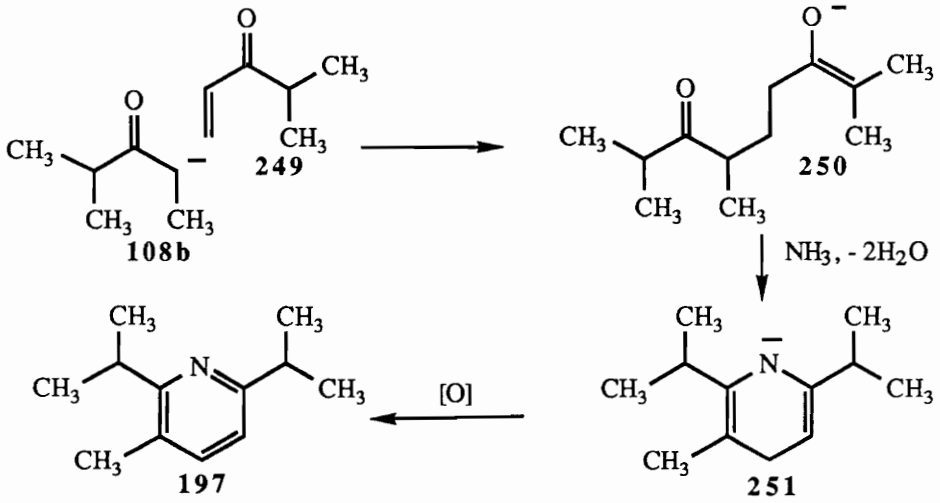
non equivalent isopropyl groups and an isolated methyl unit: δ 1.24 (d, J = 4.1 Hz, 6 H), δ 1.77 (d, J = 4.2 Hz, 6 H), δ 2.27 (s, 3 H), δ 2.96 (m, J = 4.1 Hz, 1 H), and δ 3.20 (m, J =4.1 Hz,1 H). The most convincing evidence for the pryidine structural assignment is the set of aromatic doublets centered at δ 6.83 (d, J = 7.7 Hz, 1H) and at δ 7.26 (d, J = 8.0 Hz, 1 H) in the ^{1}HNMR spectrum. The proton-decoupled ^{13}CNMR spectrum reveals ten distinct resonances. Pyridine **197** has a total of 12 carbons but chemical shift equivalence of the pairs of isopropyl methyl carbons results in only ten signals. The five aromatic signals have shifts and signal intensities that are in agreement with a 2,3,6-tri-substituted-pyridine. GC-MS analysis gave *m/z* 177 ($C_{12}H_{19}N$) M^+, 176 ($C_{12}H_{18}N$), and base peak 162 ($C_{11}H_{16}N$).

The formation of cyclohexenone **196** and pyridine **197** is readily rationalized from their respective structures and the proposed mechanism outlined in Scheme XXXI in Section III.1.3. The last step of the mechanism featured formation of unsymmetrical ketone dimer **212**. With that as a starting point, the mechanism can be extended to account for the formation of both cyclohexenone **196** and pyridine **197**. Formation of **196** is outlined in Scheme XXXII. Michael addition of enolate **108a** to enone **246** yields adduct **247**. Equilibration to enolate **248** and intramolecular aldol condensation yields cyclohexenone **196**. Formation of pyridine **197** is rationalized in Scheme XXXIII.

Scheme XXXII



Scheme XXXIII



The mechanism begins with Michael addition of enolate **108b** to enone **249** to yield adduct **250**. Condensation of **250** with NH_3 and protonation yields dihydropyridine **251**. Oxidation of **251** yields 2,3,6-trisubstituted pyridine **197**.

In summary it is suggested that the yields of the unsymmetrical ketone dimer derivatives **196** and **197** are low because the ketone dimers from which they originate apparently have other pathways in which to react further under the conditions of the $S_{RN}1$ reaction and the subsequent workup. That suggestion is based on the observation that products **196** and **197** are isolated from a complex mixture of ketone derived products. By comparison the analogous ketone dimer **198** is, by virtue of its highly branched structure, relatively inert to further transformations under the reaction conditions and can therefore be isolated in nearly quantitative yields. It should also be noted that due to the unsymmetrical nature of 2-methyl-3-pentanone, four unsymmetrical dimers derived from that ketone can be formed. Fortutitously, only one of the four combinations gives rise to a pyridine by-product, thereby allowing for the isolation of **197**.

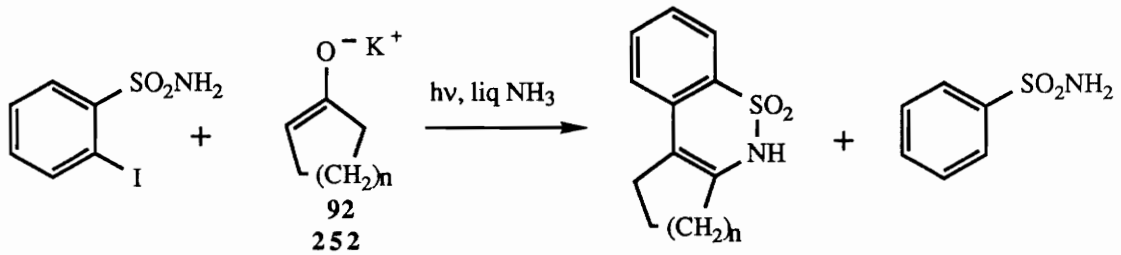
1.5 Reactions of 2-Iodobenzenesulfonamide with Enolates Derived from Cyclic Ketones.

Reactions involving nucleophiles derived from cyclic ketones were investigated in order to further explore the extent to which 2-iodobenzenesulfonamide (**1a**) will participate in aromatic substitution. It was anticipated from literature precedent and from the previously described reactions with acyclic ketone enolates that both substitution and reduction products would result. Enolate anions derived from cyclic ketones have been reported to be suitable nucleophiles for aromatic $S_{RN}1$ reactions, giving good to excellent yields of substitution products.[5e,j,m,48]

We have now found that 2-iodobenzenesulfonamide (**1a**) when treated with cyclic ketone derived nucleophiles, undergoes a photoinitiated substitution-cyclization reaction sequence. This process results in the formation of tricyclic 1,2-benzothiazine 1,1-dioxide derivatives **254a-b** and **255** in fair to good yields. The results of this study are summarized in Table V. For comparison the published results of two related studies by Bunnet and Beugelmans are summarized in Table VI.

These new heterocycles have properties that are interesting in their own right. Product **254a** is interesting due to the relative acidity of the amide proton. Unlike products **254-c**, **183a-d** and **184a-b** which are all protonated by the ammonium chloride employed to quench the reaction mixture, isolation of cyclopentanone derived heterocycle **254a** required acidification of the aqueous phase with HCl upon workup. Compound **254a** is soluble in a 10% bicarbonate solution. Heterocycles **254b** and **254c** are of interest due to their sensitivity towards oxidants. Product **254b** can be obtained in the pure form, but with difficulty. Treatment of **254b** with diethyl ether from an open can results in instantaneous darkening of the product. Presumably, this decomposition is due to oxidation of the substrate by ether peroxides. Several attempts at the isolation of **254c** were unsuccessful due to rapid air oxidation to give **255**. In order to quantitate the yield for the substitution reaction, it was necessary to treat the crude reaction mixture with an

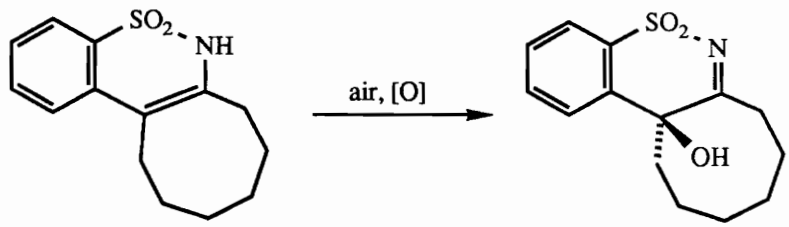
Table V. Photostimulated Reactions of 2-Iodobenzenesulfonamide with Potassium Enolates Derived from Cyclic Ketones



1a **92** **252** **253** **254** **179**

entry	n, enolate	rxn time,min	substitution, (yield, %)	reduction, yield, %
1	1, **252**	15	**254a** (45[a])	10
2	2, **92**	10	**254b** (45[a])	42
3	4, **253**	40	**254c** (65[b])	0

[a]Yields are reported after chromatography [b]Yield reported is for oxidation product **255** after chromatography and recrystallization.



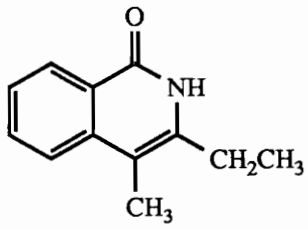
254c **255**

oxidant, monoperoxyphthalic acid magnesium salt hexahydrate (MMPP) (see Section III.3.1). The yield reported in Table V for **254c** is based on the amount of **255** isolated from the oxidative workup. Speculation as to the nature of the air sensitivity of these substrates is presented in Section III.3.1. In addition, an X-ray crystal structure of **255** is presented in that section (see Figure 2).

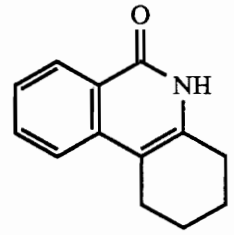
Inspection of Table V leads to the conclusion that substitution is for the most part favored over reduction for the reactions of sulfonamide **1a** with the cyclic ketone enolates employed. This was a surprising result in light of the high ratio of reduction to substitution observed for the analogous reaction of **1a** with diethyl ketone enolate **108a**. This behavior is opposite of that reported in the literature for similar studies (Tables III and VI). Other studies have shown that the yield of reduction product is greater for reactions of a particular substrate with an enolate ion derived from a five, six or seven membered cyclic ketone than it is for the analogous reaction with the enolate ion **108a** derived from 3-pentanone. For example, Bunnett reports that bromobenzene reacts with the enolate derived from 3-pentanone to yield 2-phenyl-3-pentanone in 80% and only a trace of benzene (entry 1, Table III).[50] In the same report, Bunnett indicates that the enolate derived from cyclopentanone reacts under $S_{RN}1$ conditions with bromobenzene to yield 2-phenylcyclopentanone in 64% yield, benzene in 28% yield and recovered aryl halide in 9% yield (entry 1, Table VI). Similarly, the enolates derived from cyclohexanone and cycloheptanone were reported to react with bromobenzene to give quantities of benzene that become significant when compared to the trace amount reported for the analogous reaction of diethylketone enolate **108a** (entry 2 and 3, Table VI). Beugelmans reports that 2-bromobenzamide reacts with diethylketone enolate **108a** to yield isocarbostyril **109d** in 70% yield, along with 20% of benzamide (entry 6, Table III).[5j] In contrast, Bugelmans reports that 2-bromobenzamide, when treated with the enolate derived from cyclohexanone

Table VI. Photostimulated Reactions of Certain Aryl Halides with Potassium Enolate Ions Derived from Cyclic Ketones

entry	aryl halide	ketone	Irradiation time, min	product, yield %	ref.
1	PhBr	Cyclopentanone	150	2-Phenylcyclopentanone, 64% C_6H_6, 28% C_6H_5Br, 9%	50
2	PhBr	Cyclohexanone	60	2-Phenylcyclohexanone, 72% C_6H_6, 6% C_6H_5Br, 18%	50
3	PhBr	Cycloheptanone	210	2-Phenylcycloheptanone, 58% C_6H_6, 12% C_6H_5Br, 29%	50
4	PhBr	Cyclooctanone	210	2-Phenylcyclooctanone, 95% C_6H_6, 3% C_6H_5Br, 0%	50
5	2-Bromo-benzamide	Cyclohexanone	180	**110**, 30% $C_6H_5CONH_2$, 60%	5j



109d



110

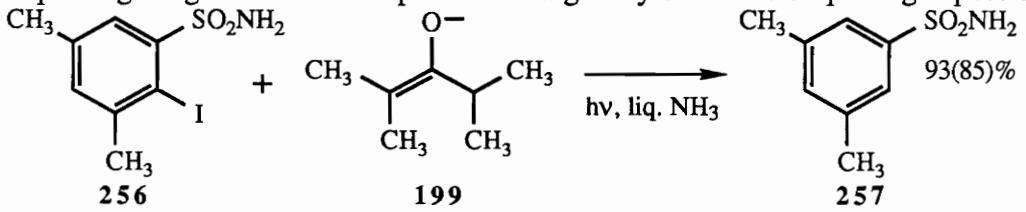
under $S_{RN}1$ conditions, yields substitution product **110** in 30% yield and benzamide in a yield of 60% (entry 5, TableVI). The apparent anomalies associated with the reactions of the various aryl halides with cyclohexanone and cyclopentanone enolates may arise from the poor solubility of both of these nucleophiles in liquid NH_3. Experimental sections of the papers cited did not indicate at which concentration the reactions involving these two nucleophiles were run. The reactions reported in Table V (entries 1 and 2) were run at sufficiently dilute concentrations to produce homogeneous solutions of the enolates. It was found that higher concentrations (i.e heterogeneous mixture of the enolates) required longer reaction periods and gave more complex product mixtures.

It is important to note that the reactions of cyclic ketone enolates are faster with 2-iodobenzenesulfonamide than with bromobenzene or 2-bromobenzamide. This difference in the rate may be the result of the competing reduction reaction acting as a chain terminating step in the case of the latter two substrates.[50] Reduction of 2-iodobenzenesulfonamide via β-hydrogen atom transfer from the cyclic enolate is likely to be a chain process. Evidence for a radical chain reduction mechanism was demonstrated for the analogous reaction with the enolate derived from 2,4-dimethyl-3-pentanone (Section III.1.3). A comparison of entries 1-3 of Table V and entries 1-4 of Table VI indicates that substitution increases with increasing ring size for both **1a** and bromobenzene. Cyclooctanone enolate appears to be a poor hydrogen atom donor.

In summary, 2-iodobenzenesulfonamide (**1a**) was found to undergo aromatic nucleophilic substitution when reacted under photostimulation in liquid NH_3 with enolates derived from cyclic ketones. This reaction provides a relatively efficient route to previously unknown tricyclic heterocycles. Difficulties associated with a competing reduction reaction result in decreased yields for reactions employing either cyclohexanone and cyclopentanone derived nucleophiles. The reaction of **1a** with enolate **253** derived from cyclooctanone yields only substitution products. However, the air sensitivity of the anticipated substitution product **254c** resulted in a deceased mass balance for the reaction.

1.6 Photostimulated Substitution Reactions of 2-Iodo-3,5-dimethylbenzenesulfonamide in Liquid NH_3

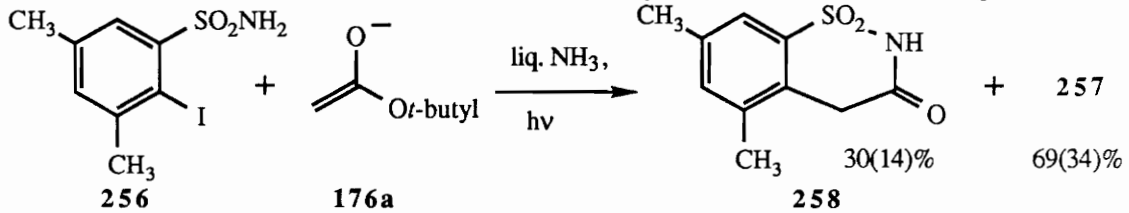
As part of an investigation of the intramolecular cyclization reactions of dianions derived from *N*-acyl-2-halobenzenesulfonamides, it was necessary to prepare 3,5-dimethylbenzenesulfonamide (**257**). Sulfonamide **257** was conveniently synthesized via the photostimulated reduction of 2-iodo-3,5-dimethylbenzenesulfonamide (**256**) by the potassium enolate, **199**, derived from 2,4-dimethyl-3-pentanone. The reaction proceeded as anticipated giving the reduction product in a good yield. The surprising aspect of the



256 **199** **257**

reaction was that the reaction mixture was homogeneous prior to irradiation. Analogous reactions of 2-iodobenzenesulfonamide (**1a**) with this and other enolates were consistently heterogeneous, with the exception of the reaction of **1a** with the anion derived from 2-benzyl-4,4-dimethyl-2-oxazoline (**180**). Recall, that in Section III.1.1 it was reported that the substrate **1a** is solubilized by the oxazoline anion nucleophile. Also recall that the oxazoline derived nucleophile was the only ester enolate equivalent that participated in a substitution reaction with sulfonamide **1a**. Based on these observations the question was asked whether the soluble sulfonamide anion derived from **256** would yield a substitution product when reacted with ester enolates under $S_{RN}1$ conditions.

As anticipated, 2-iodo-3,5-dimethylbenzenesulfonamide **256** reacted with ester enolate **176a** derived from *t*-butyl acetate under photostimulation to yield 5,7-dimethyl-1,2-benzothiazin-3(2*H*)-one 1,1-dioxide **258** 30% yield. The reaction also gave a 69%

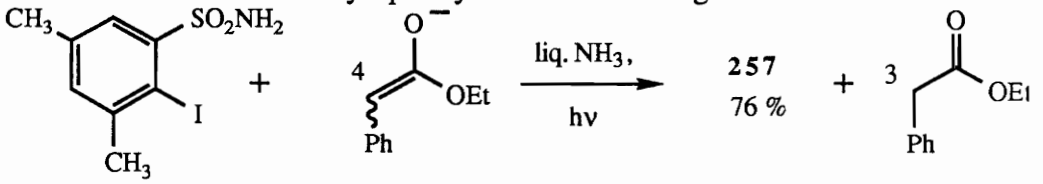


256 **176a** **258**

yield of reduction product, sulfonamide **257**. Prior to irradiation, the reaction mixture appeared to be significantly less heterogeneous than the analogous reaction of ester enolate

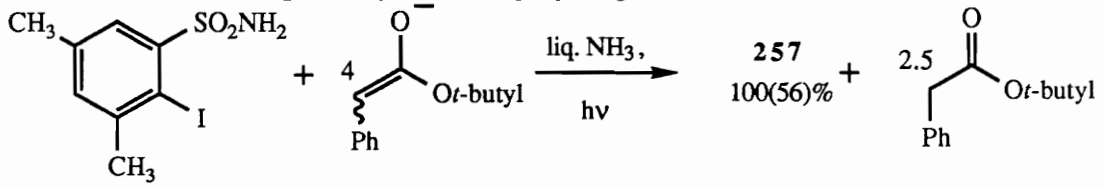
176a with sulfonamide **1a**. Furthermore, it was observed that the reaction was homogeneous at the completion of the irradiation period.

Encouraged by these results, it was sought to extend this study to include enolate anion **176b** derived from ethyl phenylacetate. Although the reaction mixture was



256 **176b** **259a**

completely homogeneous, only reduction product **257** was observed. Interestingly, one equivalent of the starting ester **259a** was consumed by the reaction. However, no byproduct derived from the ester could be isolated. Only small quantities of polar material which could not be characterized were observed. In light of the fact that the *t*-butyl ester enolate **176a** participated in the substitution reaction and yet the ethyl ester enolate **176b** did not, it was reasoned that the hydrogen atoms α to the oxygen of the ethyl ester might be involved in a reduction pathway involving hydrogen atom transfer. Therefore **256** was



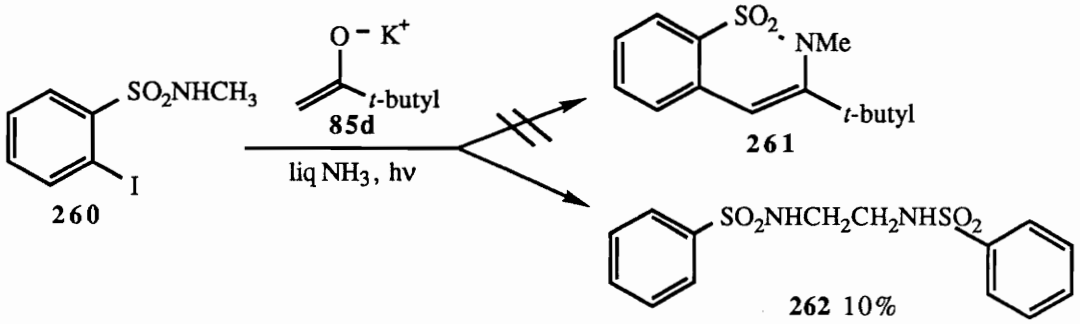
256 **176c:** **259b:**

treated under irradiation with enolate **176c** derived from *t*-butyl phenylacetate (**259b**). The result was similar to that obtained for the reaction involving the ethyl ester. Only reduction product **257** and recovered ester were observed.

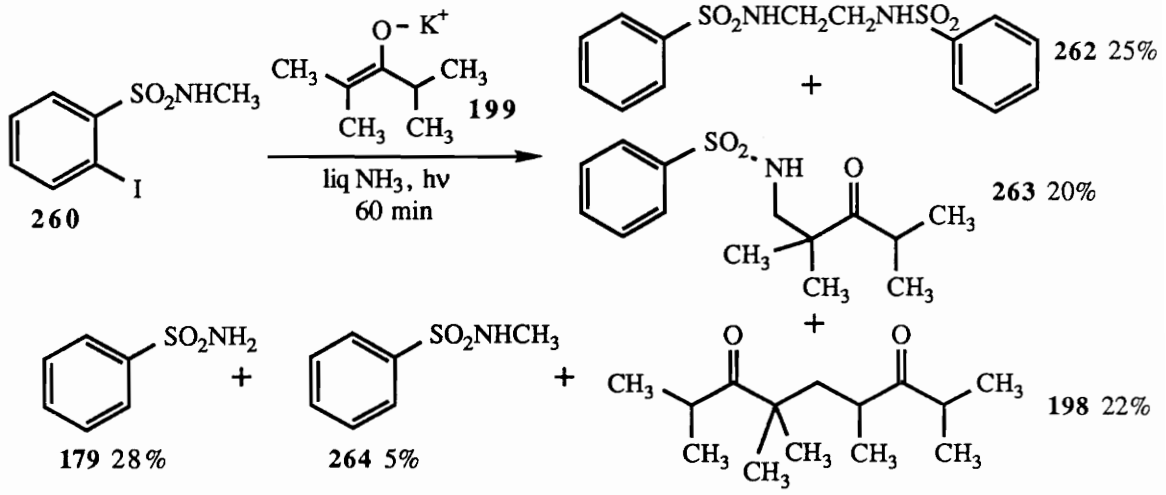
In summary, 2-iodo-3,5-dimethylbenzenesulfonamide **256** was found to participate in a photostimulated aromatic nucleophilic substitution reaction with the enolate derived from *t*-butyl acetate to yield the previously unknown heterocycle 3,5-dimethyl-2-iodobenzenesulfonamide **258**. However, sulfonamide **256** formed only reduction product **257** upon treatment with enolates derived from esters of phenylacetic acid under analogous conditions. It was also observed that the reduction reaction consumed at least one equivalent of the starting phenylacetate. The greater solubility of substrate **256** in the presence of ester enolates relative to 2-iodobenzenesulfonamide (**1a**) does however, greatly enhance the rate of consumption of the starting material.

1.7 Photostimulated Reactions of *N*-Alkyl-2-iodobenzenesulfonamides in the Presence of Enolate Ions.

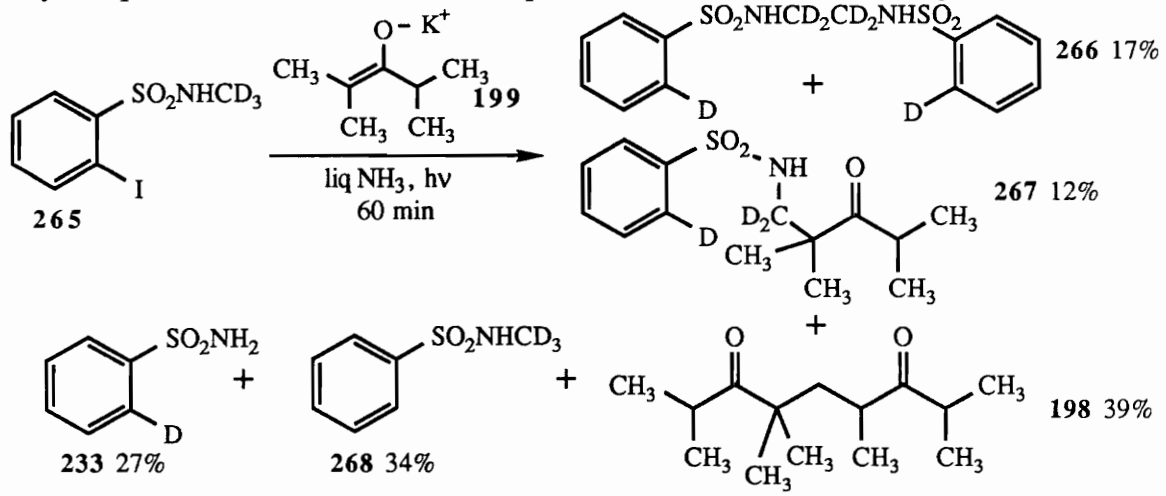
In Sections III.1.2 and III.1.5 it was reported that 2-iodobenzenesulfonamide (**1a**) reacted under photostimulation in liquid NH_3 with ketone enolate ions to yield 3-substituted and 3,4-disubstituted-2*H*-1,2-benzothiazine 1,1 dioxides. In an attempt to extend this methodology to include the preparation of 2,3-disubstituted and 2,3,4-trisubstituted-2*H*-1,2-benzothiazine 1,1 dioxides, the photostimulated reaction of *N*-methyl-2-iodobenzenesulfonamide (**260**) with the enolate anion **85d** derived from



pinacolone was investigated. Surprisingly the anticipated 2-methyl-3-*t*-butyl-2*H*-1,2-benzothiazine 1,1 dioxide (**261**) was not formed. Instead, a complex mixture of products was produced. Chromatography of this mixture gave *N,N'*-dibenzenesulfonyl-1,2-diaminoethane (**262**) in 10% yield as the only isolable product. The formation of ethylenediamine derivative **262** suggested that an intramolecular hydrogen atom transfer from the *N*-methyl carbon to an intermediate aryl radical was taking place. A further investigation of this reaction was undertaken. It was found that *N*-methyl-sulfonamide **260** reacted with the enolate ion **199** derived from diisopropyl ketone to yield a complex, yet isolable mixture of products. Ethylenediamine derivative **262** was again formed. In addition *N*-benzenesulfonyl-1-amino-2,2,4-trimethyl-3-pentanone (**263**), benzenesulfonamide (**179**), *N*-methylbenzenesulfonamide (**264**), and unsymmetrical ketone dimer **198** were formed.



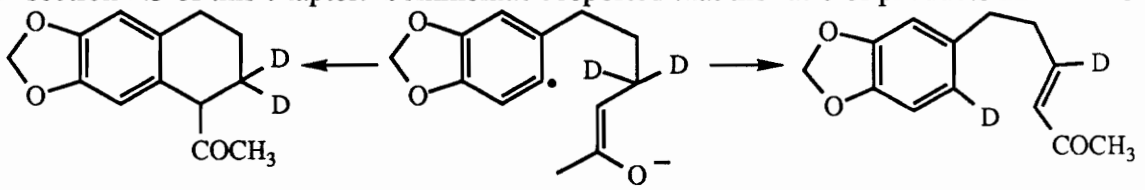
Formation of products **263** and **179** in addition to **262** supported a working hypothesis that reduction, in part, involved intramolecular hydrogen atom transfer. To provide evidence for such a mechanism, *N*-methyl-d_3-2-iodobenzene-sulfonamide (**265**) was prepared from 2-iodobenzenesulfonyl chloride and *N*-methyl-d_3-amine (98 atom% D). The reaction of labeled sulfonamide **265** with enolate **199** under analogous conditions yielded the corresponding deuterium labeled products. Of the aromatic products isolated only compound **268** did not exhibit incorporation of deuterium on the ring.



It is important to note that products **266**, **267** and **233** approach 98% d_1 for the ring label. The integrity of the amount of deuterium incorporated and the position of the label on the ring was established by ^{1}HNMR, ^{2}HNMR, ^{13}CNMR and mass spectral analysis. The ^{13}CNMR spectra of the ring labeled compounds, are worthy of note due to the interesting isotope shifts observed for the carbons *ortho* (C-2 and C-6) and *meta* (C-3

and C-5) to the sulfonyl carbon (C-1). Typically, four resonances are observed for the aromatic region of each of the proton-decoupled ^{13}CNMR spectra of the nonlabled sulfonamides. However, characteristic of each of the proton-decoupled ^{13}CNMR spectra of the labeled compounds, were six distinct aromatic carbon resonances (Figure I). Not shown in Figure I are the three resonances for the C-1 carbons of sulfonamides **266, 267** and **233**. Those signals occur between 140 and 145 ppm. The signals which occur between 132 and 133 ppm are assigned to the C-4 carbons of **266, 267** and **233** respectively. Carbons C-3 and C-5 of the unlabeled sulfonamides are equivalent producing one resonance in the range of 129 and 130 ppm. However, the C-3 and C-5 carbons of the labeled sulfonamides undergo an isotope shift producing two distinct resonances. Likewise carbons C-2 and C-6 are equivalent for the unlabeled sulfonamides producing one carbon resonance in the range of 126 - 127 ppm. For the labeled sulfonamides, the C-2 carbon is split into a triplet with a coupling constant of J_{CD} = 25 Hz. Note that in each example the triplet is not symmetrically displaced around the C-6 carbon resonances.

Based on the labeling study it is concluded that the reduction products **264** and **268** (no ring deuterium incorporation observed) arise from intermolecular hydrogen atom transfer from the β-carbon of the enolate.[51] The nearly seven fold increase in yield of labeled sulfonamide **268** relative to sulfonamide **264** is strong evidence for a primary isotope effect. Semmelhack observed similar results in the labeling study cited previously in section 1.3 of this chapter. Semmelhack reported that the ratio of products **214**:**215** is



214 **269** **215**

5:1, with substitution being the major pathway. Yet, the corresponding ratio of the analogous unlabeled products is reported to be 1:2, with reduction being the major pathway. Semmelhack argued that this could be interpreted as an isotope effect on the partitioning of the radical anion **269** toward cyclization (no primary isotope effect) and D atom transfer (slowed by a primary isotope effect).[52a]

The high degree of deuterium incorporated in products **266, 267** and **233** supports the hypothesis that the mechanism of formation of those sulfonamides involves intramolecular hydrogen atom transfer. Clearly, a hydrogen atom from the methyl group of

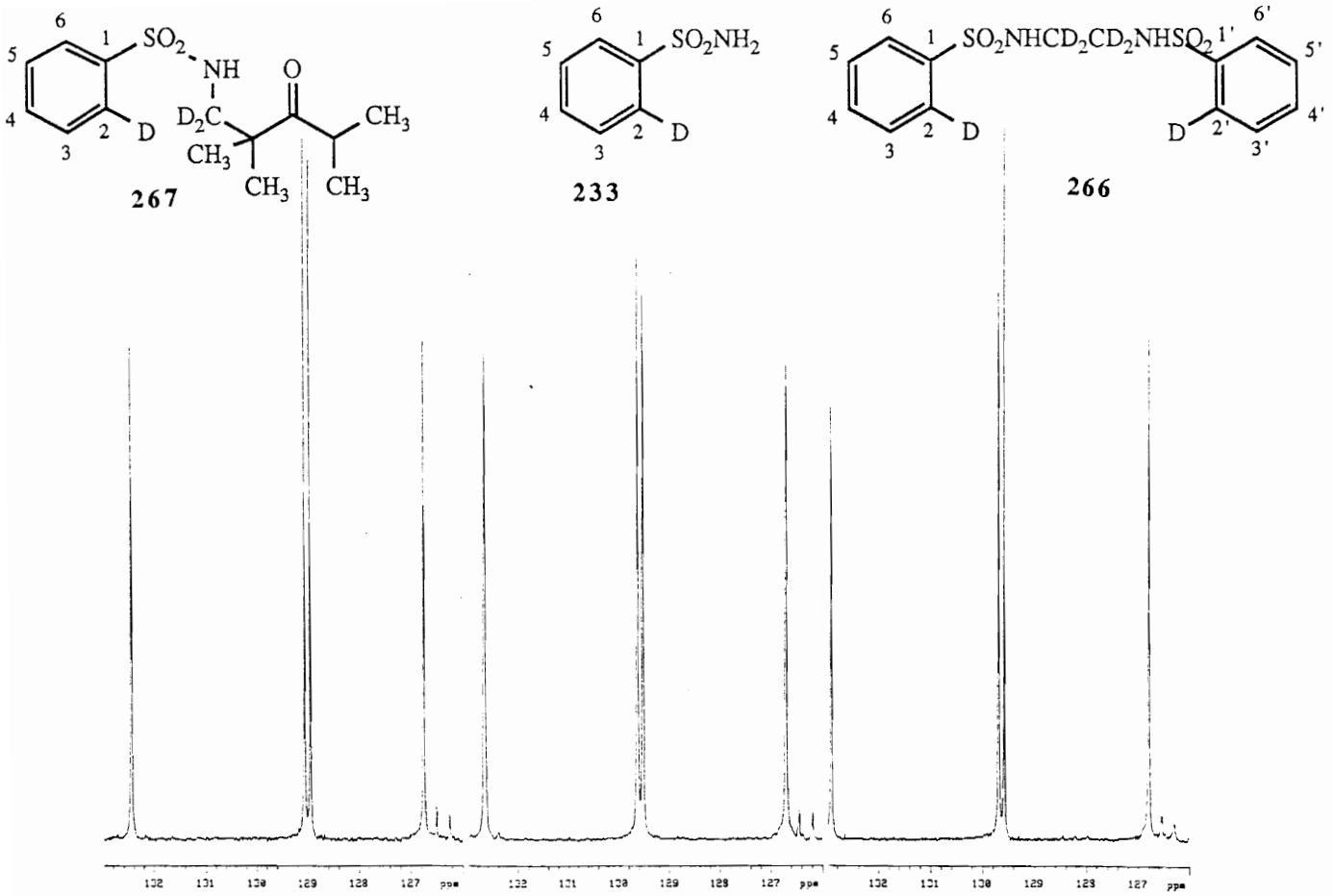
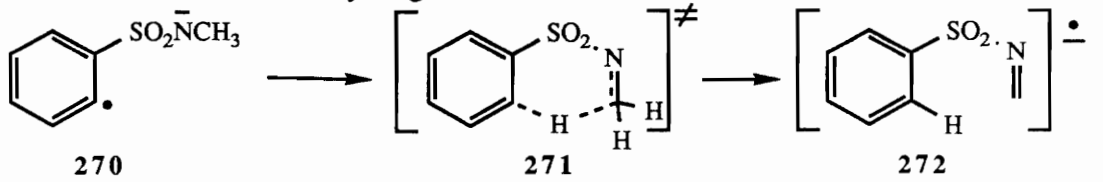


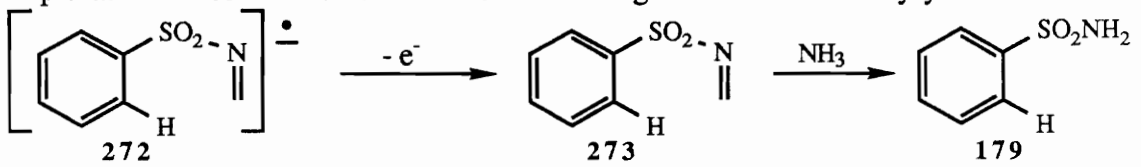
Figure 1. *100 MHz proton-decoupled ^{13}CNMR spectra of deuterium labled sulfonamides.*

the sulfonamide is transfered to intermediate aryl radical **270**. The radical anion **270** is expected to arise from the normal $S_{RN}1$ pathway involving electron transfer to the starting sulfonamide and fragmentation to liberate iodide. It is proposed that the hydrogen atom intercepts the aryl radical intermediate and the reaction mechanism diverges from the normal substitution course. This hydrogen atom abstraction can occur via a six membered



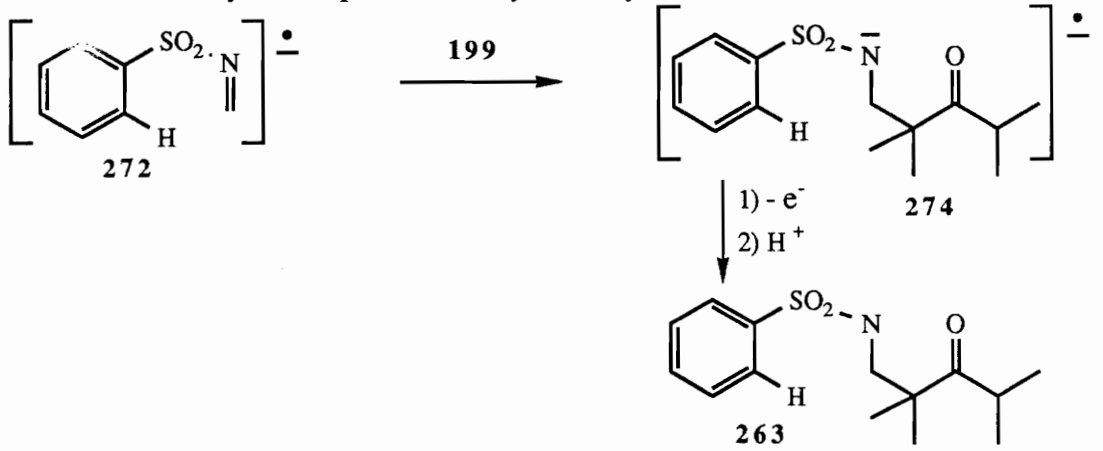
270 **271** **272**

transition state represented by activated complex **271**. Based on the products formed, radical anion **272** has three possible modes of reaction. The first mode is a propagation step that involves electron transfer to the starting halide to ultimately yield radical anion



272 **273** **179**

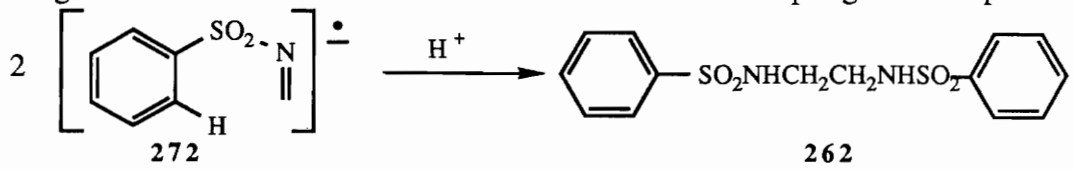
intermediate **270**, and fomaldehyde *N*-benzenesulfonylimine **273**. The imine undergoes ammonolysis to yield benzenesulfonamide **179**. A second mode involves trapping of the radical anion **272** by nucleophile **199** to yield ketyl radical **274**. Electron transfer from



272 **274** **263**

274 to the starting sulfonamide and protonation would yield the observed β-aminoketone **263**. Ketone **263** could also arise from nucleophilic attack of enolate **199** on imine **273**. However, ammonolysis of the imine may preclude such an addition. Based on arguments provided by Davis, it is reasoned that the electronegative sulfur activates the C-N double bond of **273** towards Michael-type additions.[60] Such activation facilitates ammonolysis

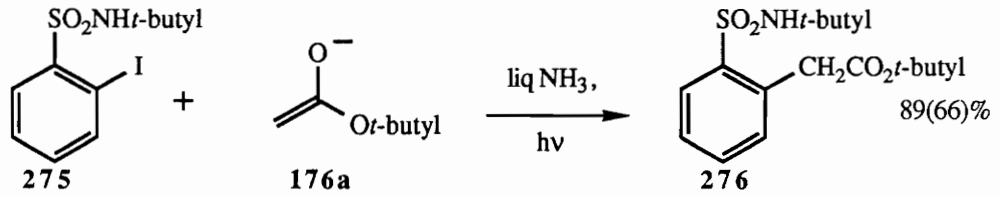
by NH_3, which is clearly in a large excess, effectively precluding Michael-type addition involving enolate **199**. The third mode of reaction involves coupling of two equivalents



272 **262**

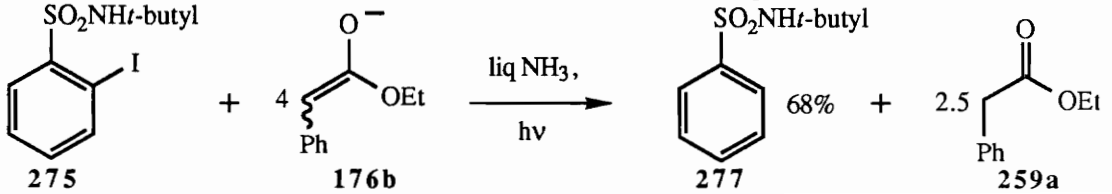
of **272** and protonation of the resulting dianion to yield ethylenediamine derivative **262**. It is noted that in both experiments more of the unsymmetrical dimer **198** is produced, than can be attributed to the formation of reduction products **264** and **268**. This may suggest that the actual reaction mechanism is more complex than the steps indicated above. It is interesting to note that Beugelmans reported that *N*-methyl-2-halobenznamides react with the enolate derived from acetone in a slow reaction (3 - 5 hours) to yield the corresponding reduction product *N*-methylbenzamide in 23-45% yield along with the corresponding 2,3-disubstituted isocarbostyrils in yields of 40-45%.[5j] Benzamides analogous to **179**, **262**, and **263** were not reported.

Although it was found that *N*-methyl-2-iodobenzenesulfonamide does not participate in aromatic substitution reactions, it was observed that the *N*-*t*-butyl analog does. Arylacetic acid ester **276** resulted when *N*-*t*-butyl-2-iodobenzenesulfonamide (**275**) was reacted in liquid NH_3 under photostimulation with the enolate anion **176a** derived



275 **176a** **276**

from *t*-butyl acetate. The reaction was particularly clean in that no reduction products nor colored impurities characteristic of many of the photostimulated reactions of the primary 2-halobenzenesulfonamides were produced. However, much like 2-iodo-3,5-dimethyl-benzenesulfonamide (**256**), sulfonamide **275** does not participate in a substitution reaction



275 **176b** **277** **259a**

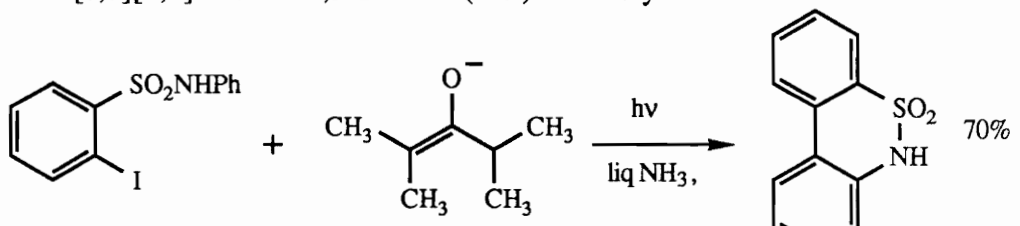
with the enolate anion **176b** derived from ethyl phenylacetate. Once again, enolate **176b** completely reduced the substrate. Also, more than one equivalent of the starting ester could not be accounted for (see Section III.1.6).

In summary, it was found that *N*-methyl-2-iodobenzenesulfonamide **260** does not participate in aromatic substitution reactions via the $S_{RN}1$ mechanism. Reduction of the aryl halide with concomitent oxidation of the *N*-methyl group precludes substitution. The mechanism of reaction involves intramolecular hydrogen atom transfer from the sulfonamide methyl group to an intermediate aryl radical. In addition it was found that *N*-*t*-butyl-2-iodobenzenesulfonamide (**275**) undergoes photostimulated aromatic nucleophilc substitution when treated with the enolate anion **176a** derived from *t*-butyl acetate. The reaction proceeds cleanly and efficiently to afford arylacetic acid ester **276.**

1.8 The Reactions of *N*-Aryl-2-iodobenzenesulfonamides in the Presence of Nucleophiles in Liquid NH_3.

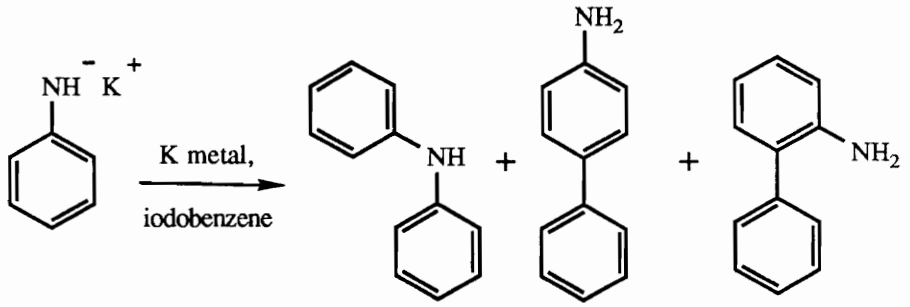
In the previous section it was reported that *N*-*t*-butyl-2-iodobenzenesulfonamide (**275**) participated in an aromatic nucleophilic substitution reaction with the enolate anion derived from *t*--butyl acetate. This result encouraged further studies of possible intermolecular substitution reactions of *N*-substituted-2-halobenzenesulfonamides. It was reasoned that *N*-phenyl-2-iodobenzenesulfonamide (**278**) had excellent potential as a participating substrate. It was thought that the electron withdrawing character of the aryl group might have a favorable affect on the reduction potential of the substrate and thereby facilitate electron transfer. Furthermore, sulfonamide **278** does not possess activated hydrogen atoms like its *N*-methyl analog, **260**, and therefore would not be liable to an intramolecular hydrogen atom transfer reaction.

In light of this reasoning, it was both surprising and interesting to find that sulfonamide **278** does not participate in intermolecular nucleophilic aromatic substitution. Instead, it was observed that *N*-phenylsulfonamide **278** when irradiated in the presence of excess diisopypyl ketone enolate (**199**), undergoes an intramolecular cyclization to form 6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide (**279**) in 70% yield.



278 **199** **279**

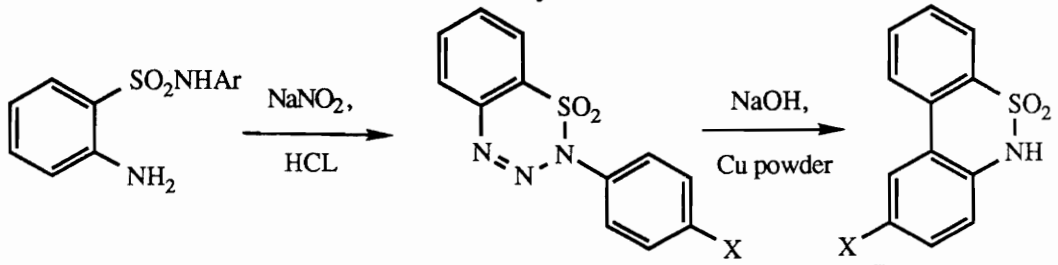
The participation of anilide ion in intermolecular aromatic substitution involving the $S_{RN}1$ mechanism has been reported earlier. The metal catalyzed reaction of aniline with iodobenzene has been described by Bunnett and Kim in some of the pioneering work on the $S_{RN}1$ reaction. These authors report that iodobenzene when treated with potassium anilide in the presence of potassium metal, reacts to form diphenylamine (**281**), *o*-



280 **281** 19% **282** 11% **283** 11%

aminobiphenyl (**282**) and *p*-aminobiphenyl (**283**).[37] A related reaction reported independently by Combellas and by Beugelmans involves intermolecular aromatic substitution by phenoxide nucleophiles. Phenoxide derivatives were reported to yield biaryl products via electrochemical as well as photoprompted $S_{RN}1$ reactions.[61,62]

The preparation of dibenzo[*c*,*e*][1,2]thiazines has been reported earlier. The preparation of dibenzothiazine **279** was first reported by Ulmann in 1910.[63] More recently, in 1977 Burmistrov et al. expanded Ulmann's work to include **287**.[64] The preparation involves the diazotization of *N*-aryl-2-aminobenzenesulfonamides **284** and

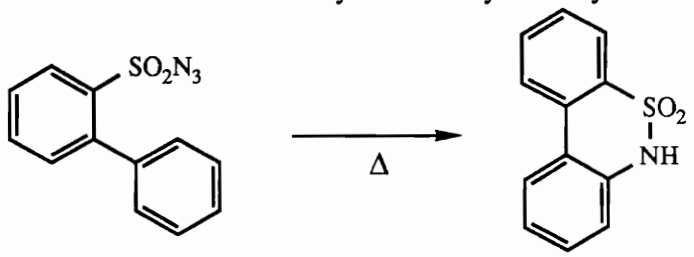


284a: X = H
284b: X = OMe

285a: X = H
285b: X = OMe

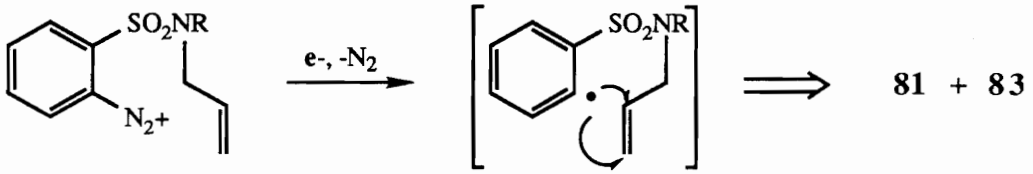
279: X = H
286: X = OMe

decomposition with hydroxide and copper powder of the isolated 2-arylbenzo-1,2,3,4-thiatriazine 1,1-dioxide intermediates **285**. In another report, Abramovitch and coworkers describe the preparation of **279** via thermolysis of biarylsulfonyl azide **287**. Intuitively,



287 **279**

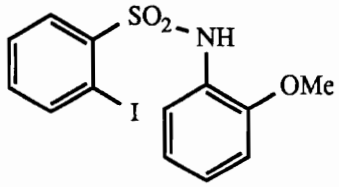
from a mechanistic stand point, Ulmann's preparation of **279** is related to the intramolecular reaction reported above for *N*-phenyl-2-iodobenzenesulfonamide **278**. Beckwith's report of the cyclization of arenediazonium salt **77** to yield benzothiazines and



77 79

benzothiazepines was cited earlier.[35] Recall, that the mechanism featured radical addition to an olefin. It would appear that this too is mechanisticly related to the photocyclization reaction of sulfonamide **278**. The reactions of arenediazonium salts and their relationship to the $S_{RN}1$ reaction has been recently reviewed by Galli.[35]

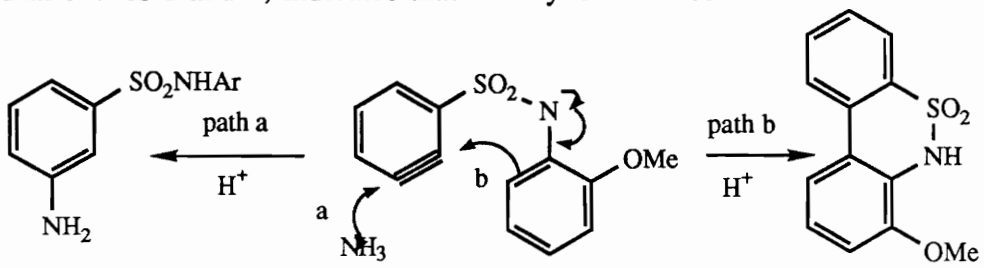
In order to help establish the mechanism of the cyclization of *N*-phenylsulfonamide **278** a systematic study was undertaken. *N*-(2-methoxyphenyl)-2-iodobenzesulfonamide



288

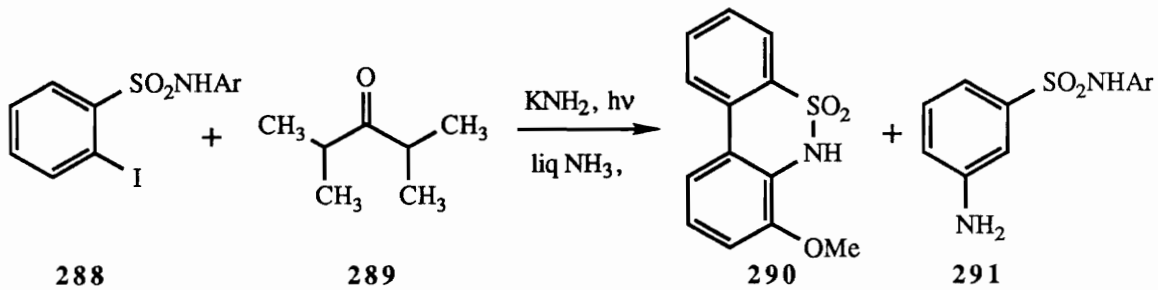
(**288**) was chosen for the mechanistic study in the place of **278** because of its increased solubility in chlorinated solvents, which greatly improved the efficiency of isolation of the reaction products via chromatography. The results of this mechanistic study are reported in Table VII.

The results presented in Table VII indicate that two mechanisms leading to dibenzothiazine **290** are possible. Formation of **291** in only the experiments that are outlined in entries 1 and 2, indicates that the aryne intermediate **294** is involved in the



291: Ar = 2-$MeOC_6H_4$ **294** **290**

Table VII. Mechanistic Study of the Intramolecular Cyclization of *N*-(2-Methoxyphenyl)-2-iodobenzenesulfonamide

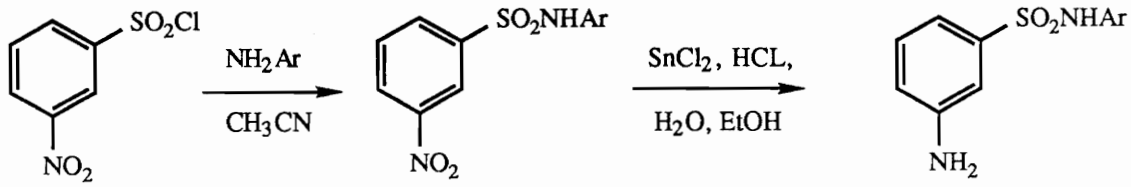


288 **289** **290** **291**

Ar = 2-MeOC$_6$H$_4$

entry	equivalents of KNH_2	equivalents of diisopropyl ketone **289**	rxn time (min)	yield % **288**	yield % **290**	yield % **291**[a]
1	2	0	90[b]	53	14	31
2	2	0	90	0	56	28
3	2	2.2	78	0	96[c]	0
4	2	2.2	15	11	75	0
5	2	2.2	15[d]	16	61	0

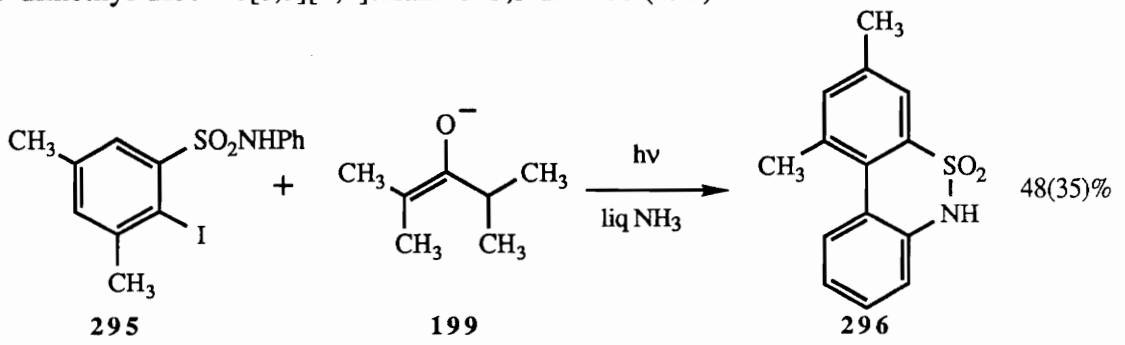
[a]Structure confirmed via independent synthesis starting with 3-nitrobenzenesulfonyl chloride **292** and *o*-anisidine. [b]Reaction was covered with a dark cloth.



292 **293** **291**

[c]Recrystallization from toluene gave **290** in 66% yield. [d]The reaction was run in the presence of 5 mole% DTBN.

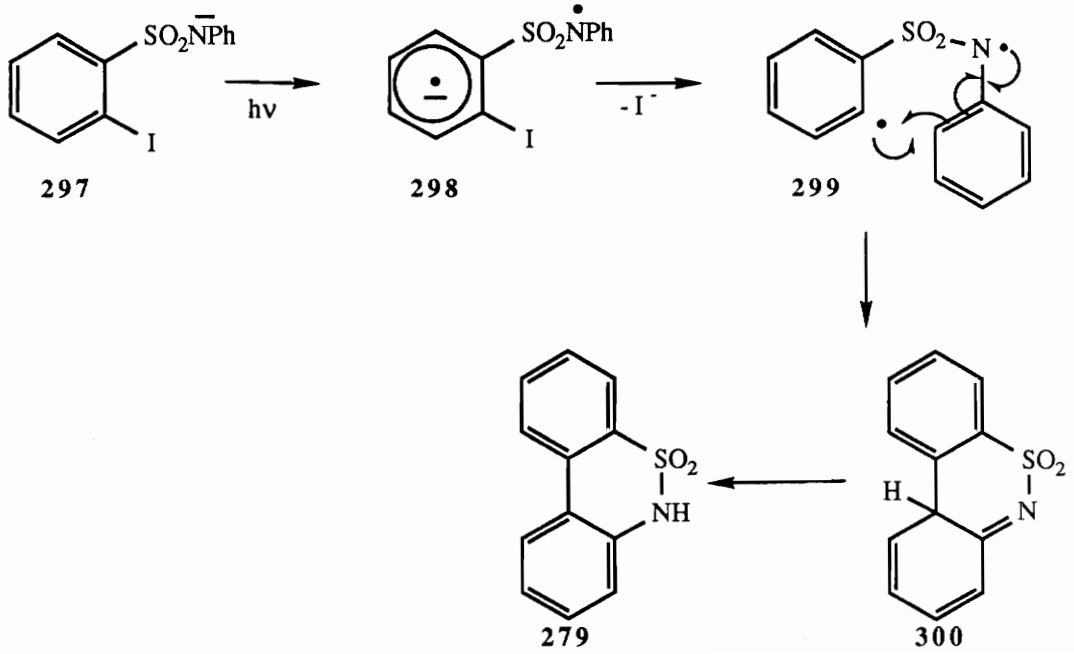
reaction mechanism when a strong base is present. The formation of **290** in small yields in the dark reaction (entry 1) indicates that cyclization can occur via intramolecular trapping of the aryne intermediate **294**.[66] The significant increase in yield of dibenzothiazine **290** in the photostimulated reactions suggests that cyclization may occur via a charge transfer process (entries 2-5). The minimal affect of DTBN may suggests that the electron transfer process is non-chain in character. To demonstrate unambiguously that the photocyclization can occur via a non-aryne mechanism *N*-phenyl-2-iodo-3,5-dimethylbenzenesulfonamide (**295**) was treated with two equivalents of enolate **199** under photostimulation to yield 1,3-dimethyl-dibenzo[*c*,*e*][1,2]thiazine 5,5 dioxide (**296**).



