STUDIES OF INTRAMOLECULAR $S_{RN}1$ REACTIONS OF CARBANIONS DERIVED FROM 2-(*o*-HALOBENZYL)AMIDES AND 3-(*o*-HALOBENZYL)IMIDES. APPLICATION TO THE SYNTHESIS OF SUCCINIMIDO[3,4-b]INDANE, A POTENTIAL ANTICONVULSANT.

by

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(ABSTRACT)

The possibility of inducing intramolecular $S_{RN}1$ reactions in two 2-(*o*-halobenzyl)-amides, 2-(*o*-iodobenzyl)-*N,N,N'N'*-tetramethylsuccinamide (**77**) and 2-(*o*-iodobenzyl)-*N,N,N'N'*-tetramethylglutaramide (**80**), and three 3-(*o*-halobenzyl)imides, 3-(*o*-iodobenzyl)succinimide (**99**), 3-(α-cyano-*o*-bromobenzyl)succinimide (**82**) and 3-(*o*-iodobenzyl)glutarimide (**108**), was investigated. All of these substrates were prepared during the course of the investigation.

Treatment of **77** and **80** with excess potassium amide in liquid ammonia under photostimulated conditions afforded reasonably good yields of the expected cyclized products, 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) and 1,3-bis-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**), respectively. When imide **99** was subjected to similar conditions, it also underwent the expected cyclization, affording succinimido[3,4-b]indane (**61**) in acceptable yield. Mechanistic investigations revealed that all of the above reactions appear to occur via intramolecular $S_{RN}1$ processes.

Attempts to induce similar cyclization reactions with 3-(α-cyano-*o*-bromobenzyl)-succinimide (**82**) and 3-(*o*-iodobenzyl)glutarimide (**108**) proved unsatisfactory. Substrate **82** failed to undergo cyclization to give the desired succinimido[3,4-b]indane-8-carbonitrile (**83**). Instead, 3-(α-cyano-α-phenylmethyleno)succinimide (**107**) was formed as the sole isolable product, presumably via an intramolecular β-hydrogen atom abstraction process. 3-(*o*-Iodobenzyl)glutarimide (**108**) did not undergo the desired cyclization to give 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine-2,4-dione (**62**) either, presumably because of steric hindrance.

This study was undertaken with the objective of investigating the possibility of inducing intramolecular $S_{RN}1$ reactions in appropriately substituted amide and imide derivatives. The specific substrates, **77**, **80**, **82**, **99** and **108**, were selected for the study because it appeared that intramolecular $S_{RN}1$ reactions with these substrates would result in the formation of products that might be useful in the development of new anticonvulsant agents. In this context, the preparation of succinimido[3,4-b]indane (**61**), which seemed likely to possess antiepileptic properties, fulfilled our proposed objective of applying novel chemistry to the preparation of a new potential anticonvulsant agent.

The successful cyclization of **77** and **80** into the expected products, 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) and 1,3-bis-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**), respectively, also represented the application of novel chemistry to the formation of two other benzo-fused systems. The synthetic and mechanistic investigations undertaken during this study are expected to extend the scope of the synthetic utility of intramolecular $S_{RN}1$ chemistry.

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I. INTRODUCTION

The scope and limitations of nucleophilic aromatic substitution reactions have been extensively investigated in our laboratories for the past several years, with particular emphasis on photoassisted substitutions involving a radical-chain mechanism, commonly referred to as $S_{RN}1$ reactions. Recently, these investigations have begun to incorporate yet another component, that of the synthesis of new, more effective anticonvulsant agents. Thus, the possible use of previously uninvestigated $S_{RN}1$ reactions in the synthesis of compounds that might possess anticonvulsant activity has been a significant part of our research efforts, and constitutes the major focus of this dissertation.

Numerous researchers have been engaged in the study of $S_{RN}1$ reactions since their discovery almost twenty years ago. These world-wide studies have explored a wide variety of substrates and nucleophiles that can participate in $S_{RN}1$ reactions. In spite of these extensive studies, a particularly attractive aspect of these reactions, the potential for intramolecular $S_{RN}1$ reactions when the potential leaving group as well as the attacking nucleophile are present and appropriately positioned on the same molecule, remains largely untapped. One can envision a variety of cyclic compounds containing carboaromatic and heteroaromatic moieties that can be accessed by this novel synthetic approach.

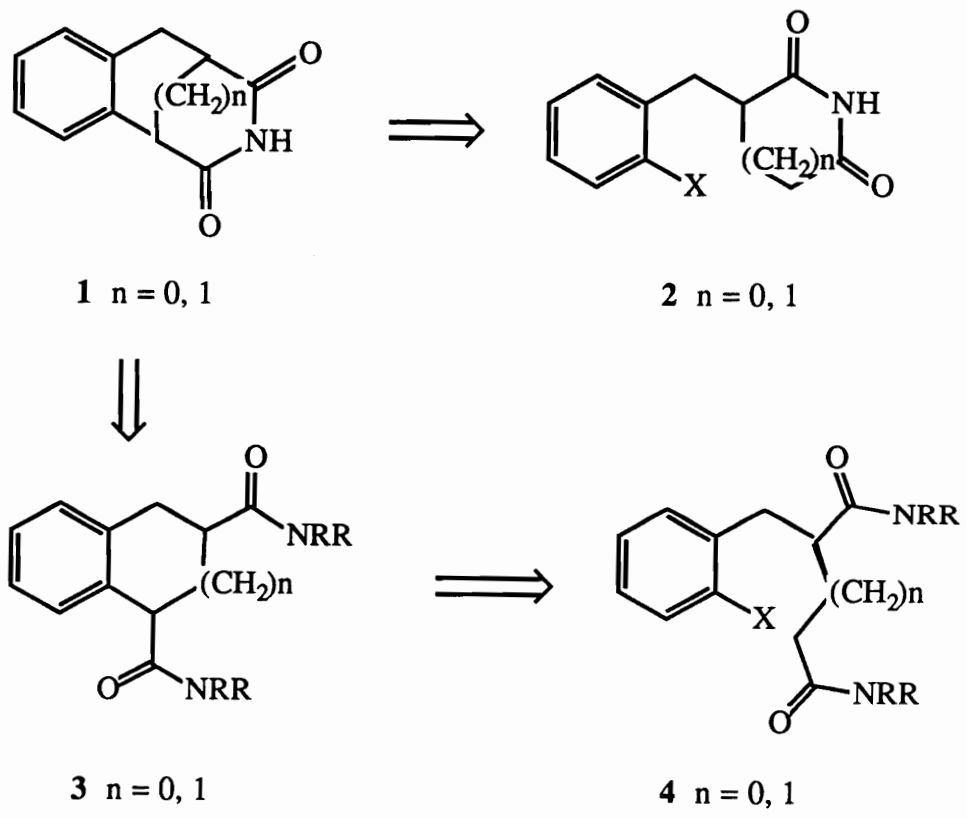
Over the past decade, several members of our research team have been engaged in studies of intramolecular $S_{RN}1$ reactions as synthetic tools. In many instances, the reactions occurred as expected, affording the corresponding cyclized products in high yields. However, other competing processes frequently led to the formation of unexpected products by reaction pathways that did not involve $S_{RN}1$ chemistry. Some of the

processes that have been shown to compete effectively with $S_{RN}1$ reactions occur via the intermediacy of arynes, while others involve β-hydrogen atom abstraction from the nucleophile by intermediate aryl radicals. The latter process has been suspected to occur via a radical chain process similar to the $S_{RN}1$ process, with some intermediate radical species being common to both reaction pathways. Thus, investigations designed to probe the mechanistic features of reactions being studied as synthetic procedures have provided extensive insight into the synthetic applicability of these reactions, and are an integral part of all such investigations.

This dissertation describes the results of our efforts to investigate the possibility of inducing intramolecular $S_{RN}1$ reactions in certain 2-(*ortho*-halobenzyl) derivatives of succinamide and glutaramide. Previous work in our laboratories had shown that amide enolates participate efficiently in intermolecular $S_{RN}1$ reactions, and formed the rationale for the conviction that the proposed reactions would occur as expected. Such reactions, if successful, would also provide a novel synthetic procedure for the preparation of indane and tetralin derivatives, thereby complementing known procedures, most of which utilize electrophilic substitution processes as key synthetic steps. Concurrent mechanistic investigations were carried out in order to provide information that would aid in assessing the synthetic utility of intramolecular $S_{RN}1$ reactions in general.

We also intended to apply these intramolecular $S_{RN}1$ reactions to the synthesis of certain cyclic imides that appeared to have promise as potential anticonvulsant agents. Previous work in our laboratories led us to believe that two such imides, succinimido[3,4-b]indane (**1**, n=0) and 1,2,3,4,5,6-hexahydro-1,5-methano-benzazocine-2,4-dione (**1**, n=1), and perhaps some of their derivatives as well, might exhibit anticonvulsant activity.

Our interest in these compounds stemmed from the observation that it might be possible to develop novel synthetic procedures for their preparation by using intramolecular $S_{RN}1$ reactions in key synthetic steps, as outlined in the following retrosynthetic scheme (Scheme 1). Earlier efforts in our laboratories to prepare these potentially active compounds by the direct cyclization of 3-(*ortho*-halobenzyl) derivatives of succinimide (**2**, n=0) and glutarimide (**2**, n=1) had proved to be unsatisfactory. We had therefore devised an alternative synthetic strategy that employed the reactions proposed below, and were hopeful that this approach would result in efficient syntheses of the desired compounds.



1 n = 0, 1 **2** n = 0, 1

3 n = 0, 1 **4** n = 0, 1

Scheme 1

Thus, this investigation was undertaken with a two-fold objective: firstly, the possibility of inducing intramolecular $S_{RN}1$ reactions in 2-(*ortho*-halobenzyl)amide derivatives (**4**, n=0,1) would be probed, and secondly, these reactions would be applied towards novel syntheses of two potential antiepileptic agents.

II. LITERATURE SURVEY

1. Nucleophilic Aromatic Substitution.

1.1 Introduction.

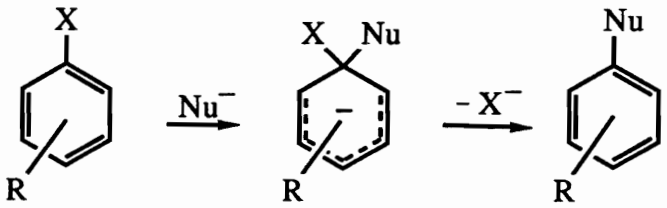
Nucleophilic aromatic substitution is a process that has been used somewhat infrequently, particularly when compared with electrophilic substitution, for the functionalization of aromatic rings. Prior to 1970, non-aryne nucleophilic aromatic substitutions had been found to occur almost exclusively with aromatic substrates containing a nucleofuge (leaving group) that was activated by one or more electron withdrawing groups placed *ortho-* and/or *para-* to it.[1] In the absence of such activating groups, extremely strenuous conditions or strong bases were required to force substitution to take place. However, in the past two decades, extensive research in the area has revealed the participation of even unactivated aryl substrates in non-aryne nucleophilic substitution, and the use of aromatic nucleophilic substitution reactions as an important synthetic tool has now been firmly established.

The mechanisms that have been proposed to describe nucleophilic aromatic substitution reactions vary greatly depending upon the aromatic moiety, the nucleophile, and the reaction conditions; those occurring more commonly will be discussed in the following sections.

1.2. S_NAr (S_NAE) Mechanism.

The S_NAr (S_NAE) mechanism is one of the earliest addition-elimination proposals used to explain nucleophilic substitutions involving activated carboaromatic substrates. The main feature of this mechanism is the formation of the σ-complex (also known as the Meisenheimer or Meisenheimer-Jackson complex) as the reaction intermediate (Scheme

2).[2] Since the process involves addition of the nucleophile followed by the elimination of the nucleofuge, X, it is sometimes referred to as the S_NAE or AE mechanism. The function of the electron withdrawing substituent R is to aid in the dispersal of the negative charge generated in the otherwise highly energetic σ-complex. In some cases, the intermediate complex may be stabilized to such an extent that it can actually be isolated.[3] Thus, the presence of strong electron withdrawing substituents such as nitro or diazonio groups is generally a prerequisite for operation of the S_NAr mechanism. The nature of the nucleofuge also plays an important role in S_NAr reactions. When more electronegative leaving (nucleofugic) groups are involved, the reaction proceeds more efficiently. Thus, for the halogen series, the ease of displacement is F > Cl > Br > I.



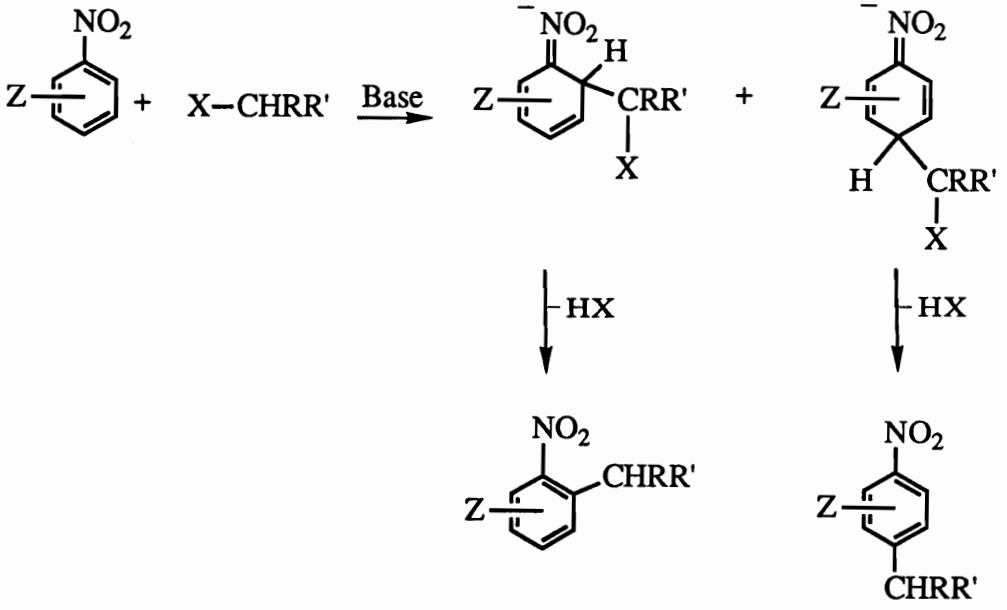
Scheme 2

There are several examples of S_NAr reactions involving unactivated substrates. However, these reactions are facilitated either by high temperature, by using crown ethers[4], by using an effective dipolar aprotic solvent[5], or by the use of chromium tricarbonyl complexes of the aryl halides.[6]

Nitrogen containing, π–deficient, heteroaromatic substrates undergo S_NAr reactions more readily than their carboaromatic counterparts. The difference is attributed to

the inductive stabilizing ability of the nitrogen atom. Anionic σ-complexes of some heteroaromatic azines and diazines have been shown to be stable enough for observation.[7]

The recent discovery of the substitution of hydrogen in aromatic nitro compounds by carbanions that have leaving groups, X, at the carbanionic centers constitutes another interesting class of S_NAr reactions.[8] The reaction, termed vicarious nucleophilic substitution of hydrogen (VNS), proceeds via the formation of σ-complexes followed by base-induced β-elimination of H-X (Scheme 3). Substituents such as PhS, MeS, and $Me_2NC(S)S$ have been shown to be efficient leaving groups in the reaction. In addition to being good leaving groups they also stabilize carbanions and are resistant to direct nucleophilic substitution (S_N2) reaction. Carbanions derived from nitriles and esters

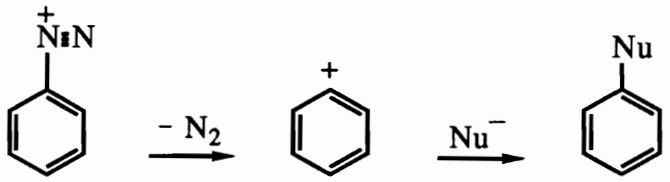


Scheme 3

containing these substituents in the α-position are suitable nucleophilic reagents for this process. Dithioacetal carbanions also react with nitroarenes according to the VNS principle.

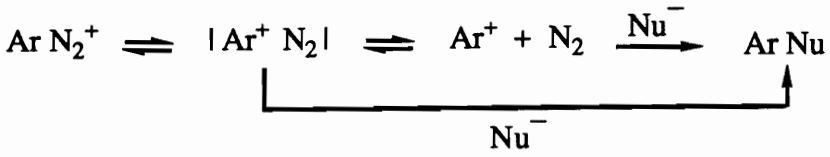
1.3. S_N1 Mechanism.

Aromatic substrates such as diazonium salts, bearing incipient molecular nitrogen as the leaving group, seem to be the only compounds able to form aryl cations. The proposed unimolecular pathway with arenediazonium salts (Scheme 4) was supported by kinetic evidence in early reports.[9]



Scheme 4

However, in 1969 Lewis and co-workers suggested that these reactions occurred via an S_N2 type, one-step mechanism.[10] Their proposal was based on the grounds that several arenediazonium salts showed rates that depended on the concentration of the nucleophile. Although subsequent papers by Swain clarified the confusion somewhat,[11] the kinetic data obtained by Zollinger and co-workers[12] could be explained only if additional steps, involving a molecular ion pair, were added to the S_N1 mechanism (Scheme 5).

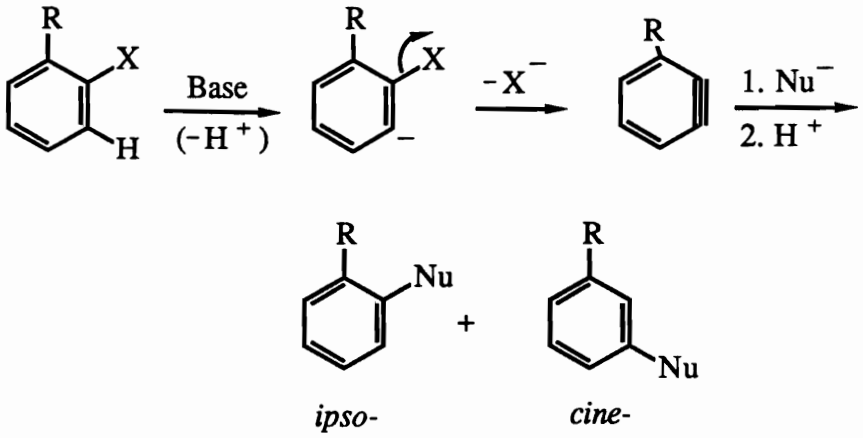


Scheme 5

Recently, reactions of arenediazonium salts in basic solution were shown to proceed via an S_N1 process along with various competing reactions which included S_NAr, aryne and radical pathways.[13] Thus, nucleophilic aromatic substitution of arenediazonium ions may not occur exclusively via an S_N1 pathway, other reaction pathways often providing competition with this process under the conditions utilized for effecting the reaction.

1.4. Aryne Mechanism.

Roberts established the existence of an aryne intermediate in 1953 in certain nucleophilic aromatic substitution reactions.[14] The formation of aryl carbanions as precursors of aryne intermediates takes place in strongly basic solution (Scheme 6). Subsequent elimination of the nucleofuge, X, gives rise to the aryne. The nucleophile can then react at either one of the two sites on the "triple bond" to yield the products. If the nucleophile attacks the position originally occupied by the leaving group X, the reaction is called *ipso-* substitution. Attack of the nucleophile at the other available site leads to the *cine* -substitution product. Thus, reactions involving benzyne intermediates have the drawback that more than one product is often obtained. However, a wide variety of substrates are known to participate readily in nucleophilic substitution by this mechanism, and many substrates bearing electron-withdrawing substituents (in addition to the nucleofuge) appear to undergo the reaction just as readily as those bearing electron-



Scheme 6

releasing substituents. Consequently, this process has proved to be useful in derivatizing otherwise unreactive carboaromatic and heteroaromatic substrates.[15]

When halogens are used as nucleofuges in aryne reactions, the order of reactivity is just the reverse of that in the S_NAr mechanism, *i.e.*, I > Br > Cl > F. The most frequently used base/solvent system for aryne reactions is an alkali metal amide in liquid ammonia, although other bases, such as LDA[16a,b], lithium diethylamide[16c], lithium tetramethyl piperidide[16d] and complex base $NaNH_2$-*t*-BuONa[16e,f] in aprotic solvents such as THF and DME have also been employed to form benzynes from halobenzenes.

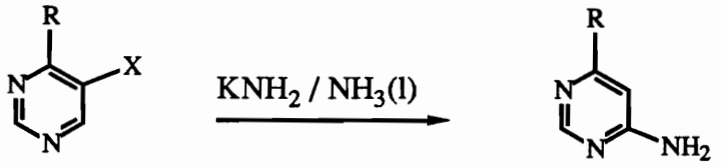
Hetaryne formation in nitrogen heterocycles is more selective than in carboaromatic systems. An annular nitrogen facilitates formation of the hetaryl anion by increasing the acidity of the hydrogens in the system. However, at the positions directly adjacent to the nitrogen, this effect is less pronounced; also, the hetaryne having the "triple bond" furthest

from the nitrogen is lower in energy. Thus, the effects of the nitrogen atom on the deprotonation and elimination steps make the formation of 2,3-pyridyne much less likely than the 3,4 analog from 3-halopyridine. Similarly, when 3-haloquinolines are subjected to hetaryne conditions, the more favorable intermediate is a 3,4-quinolyne.

The unusual structural and chemical properties of aryne and hetaryne intermediates has stimulated a great deal of research activity.[17] It is from this research that S_N(ANRORC) and $S_{RN}1$ mechanisms were discovered.

1.5. S_N(ANRORC) Mechanism.

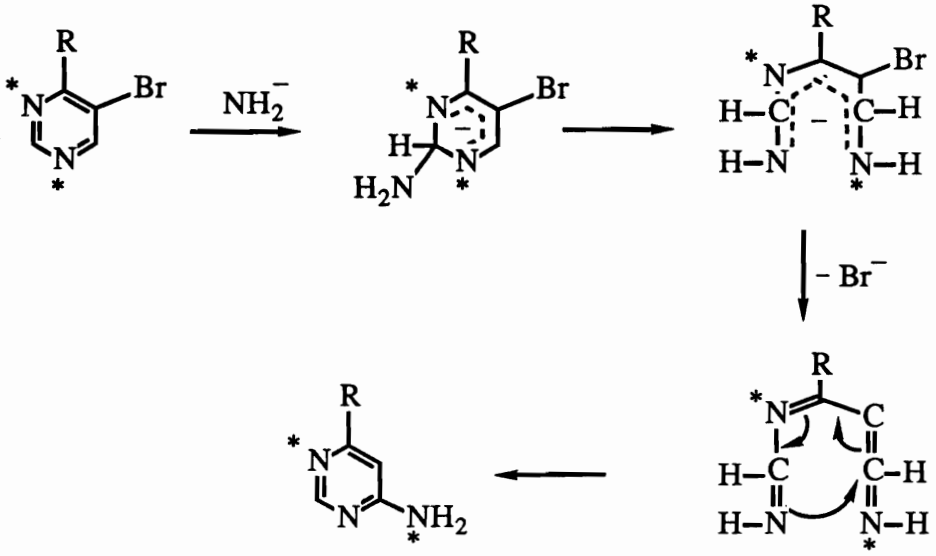
In a process that initially appeared to be a hetaryne process, 5-bromopyrimidines were found to react with potassium amide in liquid ammonia to give the *cine*- product, 6-



(1)

aminopyrimidines, exclusively (eq 1).[18] However, in subsequent reports, both the hetaryne and S_NAr mechanisms were shown to be inconsistent with the results obtained. Van der Plas and co-workers[19] then proposed a nucleophilic substitution mechanism which involved initial addition of the nucleophile followed by a ring opening and ring closure process, S_N(ANRORC), which was based on the results of a ^{15}N-labeling experiment (Scheme 7). Numerous heteroaromatic azines and diazines have been found to undergo this substitution process. A 1978 review by Van der Plas[20] treats this subject in detail, and

continuing publications from the Van der Plas research group serve to keep the interested reader apprised of recent developments in this area.

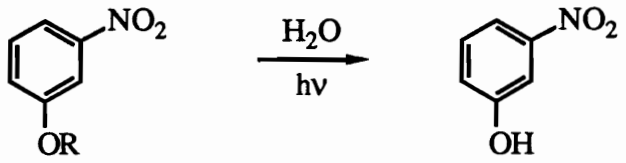


Scheme 7

1.6. Photosubstitution Processes.

In 1956, Havinga and Dorst first observed that certain photoinduced aromatic substitutions were of a heterolytic nature.[21] At that time, most known photoreactions of organic molecules were of a homolytic nature, leading to free radical chemistry. The conversion of aqueous solutions of nitrophenyl phosphates and sulfates to the corresponding nitrophenol under the influence of ultra-violet irradiation was recognized to be a nucleophilic photosubstitution process (eq 2). A peculiar feature that sparked further study was that the *meta*-nitro- derivatives rather than the *ortho*- and *para*- isomers underwent the reaction most effectively. This observation was in strong contrast to what might have been expected on the basis of the classical orientation rules for thermal addition-

elimination (S_NAr) reactions. Gradually it was recognized that this type of nucleophilic aromatic photosubstitution is a fairly general reaction, occurring in various solvents (water, alcohols, acetonitrile, etc.) and with various polycyclic and heterocyclic aromatic systems as well. A wide range of leaving groups (phosphate, sulfate, OR^-, NO_2^-, I^-, Br^-, Cl^-, F^-, SO_3^{--}, SO_2^{--}, N_2, H) and nucleophiles (H_2O, ROH, primary, secondary and tertiary amines, pyridines, OH^-, OR^-, CN^-, CNO^-, H^-, CH_3^-, COO^-, NO_2^-) are known to participate in this process.[22,23]



(2)

R = sulfate, phosphate

It is now believed that these photosubstitution reactions proceed via a multistep mechanism, represented diagrammatically in Fig.1.[22] Irradiation first leads to the excited singlet state (step 1), which then decays to the ground state (step 2) or to the triplet state (step 3). In many photosubstitutions of aromatic nitro-compounds, a π–π^* triplet is considered to be the reactive excited state. Interaction with the nucleophile leading to an "aromatic compound-nucleophile complex" (σ- complex or "exciplex") (step 5) competes with the decay of the triplet to the ground state (step 4). This complex has several reaction paths at its disposal: (i) dissociation into starting compounds (step 6); (ii) dissociation into aromatic radical anion and nucleophile radical or radical cation (step 7); and (iii) loss of a substituent to form substitution product(s) (step 8). Path (i) represents a "chemical quenching" of the excited state. Path (ii) is probably important only with nitroaromatic compounds and leads to reduction products via the radical anion (step 10). Alternatively,

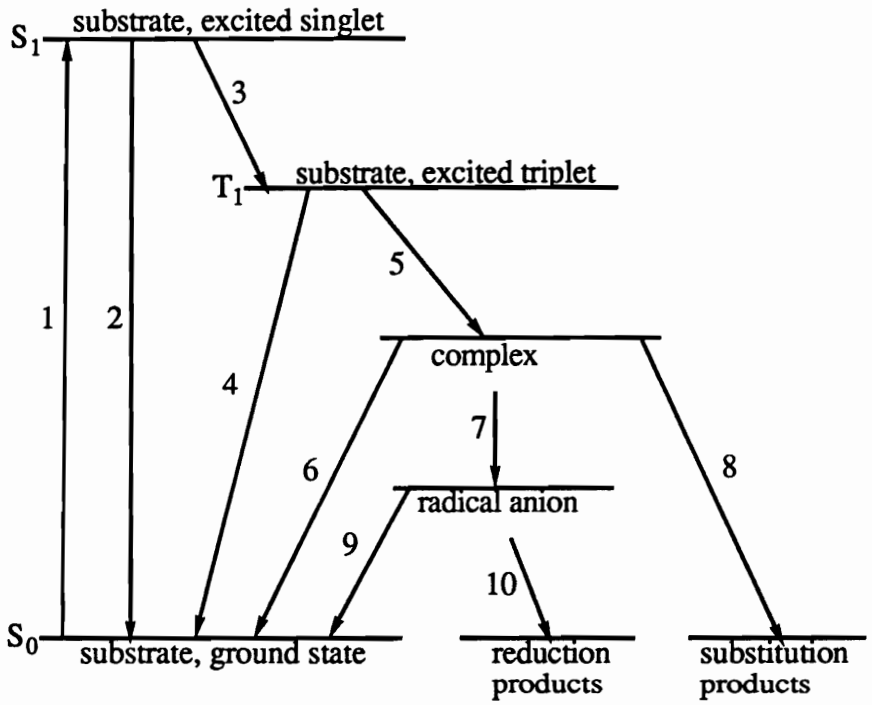

S1
substrate, excited singlet
3
T1
substrate, excited triplet
5
1
2
4
complex
7
6
8
radical anion
9
10
S0
substrate, ground state
reduction products
substitution products

Fig.1

the radical anion may also return to ground state by loss of an electron (step 9), forming another way of "chemical quenching". The photosubstitution products emerge from path (iii) (step 8), the ratio of the rate constants of processes (step 6) and (step 8) largely determining the quantum yield of this type of nucleophilic aromatic photosubstitution. Mechanistically, this represents an overall addition-elimination process (S_NAr), in which the nucleophile adds to the excited triplet state of the substrate rather than to its ground state as in thermal S_NAr processes. The steps leading to the formation of substitution products are summarized in Scheme 8, where (S-X) represents the substrate with a suitable nucleofugic group (X) and (Nu) represents the nucleophile.

$$^{0}S\text{-}X \xrightarrow[(1)]{h\nu} {}^{*}S\text{-}X^{\uparrow\uparrow} \xrightarrow[(3)]{} {}^{*}S\text{-}X^{\uparrow\downarrow} \xrightarrow[(5)]{Nu^-} [\,{}^{*}S\text{-}X\text{---}Nu] \xrightarrow[(8)]{-X^-} S\text{-}Nu$$

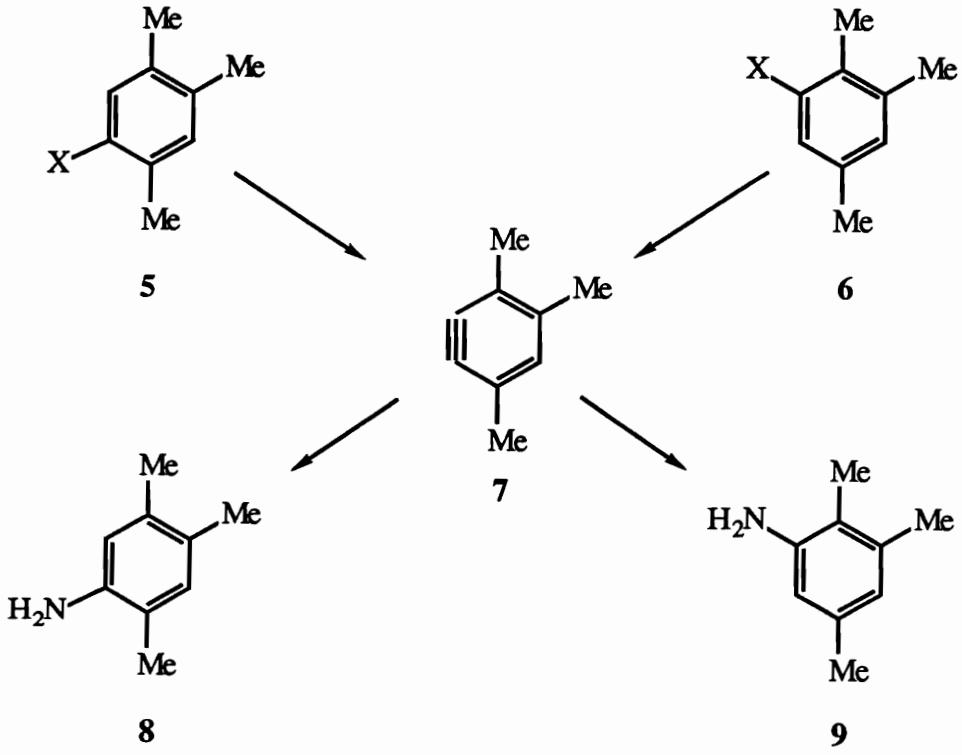
Scheme 8

1.7. The $S_{RN}1$ Mechanism:

In a series of experiments designed to investigate the aryne mechanism, Kim and Bunnet observed some unusual results that were inexplicable in terms of the aryne mechanism.[24] They were studying the effects of potassium amide in liquid ammonia on 5- and (6-halo)pseudocumenes, (**5**) and (**6**) respectively (Scheme 9). Both isomers were expected to give the same ratio of trimethylanilines, **8** and **9** respectively, since dehydrohalogenation of both **5** and **6** would lead to the same aryne intermediate, **7**. For the same reason, this ratio was also expected to be independent of the halogen employed. With X = Cl or Br, this expectation was fulfilled. However, when the leaving group was iodo, the mixture of trimethylanilines **8** and **9** obtained was always dependent upon which

starting material was used; the mixture was consistently enriched with the *ipso*-substitution product. Thus, **5** gave more of **8** and **6** gave more of **9**.

Inhibition of these reactions by small quantities (10 mol%) of radical scavengers such as di-*tert*-butyl nitroxide suggested that a chain process was in operation. Furthermore, promotion by one-electron donors such as potassium metal pointed towards

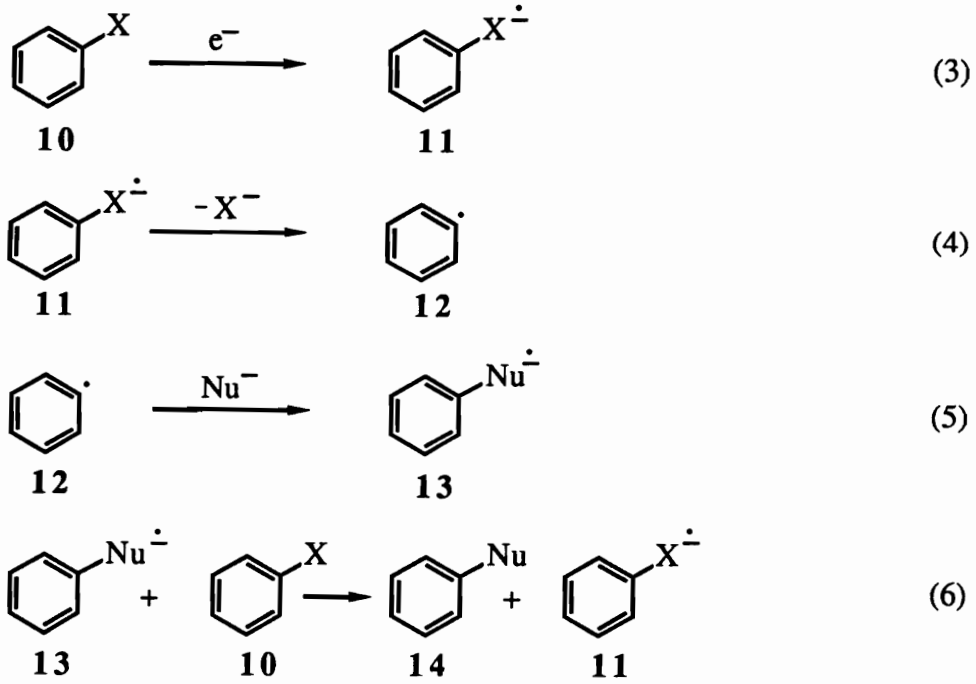


Scheme 9

single-electron transfer steps in the process leading to the *ipso*-substituted product. This was recognized as being the aromatic analog of the aliphatic nucleophilic substitutions occurring in *p*-nitrobenzylic and α-nitroalkyl halides[25]. The term *substitution, radical-*

nucleophilic, unimolecular , abbreviated as $S_{RN}1$ and first suggested by Bunnett, is widely adopted and will be used throughout this dissertation.

The steps in the general $S_{RN}1$ reaction with an unactivated aryl halide are represented in Scheme 10. Electron transfer from a suitable donor (often the nucleophile) to the substrate **10** effects initiation of the chain reaction (eq 3). The radical anion **11** then expels the leaving group X^- to give radical **12** (eq 4) and the resulting aryl radical combines with the nucleophile to form a product radical anion **13** (eq 5). The propagating cycle is completed by transfer of an electron from **13** to another substrate molecule **10** (eq 6). Three types of reactive intermediates, radical anion **11**, radical **12**, and radical anion **13** are involved in this mechanism, and the generation of any one of these can provide entry into the propagation cycle. Initiation has been shown to be effected by near -UV light, by



(3)

(4)

(5)

(6)

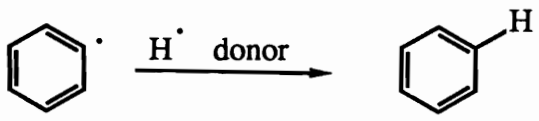
Scheme 10

dissolved alkali metals and by electrochemical means, which distinguishes the $S_{RN}1$ mechanism as being different from the photosubstitutions described in the previous section (1.6.). The aryl radical does not arise by homolytic cleavage of the carbon-halogen (or other carbon-nucleofuge) bond to any significant extent, and the origin of the aryl radicals is as represented in eq 4.[24,26,27]

It has also been observed that the expected $S_{RN}1$ product **14** is almost invariably accompanied by small amounts of **15** and/or **16** (eq 7, 8). The formation of these products can be accounted for in the following way. In addition to reacting with the nucleophile (eq 5), aryl radical **12** can also undergo two other reactions: self-coupling to yield **15** (eq 7), and hydrogen atom abstraction, ostensibly from the solvent, to yield **16** (eq 8). Since both these reactions effectively prevent the reactive intermediate **12** from

12 **15** (7)

propagating the chain reaction represented in Scheme 9, they represent two possible termination steps in the overall $S_{RN}1$ process. An analogous reaction may be responsible for the observed inhibition of $S_{RN}1$ reactions by radical scavengers such as di-*tert*-butyl



12 **16** (8)

nitroxide. Combination of the radical scavenger with **12**, with the resultant inhibition of the propagation cycle, would be reflected in the effective inhibition of the overall $S_{RN}1$ reaction.

Since the $S_{RN}1$ reaction proceeds in a completely non-rearranging manner, it is potentially more useful synthetically than aryne mediated reactions. The synthetic potential of this reaction was very quickly recognized and numerous studies have explored both the mechanistic and synthetic aspects of the trapping of an aryl radical by a nucleophile. These studies have identified a large number of nucleophiles and a wide variety of carboaromatic and heteroaromatic halides that are able to participate in this reaction. These investigations have been reviewed by several authors over the years[27-40].

1.8. Intramolecular $S_{RN}1$ Reactions.

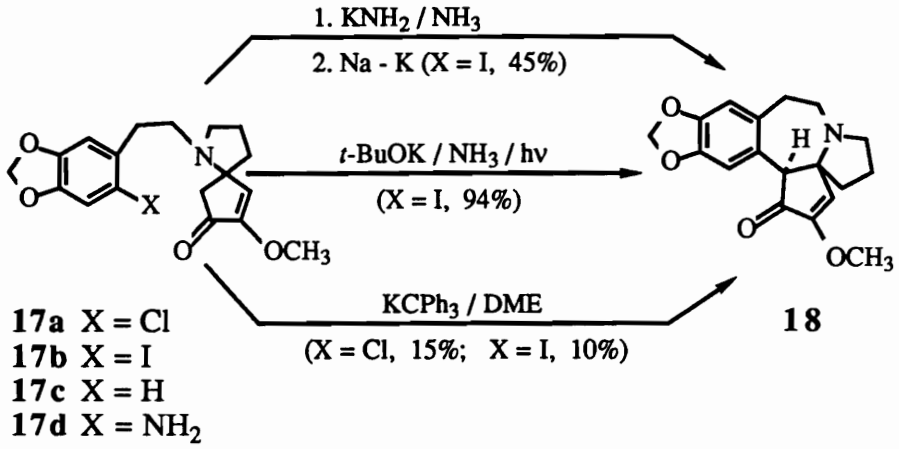
The intramolecular $S_{RN}1$ reaction of an aryl halide with a nucleophilic center already attached to the aromatic ring represents a novel cyclization process that is very attractive from a synthetic viewpoint. To date, however, only a few reports of intramolecular reactions that seem to proceed by the $S_{RN}1$ mechanism have appeared. Beugelmans[39] has recently summarized approaches to the synthesis of heterocyclic systems via both intra- and intermolecular $S_{RN}1$ reactions.

1.8.1. *Carbon Nucleophiles:*

1.8.1a. Ketone Enolate Anions.

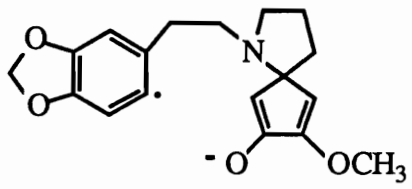
The first use of an intramolecular $S_{RN}1$reaction was reported by Semmelhack and co-workers in 1973 as being the key step in an elegant synthesis of cephalotaxinone (**18**)

(Scheme 11).[41] Product **18** was obtained in 94% yield from the iodoketone **17b** with potassium *tert*-butoxide in liquid ammonia under photostimulation with pyrex-filtered



Scheme 11

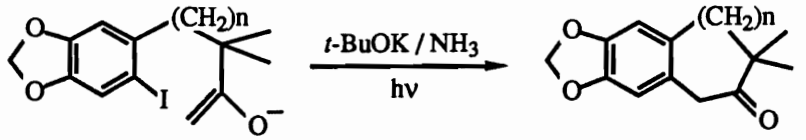
light. The photoassisted reaction was clearly superior to both the potassium metal-promoted $S_{RN}1$ and benzyne routes. In the dissolving metal $S_{RN}1$ reaction initiated by solvated electrons from potassium metal, **18** was obtained in 45% yield, accompanied by 35% of unreacted starting material **17a** and 18% of reduction product **17c**. The use of ethereal solvents gave increased yields of **17c**, suggesting that reduction may result from hydrogen atom abstraction from the ethereal solvent by radical anion **19**.[42] Alternatively, **19** could undergo reduction to a phenyl anion, protonation of which by ammonia would afford **17c**. When **17b** was treated with potassium amide in liquid ammonia in the dark



19

(*i.e.*, benzyne conditions), a 40% yield of the amino derivative **17d** was obtained. Only a trace of product **18** was observed.

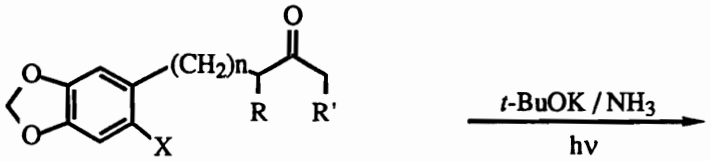
The success of this reaction prompted Semmelhack and Bargar[43] to study the viability and regioselectivity of the photostimulated ring closure of the series of iodoaryl ketones **20** (eq 9) and **22** (eq 10). Haloaryl ketones of the type **20** were expected to yield



(9)

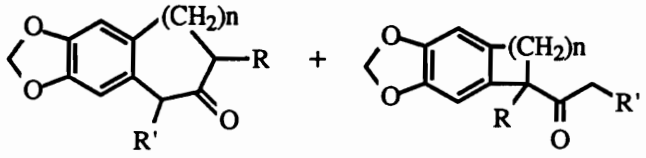
20 **21** n = 1, 99%
n = 3, 73%
n = 5, 25 - 35%

information about ring size preference in cyclizations, while those of type **22** could shed light on regioselectivity with ketones that could give two different enolate anions. Where



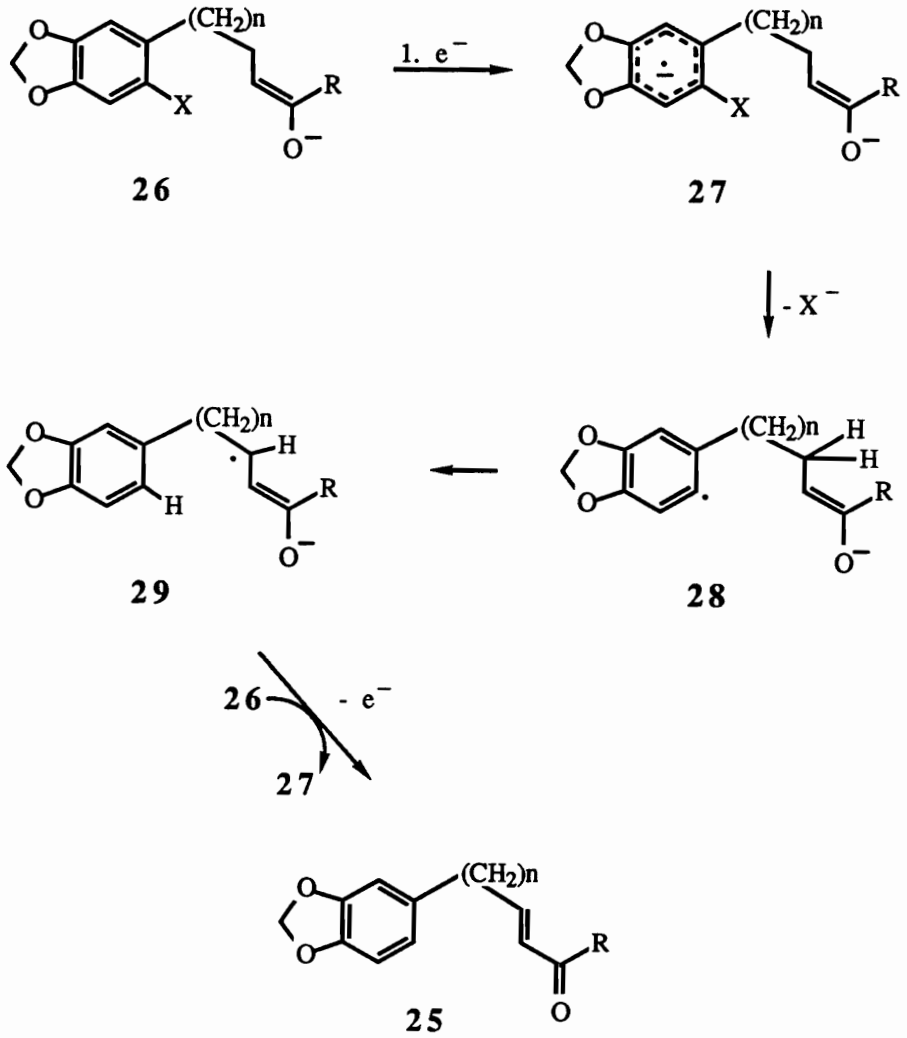
22

(10)



23 **24**

only one enolate anion was possible, as in **20**, the cyclization was fairly smooth; the six-membered ring, **21** (n = 1), was formed nearly quantitatively, and even the ten-membered ring, **21** (n = 5), was formed in 25 - 35% yield. Compounds of type **22** can form two different enolates, however, and theoretically two different products, **23** and **24**, are possible (eq 10). In actuality though, these products were obtained in only poor yields, whereas the α,β-unsaturated ketone **25** was obtained as a major product. This product

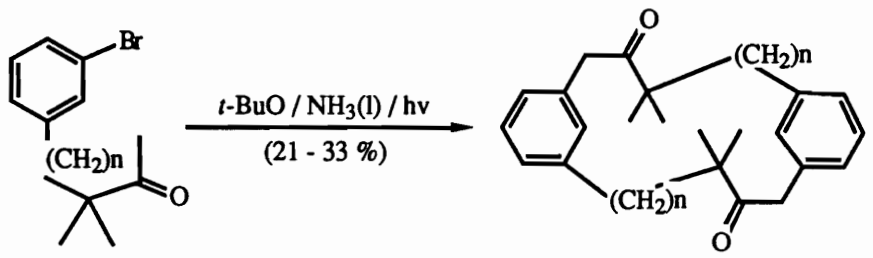


Scheme 12

was shown to arise from an intramolecular β-hydrogen atom abstraction process that competed with cyclization (Scheme 12). This was believed to be a chain process also, in which the product radical anion **29** propagated the reaction by donating an electron to a substrate enolate anion **26.**

The presence of α-methyl groups in **20** enforced regiochemical control on the reaction (eq 9) and prevented internal β-hydrogen transfer reactions, resulting in good yields of the expected $S_{RN}1$ products **21.** Although the cyclization of **22** (eq 10) was complicated by the β-hydrogen atom abstraction process described above, small quantities of the expected $S_{RN}1$ products **23** and **24** were obtained. The regiochemistry of the ring closure for the ketones **22** (X = Br; n = 3 or 4) leading to products **23** and **24** appeared to be controlled by the proportion of the respective enolate ions present; when R' = H, greater proportions of the cyclic ketones resulting from attack through the methyl group occurred to give the seven- and eight-membered cyclic ketones in preference to the products with five and six membered rings, respectively.

In an interesting, recent series of reactions which involve a combination of inter- and intramolecular $S_{RN}1$ reactions with ketone enolates, [m.m]-*meta*-cyclophanediones,



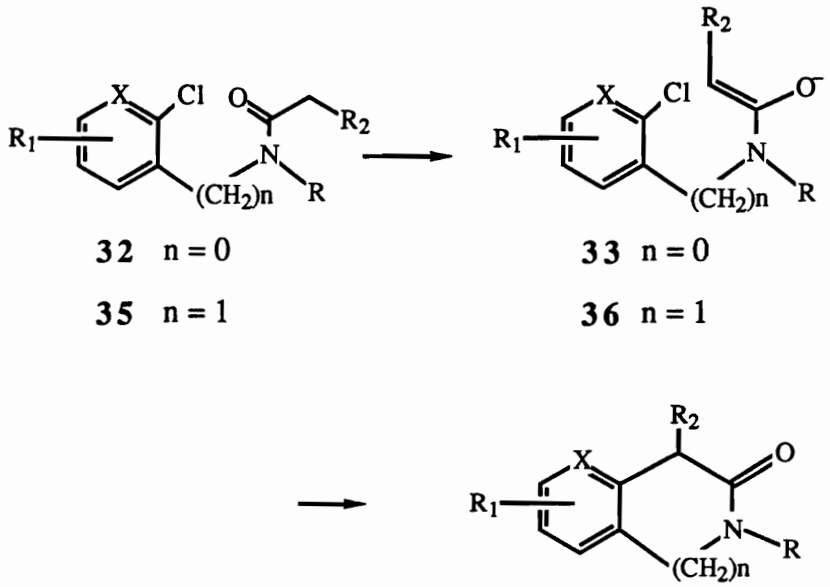
(11)

30 n = 0 - 5 **31** n = 0 - 5

31 (m = 3-8), were obtained in acceptable yields by the tandem $S_{RN}1$ reactions of ketones **30** (eq 11).[44]

1.8.1b. Amide Enolate Anions.

The photoinduced cyclization of mono- and dianions of *N*-acyl-*N*-alkyl-2-haloanilines and *N*-acyl-2-haloanilines **32** (X = CH), and that of the mono and dianions of *N*-acyl-*N*-alkyl-2-halobenzylamines **35** (X = CH) was developed by Wolfe and co-workers as a general method for the preparation of oxindoles **34** (X = CH) and 1,4-dihydro-3(2H)-isoquinolinones **37** (X = CH), respectively (Scheme 13).[45] The yields range from 32-83%, with most in excess of 60%. These reactions were assumed to



32 n = 0 **33** n = 0

35 n = 1 **36** n = 1

34 n = 0

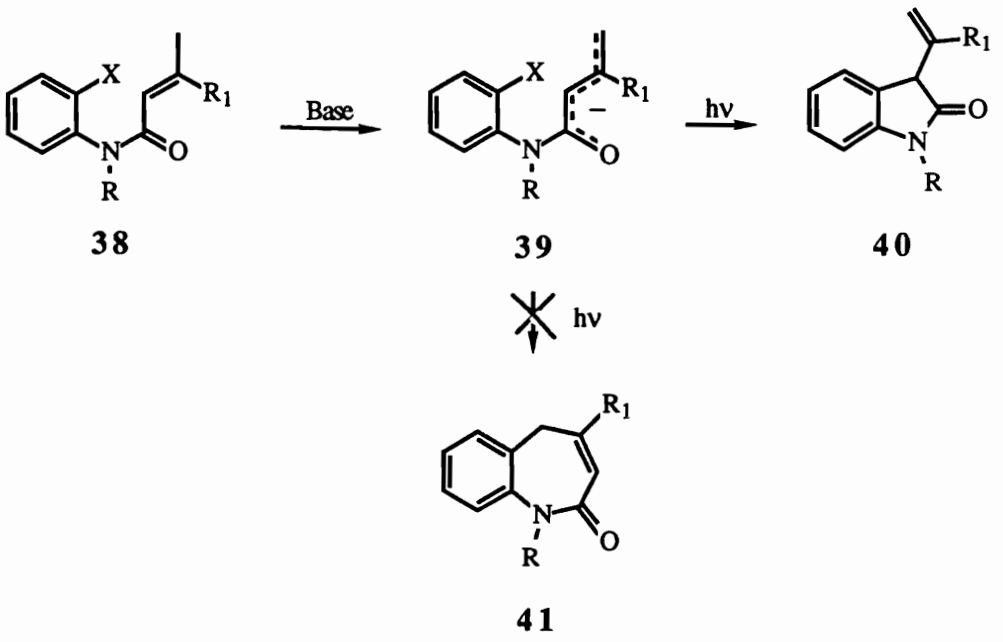
37 n = 1

Scheme 13

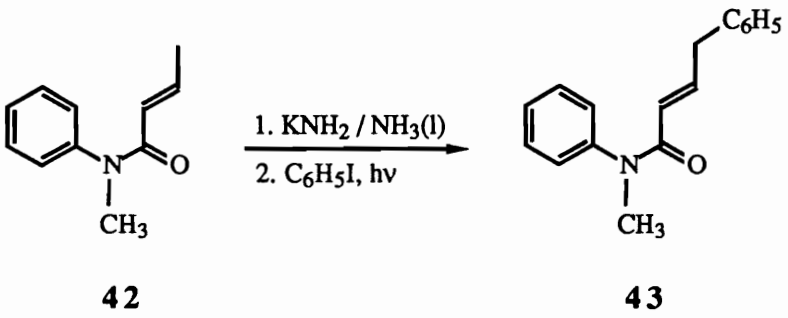
proceed via the $S_{RN}1$ mechanism as they required photostimulation and were inhibited markedly by 10 mol% of the radical scavenger, di-*tert*-butyl nitroxide. The inhibitory influence of small amounts of di-*tert*-butyl nitroxide was interpreted as precluding the possibility of diradical coupling as a major reaction pathway leading to products, since inhibition of a radical coupling pathway would require stoichiometric amounts of the radical scavenger. The reaction proceeded readily when there were substituents *ortho*- to the halogen, providing further evidence for operation of the $S_{RN}1$ pathway and ruling out the aryne mechanism.