295 **199** **296**

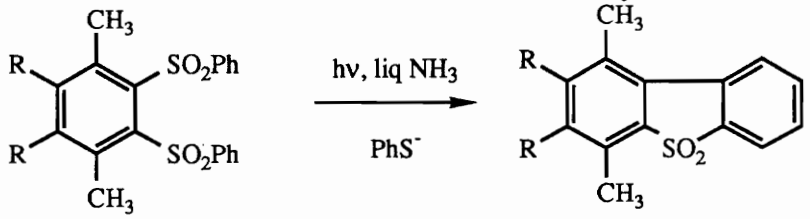
The proposed mechanism of the photostimulated intramolecular cyclization of the anion derived from *N*-aryl-2-iodobenzenesulfonamides in liquid NH_3 is outlined in Scheme XXXIV. The mechanism features photostimulated intramolecular electron transfer to yield

Scheme XXXIV



297 **298** **299** **279** **300**

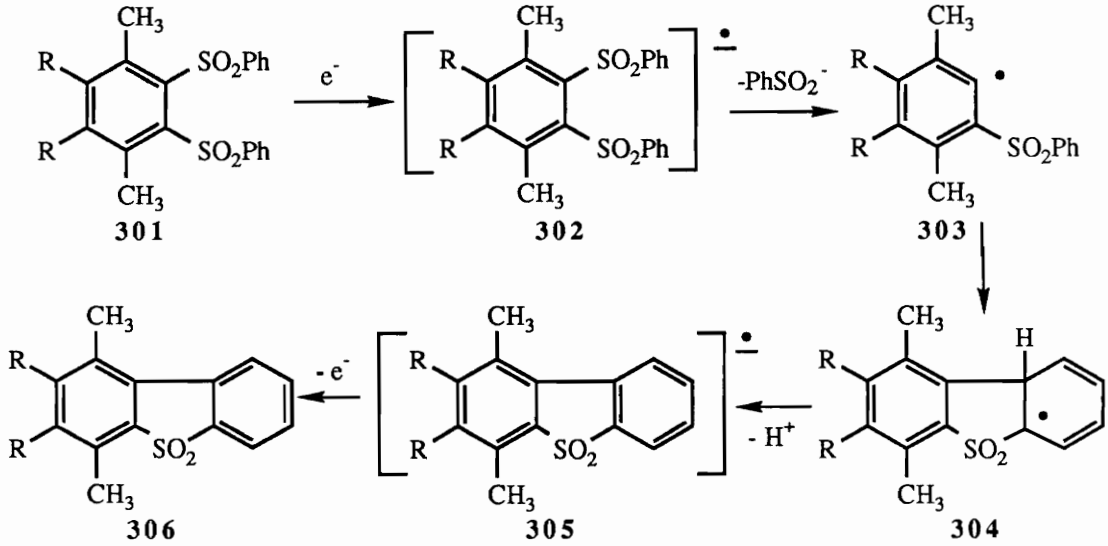
diradical anion **298**. Expulsion of iodide yields a neutral diradical **299**. Coupling of the diradical gives tautomer **300**, which rearranges to give dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide (**279**). Precedent for such intramolecular aryl coupling has been reported in the literature. Novi reported that the photostimulated reaction of *o*-bis(phenylsulfonyl) arene **301** with benzenethiolate resulted in the formation of biaryl **306**.[67] To account for



301 **306**

the formation of **129**, Novi proposed the mechanism outlined in Scheme XXXV. The mechanism features external electron transfer to yield radical anion **302**. Expulsion of

Scheme XXXV



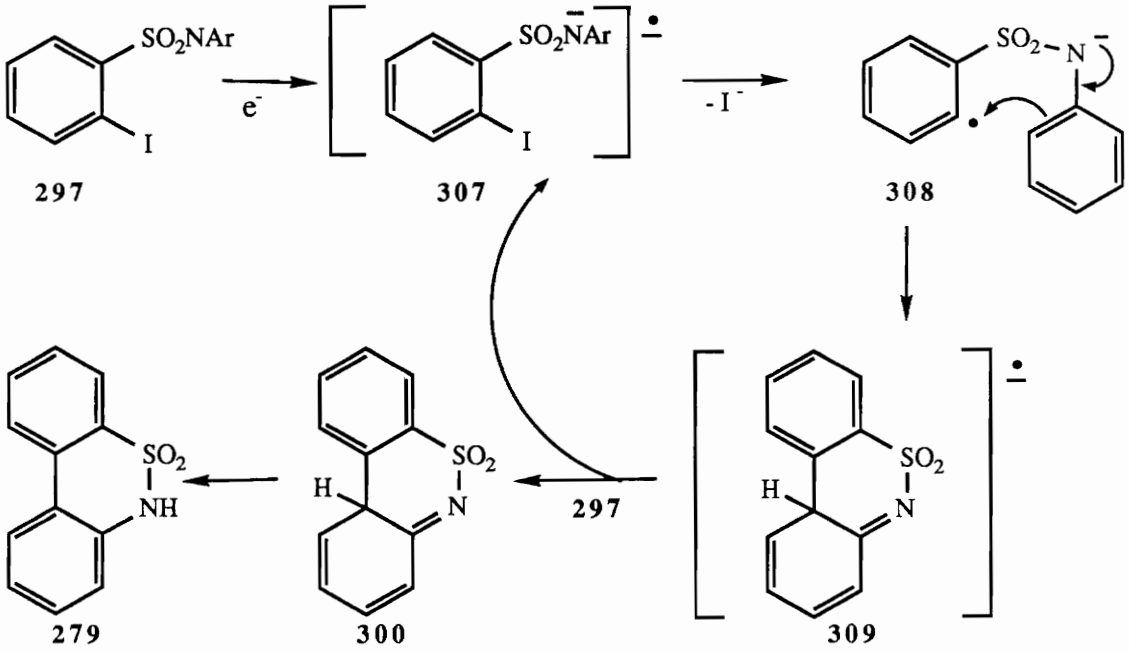
301 **302** **303**

306 **305** **304**

benzenesulfinate ion results in formation of radical **303**. Intramolecular trapping of the radical by the π-system of the phenyl ring results in sulfonyl stabilized radical **304**. Deprotonation of the π-delocalized intermediate and ejection of an electron yields the biaryl product **306**. The major difference in the two related mechanisms is the non-chain character of the reaction of the *N*-aryl-2-iodobenzenesulfonamides. A mechanism involving a chain transfer step is easily written for the sulfonamide cyclization reaction (Scheme XXXVI). This mechanism features an external electron transfer step forming radical dianion **307** analogous to **298**. Expulsion of halide and nucleophilic attack of the tethered anilide anion yields **309**. Electron transfer from **309** to the ionized starting

sulfonamide **297** propagates the chain and affords tautomer **300**. Finally, tautomerization yields the dibenzothiazine product **279**. The minor effect that DTBN has on the rate of the reaction indicates that the external electron transfer mechanism is unimportant.

Scheme XXXVI

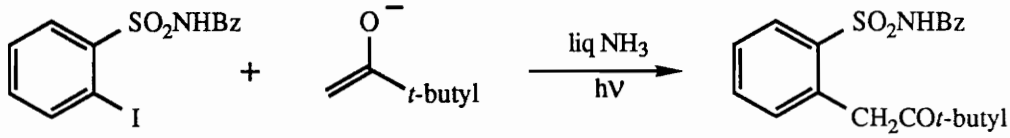


To summarize, *N*-aryl-2-iodobenzenesulfonamides were found to undergo an intramolecular cyclization reaction to yield dibenzo[*c*,*e*][1,2]thiazine 5,5 dioxides **279**. The formation of **279** can occur via two mechanisms, an intramolecular aryne and a photoinitiated intramolecular aryl radical coupling. Experimental evidence for the aryne reaction was the formation of amination product **291** when a strong base was present. Experimental evidence for the intramolecular radical coupling reaction centers around the increased yields obtained under photostimulation of dibenzothiazine **288**. The presence of 5 mole% of di-*tert*-butyl nitroxide (DTBN) had little inhibitory effect on the reaction, which might indicate a non-chain character of the photocyclization.

1.9 Reactions of *N*-Acyl-2-iodobenzenesulfonamides with Ester Enolates

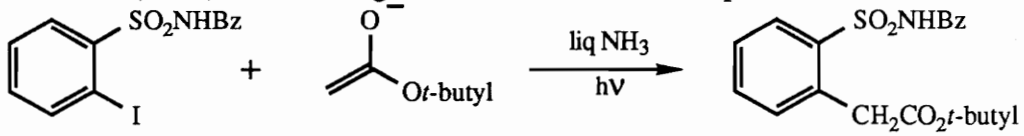
In this section we report that *N*-acyl-2-iodobenzenesulfonamides react under $S_{RN}1$ conditions with nucleophiles derived from both *t*-butyl acetate and ethyl phenyl acetate to yield substitution products. In previous sections of this report, the reactions of primary and secondary alkyl and aryl 2-iodobenzenesulfonamides with ketone and ester enolates under $S_{RN}1$ conditions have been described. Substitution reactions involving primary sulfonamides and ketone enolates met with moderate success. Yet substitution reactions involving ester enolates and primary sulfonamides have proceeded poorly if at all. Only two reactions involving primary sulfonamides and ester enolates have resulted in formation of substitution products. The reaction of 2-iodobenzenesulfonamide (**1a**) with the anion nucleophile derived from 2-benzyl-4,4-dimethyl-2-oxazoline (**180**) and that of 2-iodo-3,5-dimethylbenzenesulfonamide (**78**) with the enolate anion **80** derived from *t*-butyl acetate, yielded substitution products. Still, the yields of substitution products were less than satisfactory. Attempts at intermolecular $S_{RN}1$ reactions with secondary sulfonamide substrates have also met with little success. Intramolecular hydrogen atom transfer and intramolecular cyclization precludes intermolecular substitution for *N*-methyl and *N*-aryl-2-iodobenzenesulfonamides, respectively. Prior to this work, only the reaction of *N*-*t*-butyl-2-iodobenzenesulfonamide with enolate **80** gave preparatively useful yields of a substitution product. Still, that same substrate gave only the reduction product **106** when treated with enolate anion **82a** derived from ethyl phenylacetate.

In related work it was discovered that the dianions derived from certain *N*-acyl-2-iodo- benzenesulfonamides are susceptible to aromatic nucleophilic substitution by amide ion (see Sections III.2.1 and III.2.2). The fact that KNH_2, a hard base, participated in a substitution reaction with a dianionic substrate might suggest that the mono anions derived from these substrates would be prime candidates for substitution reactions with softer bases. In other words, it was anticipated that the mono anions derived from *N*-acyl-2-iodobenzenesulfonamides would participate in aromatic $S_{RN}1$ reactions when treated with enolates derived from ketones and esters. To test this hypothesis, *N*-benzoyl-2-iodo-benzenesulfonamide (**310**) was reacted under photostimulation with enolate anion **85d**



310 **85d** **311** 100(85)%

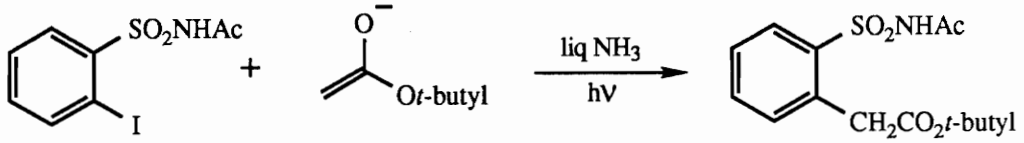
derived from pinacolone. The reaction gave the anticipated α-arylketone **311** in excellent yields. Encouraged by this result, efforts were then directed toward reactions involving ester enolates. The reaction of *N*-benzoyl-2-iodobenzenesulfonamide (**310**) with *t*-butyl acetate enolate (**176a**) was investigated. The reaction is complete in less than 30 minutes



310 **176a** **312** 84(75)%

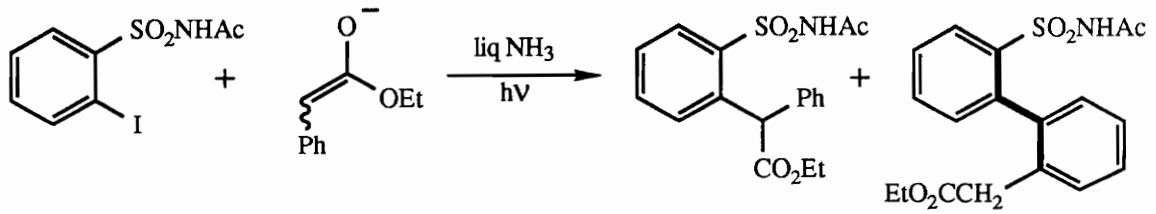
and forms the anticipated arylacetate **312** in good yields. In control experiments, **310**, upon treatment with enolate **176a** for 45 minutes without irradiation (other than ambient laboratory lighting) was only 40% converted to **312**. Under the same conditions (ambient irradiation, 45 min) but with 5 mole% DTBN present in the reaction mixture, only 10% of **310** was converted to **312**. These two experiments are consistent with an nucleophilic aromatic substitution occuring via the $S_{RN}1$ mechanism.

Having established that *N*-benzoyl-2-iodobenzenesulfonamide (**310**) would participate in substitution reactions with both pinacolone and *t*-butyl acetate enolates under $S_{RN}1$ conditions, attention was turned towards enolate anion **176b** derived from ethyl phenylacetate. For the sake of simplification of the NMR spectra of the anticipated product, *N*-acetyl-2-iodo-benzenesulfonamide **313a** was chosen for the study. In Section III.2.1 sulfonamide **313a** is reported to react via an intramolecular reaction in the presence of excess KNH_2 to yield 3,4-dihydro-1,2-benzothiazin-3(2*H*)-one 1,1 dioxide (**13d**). Therefore it was anticipated that care should be taken to exclude the presence of excess amide. To test the suitability of sulfonamide **313a** as a substrate, it was treated with excess enolate **176a** under photostimulation in liquid ammonia. The reaction



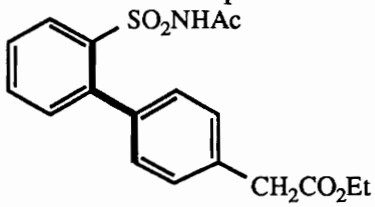
313a **176a** **314** 76(65)%

resulted in formation of arylacetate **314** in good yields. Encouraged by this result **313** was treated with enolate **176b** under analogous conditions. The reaction gave the desired

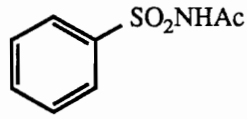


313a **176a** **315** 51(38)% **316** trace

ethyl diarylacetate **315** in a relatively good yield. In addition, *ortho*- coupled biarylacetic acid ester **316** was obtained in trace quantities. Not isolated but indicated to be present by the ^{1}HNMR spectrum of the crude reaction mixture, were the *para*- coupled biarylacetic acid ester **317** and the reduction product **318**.



317

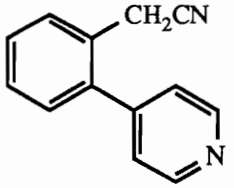


318

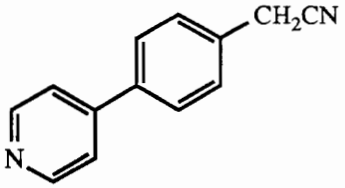
The assignment of structure **315** was made in accord with ^{1}HNMR, ^{13}CNMR, IR and MS analysis. The proton-decoupled ^{13}CNMR spectrum and MS data are in agreement with either structure **316** or **317**. Distinction between those structures is made on the basis of the ^{1}HNMR and IR spectra. Characteristic of the ^{1}HNMR is an AB pattern of δ_A = 3.34 and δ_B = 3.43 with J_{AB} = 16 Hz for the geminal protons α to the ester carbonyl. Chemical shift non-equivalency arises from the chirality resulting from restricted rotation along the biaryl linkage of **316**. Stucture **317** is achiral due to the mirror plane bisecting the *para*-substituted ring. The ^{1}HNMR of compound **317** should contain a singlet resonance for the geminal protons α to the ester carbonyl. Because sturcture **317** contains the structural features of both a 1,2- and a 1,4-disubstituted aromatic ring, the IR spectra of **317** is expected to have two absorptions for the C-H out of plane stretch. The IR spectra of the compound isolated has only one absorption in that region and occurs at 778 cm^{-1}. That absorption is consistent with a 1,2 disubstitued aromatic such as **316**.

Apparently this is the first report of the coupling of an aryl halide with the enolate anion of ethyl phenylacetate to yield biaryl products. However, the coupling reaction is not without precedent. Hermann has reported the formation of small quantities of *ortho*- and *para*- coupled benzyl cyanides **319** and **320** from the $S_{RN}1$ reaction of the anion

derived from phenylacetonitrile with 4-bromopyridine.[7] Similarly, Wong has reported



319

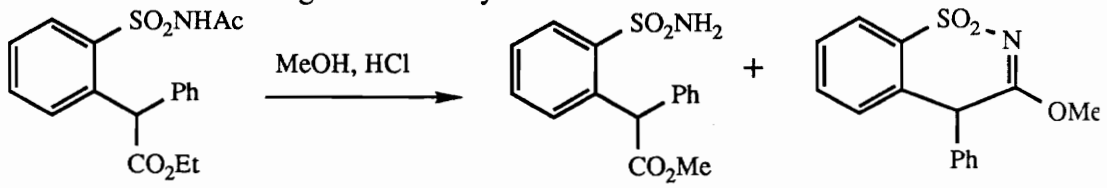


320

that the potassium dianion of phenylacetic acid when treated with iodobenzene undergoes an $S_{RN}1$ reaction to give 4-biphenylacetic acid[47]. Other researchers in our group have found that the lithium dianion of phenylacetic acid reacts under $S_{RN}1$ conditions with iodobenzene to yield the α-coupled product, diphenylacetic acid.[9]

In an attempt to optimize the yield of product **315**, sulfonamide **313a** was treated with the lithium enolate anion of ethyl phenylacetate under conditions analogous to that employed for the potassium enolate. The reaction resulted in formation of the reduction product **318** exclusively. Similar to results reported earlier for sulfonamides **256** and **275,** the reduction reaction consumed an equivalent of the starting ester. Surprisingly, treatment of **313a** with the anion **180** derived from 2-benzyl-4,4-dimethyl-2-oxazoline, gave only the reduction product **318.**

To demonstrate the potential of substrates **311, 312** and **315** for use as synthetic intermediates in the preparation of 1,2-benzothiazin-3(4*H*)one 1,1 dioxides, compound **315** was treated with methanolic HCl at 25°C overnight The reaction gave methanolysis products **182** and **321** in good over all yields.



315 **182** 53(42)% **321** 33(31)%

In summary, *N*-acyl-2-iodobenzenesulfonamides have been found to participate in nucleophilic aromatic substituion via the $S_{RN}1$ mechanism. The substrates react nearly equally as well with ester enolates as they do with ketones. The resulting substitution products can be treated with methanolic HCl to yield the corresponding primary sulfonamides.

1.10 The Relationship of Solubility to Reduction for the Reactions of 2-Iodobenzenesulfonamides with Ester Enolates in Liquid NH_3.

At the outset of this research earlier workers in our laboratories had found that irradiation of 2-halobenzensulfonamides **1a-c** in the presence of ester enolates in liquid NH_3 resulted in the sluggish formation of the reduction product, benzensulfonamide (**179**). The reaction mixtures of **1a-c** with ester enolate nucleophiles were characteristically heterogeneous suspensions. We concluded that the lack of favorable reactivity of **1a-c** with ester enolates is in part due to the unavailability of the sulfonamide in solution. This conclusion however does not account for why reduction was able to take place. We therefore speculated that reduction might be occuring out of solution. However, observations made throughout our study of the intermolecular reactions of 2-halobenzenesulfonamides with ester enolate and ester enolate equivalent nucleophiles indicate that reduction can occur in solution. The reactions of the oxazoline derived nucleophile **180** with 2-iodobenzenesulfonamide **1a** (Section III.1.1); the reactions of 2-iodo-3,5-dimethylbenzenesulfonamide **256** with the enolates **176a-c** derived from *t*-butyl acetate and esters of phenylacetic acid (Section III.1.5); the reactions of *N*-*t*-butyl-2-iodobenzene- sulfonamide **275** enolates **176a-c** (Section III.1.6); and the reactions of *N*-acetyl-2-iodobenzensulfonamide **313a** with nucleophiles **180**, **176a** and **176b**, were either homogeneous or at least only slightly heterogeneous. Yet reduction was able to compete quite efficiently with substitution in most of the reactions. In some of the examples, reduction was the sole product.

Throughout this study it was observed that the homogeneity of a reaction mixture was a function of both the substrate and the nucleophile. This observation would seem to indicate that some association or complexation of the substrate and the nucleophile exists. How well NH_3 solvates aggregates of such a complex appears to be to some extent a function of the steric features of both the substrate and the nucleophile. Apparently, sterically bulky nucleophiles (i.e. a β-aryl ester enolate) and substrates (ie. an *ortho*-disubstituted aryl halide or a *N*-*t*-butyl-2-halobenzenesulfonamide) contribute to the solvation of the complex. It is a given that other factors are involved in the solubility of the substrate such as hydrogen bonding with the solvent. Nevertheless, the greatest solubility

of the substrate was achieved when the substrate as well as the nucleophile featured spacially demanding groups near their respective electrophilic and nucleophilic sites. The clearest example of this phenomenon is the reactions of 2-iodobenzenesulfonamide (**1a**) and 2-iodo-3,5-dimethylbenzenesulfonamide (**256**) with ethyl phenylacetate and *t*-butyl acetate derived enolates. It was observed that 2-iodo-3,5-dimethylbenzenesulfonamide (**256**) was completely soluble in the presence of ethyl phenylacetate enolate (**176b**) and only partially soluble in the presence of *t*-butyl acetate enolate (**176a**). It was also observed that 2-iodobenzenesulfonamide (**1a**) was insoluble in the presence of enolate **176b** as well as **176a**. It was noted throughout the study, that qualitatively, reduction was favored over substitution when either the nucleophile or the substrate had structural features that could sterically limit the approach of the nucleophile towards the aromatic electrophile. That point has been established for reduction reactions involving β-hydrogen atom transfer and was pointed out in Section III.1.3. From this study, it is concluded that the relationship of reduction to substitution is indirect; in that factors which favor solvation of the substrate-nucleophile complex also tend to favor reduction.

A comparison of the amount of reduction to substitution observed for the reactions of ester enolates **176a-c** and the oxazoline derived anion **180** reported in previous sections, are summarized in Table VIII. The reactions of the ethyl phenylacetate enolate **176b** are particularly instructive. In entry 2, it is reported that ethyl phenylacetate enolate reduces 2-iodobenzenesulfonamide (**1a**) in a slow reaction.[9] Yet oxazoline derived nucleophile **180** efficiently consumes all of the same starting material in a reaction that gave mainly substitution product (entry 3). To the contrary, enolate **176b** participates in a substitution reaction with *N*-acetylsulfonamide **313a** (entry 10); yet oxazoline anion **180** only yields the reduction product when treated with **313a** (entry 12). It is also instructive to point out that, whereas *t*-butyl acetate enolate, **176a**, participates in substitution reactions with substrates **256** and **275** (entries 4 and 7 respectively); the ethyl phenylacetate enolate does not (entries 5 and 8).

Table VIII. Reactions of 2-Iodobenzenesulfonamide and its Derivatives with Ester and Oxazoline Derived Nucleophiles.

entry	substrate	ester or ester equivalent	nucleophile	% reduction	% substituition
1	2-iodobenzene sulfonamide, **1a**	*t*-butyl acetate	**176a**	-[a]	0
2	**1a**	ethyl phenylacetate	**176b**	-[a]	0
3	**1a**	2-benzyl-4,4-dimethyl-2-oxazoline	**180**	27	50(25)
4	2-iodo-3,4-dimethyl benzenesulfonamide, **256**	*t*-butyl acetate	**176a**	69	30(14)
5	**256**	ethyl phenylacetate	**176b**	76	0
6	**256**	*t*-butyl phenylacetate	**176c**	100	0
7	*N*-*t*-butyl-2iodo-benzenesulfonamide, **275**	*t*-butyl acetate	**176a**	0	89
8	**275**	ethyl phenylacetate	**176b**	68	0
9	*N*-acetyl-2-iodo benzenesulfonamide, **313a**	*t*-butyl acetate	**176a**	0	76(65)
10	**313a**	ethyl phenylacetate	**176b**	-[b]	51(38)
11	**313a**	ethyl phenylacetate	**176b**	80[c]	0
12	**313a**	2-benzyl-4,4-dimethyl-2-oxazoline	**180**	75	0

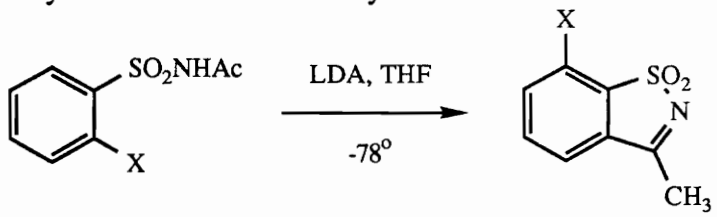
[a]The %reduction was not determined; recovered starting material was the major product. [b]The reduction product was not isolated, only observed as a minor constituent of the crude reaction mixture. [c]In this example $LiNH_2$ was used in place of KNH_2.

The reaction of the potassium enolate of ethyl phenylacetate with the *N*-acetyl sulfonamide **313a** (entry 10) represents a fine tuning of the steric requirements of substitution. Likewise, the successful substitution reaction of the oxazoline anion **180** with the parent sulfonamide **1a** represents a similar balance (entry 3). A balance between free access of the nucleophile to the substrate leading to insolubility and hence no reaction; and greatly limited access to the subtrate by the nucleophile leading to complete solubility but only reduction products. It is suggested that insufficient steric inhibition between the nucleophile and the electrophile leads to an insoluble complex and therefore a slow consumption of the starting material to form reduction products. It is also suggested that too great of an amount of steric incumberance precludes substitution and reduction predominates.

2. REACTIONS OF THE POTASSIUM DIANIONS OF *N*-ACETYL-2-HALOBENZENESULFONAMIDES IN LIQUID NH_3.

2.1 Cyclization Reactions

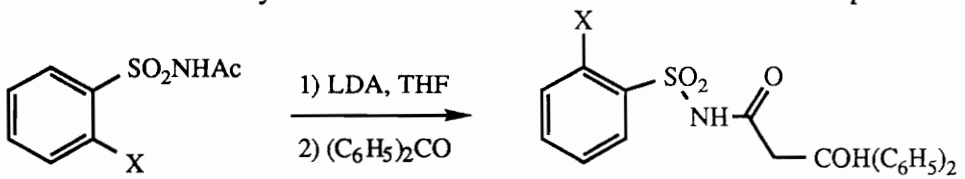
A synthetically useful feature of the dianions derived from *N*-acetyl-2-halobenzenesulfonamides is the chemistry they exhibit as a function of the conditions under which they are generated. Previous workers in the our research group have found that *N*-acetyl-2-bromo- and 2-chlorobenzenesulfonamides **313b** and **313c**, respectively, undergo a ring metalation-cyclization reaction to yield 7-halobenzoisothiazoles **322** upon



313b: X = Br
313c: X = Cl

322a: X = Br
322b: X = Cl

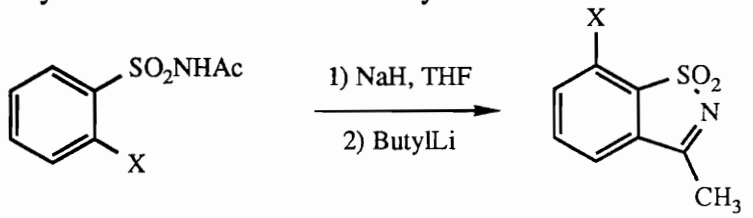
treatment with lithium diisopropyl amide in THF.[68] Quenching experiments provided evidence for the intermediacy of a lateral dianion. Thus alcohol **323** was produced when



313c: X = Cl

323: X = Cl

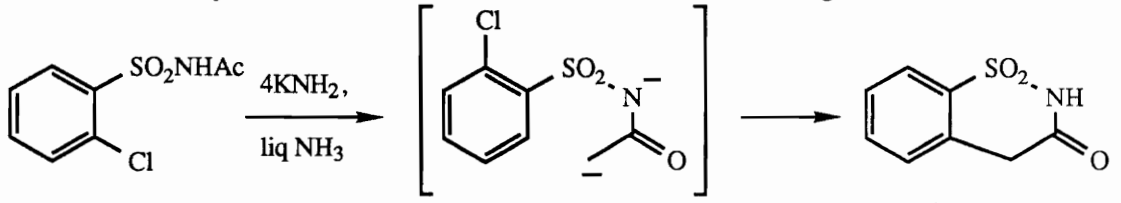
the reaction was quenched with benzophenone. Likewise our research group found that sequential NaH-butyllithium treatment of *N*-acetyl sulfonamides **313b** and **313c** gave the



313b: X = Br
313c: X = Cl

322c: X = H

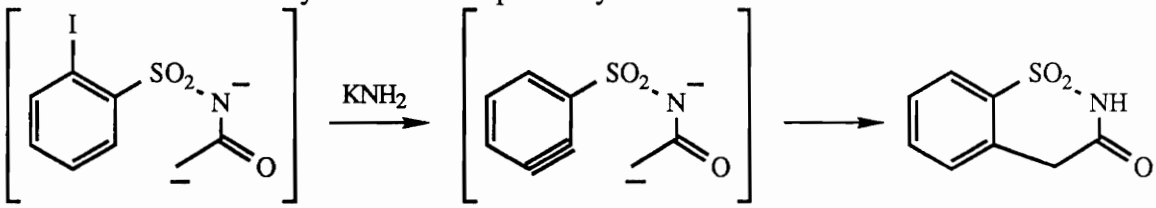
dehalogenated benzoisothiazole **322c** via a two-step mechanism involving metal halogen exchange and intramolecular trapping of the aryl anion by the carbonyl function. Campbell found that *N*-acetyl-2-chlorobenzenesulfonamide **313c** undergoes an intramolecular



313c **324c** **13d**

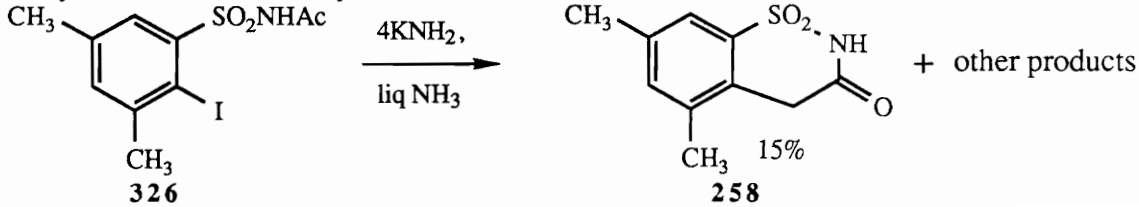
aromatic substitution reaction to yield 1,2-benzothiazin-3(2*H*)-one 1,1-dioxide **13d** upon treatment with excess KNH_2 in liquid NH_3. This reaction represents a convenient two step preparation of 1,2-benzothiazin-3-one **13d** from 2-iodobenzenesulfonamide. As indicated in the Historical Section, previous preparations of such heterocycles are much more complicated. A preliminary investigation of the mechanistic aspects of the dianion cyclization to yield the thiazine structure is reported here. Characteristics of the analogous reaction of the *N*-acetyl-2-iodobenzenesulfonamide with excess KNH_2 is reported in Table IX.

As summarized in the Table IX, the reaction characteristics of the dianion cyclization include a relatively short reaction period, the lack of the need for photostimulation, the requirement of excess base and finally, only a moderate inhibitory effect by di-*tert*-butyl nitroxide (DTBN). The results reported in Table IX are somewhat inconclusive; for they are consistent with several reaction mechanisms. The first one to be considered is the aryne reaction pathway shown below. In order to ascertain



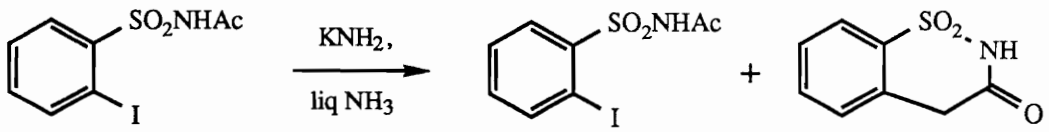
324a **325a** **13d**

whether the reaction can proceed when formation of an aryne intermediate is not possible, *N*-acetyl-2-iodo-3,5-dimethylbenzenesulfonamide **326** was treated with excess KNH_2 in



326 **258**

Table IX. An Investigation of the Cyclization Reaction of the Potassium Dianion of *N*-Acetyl-2-iodobenzenesulfonamide.



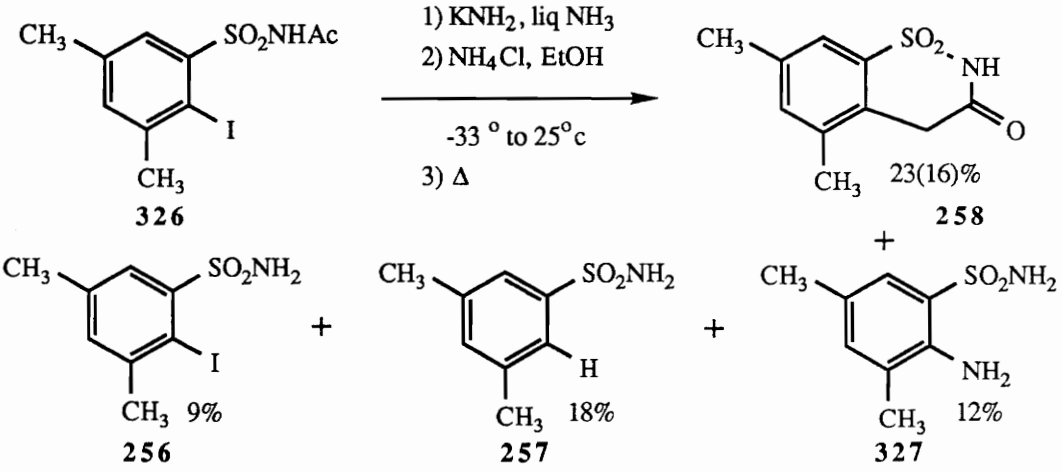
313a **313a** **13d**

entry	equiv KNH_2	rxn time min	ratio[a] **313a:13d**
1[b]	4	30	0:100
2	3	30	5:95
3	2	30	75:25
4	4	8	9:91
5[b]	4	8	37:63

[a]Ratio as estimated from the ^{1}HNMR of the crude reaction mixture. [b]The reaction gave 1,2-benzothiazin-3(2*H*)-one 1,1-dioxide **13d** in 60% after recrystallization from ethanol. mp = 197-201°c, lit. 202-204°c[11]. [c]Reaction was run in the presence of 15 mole % di-*tert*-butyl nitroxide (DTBN).

liquid NH_3. The reaction of sulfonamide **326** was not as clean as the analogous reaction of **313a** in that side products were formed. Regardless, the isolation of the previously synthesized benzothiazin-3-one **258** clearly indicates that a pathway other than or in addition to an aryne mechanism is involved.

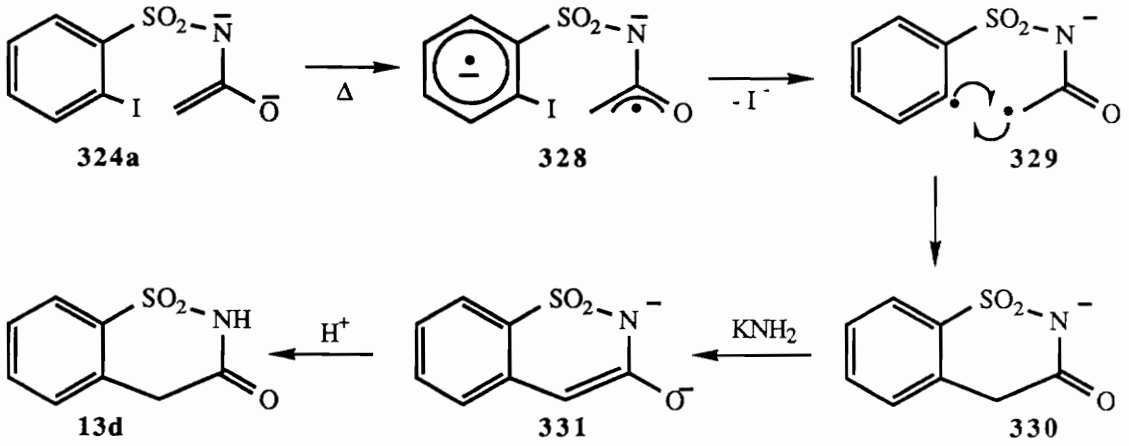
Fortuitously, benzothiazine **326** precipitated upon concentration of the solvent used for extraction during workup. Attempts at chromatography of the residue obtained upon concentration of the mother liquor failed. Alternatively, the by-products were isolated and characterized by cleavage of the acetyl moiety with ethanolic NH_3. Thus, the reaction mixture was quenched by transfering the NH_3 solution to a flask containing NH_4Cl suspended in ethanol. The resulting saturated ethanolic NH_3 solution obtained on warming to room temperature was heated at reflux to yield, in addition to cyclization



product **258**, amination product **327**, reduction product **257**, and cleaved starting amide **256**. Isolation of the acidic benzothiazin-3-one **258** from sulfonamides **327**, **257** and **256** was accomplished by a simple bicarbonate extraction. The primary sulfonamides proved to be isolable via chromatography. An investigation of the nature of the amination and reduction reaction is discussed in the next section.

In Section III.1.8 it was reported that *N*-aryl-2-iodobenzenesulfonamides undergo an intramolecular cyclization reaction to yield dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxides. The reaction was found to involve a photostimulated intramolecular radical coupling mechanism in addition to an aryne mechanism. An analogous thermally initiated intramolecular radical coupling mechanism is proposed here (Scheme XXXVII). This mechanism features

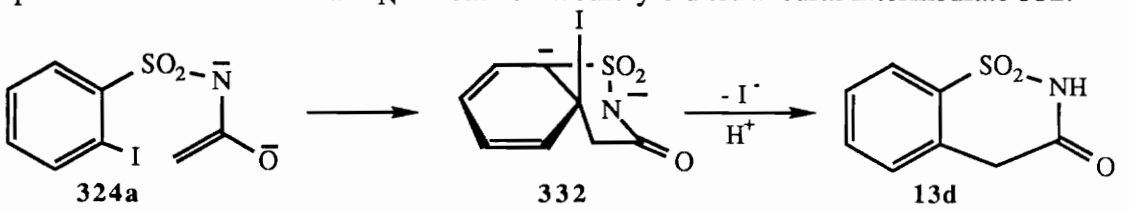
Scheme XXXVII



324a **328** **329** **330** **331** **13d**

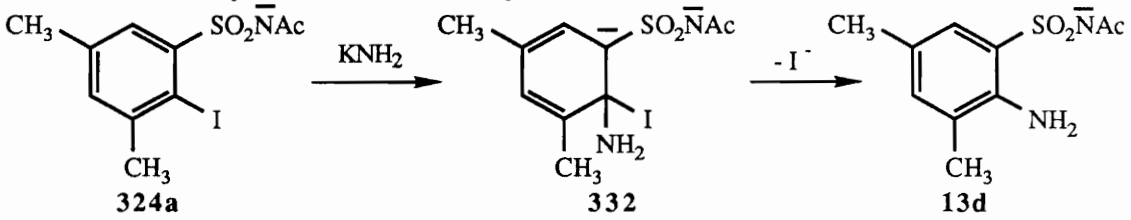
reduction of the aryl halide by the side chain dianion via thermal-initiated electron transfer. The resulting diradical dianion **328** fragments to liberate iodide and forms the diradical species **329**. Cyclization to yield **330** occurs upon coupling of the diradical. The excess base present then ionizes the product which is more acidic than the starting lateral dianion by nature of the conjugative effects of the aromatic ring. A similar mechanism for the photostimulated cyclization of the anion arising from LDA-THF treatment of 2-chloro-3-methyl-*N*-methylacetamide was considered and discarded by Wolfe.[6] Wolfe argued that the dramatic inhibitory effect (a ten fold decrease in cyclization) that the addition of 10 mole % DTBN had on the photoprompted cyclization of that ion, strongly indicated a radical chain mechanism. In Table VIII it is reported that the addition of 15 mole % of DTBN had only a moderate inhibitory effect on the cyclization of the dianions. A radical chain mechanism featuring external electron transfer to the dianion would result in a trianion and therefore seems unlikely. The inhibition study is at least consistent with the suggestion that a reaction pathway involving external electron transfer is unimportant.

Another mechanism deemed possible involves an addition-elimination reaction sequence. An intramolecular S_NAr reaction would yield tetrahedral intermediate **332**.



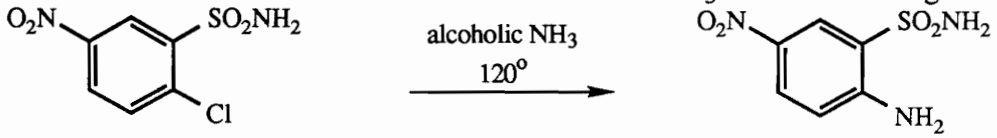
324a **332** **13d**

Elimination of iodide and protonation would yield the benzothiazine heterocycle. Similarly, amination of *N*-acetyl-2-iodo-3,5-dimethylbenzenesulfonamide **327b** could arise from an



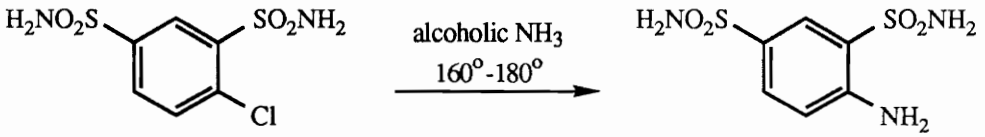
324a **332** **13d**

addition-elimination sequence if ionization to form the lateral dianion was incomplete. Such a substitution under the conditions of the reaction (-33°) would be without precedent. Amination of haloarylsulfonamides via the S_NAr mechanism requires the presence of strongly activating group and elevated temperatures. Thus, Fischer reported that treatment of 4-chloro-3-nitrobenzenesulfonamide with alcoholic NH_3 at 120° in an agitated tube



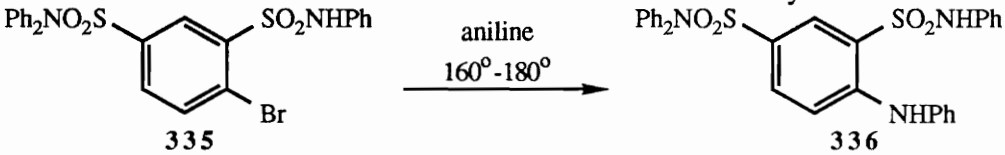
333 **334**

resulted in the substitution of the chloride by NH_3.[69] The comparison is not direct in that the literature example involves a primary sulfonamide as the substrate and NH_3 as the nucleophile. It is important to add that Fischer indicates the need of much higher temperatures and a second sulfonamide group to facilitate substitution when the strongly activating nitro group is not present. Thus similar treatment of *m*-benzenesulfonamide **335**



335 **336**

required more severe conditions to yield amination product **336**. Likewise, Fischer reported that *m*-benzeneulfonamide **337** underwent substitution by aniline under similar



335 **336**

conditions to yield amination product **338**. Based on Fischer's results it is concluded that the amination reaction does not occur by an addition elimination process in spite of the fact that NH_2^- might be a more efficient nucleophile than NH_3 or even aniline. Nevertheless, it

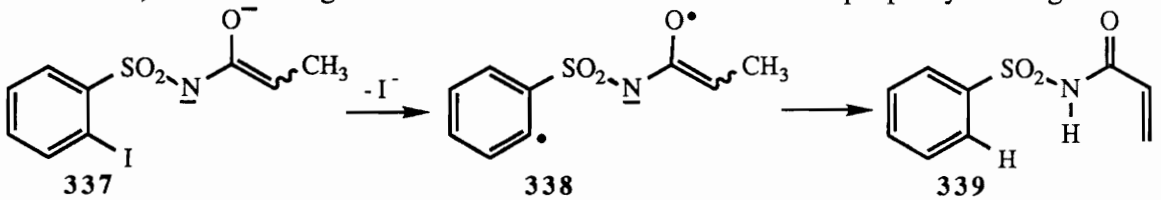
might still be argued that the cyclization reaction may involve an addition elimination sequence. It might be suggested that the lateral dianion is an infinitely more efficient nucleophile than NH_3 or aniline due to its proximity to the electrophilic site. On the other hand, it seems more plausible to argue that the cyclization products **13d** and **258**, and the amination product **327**, arise from a common intermediate. In the next section it is reported that iodide replacement by NH_2^- becomes a more efficient competing side reaction as the steric requirements for substitution to occur become more severe.

In summary, it is reported that the potassium dianion derived from *N*-acetyl-2-iodobenzenesulfonamide **313a** undergoes an intramolecular cyclization reaction to yield 1,2-benzothiazin-3-(2*H*)-one 1,1-dioxide **13d**. Although an aryne mechanism was not ruled out, it was proven by the cyclization of *N*-acetyl sulfonamide **326** that the cyclization can occur by another mechanism. It is proposed that the mechanism involves an intermolecular electron transfer initiation step. Based on an inhibition study with DTBN it is concluded that the radical reaction is non-chain in nature. A mechanism involving an addition-elimination reaction sequence was argued against due to insufficient activation of the aryl halide.

2.2 Amination and Reduction.

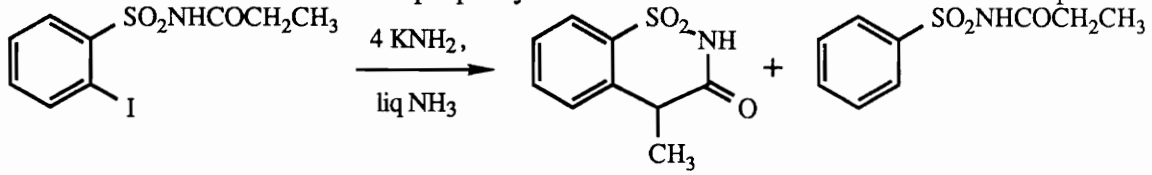
In the preceding section, it was reported that *N*-acetyl-2-halobenzensulfonamides undergo an intramolecular cyclization reaction to yield 1,2-benzothiazin-3(2*H*)-one 1,1-dioxide (**13d**). In an attempt to extend this heterocyclic annulation methodology to include 4-substituted and 4,4-disubstituted analogs of **13d**, the reactions of a series of β-substituted *N*-acyl-2-iodobenzenesulfonamides were investigated. In this section we report that anions derived from a number of *N*-acyl-2-iodobenzene sulfonamides do not participate in the analogous cyclization reactions of the parent *N*-acetyl dianon **324a**. Instead the substrates undergo amination and or reduction.

From the start of the study it was anticipated that reduction to yield the dehalogenated sulfonamide might be a serious competing side reaction. Isolation of 3,5-dimethylbenzensulfonamide (**257**) from the reaction of the dianion derived from *N*-acetyl-2-iodo-3,4-dimethylbenzensulfonamide (**326**), demonstrated that reduction will compete with cyclization (Section III.2.1). The mechanism of that reduction remains unclear. A better understood reduction pathway features hydrogen atom transfer (see Sections III.1.3 and III.1.6). It was thought that dianion **337** derived from the *N*-propionyl analog with its



337 **338** **339**

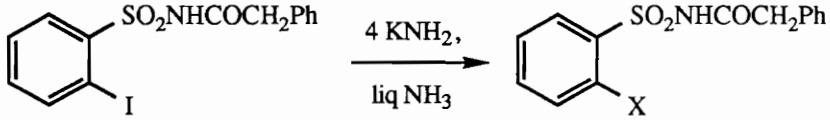
β-hydrogen atoms might be particularly susceptible to reduction. However, such a reduction was considered to be a potentially useful mechanistic probe. It was reasoned that if reduction via β-hydrogen atom transfer were to occur, then the propionyl function should in turn be oxidized to the corresponding α-β-unsaturated amide. Isolation of the oxidation product **339** or products thereof, would support the existence of an aryl radical intermediate. The reaction of *N*-propionyl-2-iodobenzensulfonamide **340** failed to provide



340 **341** not isolated **342** 25%

the mechanistic evidence sought. From ^{1}HNMR analysis of the crude product mixture, it was determined that the substitution and reduction products, **341** and **342** respectively, had formed. The reduction product **342** was the major component. Characteristic of the proton NMR spectrum was a doublet, δ 1.69 J = 7.0 Hz; a quartet, δ 4.27J = 7.0 Hz; a triplet δ 1.06 J = 7.4 Hz; and a second quartet δ 2.30 J = 7.4 Hz. The presence of the doublet resonance and the chemical shift of the methine allowed for the assignment of the 4-methyl-1,2-benzothiazin-3-one structure. Unfortunately, repeated attempts at isolation of the cyclization product failed to provide an analytical sample. Chromatography resulted in the isolation of impure reduction product, comparison of which to an authentic sample confirmed the assignment made initially from the crude ^{1}HNMR. It should be stressed that the reduction product contained the unoxidized *N*-propionyl substitutent. From that, it was concluded that the reduction reaction leading to **342** does not involve an intramolecular β-hydrogen atom transfer. Due to the poor mass balance obtained after chromatography, an intermolecular hydrogen atom transfer could not be ruled out as the mechanism of reduction.

Attention was turned to the reaction of the dianion derived from *N*-phenylacetyl sulfonamide **343**. Treatment of the sulfonamide with excess KNH_2 in liquid NH_3 gave upon purification the corresponding amination and reduction products **344** and **345**

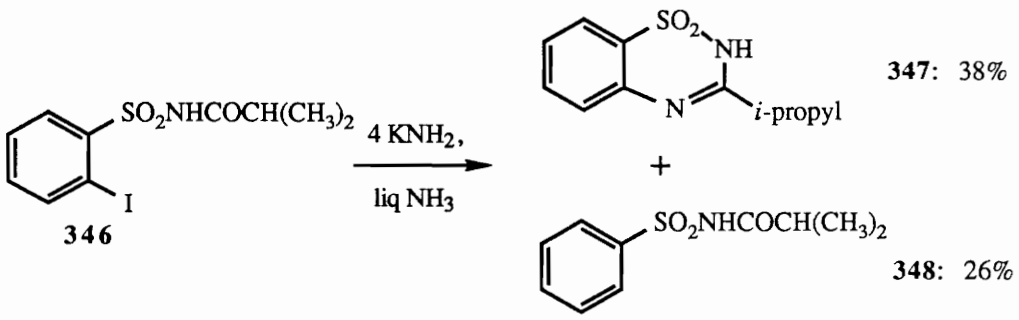


343

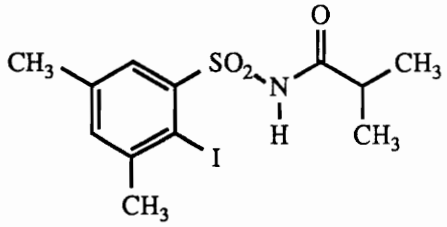
344: X = NH_2, 15%
345: X = H, 30%

respectively. The yields reported are believed to representative of the difficulties associated with the purification of these substrates and not to be representative of the actual product distribution. From this example and from the example reported earlier for the *N*-acetyl sulfonamide **326** it is clear that reduction can occur via a mechanism other than β-hydrogen atom transfer.

Amination leading to the formation of 1,2,4-benzothiadiazine 1,1-dioxide (**347**) was found to be the major mode of reaction of the *N*-isobutrylsulfonamide **346**. The amination reaction was complete within an hour. However, it was found that longer



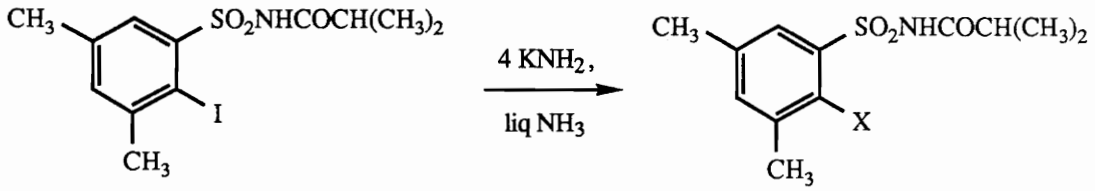
reaction periods allowed for the formation of the heterocyclic substrate and thereby simplified the workup procedure. Fortuitously, the heterocycle was found to be insoluble in ether and precipitated from the reduction product nearly quantitatively. From the three reactions which were found to result in amination products, it was reasoned that sterically demanding groups favor the amination reaction. Therefore it was decided to employ the *N*-isobutryl derivative **349**, to study the nature of the amide substitution reaction. It was



349

reasoned that the two substituents *ortho* to the iodide as well as the isobutryl group would maximize the amination reaction. The results of that study are presented in the Table X. Briefly, it was determined that the reaction was fast in that all of the starting material was consumed in less than 15 minutes. The addition of 10 mole% DTBN seemed to favor the reduction reaction over amination, but had no inhibitory effect on the consumption of the starting material. The addition of a catalytic amount of potassium metal favored the formation of the amination product over reduction. Potassium metal is known to catalyze the aromatic $S_{RN}1$ reaction of aryl halides with KNH_2.[37] The modest decrease in the amount of amination product resulting from the addition of DTBN might indicate that the substitution reaction has only a minor radical chain component. Likewise, the modest increase in the amount of amination product resulting from the addition of solvated electrons again suggests that the amination reaction is primarily non-chain in character.

Table X. Characteristics of the Reaction of the Potassium Dianion Derived from *N*-Isobutryl-2-iodo-3,5-dimethylbenzenesulfonamide and Excess KNH_2 in Liquid NH_3.



349

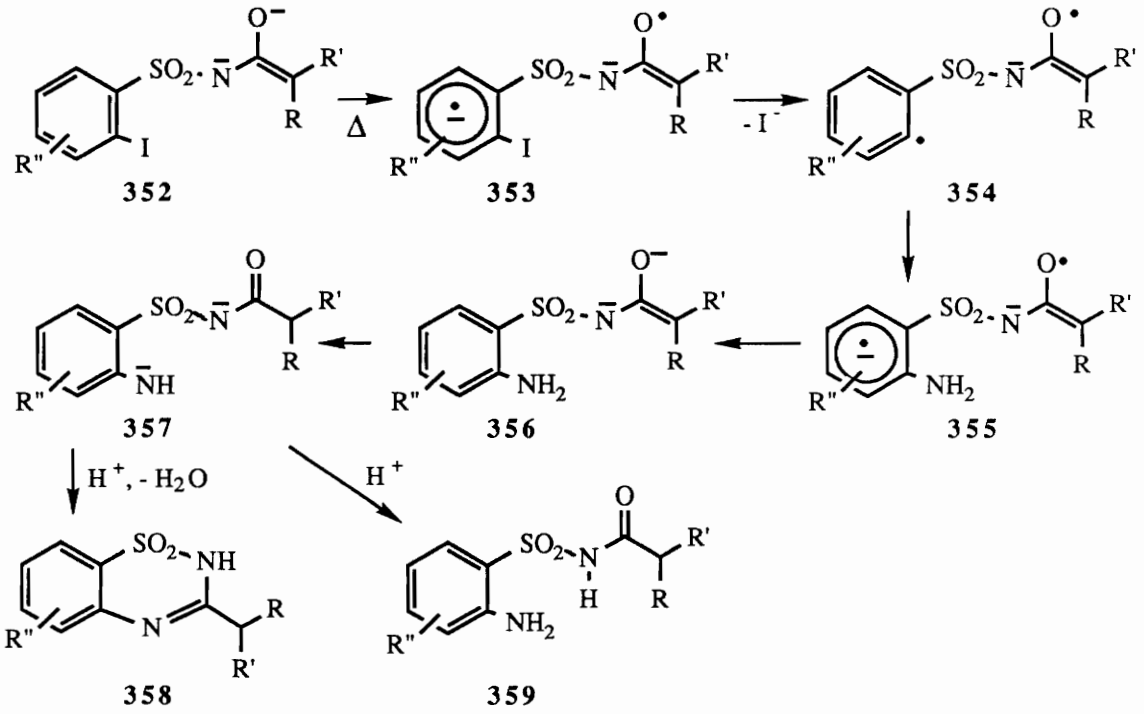
350: X = NH_2
551: X = H

entry	rxn time	conditions	ratio of **350**:**351**[a]	product, yield%[a]
1	15 min	dark	6:4	**350**, 47 **351**, 32
2	15 min	dark, 10 mole% DTBN	4:6	**350**, 32 **351**, 47[b]
2	15 min	dark, 10 mole% potassium metal	7:3	**350**, 54[c] **351**, 23

[a]Ratios and yields are estimated from the ^{1}HNMR spectra of the crude mixture, and are based on the integrals of the resonances assigned to the isopropyl methyl units of **350** and **351**. [b]Isolated yield was 23%. [c]Isolated yield was 16%.

Based on the results reported in Table X, and the conclusions drawn earlier from Fischer's results (see Section III,2,1), it is concluded that the amination reaction involves aa intramolecular electron transfer catalyzed substitution mechanism. This mechanism is outlined in Scheme XXXVIII and is analogous to the mechanism proposed earlier for the

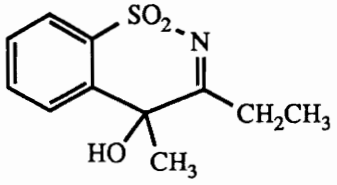
Scheme XXXVIII



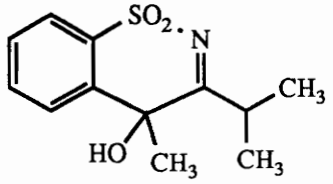
cyclization reaction of the *N*-acetyl dianion analogs of **352** (see Scheme XXXVII). The first step involves a thermal initiated intramolecular electron transfer to yield the π-aryl radical anion **353**. Ejection of iodide results in the localized aryl radical **354**. Nucleophilic trapping of that radical by NH_2^- yields the diradical dianion **355**. Intramolecular electron transfer results in dianion **356**. Proton transfer yields the anilide intermediate **357**. Intramolecular condensation would yield the 1,2,4-benzothiadiazine 1,1-dioxide **358**. Quenching of **357** with acid yields the open chain amination product **359**.

3. OXIDATION REACTIONS OF 2*H*-1,2-BENZOTHIAZINE 1,1 DIOXIDES

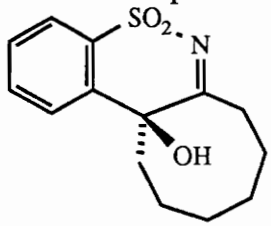
In Sections III.1.2 and III.1.5 we revealed that oxidation products **194**, **195** and **255** derived from the 1,2-benzothiazine derivatives **184a-b**, and **254c** respectively, were isolated. In this section the optimization of the yields of those oxidation products are



194



195



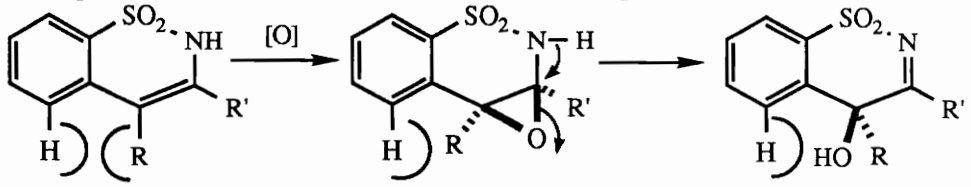
255

reported. Throughout the study of the aromatic $S_{RN}1$ reactions of 2-halobenzenesulfonamides with enolates derived from both acyclic and cyclic ketones, it was observed that the resulting benzothiazine 1,1-dioxides were susceptible to decomposition on standing in air. The 4-substituted-2H-1,2-benzothiazine 1,1-dioxides were found to be particularly air sensitive and care in limiting exposure to air was required for optimization of their yields. The benzothiazine derivative **254c** was so prone to oxidation that it could not be isolated.