The method was also extended to the preparation of azaoxindoles **34** (X = N) (Scheme 13).[45] However, these reactions must be carried out at -78°C to prevent decomposition of the enolate ions **33** (X = N), formed from the pyridine derivatives **32** (X = N). In addition, there had to be an alkyl group on the amide nitrogen (**32-34**; X = N, R = alkyl) before successful reactions occurred.

α,β-Unsaturated *N*- alkylanilides **38** reacted to give 3-alkylideneoxindoles **40** in yields usually over 65% (Scheme 14).[46] The delocalized anion **39** can potentially undergo arylation at either the α-position or the γ -position, but α-substitution occurred exclusively to yield the five-membered oxindoles **40**. Efforts to direct regioselectivity towards the γ–position to yield the benzazepinones **41** by changing the counter ion associated with the dienolate or by incorporating an α-methyl substituent proved ineffective. This was interesting in the light of the fact that the analogous intermolecular reaction between the anion of *N*-methylcrotonanilide (**42**) and iodobenzene afforded the γ-substituted product, *N*-methylstyrylanilide (**43**), exclusively (eq 12).[47]



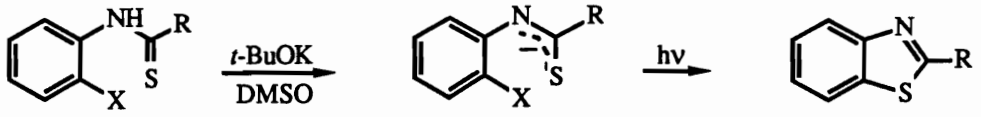
Scheme 14



(12)

1.8.2. *Sulfur Nucleophiles:*

o- Iodothiobenzanilide (**44a**) and *o*- iodothioacetanilide (**44b**) undergo ring closure through an intramolecular $S_{RN}1$ reaction on treatment with potassium t-butoxide in dimethyl sulfoxide giving high yields of 2-phenyl- and 2-methyl-1,3-benzothiazole (**46a,**



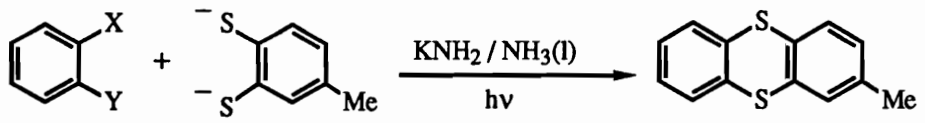
44a R = C_6H_5 **45a** R = C_6H_5 **46a** R = C_6H_5

44b R = CH_3 **45b** R = CH_3 **46b** R = CH_3

Scheme 15

46b), respectively, but only when the reaction is performed with entrainment (i.e., catalytic initiation of the chain reaction) using the acetone enolate anion as the entraining species (Scheme 15).[48] Only starting material was recovered in the absence of entrainment.

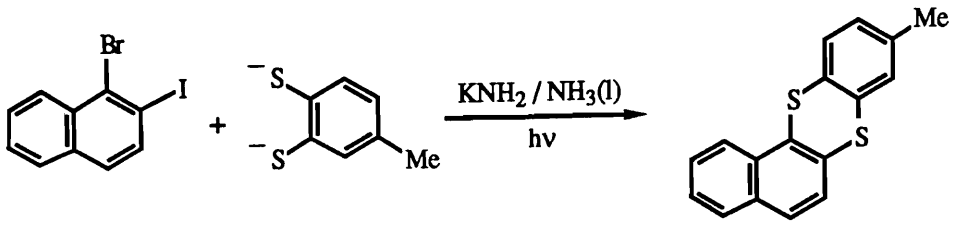
Recently, Rossi and co-workers reported the results of their studies with certain bifunctional substrates which could potentially undergo an initial intermolecular $S_{RN}1$ reaction followed by a second one in which ring closure is effected.[49] The reactions of *o*-dihalobenzenes **47a-b** with dithiolate ion **48** gave **49** in moderate yields (eq 13). The yield of the analogous product, **51**, formed from **48** and 1-bromo-2-iodonaphthalene (**50**) was 24% (eq 14), while the reaction of 1,2-ethanedithiolate (**52**) with *o*- diiodobenzene (**47b**), gave a 13% yield of benzo-1,4-dithiane (**53**) (eq 15).[49]



(13)

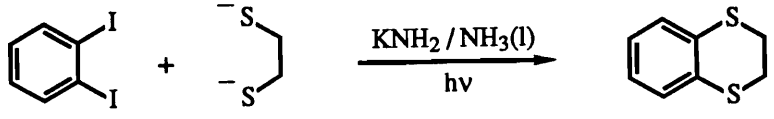
47a X = Cl, Y = Br **48** **49**

47b X = Y = I



(14)

50 **48** **51**



(15)

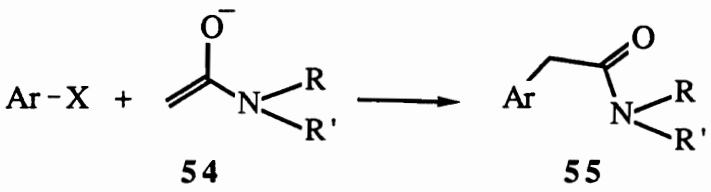
47b **52** **53**

III. THE RESEARCH PROPOSAL.

1. *N,N*-Disubstituted Amide Enolates in $S_{RN}1$ Reactions.

In addition to the *intramolecular* $S_{RN}1$ reactions involving α-anions derived from certain carboxamides described earlier (see Section 1.8.1b.), a few other workers have investigated the ability of the α-anions of *N,N*-disubstituted carboxamides to participate in *intermolecular* $S_{RN}1$ reactions. Results of these studies are described in this section, since they pertain directly to the types of reactions we wished to investigate.

Rossi and co-workers have shown that α-anions of *N,N*-disubstituted carboxamides, **54a-d**, represent nucleophiles that can successfully participate in $S_{RN}1$ reactions (eq 16).[50] The reaction between iodobenzene and **54a** in the dark afforded the



(16)

54 **55**

a R = CH_3 ; R' = Ph

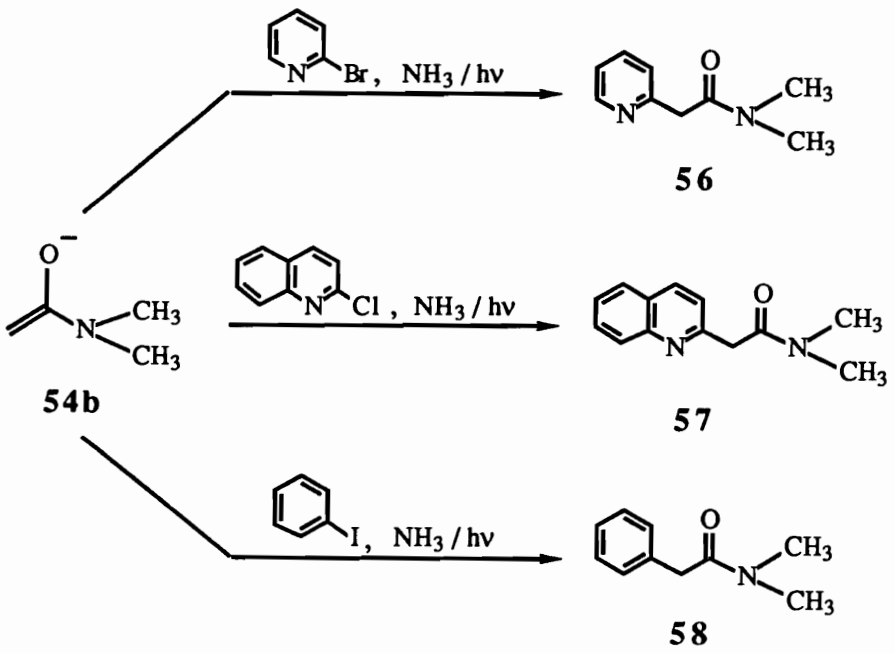
b R = R' = CH_3

c R = R' = $-(CH_2)_5-$

d R = R' = $-(CH_2)_2O(CH_2)_2-$

expected product **55a** in 34% yield, but a higher yield (80%) was obtained when the reaction was carried out under photostimulation. Photostimulated reactions of various aryl halides with **54a** or **54b** gave product yields of 50 to 80%. Since **54c** was insoluble in ammonia, there was little reaction with bromobenzene. However, **54d**, which was soluble in ammonia, gave high yields of products.

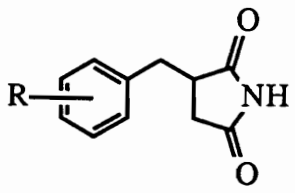
Similar results were observed by Wong in our laboratories.[51] The potassium enolate of *N,N* -dimethyl acetamide (**54b**) was found to react under near-UV irradiation with 2-bromopyridine, 2-chloroquinoline and iodobenzene to give products **56**, **57** and **58**, respectively, in yields comparable to those reported by Rossi and co-workers (Scheme 16). The discovery that these reactions were inhibited by small concentrations of the radical scavenger, di-*tert*-butyl nitroxide, as well as the fact that significantly lower yields were obtained when the reactions were carried out in the absence of photostimulation, constituted evidence supporting operation of the $S_{RN}1$ pathway.



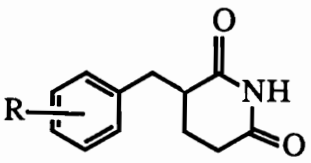
Scheme 16

2. Benzylsuccinimides and Benzylglutarimides as Anticonvulsants:

The reactivity of amide enolate **54b** was of particular interest to us in connection with other ongoing studies in our laboratories. For several years now, our research efforts have been directed towards the development of new, more effective anticonvulsant agents. As a result of previous work by Rogers[52], Goehring[53] and Pisipati[47], several 3-benzylsuccinimides (**59**) and 3-benzylglutarimides (**60**) were shown to possess antiepileptic activity in animal studies. We wished to further explore the possibilities presented by these compounds by attempting to synthesize compounds **61** and **62**, which

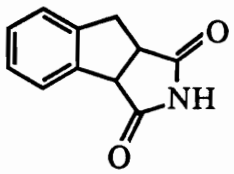


59

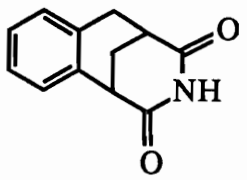


60

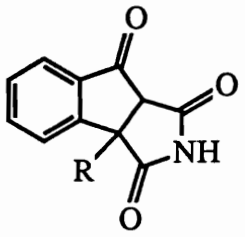
can be considered "rigid" analogs of **59** and **60**, respectively, and would therefore appear to be promising candidates for anticonvulsant activity. The anticonvulsant properties of some 8-one derivatives of **61**, such as **63** and **64**, have been described by Campaigne and co-workers,[54] further strengthening our belief that **61** and **62** might possess anticonvulsant activity.



61

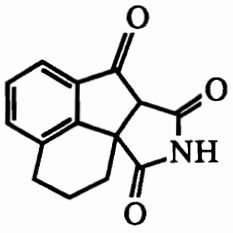


62



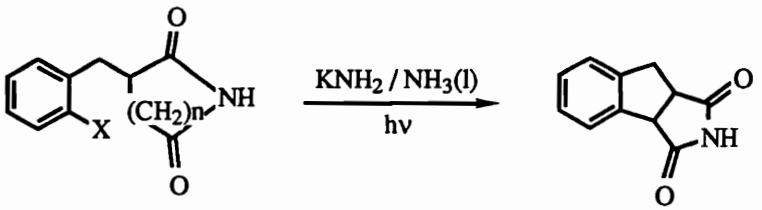
63

R = Me, Et, *i*-propyl



64

Initial speculation about the possibility of synthesizing the above-mentioned "rigid" analogs **61** and **62** by means of intramolecular $S_{RN}1$ reactions arose during the synthesis of various analogs of benzylsuccinimides **59** and benzylglutarimides **60** undertaken by Goehring in the late 1970's.[53] It appeared possible that *ortho*-halobenzylsuccinimides **65** and *ortho*-halobenzylglutarimides **66** might be induced to undergo intramolecular $S_{RN}1$ reactions, through the respective dianions, to yield the desired compounds **61** and **62** (eq 17). At the time, however, evidence regarding the $S_{RN}1$ reactivity of the α-anions of

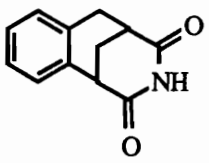


(17)

65 n = 1 ; X = Hal

66 n = 2 ; X = Hal

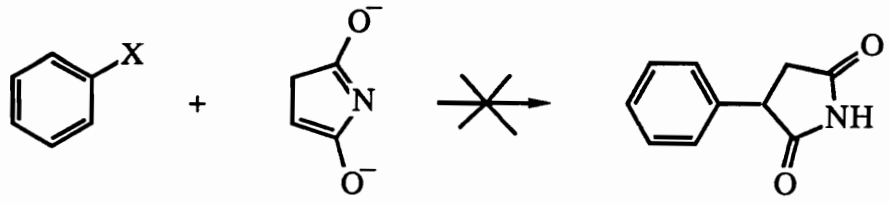
61



62

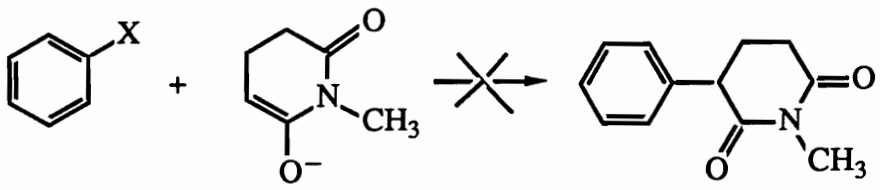
imides was virtually non-existent.[53] However, their structural resemblance to amide enolates, which were known to participate in $S_{RN}1$ reactions, formed the rationale behind the synthetic strategy proposed above for the preparation of **61** and **62**.

Prior to investigating the intramolecular reactions proposed in eq 17, it was considered appropriate to investigate the reactivity of imide α-anions in intermolecular $S_{RN}1$ reactions. Preliminary experiments performed by Goehring in this regard were somewhat discouraging.[53] The succinimide dianion, **67**, and the *N*-methylglutarimide monoanion, **68**, demonstrated poor intermolecular $S_{RN}1$ reactivity toward aryl halides, affording only low yields of the expected products **69** and **70**, respectively (eq 18, 19). Also, no cyclized product was detected upon treatment of 3-(*o*-bromobenzyl)-*N*-methylglutarimide (**71**) with excess potassium amide in liquid ammonia under photostimulation (eq 20). The lack of success in these reactions was proposed to result from an inhibition of chain propagation due to poor electron transfer from the product radical anion to the starting aromatic substrate.



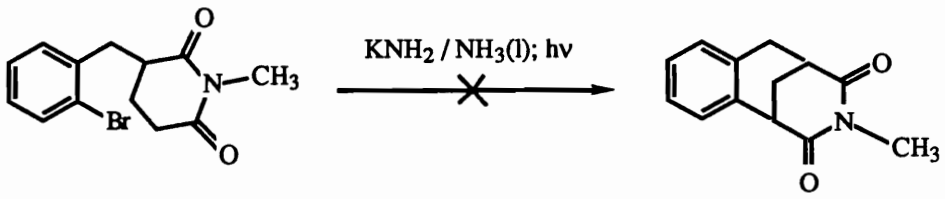
(18)

10 **67** **69**



(19)

10 **68** **70**

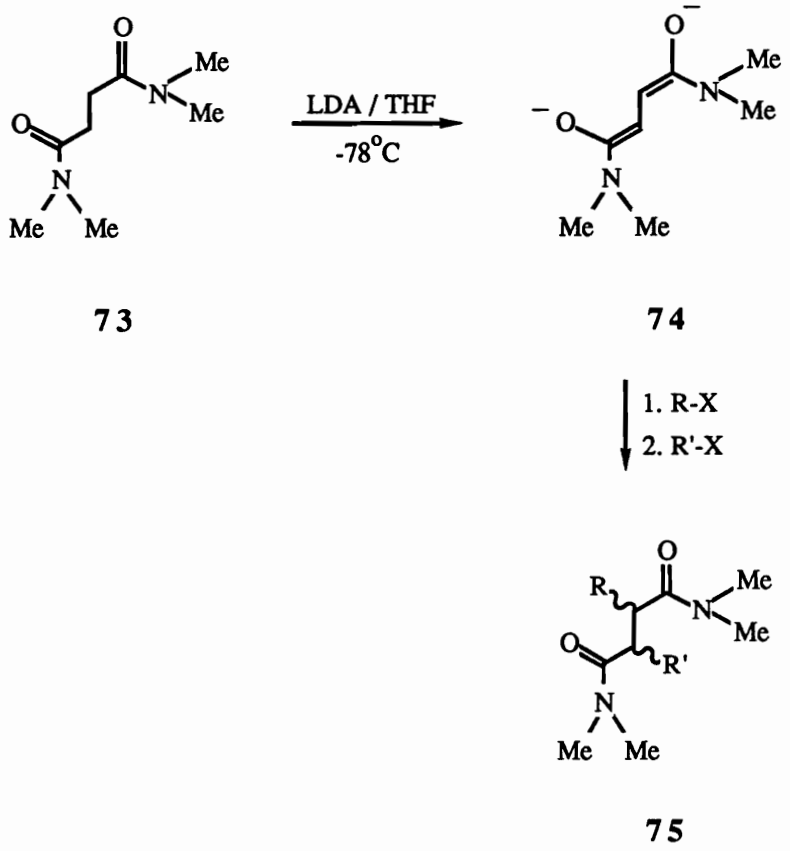


(20)

71 **72**

The preliminary results described above indicated the need for developing an alternative synthetic strategy for the preparation of the rigid analogs of benzylsuccinimides and benzylglutarimides. A report by Snieckus and co-workers[55] describing the formation and dialkylation of the lithium dianion **74** of *N,N,N',N'*-tetramethylsuccinamide (**73**) appeared to be of some significance from this standpoint. When the dianion **74** was generated with lithium diisopropylamide (LDA) in tetrahydrofuran at -78°C and subsequently treated with a variety of alkylating agents, various 2,3-dialkyl succinamides, **75**, were obtained in yields of 55-80%, depending on the type of alkylating agent used (Scheme 17). Also, excellent stereoselectivity was observed, with the *threo* isomer being favored.

It seemed likely that since sequential treatment of the dianion **74** with different alkylating agents gave dialkylated products **75** cleanly, the initial monoalkylated product

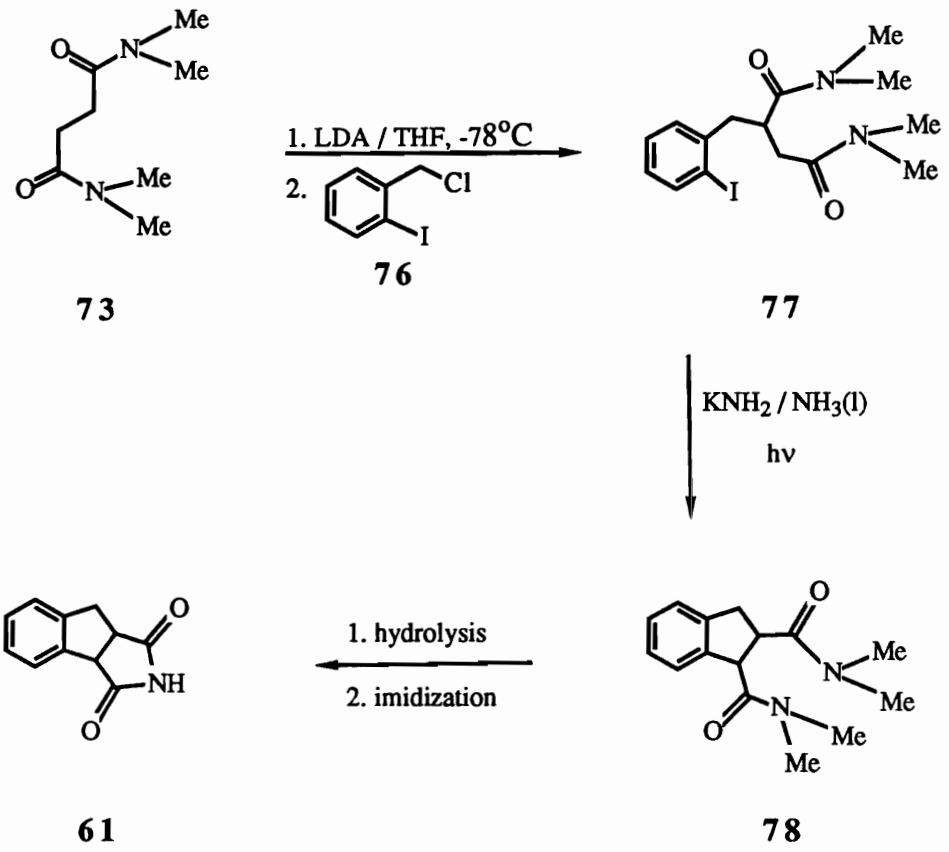


73 **74** **75**

Scheme 17

could be prepared by treating dianion **74** with 1 equiv of an alkylating agent and subsequently neutralizing the reaction mixture. Although the authors did not describe the preparation of monoalkylated products in this manner, it appeared that their procedure might be useful in the synthesis of **77** and **80**, which were potentially capable of undergoing intramolecular $S_{RN}1$ reactions to yield **78** and **81** respectively (Schemes 18, 19). Thus, our new synthetic strategy for the preparation of **61** and **62** was based on the known participation of *N,N*-disubstituted amide enolates in $S_{RN}1$ reactions. If the proposed cyclization reactions were found to be successful, the products, **78** and **81,**

could then presumably be converted into the desired synthetic objectives **61** and **62**, via known hydrolytic and imidization procedures (Schemes 18, 19).

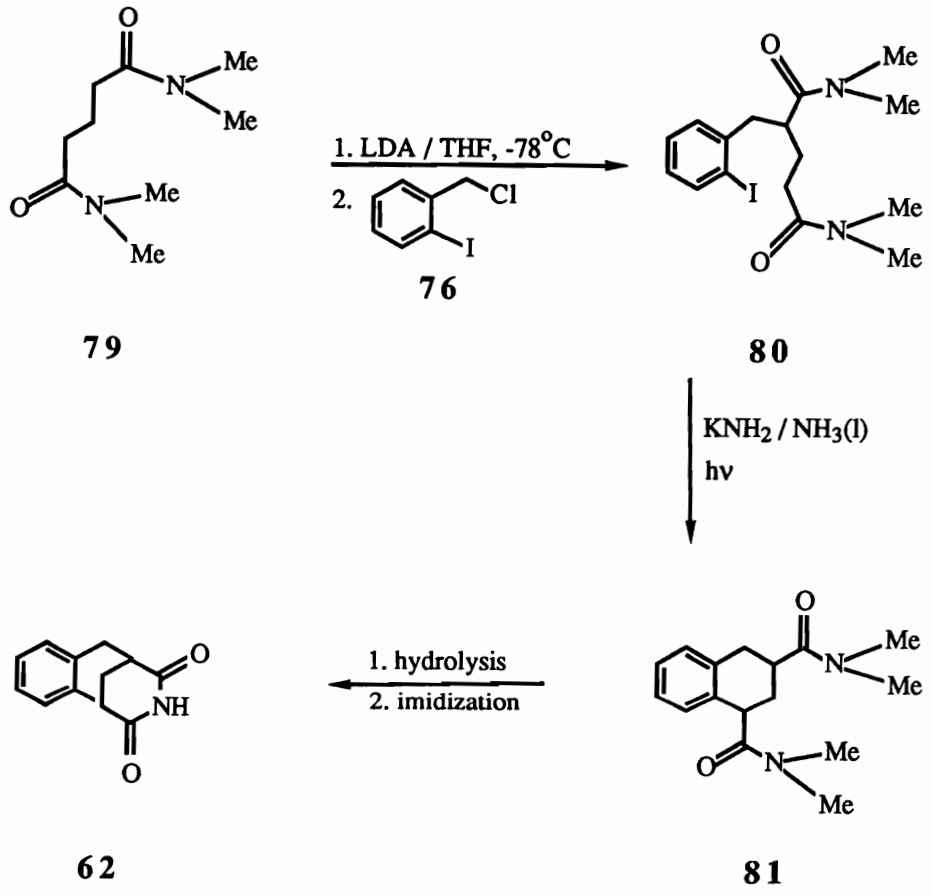


73 **76** **77** **78** **61**

Scheme 18

This proposed investigation provided a new opportunity to investigate intramolecular $S_{RN}1$ reactions. Since relatively few examples of this type were known at the time this study was undertaken, such a study was of prime interest to us. Our approach to this investigation was intended to be two-pronged, the mechanistic aspects of the reaction being of as much interest as the synthetic ones. A better understanding of the mechanistic pathways involved was expected to contribute to the extension of the synthetic

applications of the $S_{RN}1$ reaction in providing a direct access to various benzofused systems, indane and tetralin derivatives in particular. The development of new procedures such as those described above for the efficient syntheses of these types of compounds would be valuable, since they would complement the procedures presently available for these purposes.



Scheme 19

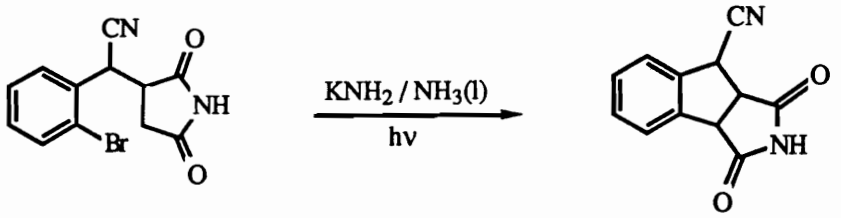
IV. RESULTS AND DISCUSSION

1. Introduction.

The investigation proposed in the previous section was undertaken with the two-fold objective of exploring both the synthetic potential and the mechanistic features of the intramolecular $S_{RN}1$ reactions that could ostensibly be induced in the 2-(*o*-iodobenzyl) amides **77** and **80**. If these reactions occurred as expected, they could perhaps be incorporated into the synthetic strategies outlined in Schemes 18 and 19 for preparing the potential anticonvulsants succinimido[3,4-b]indane (**61**) and 1,2,3,4,5,6-hexahydro-1,5-methanobenzazocine-2,4-dione (**62**). Since the first step in the scheme proposed for the synthesis of **61** (Scheme 18) involved the preparation of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) by alkylation of *N,N,N',N'*-tetramethylsuccinamide (**73**), a study of this reaction was undertaken first. If **77** were to undergo cyclization to give 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**), a parallel investigation was to be initiated to probe the mechanistic features of the cyclization step, while still proceeding with the synthetic study. Investigation of the synthesis and chemistry of the analogous glutaramide substrate **80**, was planned along similar lines.

Some interesting findings uncovered during the studies of the cyclization of **77** to form **78** suggested that it might also prove worthwhile to reinvestigate the possibility of effecting intramolecular $S_{RN}1$ reactions in 3-(*o*-halobenzyl)succinimides **65** and 3-(*o*-halobenzyl)glutarimides **66** (eq 17). The presence of excess base in the reaction mixture was found to be critical for efficient cyclization of **77** to form **78**. Therefore, a study was undertaken to determine if the same was perhaps true for the cyclization of the imides **65** (X=I) and **66** (X=I) to form **61** and **62** respectively.

The success obtained in the cyclizations mentioned above also prompted attempts to apply this approach to the possible synthesis (eq 21) of succinimido[3,4-b]indane-8-carbonitrile (**83**) from 3-(*o*-bromo-α-cyanobenzyl)succinimide (**82**), for which we had developed a new synthesis.



(21)

82 **83**

Results of these investigations appear in the next sections in the following order: First, the results of our endeavors to synthesize succinimido[3,4-b]indane (**61**) from bisamide **77** and imide **65** are described. This is followed by a discussion of the results of efforts to prepare **83** from **82**. Subsequently, the investigation conducted with the objective of preparing 1,2,3,4,5,6-hexahydro-1,5-methano-benzazocine-2,4-dione (**62**), from imide **66** and bisamide **80** respectively, is discussed. A description of the mechanistic studies associated with these synthetic endeavors appears at the end of the chapter, in the same relative order as the synthetic investigations were presented.

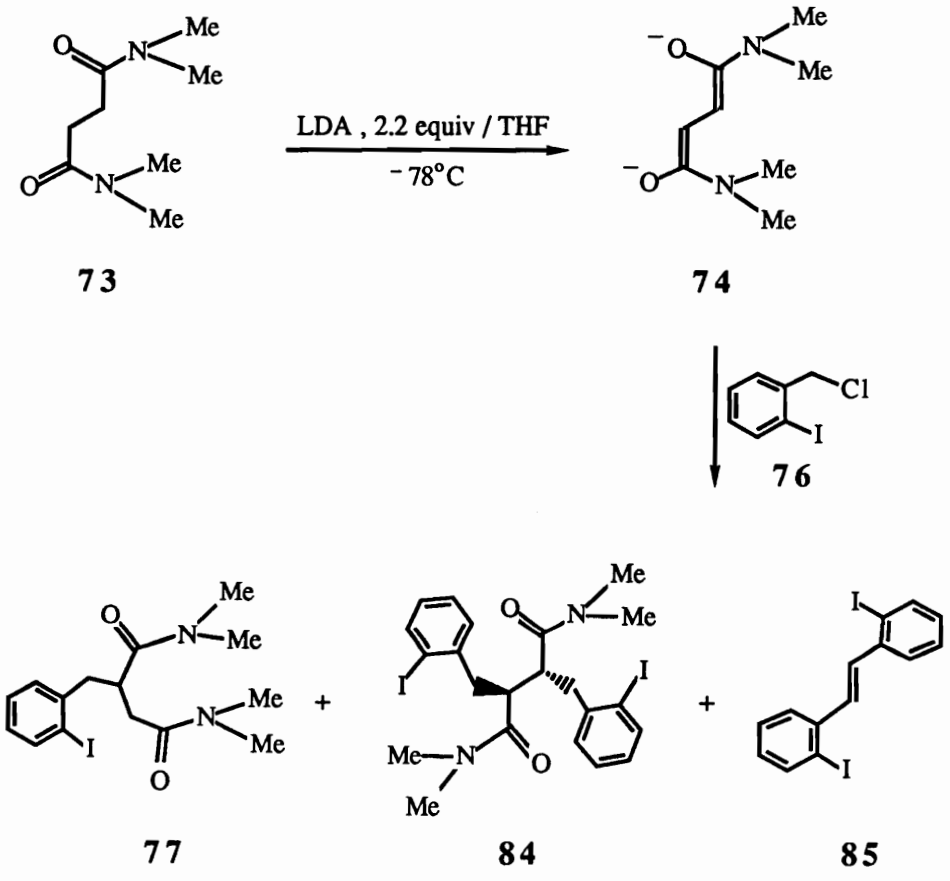
2. Synthesis of Succinimido[3,4-b]indane (61) from *N,N,N',N'*-Tetramethylsuccinamide (73).

2.1. Synthesis of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (77).

As stated earlier, the first step in the proposed synthesis of succinimido[3,4-b]indane (**61**) involved the preparation of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethyl-succinamide (**77**). The procedure described by Snieckus and co-workers[55] for the alkylation of *N,N,N',N'*-tetramethylsuccinamide (**73**) appeared to be well-suited for this purpose. An attempt was therefore made to prepare **77** by alkylating dianion **74**, generated from *N,N,N,N*-tetramethylsuccinamide (**73**) by means of 2.2 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C, with an equiv of *o*-iodobenzyl chloride (**76**) (Scheme 20). Upon separation of the crude product mixture by flash chromatography, the dialkylated derivative, 2,3-bis-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethyl succinamide (**84**) was obtained as the major product (65%). Its sharp melting point suggested that it was a single diastereomer, and on the basis of Snieckus's report, likely to be the *threo*- isomer. The desired monoalkylated derivative, 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) was obtained in only 15% yield along with a small amount of *trans-o,o'*-diiodostilbene (**85**) (10%) (entry 1, Table I). After attempting to improve the yield of the desired monoalkylated derivative **77** by carrying out the reaction under various conditions, which are summarised in Table I, the following conclusions were reached:

i) It was important that a cold (approx. -70°C), dilute (approx. 6% w/v) solution of *o* -iodobenzyl chloride in THF be added slowly (30 min) to the dianion **74**, in order to obtain the highest yields of the desired monoalkylated derivative **77** (entry 6). If a more

concentrated (17% w/v), cold (-70°C) solution of the alkylating agent was added slowly (25 min) (entry 2), or, if a more dilute (6.2%) cold (-70°C) solution was added rapidly (1 min) (entry 4), dialkylation occurred at the expense of monoalkylation. If the solution of the alkylating agent was not cooled in either of the above cases (entries 3, 5), the yield of monoalkyl derivative **77** was again significantly decreased by formation of the dialkylated product **84**.



73 **74** **76** **77** **84** **85**

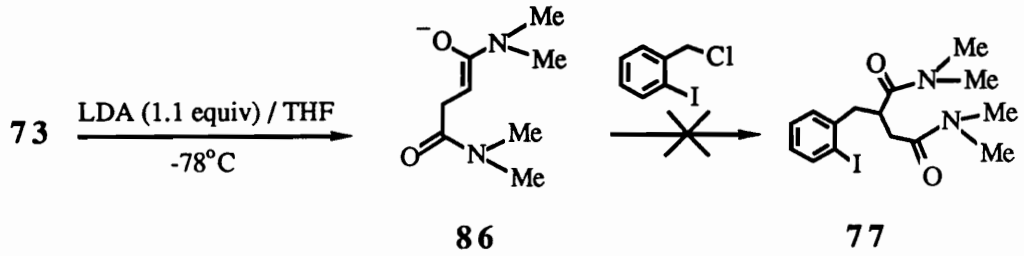
Scheme 20

Table I

Alkylation of *N,N,N',N'*-Tetramethylsuccinamide (73) with *o*-Iodobenzyl Chloride (76) Using LDA/THF at -78°C

entry	equiv of base	°C	conc of **76** in THF (%w/v),	addition time, min	yield, % **77**	**84**	**85**	**73**
1	2.2	17, r.t.	1	15	55	12	–	
2	2.2	17, -70	25	20	56	8	–	
3	2.2	17, r.t.	25	17	58	11	–	
4	2.2	6.2, -70	1	22	55	10	–	
5	2.2	6.2, r.t.	1	16	52	11	–	
6	2.2	6.2, -70	30	37	40	7	–	
7	1.1	6.2, -70	30	5	8	–	70	

ii) The dianion of *N,N,N,N* -tetramethylsuccinamide (**74**) was alkylated more efficiently than its monoanion **86**, as seen from the following results. When substrate **73** was treated with an equiv of LDA to form the monoanion **86**, addition of alkylating agent **76** resulted in the formation of a product mixture consisting of mostly starting materials along with traces of the monoalkylated product **77** and the dialkylated product **84** (entry 7) (Scheme 21).



86 **77**

Scheme 21

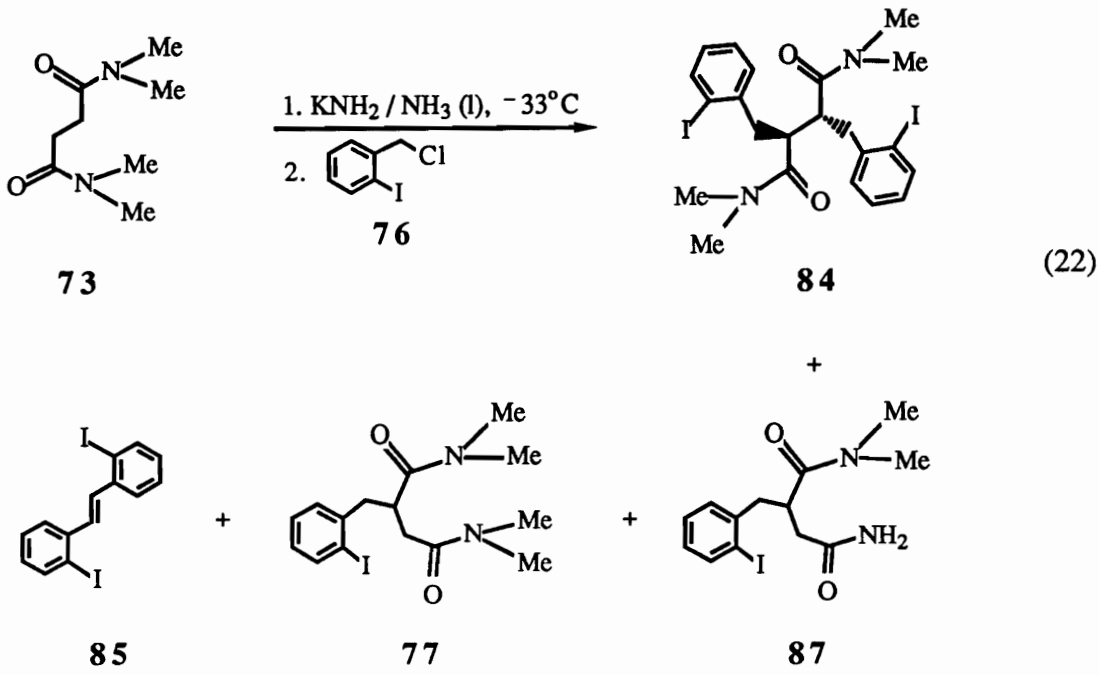
Thus, in our hands, the procedure described by Snieckus and co-workers afforded significant amounts of the undesired dialkylated derivative **84**. Therefore, prior to proceeding with the proposed investigation of the cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) to form 1,2-bis-(*N,N*-dimethylcarboxamido)-indane (**78**), optimization of the alkylation reaction was critical to the success of this overall synthetic strategy, and conditions that would give increased yields of **77**, while concomitantly suppressing dialkylation, needed to be determined.

Optimization of the Alkylation Reaction:

Since we had been unsuccessful in significantly limiting the extent of dialkylation of **73** using the procedure described by Snieckus and co-workers, the possibility of using different base/solvent systems (other than LDA/THF) for the generation and subsequent alkylation of dianion **74** was considered and tested. The suitability of potassium amide in liquid ammonia as an effective base/solvent system towards such an objective appeared to be worth investigating. However, there was no precedent in the literature for such an alkylation reaction. Although amide mono-enolates can be formed with alkali metal amides in liquid ammonia[50,51,56,57], there are no known examples of vicinal dianions such as **74** being generated under similar conditions. Thus, investigation of the possible formation and alkylation of dianion **74** using an alkali metal amide in liquid ammonia would be of value in its own right, and might well prove to be a synthetically useful procedure.

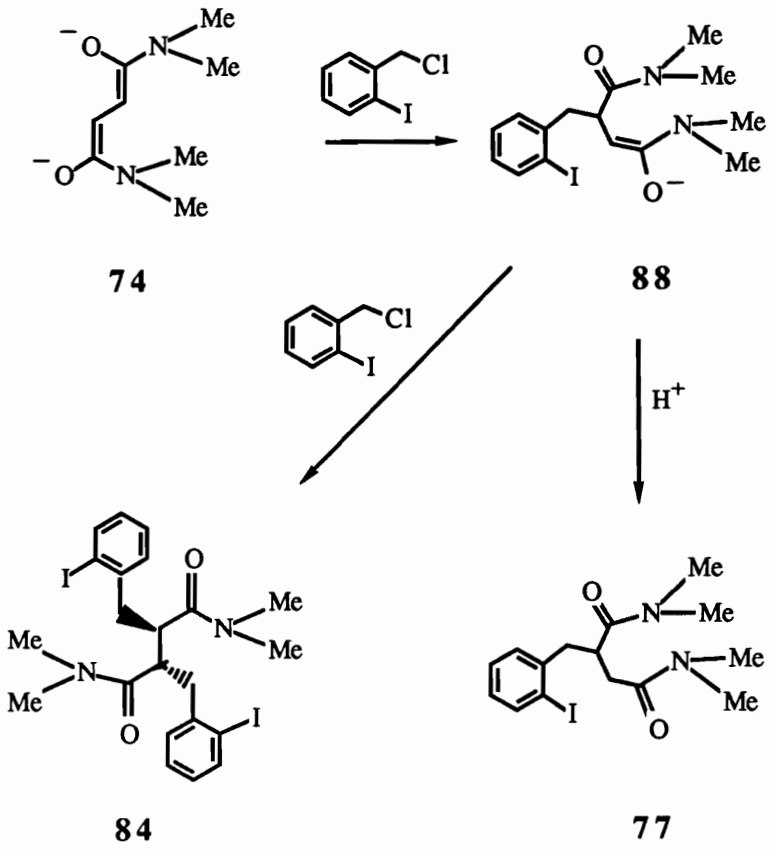
In a preliminary effort to explore the above possibility, the alkylation reaction was carried out with potassium amide (2.2 equiv) in refluxing liquid ammonia (entry 1, Table II). Examination of the ^{1}H-NMR spectrum of the crude product mixture revealed three major products, dialkylated derivative **84**, the desired monoalkylated derivative **77**, and *o,o'*-diiodostilbene (**85**), in the ratio 2:1:1 (eq 22). Upon chromatographic separation, one of the fractions consisted of a previously unidentified compound, which was shown to be 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)butanamide (**87**) (5%). Even though dialkylated product **84** was again obtained as the major product of the reaction, these results were encouraging, since they indicated that the desired dipotassium salt **74** had been formed from **73** with potassium amide in liquid ammonia. These preliminary results suggested that it might be profitable to further investigate the usefulness of alkali metal

amides in liquid ammonia in our quest for an efficient synthetic procedure for the preparation of **77** from *N,N,N',N'*-tetramethylsuccinamide (**73**).



(22)

In order to identify the conditions that would give the maximum yields of the monoalkylated product **77**, it was necessary to determine ways to suppress not only the dialkylation process, but also the formation of *o,o'*-diiodostilbene (**85**). Since lithium enolates are known to be less reactive than the corresponding potassium enolates in reactions with alkylating agents[58], it seemed possible that the difference in reactivities of dianion **74** and alkylated monoanion **87** with lithium as the counter-ion might be large enough to enable control of the alkylation reaction. Thus, the lithium salt of the alkylated monoanion **88**, once formed, might be resistant to further alkylation, thereby suppressing the formation of the dialkylated product **84**, and simultaneously increasing the yield of the desired 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) (Scheme 22). This led



Scheme 22

to the premise that the use of lithium amide (instead of potassium amide) in liquid ammonia might resolve the problem of dialkylation. Also, during the investigation of the alkylation of dianion **74** using LDA/THF as the base/solvent system, it had been observed that dialkylation had been somewhat suppressed when the solution of the alkylating agent was cooled to approximately -70°C before being slowly added to the dianion. Since the temperature of the reaction mixture had been maintained at -78°C during the course of this reaction, it appeared that at low temperatures the reactivity of the monoanion **88** was diminished to a somewhat greater extent than that of the dianion **74**. Extrapolating this to

the alkylation of the dianion **74** with an alkali metal amide in liquid ammonia, it seemed possible that if the reaction were to be carried out at temperatures below that of refluxing liquid ammonia (-33°C), reactivity differences between dianion **74** and monoanion **88** might be effectively exploited to give the desired 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) in acceptable yields, again by concomitantly limiting the extent of dialkylation. It is also known that lithium diisopropylamide in tetrahydrofuran at -78°C is less effective than potassium amide in liquid ammonia at -33°C in the conversion of benzyl halides to stilbene.[59] Therefore, it appeared reasonable to believe that lithium amide in liquid ammonia at temperatures well below -33°C might also suppress the formation of *o,o'*-diiodostilbene (**85**) in addition to suppressing dialkylation.

Each of these ideas were tested separately, in order to evaluate their viability in an acceptable synthetic procedure for the preparation of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**). These experiments are summarized in Table II. The reaction with lithium amide (2.2 equiv) as the base at -33°C (entry 2) gave the dialkylated derivative **84** as the major product. The results of this experiment were comparable to those obtained with potassium amide (2.2 equiv) in the same solvent at the same temperature (entry 1), except for the somewhat decreased formation of *o,o'*-diiodostilbene **85** with lithium amide. Thus, the use of lithium, rather than potassium, as the counterion at -33°C did not appear to improve the selectivity of the reaction as far as dialkylation was concerned.

Next, the behavior of both the lithium and the potassium dianions in liquid ammonia at lower temperatures was separately tested. When the reaction was carried out with lithium amide (2.2 equiv) in liquid ammonia at -78°C (entry 3), there appeared to be no visual signs of reaction after stirring with the alkylating agent for 15 min, so the reaction

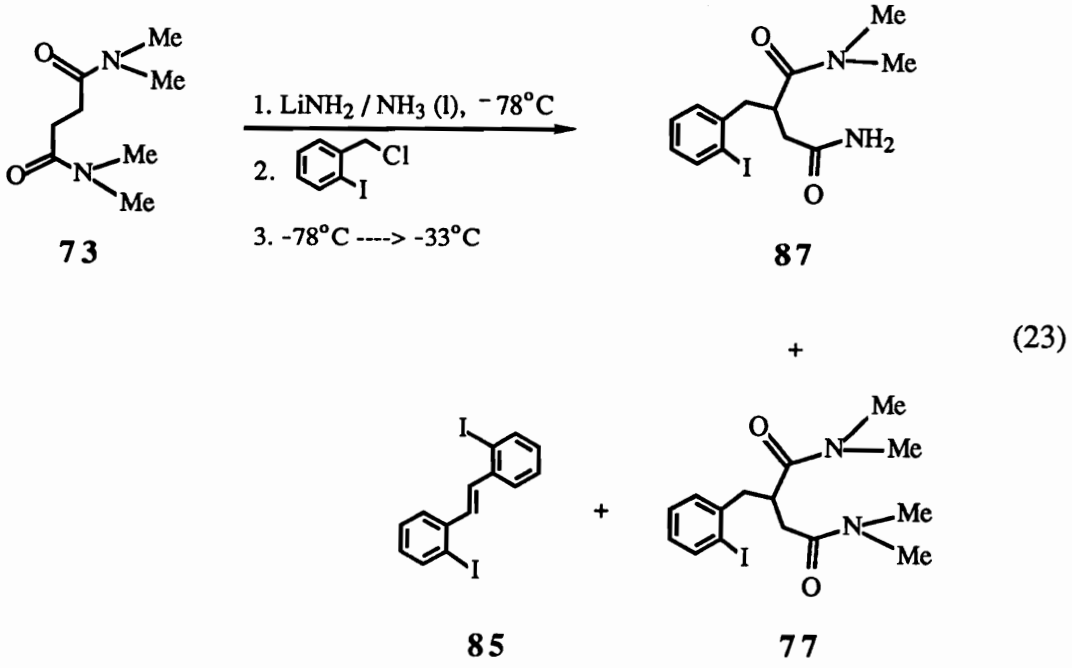
Table II

Optimization of the Monoalkylation of *N,N,N',N'*-Tetramethylsuccinamide (73) with Alkali Amides in Liquid Ammonia

entry	equiv of base	temperature °C, reaction time, h	yield, % 77	84	87	85
1	KNH_2 (2.2)	-33, 0.5	22	42	5	19
2	$LiNH_2$ (2.2)	-33, 0.5	21	37	9	15
3	$LiNH_2$ (2.2)	-78, 0.25 -->warm to -33, stir at -33 for 0.5 h,	26	-	50	8
4[a]	KNH_2 (2.2)	[c]	20	25	10	16
5[b]	$LiNH_2$ (2.2)	-60, 0.75, quench at -60	51	-	9	5
6	$LiNH_2$ (2.2)	-60, 1	65	-	15	6
7	$LiNH_2$ (2.2)	-60, 1.25	53	-	23	6

[a] Recovered 10% of unreacted **73**. [b] Recovered 8% of unreacted **73**. [c] Same as entry 3.

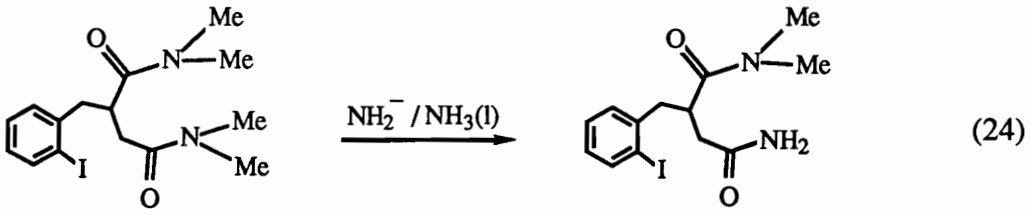
mixture was allowed to warm to -33°C and stirred for 0.5 h before being quenched. The products from this reaction were identified as the desired 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) (25%), 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)-butanamide (**87**) (50%) and *o,o'*-diiodostilbene (**85**) (8%) (eq 23). No dialkylated product **84** was observed. Also, the yield of stilbene **85** was less than that at -33°C. However, when a procedure similar to that described for entry 3 was carried out with potassium amide (entry 4), the results were quite different. Considerable amounts of the dialkylated derivative **84** were obtained; the formation of *o,o'*-diiodostilbene (**85**), although somewhat less than when the reaction was carried out at -33°C, was also still significant, indicating that even at lower temperatures, the use of potassium amide was unsatisfactory for our purposes.



73 **87** **85** **77**

(23)

The desired monoalkylated derivative **77** was not obtained as the major product from the reaction with lithium amide described in entry 3. Nonetheless, the results were encouraging, since, with the use of lithium amide in liquid ammonia at temperatures below -33°C, the two problems stated earlier, namely, dialkylation and formation of *o,o'*-diiodostilbene (**85**), had been successfully overcome to a significant extent. It appeared as if the reaction had actually occurred during the warming of the reaction mixture from -78°C to -33°C. However, a new problem had arisen: a large proportion of the newly formed alkylated monoanion **88**, or perhaps neutral **77** in equilibrium with it, had undergone partial solvolysis to form **87** (eq 24). An attempt was therefore made to determine the conditions that would minimize the solvolysis reaction without adversely affecting the selectivity of the alkylation process.

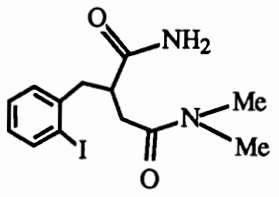


77 **87** (24)

Speculating that the alkylation might proceed efficiently at some temperature below -33°C, but above -78°C, the reaction was carried out at -60°C using lithium amide in liquid ammonia (entry 5), taking the precaution of also quenching the reaction at the same temperature. Upon separation of the product mixture, the desired 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) was obtained in 50% yield, thus representing an improvement over that obtained previously. Also encouraging was the fact that dialkylation and formation of *o,o'*-diiodostilbene (**85**) were again minimal. These results indicated that

solvolysis probably occured much more slowly at -60°C than when the reaction mixture was allowed to warm to -33°C before being quenched. However, the recovery of unreacted **73** (10%) sugested that longer reaction times would be necessary for complete reaction. From the results of subsequent experiments carried out to determine the optimum reaction time (entries 6, 7), it appears as if both temperature and time of reaction are critical in the maximization of the yield of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**). 3-(*N,N*-Dimethylcarboxamido)-4-(*o*-iodophenyl)butanamide (**87**) presumably arises from **77** by solvolysis, and this process is facilitated at higher temperatures (*i.e.*, closer to -33°C), as well as during extended reaction times (even at temperatures below -33°C) (eq 24).

Elucidation of the structure of the solvolysis product, **87**, was based on its spectral features. Its ^{1}H-NMR spectrum revealed that the molecule contained one amido group along with one *N,N*-dimethylcarboxamido- group. Since the remainder of the spectrum closely matched the ^{1}H-NMR spectrum of the monoalkylated derivative **73**, the compound was assumed to be either 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)-butanamide (**87**) or the isomeric 3-carboxamido-4-(*o*-iodophenyl)-*N,N*-dimethylbutan-amide (**89**). Theoretically, there appeared to be two possible pathways that could



89

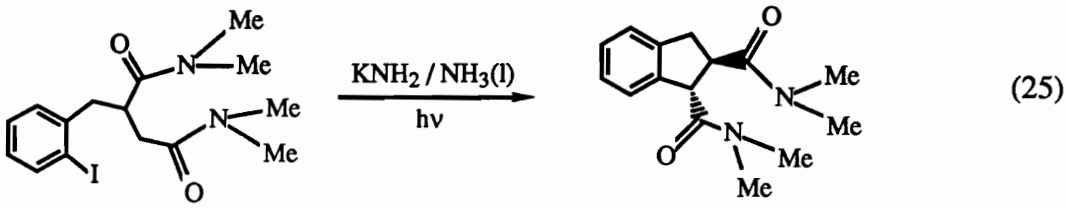
possible pathways that could lead to the formation of this compound: either it could arise from the partial solvolysis of **77** (eq 24), or it was possible that substrate **73** underwent partial solvolysis prior to alkylation. However, the latter process seemed unlikely, based on the results from entries 5, 6 and 7 (Table II). That the solvolysis product was in fact 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)butanamide (**87**) and not 3-carboxamido-4-(*o*-iodophenyl)-*N,N*-dimethylbutanamide (**89**) was determined from the fragmentation pattern of its mass spectrum. The moderately intense (55% relative intensity) peak corresponding to mass 302 could arise only from **87**, by fragmentation of (-CH_2-CO-NH_2) at the tertiary carbon site. This structural assignment was also confirmed by X-ray crystallography (see Appendix II, pp 210).[67]

Since a satisfactory procedure for the synthesis of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) in 65% isolated yield had thus been developed, attention was then turned to the possibility of inducing **77** to undergo an intramolecular $S_{RN}1$ reaction to form 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**).

2.2. Cyclization of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (77) to form 1,2-bis-(*N,N*-Dimethylcarboxamido)indane (78).

As stated earlier, the potential of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethyl-succinamide (**77**) to undergo cyclization under $S_{RN}1$ conditions was of prime interest to us, particularly in connection with ongoing studies in our laboratories involving intramolecular aromatic nucleophilic substitution reactions. A preliminary test conducted to explore the possibility of inducing such a cyclization afforded promising results. Thus, upon treatment with potassium amide (8 equiv) in liquid ammonia under photostimulation, **77** underwent cyclizaton to give the expected product, 1,2-bis-(*N,N*-dimethyl-

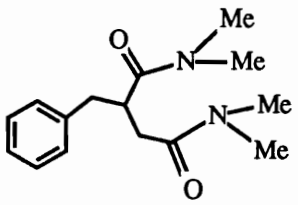
carboxamido)indane (**78**) in moderate yield (eq 25). Assignment of *trans*- configuration is discussed in greater detail later in this chapter (see Section 6.1., pp 89). Further experimentation was undertaken to determine the optimum reaction conditions for the cyclization reaction, the results of which are presented in Table III. Subsequent experiments, aimed at uncovering the mechanistic features of the cyclization reaction, appear later (see Section 7.2, 100).



(25)

77 **78**

Experiments aimed at maximizing production of **78** showed that the best yields of this product were obtained when an excess of potassium amide was used (8 equiv) (Table III, entries 1, 2, 4 and 5), either with or without photostimulation. A small percentage of substrate **77** underwent reductive dehalogenation to form 2-benzyl-*N,N,N',N'*-tetramethylsuccinamide (**90**) under these conditions. When the theoretical quantity (3



90

Table III

Investigation of the Cyclization of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (77) to 1,2-bis-(*N,N*-Dimethylcarboxamido)indane (78)

entry	base (equiv), solvent	time, h	photostimulation	----- yield, % ----- 78	90	77
1	KNH_2 (8) NH_3 (l)	3	+	65	15	–
2	KNH_2 (8) NH_3 (l)	0.25	+	68	9	–
3	KNH_2 (3.3) NH_3 (l)	3	+	38	20	18
4	KNH_2 (8) NH_3 (l)	3	–	70	10	–
5	KNH_2 (8) NH_3 (l)	0.25	–	69	8	–
6	KNH_2 (3.3) NH_3(l)	3	–	32	15	32
7	$LiNH_2$ (3.3) NH_3 (l)	3	+	–	–	89
8	$LiNH_2$ (8) NH_3 (l)	3	+	15	8	60
9	$NaNH_2$ (8) NH_3 (l)	3	+	–	–	88
10	KO*tert*-Bu NH_3 (l)	3	+	–	–	92
11[a]	LDA (3.3) THF	3	+	10	–	72
12[a]	LDA (8) THF	3	+	32	20	31

[a] Temperature was maintained between -30°C and -35°C during the reaction.

equiv) of potassium amide was used (entry 3), the reaction was incomplete after 3h of photostimulation, the product mixture containing 30% of unreacted **77**. Also, a greater proportion of the substrate underwent reductive dehalogenation to give **90** (relative to entry 1).

With excess potassium amide, the results of the dark reactions (entries 4 and 5) were comparable to those obtained with photostimulation (entries 1 and 2), good yields of the cyclized product being obtained in all four instances. The dark reaction with 3 equiv of potassium amide (entry 6) resulted in only 20% cyclization to the expected product **78**. These results indicated that the reaction perhaps proceeded via the intermediacy of an aryne, rather than by an $S_{RN}1$ pathway. Alternatively, it was possible that a thermal $S_{RN}1$ reaction was occurring. The investigation conducted to determine the mechanistic aspects of this reaction is discussed in detail later in this chapter (see Section 7.2., pp 100).

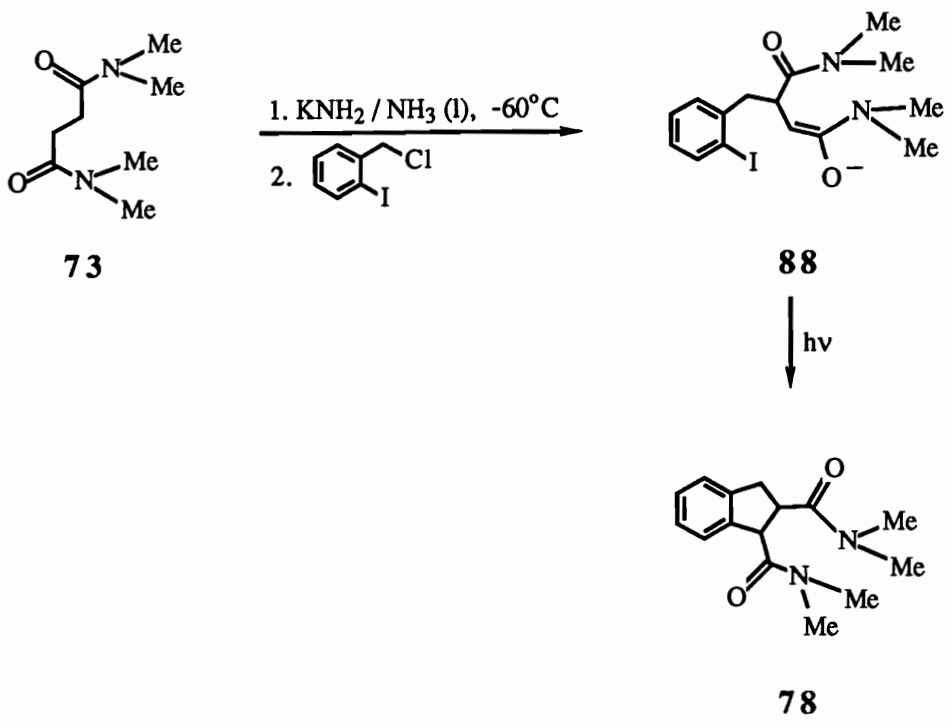
While potassium amide in liquid ammonia is known to be the base/solvent system of choice for many $S_{RN}1$ reactions, other base/solvent systems such as lithium amide, sodium amide and potassium *tert*-butoxide in liquid ammonia, as well as LDA in THF, have been shown to be effective as well. The possibility of inducing the above cyclization with other bases such as those just cited therefore deserved some scrutiny. When cyclization was attempted with lithium amide in ammonia (entries 7 and 8), the product mixtures were found to consist largely of unreacted **77**, although small amounts of the cyclized product **78** were detected when excess lithium amide was used. Excess sodium amide (entry 9) and excess potassium *tert*-butoxide (entry 10) were also ineffective in inducing the intramolecular reaction under photostimulated conditions; only unreacted **77**, along with traces of **90**, were detected in the product mixture. When LDA/THF was used as the base/solvent system (entries 11 and 12), the product mixture was found to contain

small quantities of the cyclized product **78**, although the presence of relatively large amounts of unreacted **77** (72% and 31%, respectively) indicated that the reactions were incomplete even after 3h of photostimulation. The obtention of 30% of 2-benzyl-*N,N,N',N'*-tetramethylsuccinamide (**90**) as compared to 20% of the desired 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) in the latter case, when excess LDA was used (entry 12), revealed that a greater proportion of the substrate underwent reduction rather than cyclization.

From the series of experiments described in Table III, it was found that treatment of 2-(*o*-iodobenzyl)-*N,N,N',N'*tetramethylsuccinamide (**77**) with excess potassium amide (8 equiv) in refluxing liquid ammonia for 15 min (dark) was the best synthetic procedure for effecting its cyclization to the desired 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**).

2.3. Attempted "One-Pot" Synthesis of 1,2-bis-(*N,N*-Dimethylcarboxamido)indane (78) from *N,N,N',N'*-Tetramethylsuccinamide (73).

Although the inherent possibility of accomplishing the "one-pot" synthesis of **78** outlined in Scheme 23 had presented itself as an attractive one during the developmental stages of this investigation, it was not until this time that the idea appeared more promising. Since alkali-metal amides in ammonia were used in both steps (alkylation, cyclization) leading to the most efficient synthesis of **78** from **73**, it seemed that the two reactions could perhaps be combined into a "one-pot" procedure that would afford the cyclized compound **78** from **73** in a single experimental step (Scheme 23). A series of experiments were carried out to explore this possibility.



73 **88** **78**

Scheme 23

Investigation of the alkylation and cyclization reactions, described in the two preceding sections, had revealed that efficient monoalkylation of *N,N,N',N'*-tetramethylsuccinamide (**73**) to yield 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) occurred when 2.2 equiv of lithium amide in liquid ammonia at -60°C were used (more base and higher temperatures being detrimental), while the presence of excess potassium amide (8 equiv) in liquid ammonia, was a prerequisite for efficient cyclization of **77** to 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**), the reaction proceeding equally well with or without photostimulation.

This led to the preliminary conclusion that the "one-pot " procedure might be conveniently accomplished by carrying out the two reactions (alkylation and cyclization) in a sequential manner. Thus, it appeared that if the reaction were carried out first under the conditions that gave good yields of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) (2.2 equiv lithium amide, liquid ammonia, -60°C, 1 h), followed by addition of more base (6 equiv potassium amide) and subsequent warming to -33°C, the cyclized product, 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) should be obtained in reasonably good yield. Although this idea is promising in theory, it is complicated by the *practical* problem of adding potassium amide to the reaction mixture at the end of the alkylation reaction, in order to induce effective cyclization of the newly formed alkylated monoanion **88**. With reactions carried out in liquid ammonia, the alkali metal amides are usually generated *in situ* prior to addition of the substrates, and it would become experimentally difficult to transfer potassium amide generated elsewhere (in another flask) to the reaction vessel at an intermediate stage in the reaction, *i.e.*, after the alkylation reaction is complete. Potassium amide, in particular, is the most difficult to handle of all the alkali metal amides. Sodium amide can be added as a solid and lithium amide can be quickly generated by the addition of *n*-butyllithium to liquid ammonia. Solid potassium amide, on the other hand, is extremely unstable and therefore cannot be added as such. Moreover, the formation of potassium amide by addition of potassium metal to the reaction mixture would be relatively slow, which could cause increased possibilities of undesirable side reactions such as reduction of the substrate to amide **90**.

Since neither lithium nor sodium amide was effectual in inducing the cyclization of **77** to give **78** (Table III, entries 7-9), we decided to explore the possibility of using a mixture of bases (KNH_2 + 'B', where 'B' = $LiNH_2$, $NaNH_2$ or *t*-BuOK) for the

cyclization reaction. Caubere[16e,f] has reported the use of complex base such as $NaNH_2$-*t*-BuONa in the presence of aprotic solvents such as THF and DME for generation of arynes, although there was no precedent in the literature regarding the use of complex base in $S_{RN}1$ reactions. In order to do so, it would be necessary to generate potassium amide *in situ* prior to addition of the substrate, while the second base could be added at a later stage. Furthermore, in terms of developing a 'one-pot' synthesis of **78** from **73** by this route, it meant that potassium amide would have to be used in the initial monoalkylation step (the formation of **88** from **73**, Scheme 23).

Previous experiments had shown potassium amide to be unsuitable for the monoalkylation of *N,N,N',N'*-tetramethylsuccinamide (**73**) to give 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) (Table II, entries 1,4). Our preliminary experiments now, therefore, focussed on determining optimum conditions for monoalkylation using potassium amide as the base, since efficient monoalkylation, uncomplicated by competing reactions, was critical to the success of the 'one-pot' synthesis of **78** from **73** by the route proposed above. Using, with potassium amide, conditions similar to those that had given good yields of **77** when lithium amide was employed (Table II, entry 6), afforded **77** in 50% yield, along with 12% of dialkylated product **84**, 6% of solvolysis product **87** and 14% of *o,o'*-diiodostilbene (**85**).

Having determined the reaction conditions leading to the formation of **77** in acceptable yield, we then explored the possibility of using the mixed bases (KNH_2 + 'B') for an effective "one-pot" procedure for the synthesis of **78** from **73**. In all the experiments summarized in Table IV, the first stage of alkylation was carried out with 2.2 equiv of potassium amide at -60°C for 1 h, after which time another base 'B' (6 equiv) was

added, the reaction mixture warmed to -33°C and then irradiated for 0.5 h before quenching with solid ammonium chloride. The decision to irradiate the reaction mixtures during the latter part of the experiments was based on the premise that even though the cyclization had been found to proceed equally well with or without photostimulation with potassium amide, the attempted cyclization with the complex base (KNH_2 + 'B') might possibly require photostimulation. However, the use of the bases lithium amide (entry 1), sodium amide (entry 2) and potassium *tert*-butoxide (entry 3) as 'B' failed to give any detectable cyclized product.

It had been observed previously that 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) had undergone cyclization to some extent with 3 equiv of potassium amide (Table III, entries 3 and 6). Since the reaction was slower than with excess (8 equiv) base, it seemed possible that a "one-pot" synthesis of **78** might be achieved by carrying out the initial alkylation of **73** using 3 equiv of potassium amide in liquid ammonia at -60°C (1 h), warming the reaction mixture to -33°C and stirring for longer time (4-5 h) under photostimulation to allow complete cyclization to occur. When the reaction was carried out in this way (Table IV, entry 4), the desired cyclized compound **78** was isolated in 23% yield.

Concluding that our efforts to develop an efficient procedure for the tandem alkylation-cyclization of *N,N,N',N'*-tetramethylsuccinamide (**73**) to give 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) in a single experimental step were hampered primarily by the practical difficulty of adding potassium amide at an intermediate stage of the

Table IV

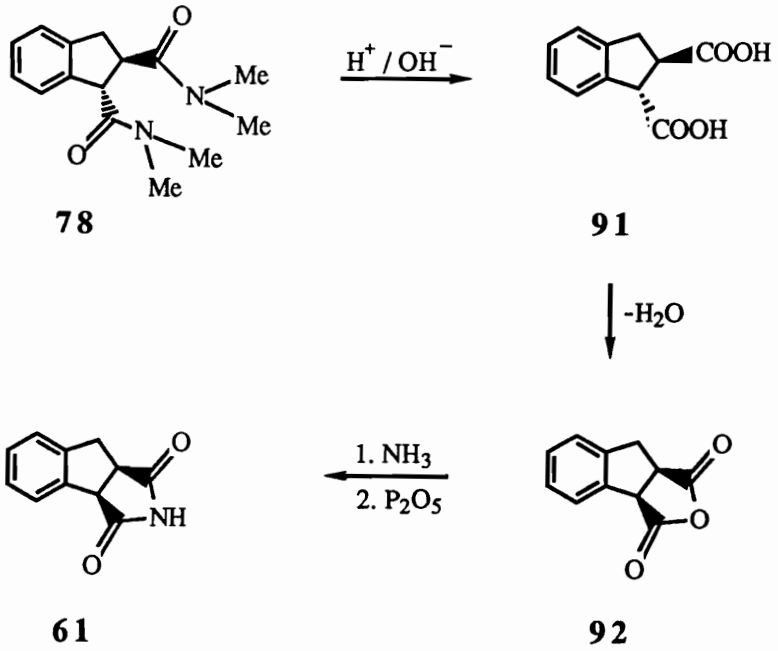
Attempted "One-Pot" Synthesis of 1,2-bis-(*N*,*N*-Dimethylcarboxamido)indane (78)

entry	base (equiv)	time, temp (°C)	photostimulation	yield, %			
				77	**78**	**90**	**85**
1	i) KNH_2 (2.2)	1h, -60	–				
	ii) $LiNH_2$ (6)	0.5h, -33	+	48	–	–	18
2	i) KNH_2 (2.2)	1h, -60	–				
	ii) $NaNH_2$ (6)	0.5h, -33	+	45	–	–	10
3	i) KNH_2 (2.2)	1h, -60	–				
	ii) KO*t*-Bu (6)	0.5h, -33	+	52	–	–	12
4	KNH_2 (3.3)	1h, -60	–				
		4.5h, -33	+	11	23	12	13

reaction, this line of investigation was terminated. Therefore, the best method for preparing **78** from **73** was by the procedure developed previously, *i.e.*, by carrying out the alkylation and cyclization reactions separately, which afforded **78** in 46% overall yield.

2.4. Conversion of 1,2-bis-(*N,N*-Dimethylcarboxamido)indane (78) to Succinimido[3,4-b]indane (61).

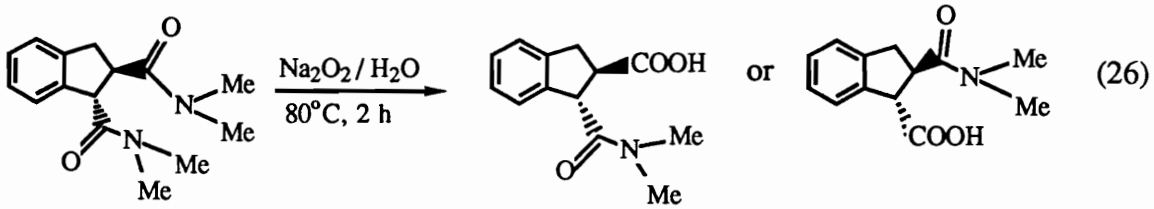
One of our synthetic objectives in undertaking this study had been to attempt to pepare succinimido[3,4-b]indane (**61**) which we believed possessed structural features that might impart anticonvulsant activity to it. One way of converting 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) to **61** appeared to be via *trans*-indane-1,2-dicarboxylic acid (**91**) which could presumably be prepared by hydrolysis of **78** (Scheme 24).



Scheme 24

Dehydration of diacid **91** was expected to afford its anhydride **92**, which could then be subjected to known imidization procedures to form the desired **61**.[60]

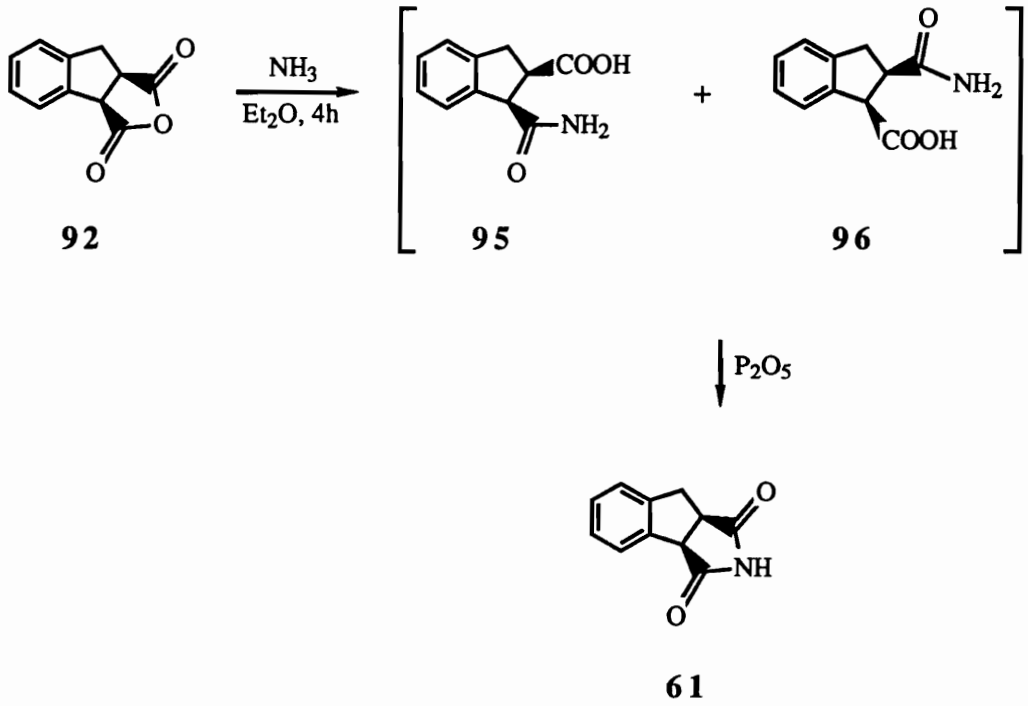
In an atempt to prepare **61** by this route, **78** was subjected to various hydrolytic conditions. Attempts to hydrolyse the *N,N*-dimethylcarboxamido groups of **78** with various mineral acids (dil. and conc HCl, dil.H_2SO_4 and polyphosphoric acid) proved ineffective, affording product mixtures that consisted mostly of unreacted **78**. However, a mild procedure, originally developed by Vaughn and Robbins,[61] that involved heating the substrate with aqueous sodium peroxide gave a product that was shown by ^{1}H-NMR to have lost one *N,N*-dimethylcarboxamido group; the other *N,N*-dimethylcarboxamido group was apparently resistant to hydrolysis under these conditions. Partial hydrolysis of **78** could result in formation of either one or both of the products, amide-acids **93** and **94** (eq 26). Nevertheless, the isolated product was a single compound as evidenced by its sharp melting point and TLC behavior. Inspection of structure **78** reveals that the *N,N*-dimethylcarboxamido- group at C-2 is somewhat less hindered than the one at C-1, and therefore more likely to undergo hydrolysis under mild conditions. Examination by X-Ray crystallography confirmed this structural assignment, identifying the product as *trans*-1-(*N,N*-dimethylcarboxamido)indane-2-carboxylic acid (**93**) (see Appendix II, pp 215).[67]



78 **93** **94**

In order to investigate the possibility of converting **78** to **61** via the route outlined in Scheme 24, it was necessary to first obtain the diacid **91**, which was accomplished in 70% yield by refluxing **78** with 15% aqueous sodium hydroxide for several hours. A procedure developed by Cook and co-workers[62] was then used to prepare the anhydride **92** in moderate yield (44%) by refluxing **91** with acetyl chloride for 6h.

This compound was expected to undergo ammonolysis to form a mixture of the *cis*-amic acids **95** and **96** upon treatment with ammonia. Presumably, these amic acids could then be dehydrated, perhaps with phosphorus pentoxide, to give the desired succinimido[3,4-b]indane (**61**) (Scheme 25).[60] When this sequence of reactions was



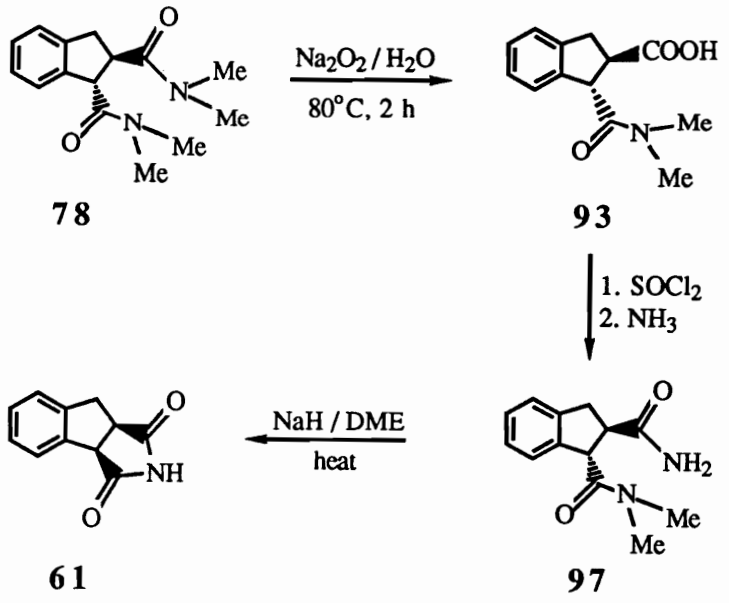
92 **95** **96** **61**

Scheme 25

attempted, without isolation of the intermediate amic acids, imide **61** was obtained in 37% yield from anhydride **92**.

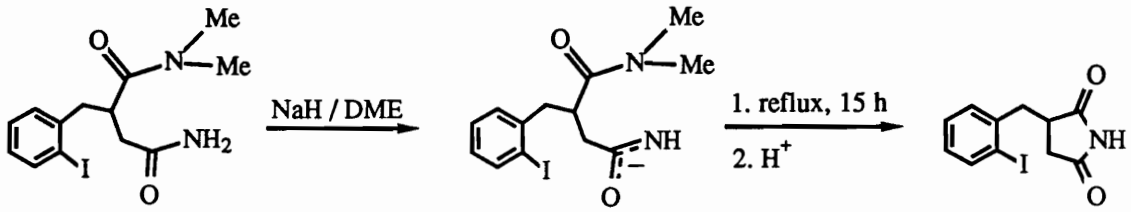
We had therefore succeeded in preparing the targeted succinimido[3,4-b]indane (**61**) from *N,N,N',N'*-tetramethylsuccinamide (**73**) by the proposed route (Scheme 18) . However, although the first three steps (from **73** to **91**) had afforded reasonably good yields of the respective products, the sequence of reactions leading from dicarboxylic acid **91** to succinimido[3,4-b]indane (**61**) had resulted in only moderate yields of the corresponding products, thereby adversely affecting the overall yield (5.5%) of the desired compound by this synthetic route.

Since the last two steps of the strategy outlined in Scheme 24 for the transformation of **78** into **61** had not proved to be very effective, an alternative route for this transformation was devised (Scheme 26), involving 1-(*N,N*-dimethylcarboxamido)indane-



Scheme 26

2-carboxylic acid (**93**), which had previously been obtained in excellent yield from **78** by treatment with aqueous sodium peroxide (eq 26). Conversion of the carboxyl group of **93** to the amido group of **97** was expected to be fairly routine, while the conjecture that **97** could be transformed into **61** was based on the observation that **87** could be converted to 3-(*o*-iodobenzyl)succinimide (**99**) in 93% yield by refluxing with sodium hydride in DME followed by acidification (Scheme 27).



87 **98** **99**

Scheme 27

An investigation was then undertaken to determine if the strategy outlined in Scheme 26 was an effective way of converting **78** into **61**. The previously isolated *trans*-1-(*N,N*-dimethylcarboxamido)indane-2-carboxylic acid (**93**) (eq 26), was converted to *trans*-1-(*N,N*-dimethylcarboxamido)indane-2-carboxamide (**97**) via its acid chloride in 89% yield. Treatment of **97** with an equivalent of sodium hydride in 1,2-dimethoxy-ethane followed by refluxing for 15 h afforded a mixture consisting of succinimido[3,4-b]indane (**61**) and unreacted **97** in the approximate ratio of 1:4 (estimated from the ^{1}H-NMR spectrum of the crude product). Increasing the reaction time to 40 h improved this ratio only slightly (1:3). Treatment of **97** with sodium hydride in refluxing toluene did not result in any significant improvement in the extent of reaction, and the product mixture still

contained considerable amounts of unreacted **97**. The reluctance of **97** to undergo the proposed reaction is attributed to the *trans*- geometry of its two amide groups. In order to undergo the intramolecular reaction that would lead to the formation of **61**, it was necessary for the two amide groups to assume a *cis*- orientation. This being a sterically unfavorable orientation, the transformation of **97** into **61** was very slow.

3. Synthesis of Succinimido[3,4-b]indane (61) from 3-(*o*-Iodobenzyl)succinimide (99).

3.1. Introduction.

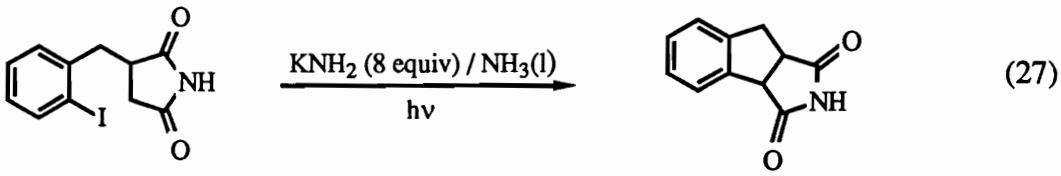
In attempting to develop a more efficient synthetic procedure for the preparation of **61**, it was felt that the possibility of inducing intramolecular $S_{RN}1$ reactions in 3-(*o*-halobenzyl)succinimides deserved further investigation. Our hopes in this approach, previously examined and rejected as being unsatisfactory, were renewed by some of the features uncovered during the investigation of the cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) to form 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**). Therefore, a series of experiments were devised to test the possibility of preparing succinimido[3,4-b]indane (**61**) by inducing 3-(*o*-iodobenzyl)succinimide (**99**) to undergo an intramolecular $S_{RN}1$ reaction.

An intriguing feature of the cyclization of **77** to form **78** (see eq 25, pp), was the fact that while the reaction proceeded only poorly with stoichiometric quantities of potassium amide, it was remarkably facile in presence of excess potassium amide in liquid ammonia. This led to a renewal of interest in the possibility that 3-(*o*-halobenzyl)-succinimides **65** also might be induced, under similar conditions, to undergo cyclization.

Earlier experiments by Goehring[53] had been carried out with **65** and stoichiometric amounts of potassium amide and the possibility that the presence of excess base might be critical seemed worth investigating. Another feature that was recognized as having a possible bearing on the reactivity of the substrate was the nature of the nucleofuge. Iodoarenes are known to be more reactive than the corresponding bromo- and chloro-

arenes, with regard to their ability to participate in $S_{RN}1$ reactions. Goehring's attempts to induce an intramolecular $S_{RN}1$ reaction in the *o*-bromo- derivative of 3-benzyl-*N*-methyl-glutarimide (**71**) had been unsuccessful, but it appeared that similar attempts with the *o*-iodo- derivative might have a different, more satisfactory, outcome.

An attempt was therefore made to incorporate the above ideas into the development of a viable synthetic route to succinimido[3,4-b]indane (**61**) from 3-(*o*-iodobenzyl)-succinimide (**99**) (eq 27). The synthesis of substrate **99** was then undertaken for the purpose of studying its cyclization to **61**.

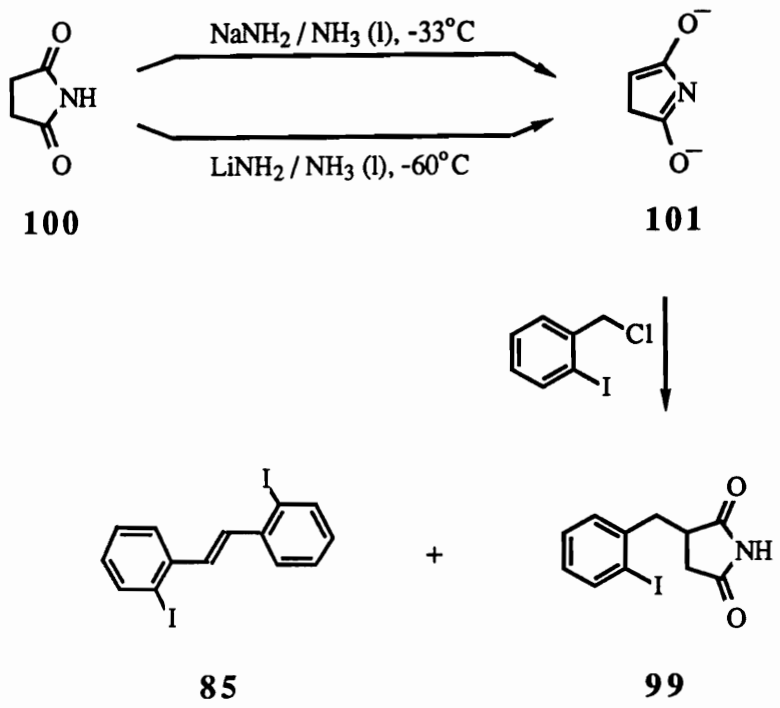


99 **61** (27)

3.2. Synthesis of 3-(*o*-Iodobenzyl)succinimide (99).

From succinimide (100).

Goehring[53] and Pisipati[47] had prepared several analogs of 3-substituted succinimides based on Rogers'[52] approach to the synthesis of 3-substituted glutarimides. This method was therefore considered as the first choice for the synthesis of 3-(*o*-iodo-benzyl)succinimide (**99**). Thus, the succinimide dianion (**101**), generated from succinimide (**100**) by treatment with 2 equiv of sodium amide in liquid ammonia, was treated with an equimolar quantity of *o*-iodobenzyl chloride (**76**) (Scheme 28). Upon chromatographic separation of the crude product, the desired product **99** was obtained in 34% yield, accompanied by 23% of *trans-o,o'*-diiodostilbene (**85**).



Scheme 28

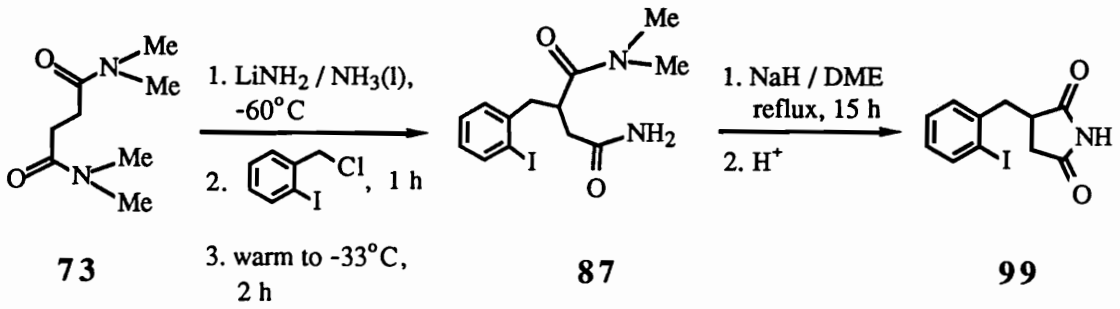
In an attempt to improve the yield of **99**, the reaction was carried out under the conditions that had been found to be optimum for the generation and alkylation of dianion **74** derived from *N,N,N',N'*-tetramethylsuccinamide (**73**), *i.e.*, the use of lithium amide in liquid ammonia at -60°C (see Table II (entry 6), Section 2.1; pp). This reaction proved to be more efficient than the procedure utilizing sodium amide in refluxing liquid ammonia, affording 3-(*o*-iodobenzyl)-succinimide (**99**) in 50% yield along with 18% of *o,o'*-diiodostilbene (**85**). Nevertheless, it was considered worthwhile to examine alternative synthetic routes that might afford **99** even more efficiently.

From N,N,N',N'-tetramethylsuccinamide (73).

An alternative synthetic route for the preparation of 3-(*o*-iodobenzyl)succinimide (**99**) emerged from the observation that 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)-butanamide (**87**) could be efficiently transformed into **99** upon treatment with sodium hydride in dimethoxyethane (Scheme 27), as described in the preceding section. Compound **87** had been initially obtained as a by-product during attempts to develop a procedure for the synthesis of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) from *N,N,N',N'*-tetramethylsuccinamide (**73**) (see eq 23, 24, Section 2.1, pp 49,50). It was believed that the intermediate formed by the monoalkylation of dianion **74** was susceptible to solvolysis, leading to the formation of **87**. Since this reaction adversely affected the yield of the desired monoalkylated product **77**, we had attempted to determine conditions that suppressed it. However, for the purpose of developing a useful synthetic procedure for the preparation of **99**, it was necessary to determine conditions that actually promoted the solvolytic formation of **87**.

During the earlier studies in the alkylation of *N,N,N',N'*-tetramethylsuccinamide (**73**) it had been observed that the yield of **87** was dependent upon two factors, temperature and reaction time. Thus, significant quantities of **87** were obtained when the reaction mixture was warmed to -33°C after the initial alkylation at -60°C. Extended reaction times, even at low temperatures, also led to high yields of **87**. These observations were successfully incorporated into the following procedure that afforded **87** in excellent yield (Scheme 29).

o-Iodobenzyl chloride (**76**) was added to dianion **74**, generated from *N,N,N',N'*-tetramethylsuccinamide (**73**) by treatment with 2.2 equiv of lithium amide in liquid ammonia at -60°C. After stirring for 1h, taking care to maintain the temperature at -60°C, the reaction mixture was allowed to warm to -33°C and stirred for an additional 2h. The crude product was shown by ^{1}H-NMR to consist of almost pure 3-(*N,N*-dimethyl-carboxamido)-4-(*o*-iodophenyl)butanamide (**87**). Purification by recrystallization afforded the desired compound in 90% yield.



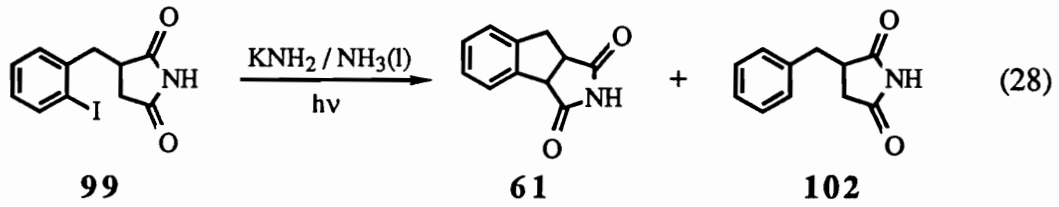
73 **87** **99**

Scheme 29

Good experimental procedures had thus been developed for the two reactions depicted in Scheme 29, which, in sequence, represent a synthetic route for the preparation of the desired 3-(*o*-iodobenzyl)succinimide (**99**) in 84% yield from *N,N,N',N'*-tetramethylsuccinamide (**73**). An investigation was then undertaken to examine the ability of imide **99** to participate in an intramolecular $S_{RN}1$ process that would lead to succinimido[3,4-b]indane (**61**).

3.3. Cyclization of 3-(*o*-Iodobenzyl)-succinimide (99) to form Succinimido[3,4-b]indane (61).

Cyclization of 3-(*o*-iodobenzyl)-succinimide (**99**) to form succinimido[3,4-b]indane (**61**) was initially attempted using excess (8 equiv) potassium amide in liquid ammonia under photostimulation for three hours. ^{1}H-NMR analysis of the crude product mixture suggested that it consisted of the expected, cyclized compound, **61**, and the product of reductive dehalogenation, 3-benzylsuccinimide (**102**) (eq 28). Separation of these compounds was accomplished by a combination of flash column chromatography and crystallization techniques, which afforded a 40% yield of the desired succinimido[3,4-b]indane (**61**), along with 28% of the reduction product **102** (eq 28, entry 1, Table V).



99 **61** **102** (28)

Having established that the proposed cyclization occured as expected, an attempt was made to determine conditions that would afford improved yields of the desired **61** from **99**, and the results of this investigation are outlined in Table V. When the reaction was carried out with 3 equiv of potassium amide under photostimulation (entry 2), only unreacted **99** was detected in the crude product mixture. However, in the presence of excess potassium amide (8 equiv), **99** reacted completely in 0.5h under photostimulation (entry 3), giving the same ratio of products **61** and **102** as obtained after a reaction time of three hours with illumination (entry 1). When the reaction was carried out with excess

potassium amide (8 equiv) in the dark, only traces of succinimido[3,4-b]indane (**61**) were obtained, even after extended reaction time (entries 4, 5). Therefore, unlike the cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) to 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**), which had been found to occur readily with excess potassium amide even in the dark, the cyclization of 3-(*o*-iodobenzyl)succinimide (**99**) was found to be a photoinduced process. In order to determine how the reaction would proceed if only a slight excess of base were used, the reaction was carried out with 4 equiv of potassium amide (entries 6, 7). The distribution of products **61** and **102** obtained upon treatment of **99** with 4 equiv of potassium amide for 1h under photostimulation was comparable to that obtained after 0.5h of photostimulated reaction with 8 equiv of the same base, indicating that the cyclization was somewhat faster when a larger excess of potassium amide was used. Either procedure could therefore be used to prepare the desired succinimido[3,4-b]indane (**61**) in approximately 40% isolated yield from 3-(*o*-iodobenzyl)succinimide (**99**).

Table V

Investigation of the Cyclization of 3-(*o*-Iodobenzyl)succinimide (99) to Form Succinimido[3,4-b]indane (61)

entry	base (equiv)	time, h	photostimulation	yield, %		
				61	**102**	**99**
1	KNH_2 (8)	3	+	40	28	–
2	KNH_2 (3.3)	3	+	–	–	82
3	KNH_2 (8)	0.5	+	41	29	–
4	KNH_2 (8)	0.5	-	10	_	73
5	KNH_2 (8)	6	-	15	–	65
6	KNH_2 (4.4)	1	+	40	30	–
7	KNH_2 (4.4)	0.5	+	28	17	22

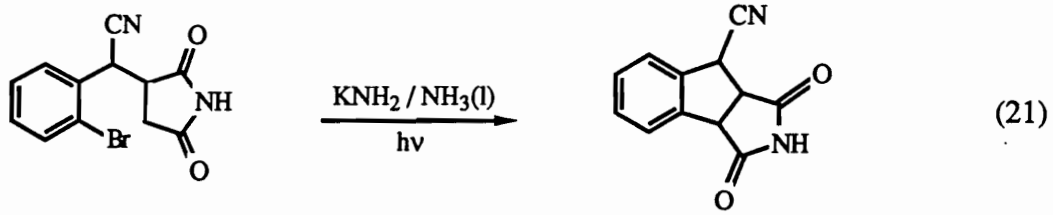
4. Attempted Synthesis of Succinimido[3,4-b]indane-8-carbonitrile (83) from (*o*-Bromophenyl)acetonitrile (103) and Maleimide (104).

4.1. Introduction.

We had been successful in developing a novel procedure, culminating in the cyclization of **99**, for the preparation of succinimido[3,4-b]indane (**61**), in 33% overall yield from *N,N,N',N'*-tetramethylsuccinamide (**73**), as discussed in the preceding section. It then seemed appropriate to seek to evaluate the usefulness of this approach for possible future application in the preparation of other compounds containing the parent tricyclic system present in **61**. From this point of view, it was considered worthwhile to attempt to prepare a cyano- derivative of **61**, succinimido[3,4-b]indane-8-carbonitrile (**83**), using a strategy similar to the one that had led to the successful synthesis of **61**. This compound was potentially valuable from a synthetic standpoint, since further derivatization of **83** via the cyano- group could lead to various other analogs of **61**.

Since 3-(*o*-iodobenzyl)succinimide (**99**) had been found to undergo intramolecular reaction successfully to form succinimido[3,4-b]indane (**61**) (eq 28), it seemed appropriate to determine if similar reactions were feasible with more highly substituted derivatives of **99**. 3-(*o*-Bromo-α-cyanobenzyl)succinimide (**82**) appeared to be a suitable substrate for such an investigation. If the expected cyclization occurred, it would lead to the formation of succinimido[3,4-b]indane-8-carbonitrile (**83**) (eq 21).

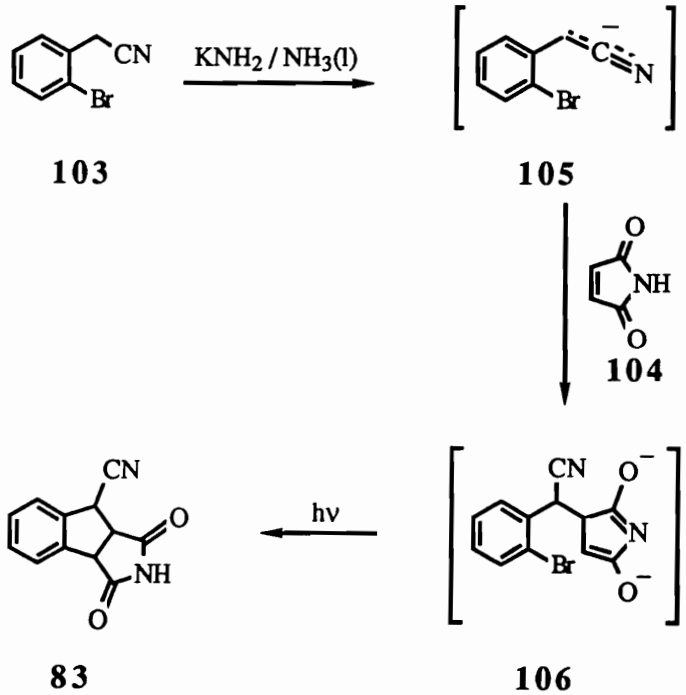
Another reason for specifically selecting **82** as a substrate whose $S_{RN}1$ reactivity was worth investigating involved the possibility of preparing **83** in a single step from



(21)

82 **83**

(*o*-bromophenyl)acetonitrile (**103**) and maleimide (**104**) by a tandem Michael addition-$S_{RN}1$ cyclization sequence (Scheme 30). Maleimide is known to be an excellent Michael acceptor,[63] while anions of various phenylacetonitriles have been shown to successfully



103 **105** **104** **83** **106**

Scheme 30

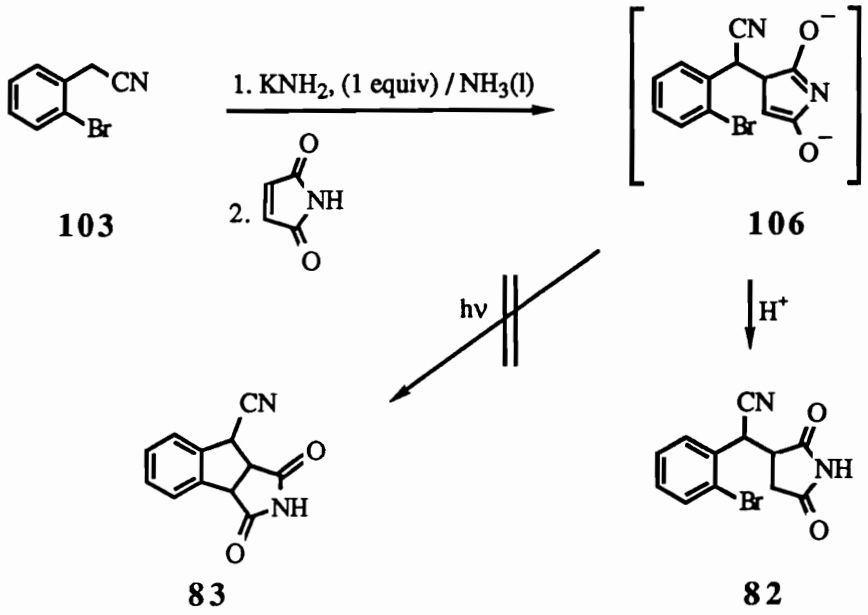
participate in Michael reactions with various Michael acceptors.[64] Moreover, potassium amide in liquid ammonia is known to be a suitable base-solvent system for this type of reaction. It was therefore envisioned that the addition of maleimide (**104**) to the anion **105** of (*o*-bromophenyl)acetonitrile, generated with potassium amide in liquid ammonia, would lead to the formation of the adduct anion **106**, which might in turn act as the nucleophile in a photostimulated intramolecular $S_{RN}1$ reaction to give the cyclized product, succinimido[3,4-b]indane-8-carbonitrile (**83**).

Thus, although specific instances where these two types of substrates have been used together in Michael reactions have not been reported, there was sufficient literature precedence to substantiate the idea that the initial Michael reaction would occur as proposed[63,64]. Further, our earlier success in inducing 3-(*o*-iodobenzyl)-succinimide (**99**) to undergo intramolecular $S_{RN}1$ cyclization to form succinimido[3,4-b]indane (**61**), formed the basis for the conjecture that the Michael adduct anion **106** might undergo further reaction under photostimulated conditions to afford succinimido[3,4-b]indane-8-carbonitrile (**83**). The results of the investigation undertaken to explore the possibility of preparing **83** by the proposed tandem Michael addition-$S_{RN}1$ cyclization sequence are discussed in the following section.

4.2. Attempted "One-Pot" Synthesis of Succinimido[3,4-b]indane-8-carbonitrile (83).

Maleimide (**104**) was added portionwise over a period of 15 min to anion **105**, generated by treatment of (*o*-bromophenyl)acetonitrile (**103**) with an equiv of potassium amide in liquid ammonia, during which time the reaction mixture was irradiated. After additional irradiation for 3 h, the crude product mixture was found to consist of mostly 3-

(*o*-bromo-α-cyanobenzyl)succinimide (**82**), the Michael adduct. However, no succinimido[3,4-b]indane-8-carbonitrile (**83**) was detected (Scheme 31).



Scheme 31

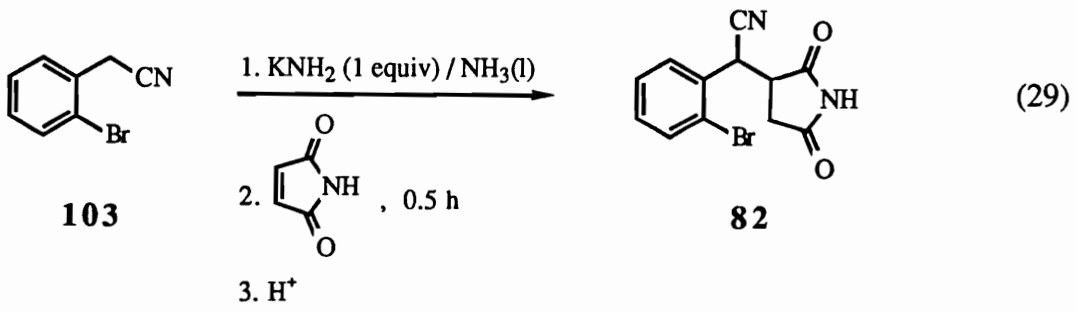
Failure of the adduct anion **106** to undergo the expected cyclization was initially attributed to the absence of sufficient potassium amide (theoretically 3 equiv of base would be required for cyclization). The reaction was then carried out using 3 equiv of potassium amide. ^{1}H-NMR spectroscopic analysis of the crude product mixture from this reaction again revealed the absence of the desired cyclized product **83**, while the Michael adduct **82** was once again obtained as the major product (40%). It was also observed that the use of excess potassium amide (3 equiv) resulted a poorer yield of **82** than the use of 1 equiv of potassium amide, which had previously afforded the Michael adduct in 62% yield. This was not entirely unexpected, since it is well known that complex mixtures result when excess base is used for carrying out Michael reactions, because the initially formed Michael

adducts may undergo the retrograde Michael reaction and/or further transformation of the initial adduct.[65]

Thus, although the proposed "one-pot" process for the preparation of succinimido[3,4-b]indane-8-carbonitrile (**83**) had initially appeared attractive, it was besieged with experimental dificulties, which we thought might be overcome if the Michael reaction and the proposed $S_{RN}1$ cyclization reaction were attempted in two discrete steps. The investigation undertaken to study the viability of this synthetic strategy for the preparation of **83** is described in the following sections.

4.3. Synthesis of 3-(*o*-Bromo-α-cyanobenzyl)succinimide (82) from (*o*-Bromophenyl)acetonitrile (103) and Maleimide (104).

During the unsatisfactory efforts to develop a "one -pot" procedure for the synthesis of **83**, the intermediate Michael adduct, 3-(*o*-bromo-α-cyanobenzyl)succinimide (**82**), had been obtained in 62% yield. When the reaction was carried out by treating the anion **105**, generated from (*o*-bromophenyl)acetonirile (**103**) with an equiv of potassium amide in



103 **82** (29)

liquid ammonia, with an equiv of maleimide (**104**), and the reaction mixture neutralized 0.5 h after the addition of **104** was complete, an 83% yield of pure **82** was obtained (eq 29).

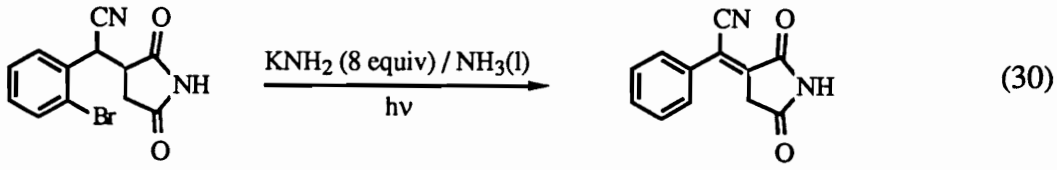
4.4. Attempted Cyclization of 3-(*o*-Bromo-α-cyanobenzyl)succinimide (82) to form Succinimido[3,4-b]indane-8-carbonitrile (83).

Having prepared 3-(*o*-bromo-α-cyanobenzyl)succinimide (**82**) in good yield, the next phase of this study involved the possible cyclization of **82** to form succinimido[3,4-b]indane-8-carbonitrile (**83**). A preliminary experiment was carried out to investigate the possibility of inducing the desired intramolecular $S_{RN}1$ reaction by treating **82** with an excess (8 equiv) of potassium amide in liquid ammonia under UV-irradiation for 3 h. Standard work-up afforded a sharp melting crystalline solid as the only isolable product in 75% yield.

Elucidation of the structure of this compound proved to be non-trivial, although it was quickly apparent that it was not the expected cyclized product, succinimido[3,4-b]indane-8-carbonitrile (**83**). ^{1}H-NMR spectroscopic analysis of this solid showed that there was one singlet in the aliphatic region of the spectrum (see Spectrum 9, Appendix I; pp. 204), along with a somewhat complex pattern in the aromatic region. Integration of the peaks yielded a ratio of 2:5 for these regions, indicating that the aliphatic singlet corresponded to 2H, while the aromatic pattern corresponded to 5H. Had the expected cyclized product **83** been formed, it would have been expected to show three separate signals for its three magnetically non-equivalent aliphatic hydrogen atoms (two doublets and a doublet of doublets, each signal integrating to 1H), along with an aromatic pattern corresponding to 4H. The ^{1}H-NMR spectrum, therefore, was instrumental in establishing

that the desired cyclization reaction had not occurred. However, it was necessary to obtain other analytical data in order to fully elucidate the structure of the isolated product. The ^{13}C-NMR spectrum of the product indicated that there was only one carbon atom, bonded to two hydrogen atoms, in the aliphatic region, all other carbon atoms appearing further downfield (see Spectrum 10, Appendix I; pp. 205). The expected cyclized compound **83** would have shown three carbon atoms, each bonded to one hydrogen atom, in the aliphatic region. Mass spectral analysis revealed a molecular ion of mass 312, identical to that expected for **83**, indicating that the unidentified product had the same molecular formula. Based on the above data, together with the information obtained from the mechanistic investigation, a tentative structure, represented by **107**, was then assigned to the compound. This structural assignment was later confirmed by X-ray crystallography (see Appendix II, pp. 225).[66]

Product **107** presumably results from a kinetically preferred intramolecular β-hydrogen atom abstraction process that competes efficiently with the expected cyclization reaction (eq 30). This is treated in more detail later in this chapter (see Section 7.4, pp 118).



82 **107** (30)

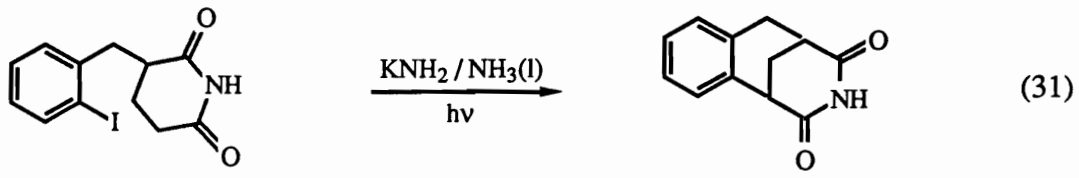
Even though the synthesis of succinimido[3,4-b]indane-8-carbonitrile (**83**) had not been accomplished by the proposed route, an interesting result that emerged from this study was the synthesis of the Michael adduct **82** in good yield. Although benzyl cyanides (as

Michael donors) as well as maleimides (as Michael acceptors) have been successfully used in the synthesis of a wide variety of compounds via the Michael reaction,[63,64] there is no report in the literature regarding specific instances where these two types of substrates have been used together to synthesize adducts such as 3-(*o*-bromo-α-cyanobenzyl)-succinimide (**82**). Further, although there are a few reports of Michael reactions carried out using alkali metal amides in liquid ammonia as the base/solvent systems,[63,64] their usefulness in this regard has not been extensively studied. Therefore, the efficient synthesis of **82** by the Michael reaction between (*o*-bromophenyl)acetonirile (**103**) and maleimide (**104**) with potassium amide in liquid ammonia represents a novel and convenient route to this new class of compounds.