The structural assignments of alcohols **194**, **195** and **255** were made in accord with IR, ^{1}HNMR, ^{13}CNMR, and MS spectral data as well as combustion analysis. The IR spectra of the alcohols exhibited strong absorptions in the range of 3400-3600 cm^{-1} (O-H) and 1600-1680 cm^{-1} ($ArSO_2N$=C). The chemical shifts and splitting patterns exhibited by the ^{1}HNMR spectra of **194**, **195**, and **255** are indicative of the assigned structures. The following spectral details were particularly informative. The ^{1}HNMR spectrum (acetone-d_6) of **194** contains an ABX pattern of δ_A 3.08, δ_B 3.00 and δ_X 1.15 with J_{AB} = 2.8 Hz, J_{AX} = 7.2 Hz, J_{BX} = 7.1 Hz. The ^{1}HNMR spectrum of **195** clearly indicates the chemical shift nonequivalence of the pair of isopropyl methyl units. Thus the spectrum exhibited two distinct doublets and a methine proton with a chemical shift consistent with the assigned structure: (acetone-d_6) δ 1.19 (d, 6.7 Hz, 3 H); δ 1.28 (d, J = 6.7 Hz, 3 H); δ 3.65 (m, J = 6.7 Hz, 1 H). The ^{1}HNMR spectrum ($CDCl_3$) of **255** exhibits very complex patterns for the α-methylene protons: δ 3.41 (m, 1H); δ 2.54 (m, 1 H). The ^{13}CNMR spectra of **194**, **195** and **255** characteristically featured an absorption in the range of 70.4-

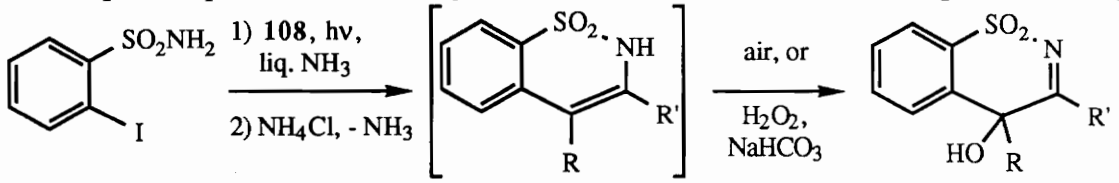
71.8 ppm which was assigned to the respective benzylic carbon. Likewise, the respective ^{13}CNMR spectra exhibited a carbonyl absorption in the range of 196.3-198.8 ppm. Mass spectral and combustion analyses were consistent with the assigned molecular formulas. Furthermore the mass spectra of the three alcohols characteristically contained an $(M-18)^+$ ion. Finally, the structural assignment of **255** was confirmed by X-ray crystal analysis (Figure 2).

The crystal structure of the oxidation product alcohol **255** seems to reveal the nature of this air sensitivity (Figure 2). It is reasoned that pyramidalization of the carbon labeled C(7) in Figure 2 would result in the relief of steric interactions associated with the C(8) methylene carbon and the proton attached to the C(5) carbon. It is proposed that the formation of products **194**, **195** and **255** involves the epoxidation of the enamide double



bond to yield intermediate **360**. Concomitant ring opening by the sulfonamide would yield the α-hydroxy-imine upon proton transfer. It is pointed out that the driving force for the air epoxidation is the relief of steric interactions just mentioned.

Optimization of the yields of the α-hydroxy-imines **194** and **195** involved quenching the reaction in a 2-litre beaker with a large excess of NH_4Cl. The residue obtained upon evaporation of the NH_3 was allowed to stand in air for 12 h, purification by



flash chromatography gave the yields indicated. A cleaner product was obtained via removal of ketone derived byproducts by extraction (refluxing hexanes) of the residue at a point prior to the complete evaporation of NH_3. Apparently, the NH_3 blanket does not allow for air oxidation of the ketone derived material. An attempt at improving the yield of the oxidation product **195** involved partial isolation of benzothiazine **184b** by partitioning between water and $CHCl_3$ the residue obtained upon filtration of the hexane wash. The $CHCl_3$ extracts were dried and then concentrated until the benzenesulfonamide which

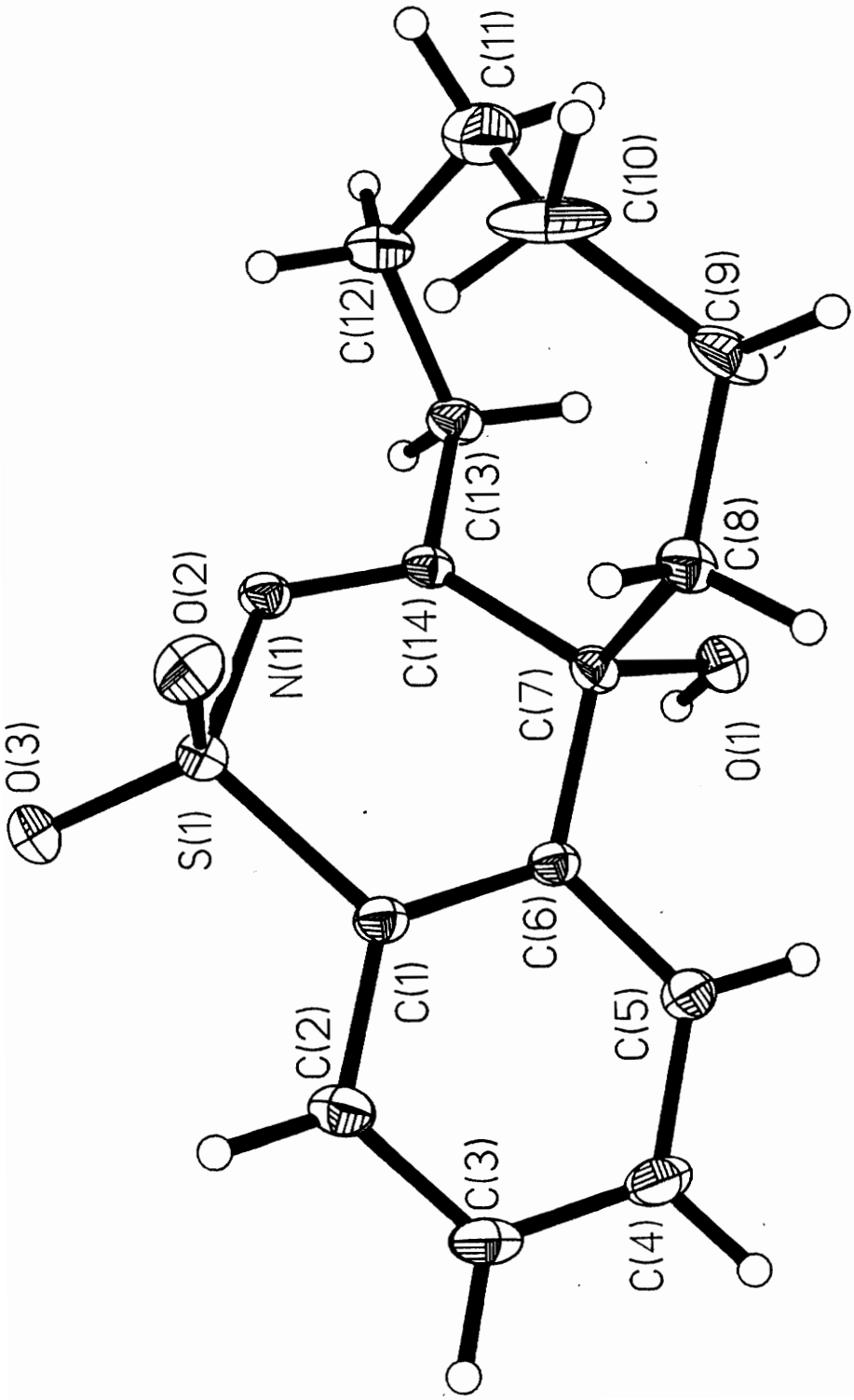
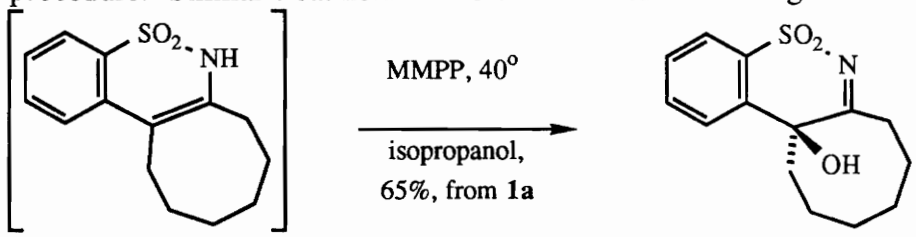


Figure 2. X-ray crystal structure of α-hydyoxyimine 255.

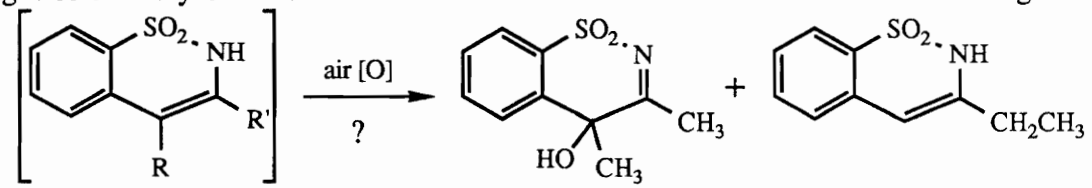
formed as a byproduct precipitated. The impure benzothiazine **184b** was stirred in a two phase mixture of $CHCl_3$ and a dilute solution of $NaHCO_3$ and H_2O_2. The reaction gave a slightly sharper melting sample of alcohol **195** in slightly improved yields to the air oxidation procedure. Similar treatment of the crude mixture resulting from the reaction



254c **255**

of sulfonamide **1a** with monoperoxyphthalic acid magnesium salt hexahydrate (MMPP) in isopropanol resulted in the optimization of the yield of alcohol **255**.[70]

In Section III.1.2 we revealed that treatment of 2-iodobenzenesulfonamide **1a** with the enolates derived from butanone results in the formation of two 1,2-benzothiazine 1,1-dioxides, **183c** and **184c**. Initial attempts at isolation of the two products failed to provide an analytical sample of either product. It was reasoned that the 3,4-dimethyl product **184c** should be significantly more air sensitive than the 3-ethyl product **183c**. The nature of that air sensitivity would result from steric interactions of the 4-methyl substituent and the C-5 proton as indicated above. It was anticipated that the air oxidative workup described above might selectively oxidize **184c** to form alcohol **361**. It was reasoned that the significant

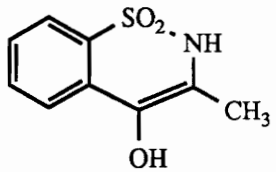


183c + 184c **361** **183c**

differences in the two products would facilitate their separation. The attempt was only partially successful in that **183c** could be isolated, but alcohol **361** was not observed It is suggested that the α-methyl group **361** allows for a sterically more accessible electrophilic *N*-sulfonyl-imine carbon. The α-ethyl and α-isopropyl groups of **194** and **195** respectively, might provide sufficient steric inhibition to the approach of a nucleophile.

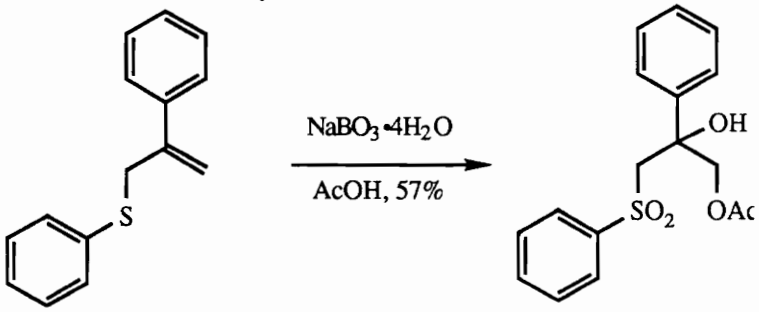
Among the 2*H*-1,2-benzothiazine 1,1-dioxides reported in this dissertation, only the the 3-methyl analog **183b** did not give satisfactory combustion data. The white solid obtained upon chromatography and recrystallization was air sensitive, becoming orange in color on standing in air. It was observed that the ^{1}HNMR spectrum of a freshly isolated sample of **183b** changed as a function of time. Thus, after a period of 24 hours new

singlet resonances at δ 2.43 and δ 3.83 were observed. It was reasoned that the resonances might be attributed to the methyl and hydroxy protons of the known benzothiazine **48**. Unfortunately the report of the preparation of **48** did not include



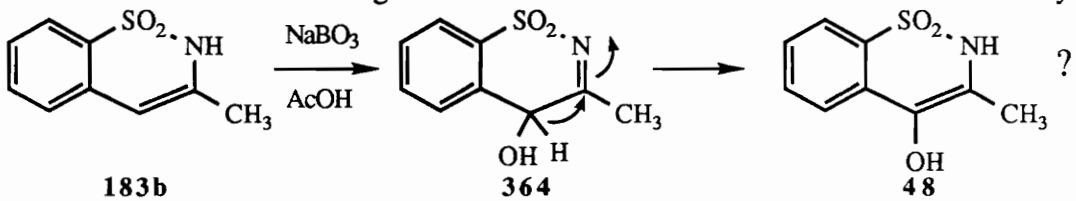
48

spectral details, only a melting point.[25] The preparation of the important antiinflammatory agent piroxicam from **48** was cited earlier in the Historical Section.[26] It was reasoned that oxidation of **183b** to **48** had potential industrial applications. A report by Gupton of the sodium perborate oxidation of allylic sulfide **362** to sulfone **363** further stimulated



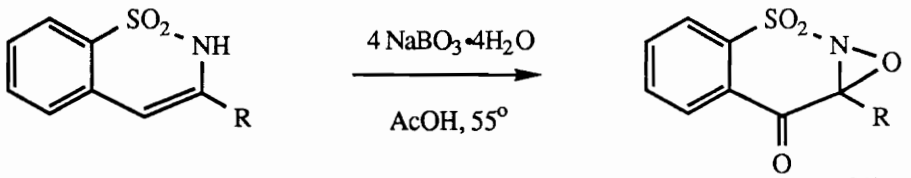
362 **363**

interest in the oxidation of **183b**.[71] Gupton provided evidence that the mechanism involved epoxidation of the styrene double bond. It was thought that the reportedly mild oxidant would epoxidize the styrene like double bond of the benzothiazine **183b** to form alcohol intermediate **364** analogous to **194** and **195**. Isomerization of **364** would yield



183b **364** **48**

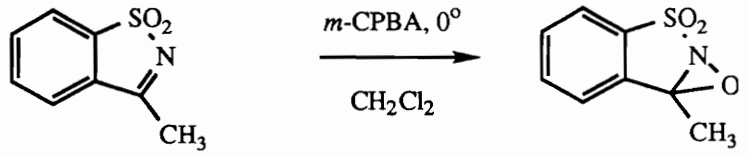
48. However, treatment of **183b** with four equivalents of sodium perborate in acetic acid gave the novel oxaziridine product **365a** instead. Likewise, it was found that the 3-*i*-



183b
183d

365a: R = Me, 70%
365b: R = *i*-propyl, 74%

propyl-1,2-benzothiazine **183d** underwent the analogous reaction to yield the corresponding oxaziridine **365b**. Davis has reported the preparation of the related 3-



366 **367**, 92%

methyl-1,2-benzothiazole 1,1-dioxide **366** derived oxaziridine **367** as well as several other synthetically important analogs.[60]

The assignment of structures **365a-b** were made in accord with IR, ^{1}HNMR, ^{13}CNMR, and MS spectral data as well as combustion analysis. The IR spectra of both substrates lacked N-H absorptions and featured strong carbonyl absorptions at 1730 cm^{-1}. The ^{1}HNMR of **365a** was not particularly informative in that the resonances exhibited could also be interpreted to indicate structure **368a**. On the other hand the ^{1}HNMR

368a **368b**

spectrum of **365b** could not be assigned to the analogous compound **368b** because of the chemical shift nonequivalency of the methyl doublets. Thus, the ^{1}HNMR spectrum of **368b** contained resonances of δ 1.20 (d, J = 6.3 Hz, 3 H), δ 1.02 (d, J = 6.8 Hz, 3 H). and δ 2.96 (m, J = 6.8 Hz, 3 H). Similarly, the ^{13}CNMR spectrum of **365b** contained three aliphatic resonances of δ 15.1, 17.1 and 26.4 which clearly indicate that the methyl carbons are nonequivalent. Characteristic of the ^{13}CNMR spectrum of **265a** and of **265b** is a carbonyl resonance of δ 185.5 and δ 185.3 respectively. Structures **368a** and **368b** require two carbonyl resonances. The chiral carbons of the oxaziridine rings were assigned to the resonances occuring at δ 82.8 and δ 86.2 for the ^{13}CNMR spectrum of **365a** and of **365b** respectively. Finally, mass spectral and combustion data for both products are in accord with the assigned formulas.

In summary it is concluded that the instability observed for the 2*H*-1,2-benzothiazine 1,1-dioxides prepared in this study is a result of the ease in which the styrene like double bond undergoes epoxidation. It is also concluded that substitution at the 4-position of the heterocycle results in greater susceptibility to oxidation. It is proposed that epoxidation resulting in pyrimidalization of the C-4 carbon negates unfavorable steric interactions associated with the C-4 substituent and the C-5 proton. Finally the characterization of oxaziridine **365a** is offered as structural proof of the parent substrate 3-methyl-2*H*-1,2-benzothiazine 1,1-dioxide **183b**.

IV CONCLUSIONS

The initial goal of this research was to apply $S_{RN}1$ heteroannulation methodologies to the preparation of 1,2-benzothiazin-3(2*H*)-one 1,1-dioxides with potential CNS activity. The chemistry involved was found to be much more complicated than anticipated. Consequently, much of our efforts were focused on understanding and characterizing reactions that competed with the desired heteroannulations. A major conclusion to be drawn from this work is that the $S_{RN}1$ reactivity of halobenzensulfonamides and related compounds is very sensitive to the functionality of the sulfonamide nitrogen. It was found that the chemistry changed dramatically each time the substituent present on nitrogen was varied. A second major conclusion to be drawn from this study is that the $S_{RN}1$ reactivity of halobenzenesulfonamides is also a function of the structure and nature of the nucleophile employed. In several examples it was observed that structural changes in the nucleophile favored competing reduction reactions at the expense of substitution.

It was found that 2-iodobenzenesulfonamide (**1a**) undergoes photoinitiated intermolecular heteroannulation to form 3-substituted-2*H*-1,2-benzothiazine 1,1-dioxides in good yields when treated with enolates derived from methyl ketones. In addition, it was found that 3,4-disubstituted-2*H*-1,2-benzothiazine 1,1-dioxide derivatives could be prepared in moderate to good yields from ethyl ketone enolates and cyclic ketone enolates. However, reduction via hydrogen atom transfer was found to be a major competing side reaction when **1a** was treated with such ketone enolates possessing β-hydrogen atoms. The yield of reduction product increased as the number of hydrogen atoms present on the ketone enolate employed increased. Diisoprpropyl ketone enolate completely reduced sulfonamide **1a** in a fast reaction that formed benzenesulfonamide and unsymmetrical ketone dimer **198** in equivalent yields.

A mechanistic study of the photostimulated reduction of 2-iodobenzenesulfonamide (**1a**) by diisopropyl ketone enolate revealed that the mechanism has a radical chain character. Labeling studies clearly indicated that β-hydrogen atom transfer is the major reduction pathway. An inhibition study employing di-*tert*-butyl nitroxide (DTBN) indicated that electron transfer to the substrate from an intermediate α,β-unsaturated ketone radical anion occurs. This study clearly indicates the problems that can be encountered when nucleophiles with activated hydrogen atoms are employed in $S_{RN}1$ chemistry.

Attempts to extend the synthetic utility of the intermolecular heteroannulation reactions of 2-halobenzenesulfonamides to include 2-alkyl- and 2-aryl-3-substituted-2*H*-1,2-benzothiazine 1,1-dioxides were in part unsuccessful. Surprisingly and interestingly, it was found that in some cases intramolecular radical reactions precluded substitution. The nature of such competing radical reactions varied with the sulfonamide functionality. For example the photostimulated reaction of *N*-methyl-2-iodobenzenesulfonamide (**260**) with dissopropyl ketone enolate resulted in a complex mixture of products. The nature of the isolated reaction products and a labeling study indicated that intramolecular hydrogen atom transfer from the α-hydrogens of the amide methyl group to an intermediate aryl radical occurred. In another example it was found that the photostimulated reaction of *N*-phenyl-2-iodobenzenesulfonamide (**278**) in the presence of excess diisopropyl ketone enolate resulted in the formation of 6*H*-dibenzo[*c*,*e*][1,1]thiazine 5,5-dioxide (**279**). In view of the apparent interest in these compounds by others, this new route to dibenzo[*c*,*e*][1,1]thiazine 5,5-dioxides might have synthetic importance.[2] Unlike the *N*-methyl and *N*-aryl analogs, it was found that *N*-*t*-butyl-2-iodobenzenesulfonamide (**275**) is a participating substrate in intermolecular nucleophilic aromatic substitution. The high yields obtained from the substitution of **275** by *t*-butyl acetate enolate might be found to be preparatively useful. It is suggested that future work might involve alkylation α to the ester carbonyl of the substitution product and then cyclization to yield 2-*t*-butyl-4-substitutied-1,2-benzothiazin-3(2*H*)-one 1,1-dioxides.

N-Acyl-2-iodobenzenesulfonamides were found to be participating substrates in $S_{RN}1$ reactions with both ketone and ester enolates. The reactions proceed sluggishly in the dark and are inhibited by DTBN. Excellent yields were obtained when pinacolone or *t*-butyl acetate enolates were employed. *N*-acetyl-2-iodobenzenesulfonamide (**313a**) underwent photosubstitution by ethyl phenylacetate enolate to give substitution products in relatively good yields. These results have synthetic significance because the acyl function is readily cleaved by methanolic HCL. Thereby, acess to previously unavailable reactive intermediates was obtained. The methanolic HCl cleavage of the acetyl group of the α-substitution product of **313a** with ethyl phenylacetate, might in future work, be followed by a cyclodehydration step to yield 4-phenyl-1,2-benzothiazin-3(2*H*)-one 1,1-dioxide. It might also prove interesting to investigate the alkylation reactions of the substitution product obtained from *N*-acyl-2-iodobenzenesulfonamides and ester enolate nucleophiles.

These compounds might be conveniently akylated α to the ester carbonyl and thereby provide a synthetic route to 4-alkyl-1,2-benzothiazin-3(2*H*)-one 1,1-dioxides.

The potassium dianions derived from *N*-acetyl-2-halobenzenesulfonamides in liquid NH_3 were found to undergo an intramolecular cyclization reaction to yield 1,2-benzothiazin-3(2*H*)-one 1,1-dioxide (**13d**) in good yields. An attempt to extend the methodology to include 4-substituted and 4,4-disubstituted analogs met with only limited success. It was found that reduction and amination were major competing side reactions. The amination reaction is apparently favored by increased steric requirements of the dianion. The convenient route to **13d** that the dianion cyclization reaction provides, might suggest that future work should be focused on developing methodology to alkylate that compound at the 4-position.

The stability of some of the products synthesized in this study varied as a function of their structures. It was found that 3,4-disubstituted-2*H*-1,2-benzothiazine 1,1-dioxide derivatives exhibited increased air sensitivity relative to 3-substituted-2*H*-1,2-benzothiazine 1,1-dioxides. Several 3,4-disubstituted-1,2-benzothiazines were found to undergo air oxidation to yield structurally interesting α-*N*-sulfonyliminoalcohols. In view of the variety of biological activitys exhibited by 1,2-benzothiazine 1,1-dioxides, it is suggested that these previously unknown analogs might be found to exhibit useful pharmocological activities.

V EXPERIMENTAL SECTION

General. Melting ponts were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are also uncorrected. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. Infrared spectra were recorded neat as thin films or KBr pellets, on a Perkin-Elmer 710B infrared spectrophotometer. Proton NMR Spectra were recorded on a Bruker WP-270 instrument. Proton chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as an internal reference (0.00 ppm). Deuterium NMR spectra were recorded on a Bruker WP-200 instrument. Deuterium chemical shifts are reported in parts per million (ppm) relative either to $CDCl_3$ (7.24 ppm) or acetone-d_6 (2.04 ppm). Carbon NMR spectra were recorded on either a Bruker WP-270 instrument or a Varian Unity 400 instrument. Carbon chemical shifts are reported relative either to the center line of the $CDCl_3$ triplet (77.0 ppm) or to the acetone-d_6 carbonyl resonance (206.0 ppm). Unless otherwise stated all chemicals were obtained from commercial sources and used as received. Photostimulated reactions were carried out in an inert atmosphere using a Rayonet RPR-240 photoreactor equipped with four 12.5-W lamps emitting maximally at 350 nm. Di-*tert*-butyl nitroxide was prepared from 2-methyl-2-nitropropane.[72] Flash chromatography was performed on Kiesegel 60 (EM Reagents, 230-400 mesh). Preparative TLC was performed on Silica Gel GF 20x20 cm 1000 micron plates obtained from Analtech, Newark DE. GC analyses were performed on a Hewlett Packard 5890A Gas Chromatograph equipped with a flame ionization detector using a Supelco Se-54 15 m, 0.25 mm ID, 0.75 μm film thickness column. The operating temperatures were as indicated. GC-MS analyses of oils were performed on a Hewlett Packard 5890A Gas Chromatograph(HP-1 methyl silicone capillary column) with a Hewlett Packard 5970 Series Mass Selective Detector. Mass spectra were recorded on a Dupont 20-4912 instrument (low resolution) or a double focusing Dupont 21-110c or VGI instrument (exact mass). X-ray crystal data was collected at 298 K on a Nicolet R3m/V diffractometer with MoKα radiation λ = .71073A.

General Procedure for the Photostimulated Reactions of Halobenzensulfonamides in Liquid NH_3. Anhydrous NH_3 (Matheson) was condensed under a blanket of nitrogen into a vacum jacketed photoreaction tube equipped

with a metal stirring bar, Y-shaped adapter and a dry ice condenser. Potassium amide, KNH_2, was generated *in situ* from the appropriate amount of potassium metal and a catalytic quantity of ferric nitrate. The ketone or ester was introduced via syringe as the neat oil. The solution was allowed to stir for 5 min prior to the addition of the sulfonamide. The sulfonamide was carefully added as the solid in portions. The reaction mixture was irradiated for the indicated period and then quenched by transferring to a 2-litre beaker containing excess solid NH_4Cl. The NH_3 solution was evaporated in a fume hood and the resulting residue treated as indicated.

Preparation of Methyl α-(2-Sulfamoylphenyl)phenylacetate (182) by the Reaction of 2-Iodobenzenesulfonamide (1a) with the Anion Derived From 2-Benzyl-4,4-dimethyl-2-oxazoline. To a stirred solution of KNH_2 in 800 mL of NH_3 was added 8.0g (42.4 mmol) of the oxazoline and 4.0 g of **1a**.[73] The slightly heterogeneous mixture was irradiated for 30 min producing a homogeneous green solution. The residue obtained upon quenching the reaction was suspended in 100 mL of H_20 containing one gram of sodium thiosulfate. The mixture was acidified to pH = 3 and then extracted with CH_2Cl_2 (3x100 mL). The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc, 7:3) of the concentrate gave recovered oxazoline, benzenesulfonamide (**179**), 0.6 g (27% yield), and 2.5 g of a mixture of substitution products. The mixture was treated with refluxing methanolic HCl overnight and then concentrated *in vacuo*. Flash chromatography (CH_2Cl_2/CH_3CN, 9:1) of the residue gave 1.04 g (25% yield) of **182** as a clear colorless oil which solidified on standing. The material was recystallized to yield 0.82 g (19%) of **182** as white needles: mp 99-101 °C; IR 3370, 3280, 1745, 1350, 1175 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 3.75 (s,3H), 4.80(s br, 2 H), 6.18 (s, 1H), 7.26-8.10 (m, ArH, 9 H); ^{13}CNMR ($CDCl_3$) δ 52.5, 127.6, 128.6, 128.9, 131.6, 132.8, 136.9, 137.5, 140.3, 172.9; mass spectrum (CI mode), *m/z* (rel intensity) 306 (15), 289 (100), 274 (20), 246 (30), 225 (25). Anal. calcd for $C_{15}H_{15}NO_4S$: C, 59.00; H, 4.95; N, 4.59. Found: C, 58.95; H, 4.97; N, 4.58.

Preparation of 3-*t*-Butyl-2*H*-1,2-benzothiazine 1,1-Dioxide (183a); A. From 2-Iodobenzenesulfonamide (1a). To a stirred solution of 56.5 mmol of KNH_2 in 800 mL of NH_3 was added 4.25g (42.4 mmol) of pinacolone and 3.0 g of **1a**.

The slightly heterogeneous mixture was irradiated for 8 min. The resulting homogeneous mixture was quenched over NH_4Cl and the NH_3 was allowed to evaporate overnight. The residue was partitioned between H_2O (80mL) and CH_2Cl_2 (3x80 mL). The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc, 7:3) of the residue and recrystallization from CCl_4 gave 2.0 g (80% yield) of **183a**: mp 193-195 °C. An analytical sample was obtained by recrystallization from toluene: mp 193-195 °C; IR (KBr) 3280, 1640, 1325, 1290, 765 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.30 (s, 9H), 6.18 (s, 1H), 7.26-7.90 (m, ArH and NH, 5H);. ^{13}CNMR ($CDCl_3$) δ 27.0, 27.9 (3C), 35.4, 103.2, 121.0, 126.9, 127.2, 131.0, 131.9, 133.6, 148.3; Anal. calcd for $C_{12}H_{15}NO_2S$; C, 60.73; H, 6.37; N, 5.90. Found: C, 60.66; H, 6.36; N, 5.89.

B. From 2-Bromobenzenesulfonamide (1b). A procedure analogous to the reaction of **1a** was followed. Thus, 2.50 g (10.6 mmol) of **1b**[74] was used in place of **1a**. The reaction gave upon workup 2.05 g (80% yield) of **183a**: mp 193-195 °C.

3-Methyl-2*H*-1,2-benzothiazine 1,1-Dioxide (183b) was prepared in 90% yield from 10.6 mmol of **1a** and 2.5 g (42.4 mmol) of acetone by a procedure analogous to the preparation of **183a**: mp 110-112 °C; IR (KBr) 3300-3100, 1665, 1425, 1315, 1180, 765 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.16 (s, 3 H), d.or (s, 1 H), 7.13 (s br, 1 H) 7.30-7.87 (m, ArH, 4 H); ^{13}CNMR ($CDCl_3$) δ 20.9, 105.3, 121.2, 126.4, 126.6, 130.1, 132.2, 133.7, 137.0; mass spectrum (70 eV), *m/z* (rel. intensity) 195 (100), 130 (100), 117 (80), 90 (20); calcd for $C_9H_9NO_2S^+$ 195.0354, found 195.0351.

3-(1-Methylethyl)-2*H*-1,2-benzothiazine 1,1-Dioxide (183d) was prepared in 67% yield from 10.6 mmol of **1a** and 3.65 g (42.4 mmol) of 3-methyl-2-butanone following a procedure analogous to the preparation of **183a**: mp 107.5-109.5 °C; IR (KBr) 3240, 1655, 1420, 1310,1180, 765 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.27 (d, J = 6.9 Hz, 6H), 2.6 (m, J =6.9 Hz, 1 H), 6.09 (s, 1 H), 7.34-7.86(m, ArH and NH, 5 H); ^{13}CNMR ($CDCl_3$) δ 20.3 (2C), 33.2, 102.9, 121.0, 126.6, 126.8, 130.7, 131.9, 133.7, 146.2; mass spectrum (70 eV), *m/z* (rel intensity) 223 (100), 208 (40), 158 (15), 144 (70), 89 940); calcd for $C_{11}H_{13}NO_2S^+$ 223.0667, found 223.0641. Anal. calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.21. Found: C, 59.18, H, 5.88, N, 6.21.

3-Ethyl-2*H*-1,2-benzothiazine 1,1-Dioxide (183c). To a stirred solution of 56.5 mmol of KNH_2 in 800 mL of NH_3 was added 3.05g (42.4 mmol) of butanone and 3.0 g (10.6 mmol) of **1a**. The heterogeneous mixture was irradiated for 15 min. The resulting homogeneous mixture was quenched over NH_4Cl and the NH_3 was allowed to evaporate to near dryness. The residue was covered with 300 mL of hexanes and then gently heated to reflux. The hexane wash was filtered on a porous glass frit and the solid residue was treated as described by one of the following workup procedures. **Method A:** The solid was crushed with a spatula and then left to stand in air for 12 h. The residue was then partitioned between H_2O (80 mL) and CH_2Cl_2 (3x80 mL). The combined methylene extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography ($CHCl_3$/EtOAc, 9:1) of the residue and recrystallization from CCl_4 gave 0.69 g (27% yield) of **183c**: mp 116.5-118.0 °C; IR (KBr) 3225, 1660, 1425, 1315, 1170, 765 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.22 (t, J = 7.5 Hz, 3 H), 2.40 (q, J = 7.4 Hz, 2 H), p.02 (s, 1 H), 7.24-1.69 (m, ArH and NH, 5 H); ^{13}CNMR ($CDCl_3$) δ 11.3, 27.2, 103.9, 121.2, 126.6 (2 H), 130.5, 132.1, 133.7, 142.2; mass spectrum (70 eV), *m/z* (rel intensity) 209 (92), 194 (2), 144 (25), 130 (100); calcd for $C_{10}H_{11}NO_2S^+$ 209.0510, found 209.0510. Anal. calcd for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69. Found C, 57.30; H, 5.28; N, 6.66. **Method B.** The residue obtained upon filtration of the hot hexane solution was partitioned between H_2O (80 mL) and CH_2Cl_2 (3x80 mL). The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography ($CHCl_3$) gave 1.2 g of an inseparable solid mixture of **183c** and 3,4-dimethyl-2*H*-1,2-benzothiazine 1,1-dioxide (**184c**). The ^{1}HNMR spectrum indicated a ratio of 2:1 for **183c**:**184c**. mass spectrum (GC inlet) calcd for $C_{10}H_{11}NO_2S^+$ 209.0510, found 209.0498 (**184c**) and 209.0510 (**183c**).

3-Ethyl-4-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide (184a) was prepared in 20% yield from 10.6 mmol of **1a** and 3.65 g (42.4 mmol) of 3-pentanone following a procedure analogous to the preparation of **183c**. The workup was similar to Method B: mp 130.5-132.5 °C; IR (KBr) 3100-3350, 1655, 1425, 1320, 1180, 785 cm^{-1}. ^{1}HNMR ($CDCl_3$) δ 1.22 (t, J = 7.5 Hz, 3 H), 2.15 (s,3 H), 2.44 (q, J = 7.6 Hz, 2 H), 6.97 (s br, 1H), 7.38-7.87 (m, ArH, 4 H); ^{13}CNMR ($CDCl_3$) δ 11.7, 13.4, 25,8, 109.9, 121.1, 124.3, 126.5, 131.9, 135.4, 137.1; mass spectrum (70 eV), *m/z* (rel intensity) 223 (100), 144 (57) 104 (35), 77(27) 56(33); calcd for $C_{11}H_{13}NO_2S^+$ 223.0667, found

223.0681. Anal. calcd for $C_{11}H_{13}NO_2S$: C, 59.20; H, 5.90; N, 6.27. Found C, 58.94; H, 5.90; N, 6.20.

(±)-3-Ethyl-4-hydroxy-4-methyl-4*H*-1,2-benzothiazine 1,1-Dioxide (194) was prepared in 12% yield from 10.6 mmol of **1a** and 3.65 g (42.4 mmol) of 3-pentanone, following a procedure analogous to the preparation of **183c**. The workup was analogous to Method A: mp 160-161 °C; IR (KBr) 3560, 1670, 1320, 1205, 800 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3 H), 1.66 (s, 3H), 2.9-2.96 (m, CH_2 and OH, 3 H), 7.44-7.80 (m, ArH, 4 H); ^{13}CNMR (acetone-d_6) δ 9.3, 70.8, 124.9, 126.1, 129.3, 133.7, 133.9, 143.3, 196.3, ($CDCl_3$) δ 9.3, 28.2, 30.6, 124.8, 124.9, 128.9, 132.5, 133.2; mass spectrum (CI mode), *m/z* (rel. intensity) 240 (45), 222 (100), 120 (15), 105 (40). Anal. calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.47; N, 5.85. Found: C, 55.18; H, 5.46; N, 5.81.

Isolation of (±)-3-Ethyl-1,6-dimethyl-2-cyclohexen-1-one (196). The hexane wash from the preparation of **184b** and **194** were combined and concentrated. Flash chromatography of the resulting oil gave 0.35 g of a yellow oil. The oil was distilled kugelrohr (Bp 40-45° 0.5mm Hg) to yield 0.15 g (11%) of **196**. GC analysis (temp program: initial temp 80°; 2 min hold; 15°/min; 10 min) indicated the oil to be 99% pure. IR (thin film) 3050-2900, 1670 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.04 (t, J = 7.6 Hz, 3 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.60 (m , 1 H), 1.74 (t, J = 1,5 Hz, 3 H), 1.92-2.33 (m, 6 H); ^{13}CNMR ($CDCl_3$) δ 10.6, 11.7, 15.7, 28.2, 49.8, 129.6, 159.0, 202.0; GC-MS (70 eV), *m/z* (rel. intensity) 152 (46), 137 (8), 123 (4), 110 (100) 67 (71).

3-(1-Methylethyl)-4-methyl-2*H*-1,2-benzothiazine 1,1-Dioxide (184b) was prepared in 9% yield from 10.6 mmol of **1a** and 4.25 g (42.4 mmol) of 2-methyl-3-pentanone following a procedure analogous to the preparation of **183c** The workup was similar to Method B: mp 143-145 °C; IR (KBr) 3300, 1315, 1190, 765 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.19 (d, J = 6.9, 6 H) 2.18 (s, 3 H), 3.18 (m, J = 6.9, 1 H), 6.90 (s br, 1 H), 7.38-7.85 (m, ArH, 4 H); ^{13}CNMR ($CDCl_3$) δ 13.4, 19.4 (2 C), 29.3, 110.1, 121.1, 124.6, 126.6, 131.8, 132.2, 135.7, 140.0; mass spectrum (70 eV), *m/z* (rel intensity) 237 (100), 222 (55) 158 (47), 104 (57), 77 (28); calcd for $C_{12}H_{15}NO_2S^+$

237.0646, found 237.0796. Anal. calcd for $C_{12}H_{15}NO_2S$: C, 60.76; H, 6.33; N, 5.91. Found C,60.48; H, 6.32; N, 6.01.

(±)-4-Hydroxy-3-(1-methylethyl)-4-methyl-4*H*-1,2-benzothiazine 1,1-Dioxide (195) was prepared from 10.6 mmol of **1a** and 4.25 g (42.4 mmol) of 2-methyl-3-pentanone, following a procedure analogous to the preparation of **183c**. The workup was analogous to Method A and gave **195** in 15% yield: mp 194-196 °C. The yield was improved to 18% by oxidation with H_2O_2. Thus, the residue obtained upon filtering the hexane wash was partitioned between H_2O (80 mL) and $CHCl_3$ (3x80 mL). The combined $CHCl_3$ extracted were concentrated until the benzensulfonamide that was also formed precipitated. The $CHCl_3$ solution was filtered and the sulfonamide **179** collected was washed with hot CCl_4 (2x10 mL). The filtrate and the washings were combined and concentrated. The residue was shown by ^{1}HNMR analysis to be mainly the unoxidized benzothiazine **184b**. The residue was then dissolved in 150 mL of $CHCl_3$ and placed into a 250 mL round bottom flask. To the flask was added 20 mL of a 1% $NaHCO_3$ solution and 0.5 mL of 30% H_2O_2. The two phase reaction mixture was allowed to stir at 25°C for 2 h. The $CHCl_3$ phase was collected, washed with a dilute sodium thiosufate solution, dried, filtered and concentrated to yield 0.48 g (18%) of **195**. Recrystallization from CCl_4 gave 0.36 g (13% yield) of clear colorless needles: mp 195.5-196.5 °C; IR (KBr) 3535, 1645, 1350, 1180, 780cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.19 (d, J = 6.7 Hz, 3 H), 1.28 (d,J = 6.7 Hz), 2.96 (s br, OH, 1 H), 3.65 (m, J = 6.7 Hz, 1 H), 7.59-7.92 (m, ArH, 4H); ^{13}CNMR (acetone-d_6) δ 21.2, 21.4, 32.8, 70.4, 124.6, 126.3, 129.2, 133,6, 143.0, 198.8; mass spectrum (CI mode), *m/z* (rel. intensity) 254 (60), 236 (100), 222 (10), 212 (17), 120 (20), 105 (60). Anal. calcd for $C_{12}H_{15}NO_3S$: C, 56.89; H, 5.97; N, 5.53. Found: C, 56.66; H, 5.97; N, 5.47.

Isolation of 2,6-(1-Methylethyl)-3-methylpyridine (197). The hexane wash from the preparation of **184b** was extracted with 5% HCl (3x15 mL). The HCl extracts were combined and neutralized with 10% NaOH. The neutral solution was extracted with $CHCl_3$ (3x30 mL). The combined $CHCl_3$ extracts were vacum filtered through a 1 inch plug of flash grade silica gel and concentrated. Preparative TLC ($CHCl_3$) gave 20mg (1% yield) of **197**. GC analysis (temp program: initial temp 80°; 2 min hold; 15°/min; 10 min) indicated a purity of 95%. IR (thin film) 1605, 1585, 1485, 1465 cm^{-1};

^{1}HNMR ($CDCl_3$) δ 1.24 (d, *J* = 4.1 Hz, 6 H), 1.77 (d, *J* = 4.2 Hz, 6 H), 2.27 (s, 3 H), 2.96 (m, *J* = 4.1 Hz, 1 H), 3.20 (m, *J* = 4.1 Hz, 1 H) 6.83 (d, *J* = 7.7 Hz, 1 H), 7.26 (d, *J* = 8.0 Hz, 1 H); ^{13}CNMR ($CDCl_3$) δ 18.1, 21.7, 22.6, 31.5, 35.9, 117.1, 126.3, 137.7, 163.6, 163.9; GC-MS (70 eV), *m/z* (rel. intensity) 177 (25), 176 (30) 162 (100), 149 (70).

Reaction of 2-Iodobenzenesulfonamide (1a) with the Enolate Anion (199) Derived From 2,4-Dimethyl-3-pentanone. To a stirred solution of 43.8 mmol of KNH_2 in 500 mL of liquid NH_3 was added 4.0 g (35.1 mmol) of 2,4-dimethyl-3-penatanone and 2.48 g (8.77 mmol) of **1a**. The heterogeneous mixture was irradiated for 500 s, becoming homogeneous within 300 s. The residue obtained upon quenching the reaction and evaporation of the NH_3, was extracted with 300 mL of hexane. The hexane solution was concentrated *in vacou* to yield 1.7 g (86%) of ketone dimer **198**.[51] Further extraction of the solid with hot EtOAc gave 1.25 g (90% yield) of benzensulfonamide (**179**): mp 150-152 °C.

Reaction of 2-Bromobenzenesulfonamide (1b) with the Enolate Anion Derived From 2,4-Dimethyl-3-pentanone. To a stirred solution of 35.3 mmol of KNH_2 in 500 mL of liquid NH_3 was added 3.22 g (28.3 mmol) of 2,4-dimethyl-3-penatanone and 1.67 g (7.06 mmol) of **1b**. The heterogeneous mixture was irradiated for 2 h, remaining heterogeneous throughout. The residue obtained upon quenching the reaction and evaporation of the NH_3, was extracted with 300 mL of hexane. The hexane solution was concentrated *in vacou* to yield 0.55 g (35%) of ketone dimer **198**.[51] Further extraction of the solid with hot ethyl acetate gave 1.15 g of a solid mixture (1:1) of **1b** and benzensulfonamide (**179**).

Reaction of 4-Iodobenzenesulfonamide (200a) with the Enolate Anion Derived From 2,4-Dimethyl-3-pentanone. To a stirred solution of 35.3 mmol of KNH_2 in 500 mL of liquid NH_3 was added 3.22 g (28.3 mmol) of 2,4-dimetyl-3-penatanone and 2.00 g (7.06 mmol) of **200a**. The heterogeneous mixture was irradiated for 2 h, remaining heterogeneous throughout. The residue obtained upon quenching the reaction and evaporation of the NH_3, was extracted with hot CCl_4 (3x100 mL). Further extraction of the solid with hot ethyl acetate gave upon concentration, 0.8 g of a solid

mixture (5:4 respectively) of **1b** and benzensulfonamide **179**. Concentration of the combined CCl_4 solution and flash chromatography ($CHCl_3$/EtOAc, 3:1) gave 0.63g (40% yield) of **198** and 0.55 g (29% yield) of 2,4-dimethyl-2-(4-sulfamoylphenyl)-3-pentanone (**200c**). An analytical sample of **299c** was obtained by recrystallization from hexane: mp 90-91.5 °C; IR (KBr) 3380, 3300, 3020, 1725, 1360, 1180, 810 cm^{-1}: ^{1}HNMR ($CDCl_3$) δ 0.87 (d, J = 6.7 Hz, 6 H), 1.49 (s, 6 H), 2.61, (m, J = 6.6 Hz, 1 H), 5.16 (s, NH, 2 H), 7.38-7.91 (m, ArH, 4H); ^{13}CNMR ($CDCl_3$) δ 20.8 (2C), 24.9 (2C), 36.0, 53.2, 126.7 (2C), 127.2 (2C), 140.7, 148.9, 216.2; mass spectrum (CI mode), *m/z* (rel. intensity) 270 (33), 198 (25), 118 (70), 88 (100). Anal. calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20. Found: C, 57.87; H, 7.14; N, 5.18.

Reaction of 4-Bromobenzenesulfonamide (200b) with the Enolate Anion Derived From 2,4-Dimethyl-3-pentanone. The reaction and workup procedure were analogous to the reaction of the **200a**. Thus the reaction of 1.67 g (7.06 mmol) of **200b** gave upon workup **198** (39% yield), **200c** (29% yield), and 0.85g of a solid mixture (7:6 respectively) of **200b** and **179**.

Inhibited Reaction of 2-iodobenzenesulfonamide (1a) and 2,4-Dimethyl-3-pentanone with Di-*tert*-butyl Nitroxide. To a stirred solution of 43.8 mmol of KNH_2 in 500 mL of liquid NH_3 was added a mixture of 4.0 g (35.1 mmol) of 2,4-dimetyl-3-penatanone and 0.13 g (.88 mmol) of DTBN. The solution was allowed to stand for 5 min prior to the introduction of 2.48 g (8.77 mmol) of **1a**. The heterogeneous mixture was irradiated for 500 s, the solution remained heterogeneous. The residue obtained upon quenching the reaction an evaporation of the NH_3, was extracted with EtOAc gave 2.17 g of recovered **1a** which was contaminated with 5 mole% benzensulfonamide (**179**). Also isolated was 0.08 g (4% yield) of ketone dimer **198**.

Preparation of *i*-Propyl Iodide-d_7 (228). A procedure analogous to that reported for the unlabeled analog was followed.[55] Into a round bottom flask equipped with a magnetic stirring bar and condenser was placed 402 mmol of $P(OPh)_3MeI$ complex and 25g (366 mmol) of isopropanol-d_8 (Aldrich). The mixture was allowed to stir under a nitrogen atmosphere for 24 h. The condenser was removed and the *i*-propyl iodide-d_7 (**228**) was collected by fractional distillation from the crude the reaction mixture. The

fraction boiling between 86-90 °C was collected to yield 49 g (76%) of **228**. The alkyl iodide was used in the next step without further purification.

Alkylation of 1,3-Dithiane with *i*-Propyl Iodide-d_7 228. A procedure analogous to that reported for the unlabeled analog was followed.[56] Thus, 101.0 mmol of 1,3-dithiane in 300 mL of dry THF was treated sequentially with 106.0 mmol of butyllithium (Aldrich) and 106.0 mmol of **228**. The sequential treatment was repeated without isolation of the monoalkylated dithiane. Work up according to Corey's and Seebach's procedure gave dithiane **230** in 82% yield, bp. 144-155 °C (10 mmHg).

Preparation of 3,4-Dimethyl-3-Pentanone-d_{14} (231). Hydrolysis of dithiane **230** was accomplished by a procedure analogous to Ghiringhelli's.[57] Thus, 6.5 g (30.0 mmol) of **230** was treated with 90.0 mmol of BF_3OEt_2, 60.0 mmol of lead dioxide, and 30 mL of a 20% solution of D_2O in THF at 0°. The mixture was allowed to warm to 25° C and was left to stir overnight. The solution was cooled in an ice bath and then neutralized by addition of 20% NaOD in portions. The mixture was filtered on a coarse glass frit and then extracted with ether (3x10 mL). The combined ethereal extracts were dried over K_2CO_3 and then concentrated by fractional distillation of the ether and THF. When the temperature of the distillate reached 80°C, 20 mL of 1,2-dichlorobenzene was added to chase the ketone. The fraction boiling between 105°-125° was collected. GC analysis indicated that the material was 95% the labeled ketone contaminated primarily with 1,2-dichlorobenzene. The ^{1}HNMR spectrum of the oil confirmed that the major contaminant was *o*-dichlorobenzene and gave some indication of minor traces of THF. The mass spectra of the ketone indicated that the product was 98 atom% D. ^{2}HNMR ($CHCl_3$, $CDCl_3$ internal reference), δ 1.00 (2 D), 2.71 (12 D); mass spectrum (GC inlet, 70 eV), *m/z* (rel intensity) 128 (33), 78 (100), 51 (20).

Reaction of 2-Iodobenzensulfonamide (1a) with the Enolate Derived From 2,4-Dimethyl-3-pentanone-d_{14} (231). To a stirred solution of 9.76 mmol of KNH_2 in 100 mL of liquid NH_3 was added 1.0 g (7.8 mmol) of **231** and, 0.55 g (1.9 mmol) of **1a**. The mixture was irradiated for 30 min and then quenched over NH_4Cl. The

NH_3 was allowed to evaporate and the residue was partitioned between H_2O (60 mL) and CH_2Cl_2 (3x80 mL). The combined organic extracts were dried, filtered and concentrated. Flash chromatography ($CHCl_3$/EtOAc, 4:1) of the residue gave 0.11 g of benzenesulfonamide: mp 150-154 °C. The mass spectrum of the solid indicated that the benzenesulfonamide produced was 80% d_1 and 20% d_0. The ^{2}HNMR (acetone) showed only one resonance of δ 7.97 relative to acetone-d_6 as an internal reference.

Reaction of 2-Iodobenzensulfonamide (1a) with the Enolate Derived From 2,4-Dimethyl-3-pentanone in Liquid ND_3. To a stirred solution of 5.5 mmol of KND_2 in 50 mL of liquid ND_3 (Cambridge Isotopes) was added 0.50 g (4.3 mmol) of diisopropyl ketone and 0.31g (1.1 mmol of) of **1a**. The reaction mixture was irradiated for 30 min and then quenched by the introduction of MeOD. The mixture was transferred to a 300 mL beaker containing 3 g on NH_4Cl. The NH_3 was allowed to evaporate and the resulting residue treated analogous to the residue obtained from the reaction of **1a** and **231**. The mass spectrum of the material showed that the benzensulfonamide produced was 95% d_0 and 5% d_1. The ^{2}HNMR spectrum shows one weak resonance at δ 7.94 relative to acetone-d_6.

Reaction of *N,N*-Dideuterio-2-iodobenzensulfonamide (1a) with the Enolate Derived From 2,4-Dimethyl-3-pentanone in Liquid ND_3. To a stirred solution of 7.0 mmol of KND_2 in 50 mL of liquid ND_3 was added 0.50 g (4.3 mmol) of diisopropyl ketone and 0.40 g (1.3 mmol of) of 2-iodobenzenesulfonyl chloride.[73] The reaction mixture was irradiated for 30 min and then quenched by the introduction of MeOD. The mixture was transferred to a 300 mL beaker containing 3 g of NH_4Cl. The NH_3 was allowed to evaporate and the resulting residue treated analogously to the residue obtained from the reaction of **1a** and **231**. The mass spectrum of the material showed that the benzensulfonamide produced was 95% d_0 and 5% d_1. The ^{2}HNMR spectrum shows two weak resonances at δ 7.96 and 7.64 relative to acetone-d_6. The ratio of the integrals of the two signals was 2:1 respectively.

Reaction of *N,N*-Dideuterio-2-iodobenzensulfonamide (1a) with the Enolate Derived From 2,4-Dideuterio-2,4-dimethyl-3-pentanone in Liquid ND_3. The labeled ketone was prepared according to the procedure reported by Subba Rao.[75] To a stirred solution of 6.4 mmol of KND_2 in 50 mL of liquid ND_3 was added 0.50 g (4.3 mmol) of 2,4-dideuterio-2,4-dimethyl-3-pentanone and 0.33 g (1.1 mmol) of 2-iodobenzenesulfonyl chloride. The reaction mixture was irradiated for 45 min and then quenched by the introduction of MeOD. The mixture was transferred to a 300 mL beaker containing 3 g of NH_4Cl. The NH_3 was allowed to evaporate and the resulting residue treated in a manner analogous to the residue obtained from the reaction of **1a** and **231**. The mass spectrum of the material showed that the benzensulfonamide produced was 94% d_0 and 6% d_1. The ^{2}HNMR spectrum shows two weak resonances at δ 7.96 and 7.65 relative to acetone-d_6. The ratio of the integrals of the two signals was 3:1 respectively.

1,2,3,4-Tetrahydrocyclopenta[*c*][1,2]benzothiazine 5,5-dioxide (254a). To a stirred solution of 21.2 mmol of KNH_2 in 800 mL of NH_3 was added 1.33 g (15.9 mmol) of cyclopentanone and 1.5 g (5.3 mmol) of **1a**. The heterogeneous mixture was irradiated for 15 min. The resulting homogeneous mixture was quenched over NH_4Cl and the NH_3 was allowed to evaporate overnight. The residue was dissolved in H_2O (80mL) and 1 gram of sodium thiosulfate was added. The aqueous phase was acidified to pH = 3 and then extracted with $CHCl_3$ (2x100 mL). The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc 6:4) of the residue and recrystallization from CCl_4 gave 0.53 g (45%) of **254a**: mp 184-187 °C. An analytical sample was obtained by recrystallization from toluene: mp 186.5-188 °C; IR (KBr) 3175, 1660, 1305, 1160, 785 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.13 (m, 2 H), 2.72-2.88 (m, 4 H), 7.00 (s br, NH, 1 H), 7.28-7.92 (m, ArH, 4 H); ^{13}CNMR ($CDCl_3$) δ 20.5, 29.1, 33.4, 115.6, 122.0, 123.7, 130.1, 132.1, 132.2, 138.4. mass spectrum (70 eV), *m/z* (rel intensity) 221 (100), 204 (12), 156 (35), 129, (20) 77 (8). Anal. calcd. for $C_{11}H_{11}NO_2S$: C, 59.70; H, 5.01; N, 6.33. Found: C, 59.61; H, 5.02; N, 6.31.

7,8,9,10-Tetrahydro-6*H*-dibenzo[*c*,*e*][1,2]thiazine 5,5-dioxide (254b). To a stirred solution of 24.7 mmol of KNH_2 in 800 mL of NH_3 was added 1.82

g (18.6 mmol) of cyclohexanone and 1.75 g (6.18 mmol) of **1a**. The heterogeneous mixture was irradiated for 15 min. The resulting homogeneous mixture was quenched over NH_4Cl and the NH_3 was evaporated. The residue was still containing traces of NH_3 was partitioned between H_2O (80 mL) and $CHCl_3$ (3x80 mL). The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc 6:4) of the residue and recrystallization from CCl_4 gave 0.66 g (45%) of **254b**: mp 146-148 °C. An analytical sample was obtained by recrystallization from toluene: mp 148.5-150 °C; IR (KBr) 3350-3150, 1650, 1315, 1170, 770 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.79 (m, 4 H), 2.40 (m, 2 H), 2.50 (m, 2 H), 6.98 (s br, NH, 1 H), 7.25-7.89 (m, ArH, 4 H); ^{13}CNMR ($CDCl_3$) δ 22.1, 22.2, 24.5,29.2, 111.9, 121.2, 123.0, 126.5, 131.8, 131.9, 134.4, 134.8. mass spectrum (70 eV), *m/z* (rel intensity) 235 (100), 221 (20), 207 (40), 170 (52) 89 (25); calcd for $C_{12}H_{13}NO_2S^+$ 335.0667, found 235.0678. Anal. calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.30; H, 5.60; N, 5.91.

(±)-8,9,10,11-Tetrahydro-11a-hydroxy-7*H*-cycloocta[*c*][1,2]benzothiazine 5,5-dioxide (255). To a stirred solution of 35.3 mmol of KNH_2 in 800 mL of NH_3 was added 3.57 g (28.3 mmol) of cyclooctanone and 2.00 g (7.06 mmol) of **1a**. The heterogeneous mixture was irradiated for 45 min. The resulting homogeneous mixture was quenched over NH_4Cl and the NH_3 was evaporated. The residue while still containing traces of NH_3 was extracted with 400 mL of refluxing hexanes. The hexane was decanted and the solid partitioned between H_2O (100 mL) and CH_2Cl_2 (3x130 mL). The combined CH_2Cl_2 extracts were dried over Na_2SO_4, filtered and concentrated to yield 2.02 g of an immobile oil. The oil was dissolved in 120 mL of 80% isopropanol and placed in a 250 mL round bottom flask. The flask was equipped with a condenser and magnetic stirring bar. To the solution was added 7.06 mmol of monoperoxyphthalic acid magnesium salt and the homogeneous mixture was heated to 40°C in an oil bath. The reaction mixture was cooled to 25°C and 2 g of sodium thiosulfate was added. The solvent was removed in vacuo and the residue partitioned between 5% $NaHCO_3$ (100 mL) and CH_2Cl_2 (150 mL). The CH_2Cl_2 extract was dried, filtered and concentrated to yield 1.6 g of a yellow solid. Flash chromatography (hexane/EtOAc 6:4) of the residue and recrystallization from CCl_4 gave 0.69 g (35% yield) of **255**: mp 182-185 °C. Concentration of the mother liquor and recrystallization from toluene gave 0.59 g (30%

yield) of **255**: mp 179-182 °C. An X-ray crystal structure was determined from the crystals that separated from CCl_4 (Figure 2). IR (KBr) 3600-3400, 2970, 1625, 1325, 1175, 765 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.23-2.15 (m, 10 H), 2.54 (m, 1 H), 3.24 (s, OH, 1 H), 3.41 (m, 1 H), 7.36-7.73 (m, ArH, 4 H); ^{13}CNMR ($CDCl_3$) δ 21.8, 25.1, 27.7, 28.0, 36.1, 46.2, 71.8, 124.2, 125.3, 128.5, 131.9, 132.8, 197.9; mass spectrum (CI mode), *m/z* (rel intensity) 280 (30), 264 (100), 262 (42). Anal. calcd. for $C_{14}H_{17}NO_3S$: C, 60.18; H, 6.13; N, 5.01. Found: C, 60.15; H, 6.09; N, 4.95.

Reaction of 2-Iodo-3,5-dimethylbenzenesulfonamide (256) with the Enolate Derived From 2,4-Dimethyl-3-pentanone. To a stirred solution of 16.1 mmol of KNH_2 in 300 mL of liquid NH_3 was added 1.47 g (12.8 mmol) of 2,4-dimethyl-3-penatanone and 1.00 g (3.21 mmol) of **256**.[76,77] The homogeneous mixture was irradiated for 15 min. The residue obtained upon quenching the reaction and evaporation of the NH_3, was extracted with 300 mL of hexane. The hexane solution was concentrated *in vacou* to yield 0.59 g (81% yield) of ketone dimer **198**. Further extraction of the solid with hot EtOAc gave 0.68 g of a brown solid. Flash chromatography (CH_2Cl_2/EtOAc, 2:1) and recrystallization from hexane/$CHCl_3$ gave 0.50 g of 3,5-dimethylbenzenesulfonamide (**257**): mp 130-135 °C; lit mp 135.5 °C;[76] ^{1}HNMR ($CDCl_3$) δ 2.38 (s, 6 H), 4.82 (s br, NH, 2 H), 7.21 (s, 1 H), 7.55 (s, 2 H).