5. Attempted Synthesis of 1,2,3,4,5,6-Hexahydro-1,5-methano -3-benzazocine-2,4-dione (62) from Glutarimide (109).

5.1. Introduction.

The successful synthesis of succinimido[3,4-b]indane (**61**) from 3-(*o*-iodobenzyl)-succinimide (**99**) suggested that the synthesis of another potential anticonvulsant, 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine-2,4-dione (**62**) might be accomplished in a similar manner by treating 3-(*o*-iodobenzyl)glutarimide (**108**) with potassium amide in liquid ammonia under photostimulation (eq 31). Although Goehring's attempts to prepare



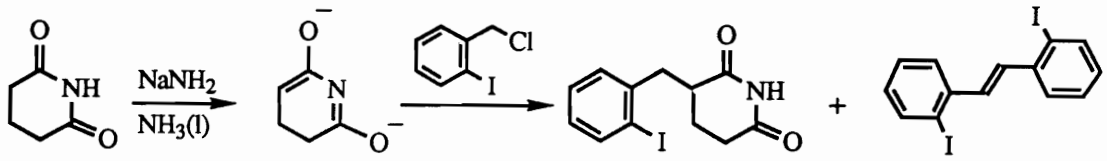
(31)

108 **62**

the *N*-methyl- derivative of **62** by subjecting 3-(*o*-bromobenzyl)-*N*-methylglutarimide (**71**) to standard photochemical $S_{RN}1$ conditions had proved unsuccessful (eq 20),[53] our subsequent investigation, reported in this dissertation, had revealed that the analogous cyclization of 3-(*o*-iodobenzyl)succinimide (**99**) to succinimido[3,4-b]indane (**61**) proceeded satisfactorily under similar conditions. This led to the premise that 3-(*o*-iodobenzyl)glutarimide (**108**) might be induced to undergo photostimulated cyclization to provide 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine-2,4-dione (**62**) upon treatment with excess potassium amide in liquid ammonia. It was considered worthwhile to explore such a possibility, and the following section describes the synthesis of the necessary substrate, 3-(*o*-iodobenzyl)glutarimide (**108**).

5.2. Preparation of 3-(*o*-Iodobenzyl)glutarimide (108).

This compound was prepared by the general procedure first developed in our laboratories by Rogers,[52] and used later (with slight modifications as necessary for specific substrates) by Goehring[53] and Pisipati[47] to prepare several 3-substituted benzyl derivatives of glutarimide and succinimide. Thus, the dianion **110**, generated from glutarimide (**109**) with 2 equiv of sodium amide in refluxing liquid ammonia, was treated with *o*-iodobenzyl chloride (**76**). Standard work-up afforded the desired 3-(*o*-iodobenzyl)glutarimide (**108**) in 42% yield, along with 26% of *trans-o,o'*-diiodo-stilbene (**85**) (Scheme 32). In an attempt to improve the yield of the desired product, the reaction was carried out with lithium amide at -60°C. However, this procedure was found to be only marginally superior, affording **108** in 48% yield.

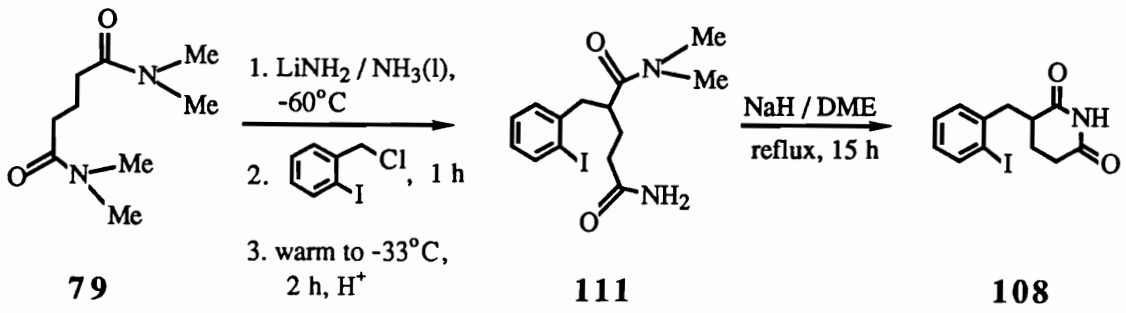


109 **110** **108** **85**

Scheme 32

Similar results during the synthesis of 3-(*o*-iodobenzyl)succinimide (**99**) via the alkylation of succinimide (**100**) had prompted a search for a more efficient procedure for the preparation of **99**, which had led to its two-step synthesis in high yields from *N,N,N',N'*-tetramethylsuccinamide (**73**) via 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)butanamide (**87**) (Scheme 29). Contemplating that a similar approach might

provide **108** in good yield from *N,N,N',N'*-tetramethylglutaramide (**79**) via 4-(*N,N*-dimethylcarboxamido)-5-(*o*-iodophenyl)pentanamide (**111**), a study was undertaken to explore such a possibility (Scheme 33). However, attempts to synthesize **111** by the alkylation of diamide **79** with *o*-iodobenzyl chloride (**76**), under the conditions that had afforded high yields of 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)butanamide (**87**) from *N,N,N',N'*-tetramethylsuccinamide (**73**), proved to be unsatisfactory, giving the desired 4-(*N,N*-dimethylcarboxamido)-5-(*o*-iodophenyl)pentanamide (**111**) in only 25% yield. This approach to the synthesis of 3-(*o*-iodobenzyl)glutarimide (**108**) was therefore not pursued further.

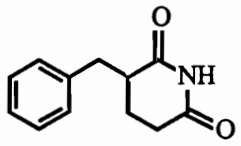


Scheme 33

5.3. Attempted Photoinduced Cyclization of 3-(*o*-Iodobenzyl)glutarimide (108) to Form 1,2,3,4,5,6-Hexahydro-1,5-methano-3-benzazocine-2,4-dione (62).

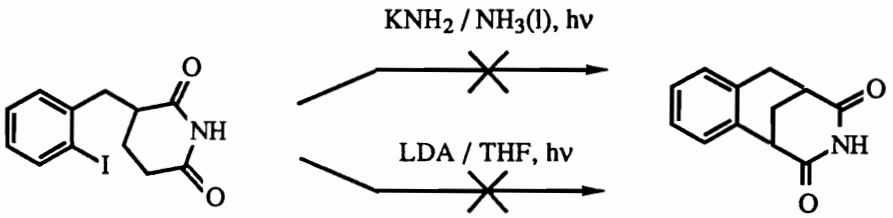
When 3-(*o*-iodobenzyl)glutarimide (**108**) was treated with excess potassium amide (8 equiv) in liquid ammonia under photostimulation for three hours, the product mixture was found to consist of mostly unreacted **108**, along with traces of 2-benzylglutarimide

(**112**), the product of reductive dehalogenation. The expected cyclized product, 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine-2,4-dione (**62**), was not detected.



112

It is known that the ability of potential substrates to undergo the $S_{RN}1$ reaction is critically affected by their solubility in liquid ammonia.[50] In the present case, it seemed that the poor $S_{RN}1$ reactivity demonstrated by 3-(*o*-iodobenzyl)glutarimide (**108**) might therefore be attributed to its poor solubility in liquid ammonia. Since **108** was found to be somewhat more soluble in THF than in liquid ammonia, an attempt was made to induce the desired photocyclization by using LDA/THF as the base/solvent system. Results from this experiment indicated that the expected cyclization reaction had not occurred, and the product mixture again consisted largely of unreacted 3-(*o*-iodobenzyl)glutarimide (**108**) along with a small quantity of reduction product **112** (Scheme 34).



108 **62**

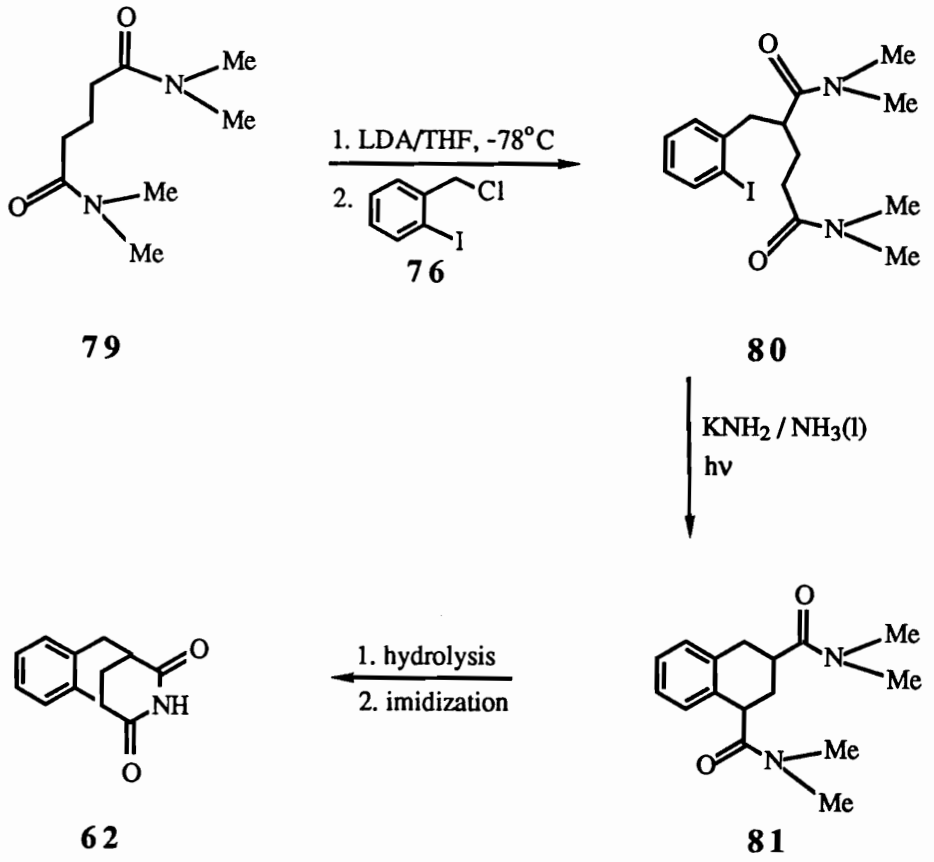
Scheme 34

These results suggested that factors other than solubility might be of some significance in the observed lack of $S_{RN}1$ reactivity of **108**. Molecular modeling studies were subsequently carried out in an effort to identify possible reasons for the inability of 3-(*o*-iodobenzyl)glutarimide (**108**) to undergo the $S_{RN}1$ reaction. The results of these studies are discussed later in this chapter (see Section 7.5., pp 123).

6. Attempted Synthesis of 1,2,3,4,5,6-Hexahydro-1,5-methano-benzazocine-2,4-dione (62) from *N,N,N',N'*-Tetramethylglutaramide (79).

6.1. Introduction.

One of the stated objectives of this investigation had been to explore the possibility of preparing 1,2,3,4,5,6-hexahydro-1,5-methano-benzazocine-2,4-dione (**62**) from *N,N,N',N'*-tetramethylglutaramide (**79**) via the synthetic scheme outlined earlier (Scheme 19, reproduced below). It now seemed especially worthwhile to investigate this synthetic



Scheme 19

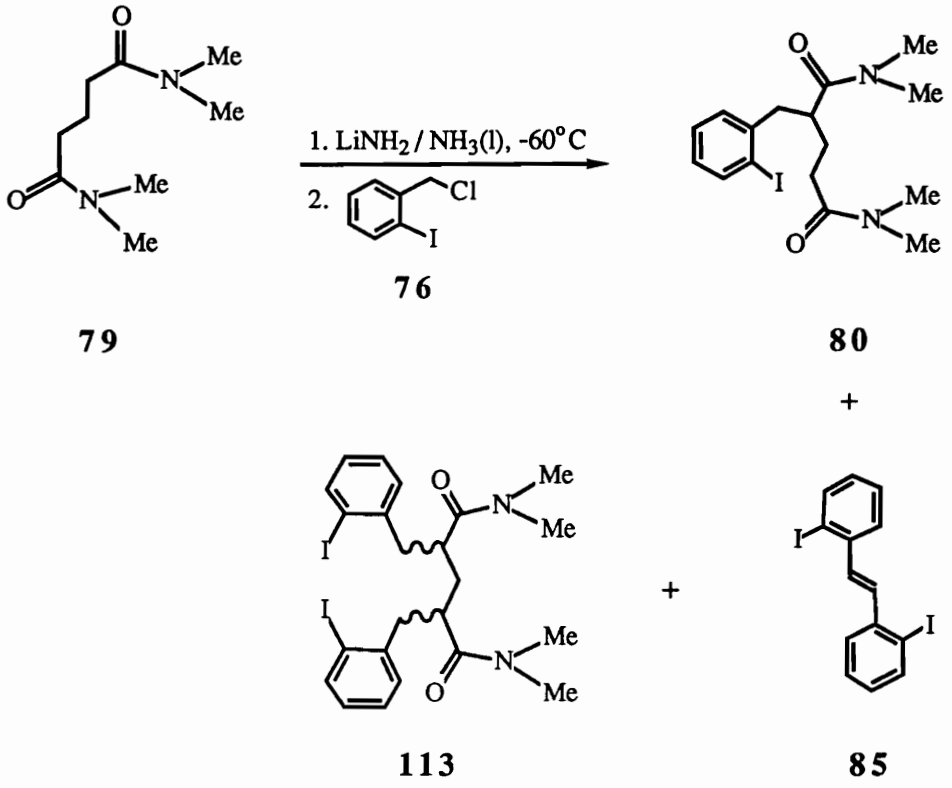
route, since we had been unable to prepare **62** directly from 3-(*o*-iodobenzyl)glutarimide (**108**).

The proposed cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) to afford 1,3-*bis*-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**) was analogous to the previously accomplished cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) to give 1,3-*bis*-(*N,N*-dimethylcarboxamido)indane (**78**) (see Section 2.2., pp .52). The product of cyclization, **81**, could presumably be converted to its imide, 1,2,3,4,5,6-hexahydro-1,5-methano-benzazocine-2,4-dione (**62**) by known procedures.[67] The following sections describe the results of our efforts to prepare 1,2,3,4,5,6-hexahydro-1,5-methano-benzazocine-2,4-dione (**62**) via the strategy outlined in Scheme 19, beginning with the synthesis of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**).

6.2. Preparation of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (80).

When the above synthetic scheme was devised, it was envisioned that 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) could be prepared by alkylation of *N,N,N',N'*-tetramethylglutaramide (**79**). We had earlier determined the reaction conditions that gave good yields of the analogous 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) from *N,N,N',N'*-tetramethylsuccinamide (**73**) (see Section 2.1., pp. 48). A preliminary experiment was carried out to examine the possibility of preparing **80** from **79** under similar conditions (eq 32). Upon treatment of the dianion of *N,N,N',N'*-tetramethyl glutaramide (**79**), generated with lithium amide (2.2 equiv) in liquid ammonia at -60°C, with *o*-iodobenzyl chloride (**76**), the product mixture was found

to contain 45% of the desired product, 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethyl-glutaramide (**80**), along with 12% of *trans-o,o'*-diiodostilbene (**85**) and 22% of the dialkylated product 2,4-*bis*-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**113**).



79 **76** **80** (32)

113 **85**

A study aimed at optimizing the yield of **80** was then initiated, the results of which are summarized in Table VI. When the reaction was carried out at -78°C with lithium amide in liquid ammonia, the product mixture consisted predominantly of unreacted starting materials (entry 2). When the reaction was carried out at -33°C with lithium amide in liquid ammonia to determine how it compared with that at -60°C, the formation of increased amounts of *o,o'*-diiodostilbene (**85**) (20%), and 2,3-*bis*-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**113**) (23%), led to poorer yields of the desired 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) (34%) (entry 3). Likewise, the use of potassium

Table VI

Investigation of the Monoalkylation of *N,N,N'N'*-Tetramethylglutaramide (79) to 2-(*o*-Iodobenzyl)-*N,N,N'N'*-tetramethylglutaramide (80) in liquid ammonia

entry	base (equiv)	temp, °C	time, h	-------yield, % ------ 80	113	85
1	$LiNH_2$ (2.2)	- 60	1	45	22	12
2	$LiNH_2$ (2.2)	- 78	1	[a]	–	–
3	$LiNH_2$ (2.2)	- 33	1	34	23	20
4	KNH_2 (2.2)	- 60	1	30	25	20
5[b]	KNH_2 (2.2)	- 78	1	20	15	10

[a] ^{1}H-NMR Spectrum of crude product showed unreacted **79** and **76**, along with traces of **80** . [b] Small amounts of unreacted **79** and **76** were also recovered.

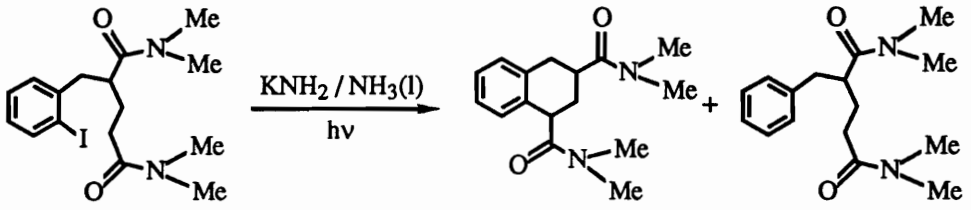
amide at -60°C afforded significant quantities of **85** (20%) and **113** (25%), thereby limiting the yield of the desired compound **80** (30%) (entry 4). Attempts to minimize dialkylation by performing the reaction with potassium amide at even lower temperatures (-78°C) proved to be unsatisfactory also (entry 5); the desired monoalkylated derivative **80** was isolated in 20% yield, along with 15% of the dialkylated product **113**, 10% of **85** and some unreacted *N,N,N',N'*-tetramethylglutaramide (**79**) and *o*-iodobenzyl chloride (**76**). Thus, although the overall reaction was slower at -78°C than at -60°C, there was no enhancement in the selectivity of the reaction, the dialkylation process being suppressed to about the same degree as the monoalkylation process.

Therefore, the use of lithium amide in liquid ammonia at -60°C emerged as the most effective synthetic procedure for the preparation of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) from *N,N,N',N'*-tetramethylglutaramide (**79**). The following section contains a description of the subsequent investigation undertaken to explore the possibility of inducing **80** to undergo cyclization to 1,3-*bis*-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**) under standard $S_{RN}1$ conditions.

6.3. Cyclization of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (80) to form 1,3-*bis*-(*N,N*-Dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (81).

The cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) was first attempted with excess potassium amide (8 equiv) in liquid ammonia under photostimulation (eq 33). The ^{1}H-NMR spectrum of the crude product of this reaction revealed that the expected cyclization had occurred, although a significant fraction of the substrate had undergone reductive dehalogenation to give 2-benzyl-*N,N,N',N'*-

tetramethylglutaramide (**114**) (entry 1, Table VII). Separation of the crude product into its constituents by flash column chromatography afforded the expected cyclized product, 1,3-*bis*-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**) in 39% yield along with 18% of the reduction product **114**.



80 **81** **114** (33)

We then attempted to determine conditions that would afford better yields of **81**, and our experiments in this regard are summarized in Table VII. 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) was treated with excess potassium amide (8 equiv) in liquid ammonia under photostimulated conditions for 0.25 h. Analysis of the crude product by ^{1}H-NMR spectroscopy revealed that the starting material had been completely consumed (entry 2) and that the ratio of cyclized product **81** to reduced product **114** was very similar to that obtained after a reaction time of 3 h, *i.e.*, approximately 2:1. In order to determine if cyclization would occur in the absence of photostimulation, the reaction was carried out in the dark with excess potassium amide (8 equiv) for 0.25 h (entry 3). ^{1}H-NMR analysis of the crude product demonstrated that it consisted of mostly unreacted 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**). The expected cyclized product, 1,3-*bis*-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**) was not detected. When the photostimulated reaction was carried out with excess lithium

Table VII

Investigation of the Cyclization of 2-(*o*-Iodobenzyl)-*N,N,N'N'*-tetramethylglutaramide (80) to Form 1,3-*bis*-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (81)

entry	base (equiv) in NH_3(l)	time, h	photostimulation	------yield, % ------ **81**	**114**	**80**
1	KNH_2 (8)	3	+	39	18	–
2	KNH_2 (8)	0.25	+	39[a]	18[a]	–
3	KNH_2 (8)	0.25	–	–	–	90[b]
4	$LiNH_2$ (8)	0.25	+	5[c]	–	80[c]
5	$LiNH_2$ (8)	2	+	23	12	48
6	KNH_2 (4.4)	0.25	+	23[d]	12[d]	48[d]

[a] Estimated from the ^{1}H-NMR spectrum of the crude product, which was almost identical to that of the crude product from the experiment described in entry 1. [b] Estimated from the ^{1}H-NMR spectrum of the crude product, which was identical to that of pure **80**. [c] Estimated from the ^{1}H-NMR spectrum of the crude product, which showed that it was comprised of mostly **80** along with traces of **81**. [d] Estimated from the ^{1}H-NMR spectrum of the crude product, which was almost identical to that of the crude product from the experiment described in entry 5.

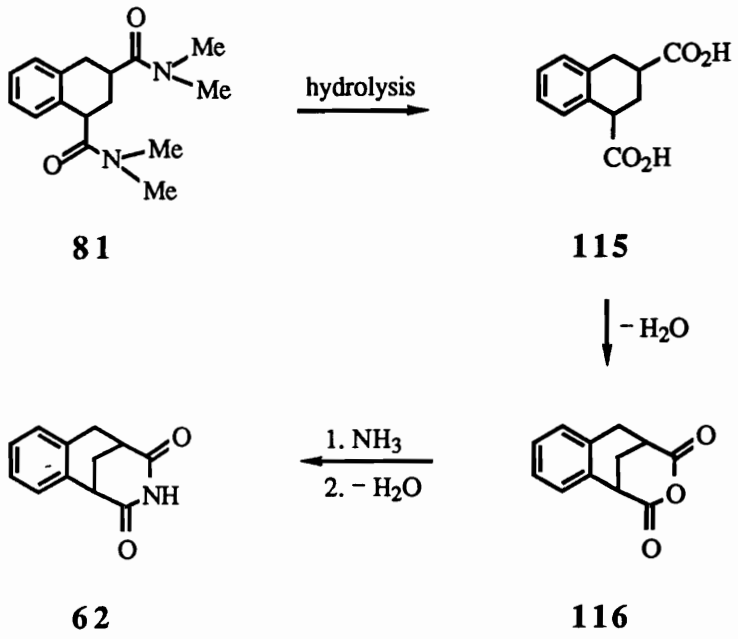
amide (8 equiv) in liquid ammonia for 0.25 h, the crude product mixture was again found to consist of mostly unreacted **80**, accompanied by traces of cyclized product **81** (entry 4). When the photoassisted reaction with excess lithium amide was carried out for 2 h, ^{1}H-NMR analysis revealed that there was still a significant quantity of unreacted **80** present in the product mixture. Separation of the crude product by flash chromatography afforded 23% of the cyclized product **81**, along with 12% of the reduction product **114** and 48% of unreacted **80** (entry 5). When **80** was treated with 4 equiv of potassium amide in liquid ammonia under photostimulation for 0.25 h, the ^{1}H-NMR spectrum of the crude product was almost identical to that of the crude product from the previous experiment (entry 6).

Thus, the procedure that emerged from this study as being the most effective one for the synthesis of 1,3-*bis*-(*N*,*N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**) consisted of treatment of 2-(*o*-iodobenzyl)-*N*,*N*,*N*′,*N*′-tetramethylglutaramide (**80**) with excess potassium amide (8 equiv) in liquid ammonia under photostimulated conditions for 0.25 h, which afforded the desired compound in 39% isolated yield. Certain mechanistic features of this cyclization reaction are described later in this chapter (see Section 7.6., pp 126).

6.4. Proposed Conversion of 1,3-*bis*-(*N*,*N*-Dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (81) into 1,2,3,4,5,6-Hexahydro-1,5-methano-benzazocine-2,4-dione (62).

The synthetic strategy envisioned for the conversion of 1,3-*bis*-(*N*,*N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**) into the desired 1,2,3,4,5,6-hexahydro-1,5-methano-benzazocine-2,4-dione (**62**) is depicted in Scheme 35. This scheme is analogous to the scheme devised for the conversion of 1,2-*bis*-(*N*,*N*-

dimethylcarboxamido)indane (**78**) to succinimido[3,4-b]indane (**61**) (see Scheme 24, pp 62). Hydrolysis of **81** was likely to afford 1,2,3,4-tetrahydronaphthalene-1,3-dicarboxylic acid (**115**), which upon dehydration could form its anhydride, **116**.



Scheme 35

Treatment of the anhydride **116** with ammonia was expected to yield a mixture of *cis*- amic acids, **117** and **118**, which could then presumably be dehydrated to give the desired compound, 1,2,3,4,5,6-hexahydro-1,5-methano-benzazocine-2,4-dione (**62**).

117 **118**

However, the analogous synthesis of succinimido[3,4-b]indane (**61**) via 1,2-*bis*-(*N,N*-dimethylcarboxamido)indane (**78**) had proved to be unsatisfactory in terms of overall yield. Although the steps leading to the formation of **78** had been reasonably efficient, some of the subsequent reactions had afforded relatively low yields of products, thereby adversely affecting the overall yield of **61** by this synthetic route (see Scheme 24, pp 62). In the present case, the prospect appeared to be somewhat worse, since even the first two steps leading to the formation of 1,3-*bis*-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**) were not very high yielding processes (45% and 39% respectively). Therefore, although Scheme 36 would appear to be a viable route for the conversion of **81** into 1,2,3,4,5,6-hexahydro-1,5-methano-benzazocine-2,4-dione (**62**), it seemed unlikely that it would result in an efficient overall synthesis of the desired compound. This conversion was therefore not undertaken. Rather, subsequent investigation was focussed on the determination of the mechanistic aspects of the cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethyl glutaramide (**80**) to form 1,3-*bis*-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**), the results being presented in the following section (see Section 7.6., pp 126).

7. Mechanistic considerations.

7.1. Introduction.

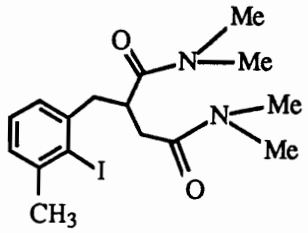
At the outset, we had stated that our interest in the study we had proposed to undertake was twofold. Along with the desire to synthesize the stated targets because of their potential as possible new antiepileptic agents, we were also keenly interested in investigating the mechanistic aspects of the key steps in the proposed synthetic routes towards these goals, namely the intramolecular nucleophilic aromatic substitution reactions, which could theoretically follow one of several possible pathways. Thus, the synthetic studies that have been described in the preceding sections were accompanied by concurrent studies designed to establish the mechanistic features of the cyclization reactions undergone by 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**), 3-(*o*-iodobenzyl)-succinimide (**99**), and 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) upon treatment with potassium amide in liquid ammonia. While the expected reactions occurred with the above substrates, they failed to occur with two other compounds, 3-(*o*-bromo-α-cyanobenzyl)succinimide (**82**) and 3-(*o*-iodobenzyl)glutarimide (**108**), that had also appeared to be potentially attractive in this context. Since substrate **82** underwent transformation into **107**, presumably via an intramolecular β-hydrogen atom abstraction process, the mechanistic features of this reaction were investigated. Substrate **108**, on the other hand, was found to be quite unreactive under the reaction conditions used, and molecular modeling studies were undertaken to probe its observed lack of reactivity. The results of all the investigations mentioned above are presented in the following sections.

7.2. Mechanism of the Cyclization of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (77) to form 1,2-*bis*-(*N,N*-Dimethylcarboxamido)indane (78).

It had been observed that the cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) to form 1,2-*bis*-(*N,N*-dimethylcarboxamido)indane (**78**) could be accomplished without photostimulation (entries 4, 5; Table III; pp 54) and required excess potassium amide (see entries 1, 2, 4, 5, Table III; pp 54). These results indicated that the above cyclization process probably occurred predominantly via an aryne pathway.[40] However, the simultaneous occurrence of another pathway, possibly $S_{RN}1$, was suggested by the obtention of small quantities of the reduction product, 2-benzyl-*N,N,N',N'*-tetramethylsuccinamide (**90**). Reductive dehalogenation, which is seldom associated with aryne reactions, is more characteristic of $S_{RN}1$ reactions. Therefore, it appeared that the two different mechanistic pathways, both of which led to the same cyclized product, **78**, possibly occurred concurrently under the conditions employed to induce the intramolecular reaction.

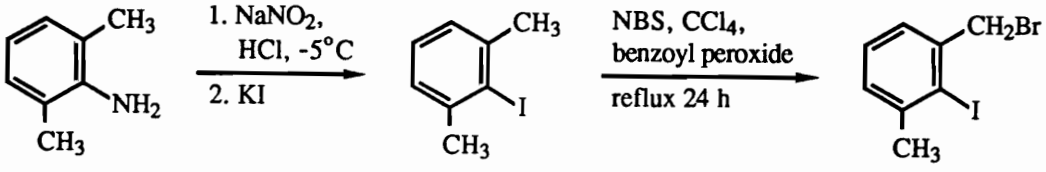
The photostimulated cyclization reaction of **77** was therefore carried out in the presence of 10 mol% of the radical-scavenger di-*tert*-butyl nitroxide for 0.25 h in order to determine if a radical-chain process was actually in operation. The ^{1}H-NMR spectrum of the crude product revealed the complete absence of **77**, and the spectrum resembled that of pure 1,2-*bis*-(*N,N*-dimethylcarboxamido)indane (**78**). The inability of di-*tert*-butyl nitroxide to inhibit the reaction could be interpreted as evidence that the reaction did not occur to any significant extent via a radical-chain process, but proceeded predominantly via an aryne pathway.

It then seemed appropriate to determine what would happen if the aryne pathway were made unavailable for the cyclization process. It was envisioned that an attempt to cyclize a substrate such as 2-(2-iodo-3-methylbenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**119**), which is analogous to **77**, but differs from it in that it cannot form an aryne intermediate, could help to ascertain if cyclization could at all occur by a radical-chain pathway.



119

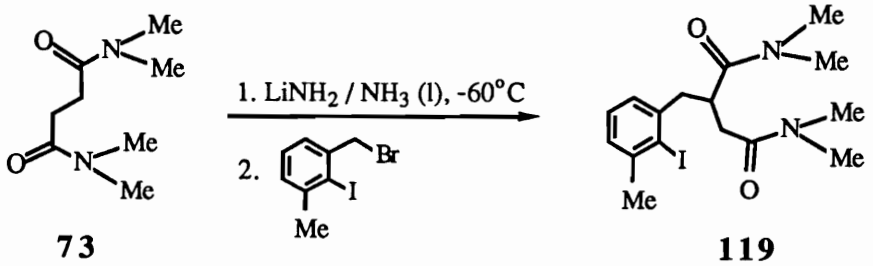
The synthesis of the substrate required for this study, 2-(2-iodo-3-methylbenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**119**), was accomplished as outlined in eq 35. The alkylating agent used in this reaction, (2-iodo-3-methyl)benzyl chloride (**120**), was prepared from 2,6-dimethylaniline (**121**) via the following synthetic scheme (Scheme 36). 2,6-Dimethylaniline (**121**) was first converted to its corresponding iodo- derivative **122**



121 **122** **120**

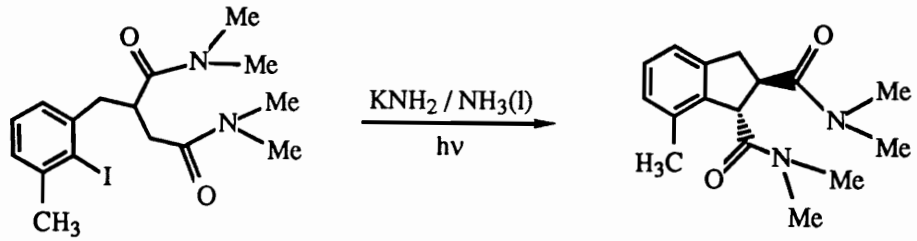
Scheme 36

(via its diazonium intermediate)[68], which was then brominated with *N*-bromosuccinimide to afford the desired (2-iodo-3-methyl)benzyl chloride (**120**).[69] *N,N,N',N'*-Tetramethylsuccinamide (**73**) was then monoalkylated with **120** under conditions previously found to be optimum for the monoalkylation of **73** with *o*-iodobenzyl chloride (**76**) [$LiNH_2$ (2.2equiv) / NH_3(l) at -60°C for 1 h], to give the desired monoalkyl derivative, 2-(2-iodo-3-methylbenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**119**) in 60% yield (eq 34).



73 **119** (34)

When **119** was treated with potassium amide in liquid ammonia under photostimulation for 3 h, the product was found to consist mainly of the expected cyclized product, 1,2-*bis*-(*N,N*-dimethylcarboxamido)-7-methylindane (**123**) (eq 35). When the reaction was repeated without photostimulation, no cyclized product, **123**, was detected

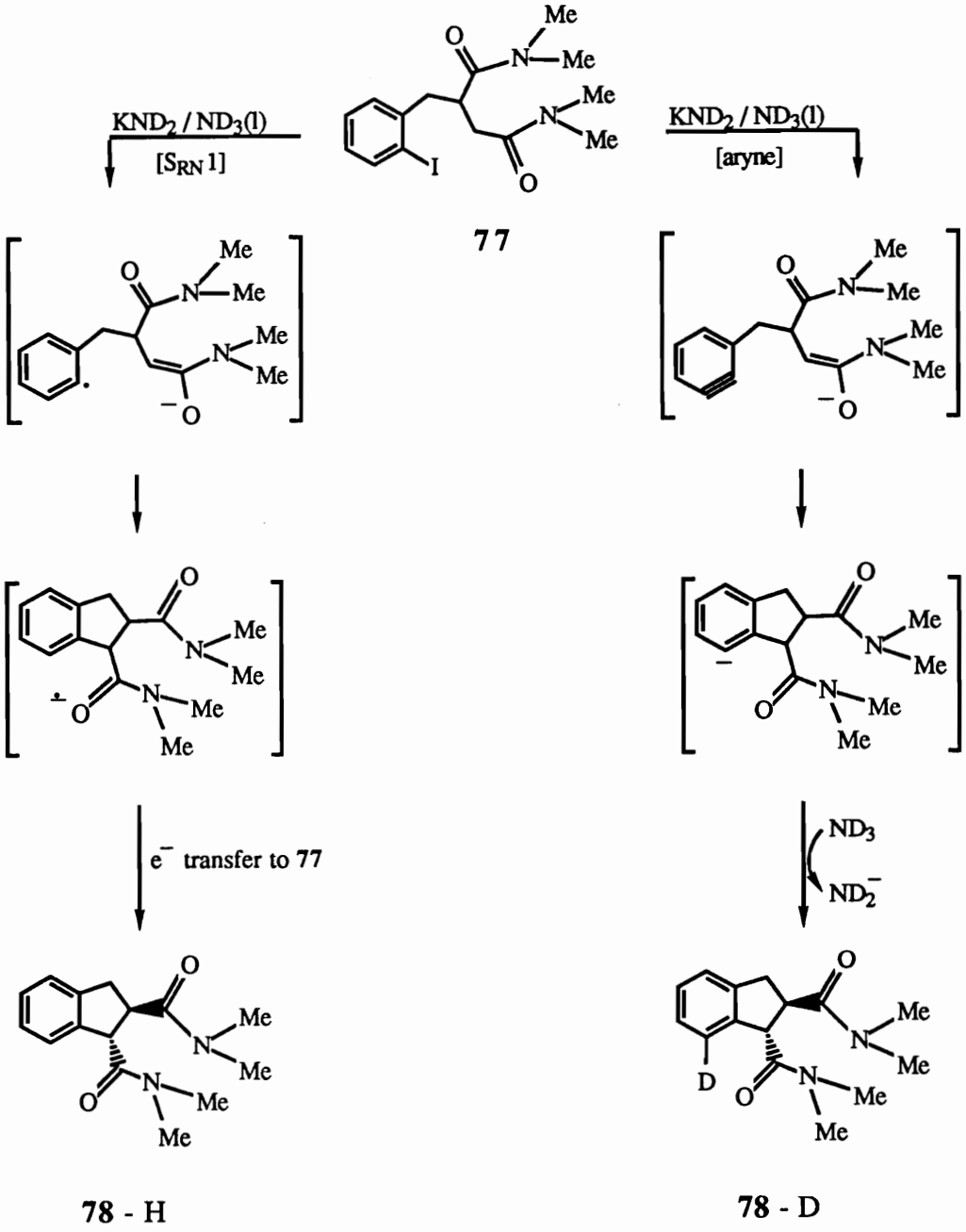


119 **123** (35)

(from the ^{1}H-NMR spectrum of the crude product). These experiments therefore established that when the aryne pathway was not available for reaction, as with **119**, the cyclization reaction could still occur by an alternate mechanism, which, in the case of **119**, appeared likely to be an $S_{RN}1$ process.

On the basis of results obtained with **119**, it appeared that in the case of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**), cyclization to form 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) probably occurred via at least two processes, aryne and $S_{RN}1$. In an attempt to detect and possibly determine the contribution of each of these putative processes, the cyclization reaction was carried out in deuterated liquid ammonia. Product molecules arising from the aryne reaction were expected to bear deuterium atoms at position C-7, whereas those formed via the $S_{RN}1$ pathway would not contain deuterium on the benzenoid moiety (Scheme 37). Thus, the ratio of deuterated and undeuterated product, **78**-D and **78**-H respectively, should be directly proportional to the contribution of the two processes leading to **78**.

When the cyclization reaction was carried out using excess potassium amide in *deuterio*- liquid ammonia at -33°C for 0.5 h, the ^{1}H-NMR spectrum of the crude product revealed that it consisted of mainly the indane **78** along with a small amount of reduction product **90** (estimated as a 7:1 mixture). The methine proton resonance at 5.0 ppm (d, J = 8.1 Hz), characteristic of the C-1 proton of **78**, was not seen at all, indicating that this site had been completely deuterated (*cf.*, spectrum 3,4; Appendix I, pp 198, 199). The resonance for the C-2 methine proton at 4.16 ppm was also significantly reduced in intensity, indicating that this site was largely deuterated as well. Deuteration at these two


KND2 / ND3(l)
[SRN1]
77
KND2 / ND3(l)
[aryne]
e⁻ transfer to 77
ND3
ND2⁻
78 - H
78 - D

Scheme 37

sites could be attributed to the equilibrium between the deuterated ammonia and the acidic protons initially attached to C-1 and C-2 of cyclized product **78**.

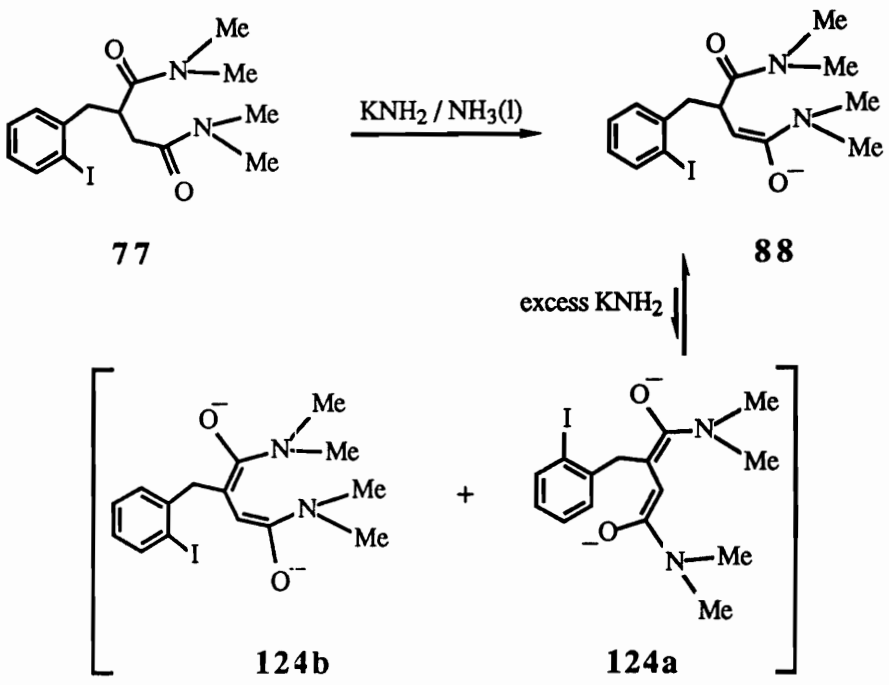
The components were separated by preparative thin layer chromatography and the cyclized product was subjected to further analysis by means of mass spectrometry, ^{2}D-NMR and ^{13}C-NMR spectrometry.[70] A comparison of the ^{13}C-NMR spectra of **78** obtained from the reactions in protio- and deuterio- liquid ammonia were quite useful in revealing the lack of any significant deuteration at the aromatic position (C-7) (*cf.*, spectrum 3,4; Appendix I, pp. 198, 199). Carbon atoms bonded to deuterium are split by residual C-D coupling into triplets.[71] If the site is incompletely deuterated, two signals for that carbon atom are expected, a singlet representing the fraction of the molecules that have C-H bonds and a triplet representing the remaining molecules which have C-D bonds. Reduction in line intensity of the singlet (when compared with the corresponding intensity of the singlet in the ^{13}C-NMR of the non-deuterated sample) identifies a site of partial deuteration. Comparison of the two ^{13}C-NMR spectra (spectrum 3 and 4) revealed that the carbon resonance at 50.35 ppm in spectrum 3 is replaced by a triplet of much lower intensity in spectrum 4, indicating complete deuteration of that site (C-1). Similarly, the line intensity of the resonance at 46.58 ppm is significantly reduced, which is consistent with the inference drawn from the ^{1}H-NMR, *i.e.*, that the C-2 site is largely, but not completely, deuterated. The line intensities of the resonances of the aromatic carbons in the two spectra were essentially identical, indicating that there was no significant deuteration at any aromatic site.

These spectral characteristics implied that the major reaction pathway for the cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) to 1,2-bis-(*N,N*-

dimethylcarboxamido)indane (**78**) *did not* involve the intermediacy of an aryne. However, before concluding that the reaction must therefore proceed via a radical pathway, it was essential to re-evaluate two observations. First, the inability of the radical scavenger di-*tert*-butyl nitroxide to inhibit the reaction, and secondly, the role played by excess base in facilitating the cyclization reaction.

Radical scavengers have proved to be an invaluable tool in revealing the participation of radicals in numerous $S_{RN}1$ reactions. However, these reactions have generally been *intermolecular* reactions, in which the radical scavenger has a competitive chance of reacting with the intermediate, short-lived radical species (thereby inhibiting the reaction) as does the reacting nucleophile, which would lead to the formation of the product in the absence of the radical scavenger.[40,47] In *intramolecular* reactions, the results with scavengers can be misleading. The close proximity of the radical and carbanion moieties in such reactions are likely to facilitate reactions which are significantly faster than the possible *intermolecular* radical-trapping reaction that would occur with the radical scavenger. In such cases, the inhibitory effects of the radical scavenger may not be observed. Thus, while inhibition of a reaction by radical scavengers constitutes strong evidence for a radical chain ($S_{RN}1$) pathway, the converse lack of inhibition does not necessarily eliminate the possibility of a radical mechanism, particularly with *intramolecular* reactions.

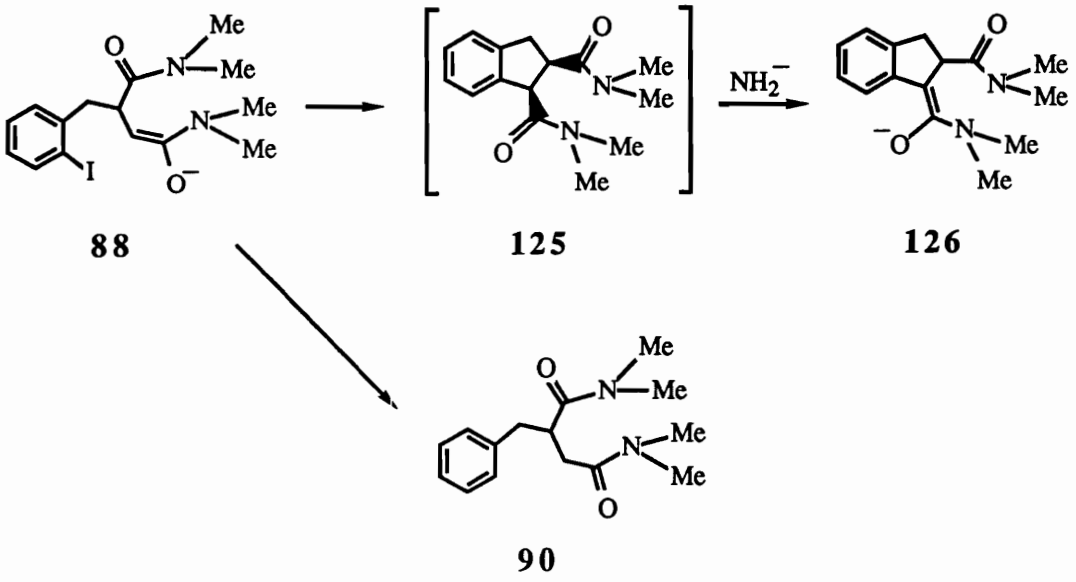
Addressing the second issue, it was assumed that in the presence of excess potassium amide, substrate **77** would be converted into the E and Z dianions, **124a** and **124b** respectively, which then undergo the cyclization reaction (Scheme 38). If the



77 88 124b 124a

Scheme 38

equilibrium for the formation of the dianions **124a-b** from the monoanion **88** were to lie largely towards **88**, then significant dianion formation would occur only in the presence of excess base. In order to establish a satisfactory rationale for why dianion formation might be required for cyclization to occur, we turned to molecular modeling techniques for possible answers.[72] These studies suggested that if monoanion **88** were to undergo cyclization, it would lead to initial formation of **125**, in which the two bulky *N,N*-dimethylamido- groups are oriented *cis*- to each other. In the basic reaction medium, this species would quickly lose its highly acidic benzylic hydrogen (at C-1) to yield **126**, thereby alleviating the steric stress associated with the *cis*- disposition of the vicinal carboxamido- groups (Scheme 39).



88 **125** **126**

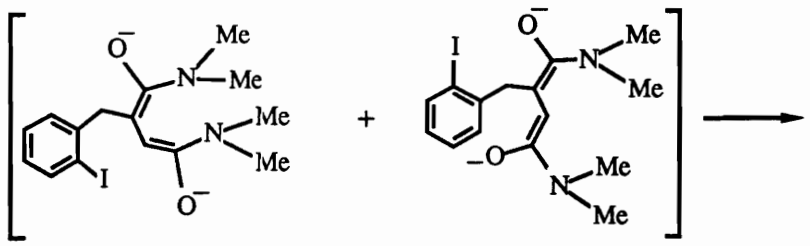
90

Scheme 39

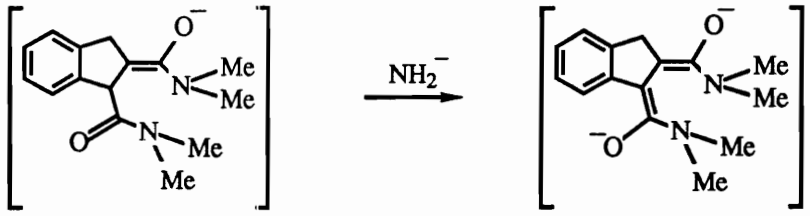
This might also account for the increased formation of the reduction product **90** when the reaction was carried out with lower concentrations of potassium amide (*c.f.* entries 2, 3 and 6, Table III, pp 54). Since the cyclization of the monoanion **88** to product indane **125** would appear to be sterically unattractive, alternative reaction pathways such as reductive dehydrohalogenation of **88** to **90** might compete more effectively, leading to increased yields of the reduction product.

Cyclization of dianions **124a-b**, on the other hand, could result in initial formation of a species, **127**, that resembles **126** in its degree of steric strain, which, as mentioned earlier, is significantly less than in **125**, the initial product formed during the cyclization of monoanion **88** (Scheme 40). Again, in presence of base, the acidic C-1 benzylic hydrogen of **127** would be lost, yielding dianion **128**, which is sterically even less hindered than

127. Therefore, it appears that cyclization of dianions **124a-b** would be more favorable and less prone to other reactions than cyclization of monoanion **88**.



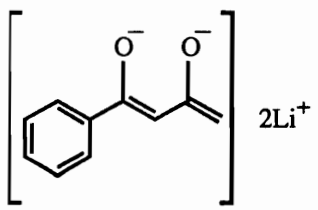
124b **124a**



127 **128**

Scheme 40

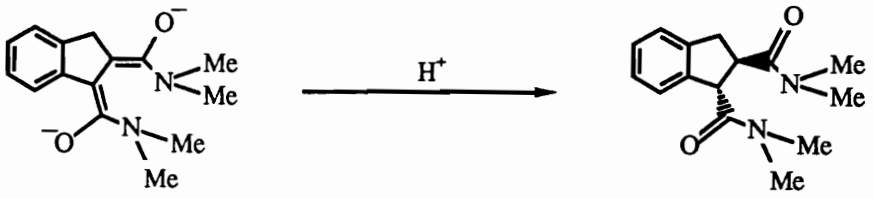
It is also possible that dianions **124a-b** are better electron-transfer agents than monoanion **88**, thus facilitating initiation of the $S_{RN}1$ process. In fact, they may well act as entraining agents. Dilithiobenzoylacetone (**129**), formed from benzoyl acetone by



129

action of lithium amide in liquid ammonia, has been shown to entrain $S_{RN}1$ reactions with monoenolates.[26] Other investigators have also observed that the rates of $S_{RN}1$ reactions are increased by basic reagents other than the nucleophilic reagent which eventually replaces the nucleofugic substituent of the substrate.[73]

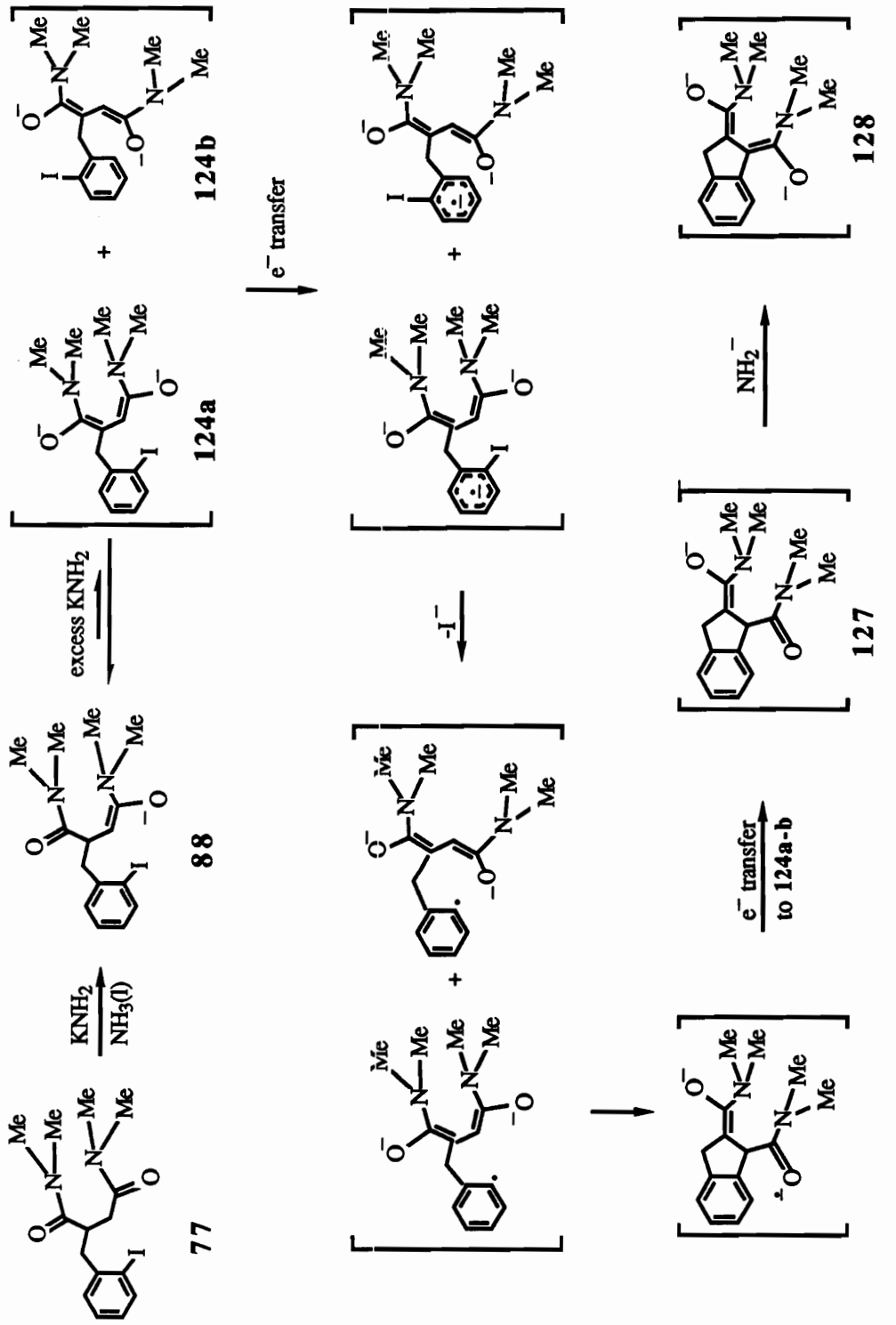
Upon neutralization of the reaction mixture with acid, protonation of dianion **128** would result in the formation of the observed product, *trans*-1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) (Scheme 41). That the *cis*- isomer, **125**, is absent, is not unexpected,



128 **78**

Scheme 41

considering the steric strain associated with the *cis*- orientation of the bulky *N,N*-dimethylcarboxamido- groups. All of the above ideas have been used to formulate the mechanistic pathway depicted in Scheme 42.



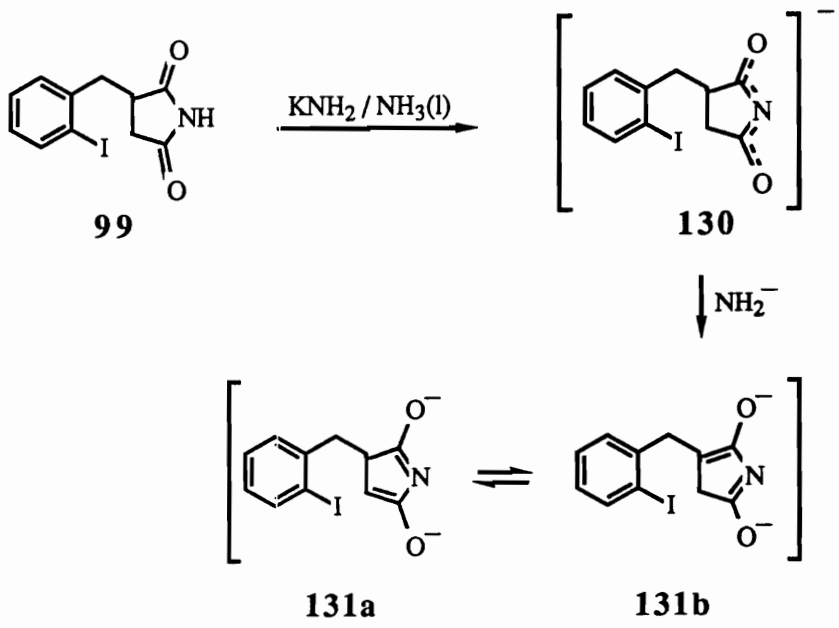
Scheme 42

7.3. Mechanistic Studies of the Cyclization of 3-(*o*-Iodobenzyl)-succinimide (99) to form Succinimido[3,4-b]indane (61).

During the investigation of the cyclization of 3-(*o*-iodobenzyl)succinimide (**99**) to form succinimido[3,4-b]indane (**61**), it had been observed that a significant proportion of the substrate also underwent reductive dehalogenation to afford 3-benzyl-succinimide (**102**). Attempts to minimize the undesirable reduction reaction had proved unsuccessful, since carrying out the reaction under a variety of conditions afforded a more or less constant product ratio (**58**:**99** = 1.4:1; see entries 1, 3, 6 and 7, Table V; pp 75). A mechanistic investigation, designed to provide insight into this intriguing phenomenon, was therefore undertaken.

Initial results of the synthetic investigation had led to the assumption that the reaction probably did not occur via an aryne pathway, since there was no appreciable reaction in the absence of photostimulation, even with excess base (see entries 4 and 5, Table V; pp 75). This observation further suggested that the reaction might proceed via a photostimulated $S_{RN}1$ pathway. In order to further explore the possibility of a radical-chain process, the reaction was carried out in the presence of 10 mol% of the radical scavenger, di-*tert*-butyl nitroxide. The ^{1}H-NMR spectrum of the crude product resembled that of pure 3-(*o*-iodobenzyl)succinimide (**99**), indicating that the reaction had been completely inhibited.

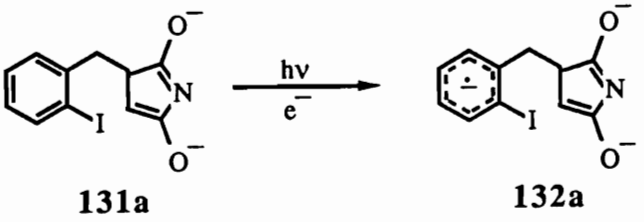
Therefore, it seems reasonable to assume that treatment of **99** with base would afford the monoanion **130** (Scheme 43). Further deprotonation of monoanion **130** would result in formation of the isomeric dianions **131a** and **131b**. Dianion **131a** could then participate in a photoassisted intramolecular $S_{RN}1$ reaction leading to the cyclized product



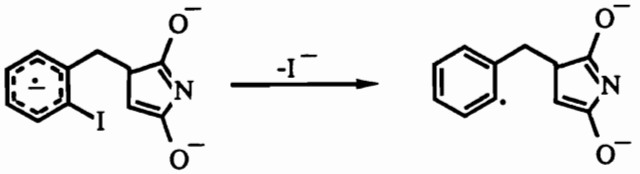
Scheme 43

anion **135** (eq 37-40, Scheme 44). Abstraction of the acidic methine proton of **135** by base would result in formation of the dianion **136** (eq 41), which upon neutralization of the reaction mixture would afford succinimido[3,4-b]indane (**61**).

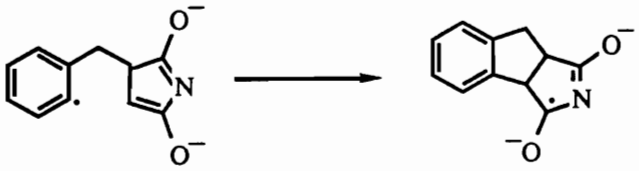
The consistent formation of the reduction product, 3-benzylsuccinimide (**102**), as a major by-product, regardless of how much base is used during the reaction, deserves explanation. Since molecular modeling calculations showed that the cyclization process involving dianion **131a** should be relatively facile, only a small fraction of **102** probably originates from this intermediate.[72] Therefore, the bulk of **102** must originate elsewhere, and the following discussion attempts to explain this phenomenon.



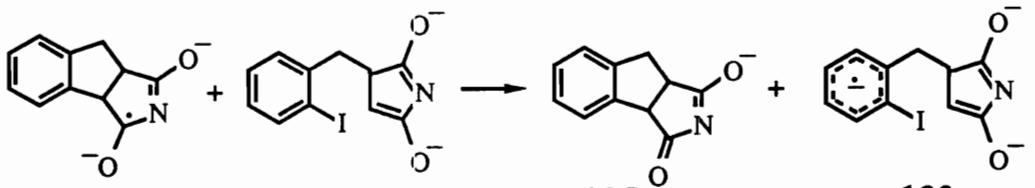
131a 132a (37)



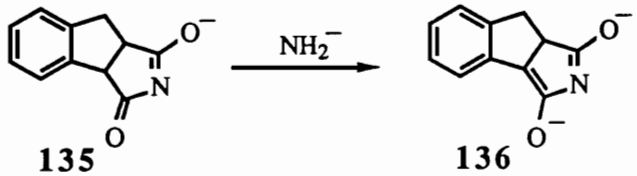
132a 133a (38)



133a 134 (39)



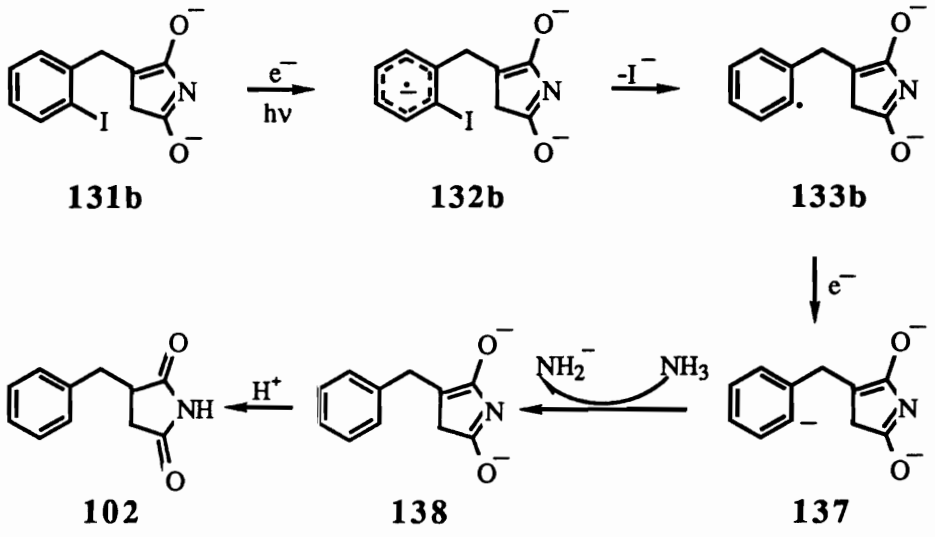
134 131a 135 132a (40)



135 136 (41)

Scheme 44

Of the two dianions **131a-b**, **131b** cannot participate in the intramolecular $S_{RN}1$ process leading to **61**. However, it could undergo photoassisted reductive dehalogenation to 3-benzylsuccinimide (**102**), as represented in Scheme 45. Addition of an electron to **131b** would form the radical anion **132b**, which would then lose iodide ion to form

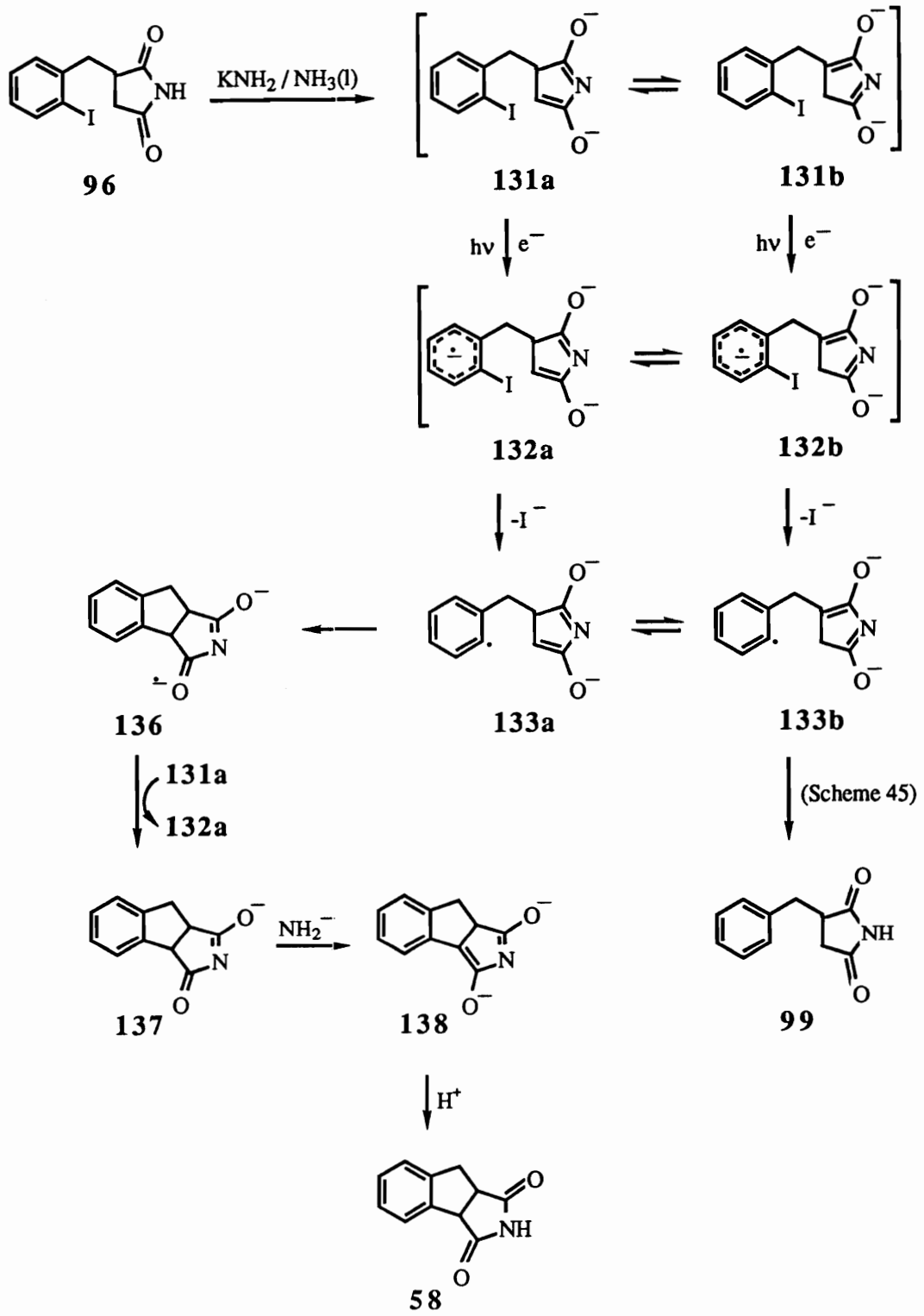


Scheme 45

radical **133b**. Addition of another electron to this species, perhaps by intramolecular electron-transfer or disproportionation, would yield anion **137**, which can then be protonated by the solvent to form dianion **138**. Alternatively, **138** may be formed via hydrogen atom abstraction from ether or THF by **133b**. Subsequent neutralization of the reaction mixture would afford the reduction product **102**.

Thus, while the cyclized product **61** originates from dianion **131a**, the reduction product **102** may originate mainly from dianion **131b**. These products are consistently formed in the ratio of approximately 4 : 2.5, which may be a measure of the distribution of

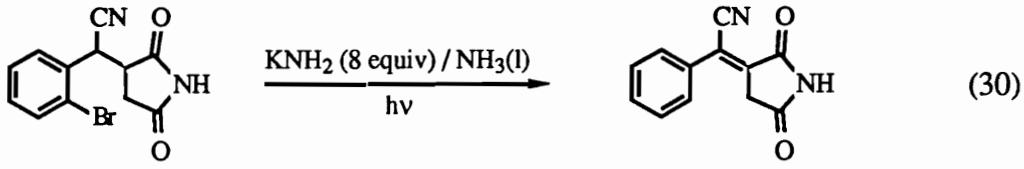
the two precursor dianions **131a-b**. The product ratio may also reflect differences in the reaction rates of the two competing processes, since the cyclization reaction, being an intramolecular chain process, is likely to be somewhat faster than the (non-chain) reduction process. The resulting shift in equilibria towards the species that is consumed faster, **133a**, would account for the observation that the cyclized product, succinimido[3,4-b]indane (**61**), is obtained in higher yield than the reduced product 3-benzylsuccinimide (**102**). These considerations have been used to propose the overall reaction pathway presented in Scheme 46.


KNH2 / NH3(l)
96
131a
131b
hν
e−
132a
132b
-I−
136
133a
133b
131a
132a
(Scheme 45)
NH2−
137
138
99
H+
58

Scheme 46

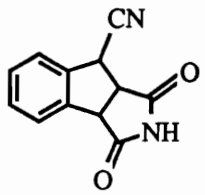
7.4. Mechanistic Studies of the Transformation of 3-(*o*-Bromo-α-cyanobenzyl)succinimide (82) into 3-(α-Cyanobenzylidene)succinimide (107).

The attempted cyclization of 3-(*o*-bromo-α-cyanobenzyl)succinimide (**82**) to succinimido[3,4-b]indane-8-carbonitrile (**83**) under standard $S_{RN}1$ conditions afforded 3-(α-cyanobenzylidene)succinimide (**107**) as the only isolable product in high yield (eq 30, reproduced below). The expected product of intramolecular $S_{RN}1$ reaction,



82 **107** (30)

succinimido[3,4-b]indane-8-carbonitrile (**83**), was not detected (see Section 4.4, pp). These results were then investigated to probe two features: first, the mechanistic aspects of the observed reaction, *i.e.*, the transformation of **82** into **107**, and second, the reasons for the complete suppression of the expected cyclization of **82** into **83**.



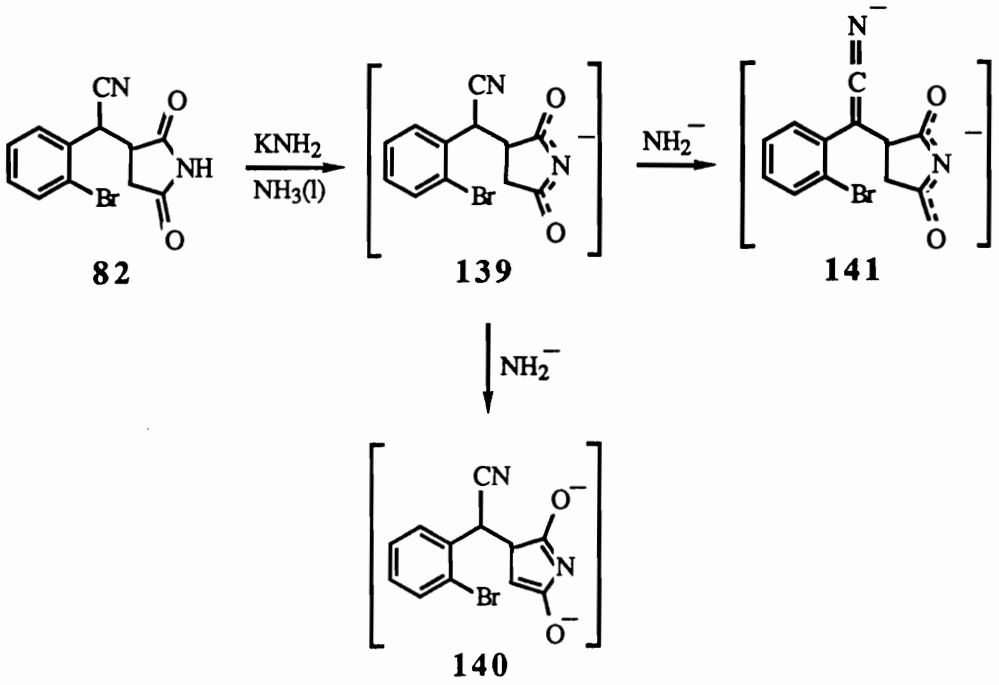
83

It seemed possible that product **107** could arise by means of an internal β-hydrogen transfer reaction. Semmelhack and Bargar had first reported the prevalence of intramolecular hydrogen atom abstraction processes over intramolecular $S_{RN}1$ reactions with certain ketone enolates.[43] They had further concluded that these reactions occurred via radical-chain processes in which the product radical-anion species propagated the chain by donating an electron to the substrate ketone enolate species (see Scheme 11, pp 20). An attempt was therefore made to determine if the observed formation of **107** from **82** occurred via an analogous radical-chain process. The reaction was carried out in the dark as well as in the presence of 10 mol% of the radical scavenger, di-*tert*-butyl nitroxide. In each case, the resulting product mixture consisted of mostly unreacted 3-(*o*-bromo-α-cyanobenzyl)succinimide (**82**). These results provided strong evidence that the conversion of **82** to **107** might proceed via a photostimulated radical-chain process.

The complete suppression of the expected intramolecular $S_{RN}1$ reaction is attributed to the presence of the α-cyano- group in substrate **82**, since the expected cyclization reaction had been found to occur satisfactorily in the absence of the cyano-group, as demonstrated by the cyclization of 3-(*o*-iodobenzyl)succinimide (**99**) to succinimido[3,4-b]indane (**61**) under standard $S_{RN}1$ conditions. Examination of the reactive intermediates that would lead to the formation of the cyclized product, succinimido[3,4-b]indane-8-carbonitrile (**83**), provides insight into possible causes for the observed reluctance of substrate **82** to undergo the expected cyclization reaction to form **83**.

Assuming that the expected cyclization of **82** to form **83** would follow a pathway similar to that previously proposed for the cyclization of 3-(*o*-iodobenzyl)succinimide (**99**)

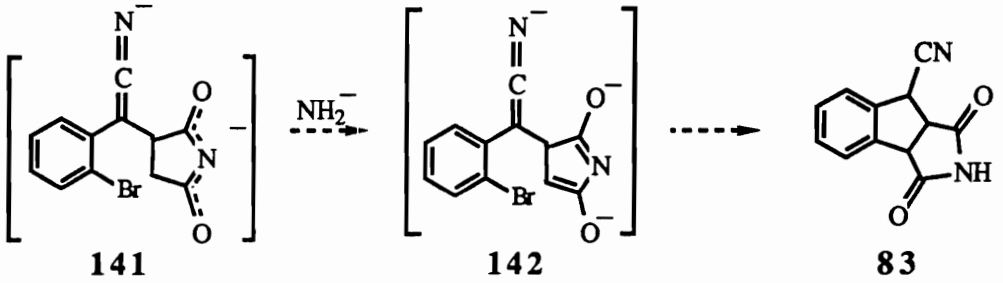
to form succinimido[3,4-b]indane (**61**) (see Scheme 44, pp 114), it appears that in order for



82 **139** **141** **140**

Scheme 47

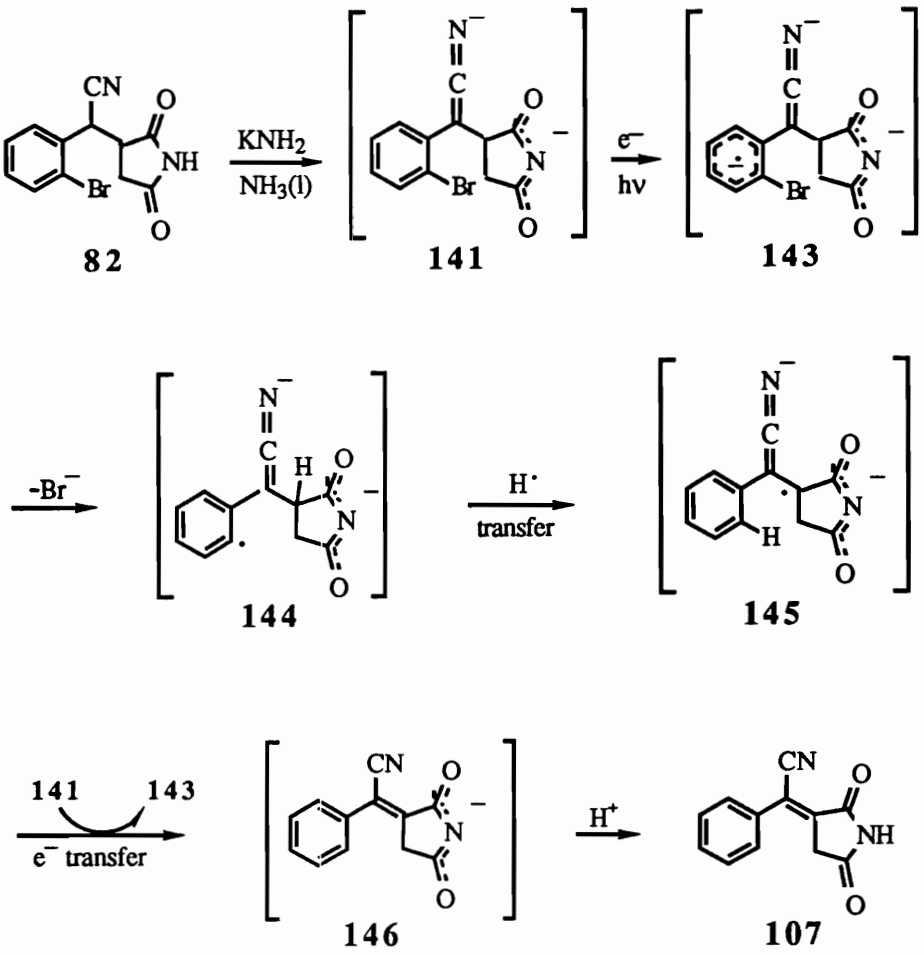
82 to undergo cyclization to form **83**, formation of dianion **140** is probably necessary (Scheme 47). However, formation of dianion **140** by deprotonation of monoanion **139** is almost certainly complicated by concomitant formation of dianion **141**. In fact, a comparison of the relative pK_as' of the respective protons suggests that deprotonation of **139** is likely to result in the formation of dianion **141**, rather than dianion **140**.[74] Then, further deprotonation to form trianion **142** would be necessary before cyclization could occur (Scheme 48). Energetically, however, deprotonation of dianion **141** is expected to be unfavorable, and may account for the observation that **82** does not undergo cyclization to form **83**.



141 142 83

Scheme 48

Although dianion **141** is unlikely to undergo further deprotonation to form trianion **142**, it could readily undergo intramolecular β-hydrogen atom transfer instead (Scheme 49). This process would lead to the formation of the product radical-anion **145**, via the intermediate species **143** and **144**, which can then propagate a chain reaction by transferring their odd-electrons to dianion **140**. The resultant product dianion **146** is stabilized by extended π-conjugation, thereby facilitating the entire process leading to its formation. Protonation of **146** upon neutralization of the reaction mixture would result in the formation of 3-(α-cyanobenzylidene)succinimide (**107**). The proposed mechanism therefore satisfactorily explains the exclusive formation of the β-hydrogen atom abstraction product **107**.

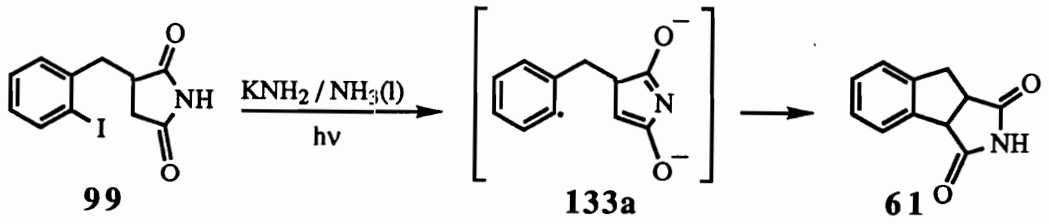

CN
O
NH
Br
O
82
KNH2
NH3(l)
N
C
O
N
Br
O
141
e⁻
hν
143
-Br⁻
144
H·
transfer
145
141
143
e⁻ transfer
146
H+
107

Scheme 49

7.5. Reluctance of 3-(*o*-Iodobenzyl)glutarimide (108) to Undergo Cyclization to form 1,2,3,4,5,6-Hexahydro-1,5-methano-3-benzazocine-2,4-dione (62): Investigation of Possible Causes.

Attempts to induce 3-(*o*-iodobenzyl)glutarimide (**108**) to undergo $S_{RN}1$ cyclization to form 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine-2,4-dione (**62**) were unsuccessful, the product mixture consisting predominantly of unreacted **108**, along with small quantities of the reduction product, 3-benzylglutarimide (**112**) (see Section 5.3., pp 86). The observed reluctance of the substrate **108** to undergo cyclization to form **62** was subsequently probed by use of molecular models. The conclusions derived from these investigations are discussed below.

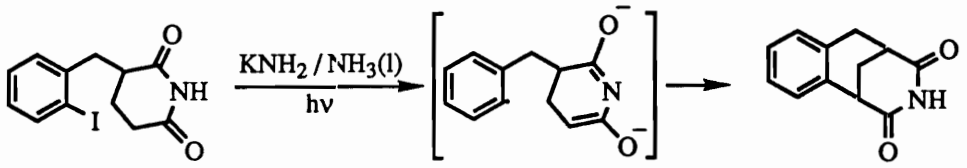
The cyclization of 3-(*o*-iodobenzyl)succinimide (**99**) to form succinimido[3,4-b]indane (**61**) presumably occurs via radical intermediate **133a** (Scheme 50) (also see



Scheme 50

Scheme 46, pp 117). The analogous transformation of 3-(*o*-iodobenzyl)glutarimide (**108**) to 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine-2,4-dione (**62**) was expected to occur via radical intermediate **147** (Scheme 51). The following assumptions were then made: First, it was presumed that in order to undergo the cyclization reaction, the

intermediate radical must assume a conformation in which the atom placement is similar to that in the most favorable conformation of the product. It was further assumed that such a conformation of radical **133a** was favorable, since the $S_{RN}1$ cyclization of **99** to form **61** occurs satisfactorily. A comparison of molecular models of radical **133a** and **61** seemed to be consistent with these assumptions.



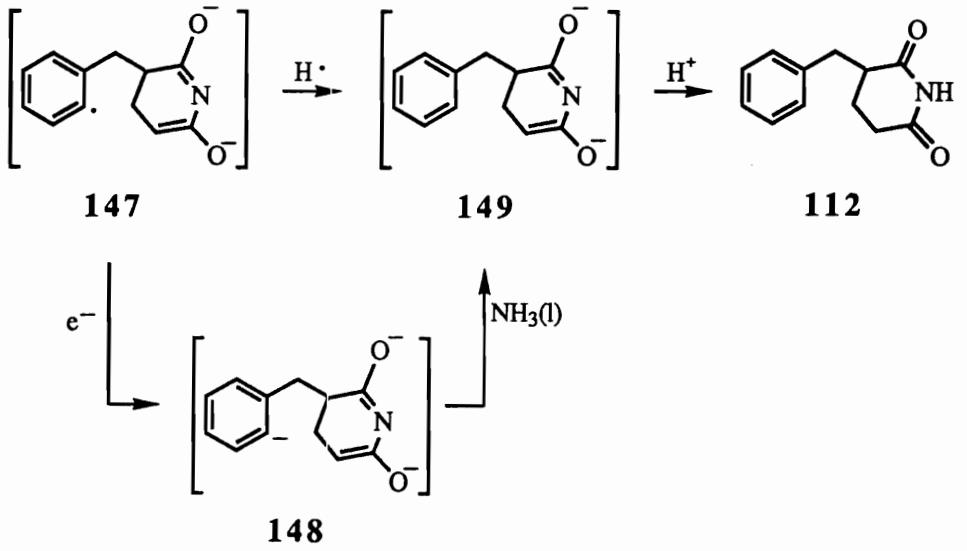
108 **147** **62**

Scheme 51

Similar examination of molecular models of intermediate species **147** and product **62** was then carried out. It appears that the conformation of **147** in which the atom placement is similar to that in product **62** may be quite strained. One of the hydrogen atoms of the benzylic methylene group is too close to the aryl carbon involved in formation of the incipient carbon-carbon bond. Consequently, the attempted cyclization of **108** to form **62** would appear to involve the formation of a sterically hindered intermediate. Therefore, steric factors might be responsible for the observed reluctance of 3-(*o*-iodobenzyl)- glutarimide (**108**) to undergo the expected photoassisted cyclization to form 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine-2,4-dione (**62**).

Since reduction product 3-benzylglutarimide (**112**) was obtained in small quantities during our attempts to induce cyclization of 3-(*o*-iodobenzyl)glutarimide (**108**), it appears that its susceptibility to undergo reductive dehalogenation is not significantly affected by the

factors discussed above. Similar amounts of reduction products are obtained in many instances of $S_{RN}1$ reactions (see Section 1.7-1.8, pp 15). Evidently, although radical **147** cannot undergo cyclization to form **62**, it can undergo reduction to form dianion **149**, presumably by either or both of the routes outlined in Scheme 52. Thus, it may directly abstract a hydrogen atom from a hydrogen-atom donor, possibly the ethereal solvent, to form **149**, or, alternatively, undergo a one-electron reduction to the phenyl anion **148**, which would then be protonated by solvent molecules to form **149**. Neutralization of the reaction mixture would afford the reduction product, 3-benzylglutarimide (**112**).



147 **149** **112**

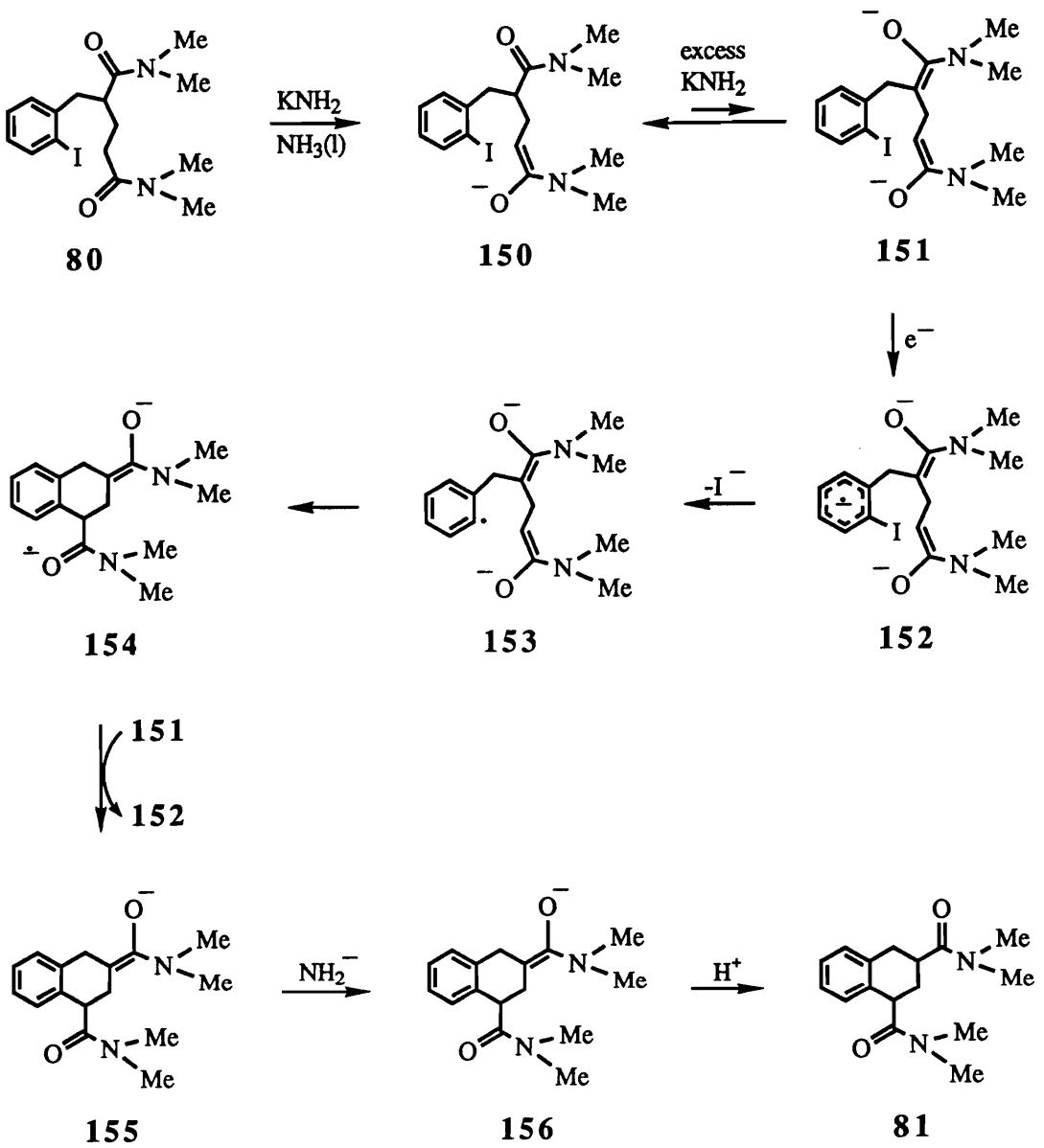
148

Scheme 52

7.6. Mechanistic Studies of the Cyclization of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (80) to form 1,3-bis-(*N,N*-Dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (81).

A series of experiments were carried out to ascertain the mechanistic features of the photoassisted cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) to 1,3-bis-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**) with potassium amide in liquid ammonia. The possibility that an aryne intermediate might be formed during the course of the reaction was probed by treating **80** with 8 equiv of potassium amide in liquid ammonia in the dark. Since no cyclized product was detected in the resulting product mixture, the aryne pathway was rejected (see entry 3, Table VII). The necessity for UV-irradiation to effect cyclization suggested the possible involvement of a radical-chain process, and was probed by carrying out the reaction in the presence of 10 mol% of the radical scavenger, di-*tert*- butyl nitroxide. The absence of **81** in the resulting product mixture indicated that the reaction was inhibited completely, thereby substantiating the premise that the reacton proceeds via an $S_{RN}1$ pathway.

The above results, along with the observation that the presence of excess base enhanced the rate of the cyclization reaction (entries 2 and 6, Table VII), support the reaction pathway outlined in Scheme 53, which is similar to that previously formulated for the cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) to form 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) (Scheme 42). Thus, upon treatment with potassium amide, substrate **80** presumably undergoes deprotonation to form mainly monoanion **150**. Further deprotonation to dianion **151** presumably occurs in presence of excess base. Addition of an electron to the aryl residue of **151** yields the radical anion **152**, which would then lose iodide to form radical dianion **153**. Attack of the enolate at



80 150 151 154 153 152 155 156 81

Scheme 53

the radical center would produce the product radical anion **154**, which can propagate the chain by transferring its odd electron to dianion **151**. The resulting species, **155**,which possesses a highly acidic benzylic hydrogen, would be expected to undergo deprotonation readily in the strongly basic reaction medium to form dianion **156**. Neutralization of the reaction mixture would afford the cyclized product 1,3-bis-(*N*,*N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**).

V. SUMMARY.

The synthesis of the 2-(*o*-iodobenzyl)- derivatives of *N,N,N'N'*-tetramethyl-succinamide and *N,N,N'N'*-tetramethyl-glutaramide (**77** and **80**, respectively) in reasonable yields was achieved by the generation of the dianions of the respective amides with lithium amide in liquid ammonia at -60°C, followed by alkylation with *o*-iodobenzyl chloride at the same temperature.

A by-product, 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)butanamide (**87**), formed during the synthesis of 2-(*o*-iodobenzyl)-*N,N,N'N'*-tetramethylsuccinamide provided the key to the development of an efficient two-step synthesis of 3-(*o*-iodobenzyl)succinimide (**99**) from *N,N,N'N'*-tetramethylsuccinamide (**73**) and represented an improvement over a previously developed procedure involving the direct alkylation of the dianion of succinimide (**100**). However, this new method could not be successfully applied to the synthesis of 3-(*o*-iodobenzyl)-glutarimide (**108**), which therefore had to be prepared by the generation and subsequent alkylation of the dianion of glutarimide (**109**).

3-(α-Cyano-*o*-bromobenzyl)succinimide (**82**) was prepared in an efficient process involving a Michael reaction between the anion of (*o*-bromophenyl)acetonitrile (**103**), generated with potassium amide in liquid ammonia, and maleimide (**104**).

The possibility of inducing intramolecular $S_{RN}1$ reactions in all of the above substrates (**77**, **80**, **82**, **99** and **108**) was investigated. Treatment of 2-(*o*-iodobenzyl)-*N,N,N'N'*-tetramethylsuccinamide (**77**) and its higher homolog 2-(*o*-iodobenzyl)-

N,N,N'N'-tetramethylglutaramide (**80**) with excess potassium amide in liquid ammonia under photostimulatIon afforded the expected cyclized products 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) and 1,3-bis-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**), respectively. When 3-(*o*-iodobenzyl)succinimide (**99**) was subjected to similar conditions, it also underwent the desired reaction, affording succinimido[2,3-b]indane (**61**) in acceptable yield. Mechanistic investigations revealed that all of the former reactions occurred via intramolecular $S_{RN}1$ processes, and indicated negligible competition from aryne pathways. However, 3-(α-cyano-*o*-bromobenzyl)-succinimide (**82**) failed to undergo the expected cyclization to form succinimido[3,4-b]indane-8-carbonitrile (**83**), affording instead, 3-(α-cyanobenzylidene)succinimide (**107**) as the sole isolable product, presumably via a facile intramolecular β-hydrogen atom abstraction process. This was proposed to occur via a radical-chain pathway similar to the $S_{RN}1$ process. 3-(*o*-Iodobenzyl)glutarimide (**108**) also did not undergo the desired cyclization to form 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine-2,4-dione (**62**). Molecular modeling studies indicated that an intermediate radical species must assume a sterically hindered conformation in order for cyclization to occur. Steric factors therefore appear to be responsible for the observed reluctance of 3-(*o*-iodobenzyl)glutarimide (**108**) to undergo the expected intramolecular reaction.

The attempted conversion of 1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) into succinimido[3,4-b]indane (**61**) was only modestly successful, affording the desired compound in poor yields. However, the direct cyclization of 3-(*o*-iodobenzyl)succinimide (**99**) to form the desired succinimido[3,4-b]indane (**61**) under standard $S_{RN}1$ conditions emerged as an acceptable method for the preparation of this potential anticonvulsant compound.

The attempted cyclization of 3-(*o*-bromo-α-cyanobenzyl)succinimide (**82**) to form succinimido-[3,4-b]-indane-8-carbonitrile (**83**) had been undertaken as a preliminary investigation for possible future use in the development of analogs of succinimido[3,4-b]indane (**61**). However, the failure of **82** to undergo the expected cyclization to form **83** suggested that strongly electron-withdrawing groups in the α-position in 3-(*o*-halobenzyl)-succinimides might be unsuitable for the purpose of analog synthesis. It appeared that in such cases, the formation of a trianionic species would be necessary for cyclization to occur. Since the formation of such a species was likely to be energetically unfavorable, competing processes, such as intramolecular β-hydrogen atom abstraction, might prevail. Nevertheless, it appears possible that the desired $S_{RN}1$ cyclization reaction may well proceed efficiently with other, non-electron-withdrawing, substituents in the α-position, and this may be the appropriate approach for future studies along these lines.

This study therefore establishes that it is possible to induce intramolecular $S_{RN}1$ cyclizations with succinamide and glutaramide derivatives that contain an appropriately positioned *o*-iodobenzyl moiety, affording reasonable yields of the expected, cyclized, products. Although amide enolates have been known to participate in intermolecular $S_{RN}1$ reactions, this is the first instance of their participation in intramolecular $S_{RN}1$ reactions.

This study also records the successful participation of 3-(*o*-iodobenzyl)succinimide in a similar intramolecular $S_{RN}1$ cyclization. Molecular modeling studies were helpful in providing insight into the reluctance of 3-(*o*-iodobenzyl)glutarimide to undergo an analogous cyclization reaction. Novel synthetic routes to three different ring systems have thus been achieved, and are expected to complement existing synthetic procedures for the preparation of compounds containing these systems.

VI. EXPERIMENTAL

1. General.

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Boiling points are also uncorrected. Elemental analysis were performed by Atlantic Microlab Inc., Norcross, Ga. Infrared spectra were recorded on a Perkin-Elmer 710 B infrared spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) and ^{13}C-NMR spectra were recorded on a Bruker WP-270 spectrometer, using deuterated chloroform as the solvent (unless otherwise stated) and TMS as the internal reference. Chemical shifts are expressed in δ units and the multiplicities of the signal are indicated as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet and any combinations as appropriate. Mass spectra were recorded on a Dupont 20-491 (low resolution) or on a double-focussing Dupont 21-110C or VG mass spectrometer (exact mass). X-ray crystal structures were obtained on a Nicolet R3m/V diffractometer with MoKα radiation λ = 0.71073A.

Thin layer chromatography (TLC) was performed using Eastman chromatogram sheets, type 13181 (silica gel) with fluorescent indicator. Flash chromatography refers to standard medium pressure column chromatography using Kiesel gel 60 (230-400 mesh) by EM reagents.

Anhydrous NH_3(l) (Matheson) was used directly from the tank since it had been previously shown that distillation from sodium did not affect the outcome of the reactions.[75] Tetrahydrofuran (THF) was distilled under nitrogen from lithium aluminum hydride or benzophenone potassium ketyl. Diisopropylamine was distilled under nitrogen

from calcium hydride. Unless otherwise stated all chemicals were obtained from commercial sources and used as received.

Solutions of organic compounds were dried using anhydrous sodium or magnesium sulfate. Photostimulated reactions were carried out in an inert atmosphere (nitrogen), using a Rayonet RPR-240 photoreactor equipped with four 12.5-W lamps emitting maximally at 350 nm. Small-scale photostimulated reactions [up to 100 mL of $NH_3(l)$] were irradiated with a portable UV-lamp. Di-*tert* -butyl nitroxide was prepared from 2-methyl-2-nitropropane.[75]

2. Synthesis and Reactions.

2.1. General Procedure for Reactions Carried Out in Liquid Ammonia.

During the course of this investigation, many of the reactions were carried out with an alkali metal amide in $NH_3(l)$. The typical experimental procedures followed for these reactions, both dark and photostimulated, are described below.

i) Dark reactions:

The type of reaction vessel used was chosen on the basis of whether the reaction was to be carried out in refluxing $NH_3(l)$ (-33°C), or whether external cooling to lower temperatures was desired. When the reaction was conducted in refluxing $NH_3(l)$, a double-jacketed photoreaction vessel was used (Fig. 8) to minimize evaporation of the solvent, whereas a three-necked round-bottomed flask was preferred for reactions that were carried out at lower temperatures. The oven-dried reaction vessel, purged with dry nitrogen and equipped with a dry-ice/acetone condenser and a bare metal magnetic stirring bar, was charged with the requisite volume of $NH_3(l)$ under a blanket of nitrogen. To this was added the theoretical amount of the appropriate alkali metal and a few crystals of ferric nitrate, $Fe(NO_3)_3.9H_2O$. After the blue color was discharged (it was assumed that formation of the alkali metal amide was then complete), the appropriate quantity of the substrate(s) was added.

After allowing the reaction to proceed for the desired time, it was quenched by carefully pouring the ammoniacal solution over a two-fold (molar) excess of solid ammonium chloride in a sufficiently large beaker. The $NH_3(l)$ was evaporated while being replaced by an appropriate volume of ether. After the ammonia had evaporated, enough water to dissolve the ammonium chloride and the alkali metal salts was added. When imides were used as substrates, the ether-water mixture was also acidified with

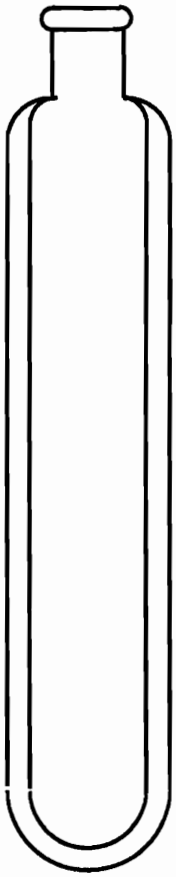


Fig. 2

concentrated HCl to ensure protonation of the imide nitrogen. The layers were then separated and the aqueous layer extracted with several portions of ether and/or methylene chloride. The combined organic extracts were dried, filtered and the solvent removed *in vacuo* to give the crude product.

ii) Photostimulated reactions:

The photostimulated reactions were usually carried out in the photoreaction tubes described earlier. However, small scale reactions (40-90 mg of substrate) were often carried out in round-bottomed flasks for the sake of convenience, using a portable UV-lamp for irradiating the reaction mixture. The remainder of the procedure was as described for the dark reactions, except that the reaction mixture was irradiated continuously with ultra-violet light of 350 nm. In cases where reaction times exceeded 0.5 h, the upper portion of the reaction vessel tended to get hot. So, in order that the $NH_3(l)$ could be poured safely, it was prudent to wait for about ten minutes to allow the photoreaction tube to cool to room temperature before quenching the reaction. In the photostimulated reactions of iodoaryls, free iodine was often detected in the organic extract containing the crude product (a pinkish-brown color); this was removed by washing the combined organic extract first with an aqueous solution of sodium bisulfite (15%, w/v), followed by a final washing with water, prior to drying with sodium sulfate.

2.2. Preparation of *N,N,N',N'*-tetramethylsuccinamide (73).

i) From dimethyl succinate:

To a one-necked round-bottomed flask (250 mL) charged with dimethyl succinate (14.6g, 100 mmol) was added an aqueous solution of dimethyl amine (40% w/v, 60 mL, 530 mmol). The reaction mixture was stirred at room temperature for 15 h. It was then exhaustively extracted with methylene chloride, saturating the aqueous layer with salt (sodium chloride) during each extraction. The organic extracts were combined, dried, filtered and the solvent was removed *in vacuo* to yield an oily white solid. Recrystallization from diethyl ether gave 5.2g (32%) of white crystals of *N,N,N',N'*-tetramethylsuccinamide (**73**): **mp**: 82-83°C (lit. mp[55] 82-83°C); **^{1}H-NMR** ($CDCl_3$) δ 2.65 (s, 4H, $-CH_2-CH_2-$); 2.8 (s, 6H, two N-CH_3); 2.9 (s, 6H, two N-CH_3).

ii) From succinyl dichloride:

An ethereal solution of dimethyl amine was obtained by the exhaustive extraction of an aqueous solution of dimethyl amine (40% w/v, 60 mL, 530 mmol) with ether (3 x 20 mL, followed by 4 x 10 mL); the combined ethereal extract was dried twice over sodium sulfate. To a 250 mL, three-necked, round-bottomed flask charged with this solution was added an ethereal solution of succinyl dichloride (7.75g, 50 mmol, 25 mL of ether) dropwise, using a pressure-equalizing addition funnel to adjust the rate of addition, thereby controlling the vigorous reaction that ensued. The vapors of hydrochloric acid that were liberated during the reaction were absorbed in a water-trap. After stirring for 0.5 h, the reaction mixture was shaken with a saturated solution of sodium bicarbonate and separated. The ethereal extract was then dried and evaporated to give 7 g of **73**. Recrystallization of the crude product from ether gave 6.88g (80%) of pure **73**.

2.3. Studies of The Alkylation of *N,N,N',N'*-Tetramethylsuccinamide (73). Preparation of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (77).

Using lithium diisopropylamide as the base in tetrahydrofuran.

The preparation of **77** by monoalkylation of **73** with *o*-iodobenzyl chloride (**76**) was first attempted using the method described by Snieckus and co-workers.[55] Several experiments were carried out to examine the effects of varying concentrations, temperatures and reaction times in an attempt to develop a useful synthetic procedure. None of these experiments afforded acceptable yields of **77**; however, one of these was found to be somewhat more effective than the others in suppressing dialkylation to some extent. This procedure is therefore described first, followed by a description of the remainder of the experiments according to their order of entry in Table I (see pp 52).

i) Lithium diisopropylamide (22 mmol) was generated *in situ* from diisopropylamine (2.22g, 22 mmol) and *n*-butyllithium (9.8mL, 22 mmol, 2.25M in hexane) in freshly distilled tetrahydrofuran (60 mL) in a dry, three-necked, round-bottomed flask under a nitrogen atmosphere at -78°C (entry 6). *N,N,N',N'*-tetramethylsuccinamide (**73**) (1.72g; 10 mmol, dissolved in 40 mL of THF) was then added and the solution was stirred for 40 min to allow complete formation of the dianion. *o* -Iodobenzyl chloride (**76**) (2.53g; 10 mmol) dissolved in THF (40 mL) and cooled to -70°C was then added dropwise (30 min), using a pressure equalizing addition funnel (the funnel was externally cooled with Dry Ice-acetone mixture) The reaction mixture was stirred at -78°C for an additional 0.33 h and then slowly warmed to room temperature. It was then quenched with a saturated solution of ammonium chloride (10 mL) and extracted several times with methylene chloride. The organic layers were combined, dried and the solvent removed *in vacuo* to yield a viscous

brown oil. This oil was separated by flash chromatography (2% methanol in methylene chloride as eluant) which afforded three products that were identified as *trans*-2,2'-diiodostilbene (**85**), *threo*-2,3-bis-(*o* -iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**84**) and 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**)

***trans*-2,2'-diodostilbene (85)** (0.21g; 10%): **mp**: 92°C; **^{1}H-NMR**: δ 7.0 (t, 2H, two aromatic CH), 7.1 (s, 2H, Ar-C<u>H</u>=C<u>H</u>-Ar), 7.2 (d, 2H, two C<u>H</u>-C(CI)-CH=CH-), 7.4 (t, 2H, two aromatic CH), 7.8 (d, 2H, two CH-C<u>H</u>-CI-); **Elemental analysis**: Calc. for $C_{14}H_{10}I_2$: C 38.89, H 2.32. Found C 38.95, H 2.44.

***threo*-2,3-bis-(*o* -iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (84)** (1.49g, 47%): **mp**: 153°C; **^{1}H NMR**: δ 2.39 (s, 6H, two N-CH_3), 2.62 (s, 6H, two N-CH_3), 2.85-2.97 (m, 4H, two Ar-CH_2), 3.6 (m, 2H, two C<u>H</u>-CO-), 6.91 (t, 2H, two aromatic CH), 7.14 (d, 2H, two -C<u>H</u>-C(CI)-CH_2-), 7.23 (t, 2H, two aromatic CH), 7.8 (d, 2H, two -CH-C<u>H</u>-CI-); **^{13}C-NMR**: δ 35.1 (CH_3), 37.0 (CH_3), 42.2 (CH_2), 44.0 (CH), 100.7 (C-I), 127.9 (CH), 128.2 (CH), 130.7 (CH), 139.1 (CH), 141.8 (<u>C</u>-CH_2), 173.9 (two CO); **Mass Spectrum** (70 eV, m/e (rel. int.)): 604 (1.2, M^+), 559 (6), 547 (10), 314 (25), 259 (85), 214 (20), 128 (20), 115 (25), 91 (20), 72 (100); **Elemental analysis**: Calc. for $C_{22}H_{26}I_2N_2O_2$: C, 41.51; H, 4.09; N, 4.40. Found C, 41.55; H, 4.17; N, 4.46.

2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (77) (1.32g, 34%): **mp**: 82-83°C; **^{1}H-NMR**: δ 2.32 (dd, 1H, -C<u>H</u>$_2$-CO-), 2.76 (s, 3H, N-CH_3), 2.88 (s, 3H, N-CH_3), 2.92 (s, 3H, N-CH_3), 2.93 (dd, 2H, Ar-CH_2), 3.06 (s, 3H, N-CH_3), 3.10 (dd, 1H, -CH_2-CO), 3.65 (m, 1 H, Ar-CH_2-C<u>H</u>-), 6.9 (t, 1 H, aromatic CH), 7.15 (d, 1 H, aromatic C<u>H</u>-C(CI)-CH2-); 7.22 (t, 1 H, aromatic CH); 7.8 (d, 1 H, aromatic CH-CI);

^{13}C-NMR: δ 35.1 (CH_3), 35.5 (CH_3), 36.9 (CH_2), 37 (CH_3), 37.1 (CH), 37.2 (CH_3), 43.5 (CH_2), 100.5 (C-I), 128 (CH), 128.5 (CH), 130.5 (CH), 139.5 (CH), 141.5 (C), 171 (CO), 174.3 (CO); **Mass Spectrum** (70 eV, m/e (rel. int.)): 388 (3, M^+), 344 (20), 316 (35), 302 (40), 272 (15), 261 (100), 217 (30), 188 (40, 174 (20), 144 (18), 115 (33), 84 (48), 72 (70); **Elemental analysis**: Calc. for $C_{15}H_{21}IN_2O_2$: C, 46.39; H, 5.41; I, 32.73; N, 7.22. Found C, 46.49; H, 5.47; I, 32.65; N, 7.19.

ii) A concentrated solution of the alkylating agent **76** (2.53g in 15 mL THF, 10 mmol) was added rapidly (1 min) to the dianion of *N,N,N',N'*-tetramethylsuccinamide [generated by treating 1.72g of **73** with 22 mmol of lithium diisopropylamide (from diisopropylamine (2.22g, 22 mmol) and *n*-butyllithium (9.8mL, 22 mmol, 2.25M in hexane))] in 60 mL of THF at -78°C) (entry 1). Work-up similar to that described above, followed by chromatographic separation of the crude product afforded 0.22g (10%) of *trans*-2,2'-diiodostilbene (**85**), 2.07g (65%) of 2,3-bis-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**84**) and 0.58g (15%) of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**).

iii) A concentrated solution of the alkylating agent **76** (2.53g in 15 mL of THF, 10 mmol, cooled to -70°C) was added slowly (25 min) to the dianion of *N,N,N',N'*-tetramethylsuccinamide [generated by treating 1.72g of **70** with 22 mmol lithium diisopropylamide (from diisopropylamine (2.22g, 22 mmol) and *n*-butyllithium (9.8mL, 22 mmol, 2.25M in hexane))] in 60 mL THF at -78°C) (entry 2). Work-up similar to that described above, followed by chromatographic separation of the crude product afforded 0.21g (10%) of 2,2'-diiodostilbene (**85**) 1.91g (60%) of 2,3-bis-(*o*-iodobenzyl)-

N,N,N',N'-tetramethylsuccinamide (**84**) and 0.78g (20%) of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**).

iv) The procedure described in iii) was repeated, except that the solution of the alkylating agent **76** was at room temp while being added to the dianion of *N,N,N',N'*-tetramethylsuccinamide (entry 3). This experiment afforded 0.24g (11%) of 2,2'-diiodostilbene (**85**) 1.97g (62%) of 2,3-bis-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**84**) and 0.66g (17%) of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**).

v) A dilute solution of the alkylating agent **76** (1.26g in 20 mL of THF, 5 mmol, cooled to -70°C) was added rapidly (1 min) to the dianion of *N,N,N',N'*-tetramethylsuccinamide [generated by treating 0.86g of **73** with 11 mmol of lithium diisopropylamide (from diisopropylamine (1.11g, 11 mmol) and *n*-butyllithium (4.9mL, 11 mmol, 2.25M in hexane))] in 30 mL of THF at -78°C (entry 4). Work-up similar to that described above, followed by chromatographic separation of the crude product afforded 0.11g (10%) of 2,2'-diiodostilbene (**85**) 0.87g (55%) of 2,3-bis-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**84**) and 0.43g (22%) of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**).

vi) The procedure described in v was repeated, except that the solution of the alkylating agent **76** was at room temp while being added to the dianion of *N,N,N',N'*-tetramethylsuccinamide (entry 5). This experiment afforded 0.12g (11%) of 2,2'-diiodostilbene (**85**) 1.01g (63%) of 2,3-bis-(*o*-iodobenzyl)-*N,N,N',N'*-

tetramethylsuccinamide (**84**) and 0.31g (16%) of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**).

vii) One equiv of lithium diisopropylamide [5.5 mmol, from diisopropylamine (0.56g, 5.5 mmol) and *n*-butyllithium (2.45mL, 5.5 mmol, 2.25M in hexane)] was used to generate the monoanion of *N,N,N',N'*-tetramethylsuccinamide (0.86g, 5 mmol), to which a dilute solution of the alkylating agent **76** (1.26g, 5 mmol, in 20 mL of THF, cooled to -70°C) was then added slowly (30 min) (entry 7). Upon chromatographic separation of the crude product, 0.69g (80%) of unreacted *N,N,N',N'*-tetramethylsuccinamide (**73**) was recovered along with 0.88g (70%) of the unreacted alkylating agent **76**. Small quantities of the alkylated products were also isolated: 0.13g (8%) of 2,3-bis-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**84**) and 0.1g (5%) of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**).