Reaction of 2-Iodo-3,5-dimethylbenzenesulfonamide (256) with the Enolate Derived From *t*-Butyl Acetate. To a stirred solution of 16.1 mmol of KNH_2 in 300 mL of liquid NH_3 was added 1.49 g (12.8 mmol) of *t*-butyl acetate and 1.00 g (3.21 mmol) of **256**. The slightly heterogeneous mixture was irradiated for 30 min. The residue obtained upon quenching the reaction and evaporation of the NH_3 was dissolved in H_2O (80 mL). To the aqueous solution was added 1 g of sodium thiosulfate. The solution was acidified to pH = 3 and then extracted with $CHCl_3$ (2x100 mL). The combined $CHCl_3$ extracts were washed with 5% $NaHCO_3$ (2x20 mL) dried, and concentrated to yield 0.41 g (69%) of **257**. The solid was recrystallized from $CHCl_3$/hexane to yield 0.20 g (34%). The aqueous phase was acidified to pH = 3 and then extracted with $CHCl_3$ (3x25 mL).

The combined $CHCl_3$ extracts were dried over Na_2SO_4 and concentrated to yield 0.22 g (30%) of 3,4-dihydro-5,7-dimethyl-1,2-benzothiazin-3(2*H*)-one 1,1-dioxide (**258**). Recystallization from ethanol gave 0.10 g (14% yield) of **258**: mp 256-258 °C; IR (KBr) 3300-2900, 1715, 1350, 1175 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.37 (s, 3 H), 2.41 (s, 3 H), 3.96 (s, 1 H), 7.28 (s, 1 H), 7.60 (s, 1 H); ^{13}CNMR (acetone-d_6) δ 18.9, 20.6, 35.7, 120.6, 127.3, 136.1, 137.2, 138.0, 138.6, 169.5; mass spectrum (CI mode), *m/z* (rel intensity) 226 (100), 210 (10), 183 (25). Anal. calcd. for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.221. Found: C, 53.17; H, 4.94; N, 6.16.

Reaction of 2-Iodo-3,5-dimethylbenzenesulfonamide (256) with the Enolate Derived From Ethyl Phenylacetate. To a stirred solution of 16.1 mmol of KNH_2 in 300 mL of liquid NH_3 was added 2.11 g (12.9 mmol) of ethyl phenylacetate and 1.00 g (3.21 mmol) of **256**. The slightly heterogeneous mixture was irradiated for 30 min. The residue obtained upon quenching the reaction and evaporation of the NH_3, was dissolved in H_2O (80 mL). To the aqueous solution was added 1 g of sodium thiosulfate. The solution was acidified to pH = 3 and then extracted with $CHCl_3$ (3x70 mL). The combined $CHCl_3$ extracts were washed with 5% $NaHCO_3$ (2x20 mL) dried, and concentrated. The bicarbonate wash was acidified to pH = 3 and then extracted with $CHCl_3$ (3x25 mL). The combined $CHCl_3$ extracts of the bicarbonate solution were dried over Na_2SO_4 and concentrated to yield only traces of phenylacetic acid. The initial $CHCl_3$ extracts were dried filtered and concentrated. Flash chromatography (hexane/EtOAc, 4:1) of the residue gave 1.6 grams (75% yield) of the recovered ester and 0.45g (76% yield) of the reduced sulfonamide **257**. Gas chromatographic analysis of the oil demonstrated that the recovered ester was pure and that it had a GC-retention time identical to an authentic sample. The ^{1}HNMR and IR spectra were shown to be identical to that of an authentic sample.

Reaction of 2-Iodo-3,5-dimethylbenzenesulfonamide (256) with the Enolate Derived From *t*-Butyl Phenylacetate. A procedure analogous to the reaction of **256** with ethyl phenylacetate was followed. Thus 2.47 g (12.9 mmol) of *t*-butyl acetate prepared from *t*-butanol/potassium *t*-butoxide and phenylacetyl chloride was

used in the place of ethyl phenylacetate. The identical workup gave recovered ester in 63% yield and the reduction product **257** in quantitative yields. Recrystallization of **257** thus obtained from toluene gave 0.33g (56% yield) of a white solid: mp 134-135.5 °C.

Reaction of *N*-Methyl-2-iodobenzenesulfonamide (260) with the Enolate Derived From 2,4-Dimethyl-3-pentanone in Liquid NH_3. To a stirred solution of 26.9 mmol of KNH_2 in 300 mL of liquid NH_3 was added 3.08 g (26.9 mmol) of 2,4-dimethyl-3-pentanone and 2.00 g (6.73 mmol) of **260**.[46] The slightly heterogeneous mixture was irradiated for 60 min. The residue obtained upon quenching the reaction and evaporation of the NH_3, was partitioned between H_2O (80 mL) and $CHCl_3$ (3x80 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography eluting first with hexane/ethyl acetate (9:4) and then with hexane/ethyl acetate (1:1) gave the following products and yields (listed in the order in which they eluted): Diisopropyl ketone dimer **198**, 0.33g (22% yield); *N*-benzenesulfonyl-1-amino-2,2,4-trimethyl-3-pentanone **263** 0.38 g (20% yield), recrystallized from hexanes to yield 0.33 g 17%: mp 90-91.5 °C; *N*-methyl-benzenzenesulfonamide **264**, 0.06 g (5% yield): mp 33-35.5 °C; benzenesulfonamide **179** 0.30 g (28% yield): mp 151.5-153.5 °C; and *N,N'*-dibenzenesulfonyl-1,2-diaminoethane **262** 0.28 g (25% yield); recrystallized from ethyl acetate to yield 0.25 g (23% yield): mp 168-170 °C. Products **198**, **264** and **179** were shown to have physical (mixture melting points) and spectral (IR and ^{1}HNMR) properties identical to authentic samples obtained either commercially or prepared independently by standard methods. Product **262** was prepared independently via the phase transfer catalyzed reaction of a CH_2Cl_2 solution of ethylenediamine, bezenesulfonyl chloride tetrabutylammonium chloride and aqueous NaOH. The physical and spectral characteristics of **263** appear below.

N-Benzenesulfonyl-1-amino-2,2,4-trimethyl-3-pentanone (**263**) exhibited the following physical and spectral characteristics: mp 90-91.5 °C; IR (KBr) 3350, 3005, 1715, 1345, 1175 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.99 (d, J = 6.7 Hz, 6 H), 1.18 (s, 6H), 2.86 (d, J = 7.0 Hz, 2 H), 3.00 (m, J = 6.7 Hz, 1 H), 5.10 (t br, 7.0 Hz, 1 H), 7.48-7.84 (m, ArH, 5 H); ^{13}CNMR ($CDCl_3$) δ 20.0, 22.2, 34.4, 48.9, 50.6, 126.9, 129.1, 132.5, 140.3, 220.3; mass spectrum (CI mode), *m/z* (rel. intensity) 284 (100), 228 (10), 210 (12), 170 (15), (70 eV), *m/z* (rel. intensity) 228 (30), 212 (15), 170 (20), 141 (40), 114 (100), 77 (70) calcd for $C_{14}H_{22}NO_3S$ $(MH)^+$ (CI mode) 284.1320, found 284.1316.

Anal. calcd for $C_{14}H_{21}NO_3S$: C, 59.33; H, 7.47; N, 4.94. Found: C, 59.24; H, 7.48; N, 4.95.

Preparation of *N*-Methyl-d_3-2-iodobenzenesulfonamide (265). A 125 mL three-neck round bottom flask was equipped with a condenser and a magnetic stirring bar. Into the flask was placed 11.7 g (38.7 mmol) of 2-iodobenezenesulfonyl chloride, 50 mL of CH_2Cl_2, 3.0 g (42.5 mmol) of methylamine-d_3•HCL (98 atom% D, Aldrich), 20 mL H_2O, and 3.40 g (85.1 mmol) NaOH). The flask was stoppered and the solution was stirred at 0° for one hour. The reaction was allowed to warm to reflux and left to stir overnight. The solution was neutralized with HCL and the phases separated. The aqueous phase was extracted with $CHCl_3$ (2x40 mL) and the extracts were combined with the organic phase. The combined solution was dried over Na_2SO_4, filtered and concentrated. The resulting material was recrystallized from ethanol to yield 10.1 g (87%) of **265**: mp 119-121 °C; ^{1}HNMR ($CDCl_3$) δ 5.17 (s br, NH, 1 H), 7.18-8.17 (m, ArH, 4 H); ^{2}HNMR ($CHCl_3$) δ 2.57 relative to $CDCl_3$.

Reaction of *N*-Methyl-d_3-2-iodobenzenesulfonamide (265) with the Enolate Derived From 2,4-Dimethyl-3-pentanone in Liquid NH_3. The reaction and work up procedure was identical to the analogous reaction of the unlabeled *N*-methyl-2-iodobenzenesulfonamide (**260**). The reaction gave the following products and yields (listed in the order in which they eluted): Diisopropyl ketone dimer **198**, 0.60g (39% yield); *N*-(2-deuteriobenzenesulfonyl)-1-amino-1,1-dideuterio-2,2,4-trimethyl-3-pentanone (**267**) 0.23 g (12% yield), recrystallized from hexanes to yield 0.19 g (10%): mp 90-91.5 °C; *N*-methyl-d_3-benzenzenesulfonamide (**268**), 0.40 g (34% yield, could not be recrystallized); 2-deuterio-benzenesulfonamide (**233**) 0.29 g (27% yield) mp 151.5-153.5 °C; and *N,N'*-di-(2-deuteriobenzenesulfonyl)-1,2-diamino-1,1,2,2-tetradeuterioethane (**266**) 0.20 g (17% yield), recrystallized from ethyl acetate to yield 0.14 g (12%): mp 168-170 °C. The physical and spectral characteristics of **267**, **268**, **233** and **266** appear below.

N-(2-deuteriobenzenesulfonyl)-1-amino-1,1-dideuterio-2,2,4-tri-methyl-3-pentanone (**267**) exhibited the following physical and spectral characteristics: mp 90-91.5 °C; IR (KBr) 3355, 3010, 1715, 1335, 1185 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 0.98 (d, J = 6.7 Hz, 6 H), 1.17 (s, 6H), 3.00 (m, J = 6.7 Hz, 1 H), 5.12 (s br, NH, 1 H), 7.48-7.84 (m,

ArH, 4 H); ^{2}HNMR ($CHCl_3$) δ 2.85 (2 D), 7.90 (1 D) (δ relative to $CDCl_3$); ^{13}CNMR (50MHz, $CDCl_3$) δ 19.8, 21.9, 34.2, 48.5, 49.7 (m, J_{CD} = 21.1 Hz), 125.9(m), 126.7, 128.9, 129.0, 132.4, 140.0, 220.0; mass spectrum (70 eV), *m/z* (rel. intensity) 287 (.5), 229 (70), 215 (35), 173 (35), 142 (100), 114 (100), 78 (100).

N-methyl-d_3-benzenzenesulfonamide (**268**) exhibited the following spectral characteristics: ^{1}HNMR ($CDCl_3$) δ 4.77 (s br, NH, 1 H), 7.46-7.87 (m, ArH, 5 H); ^{2}HNMR ($CHCl_3$) δ 2.65 relative to $CDCl_3$; mass spectrum (70 eV), *m/z* (rel. intensity) 174 (22), 141 (19), 77 (100).

2-Deuteriobenzenesulfonamide (**233**) exhibited the following physical and spectral characteristics: mp 151.5-153.5 °C; ^{1}HNMR (acetone-d_6) δ 6.59 (s br, NH, 2 H), 7.50-7.71 (m, ArH, 3 H), 7.85-7.99 (m, ArH, 1 H); ^{2}HNMR (acetone) δ 7.92 (δ relative to acetone-d_6); mass spectrum (70 eV); ^{13}CNMR (100 MHz, acetone-d_6) 126.4 (t, JCD = 25.9), 126.7,129.5, 129.6, 132.6, 144.8; mass spectrum (70 eV), *m/z* (rel. intensity) 158 (30), 142 (20), 94 (30), 78 (100), 77 (6).

N,N'-Di-(2-deuteriobenzenesulfonyl)-1,2-diamino-1,1,2,2-tetra-deuterioethane (**266**) exhibited the following physical and spectral characteristics: mp 168-170 °C; ^{1}HNMR (acetone-d_6) δ 7.53-7.63 (m, ArH, 6 H) 7.80-7.83 (m, ArH, 2 H); ^{2}HNMR (acetone) δ 2.99 (4 D), 7.87 (2 D) (δ relative to acetone-d_6). mass spectrum (70 eV); 13CNMR (100 MHz, DMSO-d_6) δ 48.1 (m), 126.1 (t, JCD = 25.0), 126.3,129.1, 129.2, 132.5, 140.1; mass spectrum (CI mode), *m/z* (rel. intensity) 347 (100), 206 (20), 173(30), 144 (20).

***N-t*-Butyl-2-iodobenzenesulfonamide (275)** was prepared in 79% yield from 2-iodobenzenesulfonyl chloride and two equivalents of *t*-butylamine in CH_2Cl_2 following standard procedures: needles from ethanol mp 152-154 °C. IR (KBr) 3395, 1360, 1200; ^{1}HNMR ($CDCl_3$) δ 1.20 (s, 9 H), 5.18 (s br, N H, 1 H), 7.13,-8.21 (m, ArH, 4 H); ^{13}CNMR ($CDCl_3$) δ 29.9 (3 C), 54.9, 92.5, 128.6, 130.3, 132.8, 142.1, 145.4. Anal.calcd for $C_{10}H_{14}INO_2S$: C, 35.41; H, 4.16, N, 4.13. Found: C, 35.37; H, 4.18, N, 4.05.

Reaction of *N-t*-Butyl-2-iodobenzenesulfonamide (275) with the Enolate Derived From *t*-Butyl Acetate. To a stirred solution of 29.5 mmol of KNH_2 in 400 mL of liquid NH_3 was added 2.47 g (23.6 mmol) of *t*-butyl acetate and 2.00

g (5.90 mmol) of **275**. The slightly homogeneous mixture was irradiated for 60 min. The residue obtained upon quenching the reaction and evaporation of the NH_3, was dissolved in H_2O (75 mL) and CH_2Cl_2 (3x100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexane/$CHCl_3$, 1:9) yielded 1.71 g (89%) of **275**. Recrystallization from hexanes gave 1.27g (66% yield) of a white solid: mp 89.0-90.5 °C; IR (KBr) 3345, 3020, 1745, 1315, 1160, 765 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.22 (s, 9 H), 1.44 (s, 9 H), 4.05 (s, 2 H) 5.21 (s br, NH, 1 H), 7.31-8.06 (m, ArH, 4 H); ^{13}CNMR ($CDCl_3$) δ 28.0 (3 C), 30.1 (3 C), 40.2, 55.3, 81.7, 127.5, 129.4, 132.2, 141.9, 171.1; mass spectrum (70 eV), *m/z* (rel intensity) 312 (10), 256 (60), 238 (30), 210 (25), 198 (30), 57 (100). Anal. calcd. for $C_{16}H_{25}NO_4S$: C, 58.72; H, 7.69; N, 4.28. Found: C, 58.79; H, 7.70; N, 4.26.

Reaction of *N*-*t*-Butyl-2-iodobenzenesulfonamide (275) with the Enolate Derived From Ethyl Phenylacetate. A procedure analogous to the reaction of **275** with *t*-butyl acetate was followed. Thus, to a stirred solution of 22.1 mmol of KNH_2 in 400 mL of liquid NH_3 was added 2.91 g (17.7 mmol) of ethyl phenylacetate and 1.50 g (4.42 mmol) of **275**. The homogeneous mixture was irradiated for 60 min. The analogous work up gave the recovered ester in 63% yield and the corresponding reduction product *N*-*t*-butylbenzensulfonamide in 68% yield. An analytical sample of the reduced sulfonamide was obtained by recrystallization from hexanes: mp 81-83 °C. Mixture melting point with an authentic sample was not depressed.

***N*-Phenyl-2-iodobenzensulfonamide (278).** Into a 100 mL round bottom flask was placed 5.0 g (16.5 mmol) of 2-iodobenzenesulfonyl chloride, 50 mL of acetonitrile and 3.38 g (36.4 mmol) of freshly distilled aniline. The flask was equipped with a magnetic stirring bar and a condenser. The reaction was slightly exothermic and becomes heterogeneous within minutes. The solution was left to stir for 4 h and then concentrated under reduced pressure. The residue was dissolved in 150 mL of $CHCl_3$ and then extracted with 10% HCl (3x15 mL). The organic extracts were vacum filtered through a 4 inch plug of flash grade silica gel to remove colored impurities. The silica gel plug was rinsed with 50 mL of fresh $CHCl_3$. The filtrate and the rinse $CHCl_3$ were combined and concentrated to yield 5.93 g (100%) of **278**. The material thus obtained could be used without further purification. Recrystallization of the solid from isopropanol

gave 5.21g (88% yield): mp 126-128 °C; IR (KBr) 3100, 1350, 1175, 765 cm^{-1}; ^{1}HNMR (acetone-d_6) δ 7.01 (m, ArH, 1 H), 7.26 (m, ArH, 5 H), 7.55 (m, ArH, 1 H), 8.09-8.16 (m, ArH, 2 H); ^{13}CNMR (acetone-d_6) δ 92.5, 120.8, 125.0, 129.2, 129.8, 132.4, 134.5, 137.8, 142.7, 143.5. Anal. calcd for $C_{12}H_{10}INO_2S$: C,40.13; H, 2.81; N, 3.90. Found: C,40.15; H, 2.82; N, 3.93.

***N*-(2-Methoxyphenyl)-2-iodobenzensulfonamide (288)** was prepared by a procedure analogous to **278**. Recrystallization from isopropanol gave a 97% yield of **288**: mp 107-109 °C; IR (KBr) 3310, 1355, 1175, 775 cm^{-1}; ^{1}HNMR (acetone-d_6) δ 3.73 (s, 3 H), 6.83-7.48 (m, ArH, 6 H), 8.02-8.13 (m, ArH and NH, 3 H); ^{13}CNMR (acetone-d_6) δ 55.9, 92.8, 11.8, 121.2, 121.7, 126.2, 128.8, 131.9, 134.4, 142.6, 143.2, 150.8. Anal. calcd for $C_{13}H_{12}INO_3S$: C, 40.12; H, 3.12; N, 3.60. Found: C, 40.13; H, 3.11; N, 3.59

***N*-Phenyl-3,5-dimethyl-2-iodobenzensulfonamide (295)** was prepared by a procedure analogous to **278** in 82% yield after recrystallization from ethanol: mp 197 199 °C; IR (KBr) 3300, 1340, 1160, 775 cm^{-1}; ^{1}HNMR (acetone-d_6) δ 2.28 (s, 3 H), 2.44 (s, 3 H), 7.00-7.83 (m, ArH, 7 H); ^{13}CNMR (acetone-d_6) δ 20.4, 95.4, 120.6, 124.8, 129.7, 130.9, 135.0, 137.9, 139.0, 143.2, 145.6. Anal. calcd for $C_{14}H_{14}INO_2S$: C, 43.42; H, 3.64; N, 3.62. Found: C, 40.40; H, 3.64; N, 3.67

6*H*-Dibenzo[*c,e*][1,2]thiazine 5,5-Dioxide (279). To a stirred solution of 11.1 mmol of KNH_2 in 300 mL of liquid NH_3 was added 1.27 g (11.1 mmol) of 2,4-dimethyl-3-pentanone and 1.00 g (2.78 mmol) of **278**. The slightly homogeneous mixture was irradiated for 30 min. The residue obtained upon quenching the reaction and evaporation of the NH_3, was dissolved in H_2O (80 mL) and the aqueous phase acidified to pH = 3 after the introduction of 1 g of sodium thiosulfate. The solution was extracted with $CHCl_3$ (3x80 mL) and the combined $CHCl_3$ were extracts dried filtered and concentrated. Flash chromatography ($CHCl_3$/CH_3CN, 97:3) of the residue gave 0.45 g (70% yield) of **279**. Recrystallization from toluene gave 0.38 g (60% yield) of **279** as a crystalline solid: mp 194-196 °C; lit[63] mp 196 °C; IR (KBr) 3300-3150, 1320, 1145, 770 cm^{-1}; ^{1}HNMR (acetone-d_6) δ 6.99-7.02 (m, ArH, 2 H), 7.29-8.21 (m, ArH, 4 H), 8.33 (m, ArH, 2 H),; ^{13}CNMR (acetone-d_6) δ 120.4, 121.8, 122.9, 124.7, 125.7, 125.9, 128.7, 130.7, 132.8,

136.0, 137.3; mass spectrum (70 eV), *m/z* (rel. intensity) 231 (100), 167 (80) 139 (35) 84 (25).

7-Methoxy-6*H*-dibenzo[*c,e*][1,2]thiazine 5,5-Dioxide (288). To a stirred solution of 10.3 mmol of KNH_2 in 300 mL of liquid NH_3 was added 1.29 g (11.3 mmol) of 2,4-dimethyl-3-pentanone and 2.00 g (5.14 mmol) of **288**. The homogeneous mixture was irradiated for 78 min. The workup of the reaction was analogous to that used to isolate **279**. The yield of **288** after chromatography was 1.29 g (96%) Recrystallization of **288** from toluene gave 0.89 g (66% yield) of a crystalline solid: mp 181.5-184 °C; IR (KBr) 3300-3200, 1605, 1320, 1175, 770 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 3.94 (s, 3H), 6.95-8.04 (m, ArH and NH, 8 H); ^{13}CNMR (acetone-d_6) δ 56.3, 112.1, 117.4, 122.1, 123.3, 124.5, 126.3, 127.0 129.0, 132.9, 133.1, 136.1, 150.1; mass spectrum (70 eV), *m/z* (rel. intensity) 261 (100), 246 (20), 182 (30), 154 (50). Anal. calcd for $C_{13}H_{11}NO_3S$: C, 59.75; H, 4.24; N, 5.36. Found: C, 59.79; H, 4.24; N, 5.38

Dark Reaction of *N*-(2-Methoxyphenyl)-2-iodobenzenesulfonamide (288) with KNH_2 in Liquid NH_3. To a stirred solution of 10.3 mmol of KNH_2 in 300 mL of liquid NH_3 was added 2.00 g (5.14 mmol) of **288**. The reaction tube was wrapped with a dark cloth and was left to stir for 1.5 h. The residue obtained upon quenching the reaction and evaporation of the NH_3, was dissolved in H_2O (80 mL) and the aqueous phase acidified to pH = 3 after the introduction of 1 g of sodium thiosulfate. The solution was extracted with $CHCl_3$ (3x80 mL) and the combined $CHCl_3$ extracts dried filtered and concentrated. Flash chromatography of the residue ($CHCl_3$) gave recovered **288** in 53% yield. Further elution with $CHCl_3/CH_3CN$ (9:1) gave 0.19 g (14% yield) of **290** and 0.44 g (31% yield) of *N*-(3-aminobenzenesulfonyl)-*o*-anisidine (**291**). Recrystallization of **291** from toluene gave 0.32 g (22% yield) of a white solid: mp 109-111 °C. The melting point of a mixture of **291** thus obtained and an independently prepared sample (described below) was not depressed: IR (KBr) 3310, 3415, 1620, 1355, 1170, 800, 775 cm^{-1}; ^{1}HNMR ($CDCl_3$, D_2O) δ 3.62 (s, 3 H), 6.71-7.50 (m, ArH, 8 H); mass spectrum (CI mode), *m/z* (rel. intensity) 279 (65) 163 (15), 123 (100).

Photostimulated Reaction of *N*-(2-Methoxyphenyl)-2-iodobenzenesulfonamide (288) with KNH_2 in Liquid NH_3. A procedure

analogous to the dark reaction was followed. However, instead of covering the tube with a dark cloth, the reaction mixture was photolyzed for 1.5 h. The analogous work up gave 0.75 g (56% yield) of **290** and 0.40 g (28% yield) of **291.**

Photostimulated Reaction of *N*-(2-Methoxyphenyl)-2-iodobenzenesulfonamide (288) with the Enolate Derived From 2,4-Dimethyl-3-penatanone in the Presence of Di-*tert*-butyl Nitroxide. The experiment was conducted under conditions analogous to that described above for the preparation of **290** Thus, to a stirred solution of 10.3 mmol of KNH_2 in 300 mL of liquid NH_3 was added a mixture of 0.04 g (.26 mmol) of DTBN and 1.29 g (11.3 mmol) of 2,4-dimethyl-3-pentanone. The solution was allowed to stir for 5 min prior to the introduction of 2.00 g (5.14 mmol) of **288**. The homogeneous mixture was irradiated for 15 min. Work up as described above gave 0.32 g (16% yield) of recovered **288** and 0.82 g (61% yield) of **290**. The analogous control experiment (photolysis for 15 min) without the addition of DTBN gave 0.22g (11% yield) of recovered **288** and 1.01 g (75% yield) of **290**.

1,3-Dimethyl-6*H*-dibenzo[*c,e*][1,2]thiazine 5,5-Dioxide (295). To a stirred solution of 10.3 mmol of KNH_2 in 300 mL of liquid NH_3 was added 1.30 g (11.4 mmol) of 2,4-dimethyl-3-pentanone and 2.00 g (5.16 mmol) of **295**. The homogeneous mixture was irradiated for 30 min. The workup of the reaction was analogous to **279**. The yield after chromatography was 0.64 g (48%) Recrystallization from toluene gave 0.46 g (34% yield) of a crystalline solid: mp 228-231.5 °C; IR (KBr) 3200, 1330, 1145 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.43 (s, 3H), 2.65 (s, 3H), 6.82 (s br, NH, 1 H), 7.12-7.88 (m, ArH , 6 H); ^{13}CNMR (acetone-d_6) δ 20.6, 23.0, 120.3, 120.9, 123.8, 124.2, 129.2, 129.7 130.0, 137.1, 137.5 (2C), 138.5, 138.7; mass spectrum (70 eV), *m/z* (rel. intensity) 259 (100), 194 (50), 180 (50), 152 (15). Anal. calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40. Found: C, 64.75; H, 5.02; N, 5.37

***N*-(3-aminobenzenesulfonyl)-*o*-anisidine (291).** This compound was prepared in two steps from starting 3-nitrobenzenesulfonyl chloride and *o*-anisidine. Thus, 10.0 g (45.0 mmol) of 3-nitrobenzenesulfonyl chloride and 12.6 g (99.1 mmol) of *o*-anisidine were combined in acetonitrile as described above for the preparation of **278**. The

analogous work up gave on recrystallization from ethanol 13.2 g (95% yield) of *N*-(2-methoxyphenyl)-3-nitrobenzenesulfonamide (**293**): mp 133-134 °C. Anal. calcd for $C_{13}H_{12}N_2O_5S$: C, 50.64; H, 3.92; N, 9.09. Found: C, 50.69; H, 3.93; N, 9.13. The reduction reaction was analogous to the procedure described by Ulmann for the preparation of *N*-phenyl-2-aminobenzenesulfonamide from the corresponding nitro compound.[64] Thus, 6.16 g (20 mmol) of **293**, 15.0 g (60 mmol) of $SnCl_2 \cdot H_2O$, 15 mL of concentrated HCl and 30 mL of ethanol were combined under an inert atmosphere at 0°C in a 125 mL round bottom flask. The flask was equipped with a magnetic stirring bar and a reflux condenser. The mixture was allowed to warm to room temperature and then was gently heated to reflux. After 20 min the yellow color of **293** had dissipated and the mixture was cooled in an ice bath. The ethanol was removed under reduced pressure and the residue treated with 100 mL of H_2O. The solution was made basic, pH = 12, by the addition of solid NaOH with cooling. The suspension was filtered through a coarse glass frit. The aqueous solution was acidified to pH = 6 and then extracted with CH_2Cl_2 (3x100 mL). The combined CH_2Cl_2 extracts were dried, filtered and concentrated to yield 4.25 g of an oil that solidified on standing. The solid was recrystallized from toluene to yield 3.61 g (65% yield) of **291**: mp 109.5-111.5 °C. Anal. calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.06; N, 10.05. Found: C, 56.00; H, 5.06; N, 10.05.

General Preparation of *N*-acyl-2-iodobenzenesulfonamindes. The *N*-acyl-2-iodobenzenesulfonamindes used in this study were prepared by refluxing the corresponding 2-iodobenzensulfonamide in a large excess of the appropriate anhydride or acid chloride. The preparation of *N*-acetyl-2-iodobenzenesulfonamide **313a** is representative. Thus, 19.5 g (68.9 mmol) of 2-iodo-benzenesulfonamide (**1a**) and 40 mL of acetic anhydride were combined in a 100 mL round bottom flask. The flask was equipped with a magnetic stirring bar and a reflux condenser. The mixture was then heated to reflux in a constant temperature oil bath; the sulfonamide dissolves on boiling. The solution was refluxed for 4 h and then allowed to cool without stirring to room temperature. The crystalline solid that separated was collected by vacum filtration. The solid was rinsed with toluene (3x15 mL) and dried *in vacuo* to yield 21.5 g (96% yield) of **313a**. The material thus obtained could be used without further purification. An analytical sample was obtained by recrystallization from 80% ethanol: mp 203.5-206 °C (dec); IR (KBr) 3270, 1740, 1450, 1355, 1170, 880, 765; ^{1}HNMR (acetone-d_6) δ 2.09 (s, 3 H),

7.33-8.27 (m, ArH, 4 H); ^{13}CNMR (acetone-d_6) δ 23.0, 92.2, 129.0, 133.3, 134.8, 142.4, 143.1, 168.3. Anal. calcd for $C_8H_8INO_3S$: C, 29.55; H, 2.48; N, 4.31. Found: C, 29.57; H, 2.49; N, 4.31.

***N*-Benzoyl-2-iodobenzenesulfonamide (310)** was prepared from benzoyl chloride and **1a** in 85% yield. An analytical sample was obtained upon recrystallization from $CHCl_3$-hexane: mp 161-171 °C; IR (KBr) 3300-3200, 1710, 1410, 1350, 1175, 840, 765; ^{1}HNMR ($CDCl_3$) δ 7.26-8.49 (m, ArH, 9 H), 9.69 (s br, NH, 1 H); ^{13}CNMR ($CDCl_3$) δ 92.2, 128.0, 128.6, 129.0, 130.9, 133.4, 133.6, 134.5, 140.8, 142.3, 164.1. Anal calcd for $C_{13}H_{10}INO_3S$: C, 40.32.10; H, 2.60; N, 3.61. Found: C, 40.20; H, 2.58; N, 3.46.

***N*-Acetyl-2-iodo-3,5-dimethylbenzenesulfonamide (326)** was prepared from acetic anydride and **256** in 88% yield. An analytical sample was obtained upon recrystallization from ethanol: mp 209.5-211.5 °C;IR (KBr) 3200-2800, 1690, 1480, 1375, 1185, 885; ^{1}HNMR (acetone-d_6) δ 2.06 (s, 3 H), 2.36 (s, 3 H), 2.49 (s, 3 H), 7.42 (s, ArH, 1 H), 7.90 (s, ArH, 1 H); ^{13}CNMR ($CDCl_3$) δ 20.74, 23.5, 30.0, 95.0, 131.3, 135.4, 138.7, 141.3, 145.1, 167.7. Anal calcd for $C_{10}H_{12}INO_3S$: C, 34.01; H, 3.43; N, 3.97. Found: C, 34.01; H, 3.45; N, 3.91.

***N*-Propionyl-2-iodobenzenesulfonamide (337)** was prepared from propionic anhydride and **1a** in 92% yield. An analytical sample was obtained upon recrystallization from $CHCl_3$/hexane: mp 155-157 °C; IR (KBr) 3200-2600, 1655, 1440, 1315, 1150, 840, 745; ^{1}HNMR (acetone-d_6) δ 1.00 (t, J = 7.4 Hz, 3 H), 2.43 (q, J = 7.4 Hz, 2 H), 7.33-8.29 (m, ArH, 4 H); ^{13}CNMR ($CDCl_3$) δ 8.2, 29.6, 92.1, 128.6, 133.0, 134.5, 139.7, 140.8, 142.4, 171.5. Anal calcd for $C_9H_{10}INO_3S$: C, 31.87.10; H, 2.96; N, 4.08. Found: C, 31.85; H, 2.96; N, 4.08.

***N*-Phenylacetyl-2-iodobenzenesulfonamide (343)** was prepared from phenylacetyl chloride and **1a** in 80% yield. An analytical sample was obtained upon recrystallization from $CHCl_3$/hexane: mp 151-153.5 °C; IR (KBr) 3350-3150, 1725, 1480, 1345, 1180, 885, 775; ^{1}HNMR ($CDCl_3$) δ 3.65 (s, 2 H), 7.22-8.36 (m, ArH, 9 H), 8.55 (s br, NH, 1 H); ^{13}CNMR ($CDCl_3$) δ 43.8, 91.9, 128.2, 128.5, 129.4, 129.6, 131.9,

133.2, 134.5, 140.6, 142.2, 167.9. Anal calcd for $C_{14}H_{12}INO_3S$: C, 41.91.10; H, 3.02; N, 4.49. Found: C, 42.03; H, 3.03; N, 4.48.

***N*-*i*-Butyryl-2-iodobenzenesulfonamide (346)** was prepared from isobutyric anhydride and **1a** in 75% yield. An analytical sample was obtained upon recrystallization from $CHCl_3$/hexane: 155.5-157.5 mp °C; IR (KBr) 3300-3100, 1705, 1450, 1365, 1190, 835, 780; ^{1}HNMR ($CDCl_3$) δ 1.15 (d, J = 7.0 Hz, 6 H), 2.52 (m, J = 6.9 Hz, 1 H), 7.24-8.39 (m, ArH, 4 H), 9.45 (s br, NH, 1 H); ^{13}CNMR ($CDCl_3$) δ 18.6, 35.8, 91.9, 128.6, 133.2, 134.5, 140.6, 142.4, 174.6. Anal calcd for $C_{10}H_{12}INO_3S$: C, 34.01; H, 3.43; N, 3.97. Found: C, 34.07; H, 3.43; N, 3.97.

***N*-*i*-Butyryl-2-iodo-3,5-dimethylbenzenesulfonamide (349)** was prepared from isobutyric anhydride and **256** in 90% yield. An analytical sample was obtained upon recrystallization from ethanol: mp 209.5-211.5 °C; IR (KBr) 3275, 1730, 1430, 1350, 1155, 905; ^{1}HNMR ($CDCl_3$) δ 1.15 (d, J = 6.9 Hz, 6 H), 2.38 (s, 3 H), 2.50 (m, COCH and $ArCH_3$, 4 H), 7.28 (m, ArH, 1 H), 8.00 (m, ArH, 1 H), 8.69 (s br, NH, 1 H); ^{13}CNMR (acetone-d_6) δ 18.9, 20.4, 35.6, 95.1, 131.8, 135.4, 139.0, 143.2, 145.3, 175.1. Anal calcd for $C_{12}H_{16}INO_3S$: C, 37.80; H, 4.23; N, 3.67. Found: C, 37.87; H, 4.27; N, 3.65.

1-(*N*-Benzoyl-2-sulfamoylphenyl)-3,4-dimethylbutanone (311). To a stirred solution of 10.3 mmol of KNH_2 in 300 mL of liquid NH_3 was added 1.04 g (10.3 mmol) of 3,3-dimethylbutanone and 1.00 g (2.58 mmol) of **310**. The homogeneous mixture was irradiated for 30 min. The residue obtained upon quenching the reaction and evaporation of the NH_3 was dissolved in H_2O (80 mL) along with 1 g of sodium thiosulfate. The solution was acidified to pH = 3 by the addition of 1 N HCl. The cloudy solution was extracted with CH_2Cl_2 (3x80 mL). The combined organic extracts were dried, filtered and concentrated. The resulting clear colorless oil, 0.85 g (100% yield), was dissolved in warm ether. On standing a white crystalline solid deposited and was collected to yield 0.72 g (85%) of **311**. An analytical sample was obtained by recrystallization from toluene: mp 157-159 °C; IR (KBr) 3260, 1710, 1425, 1365, 1180, 820, 775 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.25 (s, 9 H), 4.50 (s, 2 H), 7.14-8.33 (m, ArH, 9 H), 9.30 (s br,

NH, 1 H); ^{13}CNMR ($CDCl_3$) δ 26.7, 43.0, 44.4, 127.8, 128.8, 131.3, 131.8, 132.9, 133.2, 133.7, 135.0, 138.0, 164.3, 214.3; mass spectrum (CI mode), *m/z* (rel intensity) 360 (30), 275 (6), 262 (12), 239 (17) 122 (100), 105 (38). Anal. calcd. for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.40; H, 5.88; N, 3.83.

***t*-Butyl 2-(*N*-Acetylylsulfamoyl)phenylacetate (312).** To a stirred solution of 31.0 mmol of KNH_2 in 300 mL of liquid NH_3 was added 3.60 g (31.0 mmol) of *t*-butyl acetate and 3.00 g (7.75 mmol) of **310**. The homogeneous mixture was irradiated for 30 min. The residue obtained upon quenching the reaction and evaporation of the NH_3 was dissolved in H_2O (80 mL) along with 1 g of sodium thiosulfate. The solution was acidified to pH = 3 by the addition of 1 N HCl. The cloudy solution was extracted with CH_2Cl_2 (3x80 mL). The combined organic extracts were dried, filtered and concentrated. Flash chromatography (CH_2Cl_2/CH_3CN, 85:15) gave an oil which when dissolved in warm ether separated as a white crystalline solid on standing. The solid was collected to yield 0.2.44 g (84%) of **312**. Recrystallization from toluene gave 2.20 g (75% yield) of **312**: mp 168-171 °C; IR (KBr) 3275, 1740, 1715, 1420, 1350, 1175, 820, 775 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.33 (s, 9 H), 4.13 (s, 2 H), 7.33-7.83 (m, ArH, 9 H), 9.53 (s br, NH, 1 H); ^{13}CNMR ($CDCl_3$) δ 27.9, 40.8, 82.2, 127.9, 128.0, 128.7, 131.8, 133.1, 133.2, 133.6, 133.9, 137.8, 164.2, 171.3; mass spectrum (CI mode), *m/z* (rel intensity) 320 (18), 262 (16), 122 (100), 105 (23). Anal. calcd. for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73. Found: C, 60.68; H, 5.65; N, 3.73.

Dark Reaction of *N*-Benzoyl-2-iodobenzenesulfonamide (310) with the Enolate Anion Derived from *t*-Butyl Acetate in Liquid NH_3. A procedure analogous to the preparation of **312** was followed. Thus, to a stirred solution of 10.3 mmol of KNH_2 in 300 mL of liquid NH_3 was added 1.20 g (10.3 mmol) of *t*-butyl acetate and 1.00 g (2.58 mmol) of **310**. The photoreaction tube was left to stir for 45 min with the photoreactor turned off. The ^{1}HNMR of the crude reaction mixture indicated a 6:4 mixture of **310** and **312** respectively.

Dark Reaction of *N*-Benzoyl-2-iodobenzenesulfonamide (310) and the Enolate Anion Derived From *t*-Butyl Acetate in the Presence of Di-*tert*-

butyl Nitroxide. A procedure analogous to the preparation of **312** was followed. Thus, to a stirred solution of 10.3 mmol of KNH_2 in 300 mL of liquid NH_3 was added a mixture of 1.20 g (10.3 mmol) of *t*-butyl acetate and 20 mg (.13 mmol) of DTBN. The mixture was allowed to stir for 5 min prior to the introduction of 1.00 g (2.58 mmol) of **310**. The photoreaction tube was left to stir for 45 min with the photoreactor turned off. The ^{1}HNMR of the crude reaction mixture indicated a 9:1 mixture of **310** and **312** respectively.

***t*-Butyl 2-(*N*-Acetylsulfamoyl)phenylacetate (314).** To a stirred solution of 12.3 mmol of KNH_2 in 300 mL of liquid NH_3 was added 1.43 g (12.3 mmol) of *t*-butyl acetate and 1.00 g (3.08 mmol) of **313a**. The homogeneous mixture was irradiated for 21 min. A workup procedure analogous to the isolation of **312** was followed. The yield of **314** after chromatography and recrystallization from ether was 0.73 g (76%). Recrystallization from toluene gave 0.62 g (65% yield) of **314**: mp 116-118 °C; IR (KBr) 3300, 1740, 1345, 1165, 765 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.44 (s, 9 H), 2.07 (s, 3 H), 4.10 (s, 2 H), 7.26-8.25 (m, ArH, 4 H), 9.15 (s br, NH, 1 H); ^{13}CNMR ($CDCl_3$) δ 23.2, 28.0, 40.5, 82.2, 127.9, 131.3, 133.2, 133.7, 134.0, 137.6, 168.2, 171.1; mass spectrum (CI mode), *m/z* (rel intensity) 314 (20), 296 (16), 258 (100), 240 (40), 198 (100). Anal. calcd. for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47. Found: C, 53.72; H, 6.12; N, 4.46.

Ethyl α-(*N*-Acetyl-2-sulfamoylphenyl)phenylacetate (315). To a stirred solution of 24.6 mmol of KNH_2 in 400 mL of liquid NH_3 was added 4.04 g (24.6 mmol) of ethyl phenylacetate and 2.00 g (6.16 mmol) of **313a**. The homogeneous mixture was irradiated for 30 min. The residue obtained on quenching the reaction and evaporation of the NH_3 was extracted with hot hexanes (2x150 mL). The residue was then dissolved in H_2O (80 mL) along with 1 g of sodium thiosulfate. The solution was acidified to pH = 3 by the addition of 1 N HCl. The cloudy solution was extracted with CH_2Cl_2 (3x80 mL). The combined organic extracts were dried, filtered and concentrated. Flash chromatography ($CHCl_3$/EtOH, 97:3) gave 30 mg of **316** and 1.13 g (51% yield) of **315**. The physical and spectral properties of **316** are reported below. Recrystallization from ether of **315** gave 0.85 g (38% yield). A second recrystallization from toluene of **315** gave an analytical sample: mp 155-157 °C; IR (KBr) 3300-3175, 1760, 1705, 1480, 1180

cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz,3 H), 1.71 (s, 3 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 6.18 (s, 1 H), 7.21-8.27 (m, ArH, 9 H), 8.63 (s br, NH, 1 H); ^{13}CNMR ($CDCl_3$) δ 14.0, 22.9, 52.2, 61.8, 127.7, 128.8, 131.6, 134.0, 136.7, 137.4, 137.7, 167.7, 172.0; mass spectrum (CI mode), *m/z* (rel intensity) 362 (100), 316 (16), 303 (37), 274 (50), 239 (45). Anal. calcd. for $C_{18}H_{19}NO_5S$: C, 59.82; H, 5.30; N, 3.88. Found: C, 59.75; H, 5.29; N, 3.84.

Ethyl 2-(*N*-Acetyl-2-sulfamoylphenyl)phenylacetate (**316**) exhibited the following physical and spectral characteristics: mp 221-222 °C; IR (KBr) 3250-3150, 1740, 1700, 1460, 1320, 1180, 778 cm^{-1}; ^{1}HNMR (acetone-d_6) δ 1.09 (t, *J* = 9.6 Hz,3 H), 1.93 (s, 3 H), 3.28 (d, *J* = 21.4, 1 H), 3.44 (d, *J* = 21.4, 1 H), 3.93 (q, *J* = 9.3 Hz, 2 H), 7.12-8.28 (m, ArH, 8 H); ^{13}CNMR ($CDCl_3$) δ 11.1, 23.47, 39.7, 60.9, 127.0, 128.9, 130.5, 130.9, 133.6, 134.4, 138.8, 139.5, 140.5, 168.7, 171.7; mass spectrum (CI mode), *m/z* (rel intensity) 362 (100), 320 (30), 303 (17), 274 (10), 241 (60).

Methanolysis of Ethyl α-(*N*-Acetyl-2-sulfamoylphenyl)phenylacetate (315). A 100 ml round bottom flask was equipped with a magnetic stirring bar and a reflux condensor. Into the flask was placed 1.10 g (3.05 mmol) of **315** and 50 ml of saturated methanolic HCl. The mixture was left to stir overnight at room temperature. The solution was concentrated under reduced pressure. Flash chromatography, eluting first with CH_2Cl_2 gave 0.29 g (33% yield) of **321** as a solid. The solid was recrystallized from CCl_4 to yield 0.27 g (31%) of white needles: mp 140-142 °C The spectral characteristics of **321** are presented below. Further elution of the column with CH_2Cl_2/ CH_3CN (9/1) gave 0.49 g (53% yield) of **182** as a clear colorless oil which soldified on standing. Recystallization from hexane-CCl_4 gave 0.42 g (45% yield) of **182** as white needles: mp 99-104 °C.

(±)-3-Methoxy-4-phenyl-4*H*-1,2-benzothiazine 1,1-Dioxide (**321**) exhibited the following physical and spectral characteristics: mp 140-142 °C; IR (KBr) 1620, 1330, 1180 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 3.91 (s, 3 H), 4.94 (s, 1 H), 7.16-8.05 (m, ArH, 9 H); ^{13}CNMR ($CDCl_3$) δ 47.4, 56.0, 124.4, 128.3, 128.8, 128.9, 129.3, 132.6, 133.9, 134.0, 137.0, 171.6; mass spectrum (70 eV), *m/z* (rel intensity) 287 (60), 208 (16), 194 (10), 180 (20), 165 (100). Anal. calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.88. Found: C, 62.79; H, 4.59; N, 4.91.

General Procedure for the Reactions of The Potassium Dianions Derived From *N*-Acyl-2-iodobenzensulfonamides in Liquid NH_3. A solution of KNH_2 in liquid NH_3 was prepared in a manner analogous to the photostimulated reactions described above. The *N*-acyl-2-iodobenzensulfonamide was cautiously added in portions to a stirred solution of four equivalents of KNH_2 in 400 mL of liquid NH_3. The solution was allowed to stir for the indicated period and then quenched by transferring to a 2-litre beaker containing excess NH_4Cl. The NH_3 solution was evaporated in a fume hood and the resulting residue was dissolved in H_2O (100 mL). One gram of sodium thiosulfate was added to suppress the formation of iodine. The aqueous mixture was acidified to pH = 3 by the addition of 10% HCl. The solution was then extracted with CH_2Cl_2 (3x80 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Isolation of the product or products was as indicated.

3,4-Dihydro-1,2-benzothiazin-3(2*H*)-one 1,1-Dioxide (13d). To a stirred solution of 24.6 mmol of KNH2 in liquid NH_3 was added 2.0 g (6.15 mmol) of *N*-acetyl-2-iodo-benzenesulfonamide **313a**. The heterogeneous mixture was left to stir for 30 min. Concentration of the organic extracts obtained from the work up described above gave 1.03 g (83% yield) of **13d**. Recrystallization from ethanol resulted in 0.61 g (50 % yield): mp 197-201 °C, lit[11] mp 202-204 °C; IR (KBr) 3200-2700, 1700, 1320, 1190, 770 cm^{-1}; ^{1}HNMR (acetone-d_6) δ 4.07 (s, 3 H), 7.58-7.92 (m, ArH, 4 H); ^{13}CNMR (acetone-d_6) δ 39.1, 122.3, 128.5, 129.8, 132.1, 133.7, 137.1, 169.2.

Reaction of the Potassium Dianion Derived From *N*-Acetyl-2-iodobenzenesulfonamide (313a) in Liquid NH_3 in the Presence of Di-*tert*-butyl Nitroxide. A procedure analogous to the preparation of **13d** was followed with the exception of the addition of 13 mg (15 mole%) of DTBN. The reaction was allowed to stir for 8 min before quenching. The ^{1}HNMR spectrum of the solid obtained upon concentration of the organic extracts indicated a 3:5 mixture of **313a** and **13d** respectively. A control experiment in which the reaction was run under analogous conditions (i.e. 8 min) without the added DTBN gave a 1:10 ratio of **313a** and **13d** respectively.

Reaction of the Potassium Dianion Derived From *N*-Acetyl-2-iodo-3,5-dimethylbenzenesulfonamide (326) in Liquid NH_3 To a stirred solution of

22.7 mmol of KNH_2 in 300 mL of liquid NH_3 was added 2.00 g (5.67 mmol) of **326**. The heterrogenous mixture was allowed to stir for 70 min before quenching. The standard work up procedure was followed. The combined CH_2Cl_2 extracts were washed with 5% $NaHCO_3$ (2x30 mL) before drying. An attempt at chromatography of the material obtained from concentration of the CH_2Cl_2 extracts was unsuccessful. The bicarbonate extracts were acidified and extracted with CH_2Cl_2 (3x80 mL). The combined CH_2Cl_2 extracts were concentrated to a volume of 15 mL. The solution was filtered to yield 0.18 g of **258**. The solid was recrystallized from ethanol to yield an analytical sample of **258**: mp 255-258 °C. Attempts at further purification of the mother liquor were unsuccessful. An alternate workup invovled quenching the reaction by carefully transferring the solution to a 1000 ml three-neck round bottom flask immerced in a dry ice acetone bath. To the cooled (-78°C) NH_3 solution was carefully added a slurry of 3.0 g of NH_4Cl in 120 mL of absolute ethanol. The dry ice bath was removed and the stirred solution was left to concentrate. The resulting ethanolic NH_3 solution was left to stir overnight at 45°C and then heated to reflux for 3 h. The solution was concentrated under reduced pressure and the residue treated analogous to the previous workup of this reaction. Flash chromatography (CH_2Cl_2/CH_3CN, 95:5)) of the bicarbonate insoluable extracts gave the following products: 0.15 g (9% yield) of **256**, mp 161-163 °C; 0.19g (18% yield) of **257**, mp 132-134 °C; and 0.13 g (12% yield) of **327**, mp 125-127 °C. The spectral characteristics of **327** are presented below. Concentration the organic extracts of the acidified bicarbonate wash gave 0.29 g (23% yield) of **258** as an impure yellow solid. Recrystallization from ethanol gave 0.20g. (16% yield): mp 251-256.

2-Amino-3,4-dimethylbenzenesulfonamide (**327**) was recrystallized from toluene to yield 80 mg of a white solid: mp 125-127 °C; IR (KBr) 3550-3000, 1495, 1340, 1160 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.23 (s, 3 H), 2.70-4.90 (s br, NH, 2 H), 4.85 (s br, NH, 2 H), 7.68 (s, 1 H), 7.45 (s, 1 H); ^{13}CNMR ($CDCl_3$) δ 17.3, 20.2, 124.7, 126.0, 127.3, 136.1, 140.4; mass spectrum (70 eV), *m/z* (rel intensity) 200 (75), 183 (20), 118 (100), 104 (35), 90 (20).

Reaction of the Potassium Dianion Derived From *N*-Propionyl-2-iodobenzenesulfonamide (340) in Liquid NH_3. To a stirred solution of 29.5 mmol of KNH_2 in 300 mL of liquid NH_3 was added 2.50 g (7.37 mmol) of **340**. The heterogeneous mixture was allowed to stir for 2.5 h before quenching. The standard work

up procedure was followed. Concentration of the CH_2Cl_2 extracts gave 0.98 g of a solid. The ^{1}HNMR spectrum of the crude material indicated the presence of benzothiazine **341** and reduction product **342**. Flash chromatography (CH_2Cl_2/CH_3CN, 7:3) gave 0.37 g (24% yield) of **342** as an oil. An attempt at recrystallization of **342** was unsuccessful. The IR and ^{1}HNMR spectra of **342** were identical to an authentic sample prepared independently from benzenesulfonamide and propionic anhydride. Increasing the polarity of the solvent mixture failled to provide a sample of **341**.

Reaction of the Potassium Dianion Derived From *N*-Phenylacetyl-2-iodobenzenesulfonamide (343) in Liquid NH_3. To a stirred solution of 19.9 mmol of KNH_2 in 300 mL of liquid NH_3 was added 2.00 g (4.98 mmol) of **343**. The homogeneous mixture, which became heterogenous within 15 min, was allowed to stir for one hour before quenching. The standard work up procedure was followed. Concentration of the CH_2Cl_2 extracts gave 1.15 g of a solid. Flash chromatography (CH_2Cl_2/CH_3CN, 7:3) gave 0.85 g of a mixture of **344** and **345**. The mixture was dissolved in refluxing CCl_4 and the amination product **345** separated nearly quantitatively to yield 0.25 g (18% yield) of a white solid: mp 151-152 °C. The spectral characteristics of **345** are presented below. Concentration of the mother liquor gave 0.56 g (41% yield) of the reduction product **344** as an oil. Attempts at recrystallization of **344** were unsuccessful. The ^{1}HNMR spectrum of **344** was identical to that of an authentic sample prepared from benzene sulfonamide and phenylacetyl chloride.

N-(2-Aminobenzenesulfonyl)phenylacetamide (**345**) was recrystallized from toluene to yield an ananlytical sample: mp 151-152 °C; IR (KBr) 3550-3000, 1660, 1465, 1290, 1145, 765 cm^{-1}; ^{1}HNMR (acetone-d_6, D_2O) δ 3.71 (s, 2 H), 6.91-6.96 (m, ArH, 2 H), 7.26-7.31 (m, ArH, 5 H), 7.43 (m, ArH, 1 H), 7.65 (m, ArH, 1 H), 7.45 (s, 1H); ^{13}CNMR (acetone-d_6) δ 43.6, 118.7, 120.1, 127.8, 128.0, 129.4, 129.8, 134.9, 135.9, 155.1, 169.1; mass spectrum (CI mode), *m/z* (rel intensity) 291 (20), 274 (100), 118 (70), 104 (35), 91 (25).

Reaction of the Potassium Dianion Derived From *N*-*i*-butyryl-2-iodobenzenesulfonamide (346) in Liquid NH_3. To a stirred solution of 23.8 mmol of KNH_2 in 300 mL of liquid NH_3 was added 2.00 g (5.67 mmol) of **346**. The heterogeneous mixture was allowed to stir for 4 h before quenching. The standard work

up procedure was followed. The CH_2Cl_2 extracts were concentrated and then dissolved in ether. A solid separated as a fine precipitate and was collected on a glass frit to yield 0.52 g (38% yield) of **347**. The spectral and physical characteristics of **347** are presented below.. Flash chromatography (CH_2Cl_2/CH_3CN, 7:3) of the material obtained upon concentration of the mother liquor gave 0.33 g (26 % yield) of the reduction product **348**: mp 129-131 °C. The mixture melting point of **348** and an authentic sample was not depressed.

3-(1-Methylethyl)-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**347**) was recrystallized from toluene/isopropanol to yield an analytical sample: mp 194-196 °C, lit mp 193-194;[78] IR (KBr) cm^{-1}; ^{1}HNMR (acetone-d_6, D_2O) δ 1.27 (d, J = 6.8, 6 H), 2.85 (m,J = 6.8, 1 H), 7.30-7.83 (m, ArH, 4 H); ^{13}CNMR ($CDCl_3$) δ 20.0, 35.7, 117.8, 123.2, 124.4, 126.6, 133.2, 136.1, 136.1, 164.7.

Reaction of the Potassium Dianion Derived From *N*-*i*-butyryl-2-iodo-3,4-dimethylbenzenesulfonamide (349) in Liquid NH_3. To a stirred solution of 21.0 mmol of KNH_2 in 450 mL of liquid NH_3 was added 2.00 g (5.25 mmol) of **349**. The heterogeneous mixture was allowed to stir for 15 min before quenching. The standard work up procedure was followed. The CH_2Cl_2 extracts were concentrated to yield 1.09 g of a solid. The ^{1}HNMR spectrum of the crude product indicated a 6:4 mixture of **350** and **351** respectively. The crude material was dissoloved in hot ethyl acetate. On cooling, a crystaline solid separated and was collected on a glass frit to yield 0.21 g (15% yield) of **350**: mp 220-222 °C (spectral properties below). Flash chromatography (CH_2Cl_2/CH_3CN, 7:3) of the material obtained upon concentration of the mother liquor gave 0.26 g (20 % yield) of the reduction product **351**: mp 98-91°C; and 0.08g (3% yield) of **350.** The mixture melting point of an analytical sample of **351** obtained on recystalization from $CHCl_3/CCl_4$ and an authentic sample was not depressed: mp 102-104 °C.

Reaction of the Potassium Dianion Derived From *N*-*i*-butyryl-2-iodo-3,4-dimethylbenzenesulfonamide (349) in Liquid NH_3 in the Presence of DTBN. A procedure analogous to the reaction of the dianion derived from **349** was followed with the exception of the addition of 80 mg (10 mole%) of DTBN. The reaction was allowed to stir for 15 min before quenching. The ^{1}HNMR spectrum of the 1.06 g of

solid obtained upon concentration of the organic extracts indicated a 4:6 mixture of **350** and **351** respectively. The analogous workup gave yields of 23% for **350** and 23% for **351**.

Reaction of the Potassium Dianion Derived From *N*-*i*-butyryl-2-iodo-3,4-dimethylbenzenesulfonamide (349) in Liquid NH_3 in the Presence of Potassium Metal. A procedure analogous to the reaction of the dianion derived from **349** was followed with the exception of the addition of 20 mg (10 mole%) of potassium metal was added immediately preceding the introduction of **349**.. The reaction was allowed to stir for 15 min before quenching. The ^{1}HNMR spectrum of the 1.06 g of solid obtained upon concentration of the organic extracts indicated a 7:3 mixture of **350** and **351** respectively. The analogous workup gave yields of 25% for **350** and 20% for **351.**

***N*-(2-Amino-3,5-dimethylbenzenesulfonyl)methylpropanamide (350).** The combined samples of **350** were recrystallized from toluene to yield a white crystalline solid: mp 224-224 °C; IR (KBr) 3400-3200, 1660, 1545, 1345, 1175 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.31 (d, *J* = 6.9 Hz, 6 H), 2.23 (s, 3 H), 2.37 (s, 3 H), 2.67 (m, *J* =6.9 Hz) 4.93 (s br, NH, 2 H) 7.28 (s, ArH, 1 H), 7.53 (s br, NH, 1 H), 7.68 (s, ArH, 1 H) ; ^{13}CNMR ($CDCl_3$) δ 18.3, 19.6 (2 C), 20.6, 35.9, 126.9, 135.2, 135.7, 137.2, 138.7, 140.0, 176.5; mass spectrum (70 eV), *m/z* (rel intensity) 270 (5), 252 (40), 190 (70), 119 (100), 91 (35). Anal. calcd. for $C_{12}H_{18}N_2O_3S$: C, 53.30; H, 6.68; N, 10.36. Found: C, 53.14; H, 6.68; N, 10.32.