Using an alkali metal amide as base in liquid ammonia.

Since Snieckus's procedure had not afforded acceptable yields of **77**, a series of experiments probing the suitability of using alkali-metal amides in NH_3(l) as the base/solvent system was conducted. The procedure that afforded the best yield of **77** is described first, followed by a description of the other experiments according to their order of entry in Table II. All the experiments followed the general procedure outlined previously in section 2.1. of this chapter.

i) To a solution of $LiNH_2$ (44 mmol, from 0.3g of lithium metal) in NH_3(l) (500 mL) in a three-necked round-bottomed flask equipped with a Dry Ice condensor and a thermometer was added solid *N,N,N',N'* -tetramethylsuccinamide (**73**) (3.44g, 20 mmol)

(entry 6). The mixture was stirred while cooling to -60°C using a Dry Ice-chloroform cooling bath. After stirring for 40 min to permit complete formation of the dianion, *o*-iodobenzyl chloride (**76**) (5.05g, 20 mmol) dissolved in ether (150 mL) was added dropwise from a pressure-equalizing addition funnel, adjusting the rate of addition so that the temperature of the reaction mixture was maintained below -50°C (approximately 0.5 h for the entire addition). After stirring at -55°C for an additional 1 h, the reaction was quenched by pouring over solid ammonium chloride (7g) contained in a large beaker. The NH_3(l) was evaporated on a steam cone while being replaced with ether. After shaking with water (25 mL), the ethereal layer was separated; the aqueous layer was then extracted several times with methylene chloride. The organic extracts were combined, dried and the solvent removed *in vacuo*. The oily brown residue was triturated with ether (20 mL) to afford a white solid. Filtration of this solid under suction followed by recrystallization from chloroform/hexane yielded shiny white crystals of 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)-butanamide (**87**) (1.08g, 15%) **mp**: 132°C; **^{1}H-NMR**: δ 2.34 (dd, 2H, -CH_2-CO), 2.67 (s, 3H, N-CH_3), 2.77 (dd, 1H, Ar-C$\underline{H}_2$-), 2.79 (s, 3H, N-CH_3), 2.80 (dd, 1H, Ar-C$\underline{H}_2$-), 3.66 (m, 1H, methine), 5.8 (br s, 1H, N$\underline{H}$), 6.5 (br s, 1H, N$\underline{H}$), 7.1 (t, 1 H, aromatic), 7.2 (t, 1 H, aromatic); 7.22 (d, 1 H, aromatic); 7.8 (d, 1 H, aromatic); **^{13}C-NMR**: δ 35.5 (CH_3), 37.1 (CH_3), 37.5 (CH), 38.6 (CH_2), 43.6 (CH_2), 100.5 (C-I), 128.1 (CH), 128.4 (CH), 130.4 (CH), 139.7 (CH), 141.3 (C), 174.0 (CO), 174.3 (CO); **Mass Spectrum** (70 eV, m/e (rel. int.)): 360 (0.9, M^+), 302 (55), 233 (100), 217 (30), 188 (40), 174 (25), 144 (20), 115 (35), 84 (45), 72 (70); **Elemental analysis**: Calc. for $C_{13}H_{17}IN_2O_2$: C, 43.33; H, 4.72; I, 35.28; N, 7.78. Found C, 43.40; H, 4.78; I, 35.20; N, 7.70.

An oil was obtained upon evaporation of the ether soluble material; its ^{1}H-NMR spectrum closely resembled that of **77**. Purification by flash chromatography (gradient

elution with 0-2% methanol in methylene chloride) afforded 5.04 g (65%) of **77** and 0.26g (6%) 2,2'-diiodostilbene (**85**).

ii) To a solution of KNH_2 (11 mmol; from 0.43 g of potassium metal) in NH_3(l) (150 mL), *N,N,N',N'*-tetramethylsuccinamide (**73**) (0.86 g; 5 mmol) was added and stirred for 40 min (entry 1). *o*-Iodobenzyl chloride (**76**) (1.26 g; 5 mmol) dissolved in ether (10 mL) was then added dropwise (7 min, pressure-equalizing addition funnel) and the reaction was stirred for 0.5 h before quenching with solid ammonium chloride (1.8 g). Standard work-up followed by trituration of the crude product with ether (10 mL) afforded 0.09g (5%) of **87**; evaporation of the ether extract *in vacuo* gave an oil, which was then separated by flash chromatography (gradient elution with 0-2% methanol in methylene chloride) to give 0.67g (42%) of the dialkylated derivative **84** along with 0.43g (21%) of **77** and 0.21g (19%) of 2,2'-diiodostilbene (**85**).

iii) To a solution of $LiNH_2$ (22 mmol; from 0.15 g of Li wire) in NH_3(l) (200 mL), *N,N,N',N'* -tetramethylsuccinamide (1.72 g; 10 mmol) was added as a solid (entry 2). After stirring for 40 min to ensure complete formation of the dianion, *o*-iodobenzyl chloride (**76**) (2.53 g; 10 mmol) dissolved in ether (25 mL) was then added dropwise (10 min for complete addition using a pressure equalizing addition funnel) and the reaction further stirred for 0.5 h before quenching with solid ammonium chloride (3.8 g). Standard work-up followed by flash chromatography gave 1.18g (37%) of the dialkylated derivative **84** along with 0.81g (21%) of the desired monoalkylated product **77**, 0.32 g (15%) of 2,2'-diiodostilbene (**85**) and 0.32g (9%) of 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)-butanamide (**87**).

iv) To a solution of $LiNH_2$ (11 mmol; from 0.08 g of Li wire) in NH_3(l) (100 mL), *N,N,N',N'*-tetramethylsuccinamide (**73**) (0.86 g; 5 mmol) was added as a solid (entry 3). The mixture was stirred while cooling to -78°C using a Dry Ice-acetone cooling bath (40 min). *o*-Iodobenzyl chloride (**76**) (1.26 g; 5 mmol) dissolved in ether (10 mL) was then added dropwise (7 min, pressure-equalizing addition funnel) and the reaction was stirred for 0.25 h. Since there seemed to be no visual sign of reaction, the reaction mixture was allowed to warm to -33°C and stirred for an additional 0.5 h before quenching with solid ammonium chloride (1.8 g). Standard work-up followed by trituration with ether (20 mL) afforded 0.9g (50%) of **87** as the major product. Flash chromatography (gradient elution with 0-2% methanol in methylene chloride) of the oily residue obtained from evaporation of the ether extract gave 0.50g (26%) of **77** along with 0.09 g (8%) of 2,2'-diiodostilbene (**85**).

v) To a solution of KNH_2 (11 mmol; from 0.43 g of potassium metal) in NH_3(l) (150 mL), *N,N,N',N'*-tetramethylsuccinamide (**73**) (0.86 g; 5 mmol) was added as a solid (entry 4). The mixture was stirred while cooling to -78°C using a Dry Ice-acetone cooling bath (40 min). *o*-Iodobenzyl chloride (**76**) (1.26 g; 5 mmol) dissolved in ether (10 mL) was then added dropwise (7 min, pressure-equalizing addition funnel) and the reaction was stirred for 0.25 h. The reaction mixture was then allowed to warm to -33°C and stirred for an additional 0.5 h before quenching with solid ammonium chloride (1.8 g). Standard work-up followed by trituration with ether (20 mL) afforded 0.18g (10%) of **87**. Flash chromatography (gradient elution with 0-2% methanol in methylene chloride) of the oily residue obtained from evaporation of the ether extract gave 0.40g (25%) of the dialkylated derivative **84** as the major product along with 0.39g (20%) of **77** and 0.17g (16%) of 2,2'-diiodostilbene (**85**).

vi) To a solution of $LiNH_2$ (11 mmol; from 0.08 g of Li wire) in NH_3(l) (100 mL), *N,N,N',N'*-tetramethylsuccinamide (**73**) (0.86 g; 5 mmol) was added as a solid (entry 5). The mixture was stirred while cooling to -60°C using a Dry Ice-chloroform cooling bath (40 min). *o*-Iodobenzyl chloride (**76**) (1.26 g; 5 mmol) dissolved in ether (10 mL) was then added dropwise (7 min, pressure-equalizing addition funnel), taking care to maintain the temperature of the reaction mixture below -50°C, and stirred (-55°C) for an additional 0.75 h. Standard work-up, followed by ^{1}H-NMR spectroscopy of the crude product revealed that the reaction was incomplete. Trituration of the crude product with ether resulted in the separation of 0.16g (9%) of **87**; evaporation of the ether extract *in vacuo* gave an oily residue, which upon flash chromatographic separation (gradient elution, 0-2% methanol in methylene chloride) afforded 0.99g (51%) of **77**, along with 0.05g (5%) of **85**, 0.07g (8%) of unreacted **73** and 0.06g of unreacted **76** (5%).

vii) The procedure described above in vi) was repeated, increasing reaction time to 1.25 h (instead of 0.75 h) (entry 7). Standard work-up followed by separation of the product mixture gave 1.02g (53%) of **77** as the major product along with 0.41g (23%) of **87** and 0.065g (6%) of 2,2'-diiodostilbene (**85**).

2.4. Studies of the Cyclization of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (77) to 1,2-bis-(*N,N*-Dimethylcarboxamido) indane (78).

Several experiments were carried out to ascertain the optimum conditions for the cyclization of **77** to **78**. The procedure that emerged from this study as the most efficient is described first, followed by a description of the remainder of the experiments according

to their order of entry in Table III. All the reactions carried out in NH_3(l) followed the general procedure described previously (entries 1-10). The remaining two experiments (entries 11, 12) were carried out in tetrahydrofuran.

i) To a solution of KNH_2 (8 mmol; from 0.31g of potassium metal) in NH_3(l) (200 mL) was added 0.39g (0.23 mmol) of 2-(*o* -iodobenzyl)-*N,N,N',N'* -tetramethyl-succinamide (**77**) (entry 5). The reaction mixture was stirred in the dark for 0.25 h and quenched with solid ammonium chloride (3.5g). After evaporation of the NH_3(l) followed by standard work-up, a yellow oil was obtained, which upon flash chromatographic separation (2% methanol in methylene chloride as the eluant) afforded 0.18g (70%) of *trans*-1,2-bis-(*N,N*-dimethylcarboxamido)indane (**78**) along with 0.02g (8%) of 2-benzyl-*N,N,N',N'*-tetramethylsuccinamide (**90**).

***trans*-1,2-bis-(*N,N*-dimethylcarboxamido)indane (78) mp** 97°C; **^{1}H-NMR**: δ 2.95 (s, 3H, N-CH_3), 3.01 (dd, 1H, Ar-C$\underline{H}_2$-CH), 3.05 (s, 3H, N-CH_3), 3.14 (s, 3H, N-CH_3), 3.24 (dd, 1H, Ar-C$\underline{H}_2$-CH), 3.29 (s, 3H, N-CH_3), 4.15 (m, 1H, -CH_2-C$\underline{H}$-CO), 5.0 (d, 1H, Ar-C$\underline{H}$-CO), 7.01 (t, 1H, aromatic CH), 7.16 (m + s, 3H, aromatic CH); **^{13}C-NMR**: δ 35.63 (CH_3), 35.72 (CH_2), 35.84 (CH_3), 37.17 (CH_3),, 37.60 (CH_3), 46.58 (CH), 50.35 (CH), 122.83 (CH), 124.28 (CH), 126.78 (CH), 127.26 (CH), 141.23 (C), 141.40 (C), 172.66 (CO), 173.39(CO); **Mass Spectrum** (70 eV, m/e): 260 (5, M^+), 214 (85), 188 (20), 143 (13), 115 (33), 72 (100); **Elemental analysis**: Calc. for $C_{15}H_{20}N_2O_2$: C, 69.23; H, 7.69; N, 10.77. Found C, 69.26; H, 7.74; N, 10.71.

2-Benzyl-*N,N,N',N'*-tetramethylsuccinamide (90) mp 123°C; **^{1}H-NMR**: δ 2.28 (dd, 1H, CH-C$\underline{H}_2$-CO), 2.65 (dd, 1H, CH-C$\underline{H}_2$-CO), 2.78 (s, 3H, N-CH_3), 2.8-

2.91 (dd, 1H, Ar-C<u>H</u>$_2$-), 2.86 (s, 3H, N-CH_3), 2.88 (s, 3H, N-CH_3), 2.98 (s, 3H, N-CH_3), 3.1 (dd, 1H, Ar-C<u>H</u>$_2$-), 3.5 (m, 1H, Ar-CH_2-C<u>H</u>-CO), 7.12-7.29 (complex pattern, 5H, aromatic CH); **^{13}C-NMR**: δ 35.61 (CH_3), 35.74 (CH_3), 36.17 (CH_3), 36.60 (CH_3), 36.88 (CH_2), 38.68 (CH), 40.05 (CH), 124.26 (CH), 127.08 (CH), 127.86 (CH), 128.83 (CH), 129.56 (CH), 141.30 (C), 172.76 (CO), 173.82 (CO); **Mass Spectrum** (70 eV, m/e): 262 (25, M^+), 218 (22), 190 (15), 176 (83), 145 (28), 131 (19), 117 (14), 91 (22), 72 (100); **Elemental analysis**: Calc. for $C_{15}H_{22}N_2O_2$: C, 68.70; H, 8.40; N, 10.69. Found C, 68.73; H, 8.45; N, 10.76.

ii) To a solution of KNH_2 (8 mmol; from 0.31g of potassium metal) in NH_3(l) (200 mL) was added 0.39 g (1mmol) of **77** (entry 1). The reaction mixture was irradiated for 3 h and quenched with solid ammonium chloride (3.5 g). After evaporation of the NH_3(l) followed by standard work-up, the yellow oil obtained as the crude product was purified by flash chromatography (eluant: 2% methanol in methylene chloride) affording 0.17g (65%) of cyclized product **78** and 0.04g (15%) of the reduced product **90**.

iii) To a solution of KNH_2 (16 mmol; from 0.62g of potassium metal) in NH_3(l) (400 mL) was added 0.78 g (2 mmol) of **77** (entry 2). The reaction mixture was irradiated for 0.25 h and quenched with solid ammonium chloride (7 g). After evaporation of the NH_3(l) followed by standard work-up, a yellow oil was obtained. Purification by flash chromatography (eluant: 2% methanol in methylene chloride) afforded 0.35g (68%) of cyclized product **78** along with 0.05g (9%) of the reduced product **90**.

iv) To a solution of KNH_2 (3.3 mmol; from 0.13g of potassium metal) in NH_3(l) (200 mL) was added 0.39 g (1 mmol) of **77** (entry 3). The reaction mixture was irradiated

for 3 h and quenched with solid ammonium chloride (1.7 g). After evaporation of the NH_3(l) followed by standard work-up, a yellow oil was obtained. Purification by flash chromatography (eluant: 2% methanol in methylene chloride) afforded 0.1g (38%) of indane **78** along with 0.05g (20%) of the reduced product **90** and 0.07g (18%) of unreacted **77**.

v) To a solution of KNH_2 (8 mmol; from 0.31g of potassium metal) in NH_3(l) (200 mL) was added 0.39g (1 mmol) of **77** (entry 4). The reaction mixture was stirred in the dark for 3 h and quenched with solid ammonium chloride (3.5g). Standard work-up afforded a yellow oil, which upon chromatographic separation gave 0.18g (70%) of **78** along with 0.03g (10%) of **90**.

vi) To a solution of KNH_2 (3.3 mmol; from 0.13g of potassium metal) in NH_3(l) (200 mL) was added 0.39 g (1 mmol) of **77** (entry 6). The reaction mixture was stirred in the dark for 3 h and quenched with solid ammonium chloride (1.7 g). After standard work-up, a yellow oil was obtained. Purification by flash chromatography (eluant: 2% methanol in methylene chloride) afforded 0.08g (32%) of **78** along with 0.04g (16%) of the reduced product **90** and 0.12g (32%) of unreacted **77**.

vii) To a solution of $LiNH_2$ (1.52 mmol; from 0.014g of lithium wire) in NH_3(l) (100 mL) was added 0.18g (0.46 mmol) of **77** (entry 7). The reaction mixture was irradiated for 3 h and quenched with solid ammonium chloride (0.8g). Evaporation of the NH_3(l) followed by standard work-up afforded a yellow oil. No cyclized product was detected in the ^{1}H-NMR spectrum of the crude product, which was found to consist of

mostly unreacted **77**. Filtration through a plug of silica gel enabled recovery of 0.16g (89%) of unreacted **77**.

viii) To a solution of $LiNH_2$ (8 mmol; from 0.074g of lithium wire) in NH_3(l) (100 mL) was added 0.39g (1 mmol) of **77** (entry 8). The reaction mixture was stirred under photostimulation for 3 h and quenched with solid ammonium chloride (3.5g). After evaporation of the NH_3(l) followed by standard work-up, a yellow oil was obtained, which was found to consist predominantly of unreacted **77** along with small amounts of **78** and **90** (from its ^{1}H-NMR spectrum). Upon chromatographic separation (gradient elution with 0.5-2% methanol in methylene chloride), 0.23g (60%) of unreacted **73** was recovered along with 0.04g (15%) of **78** and 0.02g (8%) of **90**.

ix) To a solution of $NaNH_2$ (1.86 mmol; from 0.05g of sodium metal) in NH_3(l) (50 mL) was added 0.1g (0.25 mmol) of **77** (entry 9). The reaction mixture was stirred under photostimulation for 3 h and quenched with solid ammonium chloride (0.75g). After evaporation of the NH_3(l) followed by standard work-up, a yellow oil was obtained, which was found to consist of mostly unreacted **77** (from its ^{1}H-NMR spectrum). Filtration through a plug of silica gel enabled the recovery of 0.09g (90%) of **77**.

x) To a solution of potassium *tert*-butoxide (0.179g, 1.6 mmol) in NH_3(l) (50 mL) was added 0.08g (0.2 mmol) of **77** (entry10). The reaction mixture was irradiated for 3 h and quenched with solid ammonium chloride (0.75g). After standard work-up, the yellow oil obtained as the crude product was found to consist of mostly unreacted **77** along with traces of **90** (from its ^{1}H-NMR spectrum). Filtration through a plug of silica gel enabled the recovery of 0.07g (89%) of **77**.

xi) To a solution of lithium diisopropylamide (0.76 mmol), generated *in situ* from diisopropylamine (0.08g, 0.76 mmol) and *n*-butyllithium (0.30mL, 0.76 mmol, 2.5M in hexane), in tetrahydrofuran (50 mL) at -35°C was added a solution of **77** (0.09g, 0.23 mmol, 7 mL THF) (entry 11). The temperature of the reaction mixture was maintained between -30°C and -35°C while being stirred under photostimulation for 3 h. It was then quenched with a solution of ammonium chloride (7.5% w/v; 10 mL) and extracted several times with methylene chloride. The organic extracts were combined, dried and the solvent removed *in vacuo* to afford a yellow oil, which was found to consist of mostly unreacted **77** along with a small amount of **78** (estimated ratio of 7:1 from its ^{1}H-NMR spectrum).

xii) To a solution of lithium diisopropylamide (8 mmol), generated *in situ* from diisopropylamine (0.81g, 8 mmol) and *n*-butyllithium (3.56mL, 8 mmol, 2.25M in hexane), in tetrahydrofuran (100 mL) at -35°C was added a solution of **77** (0.39g, 1 mmol, 15 mL THF) (entry 12). The temperature of the reaction mixture was maintained between -30°C and -35°C while being stirred under photostimulation for 3 h. It was then quenched with a solution of ammonium chloride (7.5% w/v; 10 mL) and extracted several times with methylene chloride. The organic extracts were combined, dried and the solvent removed *in vacuo* ; the yellow oil that was left as the residue was separated by flash chromatography (gradient elution, 0-2% methanol in methylene chloride) which afforded 0.08g (32%) of the cyclized product **78**, 0.05g (20%) of **90** and 0.12g (31%) of unreacted **77**.

2.5. Studies of the "One-Pot" Synthesis of 1,2-bis-(*N,N*-Dimethylcarboxamido)indane (78) from *N,N,N',N'*-Tetramethylsuccinamide (73).

Prior to investigating the possibility of the "one-pot" synthesis of **78** from **73**, it was necessary to ascertain the efficacy of KNH_2 (rather than $LiNH_2$) in the monoalkylation of **73** to **77**; the experiment carried out with this objective in mind is described below.

To a solution of KNH_2 (11 mmol; from 0.43 g of potassium metal) in NH_3(l) (150 mL), *N,N,N',N'*-tetramethylsuccinamide (**73**) (0.86 g; 5 mmol) was added. It was then cooled to -60°C and stirred for 40 min to ensure complete formation of the dianion. *o*-Iodobenzyl chloride (**76**) (1.26 g; 5 mmol) dissolved in ether (10 mL) was then added dropwise (7 min, pressure equalizing addition funnel), taking care to maintain the reaction temperature below -55°C, after which the reaction was stirred for an additional 1 h before quenching with solid ammonium chloride (1.8 g). Standard work-up followed by flash chromatography (gradient elution 0-2% methanol in methylene chloride) gave 0.97g (50%) of the desired monoalkylated derivative **77**, along with 0.19 g (12%) of the dialkylated derivative **84**, 0.09g (5%) of the partially solvolysed product **87** and 0.19g (18%) of *o,o'*-diiodostilbene (**85**).

The possibility of developing a sequential "one-pot " tandem alkylation-cyclization was then explored via the following experiments, described in their order of entry in Table IV.

i) To a solution of KNH_2 (4.4 mmol; from 0.17g of potassium metal) in NH_3(l) (75 mL) was added *N,N,N',N'*-tetramethylsuccinamide (**73**) (0.34g, 2 mmol). The solution was then cooled to -60°C and stirred for 40 min to ensure complete formation of

the dianion (entry 1). An ethereal solution of *o*-iodobenzyl chloride (**80**) (0.51g, 2 mmol, 15 mL of ether) was then added dropwise (10 min), taking care to maintain the temperature below -50°C, after which the reaction mixture was stirred for 1 h. *n*-Butyllithium (5.33 mL, 12 mmol, 2.25 M in hexane) was then added, the reaction mixture warmed to -33°C and irradiated for 0.5 h before quenching with ammonium chloride (1.7g). ^{1}H-NMR spectroscopic analysis of the crude product obtained after standard work-up revealed only traces of the cyclized product **78**. Chromatographic separation (gradient elution with 0-2% methanol in methylene chloride) of the product afforded 0.37g (48%) of the monoalkylated derivative **77** and 0.1g (18%) of **87**.

ii) To a solution of KNH_2 (5.5mmol; from 0.22g of potassium metal) in NH_3(l) (100 mL) was added *N,N,N',N'*-tetramethylsuccinamide (**73**) (0.43g, 2.5 mmol). The solution was then cooled to -60°C and stirred for 40 min to ensure complete formation of the dianion (entry 2). An ethereal solution of *o*-iodobenzyl chloride (**80**) (0.63g, 2.5 mmol, 15 mL of ether) was added dropwise (10 min), taking care to maintain the temperature below -50°C, after which the reaction mixture was stirred for 1 h. Sodium amide (0.59g; 15 mmol) was then added, the reaction mixture warmed to -33°C and irradiated for 1 h before quenching with ammonium chloride (2g). ^{1}H-NMR spectroscopic analysis of the crude product obtained after standard work-up revealed the absence of cyclized product **78**. Chromatographic separation (gradient elution with 0-2% methanol in methylene chloride) of the product afforded 0.44g (45%) of the monoalkylated derivative **77** and 0.09g (10%) of **87**.

iii) To a solution of KNH_2 (5.5mmol; from 0.22g of potassium metal) in NH_3(l) (100 mL) was added *N,N,N',N'*-tetramethylsuccinamide (**70**) (0.43g; 2.5 mmol). The

solution was then cooled to -60°C and stirred for 40 min to ensure complete formation of the dianion (entry 2). An ethereal solution of *o*-iodobenzyl chloride (**76**) (0.63g, 2.5 mmol 15 mL of ether) was added dropwise (10 min), taking care to maintain the temperature below -50°C, after which the reaction mixture was stirred for 1 h. Potassium *tert*-butoxide (1.68g, 15 mmol) was then added, the reaction mixture warmed to -33°C and irradiated for 1 h before quenching with ammonium chloride (2g). ^{1}H-NMR spectroscopic analysis of the crude product obtained after standard work-up revealed the absence of cyclized product **78**. Chromatographic separation (gradient elution with 0-2% methanol in methylene chloride) of the product afforded 0.51g (52%) of the monoalkylated derivative **77** and 0.11g (12%) of **87**.

iv) To a solution of KNH_2 (11 mmol; from 0.44g of potassium metal) in NH_3(l) (150 mL) was added *N,N,N',N'*-tetramethylsuccinamide (**73**) (0.86g, 5 mmol). The solution was then cooled to -60°C and stirred for 40 min to ensure complete formation of the dianion (entry 4). An ethereal solution of *o*-iodobenzyl chloride (**76**) (1.26g, 5 mmol, 30 mL of ether) was then added dropwise (10 min), taking care to maintain the temperature below -50°C, after which the reaction mixture was stirred for 1 h. The reaction mixture was stirred for 1 h, after which it was warmed to -33°C and irradiated for 4.5 h before quenching with ammonium chloride (4g). Chromatographic separation (gradient elution with 0-2% methanol in methylene chloride) of the product afforded 0.30g (23%) of the cyclized product **78**, along with 0.0.48g (11%) of the monoalkylated derivative **77**, 0.19g (12%) of **90** and 0.14g (13%) of **87**.

2.6. Hydrolysis of 1,2-bis-(*N,N'*-Dimethylcarboxamido)indane (78).

i) *trans*-1-(*N,N'*-Dimethylcarboxamido)indane-2-carboxylic acid (93).

Attempts to hydrolyse **78** with sodium peroxide using the procedure described by Vaughn and Robbins[61] resulted in the hydrolysis of only one of the two *N,N'*-dimethylcarboxamido groups of **78** to form 1-(*N,N'*-dimethylcarboxamido)indane-2-carboxylic acid (**93**). Thus, to a suspension of 0.26g (1 mmol) of 1,2-bis-(*N,N'*-dimethylcarboxamido)indane (**78**) in water (10 mL) was added, portionwise, solid sodium peroxide (0.17g, 2.2 mmol). The reaction mixture was heated on a steam bath for 2 h (~80°C). The reaction mixture was then cooled to 0°C and extracted once with methylene chloride (5 mL) to remove any unreacted **78** and set aside. The aqueous layer was acidified (dropwise) with conc HCl and extracted several times with methylene chloride. The organic extracts were combined, washed with aqueous sodium chloride (10 mL, 2% w/v) and dried. Removal of the solvent *in vacuo* afforded 0.21g (80%) of a white solid that was identified as *trans*-1-(*N,N'*-dimethylcarboxamido)indane-2-carboxylic acid (**93**) **mp** 188°C; **^{1}H-NMR**: δ 3.10 (s, 3H, N-CH_3), 3.21 (dd, 1H, Ar-C$\underline{H}_2$), 3.30 (s, 3H, N-CH_3), 3.39 (dd, 1H, Ar-C$\underline{H}_2$), 3.98 (dd, 1H, Ar-CH_2-C$\underline{H}$-), 4.67 (d, 1H, Ar-C$\underline{H}$-), 7.01 (m, 1H, aromatic CH), 7.12-7.24 (complex pattern, 3H, three aromatic CH); **^{13}C-NMR**: δ 35.6 (CH_3), 35.8 (CH_2), 36.2 (CH_3), 46.8 (CH), 50.7 (CH), 124.9 (CH), 125.1 (CH), 126.7 (CH), 127.4 (CH), 140.6 (C), 141.5 (C), 173.6 (CO), 174.1 (CO); **Mass Spectrum** (70eV, m/e, rel. int.): 233 (12, M^+), 188 (9), 161 (2), 115 (30), 72 (100); **Elemental analysis**: calc. for $C_{13}H_{15}NO_3$, C 66.95, H 6.44, N 6.01; found C 66.87, H 6.39, N 5.92.

ii) ***trans*-Indane-1,2-dicarboxylic acid (91).**

Aqueous sodium hydroxide (25 mL, 15% w/v) was added to a one-necked round-bottomed flask containing 0.52g (2 mmol) of 1,2-bis-(*N,N'*-dimethylcarboxamido)indane (**78**) and the mixture was refluxed for 8 h. It was then cooled to 0°C and extracted once with methylene chloride to remove any unreacted **78**. The aqueous layer was then acidified (dropwise) with conc HCl and then extracted several times with methylene chloride. The organic extracts were combined, washed with aqueous sodium chloride (10 mL, 2% w/v) and dried. Removal of the solvent *in vacuo* afforded 0.15g (70%) of a white solid that was identified as *trans*-indane-1,2-dicarboxylic acid (**91**) **mp.** 226°C (lit. mp. 228°C[62ii]); **^{1}H-NMR**: δ 3.18 (dd, 1H, Ar-C$\underline{H}_2$-), 3.35 (dd, 1H, Ar-C$\underline{H}_2$-), 3.76 (dd, 1H, Ar-CH$_2$-C$\underline{H}$-COOH), 4.41 (d, 1H, Ar-C$\underline{H}$-COOH), 7.16-7.28 (complex pattern, 3H, aromatic CH), 7.48 (t, 1H, aromatic CH); **^{13}C-NMR**: δ 35.9 (CH_2), 46.9 (CH), 53.7 (CH), 125.0 (CH), 125.1 (CH), 127.7 (CH), 128.4 (CH), 140.2 (C), 142.5 (C), 173.6 (CO), 175.1 (CO); **Mass Spectrum** (70 eV, m/e, rel. int.): 206 (1, M^+), 188 (16), 160 (50), 133 (10), 116 (100), 91 (14), 77 (12), 63 (15).

2.7. Preparation of Succinimido[3,4-b]-indane (61).

i) From *trans*-indane-1,2-dicarboxylic acid (**91**).

The conversion of **91** into **61** was accomplished via the anhydride **92** and the amic acids **95** and **96** in the following way (see Scheme 23, pp). The anhydride **92** was first prepared by the method of Cook and Preston[62ii]. Thus, *trans*-indane-1,2-dicarboxylic acid, **91** (0.21g, 1 mmol) was refluxed with acetyl chloride (5 mL) for 6 h under a nitrogen atmosphere. The acetyl chloride was then removed *in vacuo* and the crude anhydride distilled under reduced pressure, to give 0.08g (44%) of indane-1,2-dicarboxylic acid anhydride (**92**): **mp** 97°C (lit.mp 97-98°C[62ii]).

This was then treated without further purification with a saturated ethereal solution of ammonia (20mL). After stirring for 3 h, the solution was evaporated *in vacuo* to give a white solid, which was identified as a mixture of the amic acids **95** and **96**: **Mass Spectrum** (70eV, m/e, rel. int.): 205 (2, M^+), 188 (11), 116 (100), 89 (12), 63 (15), 58 (10).

This was then dehydrated by heating with P_2O_5. After work-up, the crude product was filtered through a plug of silica gel, to afford 0.03g (37%) of pure succinimido[3,4-b]indane (**61**) **mp**: 103°C; **^{1}H-NMR**: δ 3.43 (dd, 2H, Ar-CH_2), 3.69 (m, 1H, Ar-CH_2-CH), 4.38 (d, 1H, Ar-CH), 7.29 (complex pattern, 3H, three aromatic CH), 7.55 (d, 1H, aromatic CH), 8.55 (bs, 1H, NH); **^{13}C-NMR**: δ 34.41 (CH_2), 45.04 (CH), 53.01 (CH), 125.09 (CH), 127.55 (CH), 128.81 (CH), 130.22 (CH), 136.93 (C), 141.14 (C), 177.48 (CO), 180.15 (CO); **Mass Spectrum** (70eV, m/e, rel. int.): 187 (45, M^+), 116 (100), 115 (35), 84 (25), 63 (10), 58 (12); **Elemental Analysis** Calcd. for $C_{11}H_9NO_2$: C 70.58, H 4.81, N 7.49; Found C 70.63, H 4.89, N 7.53.

ii) From *trans*-1-(*N,N'*-dimethylcarboxamido)indane-2-carboxylic acid (**93**).

The conversion of 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)butanamide (**87**) to 2-(*o*-iodobenzyl)succinimide (**99**) (see Scheme 28, pp) was undertaken as a model reaction to test the feasibility of the proposed conversion of **97** into **61** (see Scheme 25, pp 64). Solid **87** (0.4g; 1.11mmol) was added to a suspension of sodium hydride (0.03g; 1.11mmol) in freshly distilled 1,2-dimethoxyethane (25 mL) in a 100 mL, three-necked, round bottomed flask under a blanket of nitrogen. The reaction mixture was then refluxed for 18 h, after which it was cooled to room temperature before addition of an aqueous solution of ammonium chloride (10 mL; 10% w/v). Concentrated hydrochloric

acid (1 mL) was then added and the mixture was separated after vigorous shaking. The aqueous layer was further extracted several times with methylene chloride. The combined organic extracts were washed with aqueous sodium chloride (10 mL, 2% w/v) and dried. Removal of the solvent *in vacuo* afforded a white solid that was identified as 2-(*o*-iodobenzyl)succinimide (**99**). Upon recrystallization from chloroform/hexane, 0.33g (93%) of pure **99** was obtained. **mp** 133°C; **^{1}H-NMR**: δ 2.52-2.62 (dd, 1H, $C\underline{H}_2$-CO), 2.7-2.8 (dd, 1H, $C\underline{H}_2$-CO), 2.92-3.01 (dd, 1H, Ar-$C\underline{H}_2$), 3.29-3.40 (m, 1H, Ar-CH_2-$C\underline{H}$), 3.41-3.5 (dd, 1H, Ar-$C\underline{H}_2$), 6.95 (t, 1H, aromatic CH), 7.21 (d, 1H, aromatic CH), 7.21 (t, 1H, aromatic CH), 7.86 (d, 1H, aromatic CH), 8.63 (bs, 1H, NH); **^{13}C-NMR**: δ 34.91 (CH_2), 41.01 (CH_2), 41.96 (CH), 100.95 (CI), 128.82 (CH), 128.99 (CH), 130.02 (CH), 140.01 (CH), 140.09 (C), 176.48 (CO), 179.08 (CO); **Elemental analysis** Calc for $C_{11}H_{10}INO_2$: C 41.90, H 3.17, N 4.44; Found C 42.01, H 3.26, N 4.52.

The proposed transformation of *trans*-1-(*N,N*-dimethylcarboxamido)indane-2-carboxamide (**97**) to succinimido[3,4-b]indane (**61**) involved the initial preparation of **97** from *trans*-1-(*N,N'*-dimethylcarboxamido)indane-2-carboxylic acid (**93**), which was undertaken in the following way. An ethereal solution of **93** (0.4 g, 1.72 mmol; 25 mL ether) was added dropwise from a pressure-equalizing addition funnel to a 100 mL, three-necked, round bottomed flask charged with thionyl chloride (0.3 g; 2.58 mmol). A water trap was used for absorbing the acidic fumes (HCl) evolved during the reaction. The reaction mixture was heated in a hot water bath for 2 h. A saturated ethereal solution of ammonia was then added slowly to the cooled reaction mixture until further addition did not result in evolution of white fumes. The reaction mixture was cooled again and washed, first with aqueous sodium bicarbonate (10 mL, saturated) and then with aqueous sodium

chloride (10 mL, 2% w/v). The ethereal layer was dried before being evaporated *in vacuo* to give a white solid that was identified as **97**. Recrystallization from chloroform/hexane afforded 0.36 g (89%) of *trans*-1-(*N,N*-dimethylcarboxamido)indane-2-carboxamide (**97**) **mp**: 171°C; **^{1}H-NMR**: δ 3.10 (s, 3H, N-CH_3), 3.18 (dd, 1H, Ar-C$\underline{H}_2$), 3.31 (s, 3H, N-CH_3), 3.36 (dd, 1H, Ar-C$\underline{H}_2$), 4.04 (dd, 1H, Ar-CH_2-C$\underline{H}$-), 4.71 (d, 1H, Ar-C$\underline{H}$-), 6.68 (bs, 1H, NH_2), 6.85 (bs, 1H, NH_2), 7.04 (d, 1H, aromatic CH), 7.12-7.23 (complex pattern, 3H, three aromatic CH); **Mass Spectrum** (70eV, m/e, rel. int.): 232 (22, M^+), 214 (6), 188 (14), 160 (4), 149, (15), 115 (28), 72 (100).

The transformation of *trans*-1-*N,N*-(dimethylcarboxamido)indane-2-carboxamide (**97**) into succinimido[3,4-b]indane (**61**) was attempted under a variety of reaction conditions. A description of these experiments is presented below.

With sodium hydride in 1,2-dimethoxyethane

Solid *trans*-1-(*N,N*-dimethylcarboxamido)indane-2-carboxamide (**97**) (0.4 g; 1.72 mmol) was added to a suspension of 0.045 g (0.075 g of a 60% disp. in oil, 1.89 mmol) of sodium hydride in freshly distilled 1,2-dimethoxyethane (25 mL) in a three-necked round-bottomed flask under a blanket of nitrogen. The reaction mixture was then refluxed for 18 h, after which it was cooled to room temperature before addition of an aqueous solution of ammonium chloride (10 mL; 10%w/v). Concentrated hydrochloric acid (1 mL) was then added and the mixture was separated after vigorous shaking. The aqueous layer was further extracted several times with methylene chloride. The combined organic extracts were washed with aqueous sodium chloride (10 mL, 2% w/v), and dried. Removal of the solvent *in vacuo* afforded a solid that was identified from its ^{1}H-NMR spectrum as a 1: 4 mixture of the imide **61** and unreacted **97**.

With sodium hydride in 1,2-dimethoxyethane, extended reaction time

The above procedure was repeated with a modification: the reaction mixture was refluxed for 48 h. The crude product was identified as a 1:3 mixture of **61** and unreacted **97** from its ^{1}H-NMR spectrum.

With sodium hydride in toluene

Solid *trans*-(1-*N*,*N*-dimethylcarboxamido)indane-2-carboxamide (**97**) (0.4 g; 1.72 mmol) was added to a suspension of 0.045 g (0.075 g of a 60% disp. in oil, 1.89 mmol) of sodium hydride in toluene (25 mL) in a three-necked round bottomed flask under a blanket of nitrogen and refluxed for 48 h. The product obtained after work-up similar to that described above was found to be a 1:2.5 mixture of **61** and unreacted **97** from its ^{1}H-NMR spectrum.

2.8. 2-(*o*-Iodobenzyl)succinimide (99) from Succinimide (100).

i) Succinimide (**100**) (0.50 g, 5 mmol) was added to a solution of KNH_2 (11 mmol; from 0.43 g of potassium metal) in NH_3(l) (200 mL) and stirred for 40 min. *o*-Iodobenzyl chloride (**76**) (1.26 g, 5 mmol) dissolved in ether (15 mL) was then added dropwise (7 min, pressure-equalizing addition funnel) and the reaction mixture was stirred for 0.5 h before quenching with solid ammonium chloride (1.8 g). Standard work-up followed by evaporation of the solvent *in vacuo* gave a viscous oil, which was then separated by flash chromatography (gradient elution with 0-2% methanol in methylene chloride) to give 0.53g (34%) of 2-(*o*-odobenzyl)succinimide (**99**) along with 0.25g (23%) of *trans*-2,2'-diiodo- stilbene (**85**).

ii) Succinimide (**100**) (0.50 g; 5 mmol) was added to a solution of $LiNH_2$ (11 mmol; from 0.43 g of lithium wire) in NH_3(l) (250 mL). The mixture was stirred while cooling to -60°C using a Dry Ice-chloroform cooling bath (40 min). *o*-Iodobenzyl chloride (**76**) (1.26 g; 5 mmol) dissolved in ether (30 mL) was then added dropwise (15 min, addition funnel), taking care to maintain the temperature of the reaction mixture below -50°C, and the reaction mixture was stirred (-55°C) for an additional 0.5 h. Standard work-up followed by evaporation of the solvent *in vacuo* gave a viscous oil, which was then separated by flash chromatography (gradient elution with 0-2% methanol in methylene chloride), affording 0.79g (50%) of **96** along with 0.19g (18%) of **85**.

2.9. 2-(*o*-Iodobenzyl)-succinimide (99) from *N,N,N',N'*-Tetramethyl succinamide (73) via 3-(*N,N*-Dimethylcarboxamido)-4-(*o*-iodophenyl)butanamide (87).

i) To a solution of $LiNH_2$ (44 mmol, from 0.3g of lithium metal) in NH_3(l) (500 mL) in a 1 L, three-necked, round-bottomed flask equipped with a dry-ice condensor and a thermometer was added solid *N,N,N',N'* -tetramethylsuccinamide (**73**) (3.44g, 20 mmol) (entry 6). The mixture was stirred while cooling to -60°C using a Dry Ice-chloroform cooling bath. After stirring for 40 min to permit complete formation of the dianion, 5.05 g (20 mmol) of *o*-iodobenzyl chloride (**76**) dissolved in ether (150 mL) was added dropwise from a pressure-equalizing addition funnel, adjusting the rate of addition so that the temperature of the reaction mixture was maintained below -50°C (approximately 0.5 h for the entire addition). After stirring at -55°C for an additional 1 h, the reaction mixture was warmed to -33°C and stirred for a further 2h before pouring over solid ammonium chloride (7g) contained in a large beaker. The NH_3(l) was evaporated on a steam cone while being replaced with ether. After shaking with water (25 mL), the ethereal layer was separated;

the aqueous layer was then (further) extracted several times with methylene chloride. The organic extracts were combined, dried and the solvent removed *in vacuo*. The oily brown residue was triturated with ether (20 mL), when **87** separated out as a white solid. Filtration, followed by recrystallization from chloroform/hexane yielded shiny white crystals of 3-(*N,N*-dimethylcarboxamido)-4-(*o*-iodophenyl)butanamide (**87**) (6.48g, 90%). The ether extract yielded 0.26g (6%) of almost pure **85**.

ii) Solid **87** (4g; 11.1mmol) was added to a suspension of sodium hydride (0.3g; 11.1mmol) in freshly distilled dimethoxyethane (150 mL) in a three-necked round-bottomed flask under a blanket of nitrogen. The reaction mixture was then refluxed for 18 h, after which it was cooled to room temperature before addition of an aqueous solution of ammonium chloride (100 mL; 10% w/v). Subsequent work-up similar to that described in Section 2.7.ii) afforded 3.2g (91%) of 2-(*o*-odobenzyl)succinimide (**99**).

2.10. Studies of the Cyclization of 2-(*o*-Iodobenzyl)succinimide (99) to Succinimido[3,4-b]indane (61).

Several experiments were carried out to ascertain the optimum conditions for the cyclization of 2-(*o*-odobenzyl)succinimide (**99**) to succinimido[3,4-b]indane (**61**). The procedure that emerged from this study as the most efficient is described first, followed by a description of the remainder of the experiments according to their order of entry in Table V. All reactions were carried out in NH_3(l) in accordance with the general procedure described previously.

i) To a solution of KNH_2 (13.2 mmol, from 0.52g of potassium metal) in $NH_3(l)$ (400 mL) was added 0.95g (3 mmol) of 2-(*o* -iodobenzyl)succinimide (**99**) (entry 6). The reaction mixture was stirred under irradiation for 1 h and quenched with solid ammonium chloride (2.5g). After evaporation of $NH_3(l)$ followed by standard work-up, a yellow oil was obtained, which upon flash chromatographic separation (2% methanol in methylene chloride as the eluant) afforded 0.22g (40%) of succinimido[3,4-b]indane (**61**) along with 0.17g (30%) of 2-benzylsuccinimide (**102**).

ii) To a solution of KNH_2 (8 mmol, from 0.31g of potassium metal) in $NH_3(l)$ (200 mL) was added 0.32g (1 mmol) of 2-(*o* -iodobenzyl)succinimide (**99**) (entry 1). The reaction mixture was stirred under irradiation for 1 h and quenched with solid ammonium chloride (0.8g). After evaporation of $NH_3(l)$ followed by standard work-up, a yellow oil was obtained, which, upon flash chromatographic separation (2% methanol in methylene chloride as the eluant), afforded 0.07g (40%) of **61** along with 0.05g (30%) of **102**.

iii) To a solution of KNH_2 (3.3 mmol, from 0.13g of potassium metal) in $NH_3(l)$ (200 mL) was added 0.32g (1 mmol) of 2-(*o* -iodobenzyl)succinimide (**99**) (entry 2). The reaction mixture was irradiated for 3 h and quenched with solid ammonium chloride (0.35g). After evaporation of $NH_3(l)$ followed by standard work-up, a viscous yellow oil was obtained, which was found to consist predominantly of unreacted **99**. Filtration through a plug of silica gel enabled recovery of 0.26g (82%) of **99**.

iv) To a solution of KNH_2 (8 mmol; from 0.31g of potassium metal) in $NH_3(l)$ (200 mL) was added 0.32g (1 mmol) of 2-(*o* -iodobenzyl)succinimide (**99**) (entry 3). The reaction mixture was stirred under irradiation for 0.5 h and quenched with solid ammonium

chloride (0.8g). After evaporation of NH_3(l) followed by standard work-up, a yellow oil was obtained. Upon flash chromatographic separation (2% methanol in methylene chloride as the eluant) 0.08g (41%) of **61** was obtained along with 0.05g (30%) of 2-benzylsuccinimide (**102**).

v) To a solution of KNH_2 (8 mmol; from 0.1g of potassium metal) in NH_3(l) (75 mL) was added 0.1g (1 mmol) of 2-(*o* -iodobenzyl)succinimide (**99**) (entry 4). The reaction mixture was stirred in the dark for 0.5 h and quenched with solid ammonium chloride (0.25g). After evaporation of NH_3(l) followed by standard work-up, a light yellow oil was obtained, which was found by ^{1}H-NMR to consist of a 1:7 ratio of **61** and unreacted **99**.

vi) To a solution of KNH_2 (8 mmol; from 0.1g of potassium metal) in NH_3(l) (75 mL) was added 0.1g (1 mmol) of 2-(*o* -iodobenzyl)succinimide (**99**) (entry 5). The reaction mixture was stirred in the dark for 6 h and quenched with solid ammonium chloride (0.25g). Evaporation of NH_3(l) followed by standard work-up, afforded a light yellow oil, which was found by ^{1}H-NMR to consist of a 1:4 ratio of **61** and unreacted **99**.

vii) To a solution of KNH_2 (13.2 mmol; from 0.52 g of potassium metal) in NH_3(l) (400 mL) was added 0.95g (3 mmol) of 2-(*o*-iodobenzyl)succinimide (**99**) (entry 6). The reaction mixture was irradiated for 1 h and quenched with solid ammonium chloride (2.5g). After evaporation of NH_3(l) followed by standard work-up, a yellow oil was obtained, which, upon flash chromatographic separation (2% methanol in methylene chloride as the eluant), afforded 0.16g (28%) of **61** along with 0.10g (17%) of **102** and 0.21g (22%) of unreacted **99**.

2.11. Studies of the Attempted Preparation of Succinimido[3,4-b]indane-8-carbonitrile (83) from *o*-Bromophenylacetonitrile (103) and Maleimide (104).

i) Attempted "one-pot" synthesis of succinimido[3,4-b]indane-8-carbonitrile (**83**) via tandem Michael-$S_{RN}1$ reactions:

With one equivalent of potassium amide

o-Bromophenylacetonitrile (**103**) (0.49g, 2.5 mmol) was added to a solution of KNH_2 (2.75 mmol; from 0.11g of potassium metal) in $NH_3(l)$ (150 mL) and stirred for 0.25 h. Maleimide (**104**) (0.24g, 2.5 mmol) was then added portionwise, during which time the reaction mixture was irradiated. After additional irradiation for 3 h, the reaction mixture was neutralized with ammonium chloride (0.45g). Evaporation of $NH_3(l)$ was followed by the addition of ice (10g) and concentrated hydrochloric acid (2 mL). During extraction with methylene chloride, a white solid separated out, which was identified as 3-(*o*-bromo-α-cyanobenzyl)-succinimide (**82**). Filtration of this solid, followed by recrystallization from chloroform/hexane afforded white crystals of pure **82** (0.21g). Meanwhile, the filtrate was separated and the aqueous layer extracted further with methylene chloride. After drying the combined organic extracts, the solvent was removed *in vacuo* to give a suspension of a white solid in a yellow oil. Upon trituration with chloroform/hexane (3:1), a white solid separated out, which was filtered and identified as **82**. The filtrate yielded a brown oil that was found to consist of a complex mixture. No succinimido[3,4-b]indane-8-carbonitrile (**83**) was detected (Scheme 32). A total of 0.45g (62%) of **82** was obtained from this experiment.

3-(*o*-Bromo-α-cyanobenzyl)succinimide (82): mp 210-211°C; **^{1}H-NMR:** δ 1.81 (d, 2H, CH_2), 2.77 (m, 1H, CH_2-C<u>H</u>), 4.18 (d, 1H, Ar-CH-CN), 6.52 (t, 1H, aromatic CH), 6.63 (t, 1H, aromatic CH), 6.79 (d, 1H, aromatic CH), 6.89 (d, 1H,

aromatic CH-Cl), 10.73 (bs, 1H, NH); **^{13}C-NMR:** δ 31.99 (CH_2), 37.08 (CH), 43.09 (CH), 117.7 (C-Br), 122.41 (CN), 128.31 (CH), 129.22 (CH), 130.51 (CH), 132.09 (C), 133.08 (CH), 176.31 (CO), 177.18 (CO); **Mass Spectrum** (70eV, m/e, rel. int.): 194 (3, M^+), 293 (4, M^+), 213 (100), 196 (80), 140 (65), 115 (100), 88 (65), 75 (53), 63 (82); **Elemental Analysis** Calcd. for $C_{12}H_9BrN_2O_2$: C 49.15, H 3.07, N 9.56; Found C 48.95, H 3.12, N 9.49.

With three equivalents of potassium amide

o-Bromophenylacetonitrile (**103**) (0.49g, 2.5 mmol) was added to a solution of KNH_2 (8.25 mmol; from 0.33g of potassium metal) in NH_3(l) (150 mL) and stirred for 0.25 h. Maleimide (**104**) (0.24g, 2.5 mmol) was then added portionwise, during which time the reaction mixture was irradiated. After additional irradiation for 3 h, the reaction mixture was neutralized with ammonium chloride (1.3g). Evaporation of NH_3(l) was followed by the addition of ice (20g) and concentrated hydrochloric acid (3 mL). During extraction with methylene chloride, a white solid separated out, which was identified as **82**. After work-up similar to that described above, a total of 0.29g (40%) of **82** was obtained; again, no succinimido[3,4-b]indane-8-carbonitrile (**83**) was detected.

ii) Attempted two-step synthesis of succinimido[3,4-b]indane-8-carbonitrile (**83**).

Preparation of the Michael adduct, 3-(o-bromo-α-cyanobenzyl)-succinimide (82).

o-Bromophenylacetonitrile (**103**) (3.92g, 20 mmol) was added to a solution of KNH_2 (22 mmol; from 0.88g of potassium metal) in NH_3(l) (500 mL) and stirred for 0.5 h.. Maleimide (**104**) (1.94g, 20 mmol) was then added portionwise. After stirring for 1h, the reaction mixture was neutralized with ammonium chloride (3.6g). Work-up similar to

that described above, followed by recrystallization of the crude **82** from chloroform/hexane afforded 4.89g (83%) of 3-(*o*-bromo-α-cyanobenzyl)succinimide (**82**).

Attempted cyclization of 3-(o-bromo-α-cyanobenzyl)succinimide (82).

3-(*o*-Bromo-α-cyanobenzyl)succinimide (**82**) (0.5g, 1.71mmol) was added to a solution of KNH_2 (13.65 mmol; from 0.53g of potassium metal) in NH_3(l) (300 mL) and irradiated for 0.5 h. after which the reaction mixture was neutralized with ammonium chloride (1.8g). Standard work-up gave a brown solid, which, upon purification by flash chromatography (2.5 % methanol in methylene chloride), afforded white crystals of **107**. Further purification by crystallization from acetone/water gave 0.27g (75%) of 3-(α-cyano-α-phenylmethyleno)succinimide (**107**): **mp** 205-206°C; **^{1}H-NMR** (*d*-6 DMSO): δ 3.69 (s, 2H, -C<u>H</u>$_2$-CO), 7.53-7.59 (complex pattern, 3H, aromatic C-CH-C<u>H</u>-C<u>H</u>-C<u>H</u>-CH-), 7.65-7.67 (two overlapping d, 2H, aromatic C-C<u>H</u>-CH-CH-CH-C<u>H</u>-); **^{13}C-NMR** (*d*-6 DMSO): δ 36.33 (CH_2), 113.21 (C), 115.95 (C), 127.98 (double intensity, two CH), 128.58 (double intensity, two CH), 130.23 (CH), 132.19 (C), 141.76 (C), 168.03 (CO), 173.15 (CO); **Mass Spectrum** (70eV, m/e, rel. int.): 212 (19, M^+), 183 (2), 169 (2), 156 (2), 141 (100), 114 (50), 102 (12), 88 (28), 75 (25), 70 (12), 63 (62), 57 (11); **Elemental analysis** Calcd. for $C_{12}H_8N_2O_2$: C 67.92, H 3.77, N 13.21; Found C 67.93, H 3.83, N 13.13.