The Oxidation reaction of 3-(1-Methylethyl)-2*H*-1,2-benzothiazine 1,1-Dioxide (183d) with Sodium Perborate in Acetic Acid. Into a 100mL round bottom flask was placed 0.50 g of **183d** (2.24 mmol), 1.38 g (8.97 (mmol) of $NaBO_3 \cdot 4H_2O$ and 40 mL of glacial acetic acid. The flask was equipped with a reflux condensor and magnetic stirring bar. The reaction was heated overnight at 55 °C in a constant temperature oil bath. The condensor was replaced witha 6-inch fractionating column and the flask was shielded with a polycarbonate shield [caution]. The solvent was removed under reduced pressure at 25 °C. The residue was partitioned between $CHCl_3$ (3x30 mL) and saturated $NaHCO_3$. The combined $CHCl_3$ extracts were dried and then vacum filtered through a three inch plug of silica gel. The solution was concentrated to

yield 0.42 g (74%) of (±)-7a-(1-methylethyl)oxazirino[2,3-*b*][1,2]benzothiazin-7(2*H*)-one 2,2-dioxide (**236b**): mp 89-91 °C. An analytical sample was obtained by recrystallization from hexanes: mp 92-94 °C; IR (KBr) 1730, 1370, 1200, 780 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.02 (d, *J* = 6.8 Hz, 3 H), 1.20 (d, *J* = 6.8 Hz, 3 H), 2.96 (m, *J* =6.8 Hz, 1 H) 7.83-8.03 (m, ArH, 4 H) ; ^{13}CNMR ($CDCl_3$) δ 15.1, 19, 26.4, 86.2, 126.1, 127.9, 128.7, 134.0, 134.6, 135.7, 180.4; mass spectrum (CI mode), *m/z* (rel intensity) 254 (90), 240 (30), 190 (100), 184 (25), 85 (48). Anal. calcd. for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53. Found: C, 52.20; H, 4.39; N, 5.53.

(±)-7a-Methyloxazirino[2,3-*b*][1,2]benzothiazin-7(2*H*)-one 2,2-dioxide (236a). A procedure analogous to the reaction of **183d** with sodium perborate was followed. Thus, 1.00 g (5.12 mmol) of **183b** was treated 20.5 mmol of $NaBO_3$ in glacial acretic to yield 0.81 g (70%) of **236a**: mp 94-99 °C. An analytical sample was obtained by recrystallization from hexanes: mp 99.5-101.5 °C; IR (KBr) 1730, 1375, 1195, 765 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ1.91 (s, 1 H) 7.81-7.99 (m, ArH, 4 H) ; ^{13}CNMR ($CDCl_3$) δ 16.3, 82.8, 126.3, 127.0, 128.6, 134.4, 134.7, 135.9, 185.6; mass spectrum (CI mode), *m/z* (rel intensity) 226 (100), 212 (20), 184 (50), 162 (20). Anal. calcd. for $C_9H_7NO_4S$: C, 47.99; H, 3.13; N, 6.22. Found: C, 48.09; H, 3.13; N, 6.18.

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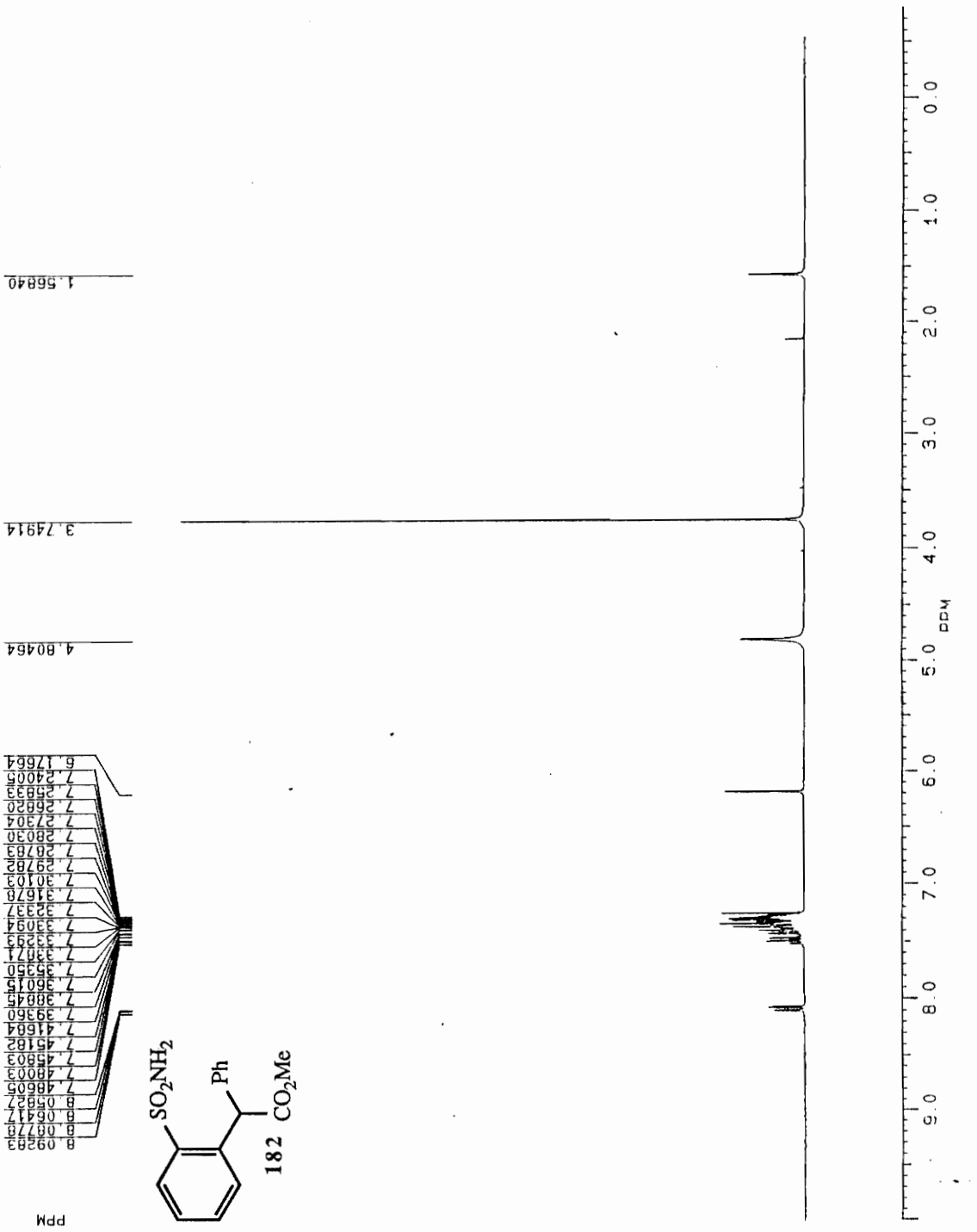
VII APPENDIX

SELECTED SPECTRA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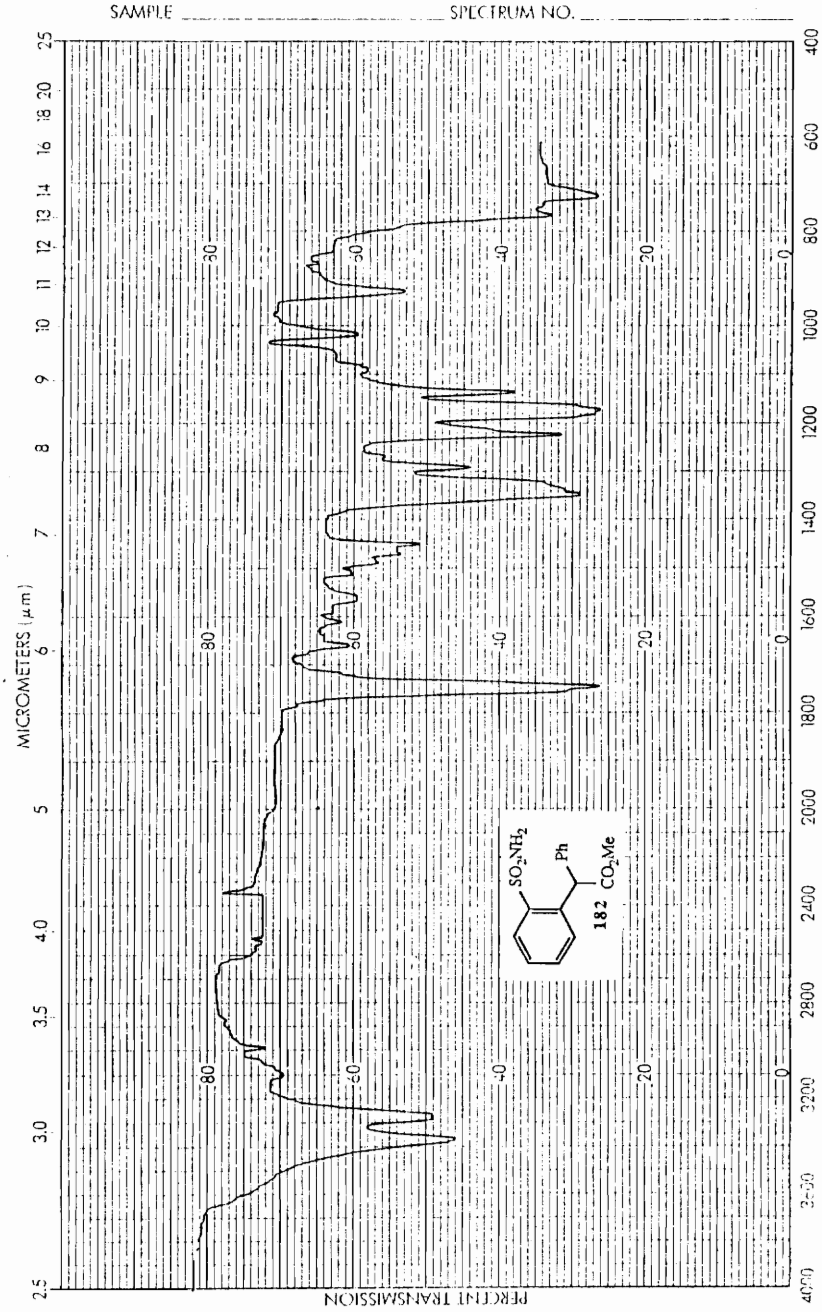
CO_2Me
182
PPM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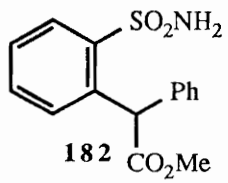
MICROMETERS (μm)
PERCENT TRANSMISSION
182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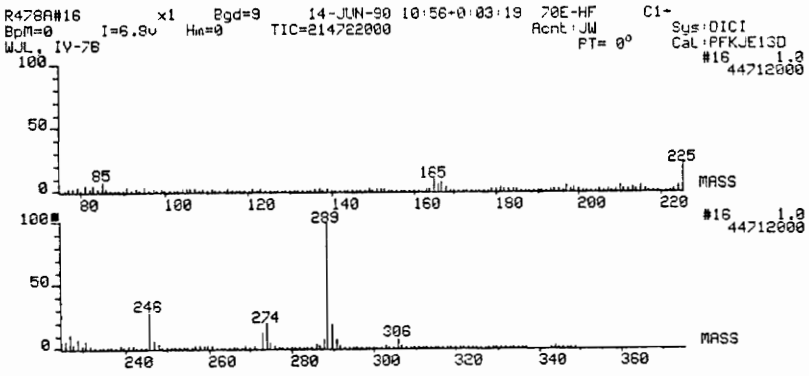
182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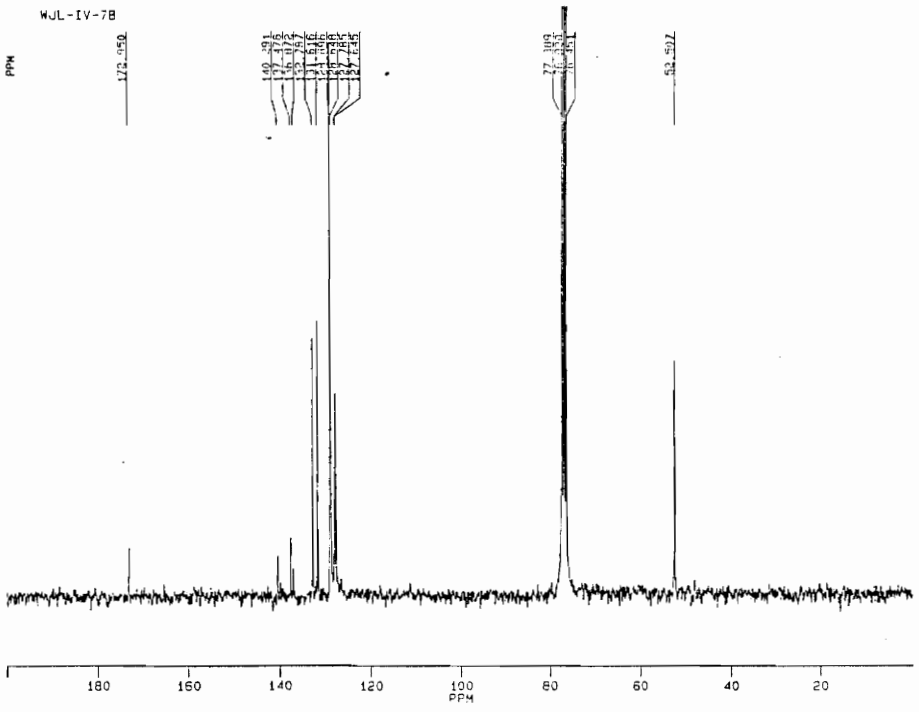
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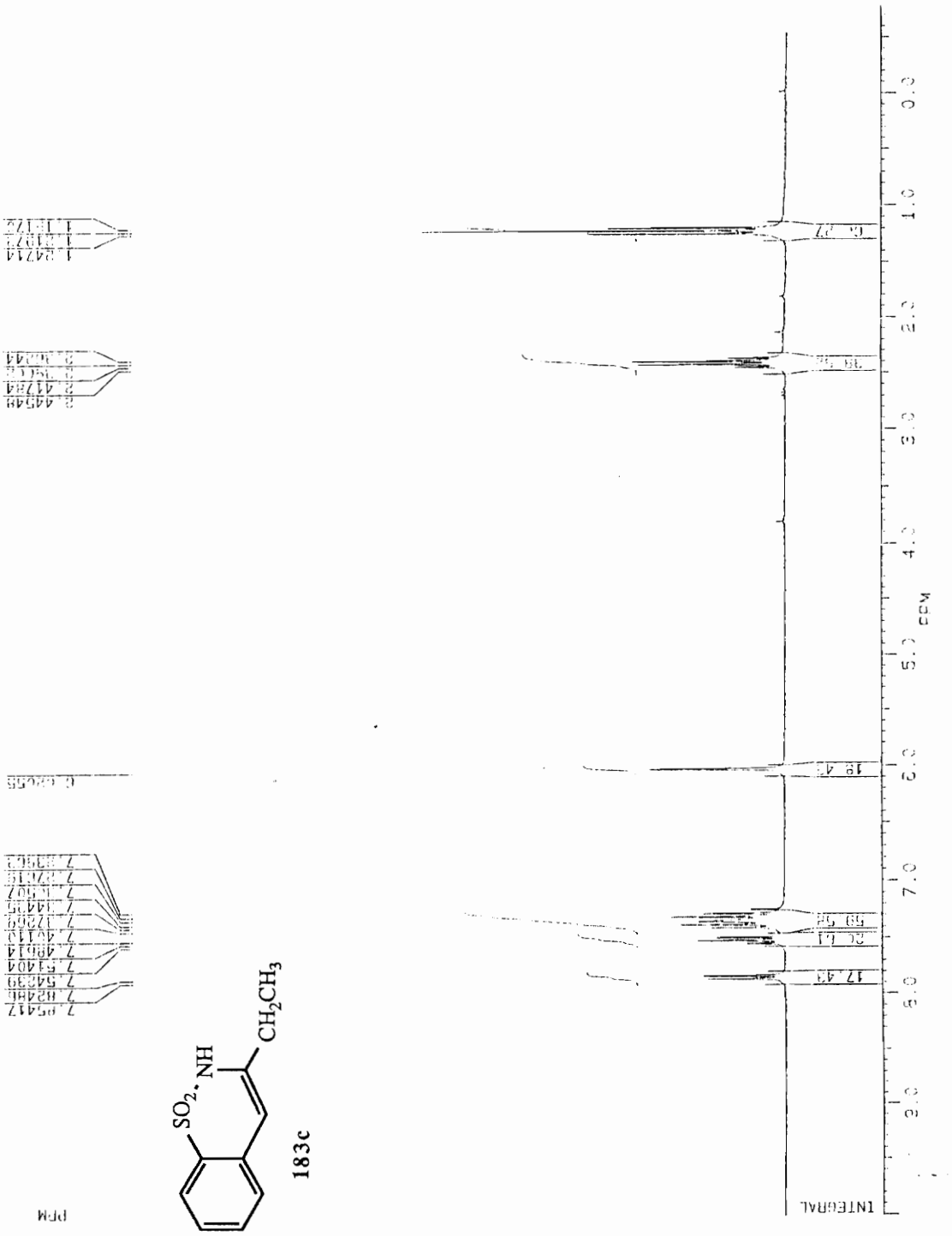
PPM



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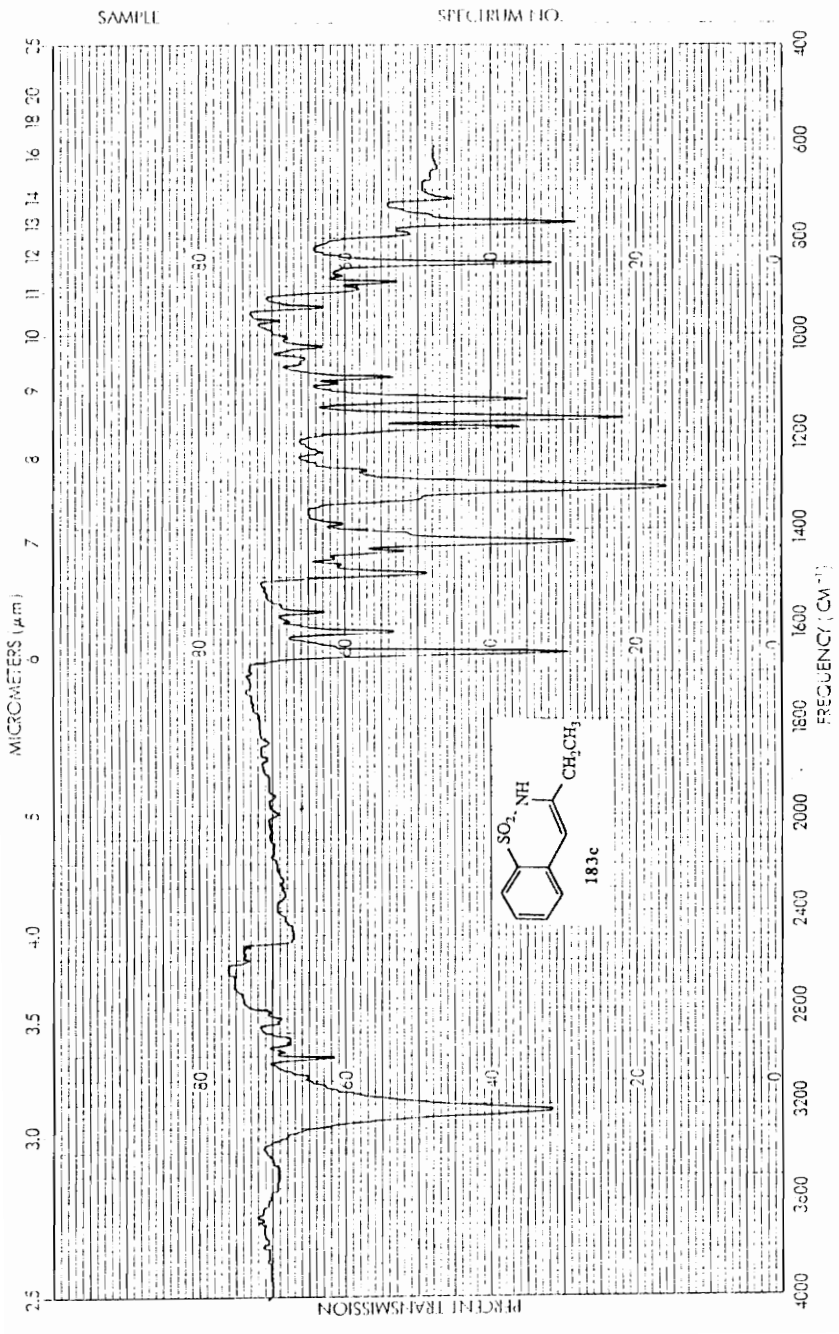
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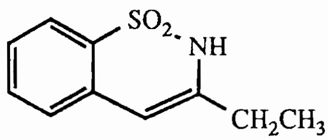
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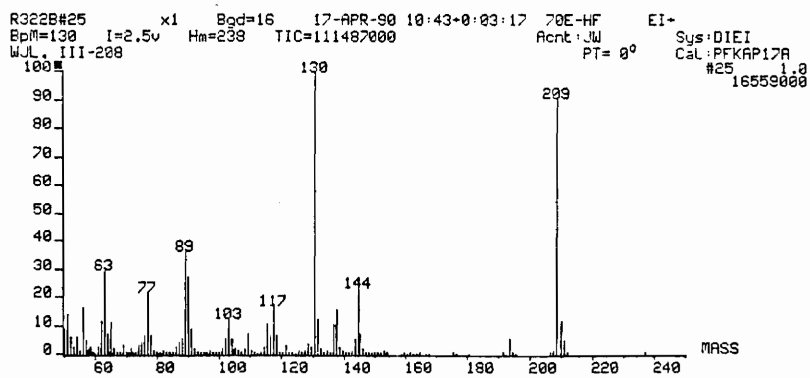
183c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209
89
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77
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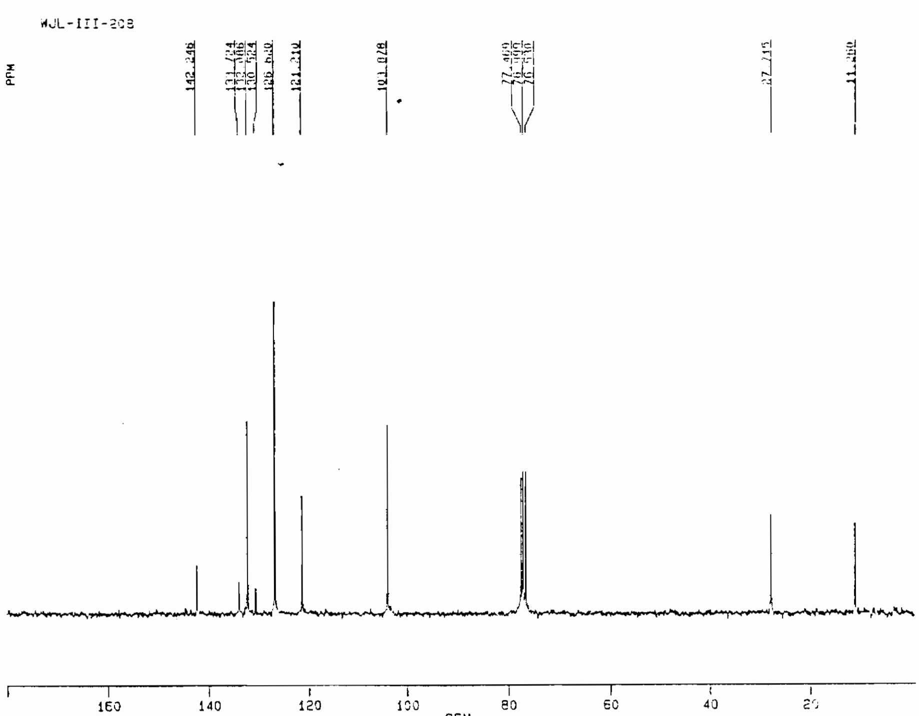
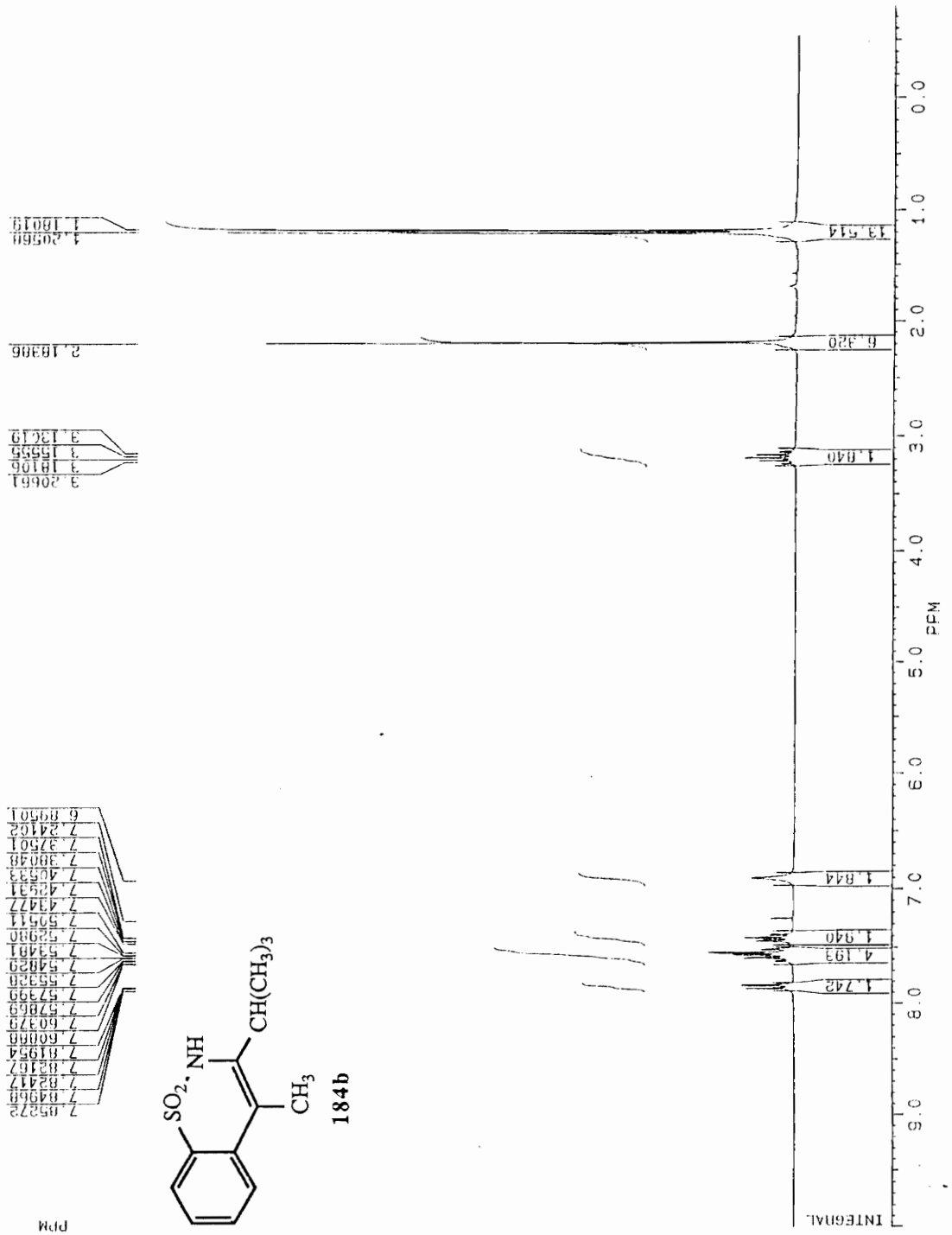
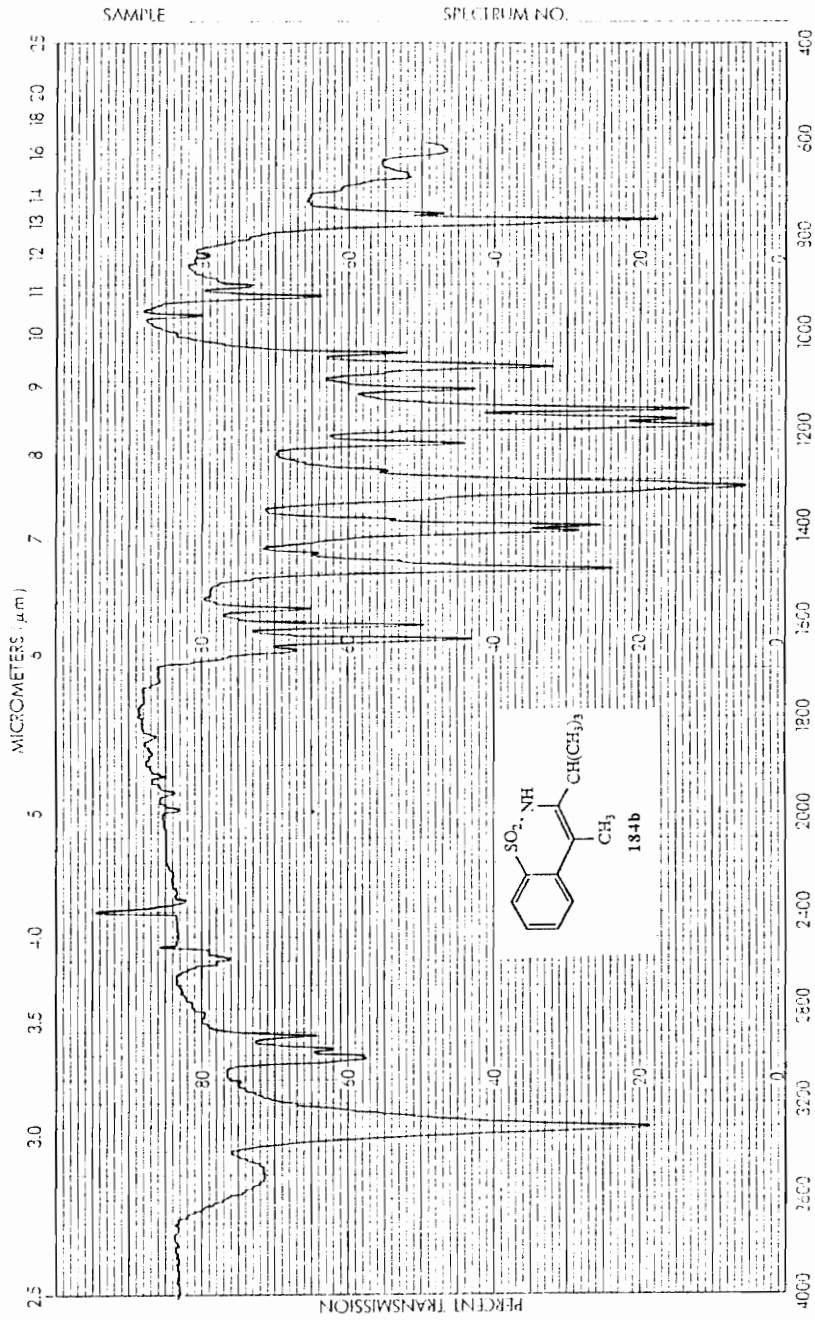
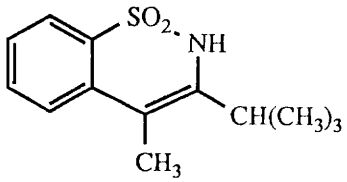
117
103
MASS


WJL-III-208
PPM
142.246
121.210
103.828
PPM

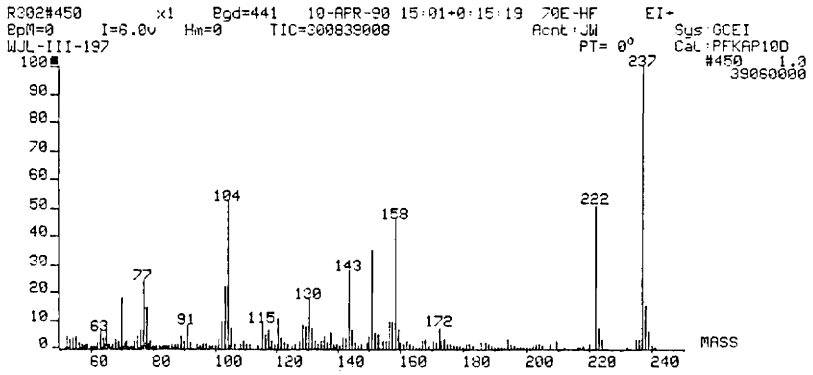

13.514
6.320
1.840
1.844
1.940
4.193
1.742
INTEGRAL
PPM
CH(CH3)3
NH
SO2
CH3

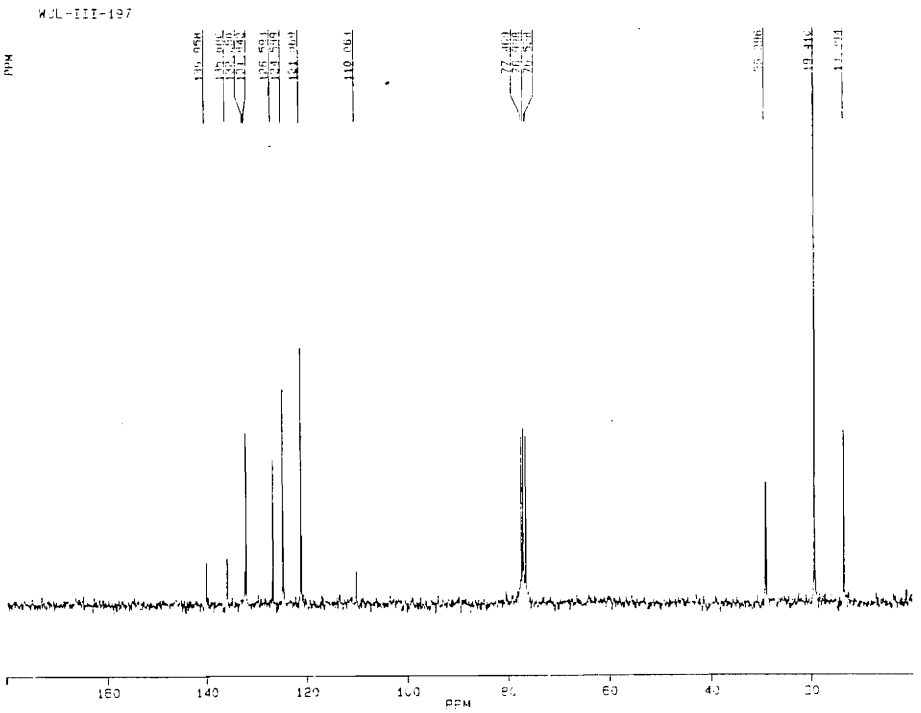
184b

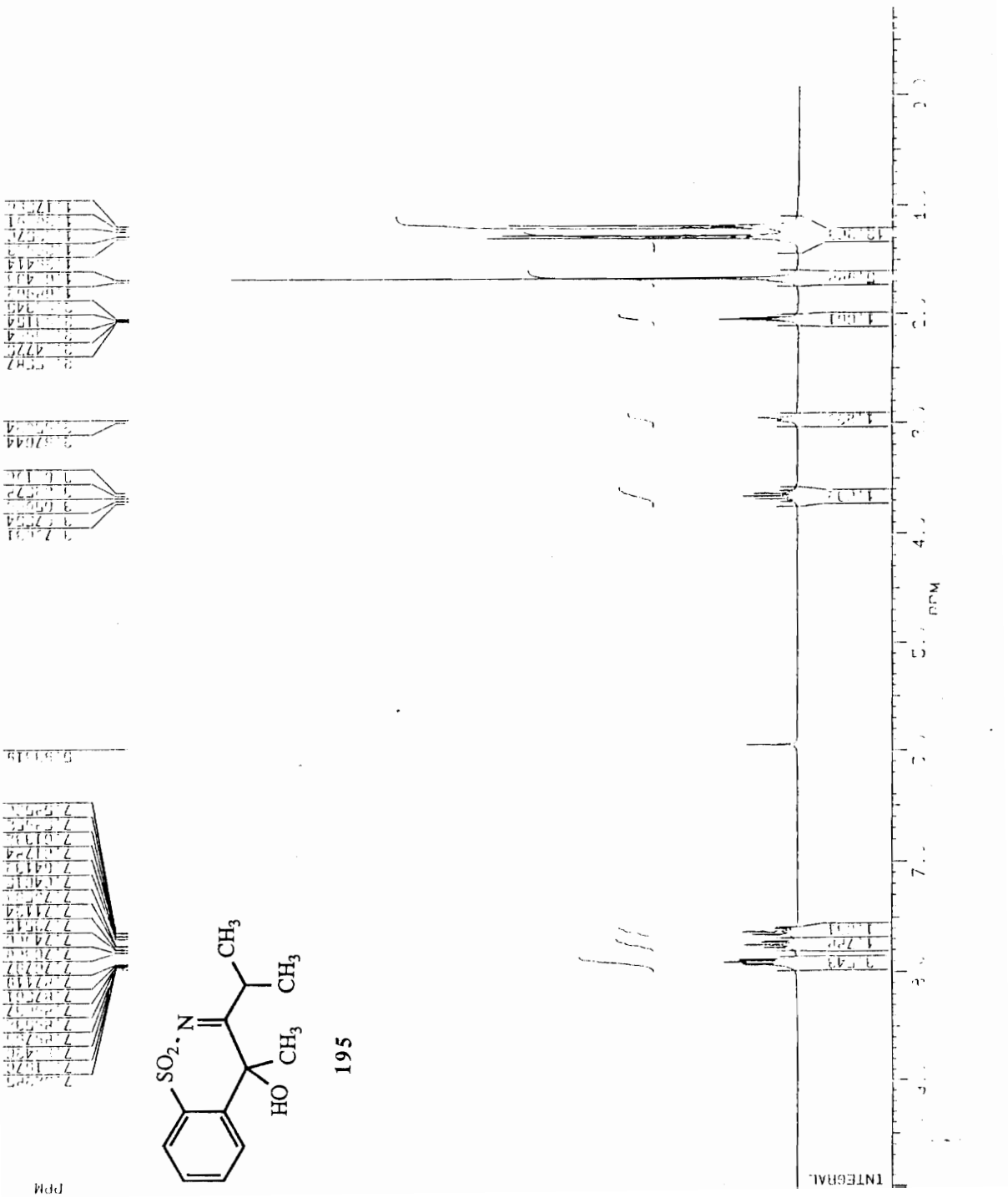

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
PERCENT TRANSMISSION
SO2, NH
CH(CH3)2
CH3
184b


SO2
NH
CH(CH3)3
CH3

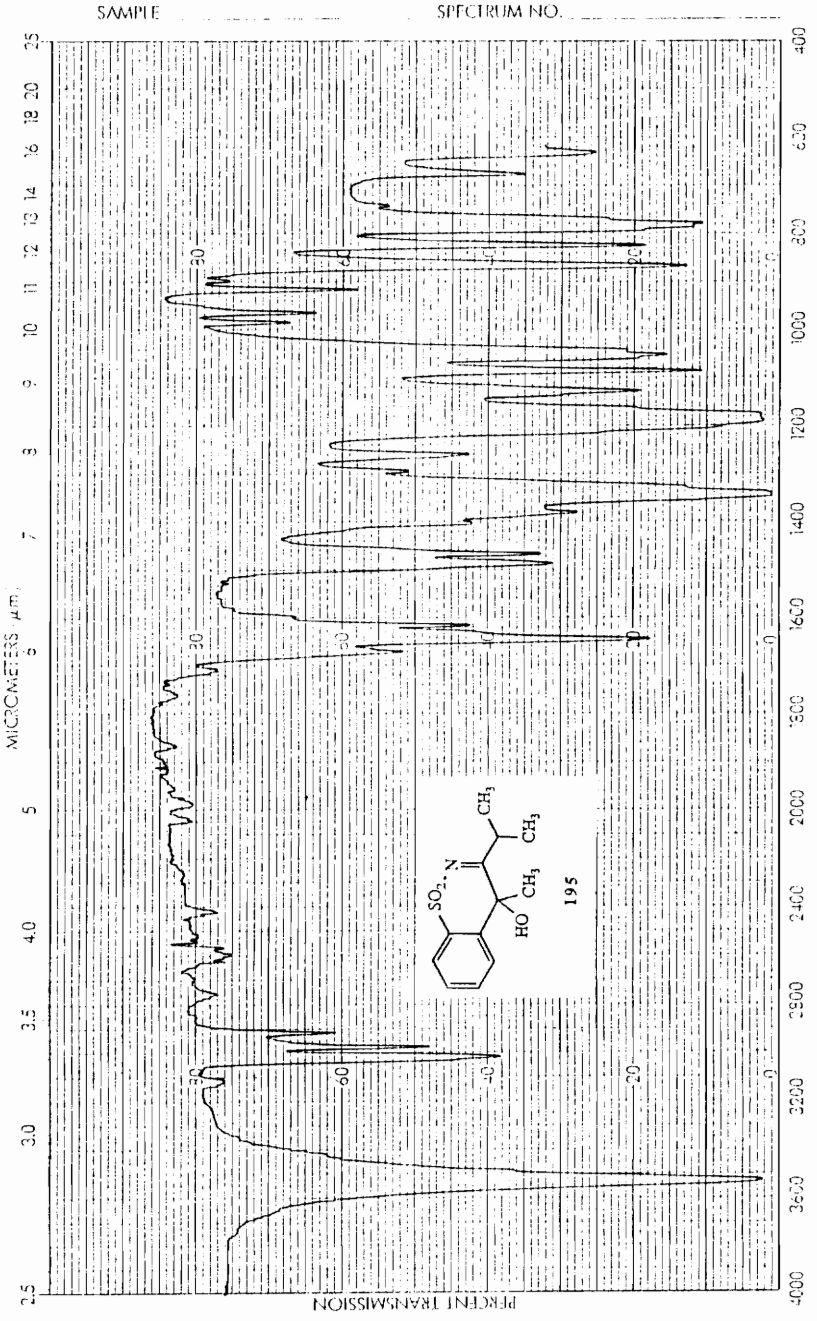
184b

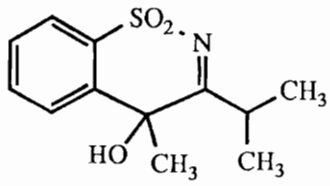

R302#450 x1 Bgd=441 10-APR-90 15:01+0:15:19 70E-HF EI+
BpM=0 I=6.0v Hm=0 TIC=300839008 Acnt:JW Sys:GCEI
WJL-III-197 PT= 0° Cal:PFKAP10D
#450 1.3
39050000
MASS


WJL-III-197
PPM

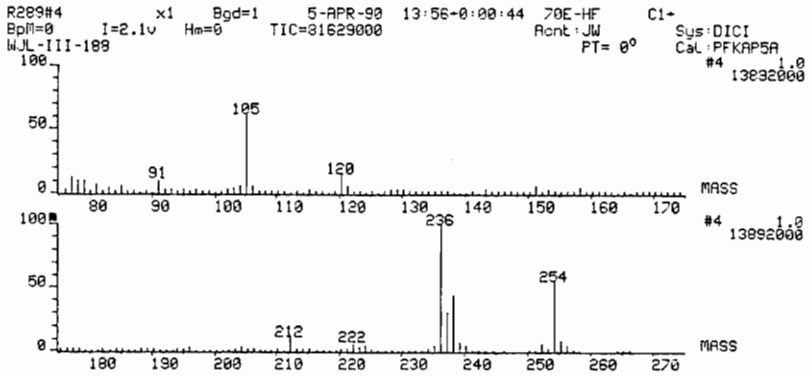


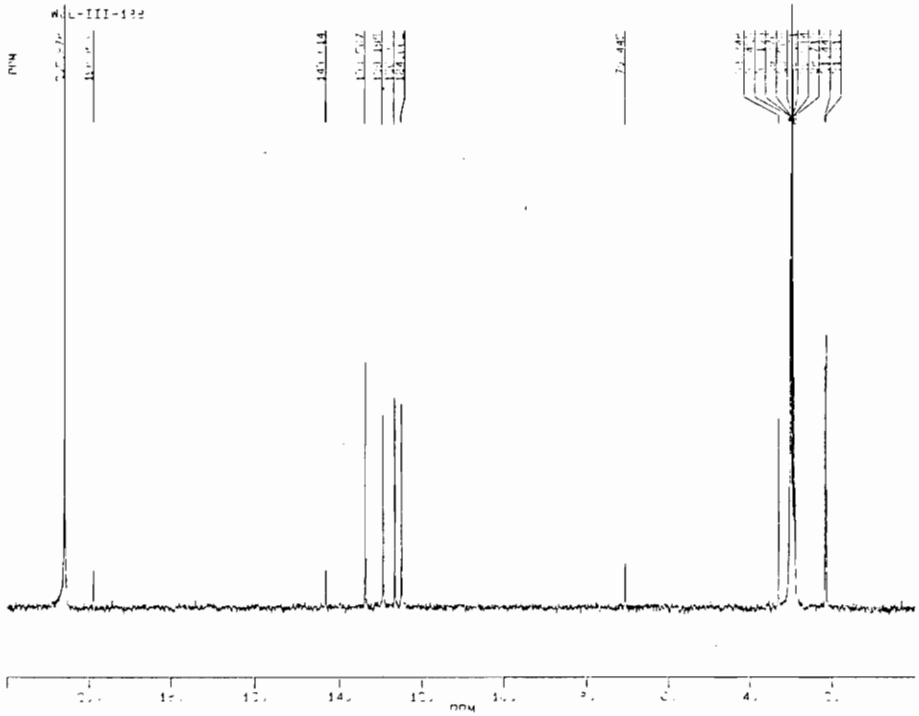
195

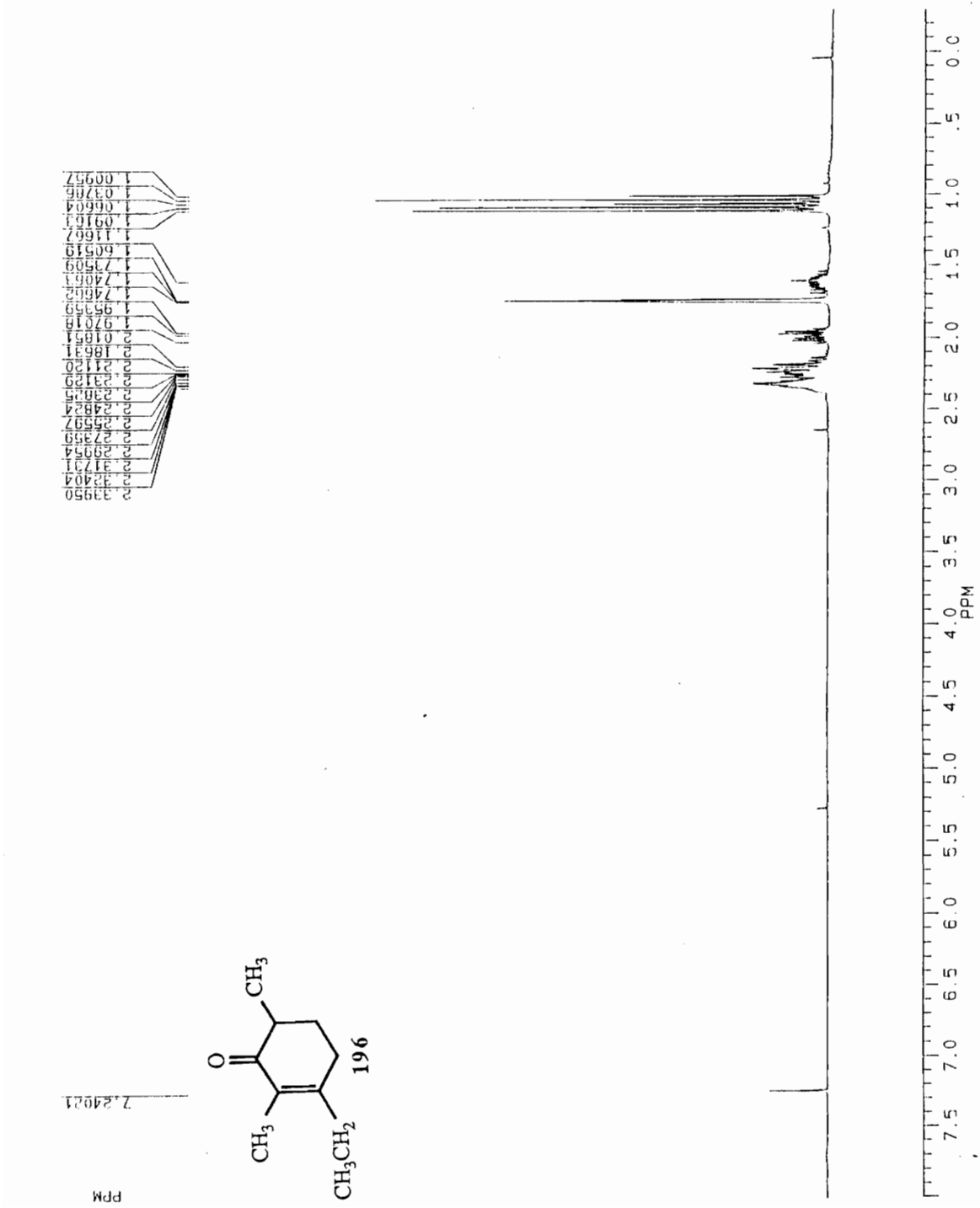

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
PERCENT TRANSMISSION
195

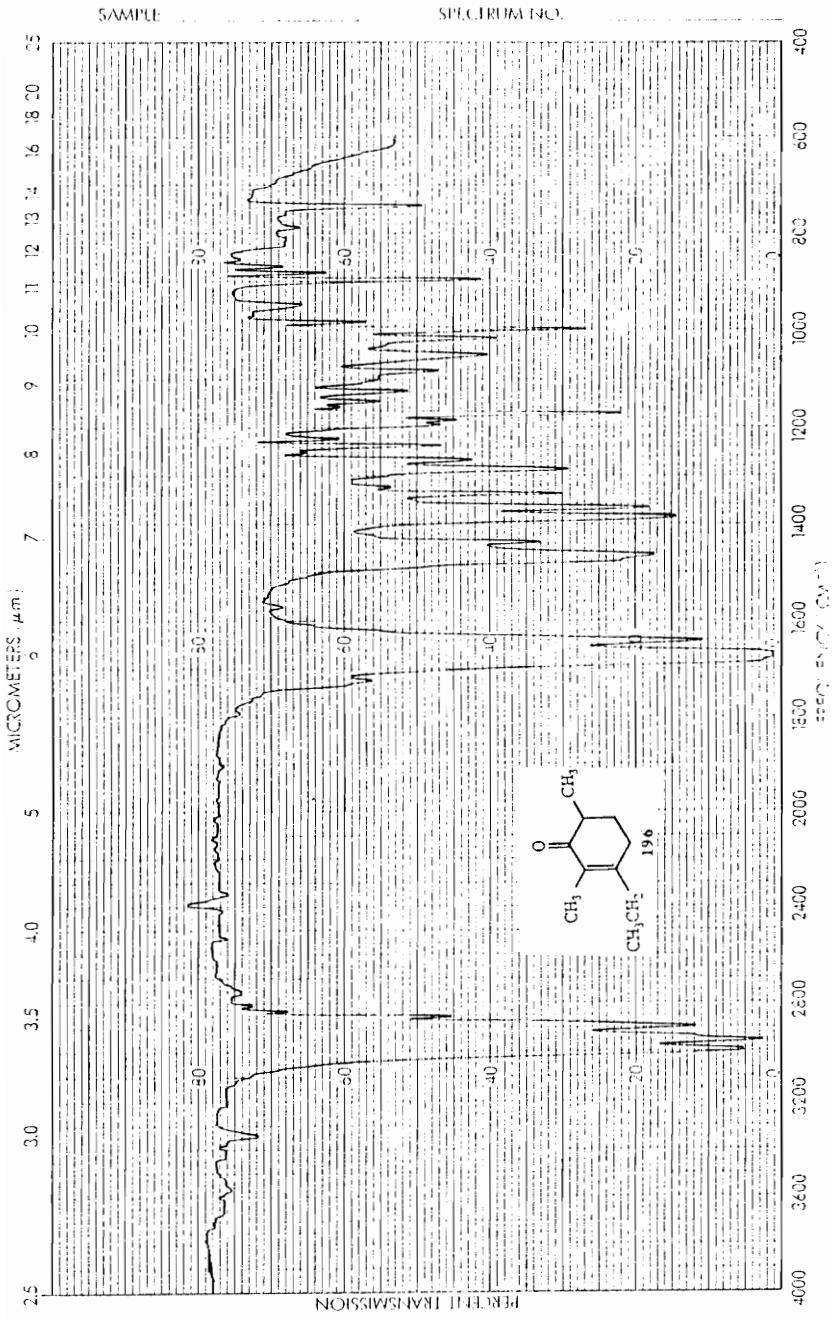

SO2
N
CH3
HO
CH3
CH3

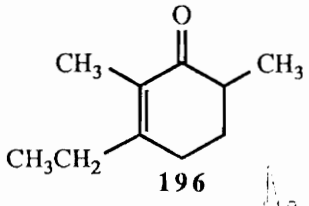
195


R289#4 x1 Bgd=1 5-APR-90 13:56-0:00:44 70E-HF C1+
BpM=0 I=2.1v Hm=0 TIC=31629000 Acnt:JW Sys:DICI
WJL-III-188 PT= 0° Cal:PFKAP5A
#4 1.0
13092000
105
91
120
MASS
236
254
212
222
MASS