2.12. Preparation of 3-(*o*-Iodobenzyl)glutarimide (108).

i) With sodium amide in liquid ammonia.

Glutarimide (**109**) (3.39 g; 30 mmol) was added to a solution of $NaNH_2$ (66 mmol; from 1.52 g of sodium metal) in NH_3(l) (400 mL) and stirred for 30 min.

o-Iodobenzyl chloride (**76**) (8.33 g; 33 mmol) dissolved in ether (90 mL) was then added dropwise (20 min, addition funnel) and the reaction stirred for 0.5 h before quenching with solid ammonium chloride (15 g). Evaporation of NH_3(l) was followed by the addition of ice (100g) and concentrated hydrochloric acid (10 mL). During extraction with methylene chloride, a white solid separated out, which was identified as 3-(*o*-odobenzyl)glutarimide (**108**). Filtration of this solid, followed by recrystallization from methanol/water afforded white crystals of **108**. Meanwhile, the filtrate was separated and the aqueous layer extracted further with methylene chloride. After drying the combined organic extracts, the solvent was removed *in vacuo*, giving a suspension of a white solid in a yellow oil. Upon trituration with chloroform/hexane (3:1 v/v, 16 ml), a small quantity of white solid separated out, which was filtered and identified as **108**. The filtrate yielded a viscous brown oil upon evaporation that was found to consist almost enirely of *trans*-2,2'-diiodostilbene (**85**) (1.85g, 26%, after filtration through a plug of silica gel). A total of 4.15g (42%) of 3-(*o*-odobenzyl)glutarimide (**108**) was obtained from this experiment: **mp** 110°C; **^{1}H-NMR** (*d*-6 DMSO): δ 1.69 (m, 2H, CH-C$\underline{H_2}$-CH_2), 2.08 (m, 1H, CH-CH_2-C$\underline{H_2}$), 2.19 (m, 1H, CH-CH_2-C$\underline{H_2}$), 2.61 (m, 1H, Ar-CH_2-C$\underline{H}$), 2.73 (m, 1H, Ar-C$\underline{H_2}$), 2.92 (m, 1H, Ar-C$\underline{H_2}$), 6.97 (t, 1H, aromatic CH), 7.24 (t, 1H, aromatic CH), 7.31 (d, 1H, aromatic CH), 7.81 (d, 1H, aromatic CH); **Mass Spectrum** (70eV, m/e, rel. int., CI): 330 (100, $(M+1)^+$), 204 (70), 176 (18), 130 (45), 112 (25), 85 (15); **Elemental analysis** Calcd. for $C_{12}H_{12}INO_2$ C 43.77, H 3.65, N 4.25; Found C 43.66, H 3.68, N 4.32.

ii) With lithium amide in liquid ammonia.

Glutarimide (**109**) (2.26 g; 20 mmol) was added to a solution of $LiNH_2$ (44 mmol; from 0.31 g of lithium wire) in NH_3(l) (250 mL). The mixture was stirred while cooling

to -60°C using a Dry Ice-chloroform cooling bath (40 min). *o*-Iodobenzyl chloride (**76**) (5.05 g; 20 mmol) dissolved in ether (60 mL) was then added dropwise (15 min, pressure-equalizing addition funnel), taking care to maintain the temperature of the reaction mixture below -50°C, and stirred (-55°C) for an additional 0.5 h before quenching with solid ammonium chloride (10 g). Work-up similar to that described above in i) gave 3.16g (48%) of **108** along with 0.82g (19%) of **85**.

2.13. Studies of the Attempted Preparation of 1,2,3,4,5,6-Hexahydro-1,5-methano-3-benzazocine-2,4-dione (62) from 3-(*o*-Iodobenzyl)-glutarimide (108).

i) With potassium amide in liquid ammonia.

3-(*o*-Iodobenzyl)-glutarimide (**108**) (0.99g, 3 mmol) was added to a solution of KNH_2 (24 mmol; from 0.94g of potassium metal) in NH_3(l) (250 mL) and irradiated for 3 h, after which the reaction mixture was neutralized with ammonium chloride (4.2g). During subsequent partitioning of the crude product mixture between water and methylene chloride, a light brown solid separated, which was filtered and identified as unreacted **108** (0.79g) from its ^{1}H-NMR spectrum. The methylene chloride extract was evaporated *in vacuo* to give a dark brown viscous oil that was found to consist predominantly of 3-benzylglutarimide (**112**) (0.09g; spectral properties match those of independently prepared sample).

ii) With lithium diisopropylamide in tetrahydrofuran.

To a solution of lithium diisopropylamide (8 mmol), generated *in situ* from diisopropylamine (0.81g, 8 mmol) and *n*-butyllithium (3.56mL, 8 mmol, 2.25M in hexane), in tetrahydrofuran (120 mL) at -78°C was added a cold solution of **108** (0.33g,

1 mmol, 50 mL THF) (entry 12). The temperature of the reaction mixture was then maintained between -30°C and -35°C while being stirred under photostimulation for 3 h, after which time it was quenched with a solution of ammonium chloride (10 mL; 7.5% w/v) and extracted several times with methylene chloride. During subsequent partitioning with methylene chloride, a light brown solid separated, which was filtered and identified as unreacted **108** (0.26g) from its ^{1}H-NMR spectrum. The methylene chloride extract was evaporated *in vacuo* to give 0.05g of a dark brown viscous oil that was again found to consist predominantly of 3-benzylglutarimide (**112**).

2.14. Preparation of *N,N,N',N'*-Tetramethylglutaramide (79).

An ethereal solution of dimethyl amine was obtained by the exhaustive extraction of an aqueous solution of dimethylamine (40% w/v, 60 mL, 530 mmol) with ether (3 x 20 mL, followed by 4 x 10 mL); the combined ether extract was dried twice over sodium sulfate. To a three-necked round-bottomed flask charged with this solution was added an ethereal solution of glutaryl dichloride (7.75g, 50 mmol, 25 mL ether) dropwise, using a pressure-equalizing addition funnel to adjust the rate of addition, thereby controlling the vigorous reaction that ensued. The vapors of hydrochloric acid that were liberated during the reaction were absorbed in a water-trap. After stirring for 0.5 h, the reaction mixture was shaken with a saturated solution of sodium bicarbonate and separated. The ethereal extract was then dried and evaporated to give 8.05 g of **79**. Recrystallization of the crude product from ether gave 7.35g (79%) of pure *N,N,N',N'*-tetramethylglutaramide (**79**): **^{1}H-NMR**: δ 1.96 (m, 2 H, CH_2-C$\underline{H_2}$-CH_2), 2.43 (t, 4H, C$\underline{H_2}$-CH_2-C$\underline{H_2}$), 2.95 (s, 6H, two N-CH_3s), 3.04 (s, 6H, two N-CH_3s); **^{13}C-NMR**: δ 20.79 (CH_2), 32.51 (double intensity, two CH_2s), 35.29 (double intensity, two N-CH_3), 37.25 (double intensity, two

N-CH_3), 172.88 (two CO); **Mass Spectrum** (70eV, m/e, rel. int.): 186 (36, M^+), 149 (20), 142 (42), 114 (66), 100 (58), 87 (57), 72 (100), 55 (20).

2.15. Studies of the Alkylation of *N,N,N',N'*-Tetramethylglutaramide (79). Preparation of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (80).

A series of experiments were carried out to determine the optimum conditions for the preparation of 2-(*o* -iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) by the monoalkylation of *N,N,N',N'*-tetramethylglutaramide (**79**) with *o*-iodobenzyl chloride (**76**) (Table VI). They are described below according to their order of entry in Table VI.

i) *N,N,N',N'*-Tetramethylglutaramide (**79**) (0.93g, 5 mmol) was added to a solution of $LiNH_2$ (11 mmol; from 0.076g of lithium wire) in NH_3(l) (150 mL) (entry 1). The mixture was stirred while cooling to -60°C using a Dry Ice-chloroform cooling bath (40 min). *o*-Iodobenzyl chloride (**76**) (1.38 g; 5.5 mmol) dissolved in ether (20 mL) was then added dropwise (15 min, addition funnel), taking care to maintain the temperature of the reaction mixture below -50°C, and stirred (-55°C) for an additional 1 h before quenching with solid ammonium chloride (3 g). Standard work-up yielded a viscous yellow oil which upon separation by flash chromatography (gradient elution with 0-2% methanol in methylene chloride) afforded 0.9g (45%) of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) along with 0.34g (22%) of the 2,4-*bis*-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide **113** and 0.13g (12%) of *trans*-2,2'-diiodostilbene **85**.

2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (80): mp: 110°C

^{1}H-NMR: δ 1.79 (m, 1H,), 1.95 (m, 1H), 2.15 (m, 1H), 2.34 (m, 1H), 2.59 (s, 3H), 2.77 (s, 3H), 2.79 (dd, 1H), 2.87 (s, 3H), 2.88 (dd, 1H), 2.95 (s, 3H), 3.22 (m, 1H), 6.81 (t, 1H), 7.11 (t, 1H), 7.14 (d, 1H), 7.7 (d, 1H); **^{13}C-NMR**: δ 27.7 (CH2), 30.61

(CH2), 35.5 (CH3), 37.0 (CH3), 37.21 (CH3), 40.01 (CH), 43.5 (CH2), 100.9 (CI), 128.02 (CH), 128.1 (CH), 130.52 (CH), 139.5 (CH), 142.0 (C), 172.53 (CO), 174.60 (CO); **Mass Spectrum** (70eV, m.e, rel. int.): 402 (7, M^+), 358 (8), 329 (20), 316 (18), 302 (32), 275 (40), 230 (15), 217 (15), 188 (22), 176 (20), 149 (15), 140 (22), 131 (10), 116 (15), 100 (12), 84 (100), 72 (90), 55 (20); **Elemental Analysis** Calcd. for $C_{16}H_{23}IN_2O_2$: C 47.76, H 5.72, N 6.96; Found C 47.83, H 5.77, N 6.90.

2,4-*bis*-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (113): mp: 126°C; **^{1}H-NMR**: δ 1.82 (m, 1H, CO-C$\underline{H}_2$-CO), 2.25 (m, 1H, CO-C$\underline{H}_2$-CO), 2.62 (s, 6H, two CH_3), 2.80 (s, 6H, two CH_3), 2.89 (m, 4H, two Ar-CH_2), 3.29 (m, 2H, two Ar-CH_2-C$\underline{H}$), 6.91 (t, 2H, two aromatic CH), 7.19 (t, 2H, two aromatic CH), 7.22 (d, 2H, two aromatic CH), 7.79 (d, 2H, two aromatic CH); **^{13}C-NMR**: δ 36.78 (CH_3), 36.81 (CH_2), 38.0 (CH_3), 39.1 (CH), 44.71 (CH_2), 100.62 (C-I), 128.5 (CH), 128.6 (CH), 131.4 (CH), 139.8 (CH), 142.5 (C), 172.2 (CO), 174.6 (CO); **Mass Spectrum** (70eV, m.e, rel. int.): 618 (20, M^+), 574 (18), 546 (21), 491 (90), 446 (32), 418 (10), 374 (26), 303 (55), 246 (15), 217 (35), 188 (30), 116 (22), 84 (24), 72 (100); **Elemental Analysis** Calcd. for $C_{23}H_{28}I_2N_2O_2$: C 44.66, H 4.53, N 4.53; found C 44.60, H 4.73, N 4.43.

ii) *N,N,N',N'*-tetramethylglutaramide (**79**) (0.23g, 1.25 mmol) was added to a solution of $LiNH_2$ (2.75 mmol; from 0.019g of lithium wire) in NH_3(l) (50 mL) (entry 2). The mixture was stirred while cooling to -78°C (30 min). *o*-Iodobenzyl chloride (**76**) (0.34 g; 1.37 mmol) dissolved in ether (10 mL) was then added dropwise (7 min, pressure-equalizing addition funnel), taking care to maintain the temperature of the reaction mixture below -70°C, and stirred (-78°C) for an additional 1 h before quenching with solid

ammonium chloride (0.8 g). Standard-work-up yielded a viscous yellow oil which was found by ^{1}H-NMR to consist predominantly of unreacted **79** and **76**, along with traces of **80**.

iii) *N,N,N',N'*-tetramethylglutaramide (**79**) (0.23g, 1.25 mmol) was added to a solution of $LiNH_2$ (2.75 mmol; from 0.019g of lithium wire) in NH_3(l) (50 mL) (entry 2). The mixture was stirred for 0.5 h; *o*-iodobenzyl chloride (**76**) (0.34 g; 1.37 mmol) dissolved in ether (10 mL) was then added dropwise (7 min, pressure-equalizing addition funnel), taking care to maintain the temperature of the reaction mixture below -70°C, and stirred (-78°C) for an additional 1 h before quenching with solid ammonium chloride (0.8 g). Standard work-up yielded a viscous yellow oil which was separated by flash chromatography (gradient elution with 0-2% methanol in methylene chloride) to give 0.17g (34%) of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) along with 0.09g (23%) of the dialkylated derivative **113** and 0.06g (20%) of **85**.

iv) *N,N,N',N'*-tetramethylglutaramide (**79**) (0.23g, 1.25 mmol) was added to a solution of KNH_2 (2.75 mmol; from 0.11g of potassium metal) in NH_3(l) (50 mL) (entry 4). The mixture was stirred while cooling to -60°C (30 min). *o*-Iodobenzyl chloride (**76**) (0.34 g; 1.37 mmol) dissolved in ether (10 mL) was then added dropwise (7 min, addition funnel), taking care to maintain the temperature of the reaction mixture below -50°C, and stirred (-55°C) for an additional 1 h before quenching with solid ammonium chloride (0.8 g). Standard work-up yielded a viscous yellow oil which was separated by flash chromatography (gradient elution with 0-2% methanol in methylene chloride) to give 0.15g (30%) of 2-(*o* -iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) along with 0.10g (25%) of the dialkylated derivative **113** and 0.06g (20%) of **85**.

v) *N,N,N',N'*-tetramethylglutaramide (**79**) (0.23g, 1.25 mmol) was added to a solution of KNH_2 (2.75 mmol; from 0.11g of potassium metal) in NH_3(l) (50 mL) (entry 5). The mixture was stirred while cooling to -78°C (30 min); *o*-iodobenzyl chloride (**76**) (0.34 g; 1.37 mmol) dissolved in ether (10 mL) was then added dropwise (7 min, addition funnel), taking care to maintain the temperature of the reaction mixture below -70°C, and stirred (-78°C) for an additional 1 h before quenching with solid ammonium chloride (0.8 g). Standard work-up yielded a viscous yellow oil which was separated by flash chromatography (gradient elution with 0-2% methanol in methylene chloride) to give 0.10g (20%) of 2-(*o* -iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) along with 0.06g (15%) of the dialkylated derivative **113** and 0.03g (10%) of **85**; small quantities of unreacted **79** (0.02g) and **76** (0.03g) were recovered as well.

2.16. Studies of the Cyclization of 2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (80) to 1,3-*bis*-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (81).

A series of experiments were carried out in a search for the optimum conditions for the cyclization of 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) to 1,3-*bis*-(*N,N*-dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (**81**) (Table VII). They are described below according to their order of entry in Table VII.

i) 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) (0.2g, 0.5 mmol) was added to a solution of KNH_2 (4 mmol; from 0.16g of potassium metal) in NH_3(l) (150 mL) (entry 1). The mixture was irradiated for 3 h and then poured over solid ammonium chloride (1g). Standard work-up yielded a viscous brown oil which was separated by flash chromatography (gradient elution with 0-2% methanol in methylene chloride) to give 0.05g

(39%) of 1,3-*bis*-(*N,N*-Dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene **(81)** along with 0.02g (18%) of the reduction product **114**.

1,3-*bis*-(*N,N*-Dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (81): **^{1}H-NMR**: δ 2.11 (m, 1H, CH-C$\underline{H}_2$-CH), 2.21 (m, 1H, CH-C$\underline{H}_2$-CH), 2.9 (d, 2H, Ar-C$\underline{H}_2$), 2.98 (s, 3H, N-CH_3), 3.01 (s, 3H, N-CH_3), 3.12 (s, 3H, N-CH_3), 3.29 (s, 3H, N-CH_3), 3.58 (m, 1H, Ar-CH_2-C$\underline{H}$), 4.21 (d, 1H, Ar-C$\underline{H}$), 6.95 (d, 1H, aromatic CH), 7.18 (complex pattern, 3H, three aromatic CH); **^{13}C-NMR**: δ 29.21 (CH_2), 32.02 (CH_2), 33.5 (CH), 35.71 (CH_3), 35.93 (CH_3), 37.24 (CH_3), 38.01 (CH_3), 39.52 (CH), 126.12 (CH), 126.71 (CH), 128.11 (CH), 129.43 (CH), 135.02 (C), 137.13 (C),175.85(CO), 176.54 (CO); **Mass Spectrum** (70eV, m.e, rel. int.): 274 (22, M^+), 229 (4), 202 (22), 129 (30), 72 (100)

ii) 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide **(80)** (0.1g, 0.25 mmol) was added to a solution of KNH_2 (2 mmol; from 0.08g of potassium metal) in NH_3(l) (75 mL) (entry 2). The mixture was irradiated for 0.25 h and then poured over solid ammonium chloride (0.5g). Standard work-up yielded a viscous brown oil which was found to consist of a 2:1 mixture of **81** and **114** (estimated from its ^{1}N-NMR spectrum).

iii) 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide **(80)** (0.1g, 0.25 mmol) was added to a solution of KNH_2 (2 mmol; from 0.08g of potassium metal) in NH_3(l) (75 mL) (entry 3). The mixture was stirred in the dark (covered with a black cloth to ensure complete exclusion of light) for 0.25 h and then poured over solid ammonium chloride (0.5g). The ^{1}H-NMR spectrum of the crude product obtained after standard work-up was identical to that of **80**.

iv) 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) (0.1g, 0.25 mmol) was added to a solution of $LiNH_2$ (2 mmol; from 0.014g of lithium wire) in NH_3(l) (75 mL) (entry 4). The mixture was irradiated for 0.25 h and then poured over solid ammonium chloride (0.5g). Standard work-up yielded a viscous brown oil which was found by ^{1}H-NMR to consist predominantly of unreacted **80** along with traces of the cyclized product **81**.

v) 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) (0.40g, 1 mmol) was added to a solution of $LiNH_2$ (8 mmol; from 0.055g of lithium wire) in NH_3(l) (250 mL) (entry 5). The mixture was irradiated for 2 h and then poured over solid ammonium chloride (2g). Standard work-up yielded a viscous brown oil which was separated by flash chromatography (gradient elution with 0-2% methanol in methylene chloride) to give 0.06g (23%) of **81** along with 0.03g (12%) of the reduction product **114** and 0.19g (48%) of unreacted **80**.

vi) 2-(*o*-iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (**80**) (0.1g, 0.25 mmol) was added to a solution of KNH_2 (1.1 mmol; from 0.05g of potassium metal) in NH_3(l) (60 mL) (entry 6). The mixture was irradiated for 0.25 h and then poured over solid ammonium chloride (0.25g). The ^{1}H-NMR spectrum of the crude product obtained after standard work-up was identical to that of the crude product from the previous experiment; it was therefore concluded that it consisted of the same components in the same proportions, *i.e.*, **81** (23%), **114** (12%) and unreacted **80** (48%).

2.17. Investigation of the Mechanism of the Cyclization of 77 to Form 78.

i) Attempted cyclization of **77** to **78** in presence of 10 mol% of di-*tert*-butyl-nitroxide.

To a solution of KNH_2 (1.86 mmol; from 0.08g of potassium metal) in NH_3(l) (50 mL) was added a mixture of 0.09g (0.23 mmol) of **77** and 0.0033g (0.023 mmol) of di-*tert*-butyl nitroxide (DTBN; 1 mL of a 0.33% solution of DTBN in ether) dissolved in ether (5 mL). The reaction mixture was stirred under irradiation for 0.25 h and quenched with solid ammonium chloride (0.5g). After evaporation of NH_3(l) followed by standard work-up, a yellow oil was obtained, which was found by ^{1}H-NMR to consist of a 7:1 ratio of **78** and **90**. No unreacted **77** was detected.

ii) Preparation of 2,6-dimethyl-iodobenzene (**122**).

This compound was prepared according to the method described by Jacobs, Reed and Pacovska[68] from 2,6-dimethylaniline. To a beaker containing 2,6-dimethylaniline (**121**) (60.59 g, 0.5 mol), were added 220mL (2.72 mol, S.G. 1.19) of concentrated hydrochloric acid, 220 mL of water and 500 g of ice. The mixture was cooled, with stirring, to -5°C in an ice-salt cooling bath. Cold aqueous sodium nitrite (36.26g, 0.53 mol, dissolved in 250 mL of cold water) was then added from a separatory funnel, the stem projecting below the surface of the reaction mixture, taking care to maintain the temperature below 0°C. The last 5% of the sodium nitrite solution was added slowly, testing with starch-potassium iodide paper for excess nitrous acid. After stirring for 10 min, potassium iodide (116.21g, 0.7 mol, dissolved in water) was added and the mixture allowed to stand overnight. It was then transferred to two smaller flasks and heated on steam cones, using air cooled reflux condensors, until no more gas was evolved, then cooled and allowed to stand undisturbed (2 h). Most of the upper aqueous layer was then siphoned off. The

remaining solution was then carefully neutralized with aqueous sodium hydroxide (40% w/v) and steam-distilled immediately. When the color of the steam distillate began to darken (the initial portion was almost colorless), it was collected separately (the last one-third portion). The first portion was separated and the product was kept aside. The aqueous layer was combined with the separately collected last portion of the steam-distillate. It was then acidified with concentrated hydrochloric acid and steam-distilled again. After separation of the aqueous layer, the products were combined (39 g total), dried and distilled under reduced pressure, affording 29.5g (25%) of pure 2,6-dimethyliodobenzene (**122**). **bp**: 93-95°C (5.5 mmHg) [lit.[68,76] bp 58-59°C (0.5 mmHg), 102-103°C (14mmHg) respectively]; **Elemental analysis:** Calc. for C_8H_9I: C, 41.37; H, 3.88. Found C, 43.30; H, 4.12.

iii) Preparation of 2-iodo-3-methylbenzyl bromide (**120**).

This compound was prepared according to the procedure described by Bacon and Lindsay.[69] To a 250 mL round-bottomed flask containing **122** (28.3g, 122 mmol) were added 100 mL of carbon tetrachloride, 21.7g (122 mmol) of *N*-bromosuccinimide and 1.1g of benzoyl peroxide. The reaction mixture was then refluxed for 24 h. The succinimide that crystallized upon cooling was filtered under suction. The succinimide residue was washed twice with cold carbon tetrachloride (2 x 5mL) and the washings combined with the initial filtrate. The solvent was removed *in vacuo* and the crude product distilled under reduced pressure, which afforded 14.3g (50%, 56°C, 0.06 mmHg) of unreacted **122**, along with 9.1g (24%, 82°C, 0.06 mmHg) of 2-iodo-3-methylbenzyl bromide (**120**). The product solidified to a low melting solid upon cooling to room temperature: **bp** 82°C (0.06 mmHg) (lit.[69] bp 144°C, 1.5 mmHg); **^{1}H-NMR**: δ 2.51 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 6.95 (t, 1H, aromatic CH-C<u>H</u>-CH), 7.03-7.20 (two overlapping d, 2H,

aromatic C<u>H</u>-CH-C<u>H</u>); **^{13}C-NMR**: δ 29.51 (CH_3), 40.35 (CH_2), 107.19 (CI), 127.41 (CH), 128.03 (CH), 129.61 (CH), 140.72 (CH), 143.09 (CH); **Elemental analysis**: Calc. for C_8H_8BrI: C 30.87, H 2.57. Found C 30.94, H 2.54.

iv) Preparation of 2-(2-iodo-3-methylbenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**119**).

N,N,N',N'-tetramethylsuccinamide (**73**) (1.72g, 10 mmol) was added to a solution of $LiNH_2$ (22 mmol; from 0.15g lithium wire) in NH_3(l) (300 mL); the mixture was stirred while cooling to -60°C (40 min); 2-iodo-3-methylbenzyl bromide (**120**) (3.11g, 10 mmol; 25 mls ether) was then added dropwise (15 min), taking care to maintain temperature below -50°C. After stirring (at -55°C) for 1 h, the reaction mixture was neutralized with solid ammonium chloride (4g). Standard work-up afforded a pale yellow oil. A white solid separated out upon trituration with ether (10 mL). This was filtered under suction and recrystallized from chloroform/hexane to give 0.6g (16%) of shiny white crystals identified as 3-(*N,N*-dimethylcarboxamido)-4-(2-iodo-3-methylphenyl)butanamide. The filtrate was evaporated *in vacuo*, affording a white crystalline residue, which was identified as 2-(2-iodo-3-methylbenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**119**). Recrystallization from chloroform/hexane gave 2.41g (60%) of pure **119**.

3-(*N,N*-Dimethylcarboxamido)-4-(2-iodo-3-methylphenyl)butanamide: **mp**: 159-160°C; **^{1}H-NMR**: δ 2.34 (dd, 1H, C<u>H</u>$_2$-$CONH_2$), 2.48 (s, 3H, Ar-CH_3), 2.71 (s, 3H, N-CH_3), 2.78-2.89 (dd, 1H, C<u>H</u>$_2$-$CONH_2$), 2.83 (s, 3H, N-CH_3), 2.99 (d, 2H, Ar-CH_2), 3.70 (m, 1H, Ar-CH_2-C<u>H</u>), 5.68 (bs, 1H, NH), 6.25 (bs, 1H, NH), 6.93 (t, 1H, aromatic CH-C<u>H</u>-CH), 7.01-7.18 (two overlapping d, 2H, aromatic C<u>H</u>-CH-C<u>H</u>); **^{13}C-NMR**: δ 30.01 (CH_3), 35.88 (CH_3), 37.31 (CH), 37.53 (CH_3), 38.41 (CH_2),

44.95 (CH_2), 107.97 (CI), 127.28 (CH), 127.74 (CH), 128.02 (CH), 142.02 (C), 142.54 (C), 173.85 (CO), 174.18 (CO); **Elemental analysis:** Calc. for $C_{14}H_{19}IN_2O_2$: C 44.92, H 5.08, N 7.48. Found C 44.68, H 4.97, N 7.61.

2-(2-Iodo-3-methylbenzyl)-*N,N,N',N'*-tetramethylsuccinamide (119): mp 127°C; **^{1}H-NMR**: δ 2.34 (dd, 1H, C<u>H</u>$_2$-CONMe$_2$), 2.49 (s, 3H, Ar-CH_3), 2.74 (s, 3H, N-CH_3), 2.83 (s, 3H, N-CH_3), 2.90 (s, 3H, N-CH_3), 2.99 (d, 2H, Ar-C<u>H</u>$_2$), 3.08 (s, 3H, N-CH_3), 3.1 (dd, 1H, C<u>H</u>$_2$-CONMe$_2$), 3.69 (m, 1H, Ar-CH_2-C<u>H</u>), 6.96 (dd, 1H, aromatic CH-C<u>H</u>-CH), 7.11-7.23 (two overlapping d, 2H, aromatic C<u>H</u>-CH-C<u>H</u>); **^{13}C-NMR**: δ 30.01 (CH_3), 35.22 (double intensity, two CH_3), 35.68 (double intensity, two CH_3), 36.71 (CH_2), 37.15 (CH), 45.17 (CH_2), 108.03 (CI), 127.28 (CH), 127.74 (CH), 127.98 (CH), 142.22 (C), 142.24 (C), 171.07 (CO), 174.66 (CO); **Elemental analysis:** Calc. for $C_{16}H_{23}IN_2O_2$: C 47.76, H 5.72, N 6.97. Found C 47.87, H 5.77, N 6.91.

v) Preparation of 1,2-bis-(*N,N*-dimethylcarboxamido)-7-methylindane (**123**).

2-(2-Iodo-3-methylbenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**119**) (0.40g, 1 mmol) was added to a solution of KNH_2 (8 mmol; from 0.31g of potassium metal) in NH_3(l) (200 mL) and irradiated for 3 h. The reaction mixture was then neutralized with solid ammonium chloride (2g). After standard work-up, the crude product was separated by flash chromatography (with 2% methanol in methylene chloride), which afforded 0.11g (40%) of 1,2-bis-(*N,N*-dimethylcarboxamido)-7-methylindane (**123**) along with 0.01g (4%) of the reduction product, 2-(3-methylbenzyl)-*N,N,N',N'*-tetramethylsuccinamide. **1,2-bis-(*N,N*-dimethylcarboxamido)-7-methylindane (123): ^{1}H-NMR**: δ 2.13 (s, 3H, Ar-CH_3), 2.85-3.0 (m, 1H, Ar-C<u>H</u>$_2$), 3.01 (s, 3H, N-CH_3), 3.04 (s, 3H,

N-CH_3), 3.12 (s, 3H, N-CH_3), 3.33 (s, 3H, N-CH_3), 3.3-3.48 (m, 1H, Ar-$C\underline{H}_2$), 3.81 (m, 1H, Ar-CH_2-C$\underline{H}$), 5.07 (d, 1H, Ar-C$\underline{H}$), 6.92-7.15 (complex pattern, 3H, three aromatic CH); **^{13}C-NMR**: δ 18.95 (CH_3), 25.93 (CH_3), 26.06 (CH_3), 26.88 (CH_2), 27.29 (CH_3), 28.08 (CH_3), 38.03 (CH), 39.65 (CH), 121.76 (CH), 127.66 (CH), 128.94 (CH), 133.70 (C), 140.82 (C), 141.42 (C), 173.39 (CO), 174.48 (CO)

2-(3-methylbenzyl)-*N,N,N',N'*-tetramethylsuccinamide: **^{1}H-NMR**: δ 2.33 (dd, 1H, C$\underline{H}_2$-$CONMe_2$), 2.19 (s, 3H, Ar-CH_3), 2.74 (s, 3H, N-CH_3), 2.83 (s, 3H, N-CH_3), 2.87 (s, 3H, N-CH_3), 2.96 (s, 3H, N-CH_3), 2.99 (d, 2H, Ar-$C\underline{H}_2$), 3.1 (dd, 1H, C$\underline{H}_2$-$CONMe_2$), 3.58 (m, 1H, Ar-CH_2-C$\underline{H}$), 6.96 (dd, 1H, aromatic CH-C$\underline{H}$-CH), 7.09-7.21 (two overlapping d, 2H, aromatic C$\underline{H}$-CH-C$\underline{H}$).

vi) Attempted cyclization of **119** to **123** without photostimulation.

2-(2-Iodo-3-methylbenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**119**) (0.10g, 0.25 mmol) was added to a solution of KNH_2 (2 mmol; from 0.08g of potassium metal) in NH_3(l) (50 mL) and stirred in the dark (covered with a black cloth to ensure complete exclusion of light) for 2.5 h. The reaction mixture was then neutralized with solid ammonium chloride (0.5g). The crude product obtained after standard work-up was found by ^{1}H-NMR to consist predominantly of unreacted **119**. No cyclized product **123** was detected.

vii) Cyclization of **77** to **78** in deuterated liquid ammonia.

2-(*o*-Iodobenzyl)-*N,N,N',N'*-tetramethylsuccinamide (**77**) (0.04g, 0.1 mmol) was added to a solution of potassium *d*-amide (0.8 mmol; from 0.04g of potassium metal) in ND_3(l) (25 mL) and irradiated for 0.5 h. The reaction mixture was then neutralized with

solid ammonium chloride (0.2g). After standard work-up, the crude product was separated by preparative thin layer chromatography (methylene chloride), affording 0.01g (38%) of the deuterated cyclized product **78**: **^{1}H-NMR**: δ 2.95 (s, 3H, N-CH_3), 3.01 (dd, 1H, Ar-C$\underline{H}_2$-CH), 3.05 (s, 3H, N-CH_3), 3.14 (s, 3H, N-CH_3), 3.24 (dd, 1H, Ar-C$\underline{H}_2$-CH), 3.29 (s, 3H, N-CH_3), 4.18 (m, low intensity, Ar-CH_2-C$\underline{H}$), 7.01 (t, 1H, aromatic CH), 7.16 (m + s, 3H, aromatic CH); **^{2}D-NMR**: δ 4.18 (s, 1D), 5.01 (s, 1D); **^{13}C-NMR**: δ 35.63 (CH_3), 35.72 (CH_2), 35.84 (CH_3), 37.17 (CH_3), 37.60 (CH_3), 46.98 (low intensity, CH), 122.83 (CH), 124.38 (CH), 127.08 (CH), 127.76 (CH), 141.63 (C), 141.80 (C), 173.06 (CO), 173.79(CO) ; **Mass Spectrum** (70 eV, m/e, rel. int.): 262 (5, M^+), 261 (2), 216 (9), 215 (3), 190 (20), 189 (15), 145 (16), 144 (12) 117 (30), 116 (20), 72 (100), 56 (10).

2.18. Investigation of the Mechanism of Cyclization of 2-(*o*-Iodobenzyl)-succinimide (99) to succinimido[3,4-b]indane (61).

The cyclization of **99** to **61** in the presence of 10 mol% of di-*tert*-butyl nitroxide was attempted in the following way. To a solution of KNH_2 (1.1 mmol; from 0.04g of potassium metal) in NH_3(l) (50 mL) was added a mixture of **99** (0.08g, 0.25 mmol) and 0.0036g (0.025 mmol) of di-*tert*-butyl nitroxide (DTBN; 1 mL of a 0.36% solution of DTBN in ether) dissolved in ether (5 mL). The reaction mixture was irradiated for 0.25 h and quenched with solid ammonium chloride (0.2g). After evaporation of ammonia followed by standard work-up, a yellow solid was obtained, which was identified as unreacted **99** (from its ^{1}H-NMR spectrum). The expected cyclized product **61** was not detected.

2.19. Investigation of the Transformation of 3-(*o*-Bromo-α-cyanobenzyl)-succinimide (82) into 3-(α-cyano-α-phenylmethyleno)succinimide (107).

i) Treatment of **82** with excess potassium amide in the dark.

3-(*o*-bromo-α-cyanobenzyl)-succinimide (**82**) (0.1g, 0.34 mmol) was added to a solution of KNH_2 (2.73 mmol; from 0.11g of potassium metal) in NH_3(l) (50 mL) and stirred in the dark (covered with a black cloth to ensure complete exclusion of light) for 0.5 h, after which the reaction mixture was neutralized with ammonium chloride (1.5g). Standard work-up gave a brown solid which was identified by ^{1}H-NMR as unreacted **78**. 3-(α-Cyano-α-phenylmethyleno)succinimide (**107**) was not detected.

ii) Treatment of **82** with excess potassium amide in the presence of di-*tert*-butyl nitroxide.

To a solution of KNH_2 (2 mmol; from 0.08g of potassium metal) in NH_3(l) (50 mL) was added a mixture of **82** (0.07g, 0.25 mmol) and 0.0036g (0.025 mmol) of di-*tert*-butyl nitroxide (DTBN; 1 mL of a 0.36% solution of DTBN in ether) dissolved in ether (5 mL). The reaction mixture was irradiated for 0.25 h and quenched with solid ammonium chloride (0.3g). After evaporation of NH_3(l) followed by standard work-up, a yellow solid was obtained, which was identified by ^{1}H-NMR as unreacted **82**. 3-(α-Cyano-α-phenylmethyleno)succinimide (**107**) was not detected.

2.20. Investigation of the Mechanism of Cyclization of 2-(*o* -Iodobenzyl)-*N,N,N',N'*-tetramethylglutaramide (80) to Form 1,3-*bis*-(*N,N*-Dimethylcarboxamido)-1,2,3,4-tetrahydronaphthalene (81).

The cyclization of **80** to form **81** in the presence of 10 mol% of di-*tert*-butyl nitroxide was attempted in the following way. To a solution of KNH_2 (1.1 mmol; from 0.04g of potassium metal) in NH_3(l) (50 mL) was added a mixture of **80** (0.1g, 0.25 mmol) and 0.0036g (0.025 mmol) of di-*tert*-butyl nitroxide (DTBN; 1 mL of a 0.36% solution of DTBN in ether) dissolved in ether (5 mL). The reaction mixture was irradiated for 0.25 h and quenched with solid ammonium chloride (0.2g). After evaporation of NH_3(l) followed by standard work-up, a yellow solid was obtained, which was identified by ^{1}H-NMR as unreacted **80**. The expected cyclized product, 1,3-*bis*-(*N,N*-dimethyl-carboxamido)-1,2,3,4-tetrahydronaphthalene (**81**), was not detected.

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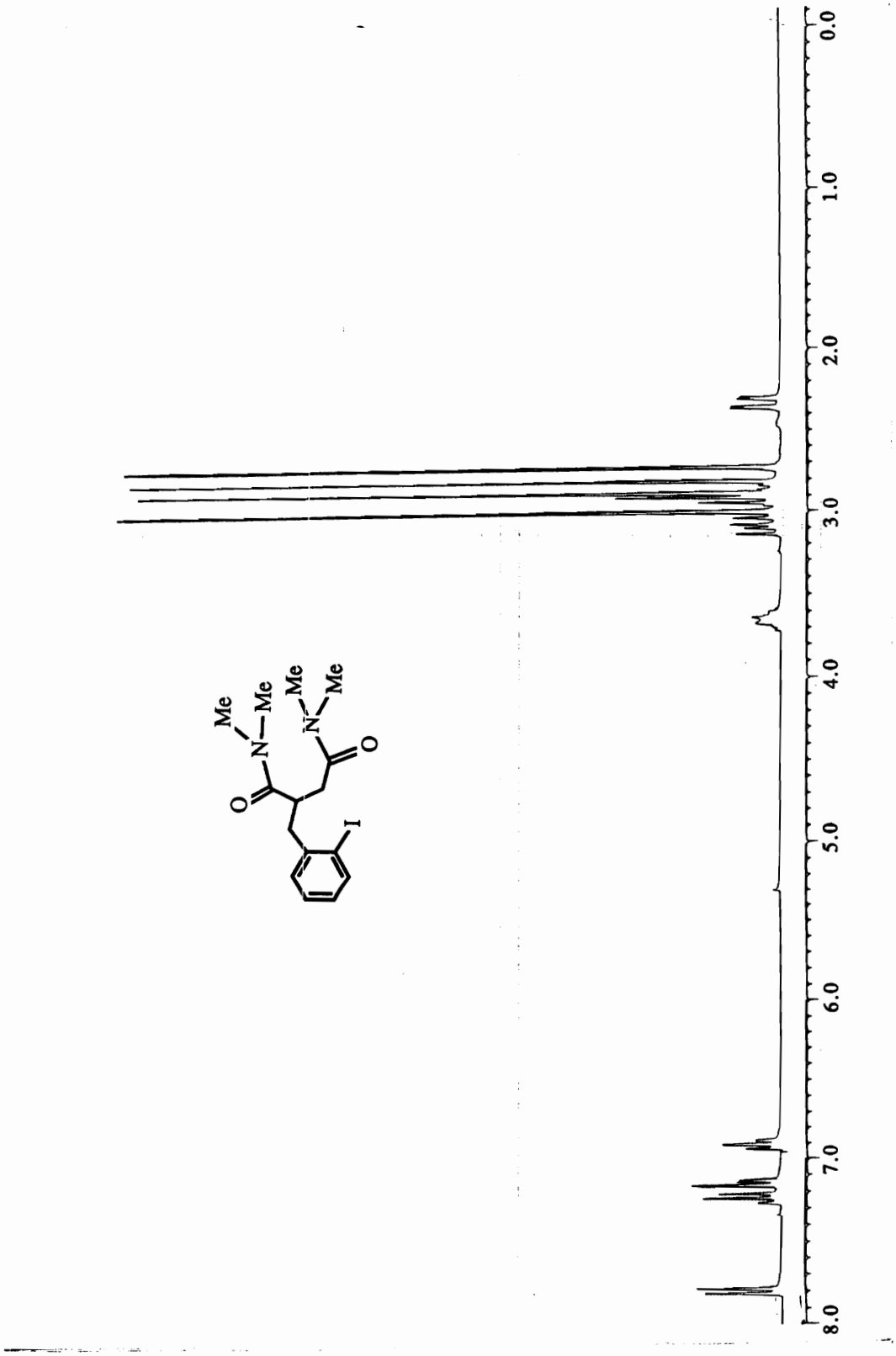
VIII. APPENDIX I