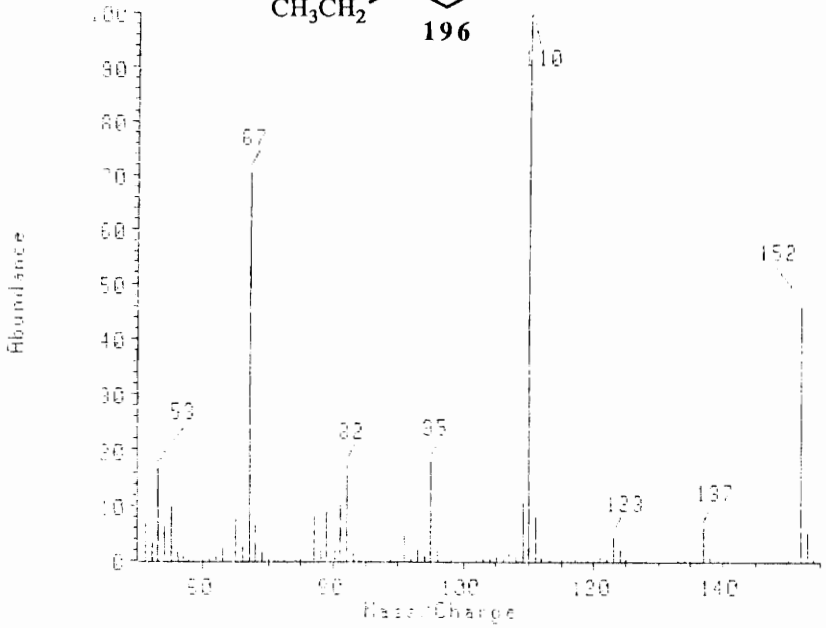


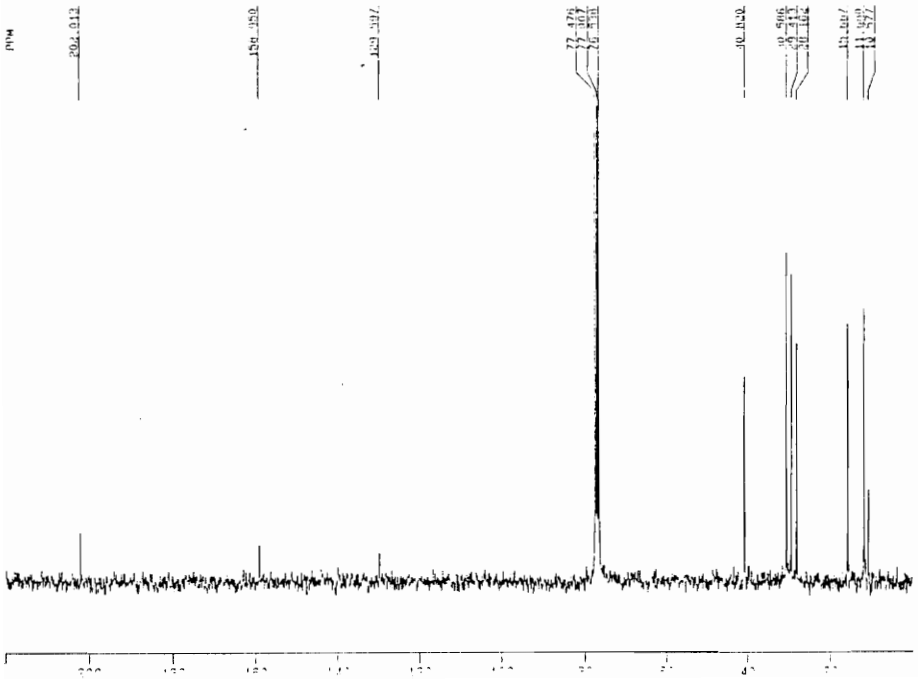

O
CH3
CH3
CH3CH2
196
PPM

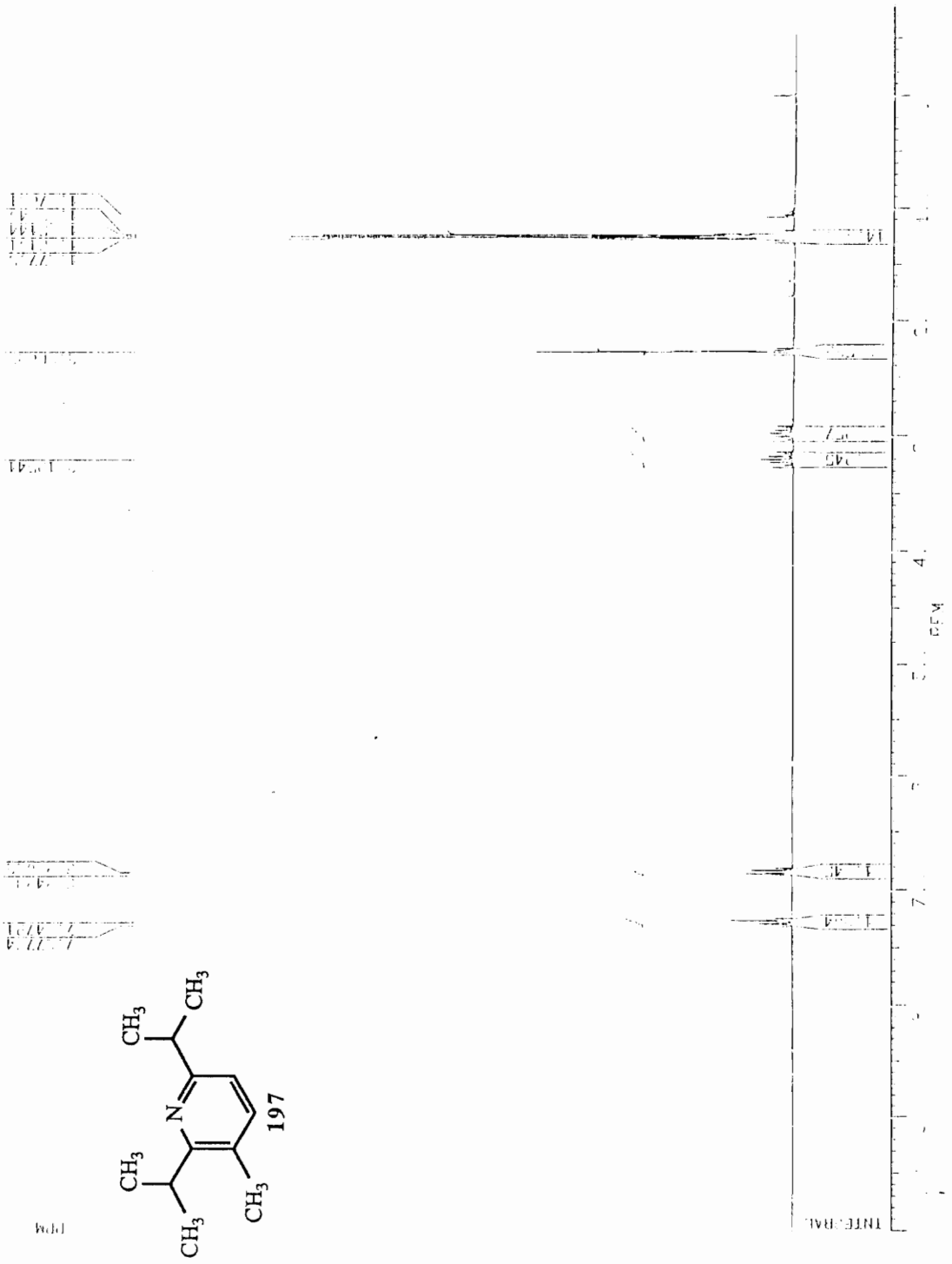

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
PERCENT TRANSMISSION
196


O
CH3
CH3
CH3CH2

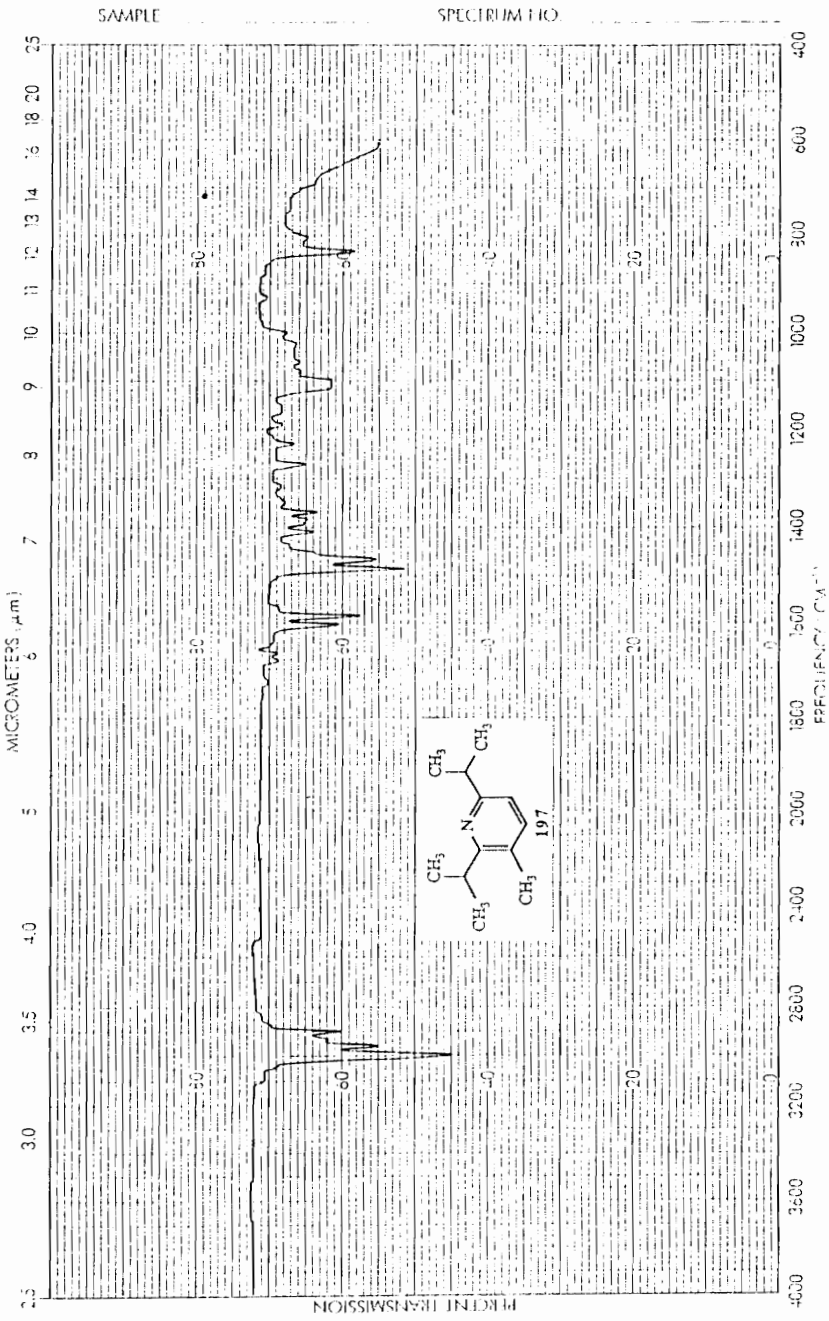
196

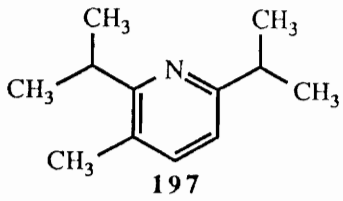

Abundance
Mass/Charge
53
67
82
95
110
123
137
152
50
90
130
120
140



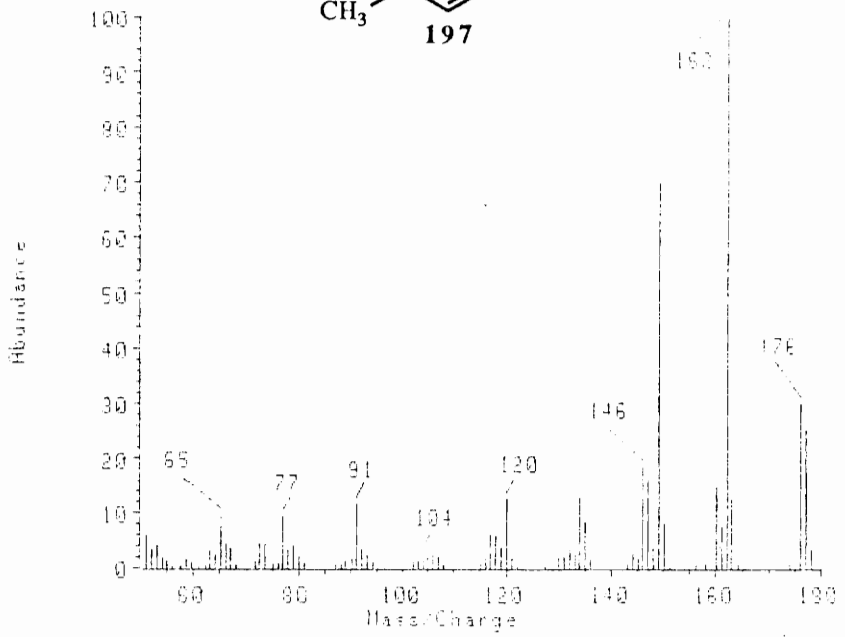


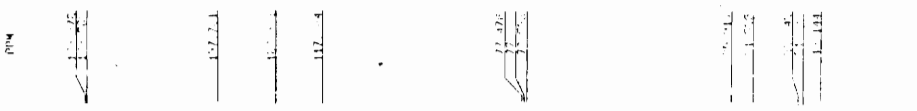
197

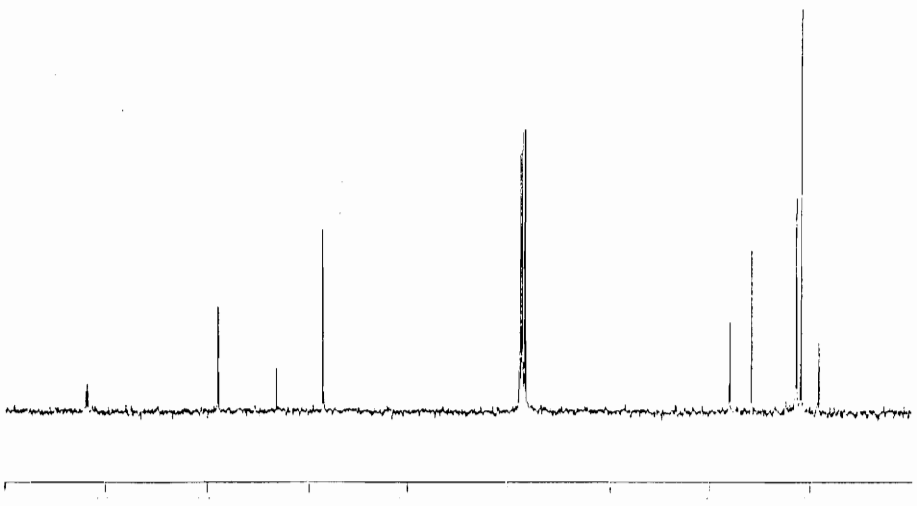

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
PERCENT TRANSMISSION
FREQUENCY (CM⁻¹)
197

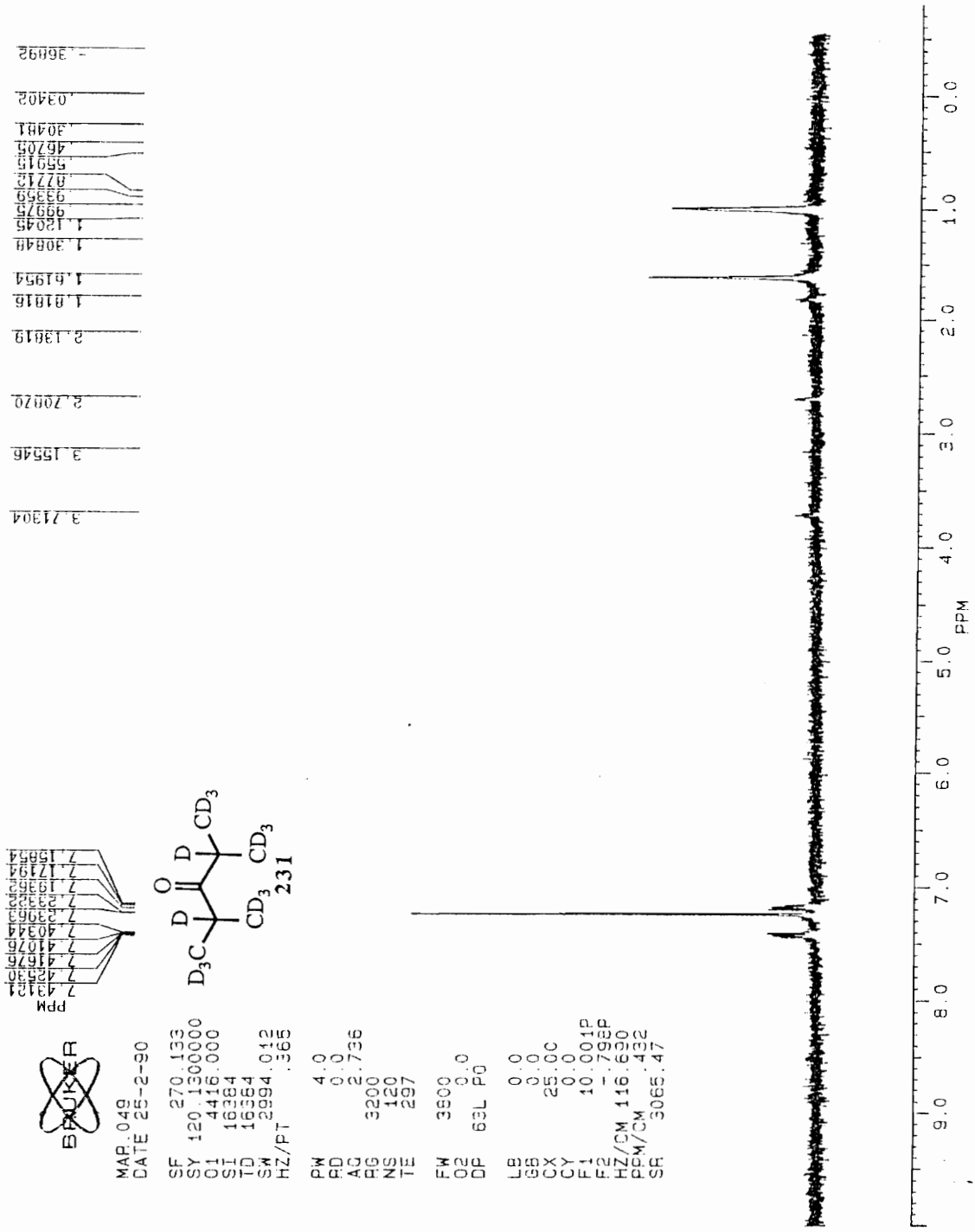

CH3
CH3
N
CH3
CH3

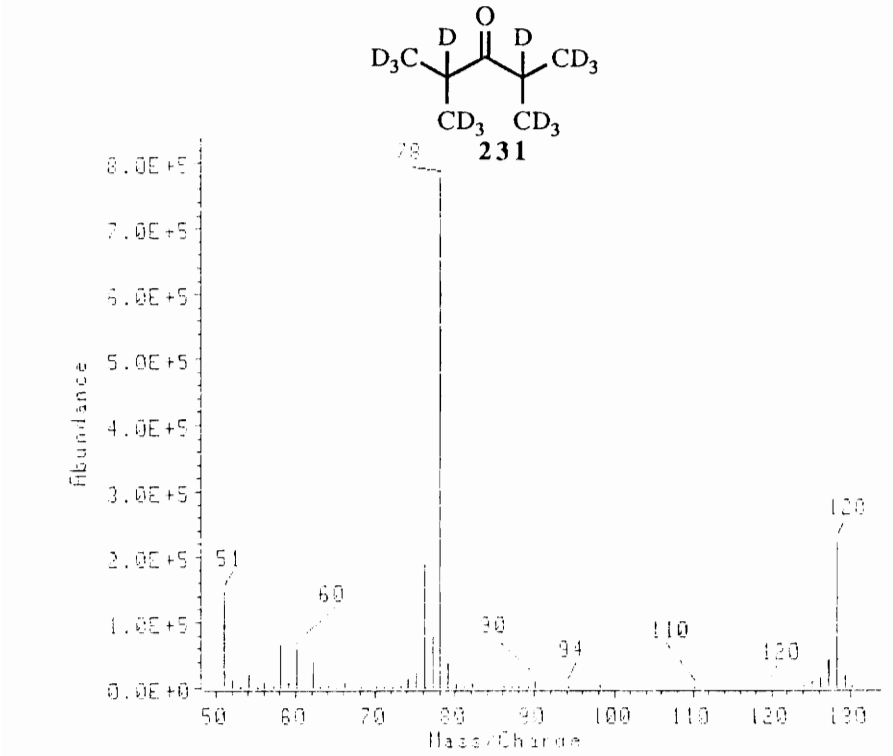
197

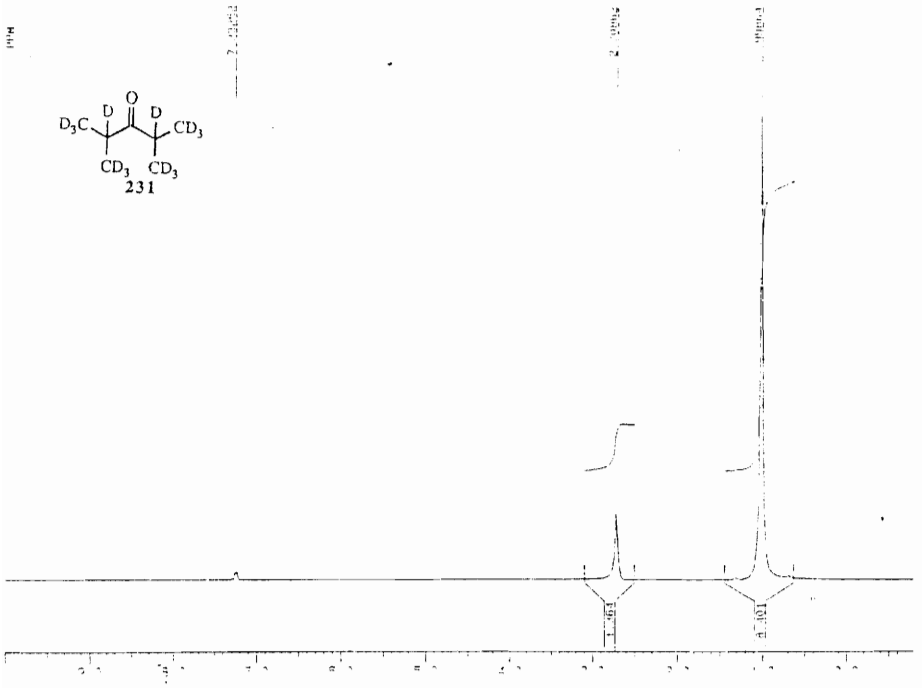

Abundance
Mass/Charge
65
77
91
104
120
146
160
176

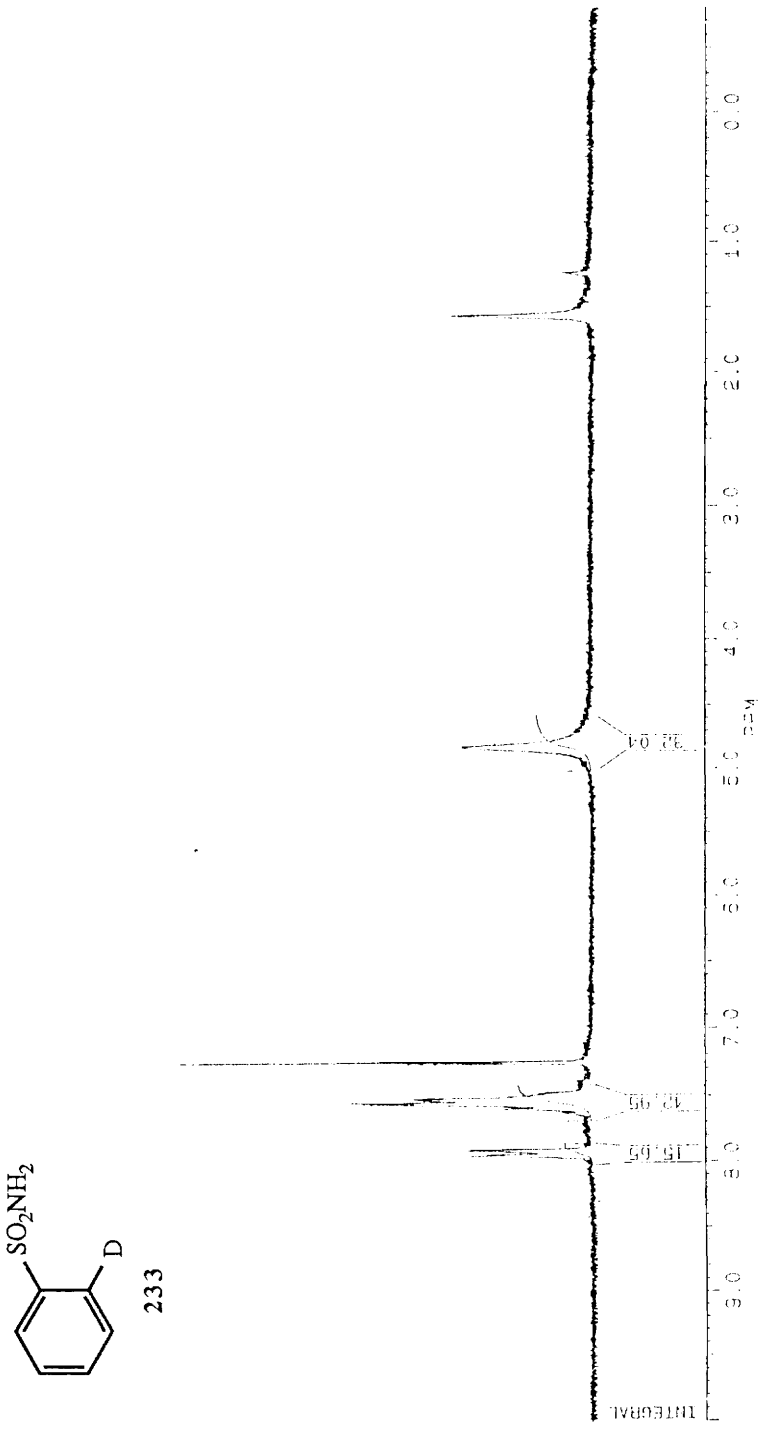




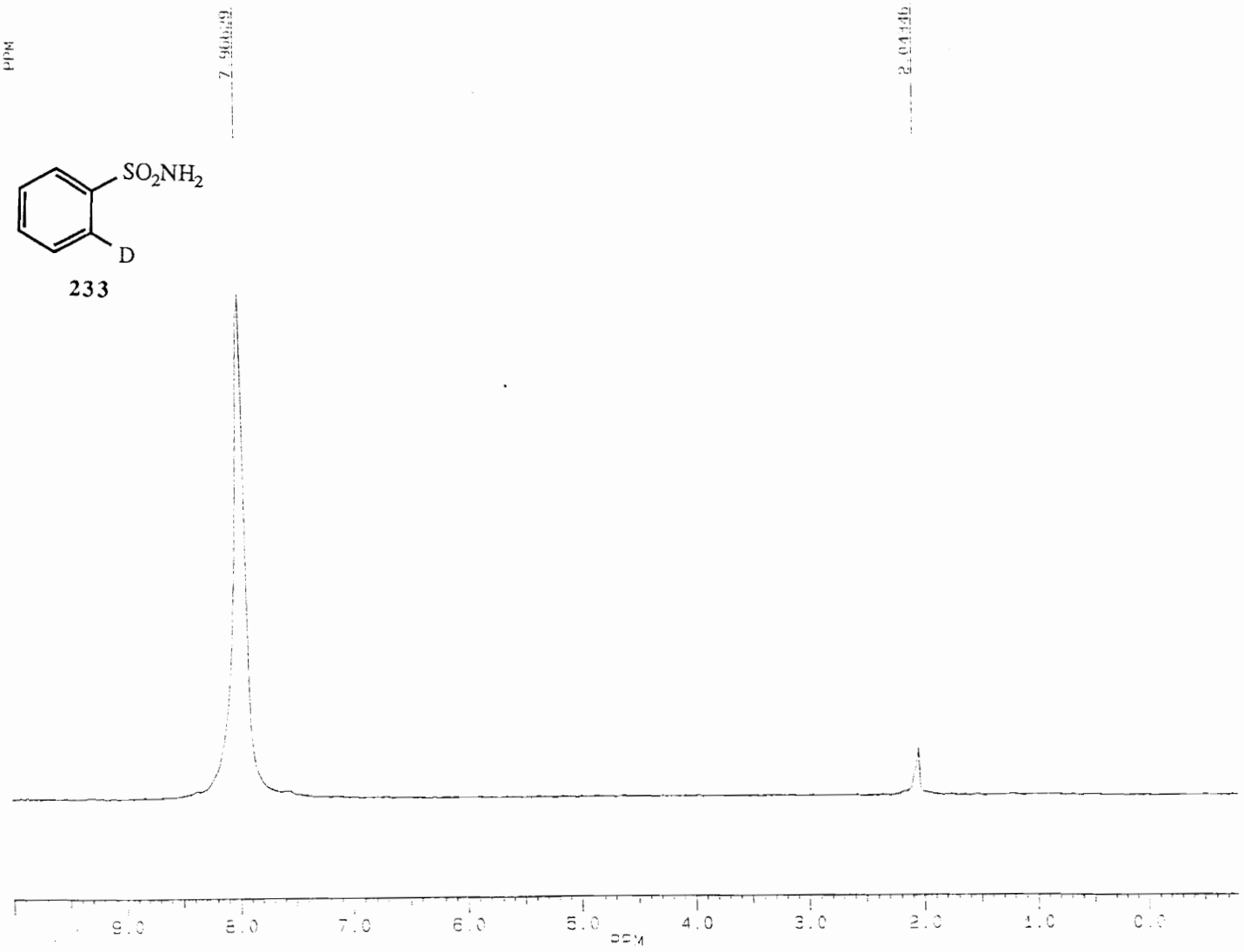

BRUKER
MAR.049
DATE 25-2-90
SF 270.133
SY 120.1300000
O1 4416.000
SI 16384
TD 16384
SW 2994.012
HZ/PT .365
PW 4.0
RD 0.0
AQ 2.736
RG 3200
NS 120
TE 297
FW 3800
O2 0.0
DP 63L PO
LB 0.0
GB 0.0
CX 25.0C
CY 0.0
F1 10.0018P
F2 -.798P
HZ/CM 116.690
PPM/CM .432
SR 3065.47
PPM
231


O
D
D
D3C
CD3
CD3
CD3
231
8.0E+5
7.0E+5
6.0E+5
5.0E+5
4.0E+5
3.0E+5
2.0E+5
1.0E+5
0.0E+0
Abundance
78
51
60
90
94
110
120
120
50
60
70
80
90
100
110
120
130
Mass/Charge

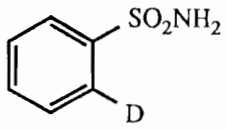

O
D
D
D3C
CD3
CD3
CD3
231



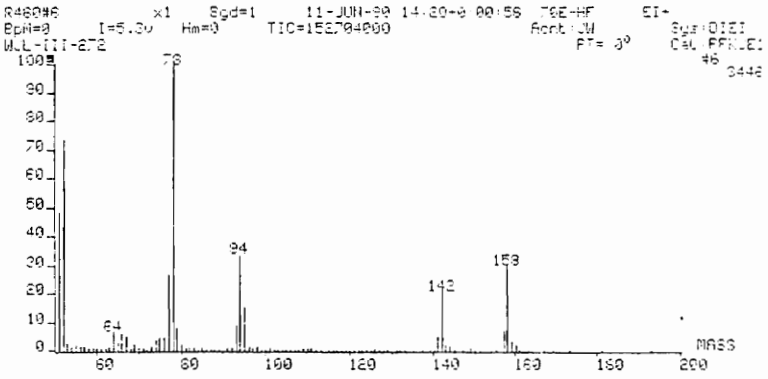
233

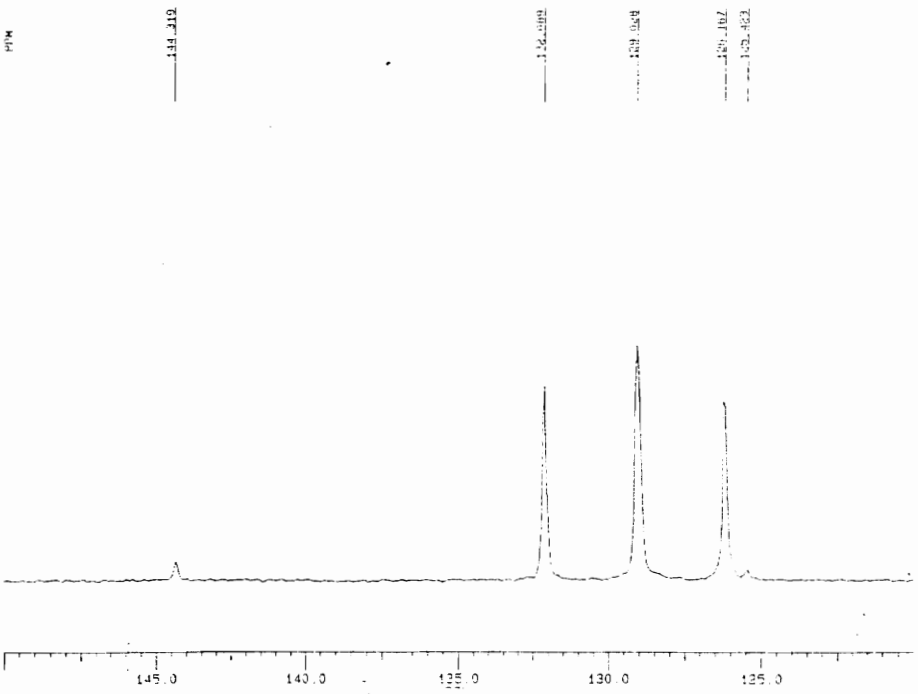


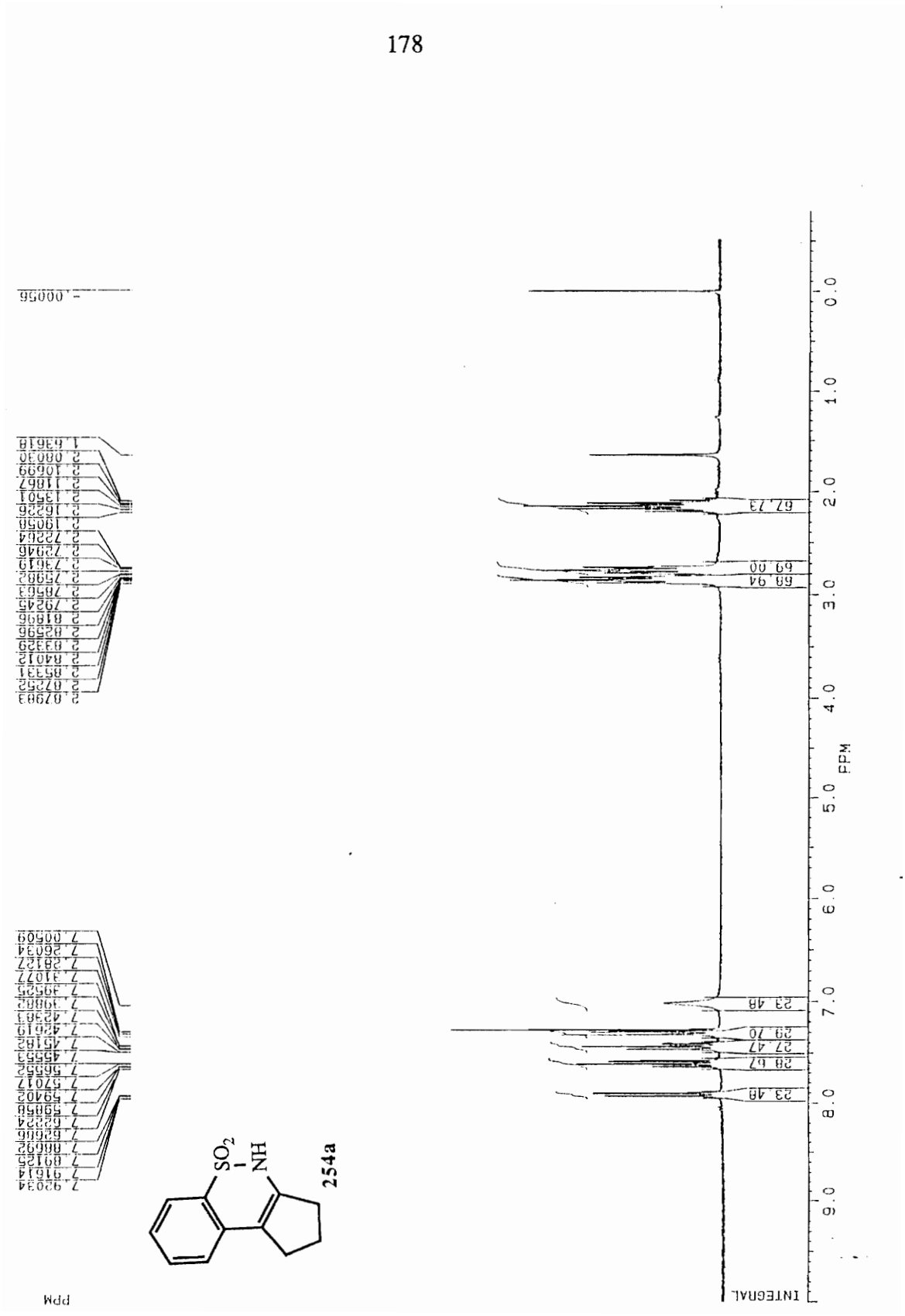
233

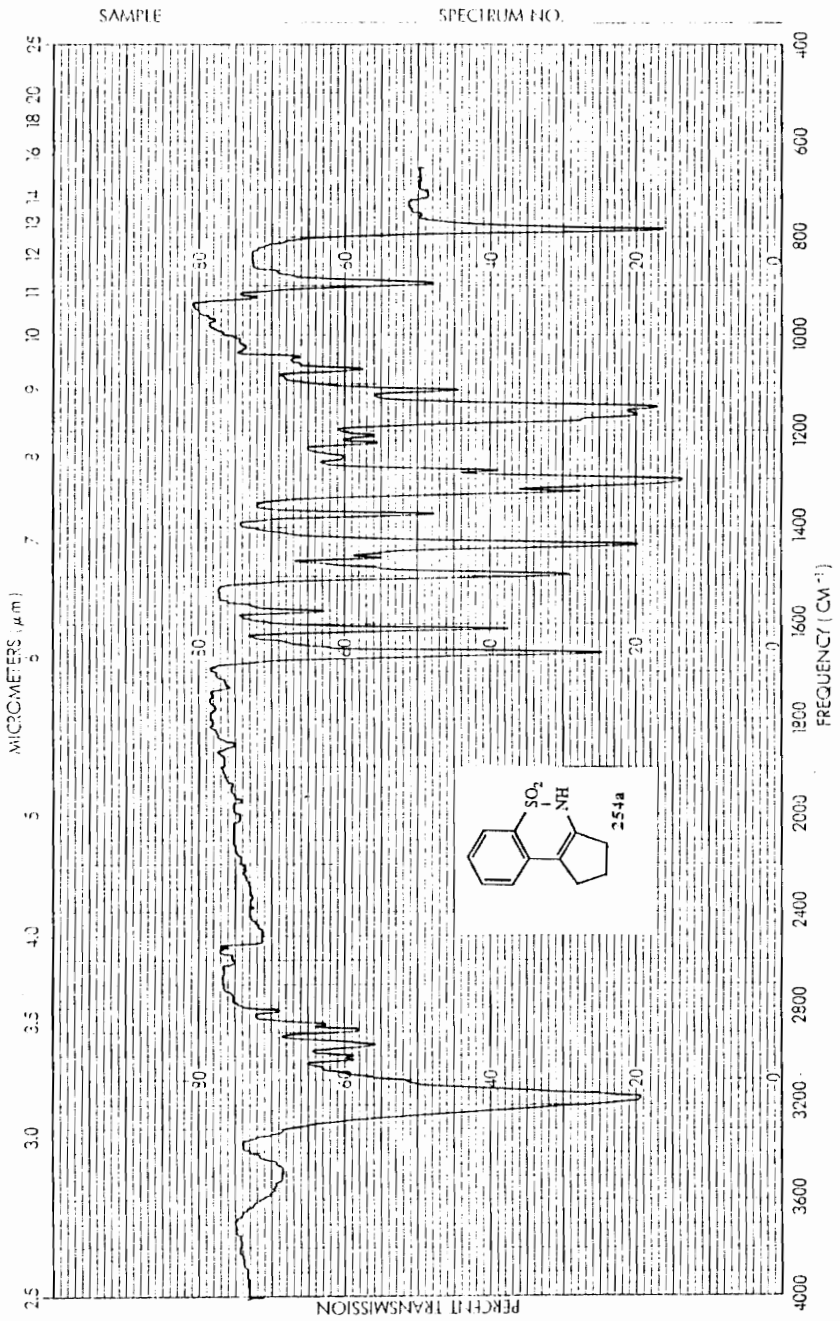

SO2NH2
D

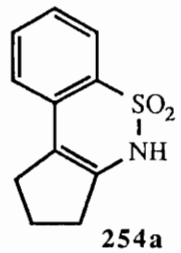
233


R460#6 x1 Bgd=1 11-JUN-90 14:20+0 00:58 70E-HF EI+
BpM=0 I=5.3V Hm=0 TIC=152704000 Acct:JW Sys:DIEI
WLL-III-272 PT= 0° CAL FILE:
#6
3448
100
90
80
70
60
50
40
30
20
10
0
78
94
142
158
64
MASS
60
80
100
120
140
160
180
200

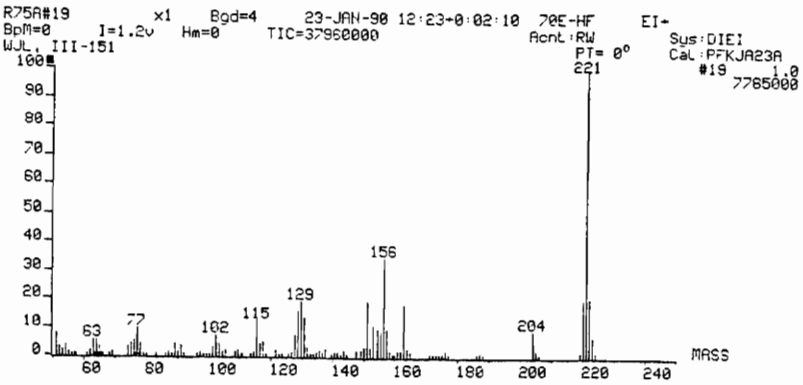

PPM
144.919
136.999
158.968
160.182
162.463
145.0
140.0
135.0
130.0
125.0

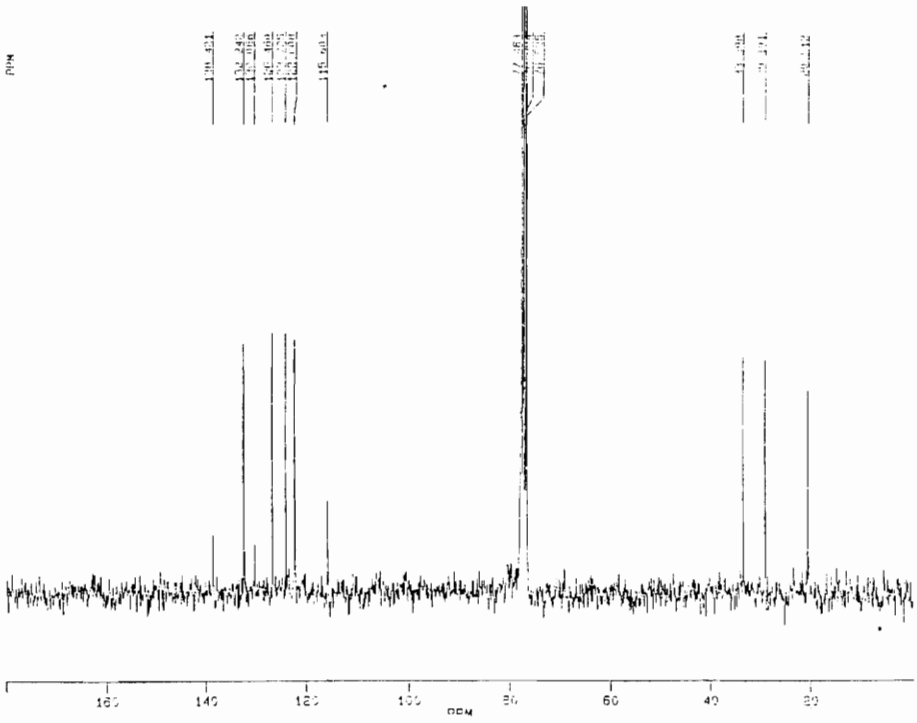

67.23
69.00
68.94
23.48
29.70
27.47
28.67
23.48
INTEGRAL
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
SO2
NH
254a

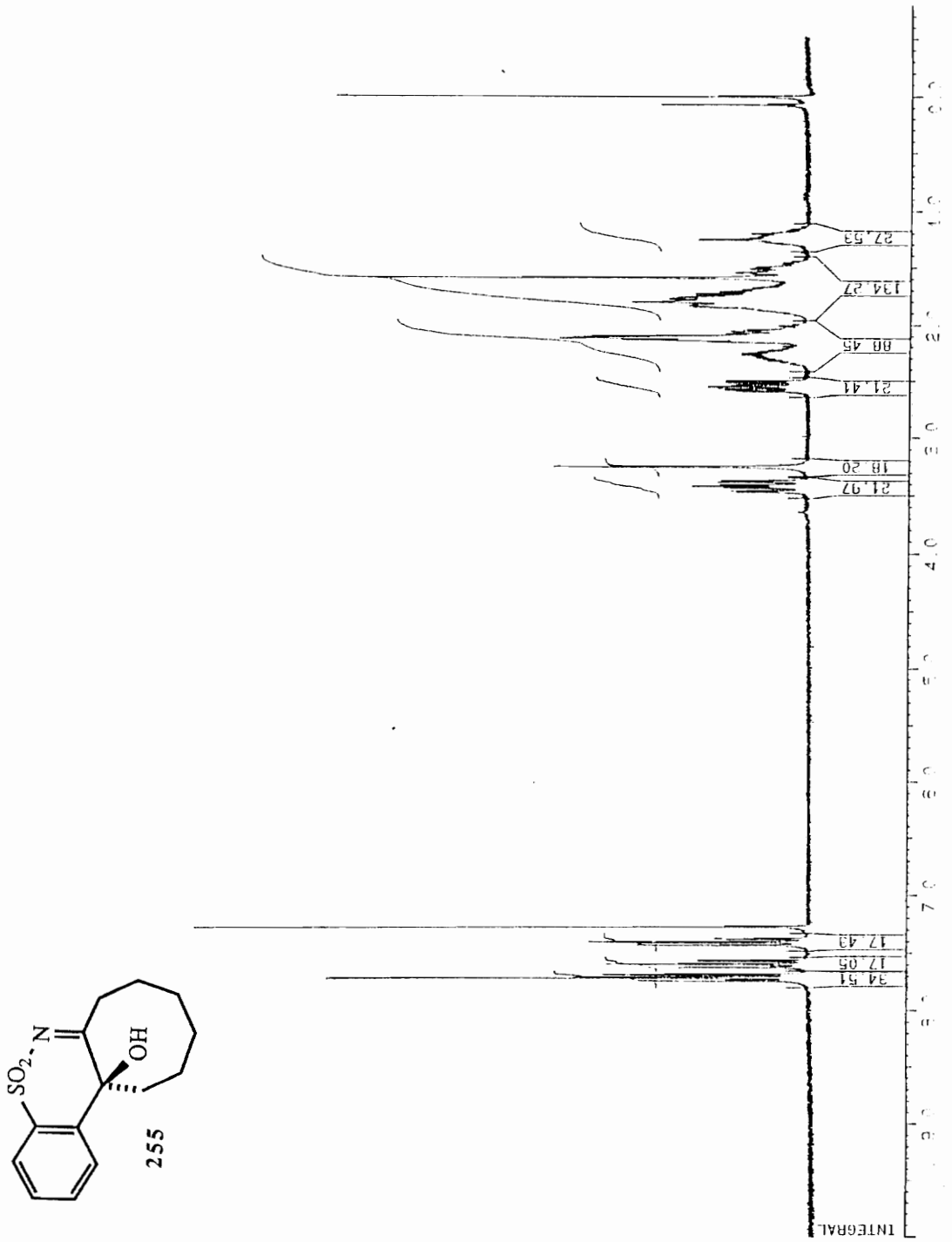

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
254a


SO2
NH

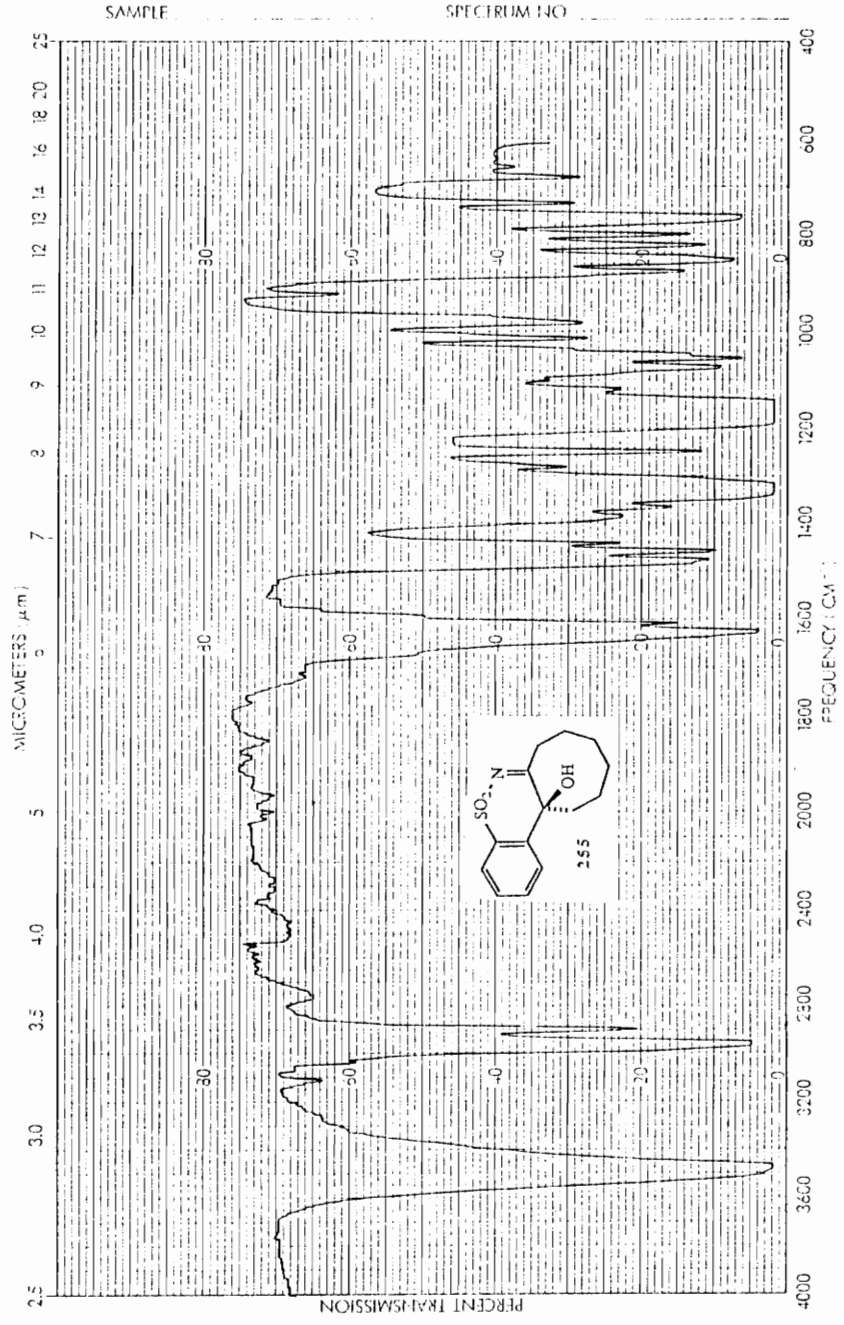
254a

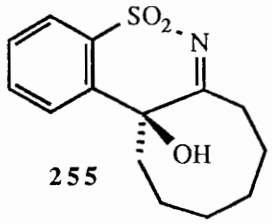

R75A#19 x1 Bgd=4 23-JAN-90 12:23-0:02:10 70E-HF EI+
BpM=0 I=1.2v Hm=0 TIC=37960000 Acnt:RW Sys:DIEI
WJL, III-151 PT= 0° Cal:PFKJA23A
#19 1.0
7765000
100
90
80
70
60
50
40
30
20
10
0
63
77
102
115
129
156
204
221
MASS
60
80
100
120
140
160
180
200
220
240


PPM
160
140
120
100
80
60
40
20
PPM

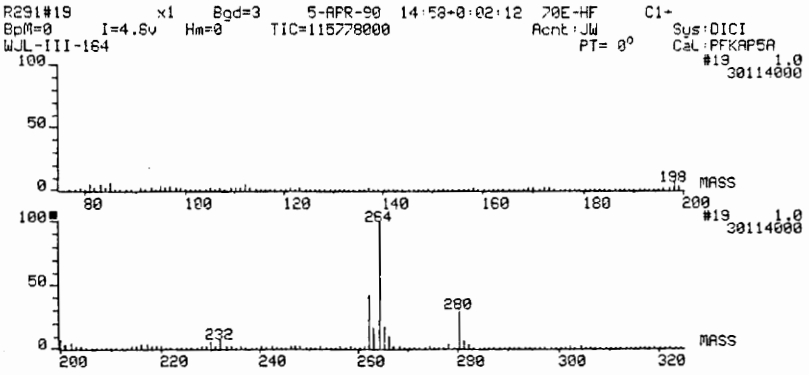

27.53
134.27
80.45
21.41
18.20
21.97
17.43
17.05
34.51
INTEGRAL
OH
N
SO2

255

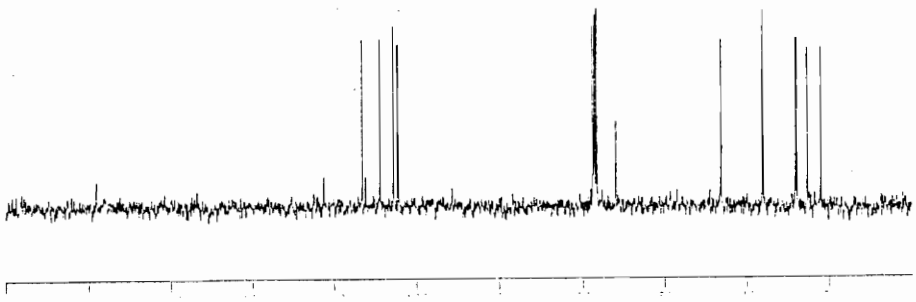

SAMPLE
SPECTRUM NO
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
OH
255

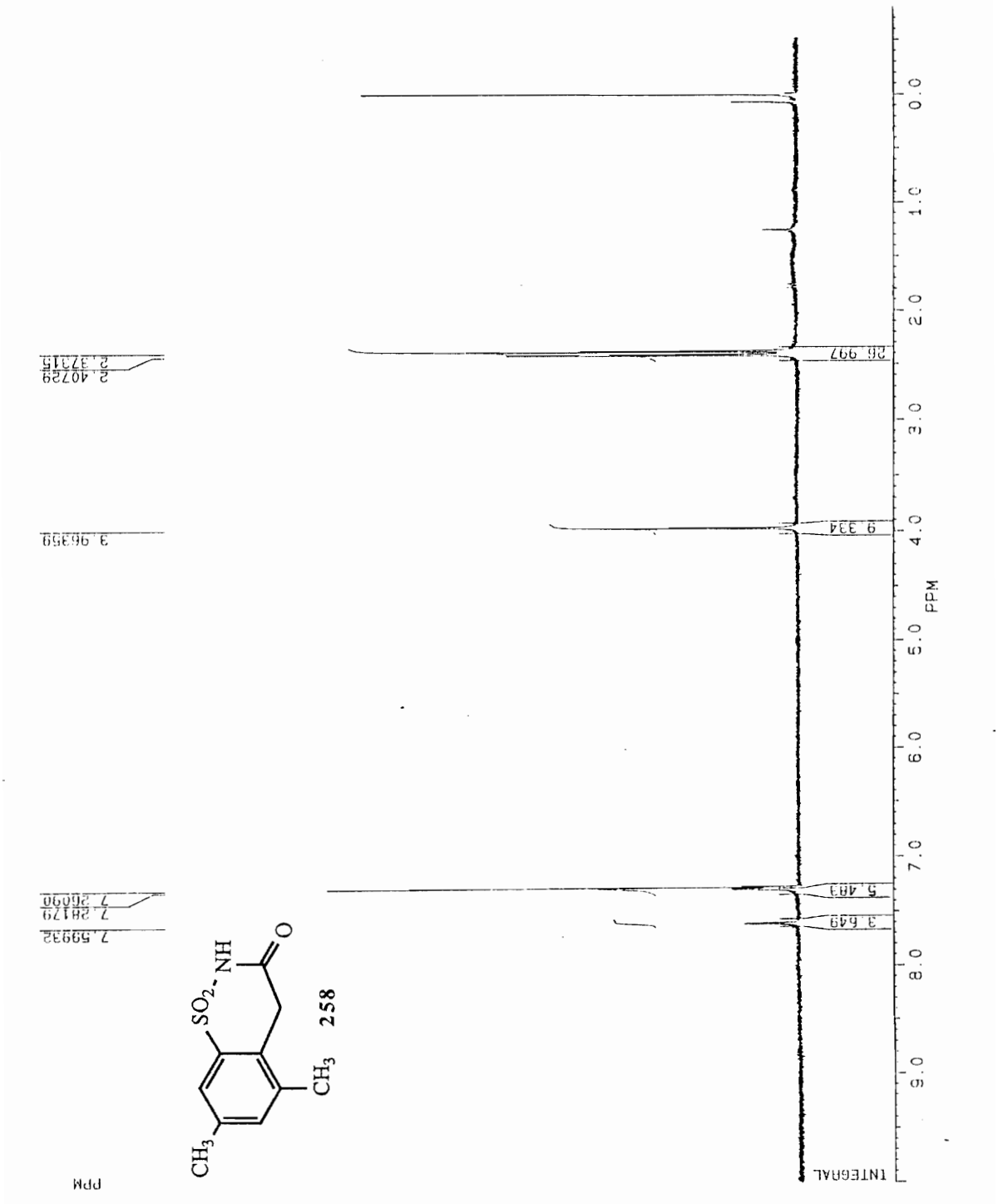

SO2
N
OH

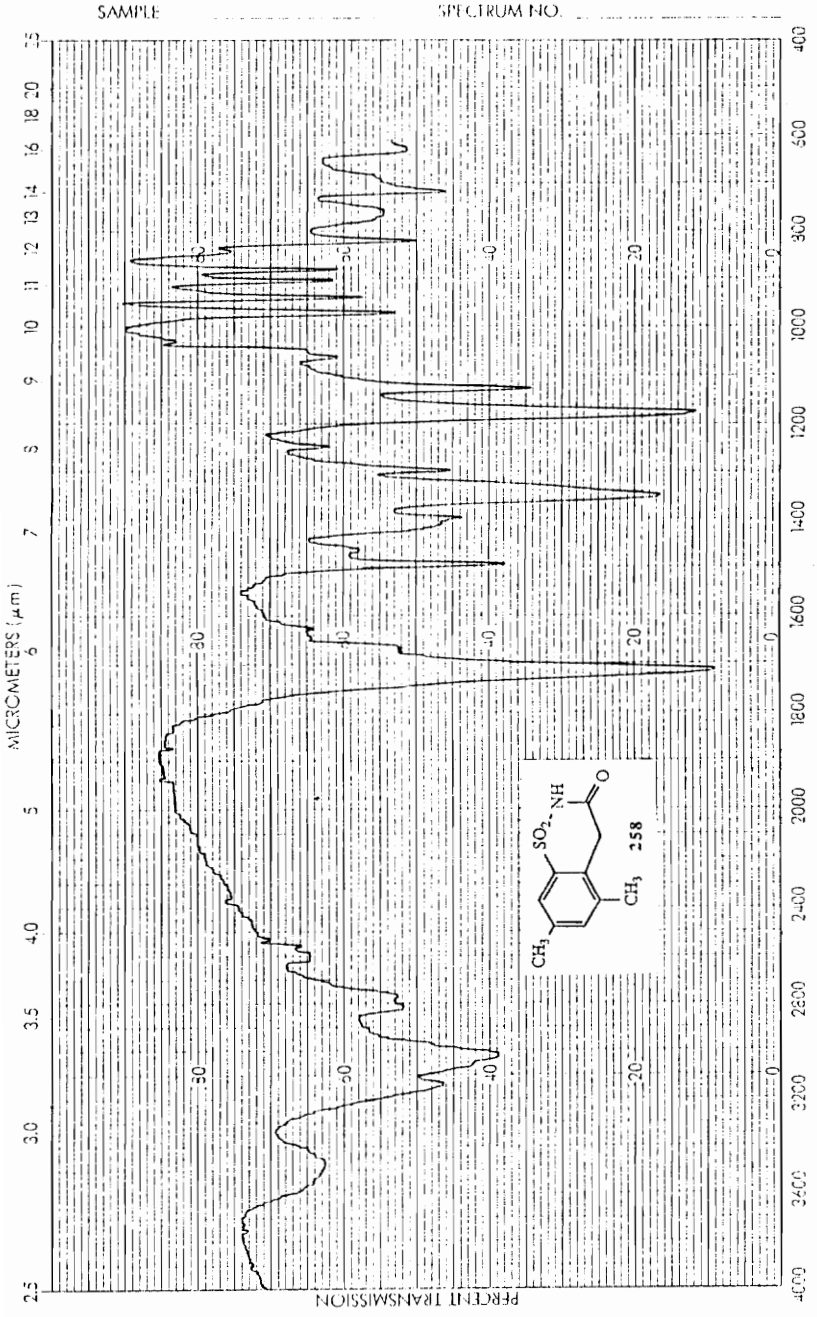
255

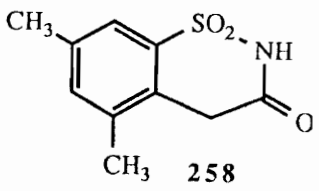

R291#19 x1 Bgd=3 5-APR-90 14:58+0:02:12 70E-HF C1+
BpM=0 I=4.8v Hm=0 TIC=115778000 Acnt:JW Sys:DICI
WJL-III-164 PT= 0° Cal:PFKAP5A
#19 1.0
30114000
MASS
198
264
280
232


PPM

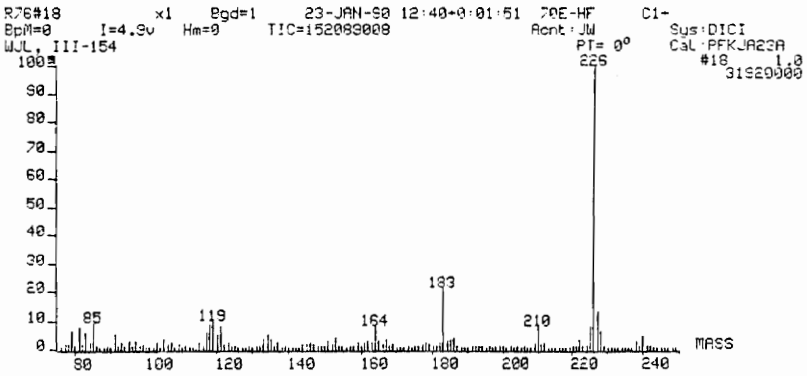


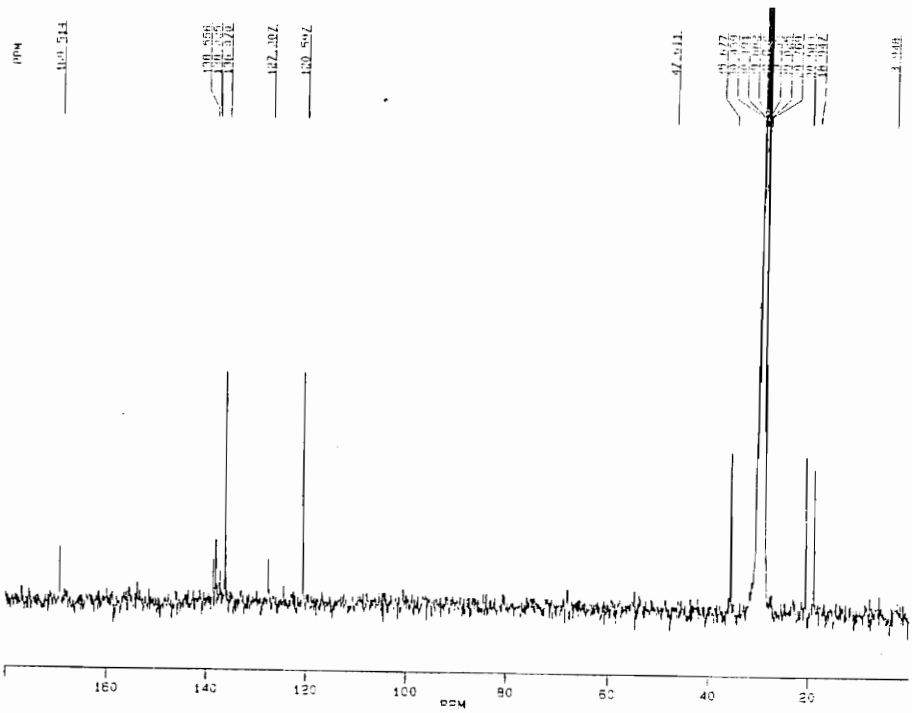

INTEGRAL
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
26.997
9.334
5.403
3.649
2.40729
2.37215
3.96359
7.59932
7.28179
7.26090
NH
O
SO_2
CH_3
CH_3
258

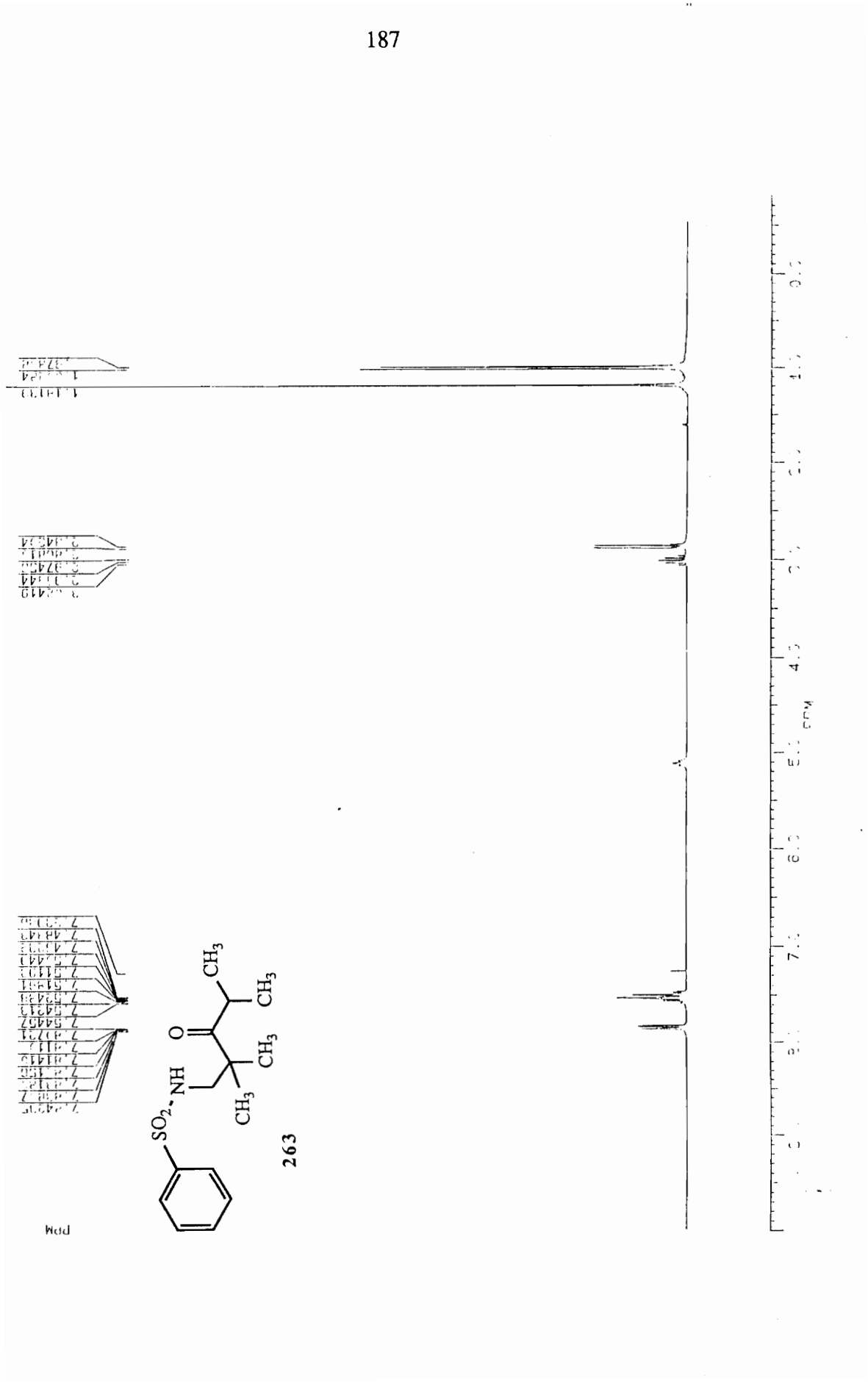

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
PERCENT TRANSMISSION
258


CH3
SO2
NH
O
CH3

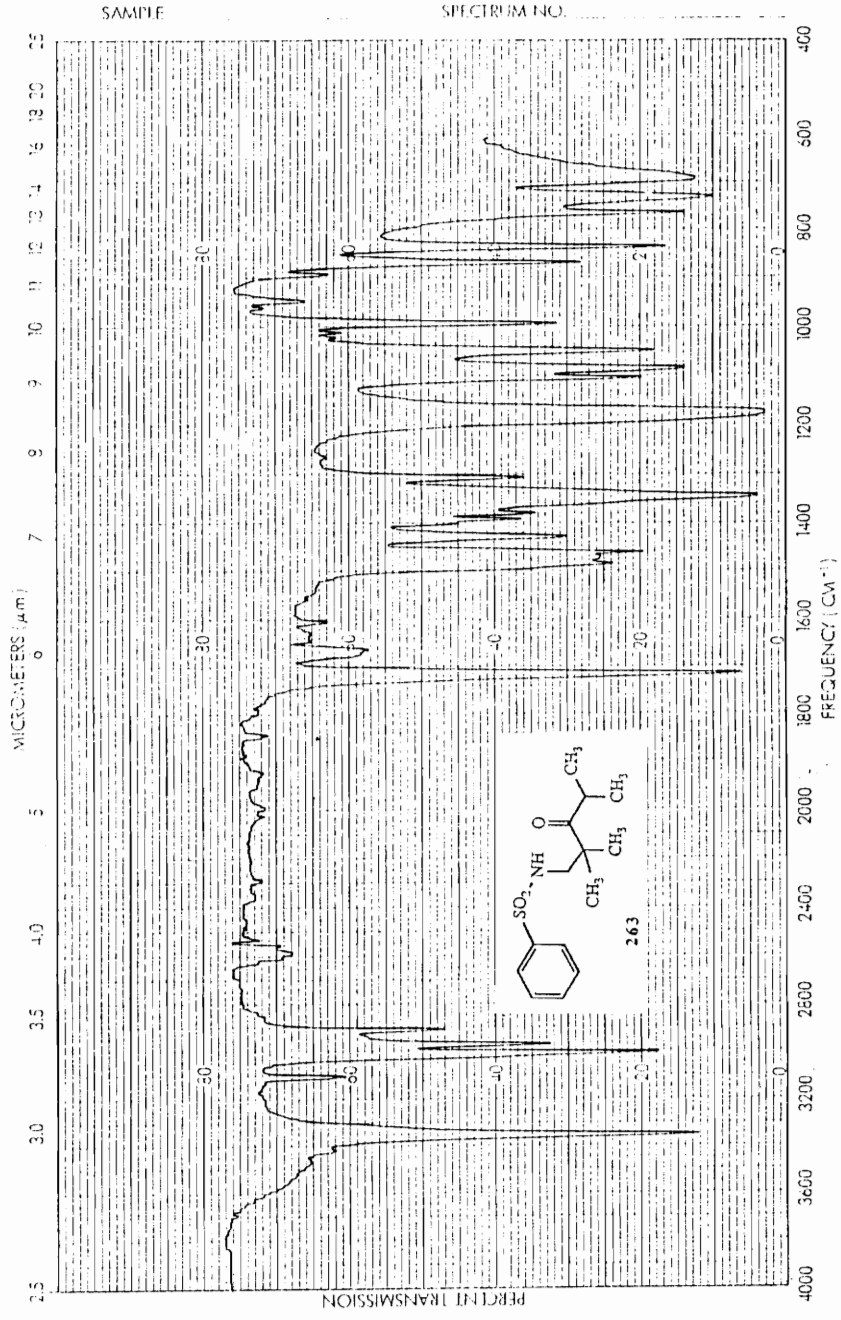
258

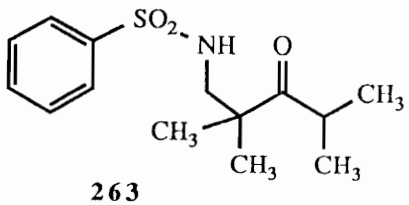

R76#18 x1 Bgd=1 23-JAN-90 12:40+0:01:51 70E-HF CI-
BpM=0 I=4.9v Hm=9 TIC=152083008 Acnt:JW Sys:DICI
WJL, III-154 PT= 0° Cal:PFKJA23A
#18 1.0
31920000
225
183
85
119
164
210
MASS


PPM
ppm

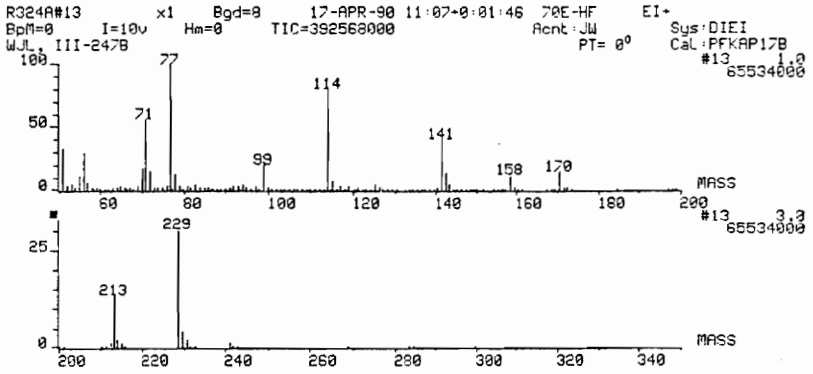


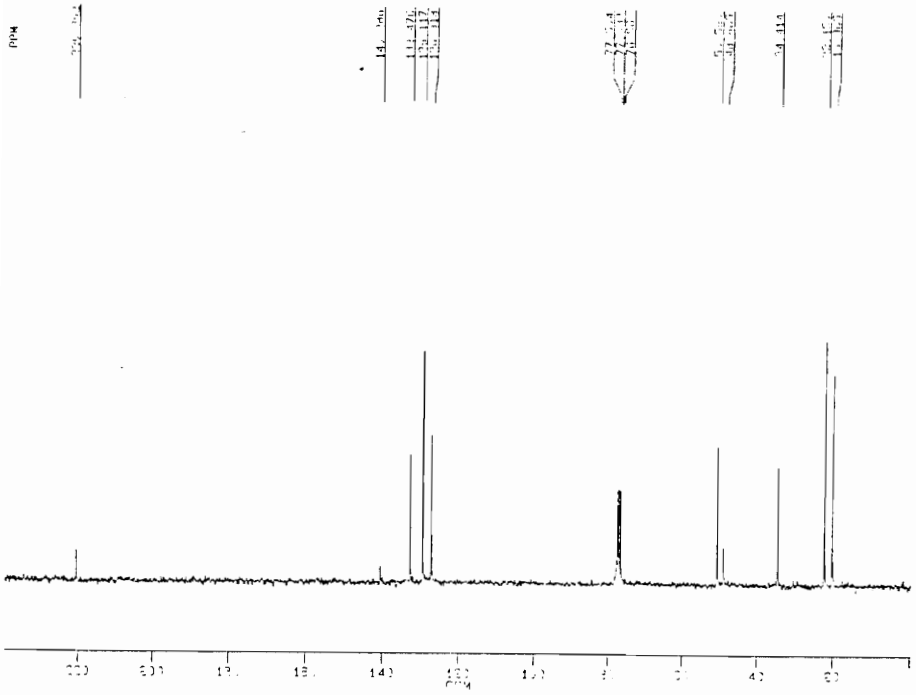
263

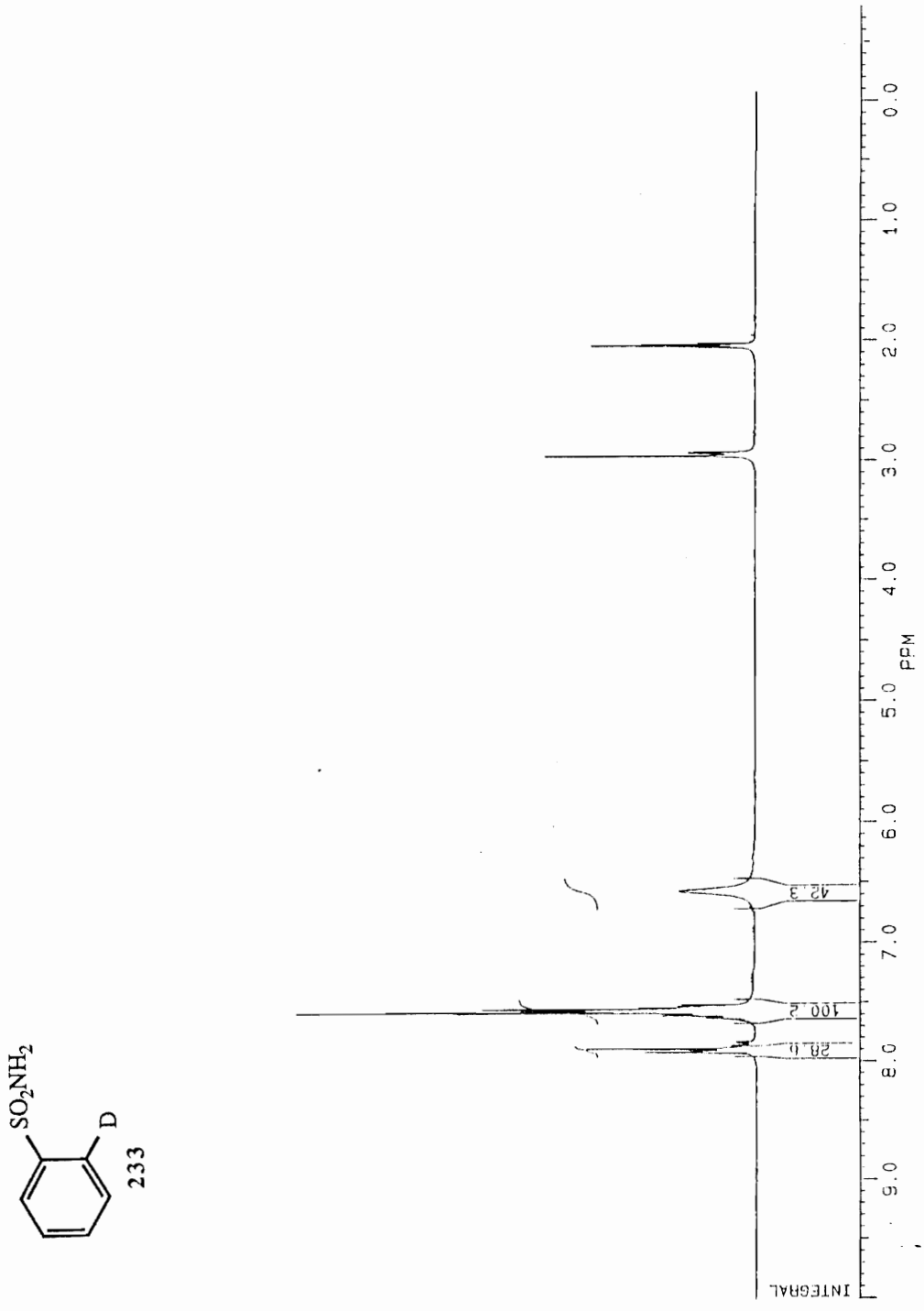

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
263

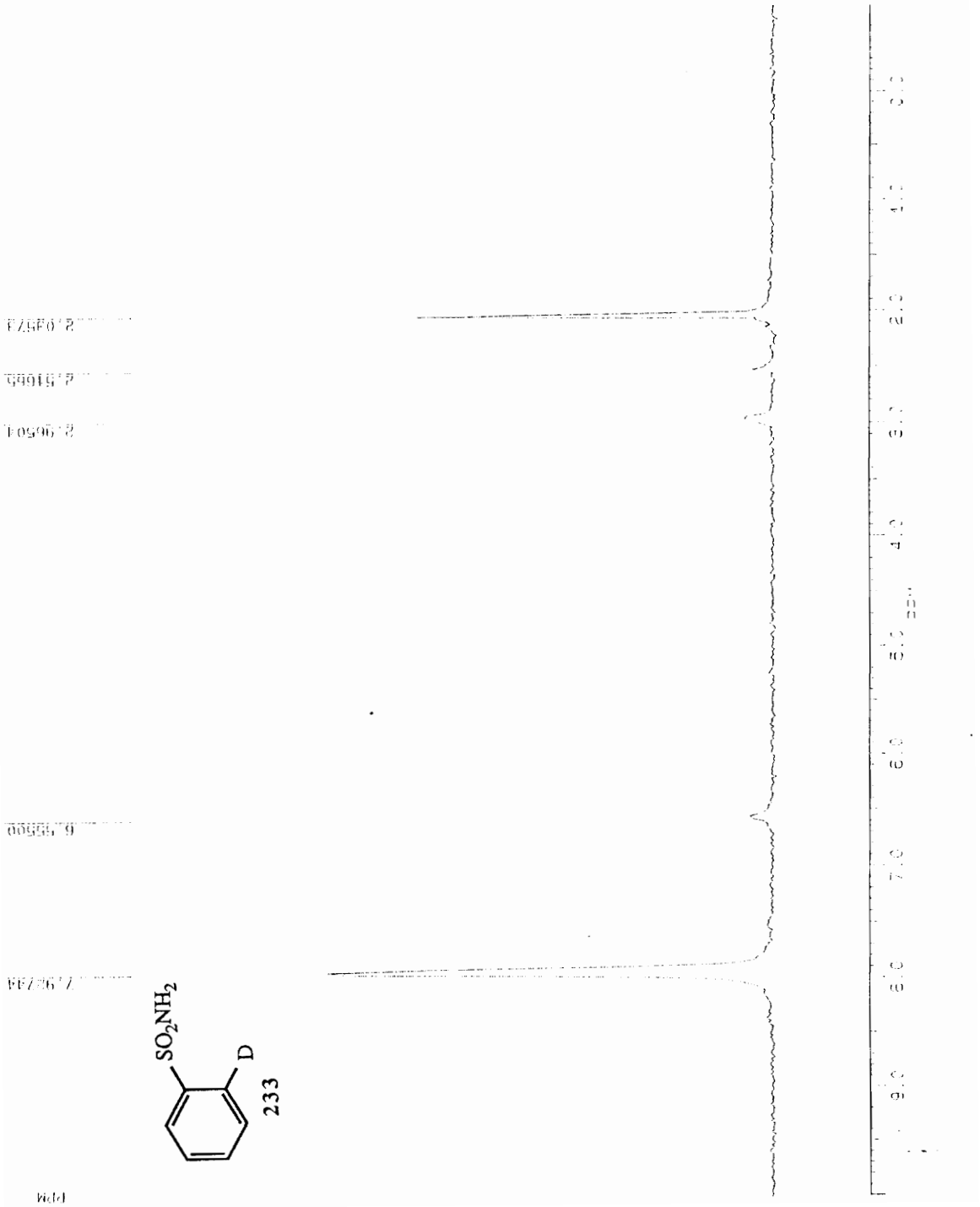

SO2
NH
O
CH3
CH3
CH3
CH3

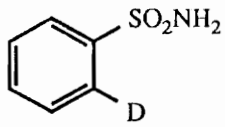
263


R324A#13 x1 Bgd=8 17-APR-90 11:07+0:01:46 70E-HF EI+
BpM=0 I=10v Hm=0 TIC=392568000 Acnt:JW Sys:DIEI
WJL, III-247B PT= 0° CaL:PFKAP17B
#13 1.0
65534000
100
50
0
77
71
114
99
141
158
170
MASS
60 80 100 120 140 160 180 200
#13 3.3
65534000
25
0
229
213
MASS
200 220 240 260 280 300 320 340

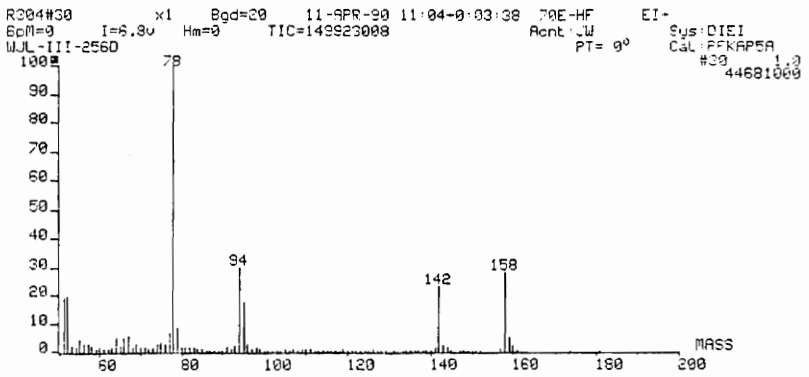


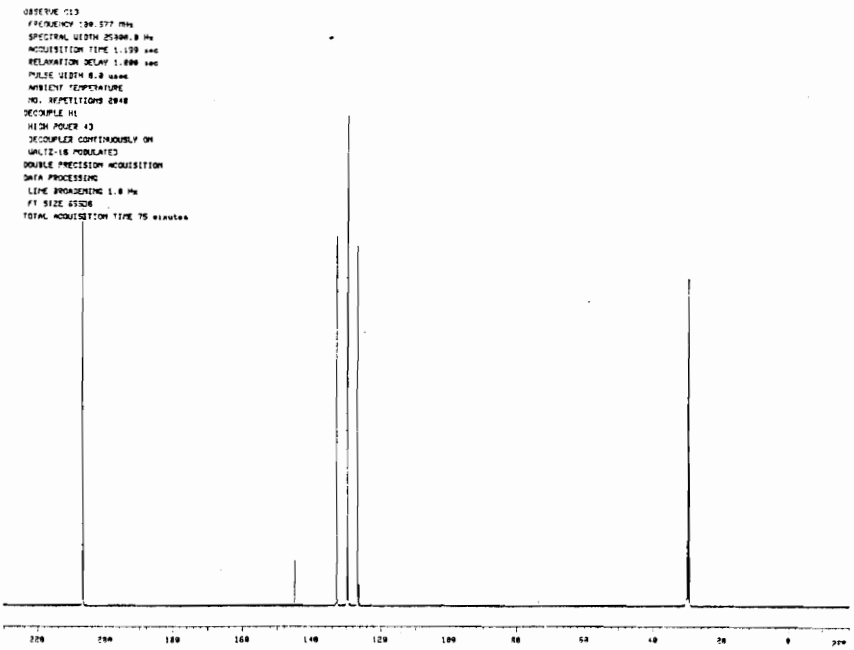

SO2NH2
D
233
INTEGRAL
42.3
100.2
28.0
PPM
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

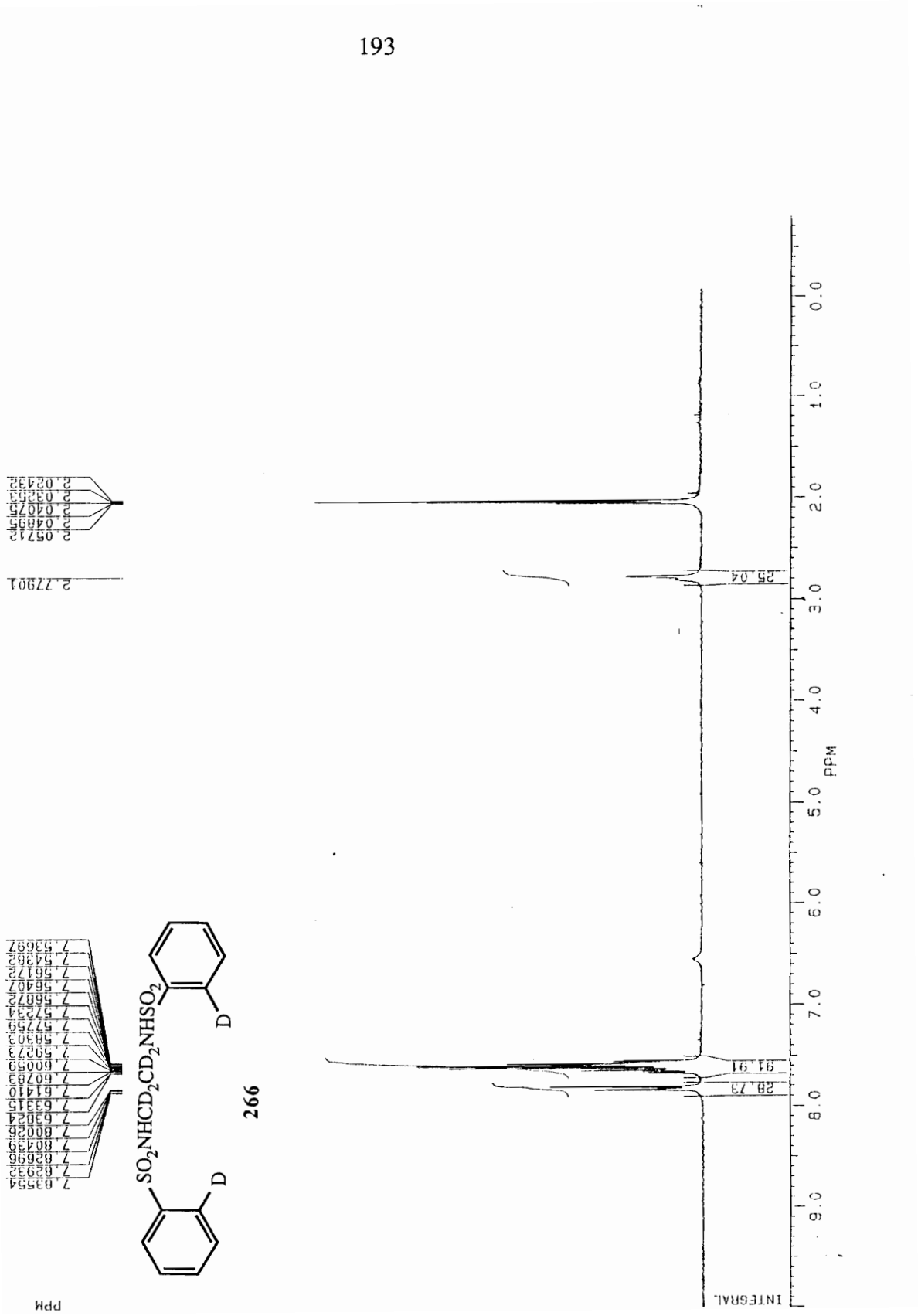

SO2NH2
D
233

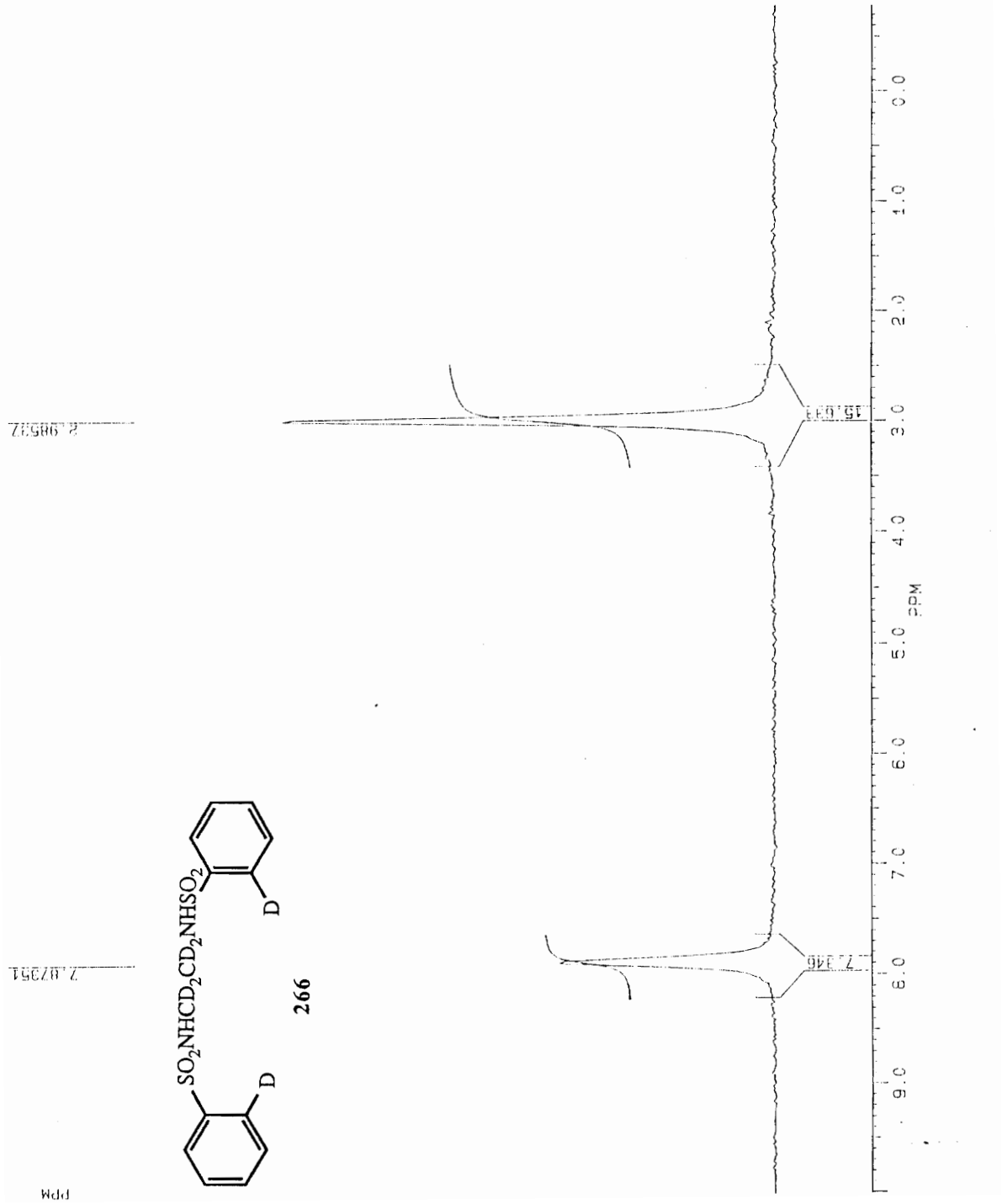

SO2NH2
D

233

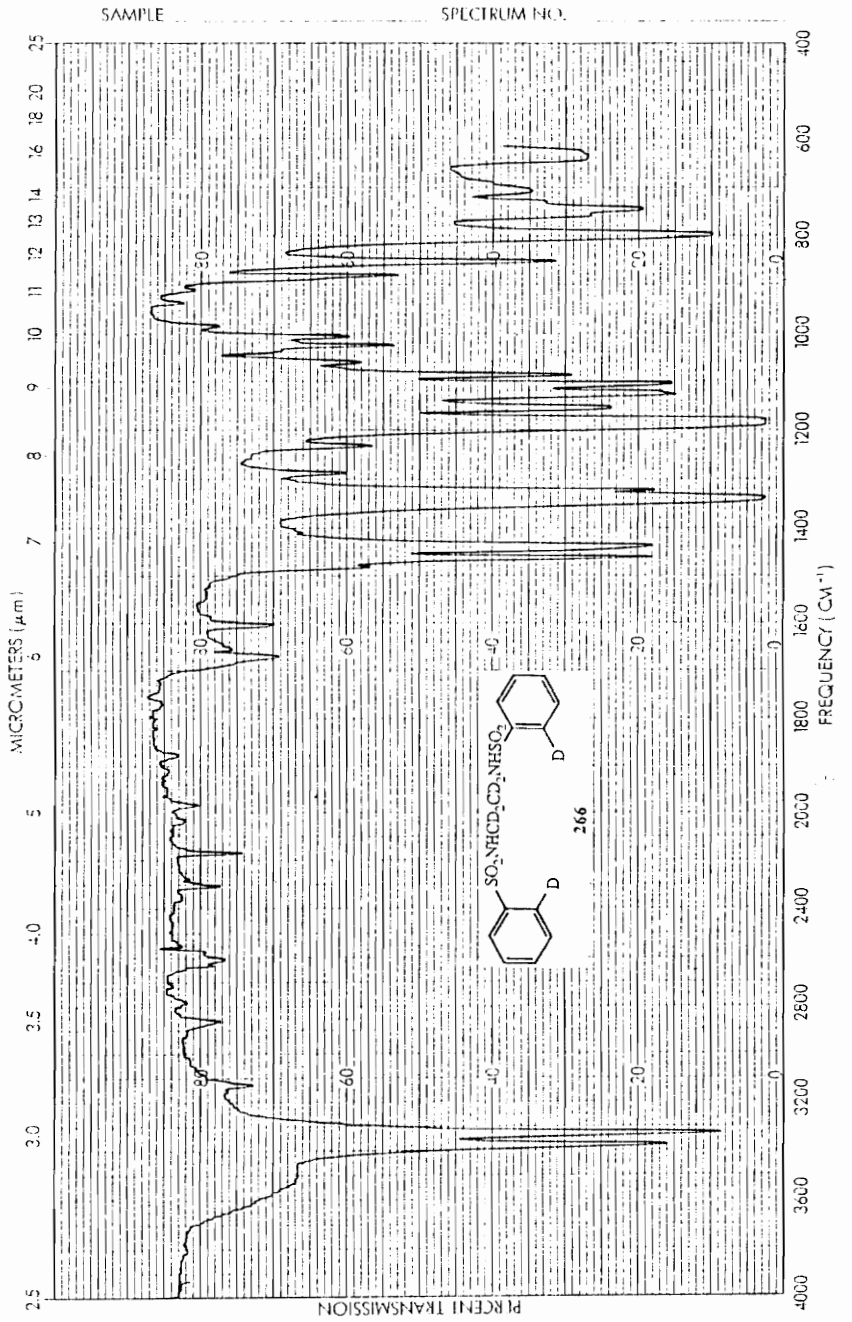

R304#30 x1 Bgd=20 11-APR-90 11:04-0:03:38 70E-HF EI+
BpM=0 I=6.8v Hm=0 TIC=14992308 Acnt:JW Sys:DIEI
WJL-III-256D PT= 0° Cal:FFKAP5A
#30 1.0
44681000
100
90
80
70
60
50
40
30
20
10
0
78
94
142
158
MASS
60
80
100
120
140
160
180
200

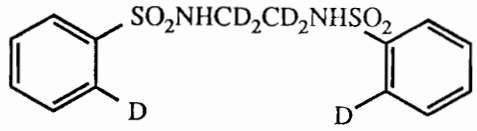

OBSERVE C13
FREQUENCY 100.577 MHz
SPECTRAL WIDTH 25000.0 Hz
ACQUISITION TIME 1.139 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 6.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 2048
DECOUPLE H1
HIGH POWER 43
DECOUPLER CONTINUOUSLY ON
WALTZ-16 MODULATED
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 75 minutes


$SO_2NHCD_2CD_2NHSO_2$
D
D
266
INTEGRAL
PPM
25.04
28.73
91.91
2.27901

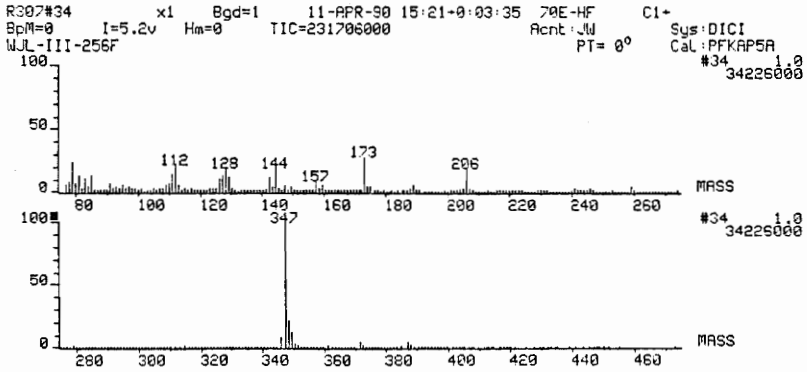


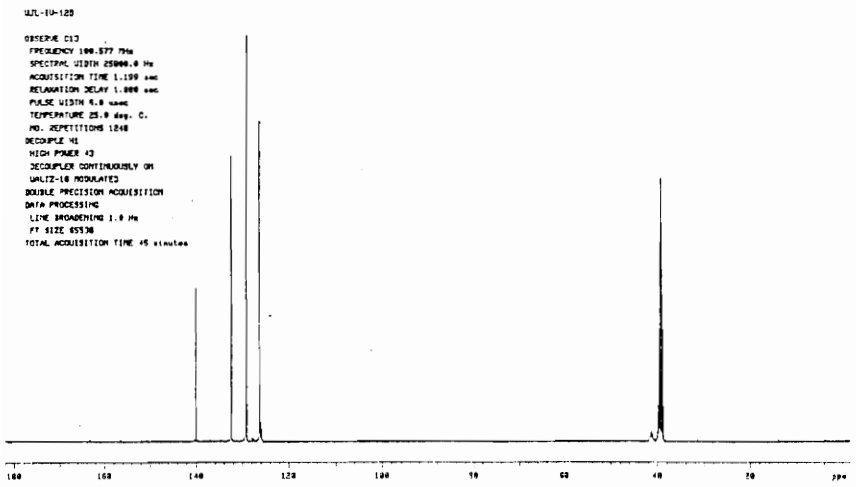
266

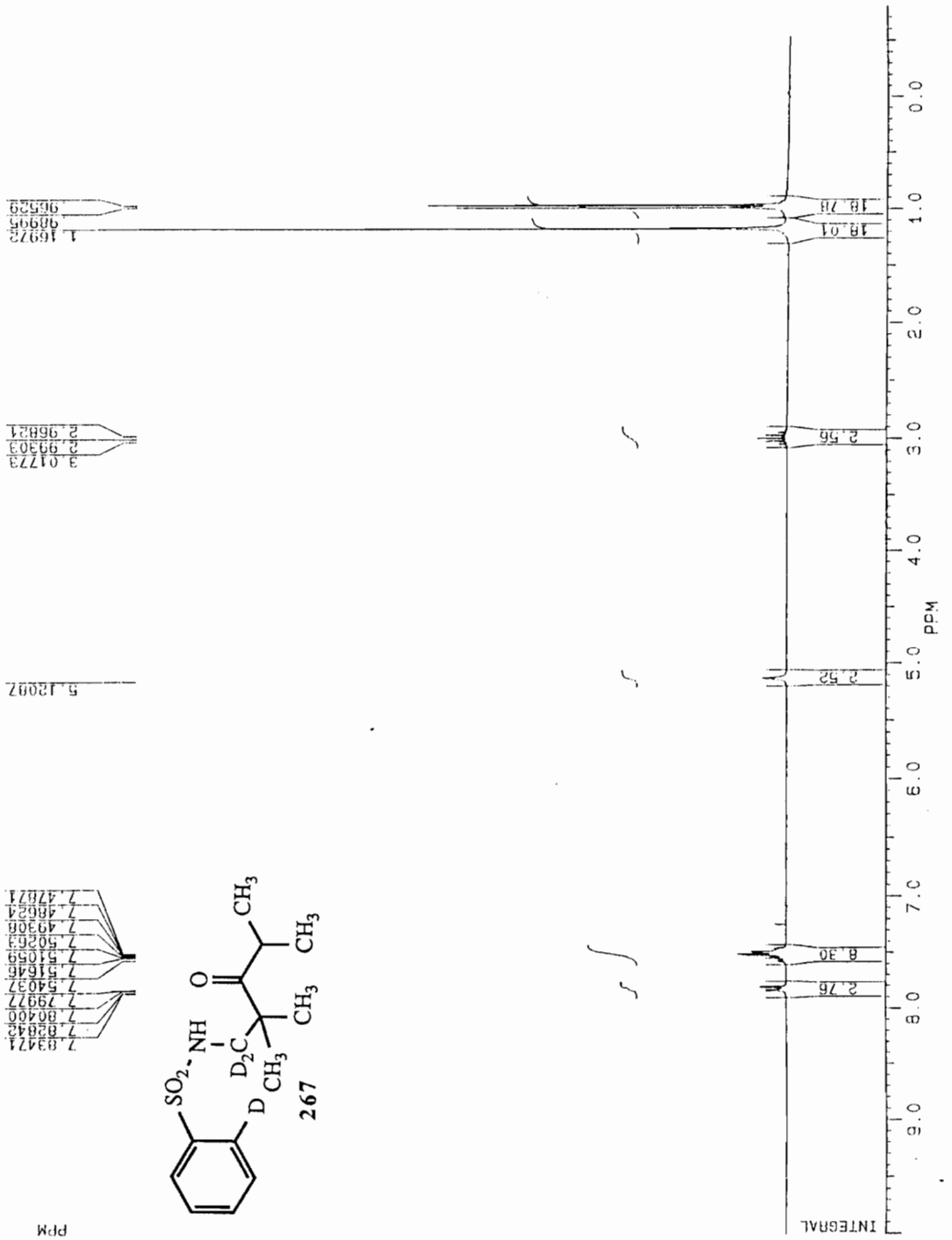

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
SO2NHCD2CD2NHSO2
D
D
266

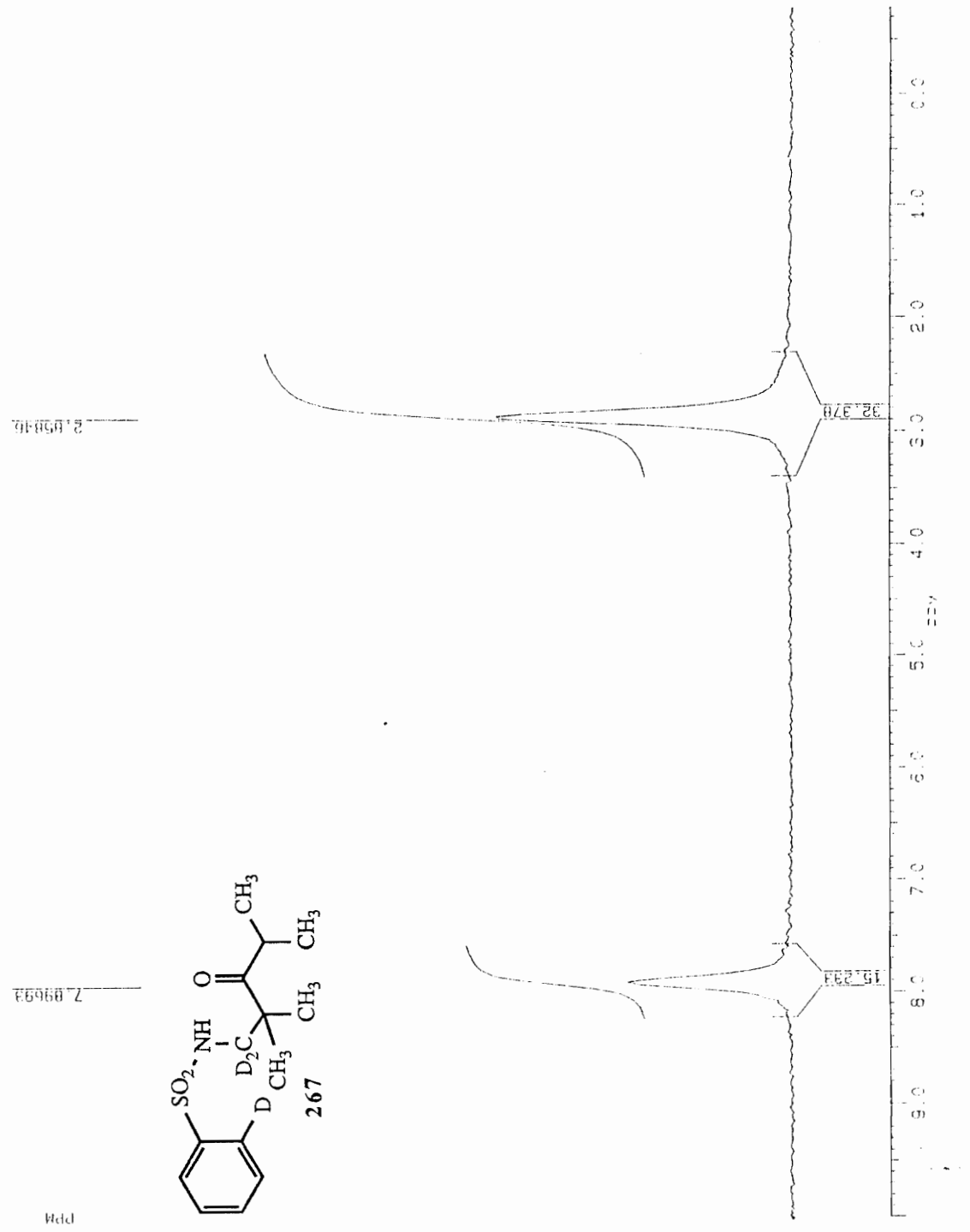

SO2NHCD2CD2NHSO2
D
D

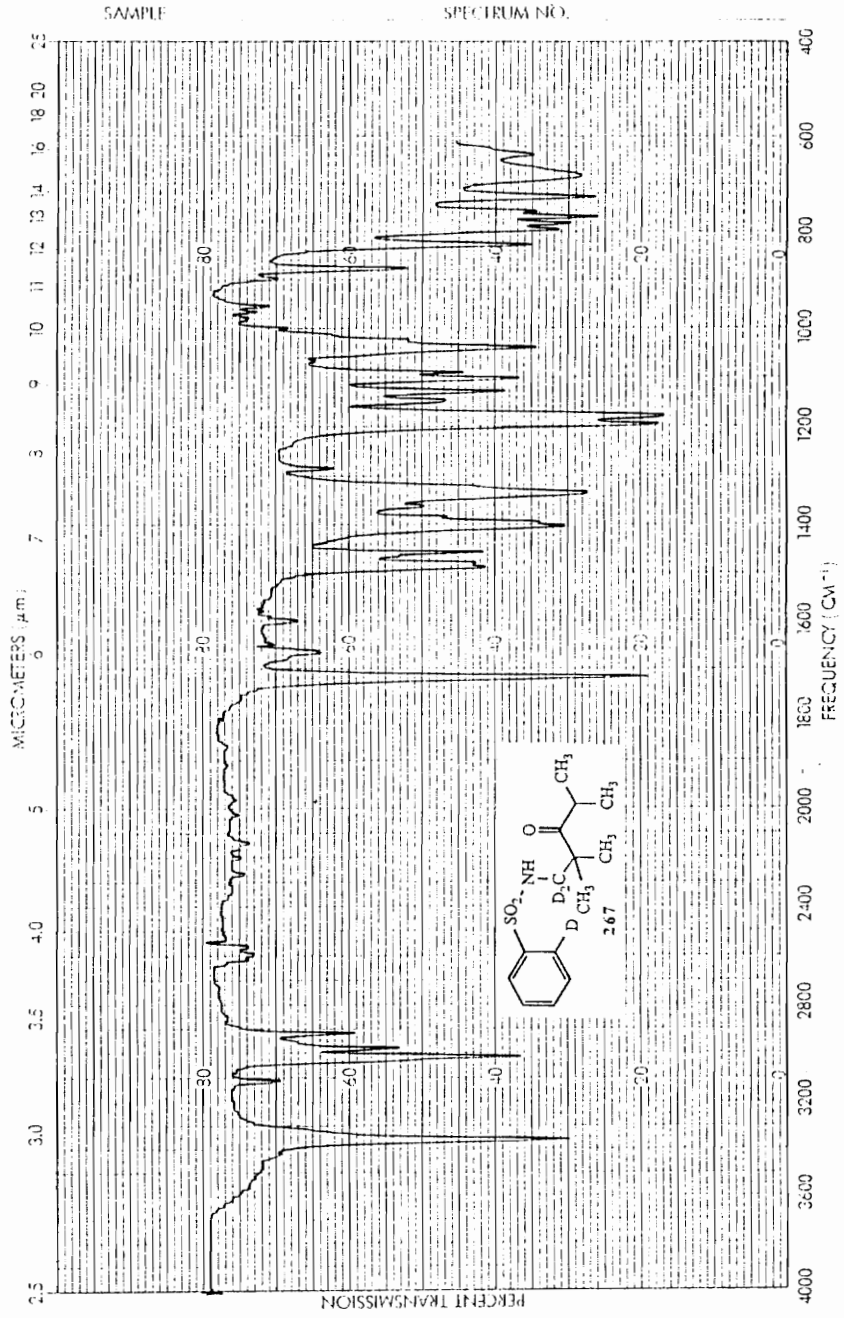
266

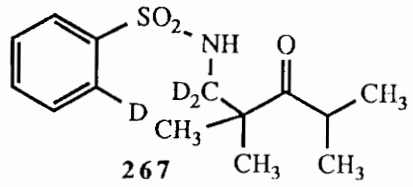

R307#34 x1 Bgd=1 11-APR-90 15:21+0:03:35 70E-HF CI+
BpM=0 I=5.2v Hm=0 TIC=231706000 Acnt:JW Sys:DICI
WJL-III-256F PT= 0° Cal:PFKAP5A
#34 1.0
34225000
MASS
347
MASS


WJL-IV-128
OBSERVE C13
FREQUENCY 100.577 MHz
SPECTRAL WIDTH 25000.0 Hz
ACQUISITION TIME 1.199 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 6.0 usec
TEMPERATURE 25.0 deg. C.
NO. REPETITIONS 1248
DECOUPLE H1
HIGH POWER 43
DECOUPLER CONTINUOUSLY ON
WALTZ-16 MODULATED
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 45 minutes

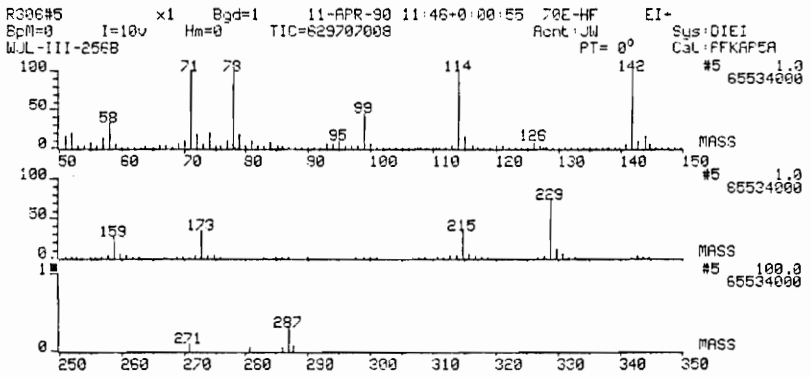

267
INTEGRAL
PPM

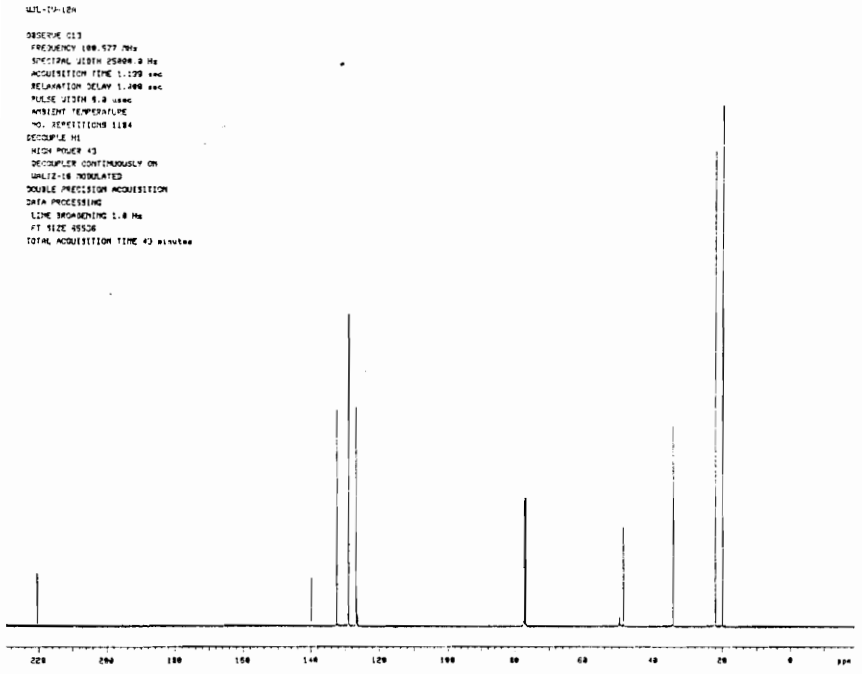

267
PPM

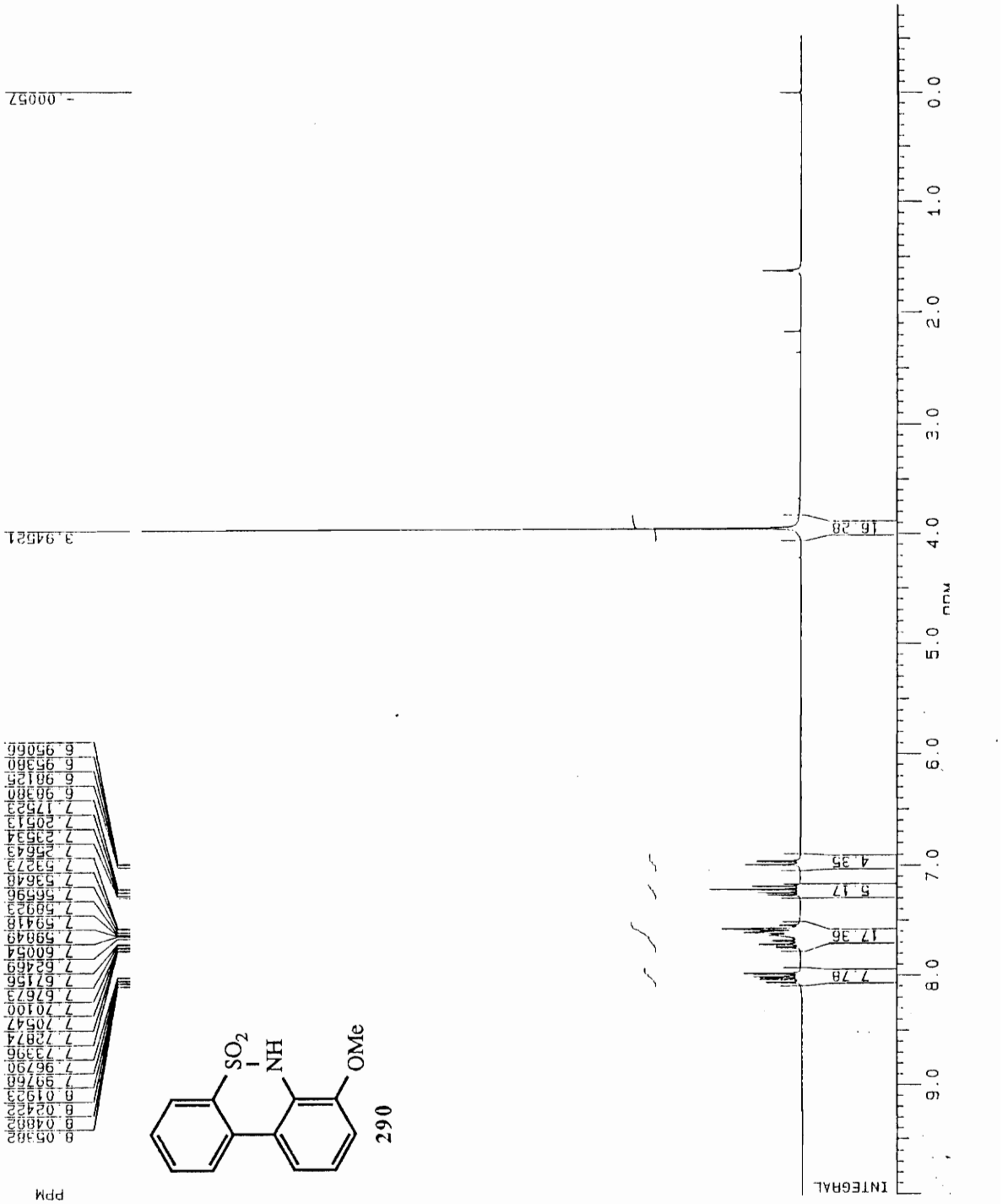

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
267

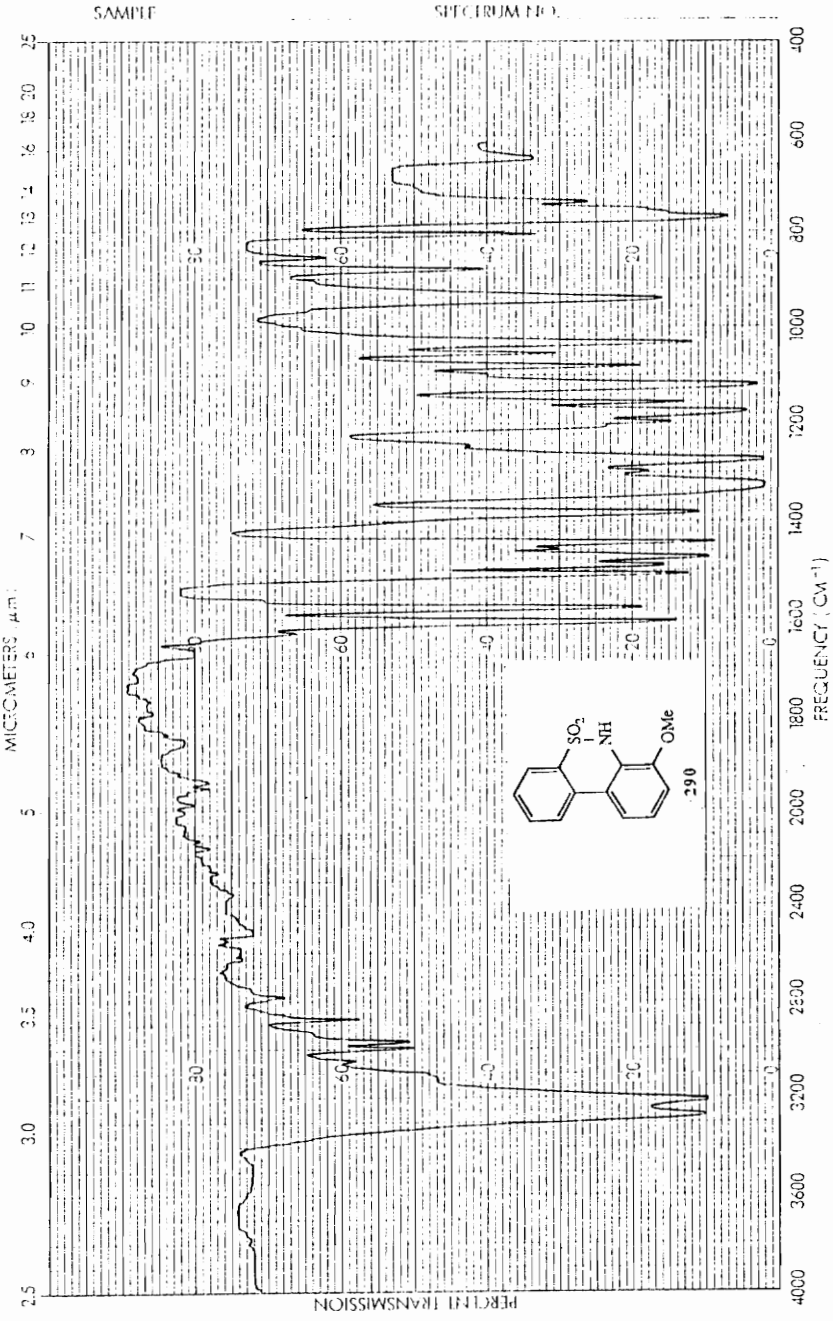

SO2
NH
O
D2C
CH3
D
CH3
CH3
CH3

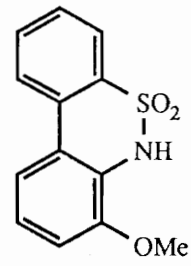
267


R306#5 x1 Bgd=1 11-APR-90 11:46+0:00:55 70E-HF EI+
BpM=0 I=10v Hm=0 TIC=829707008 Acnt:JW Sys:DIEI
WJL-III-256B PT= 0° CaL:FFKAFEA
#5 1.0 65534000
MASS
#5 100.0 65534000
MASS

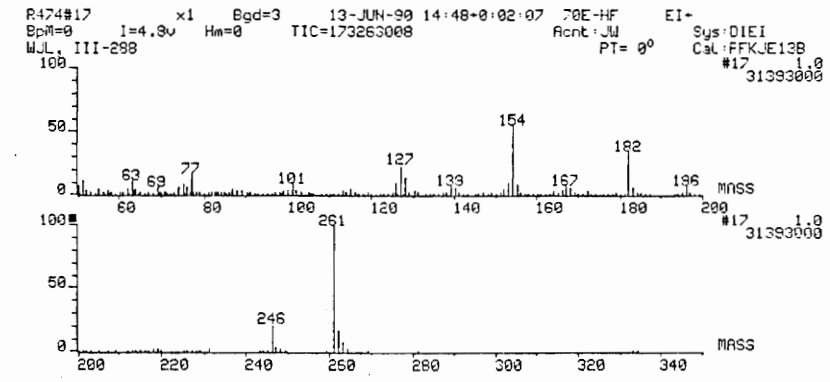

WJL-IV-12A
OBSERVE C13
FREQUENCY 100.577 MHz
SPECTRAL WIDTH 25000.0 Hz
ACQUISITION TIME 1.199 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 6.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 1184
DECOUPLE H1
HIGH POWER 43
DECOUPLER CONTINUOUSLY ON
WALTZ-16 MODULATED
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 43 minutes

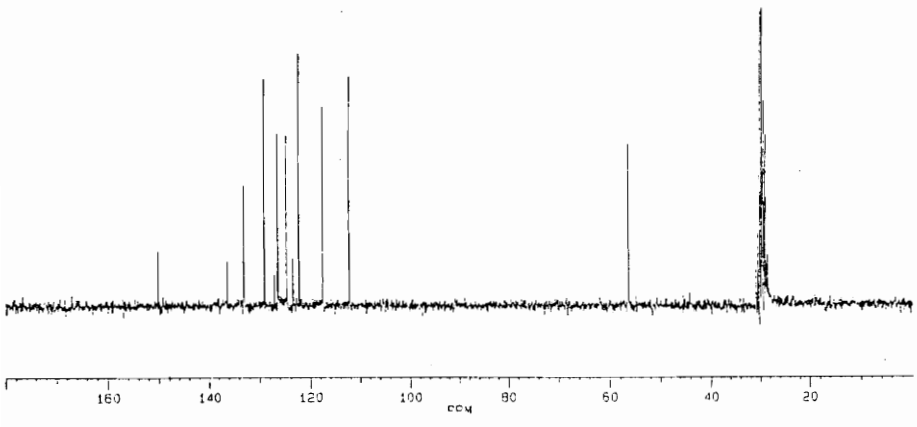

SO2
NH
OMe
290
INTEGRAL
PPM

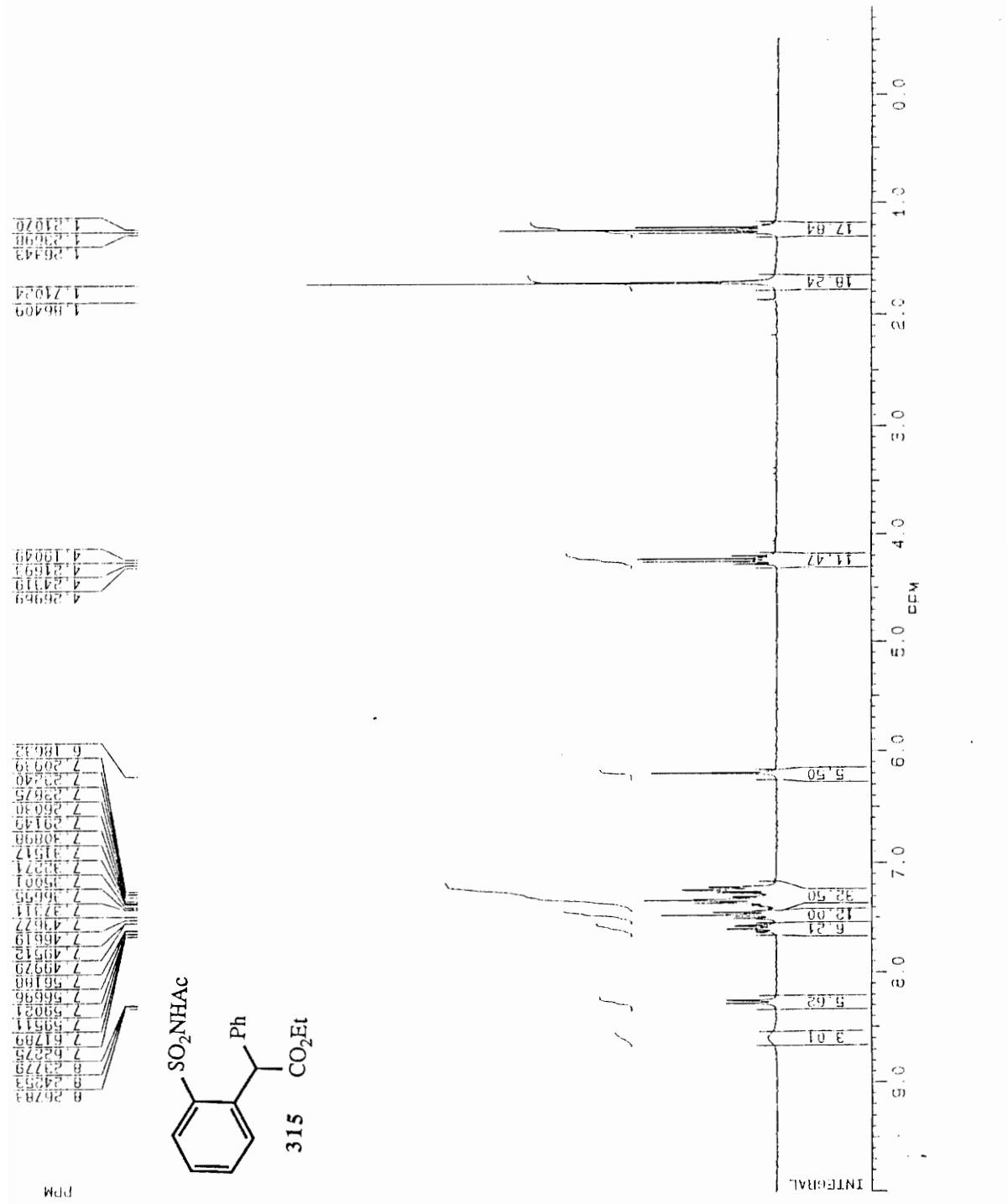

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
SO2
NH
OMe
290

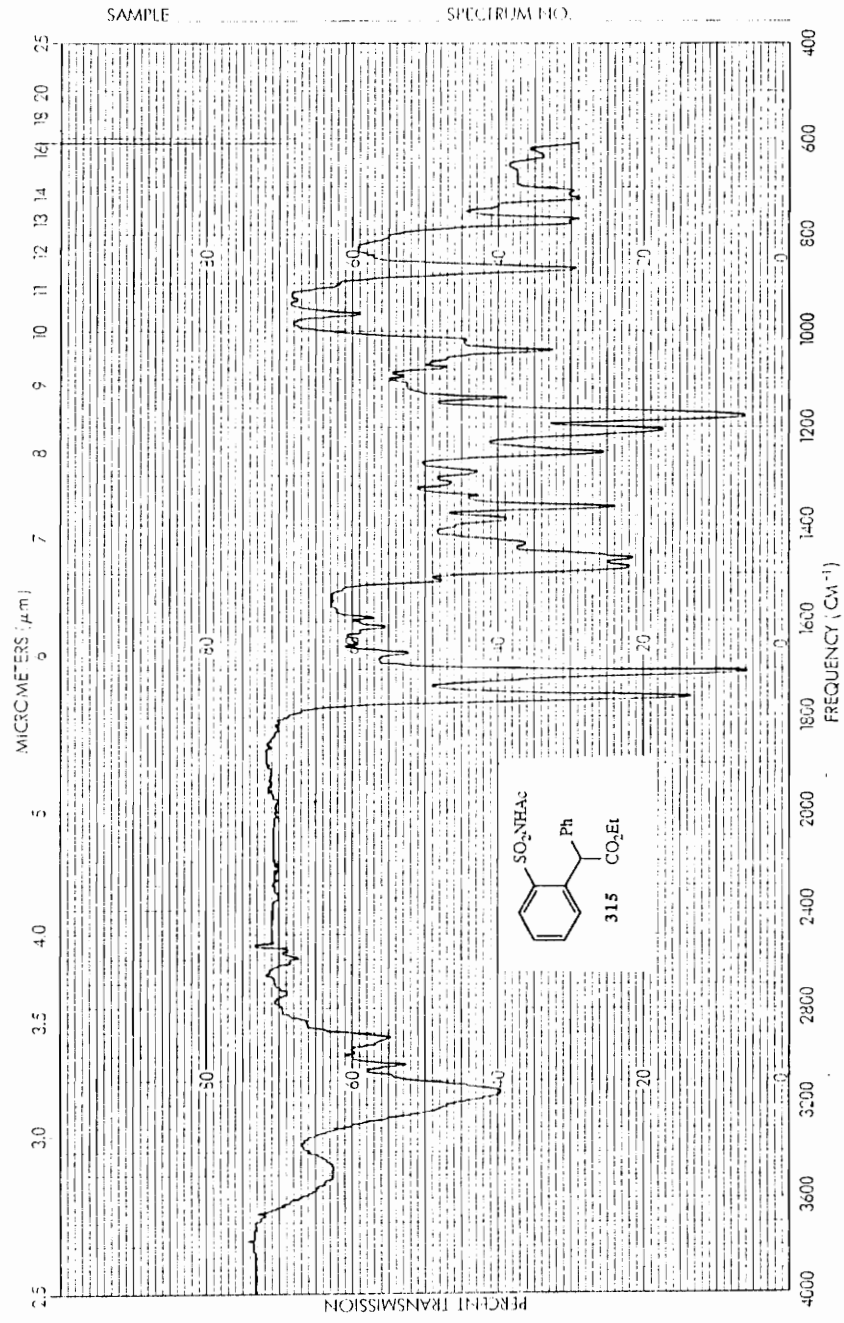

SO2
NH
OMe

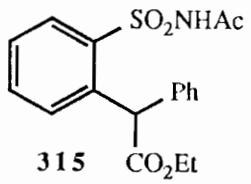
290


R474#17 x1 Bgd=3 13-JUN-90 14:48+0:02:07 70E-HF EI+
BpM=0 I=4.8v Hm=0 TIC=173263008 Acnt:JW Sys:DIEI
WJL, III-298 PT= 0° Cal:FFKJE13B
#17 1.0
31393000
MASS
#17 1.0
31393000
MASS

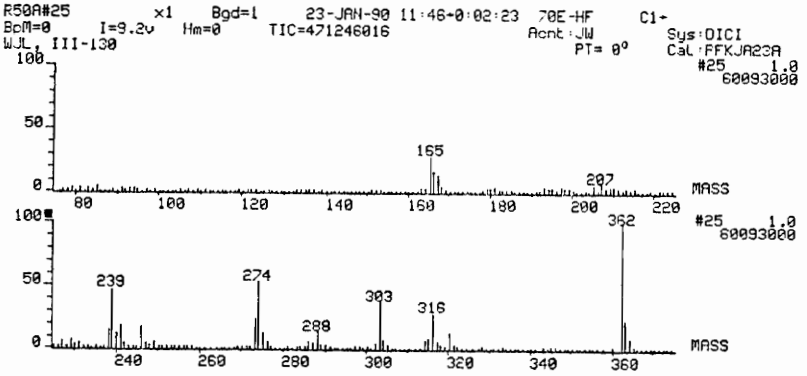

ppm

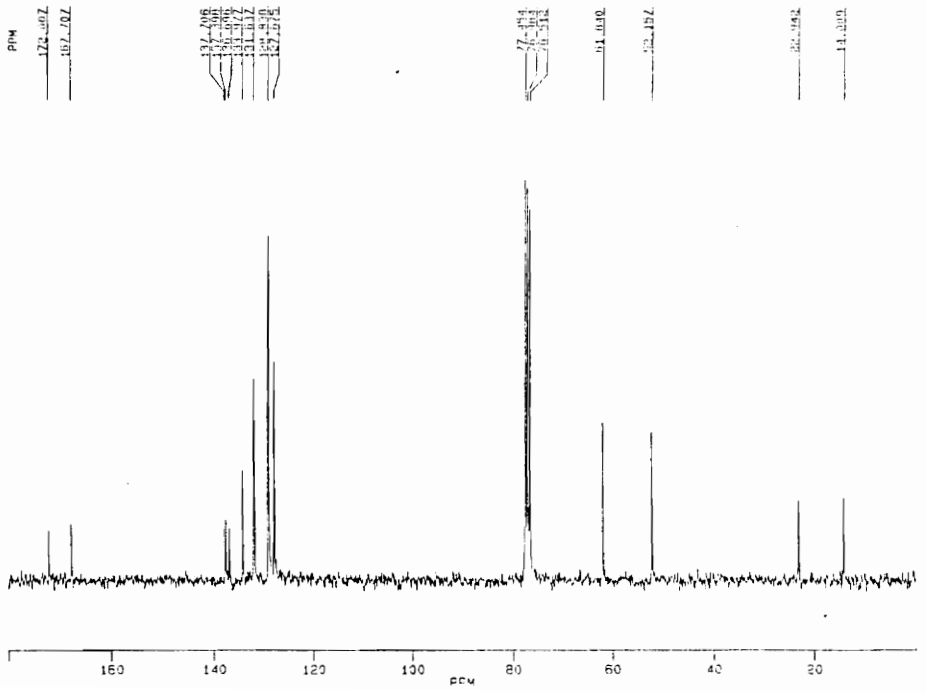

SO2NHAc
Ph
CO2Et
315
PPM
INTEGRAL
17.84
18.24
11.47
5.50
32.50
12.00
6.21
5.62
3.01

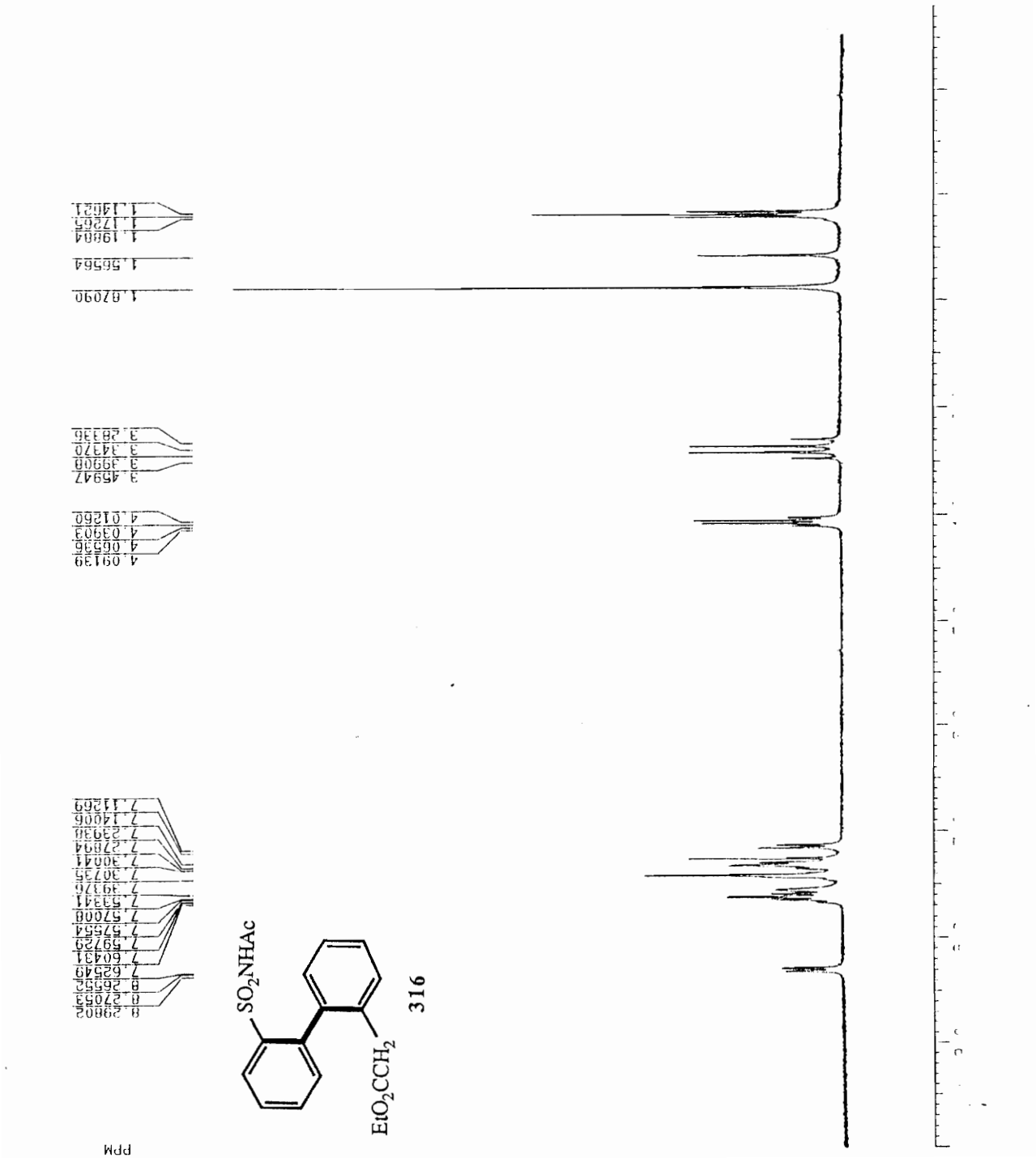

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
SO2NHAc
Ph
CO2Et
315

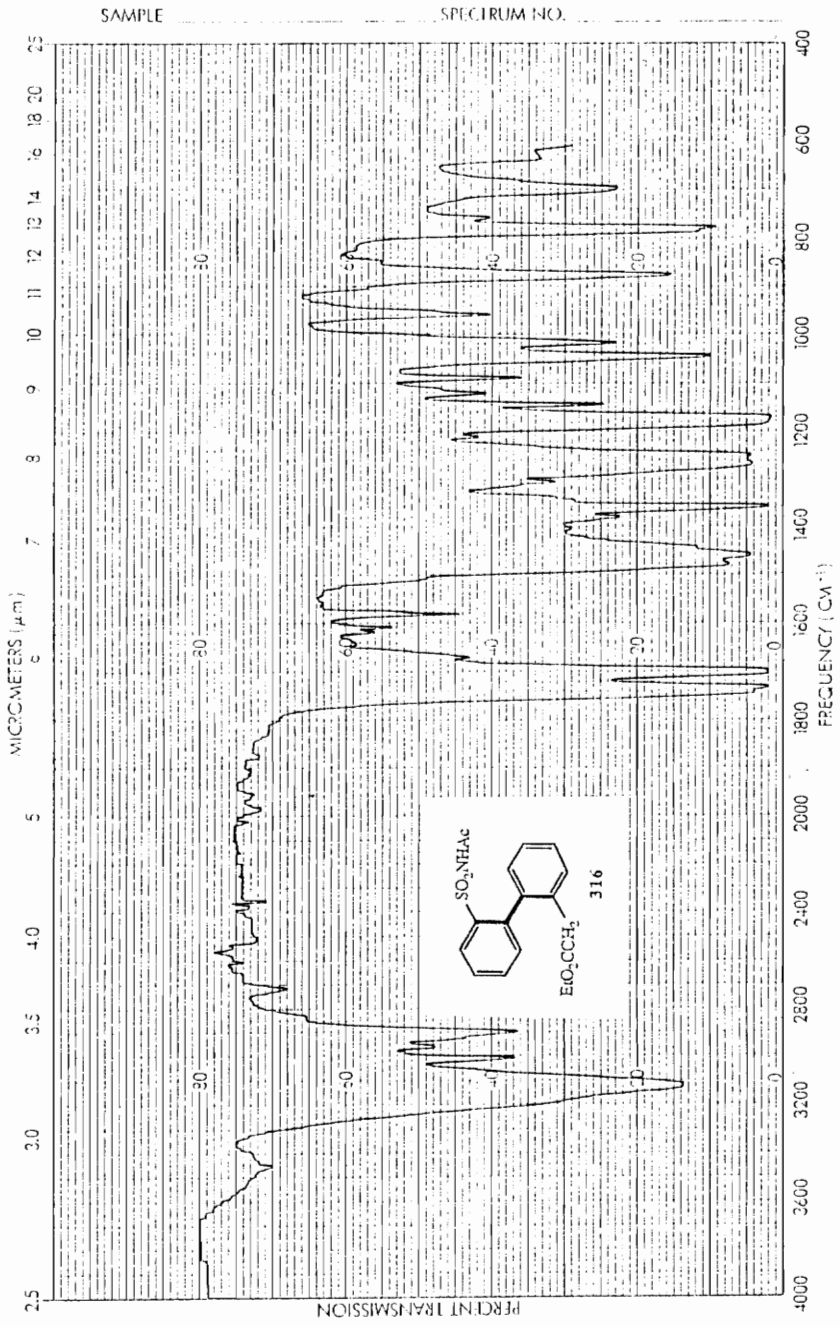

SO2NHAc
Ph
CO2Et

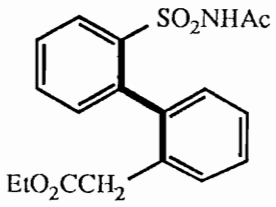
315


R50A#25 x1 Bgd=1 23-JAN-90 11:46+0:02:23 70E-HF C1+
BcM=0 I=9.2v Hm=0 TIC=471246016 Acnt:JW Sys:DICI
WJL, III-130 PT= 0° Cal:FFKJA23A
#25 1.0
60093000
MASS
#25 1.0
60093000
MASS

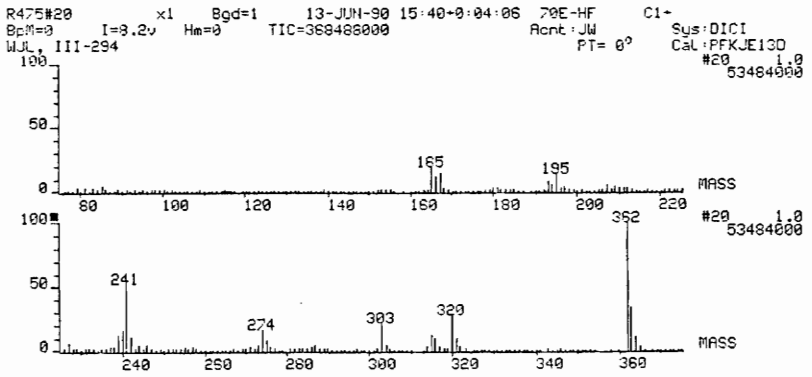

PPM
ppm

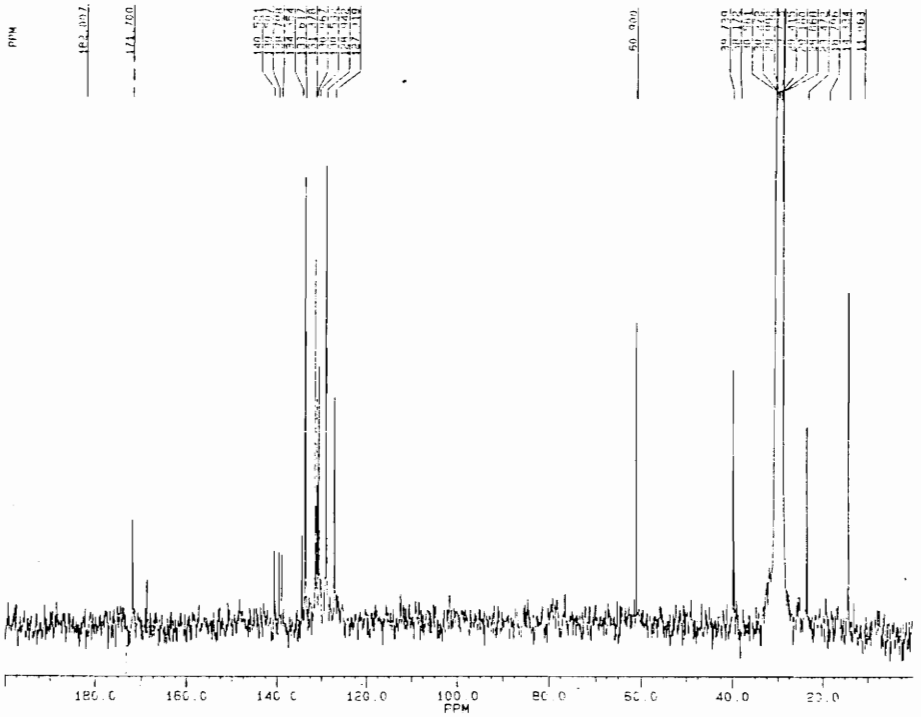

1.14021
1.17265
1.19804
1.56564
1.87090
3.28136
3.34170
3.39908
3.45947
4.01260
4.03903
4.06536
4.09139
7.11269
7.14006
7.23930
7.27894
7.30041
7.30735
7.39176
7.53341
7.57008
7.57554
7.59729
7.60431
7.62549
8.26552
8.27053
8.29802
SO_2NHAc
EtO_2CCH_2
316
ppm

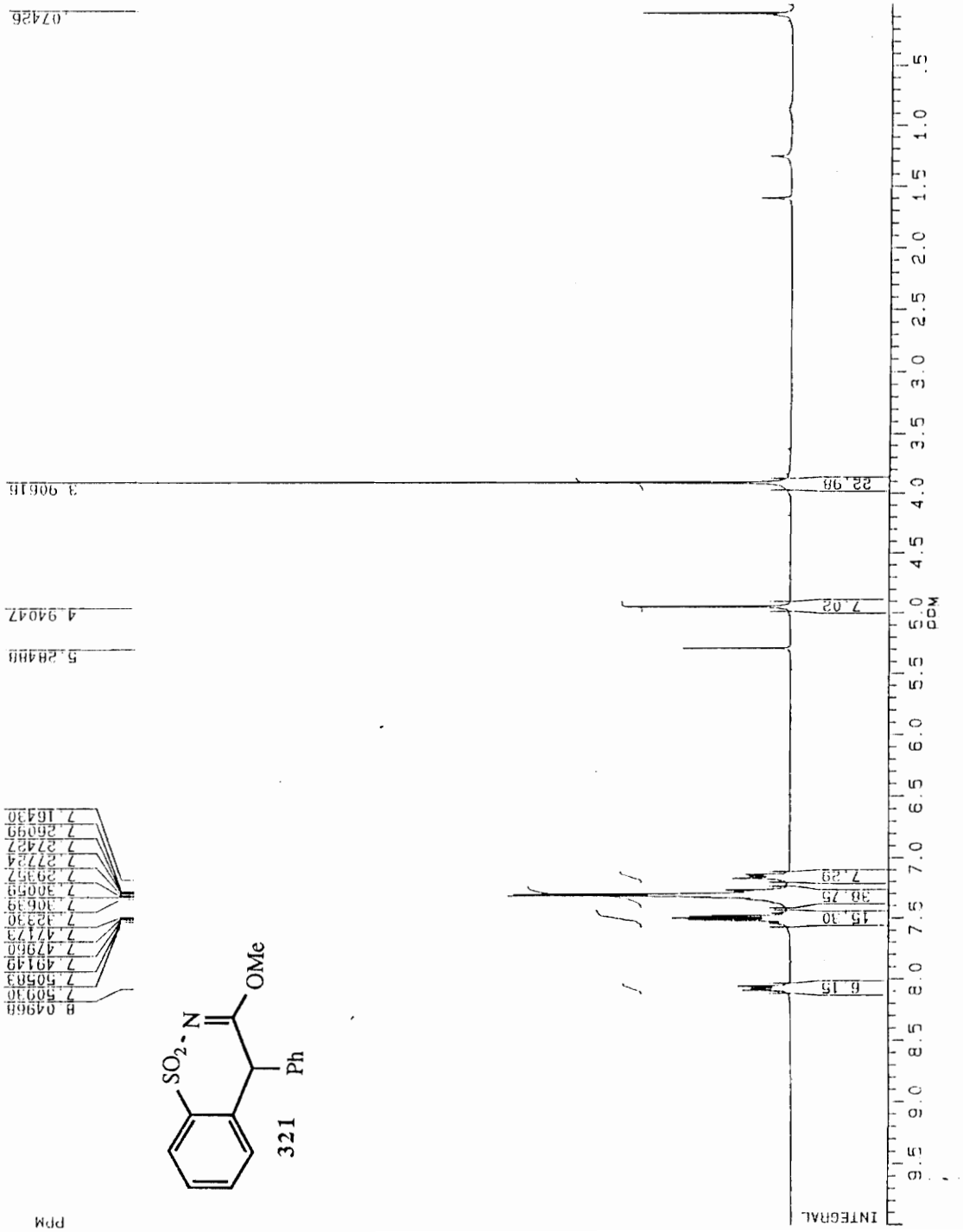

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
SO2NHAc
EtO2CCH2
316

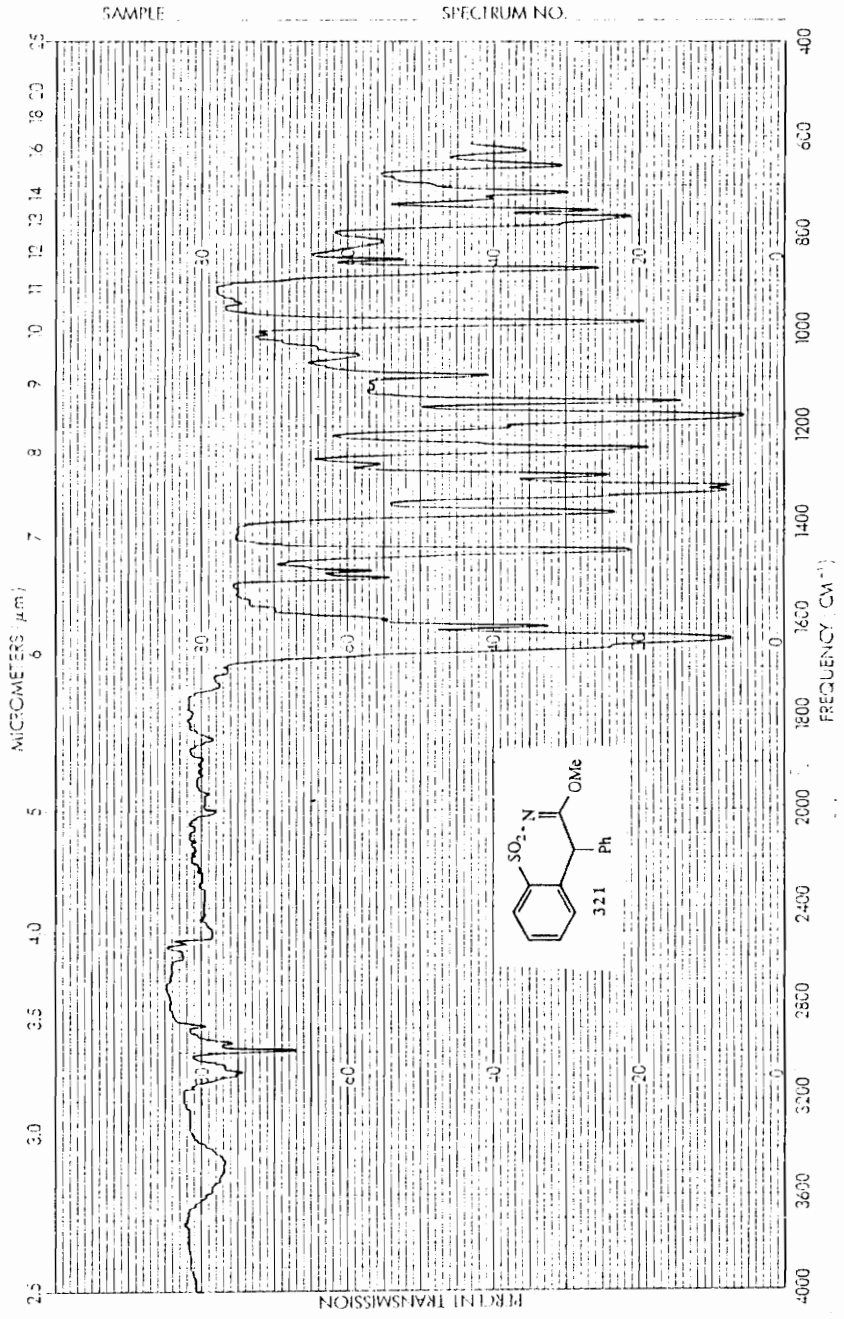

SO2NHAc
EtO2CCH2

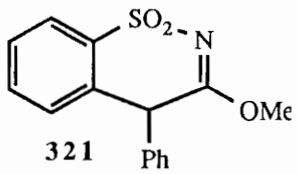
316


R475#20 x1 Bgd=1 13-JUN-90 15:40+0:04:06 70E-HF CI+
BPM=0 I=8.2v Hm=0 TIC=368486000 Acnt:JW Sys:DICI
WJL, III-294 PT= 0° Cal:PFKJE13D
#20 1.0
5348400
MASS
#20 1.0
53484000
MASS

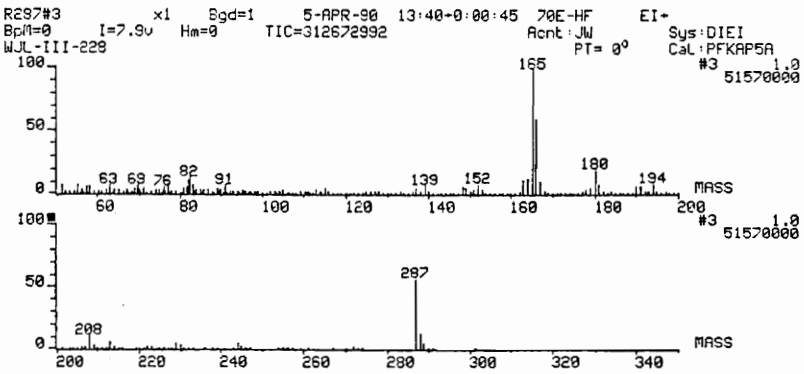

PPM
PPM

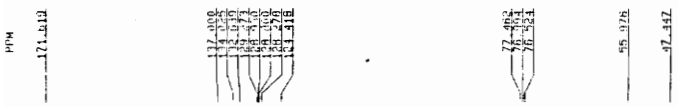

321
Ph
OMe
N
SO_2
PPM
INTEGRAL

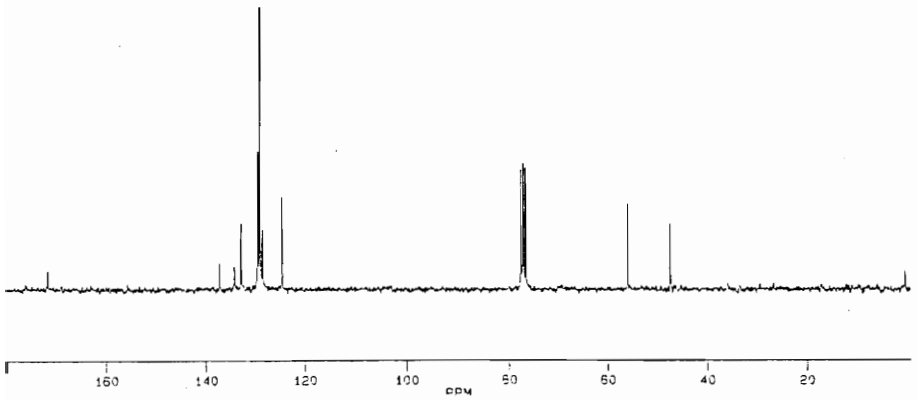

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
OMe
Ph
321

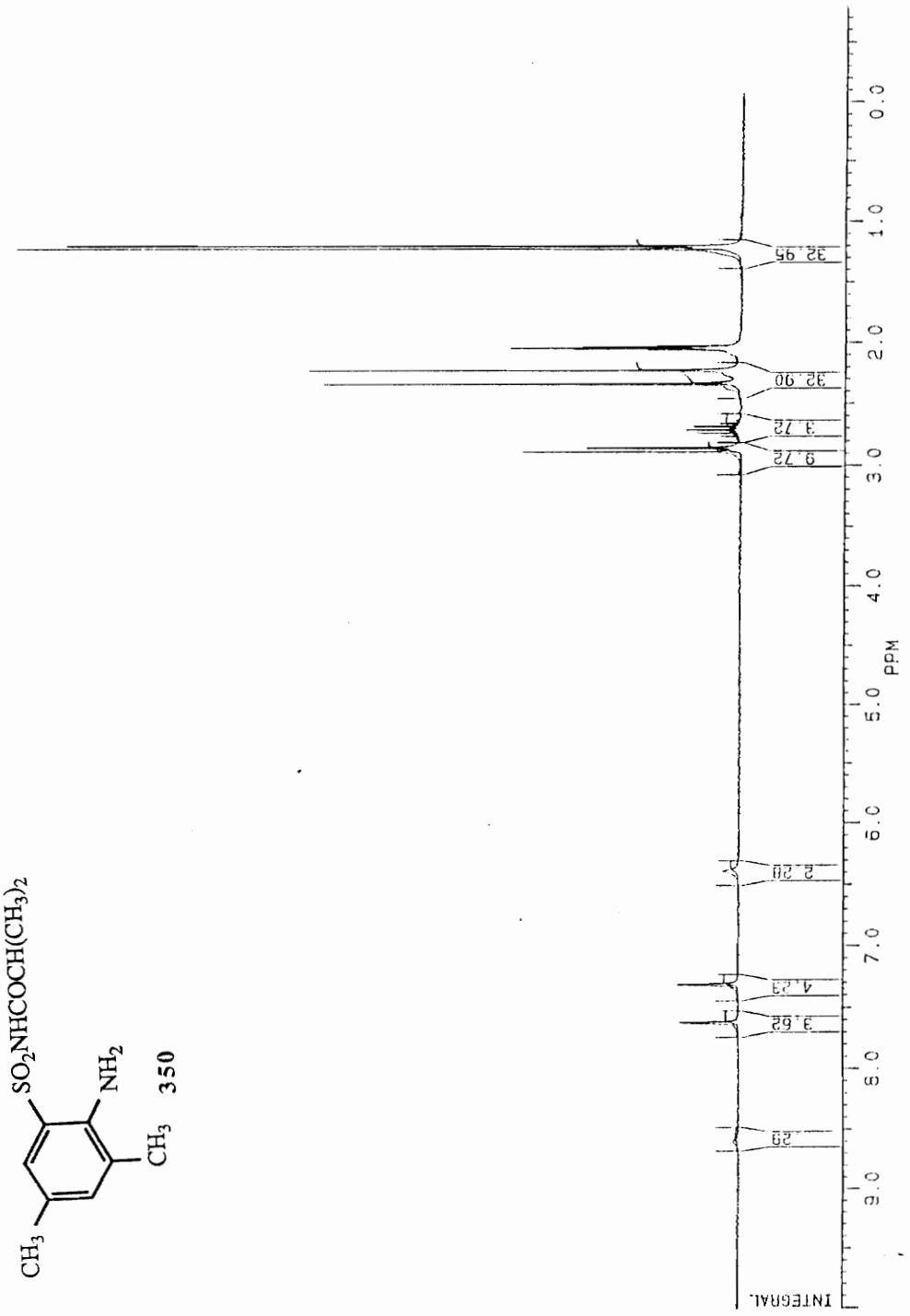

SO2
N
OMe
Ph

321


R297#3 x1 Bgd=1 5-APR-90 13:40+0:00:45 70E-HF EI+
BpM=0 I=7.9v Hm=0 TIC=312672992 Acnt:JW Sys:DIEI
WJL-III-229 PT= 0° Cal:PFKAP5A
#3 1.0
51570000
MASS
#3 1.0
51570000
MASS

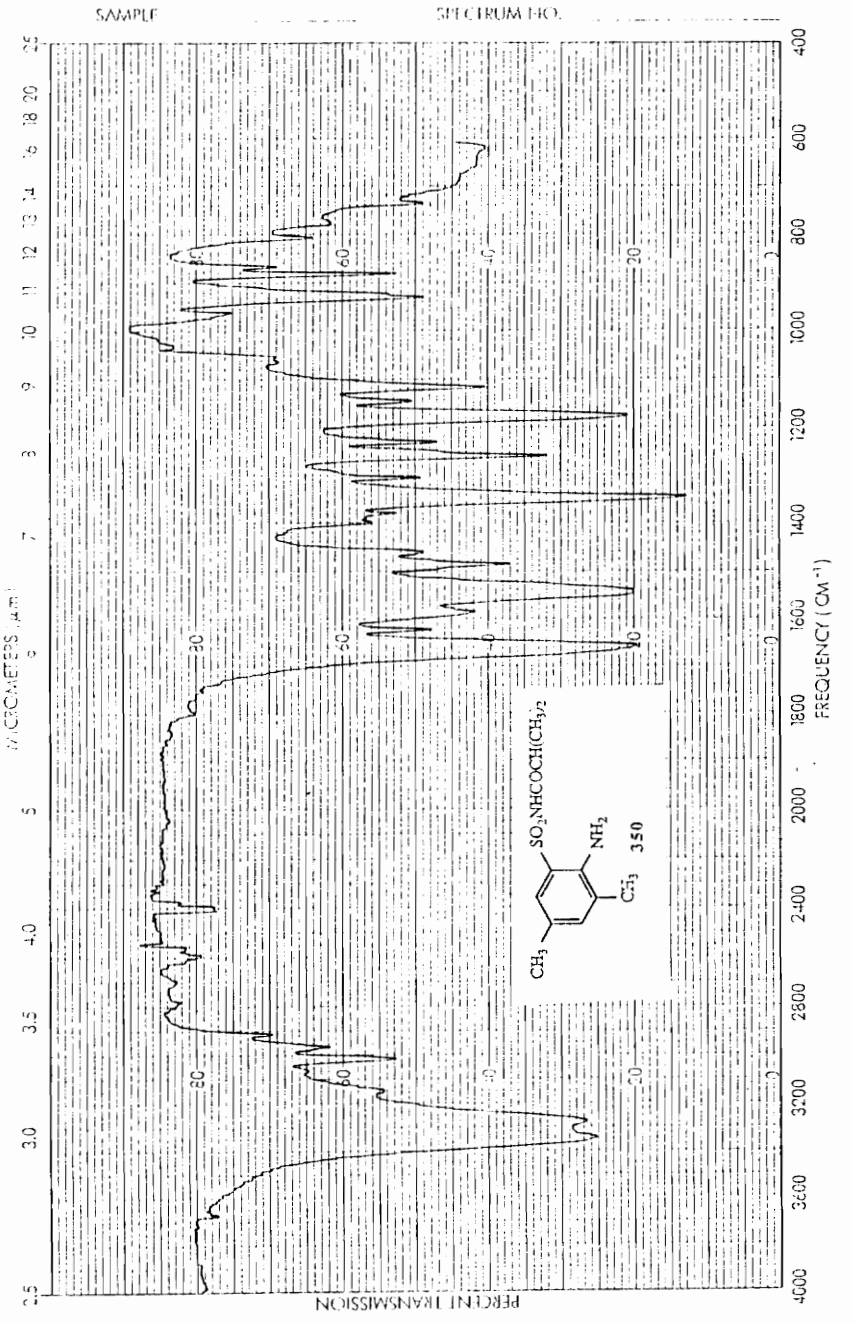


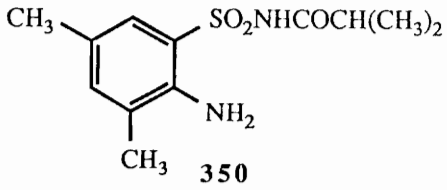

ppm


32.95
32.90
3.72
9.72
2.20
4.23
3.62
29
INTEGRAL
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0

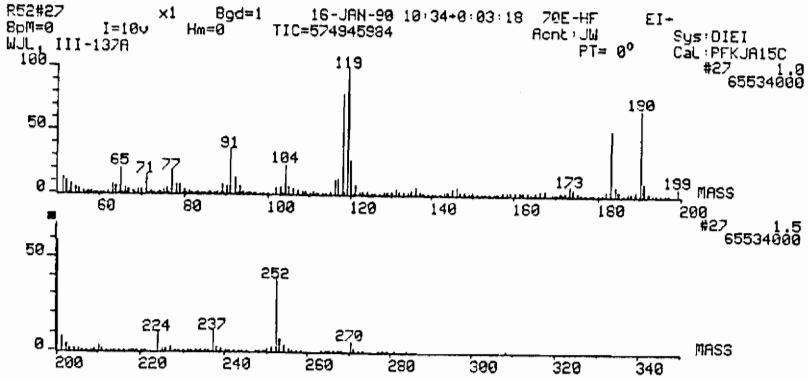
SO2NHCOCH(CH3)2
NH2
CH3
CH3

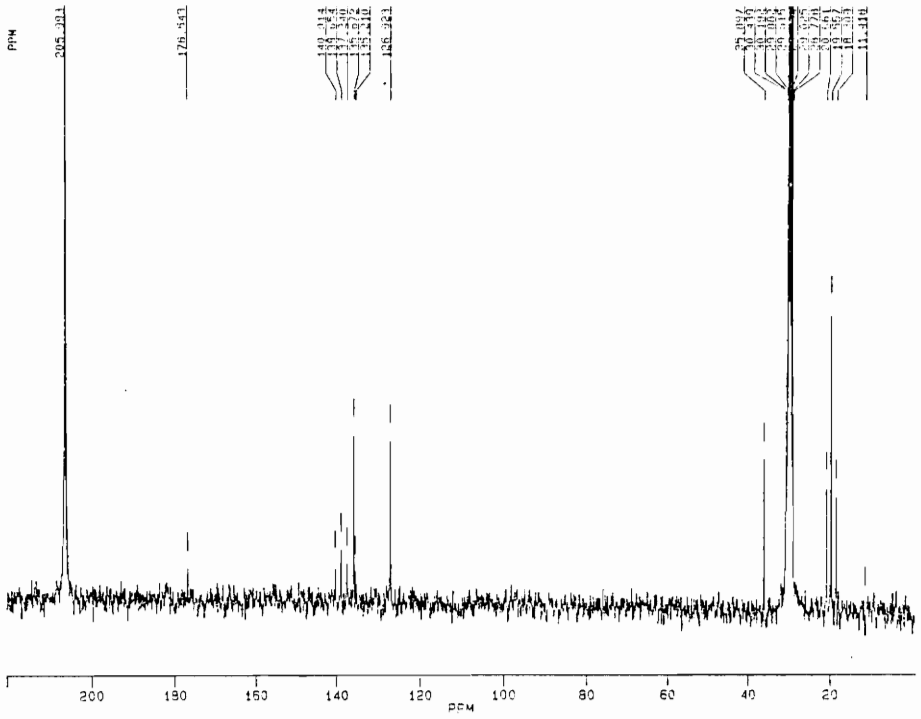
350

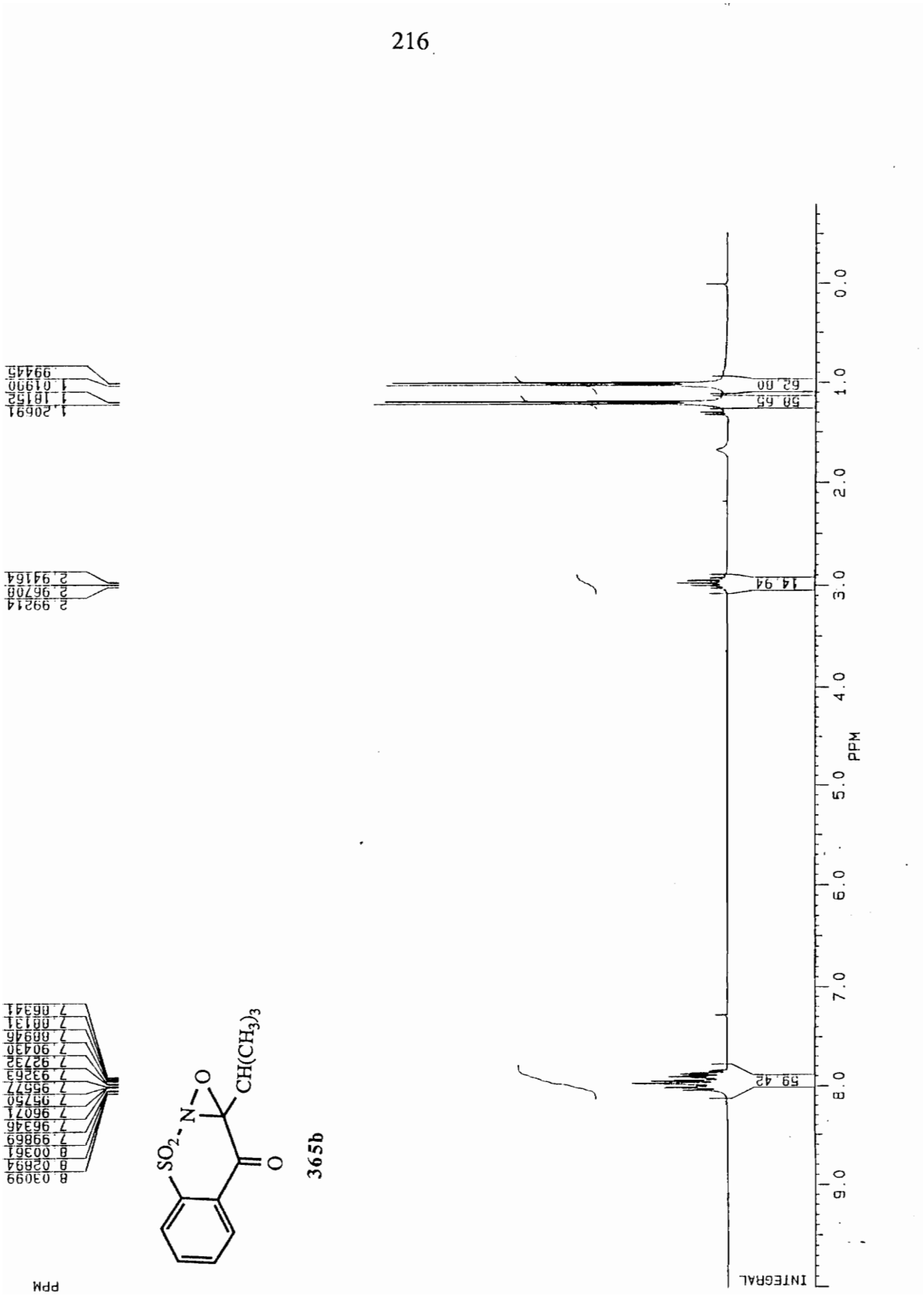

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
SO2NHCOCH(CH3)2
NH2
CF3
CH3
350

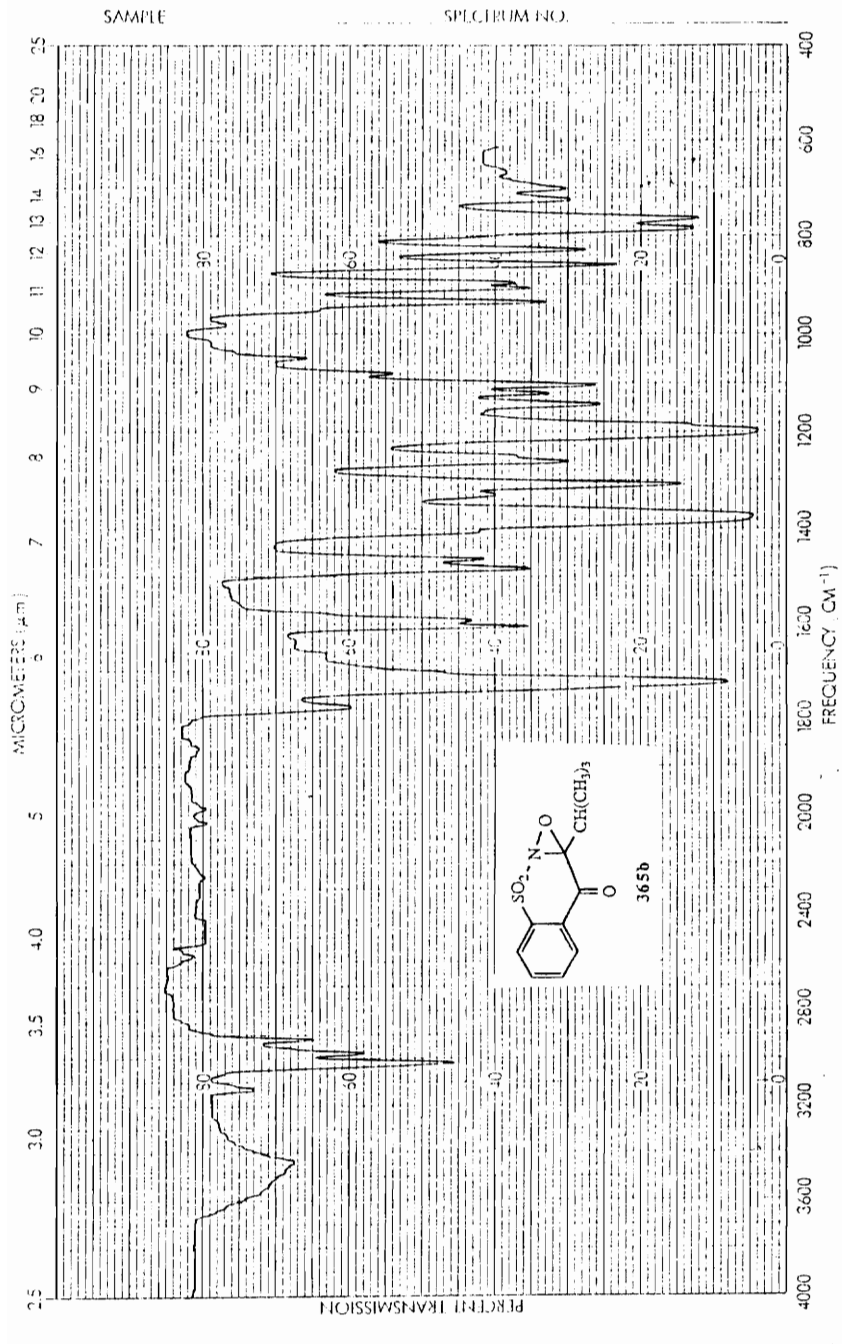

CH3
SO2NHCOCH(CH3)2
NH2
CH3

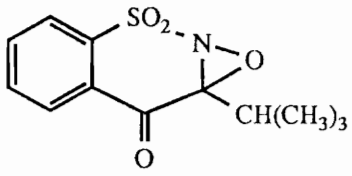
350


R52#27 x1 Bgd=1 16-JAN-90 10:34+0:03:18 70E-HF EI+
BpM=0 I=10v Hm=0 TIC=574945984 Acnt:JW Sys:DIEI
WJL, III-137A PT= 0° Cal:PFKJA15C
#27 1.0
65534000
119
190
91
65
71
77
104
173
199
MASS
#27 1.5
65534000
252
224
237
270
MASS

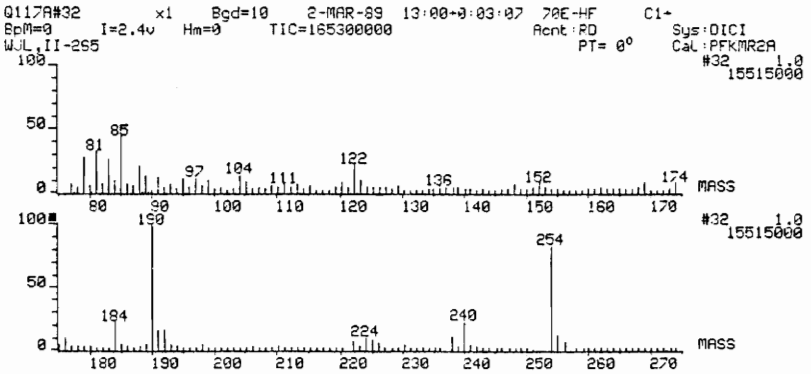

PPM
PPM

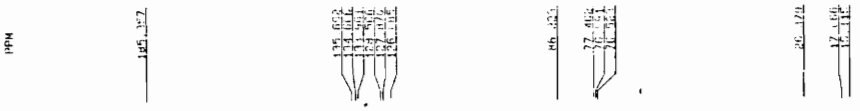

365b
SO2
N
O
CH(CH3)3
O
PPM
INTEGRAL
59.42
14.94
62.00
59.65
8.03099
8.02894
8.00361
7.99869
7.96346
7.96071
7.95750
7.95577
7.93263
7.92732
7.90430
7.88946
7.88131
7.86341
2.99214
2.96708
2.94164
1.20691
1.18152
1.01900
.99445

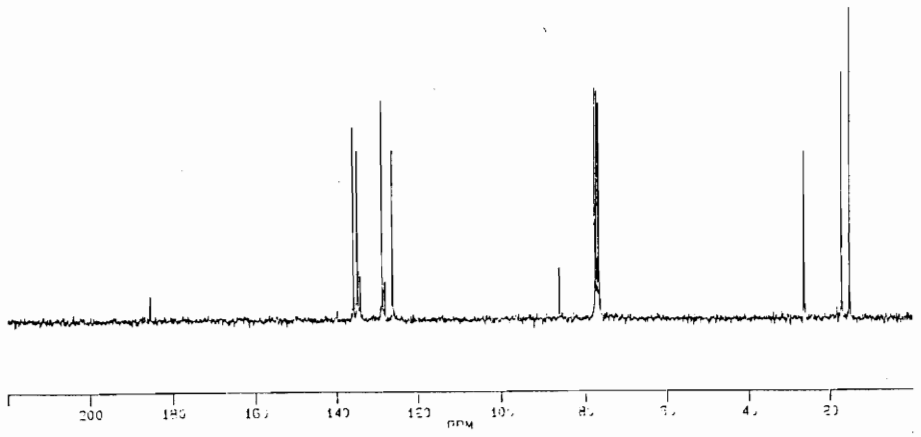

SAMPLE
SPECTRUM NO.
MICROMETERS (μm)
FREQUENCY (CM⁻¹)
PERCENT TRANSMISSION
365b


SO2
N
O
CH(CH3)3
O

365b


Q117A#32 x1 Bgd=10 2-MAR-89 13:00+0:03:07 70E-HF C1+
BpM=0 I=2.4v Hm=0 TIC=165300000 Acnt:RD Sys:DICI
WJL,II-265 PT= 0° Cal:PFKMR2A
#32 1.0
15515000
MASS
#32 1.0
15515000
MASS




PPM

VIII VITA

William Joseph Layman Jr. was born in Baltimore, MD on October 30, 1963 to William Joseph and Mildred Patterson Layman. In December 1984 he received his A.A. degree from Valencia Community College, Orlando, FL. In May 1986 he received his B.S degree in chemistry from the University of Central Florida, where he graduated *cum laude*. In September of 1986 he began graduate studies in chemistry at Virginia Polytechnic Institute and State University under the supervision of Dr. James F. Wolfe. In September of 1990 he will accept a position with the Ethyl Corporation, Baton Rouge, Louisiana.