LIST OF SELECTED SPECTRA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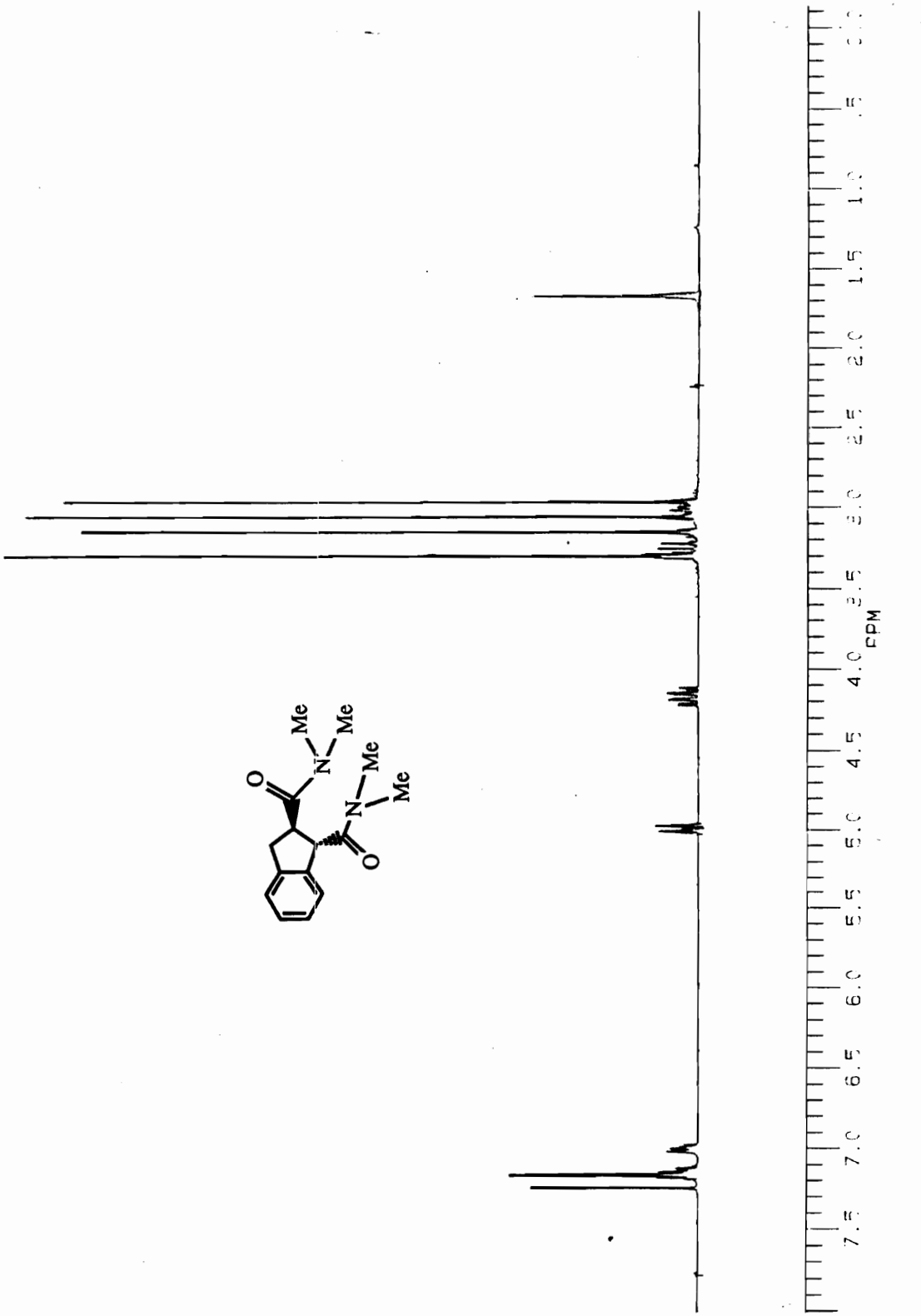
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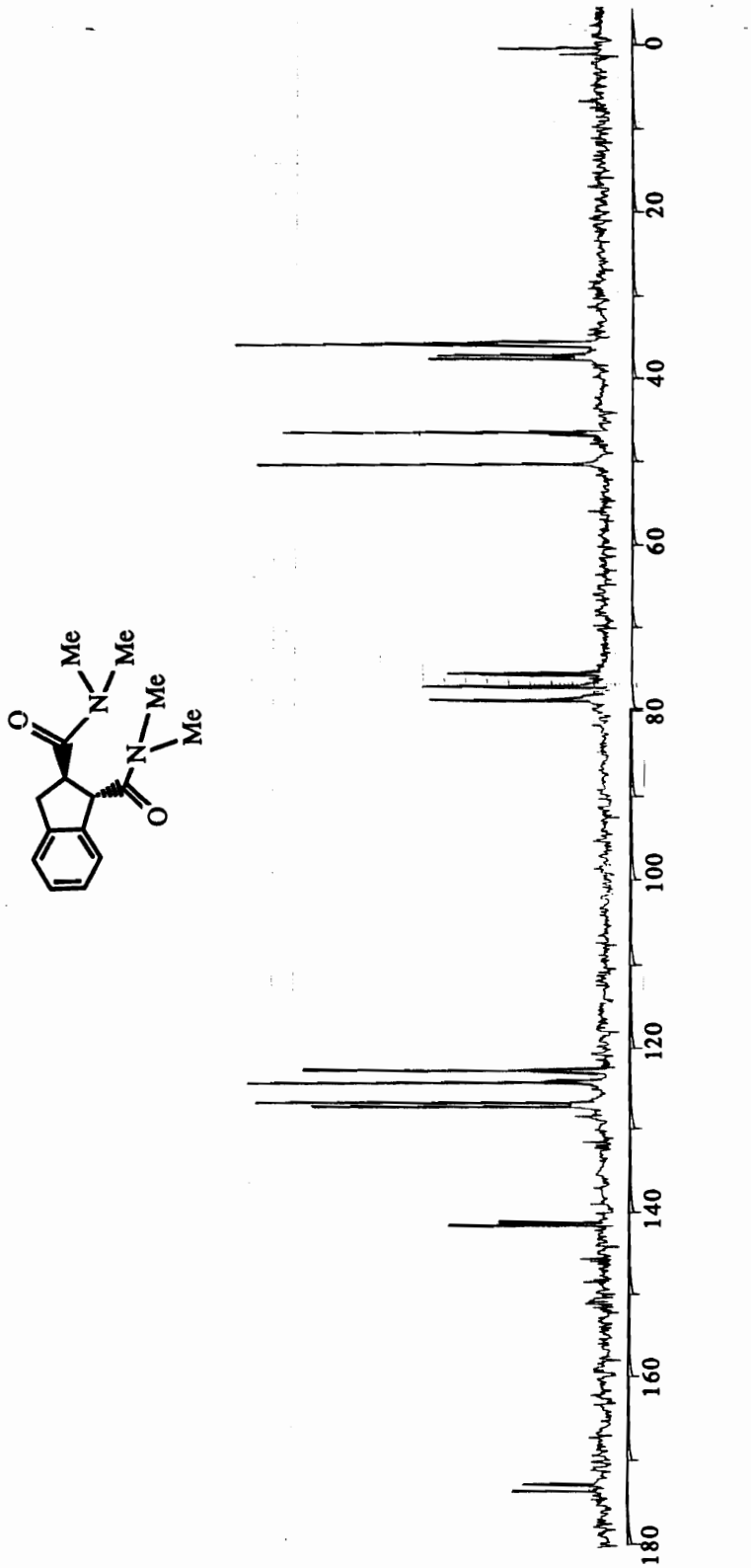
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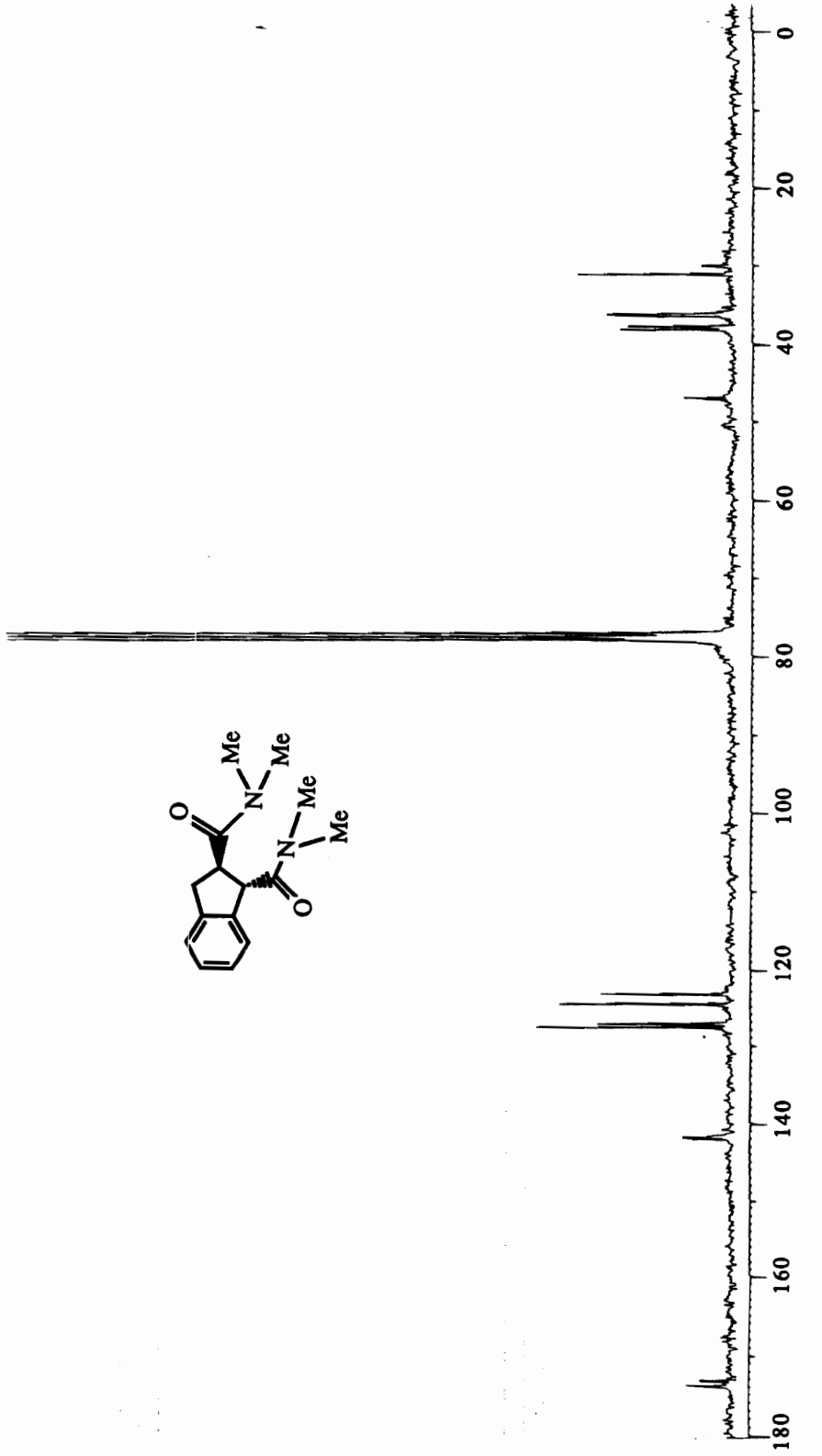
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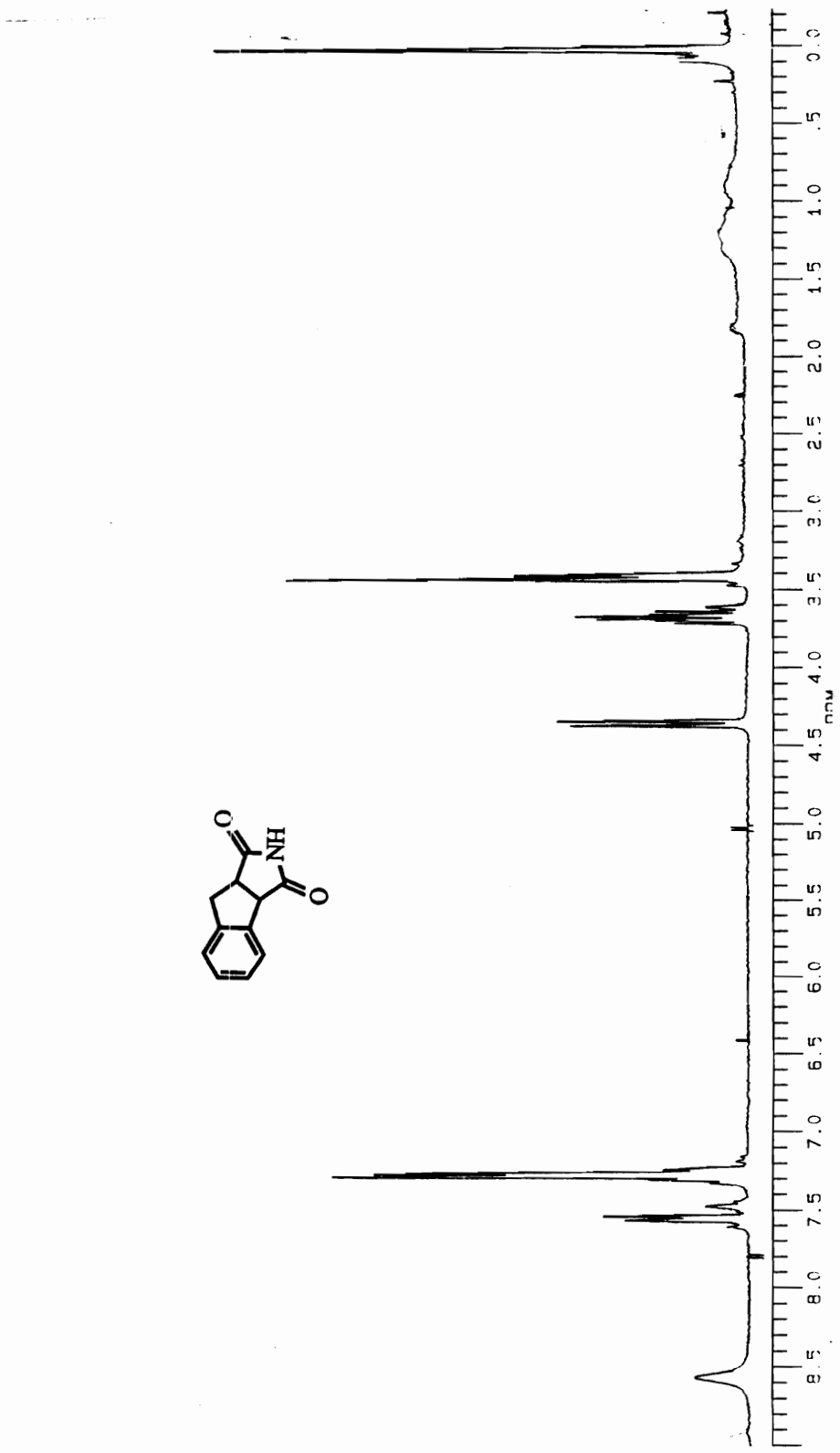
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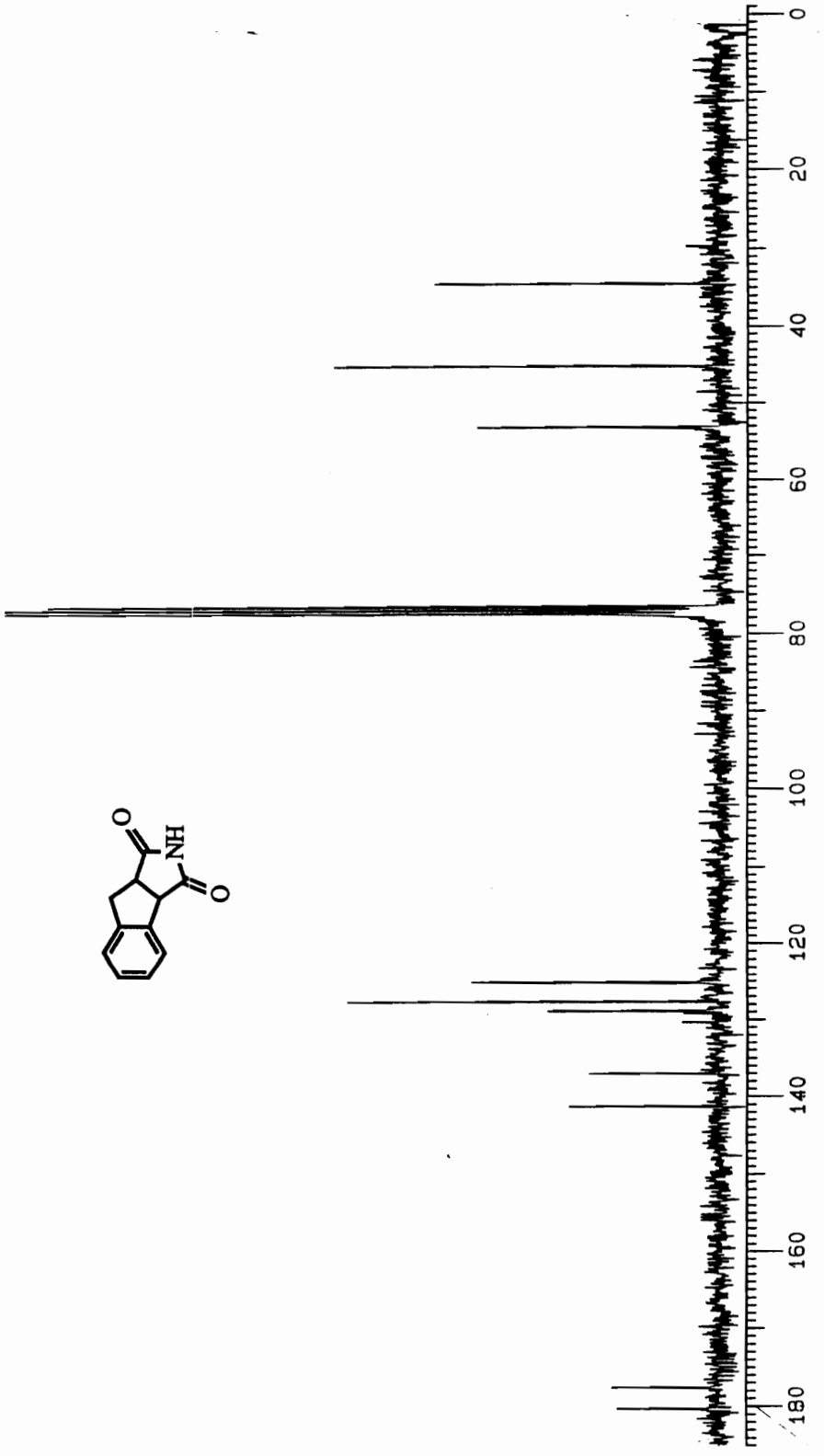
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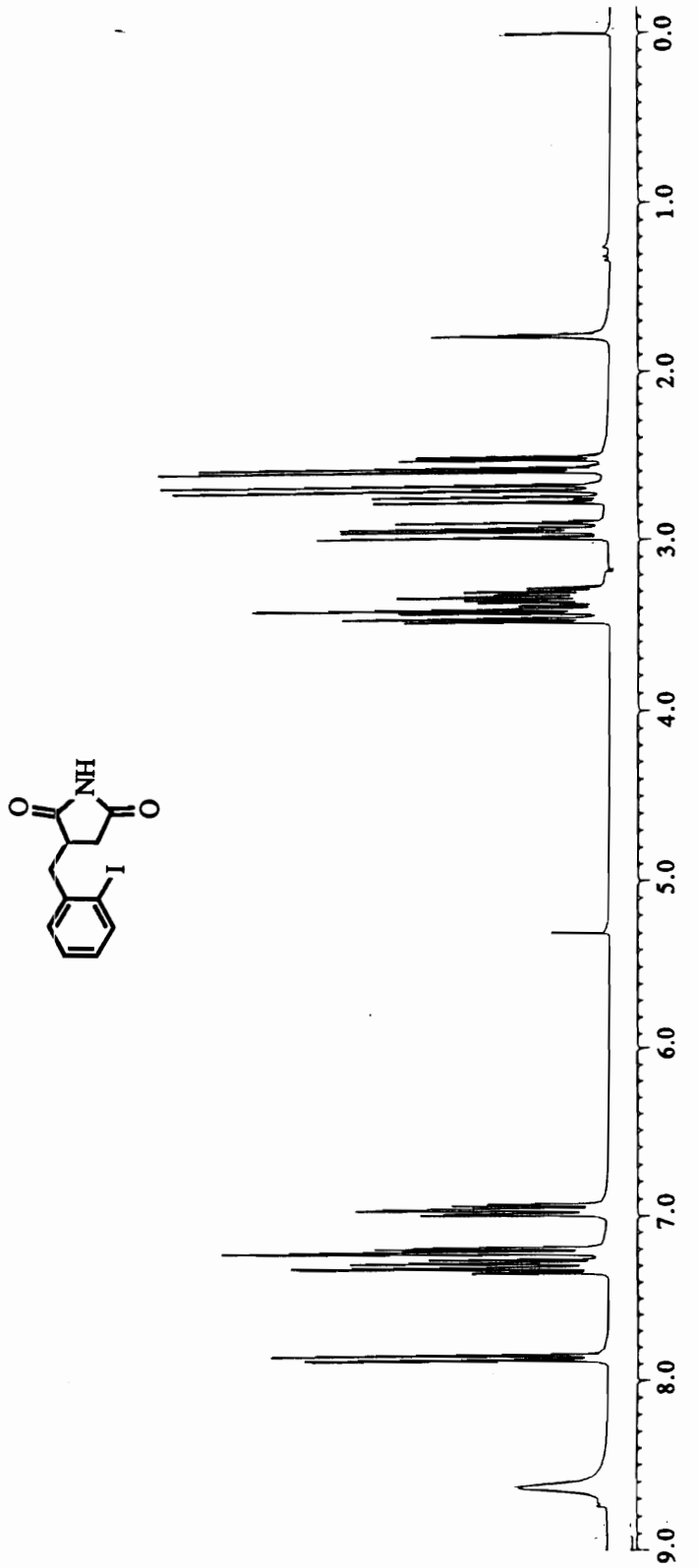
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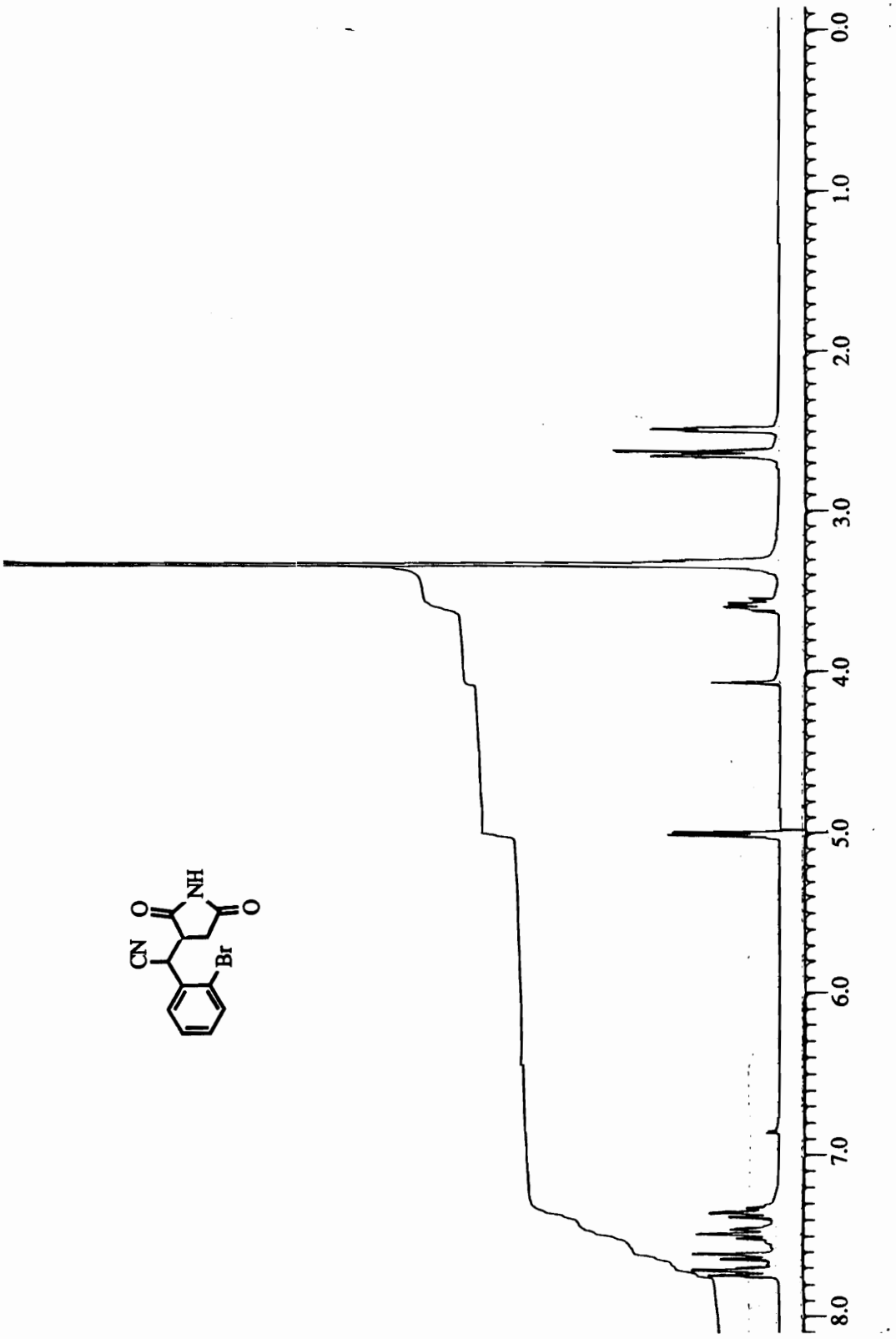
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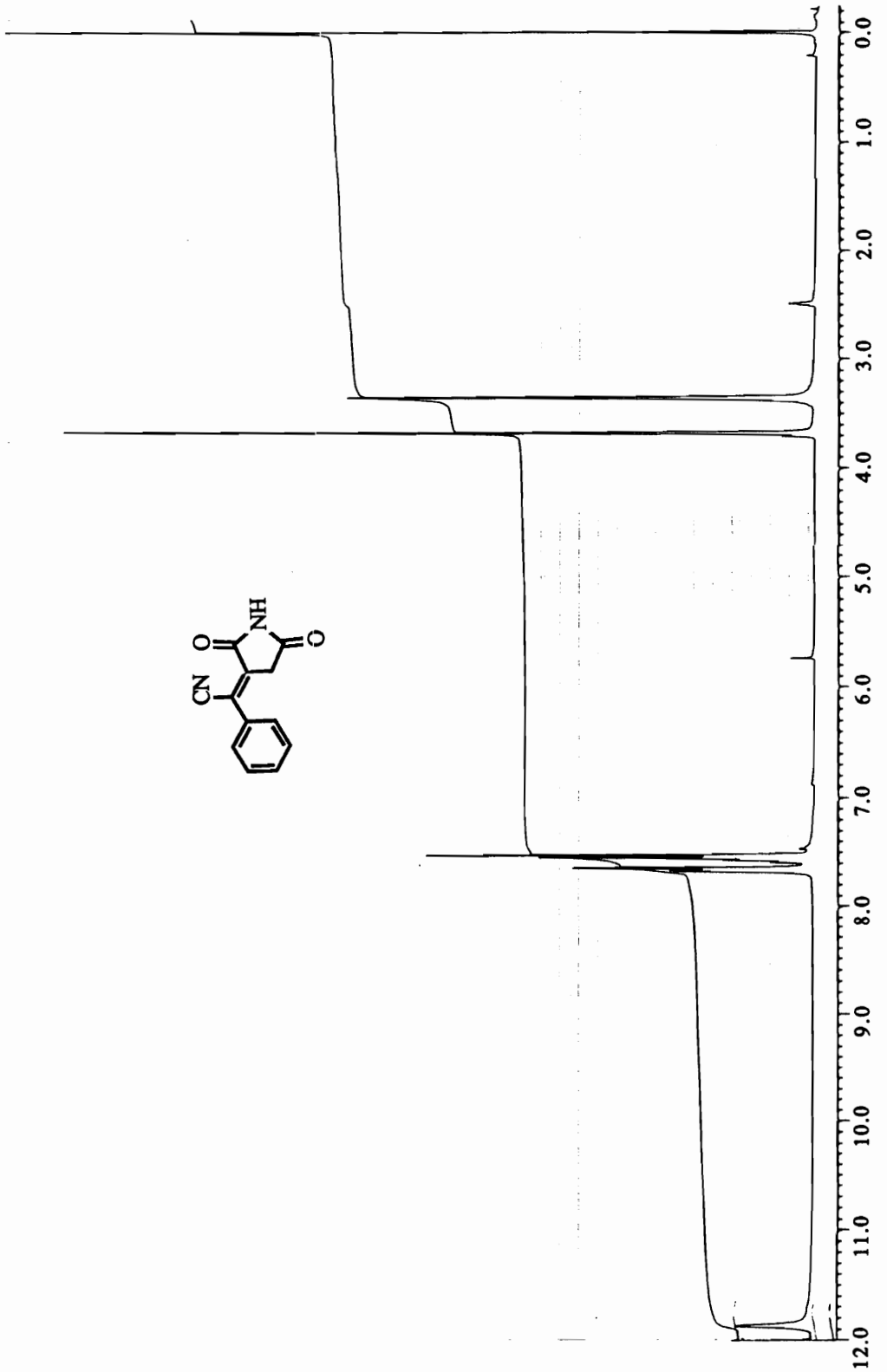
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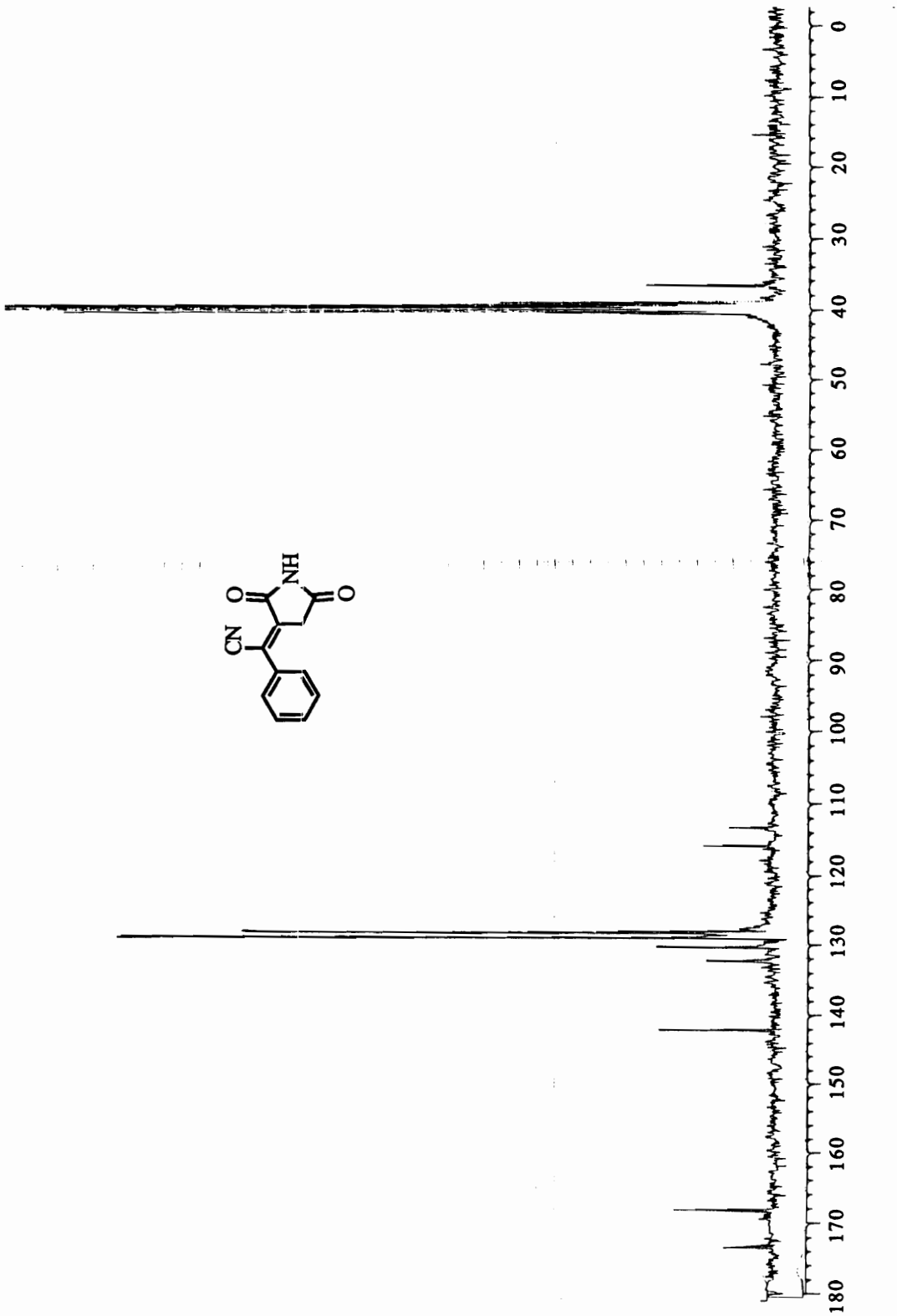
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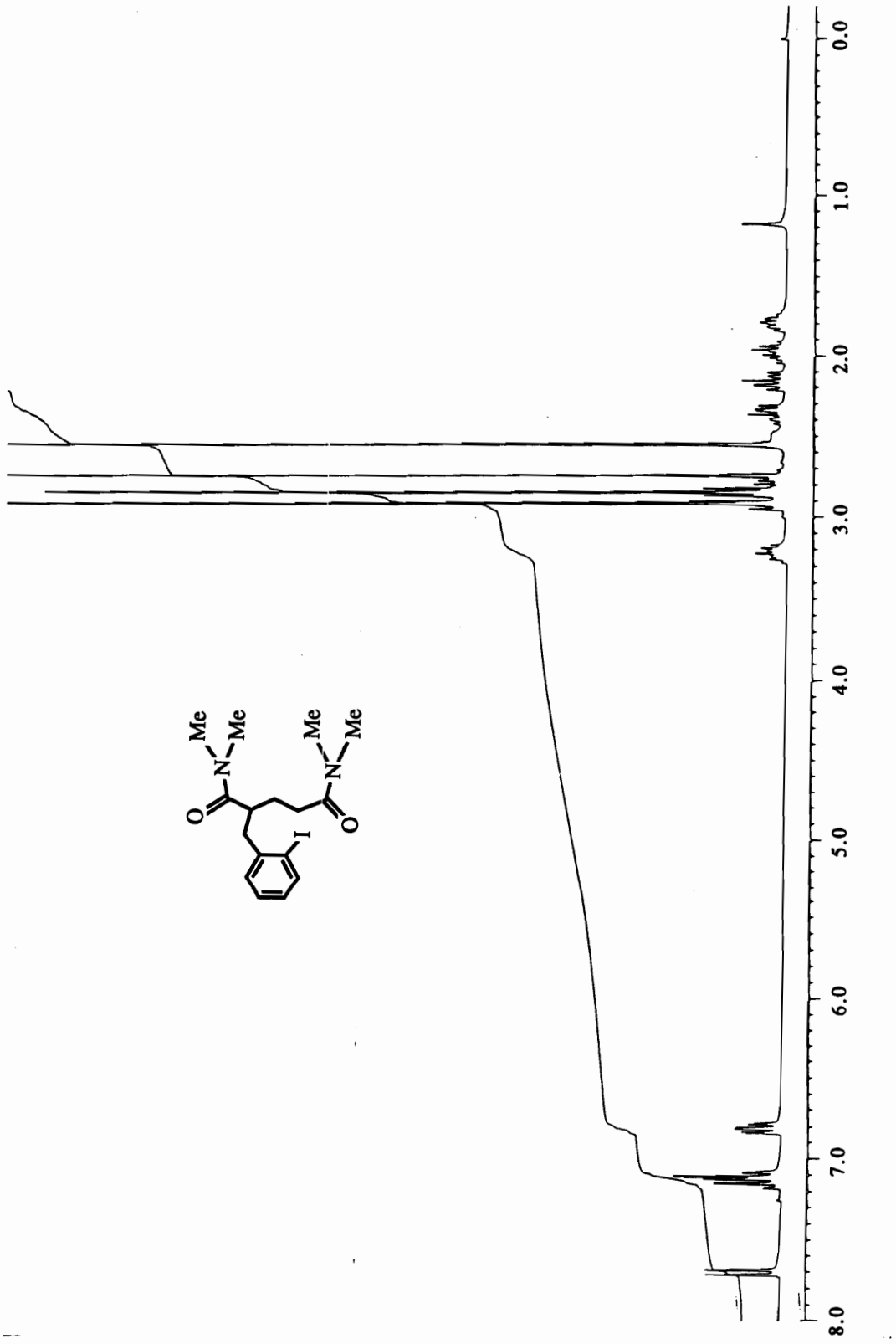
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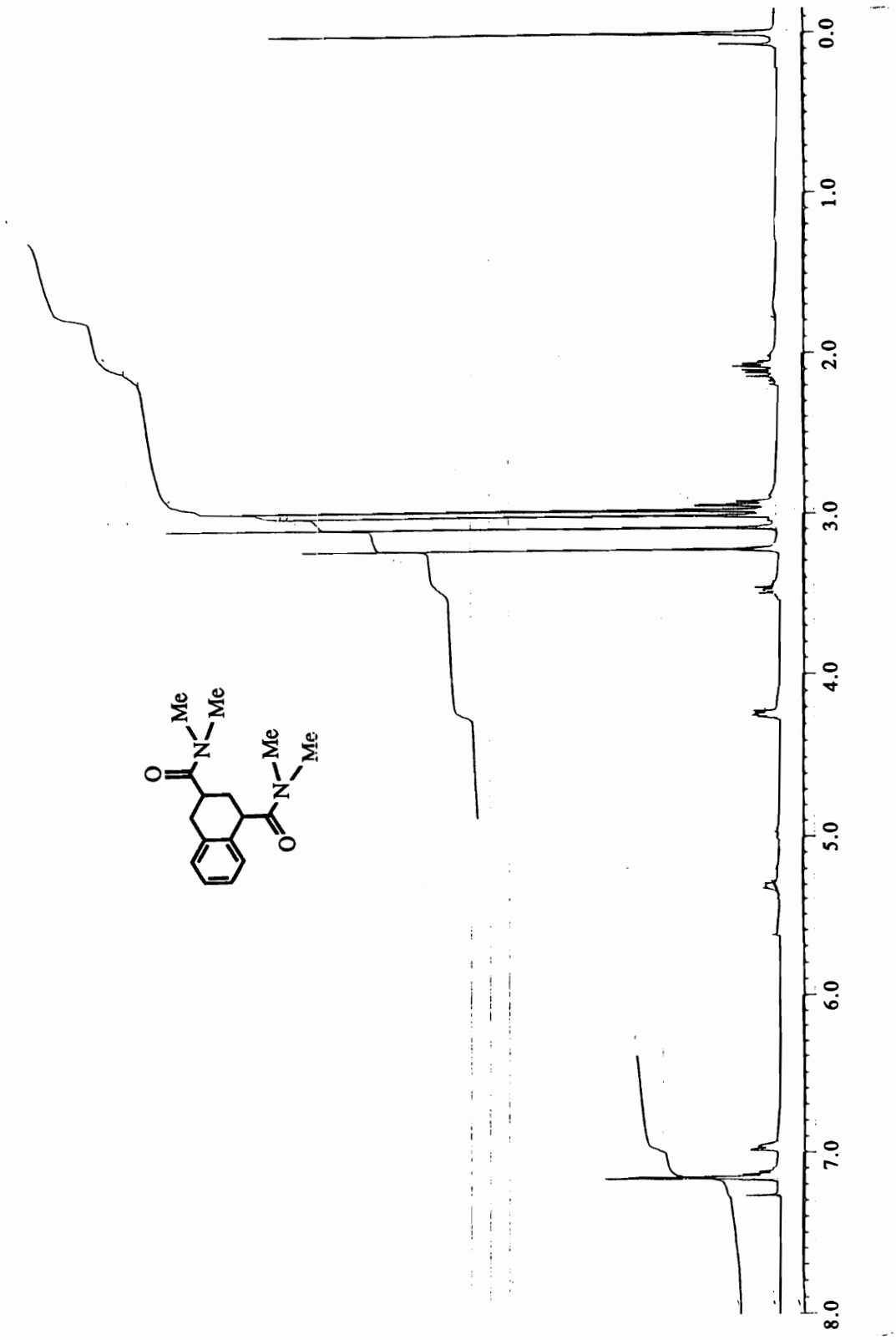
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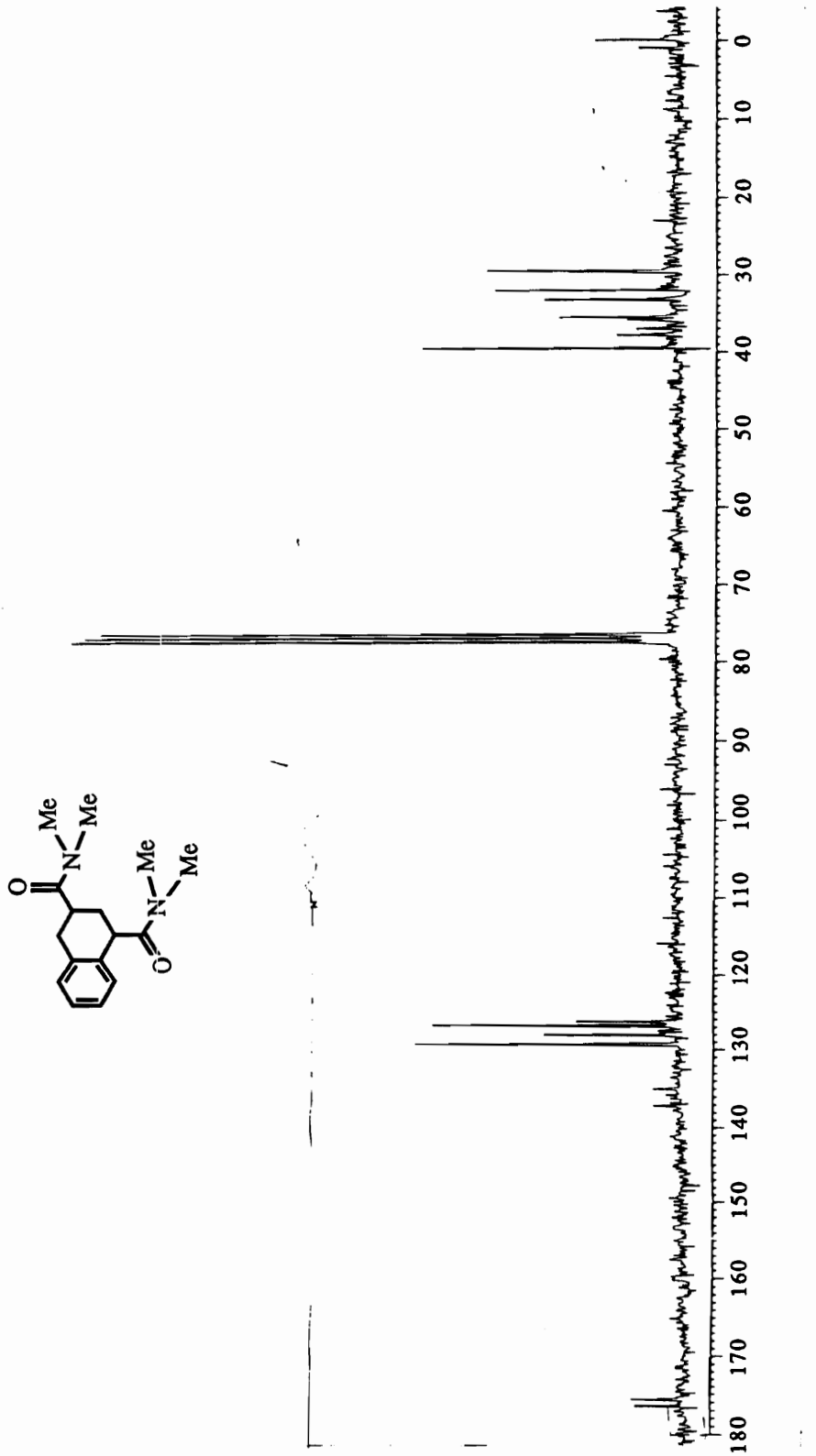
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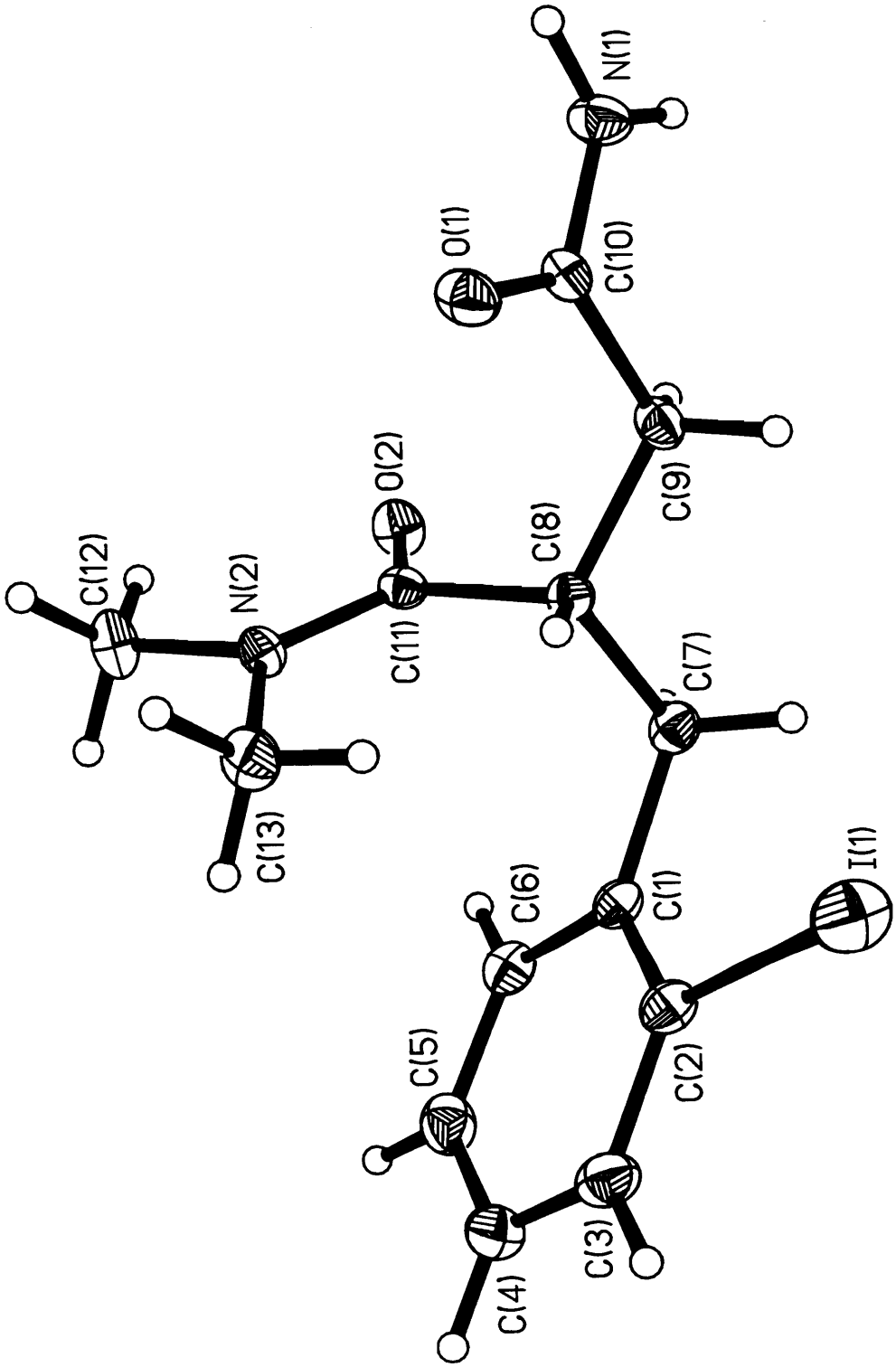
IX. APPENDIX II

LIST OF SELECTED X-RAY CRYSTAL STRUCTURES[a]

[a]A summary of x-ray crystallographic data for each of the compounds listed here appears immediately following the ORTEP representation.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C(11)
C(7)
C(13)
C(6)
C(1)
I(1)
C(5)
C(2)
C(4)
C(3)

STRUCTURE DETERMINATION SUMMARY

Crystal Data

Empirical Formula	$C_{13}\ H_{17}\ I\ N_2\ O_2$
Color; Habit	Clear Rectangular Prism
Crystal Size (mm)	0.9 x 0.4 x 0.5
Crystal System	Monoclinic
Space Group	P21/n
Unit Cell Dimensions	$\underline{a}$ = 11.597(2) A
	$\underline{b}$ = 9.064(2) A
	$\underline{c}$ = 13.660(3) A
	β = 93.85(2)^{o}
Volume	1432.7(5) A^3
Z	4
Formula weight	360.2
Density(calc.)	1.670 Mg/m^3
Absorption Coefficient	2.206 mm^{-1}
F(000)	712

Data Collection

Diffractometer Used	Siemens R3m/V
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	0
Monochromator	Highly oriented graphite crystal
2θ Range	3.5 to 55.0°
Scan Type	2θ-θ
Scan Speed	Variable; 3.00 to 15.00°/min. in ω
Scan Range (ω)	1.20° plus Kα-separation
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 200 reflections
Index Ranges	$0 \leq h \leq 15$, $0 \leq k \leq 11$ $-17 \leq \ell \leq 17$
Reflections Collected	3660
Independent Reflections	3283 (R_{int} = 3.23%)
Observed Reflections	2792 ($F > 3.0\sigma(F)$)
Absorption Correction	N/A

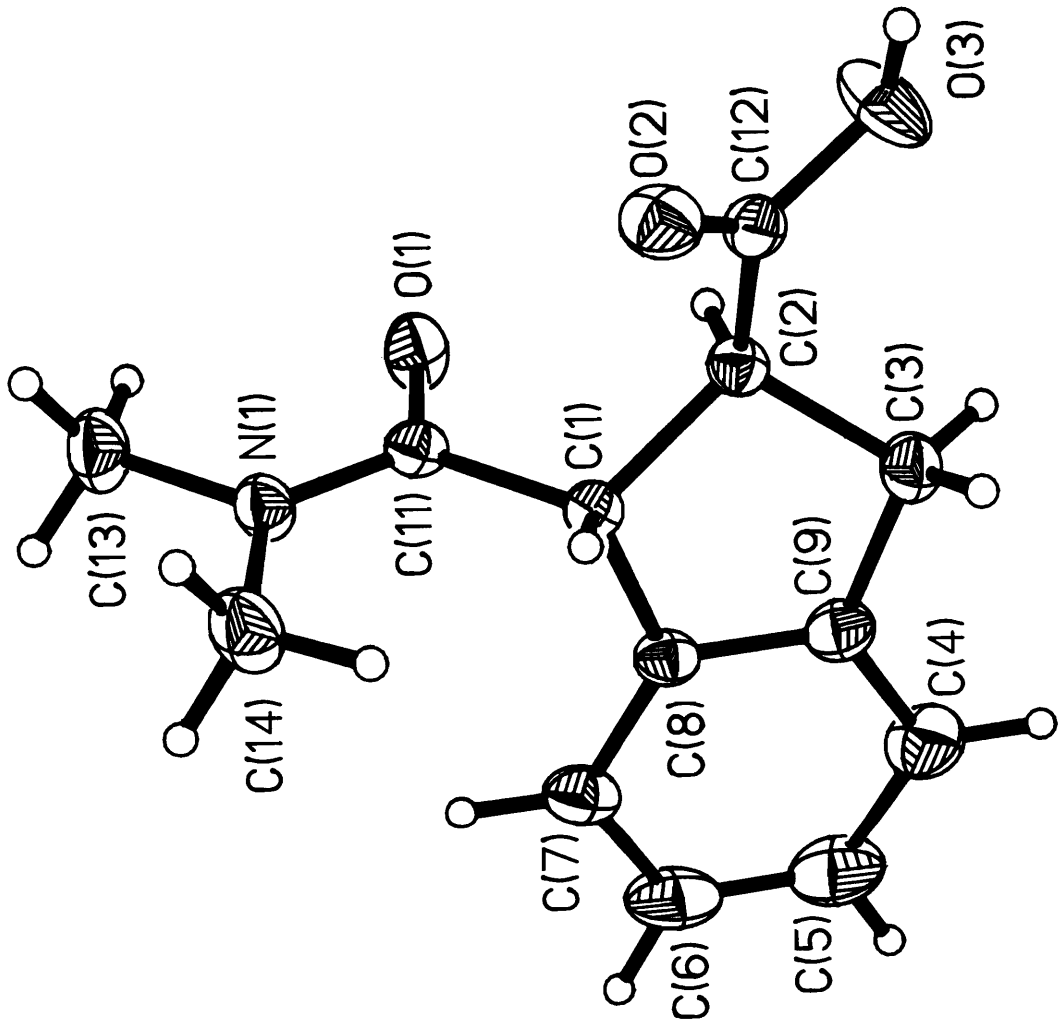
Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o - F_c)^2$
Absolute Structure	N/A
Extinction Correction	χ = 0.0014(2), where $F^* = F [1 + 0.002\chi F^2/\sin(2\theta)]^{-1/4}$
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0004F^2$
Number of Parameters refined	164
Final R indices (obs. data)	R = 4.66 %, wR = 6.64 %
R Indices (all data)	R = 5.35 %, wR = 6.76 %
Goodness-of-Fit	2.35
Largest and Mean Δ/σ	2.115, 0.434
Data-to-Parameter Ratio	17.0:1
Largest Difference Peak	1.33 eA^{-3}
Largest Difference Hole	-0.80 eA^{-3}

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients (A^2x10^3)

	x	y	z	U(eq)
I(1)	2492(1)	1043(1)	3670(1)	70(1)
O(1)	4761(3)	3266(3)	739(2)	50(1)
O(2)	7217(2)	1115(3)	2143(2)	47(1)
C(1)	4903(3)	-338(4)	3750(2)	37(1)
C(2)	3728(3)	-648(5)	3799(3)	43(1)
C(3)	3318(4)	-2083(5)	3913(3)	54(1)
C(4)	4102(5)	-3240(5)	3967(3)	59(2)
C(5)	5259(4)	-2987(6)	3900(3)	57(1)
C(6)	5662(4)	-1544(5)	3806(3)	46(1)
C(7)	5366(3)	1184(4)	3596(3)	41(1)
C(8)	5283(3)	1656(4)	2507(3)	33(1)
C(9)	5503(3)	3313(4)	2420(3)	41(1)
C(10)	5379(3)	3881(4)	1371(3)	37(1)
C(11)	6185(3)	803(3)	1978(3)	33(1)
C(12)	6755(4)	-1122(5)	903(3)	55(1)
C(13)	4685(4)	-893(5)	1222(3)	53(1)
N(1)	5949(3)	5122(4)	1215(3)	50(1)
N(2)	5858(3)	-296(3)	1364(2)	37(1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor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C(3)
N(1)
C(1)
C(13)
C(11)
C(9)
C(4)
C(14)
C(8)
C(7)
C(5)
C(6)

STRUCTURE DETERMINATION SUMMARY

Crystal Data

Empirical Formula	$C_{13} H_{15} N O_3$
Color; Habit	Clear rectangular prism
Crystal Size (mm)	0.1 x 0.2 x 0.3
Crystal System	Monoclinic
Space Group	$P2_1/n$
Unit Cell Dimensions	a = 10.249(5) Å
	b = 11.263(6) Å
	c = 11.330(5) Å
	β = 107.30(4)°
Volume	1248.8(10) $Å^3$
Z	4
Formula weight	233.3
Density(calc.)	1.241 Mg/m^3
Absorption Coefficient	0.083 mm^{-1}
F(000)	496

Data Collection

Diffractometer Used	Siemens R3m/V
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	0
Monochromator	Highly oriented graphite crystal
2θ Range	3.5 to 55.0^{o}
Scan Type	2θ-θ
Scan Speed	Variable; 3.00 to 15.00^{o}/min. in ω
Scan Range (ω)	1.20^{o} plus Kα-separation
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 200 reflections
Index Ranges	$0 \leq h \leq 11$, $0 \leq k \leq 12$ $-12 \leq \ell \leq 11$
Reflections Collected	1842
Independent Reflections	1639 (R_{int} = 1.68%)
Observed Reflections	1160 ($F > 4.0\sigma(F)$)
Absorption Correction	N/A

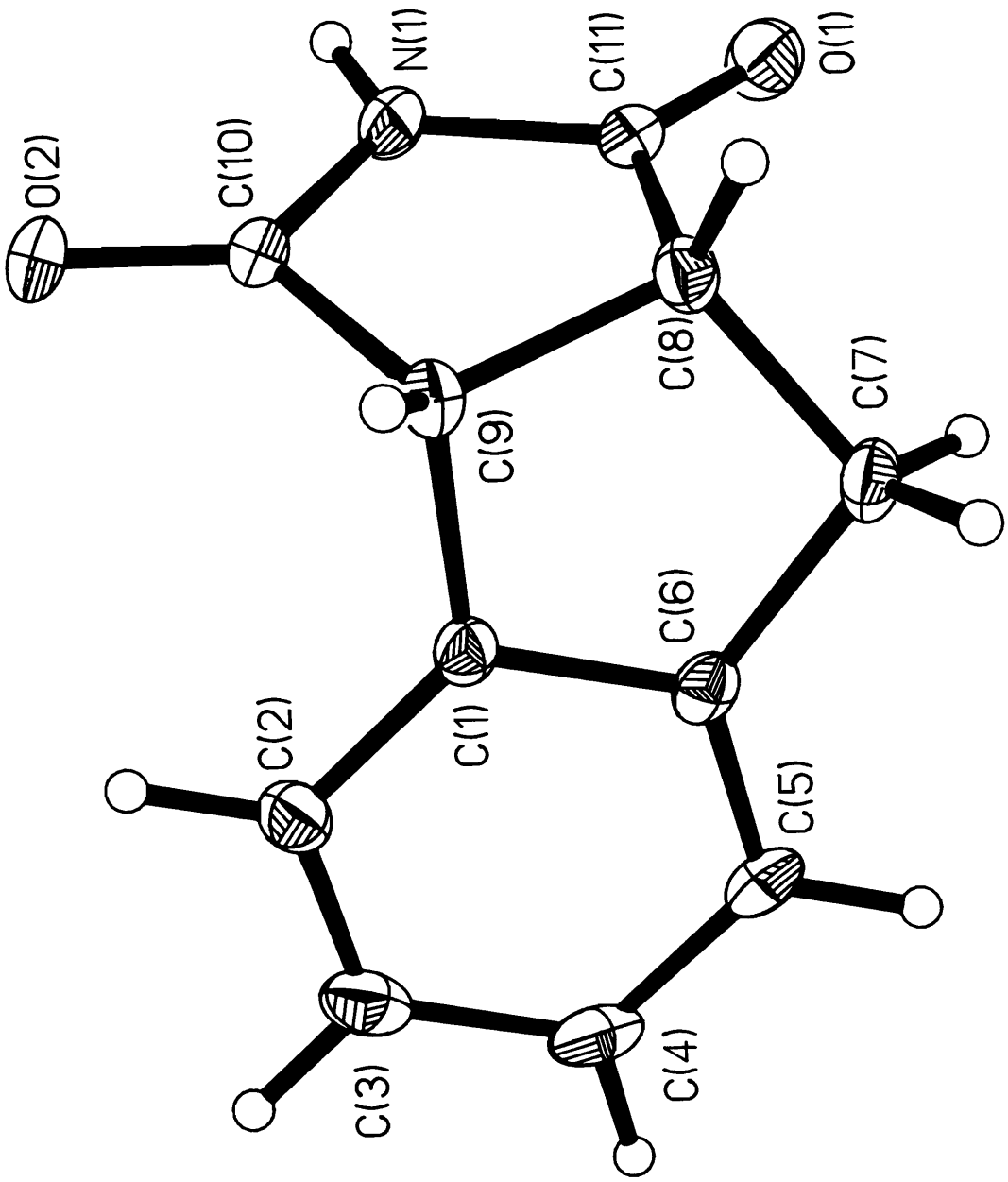
Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o - F_c)^2$
Absolute Structure	N/A
Extinction Correction	χ = 0.0049(8), where $F^* = F [1 + 0.002\chi F^2/\sin(2\theta)]^{-1/4}$
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0004F^2$
Number of Parameters refined	155
Final R indices (obs. data)	R = 5.53 %, wR = 6.41 %
R Indices (all data)	R = 7.97 %, wR = 6.74 %
Goodness-of-Fit	1.98
Largest and Mean Δ/σ	0.018, 0.004
Data-to-Parameter Ratio	7.5:1
Largest Difference Peak	0.23 eA^{-3}
Largest Difference Hole	-0.22 eA^{-3}

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($Å^2 x10^3$)

	x	y	z	U(eq)
C(1)	3633(3)	5099(3)	7601(3)	46(1)
C(2)	4856(3)	5951(3)	7855(3)	49(1)
C(3)	6066(4)	5197(3)	7717(3)	66(2)
C(4)	5894(6)	3515(4)	6117(5)	92(2)
C(5)	5032(8)	2703(5)	5345(5)	106(3)
C(6)	3682(7)	2622(4)	5284(4)	97(3)
C(7)	3129(5)	3370(3)	5990(4)	72(2)
C(8)	3982(4)	4187(3)	6747(3)	52(1)
C(9)	5349(4)	4261(3)	6814(3)	62(2)
C(11)	2286(4)	5720(3)	7018(3)	49(1)
C(12)	5159(4)	6586(3)	9079(4)	52(2)
C(13)	-149(4)	5938(4)	6678(4)	83(2)
C(14)	1131(4)	4406(4)	8130(4)	87(2)
N(1)	1162(3)	5353(3)	7256(3)	58(1)
O(1)	2255(3)	6558(2)	6292(2)	72(1)
O(2)	4546(3)	6466(2)	9814(3)	72(1)
O(3)	6212(3)	7302(3)	9251(3)	100(2)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor


O(2)
C(10)
N(1)
C(11)
O(1)
C(8)
C(7)
C(9)
C(6)
C(2)
C(1)
C(5)
C(3)
C(4)

STRUCTURE DETERMINATION SUMMARY

Crystal Data

Empirical Formula	$C_{11} H_9 N O_2$
Color; Habit	White rectangular prism
Crystal Size (mm)	0.3 x 0.3 x 0.4
Crystal System	Monoclinic
Space Group	$P2_1/n$
Unit Cell Dimensions	a = 13.439(6) Å
	b = 4.633(2) Å
	c = 14.964(7) Å
	β = 107.69(4)°
Volume	887.7(7) $Å^3$
Z	4
Formula weight	187.2
Density(calc.)	1.401 Mg/m^3
Absorption Coefficient	0.091 mm^{-1}
F(000)	392

Data Collection

Diffractometer Used	Siemens R3m/V
Radiation	MoKα (λ = 0.71073 Å)
Temperature (K)	0
Monochromator	Highly oriented graphite crystal
2θ Range	3.5 to 55.0°
Scan Type	2θ-θ
Scan Speed	Variable; 2.50 to 20.00°/min. in ω
Scan Range (ω)	1.20° plus Kα-separation
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 200 reflections
Index Ranges	$0 \leq h \leq 17$, $0 \leq k \leq 6$ $-19 \leq \ell \leq 18$
Reflections Collected	2308
Independent Reflections	1980 (R_{int} = 4.24%)
Observed Reflections	1594 ($F > 4.0\sigma(F)$)
Absorption Correction	N/A

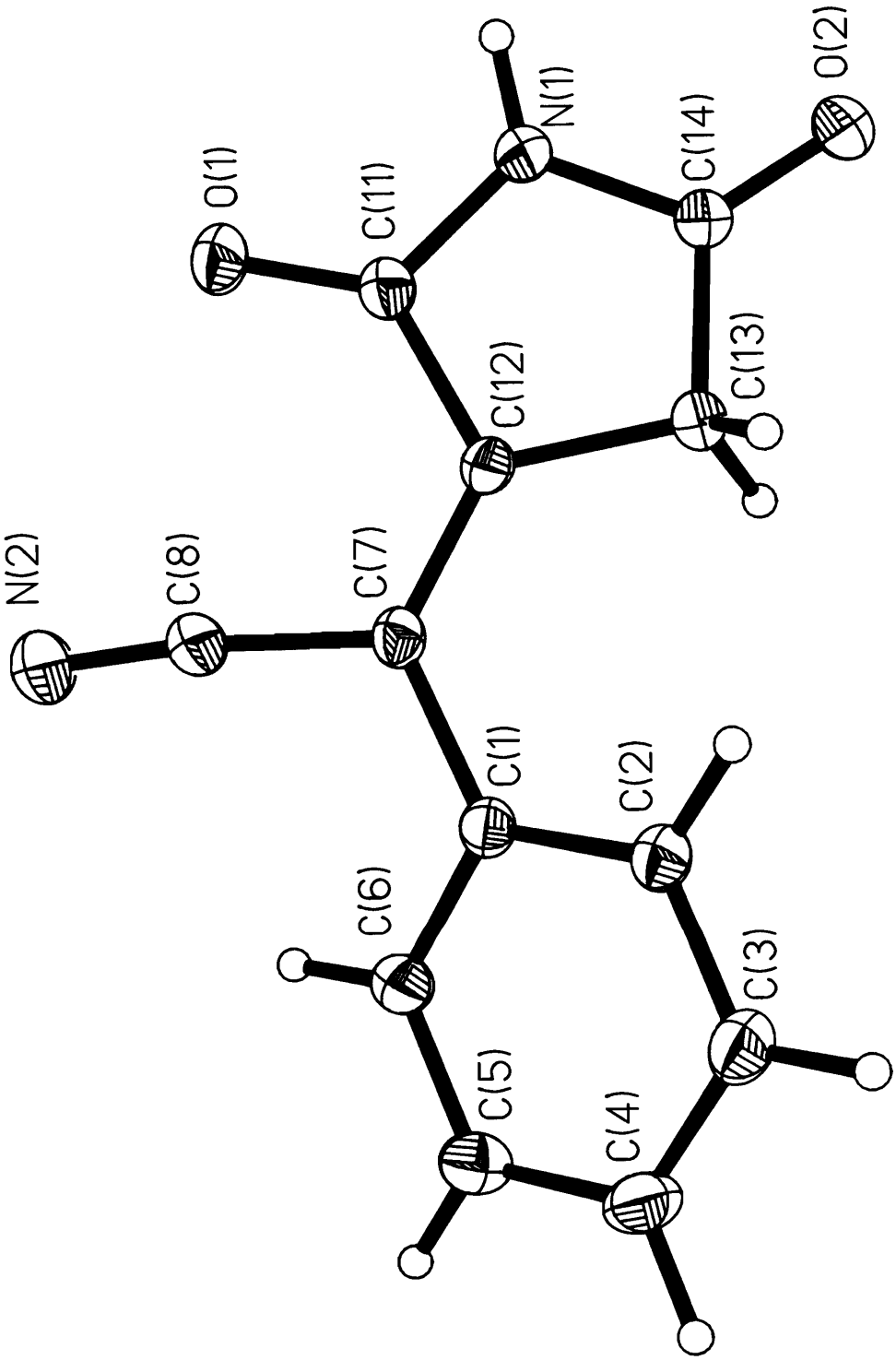
Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o-F_c)^2$
Absolute Structure	N/A
Extinction Correction	N/A
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	Unit weights
Number of Parameters refined	127
Final R indices (obs. data)	R = 8.20 %, wR = 9.18 %
R Indices (all data)	R = 9.67 %, wR = 9.76 %
Goodness-of-Fit	1.04
Largest and Mean Δ/σ	0.001, 0.000
Data-to-Parameter Ratio	12.6:1
Largest Difference Peak	0.41 eA^{-3}
Largest Difference Hole	-0.41 eA^{-3}

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients ($A^2 x10^3$)

	x	y	z	U(eq)
C(1)	1886(3)	2101(10)	4582(2)	34(1)
C(2)	863(3)	3064(12)	4363(3)	47(2)
C(3)	511(3)	4984(13)	3655(3)	55(2)
C(4)	1164(4)	6091(13)	3158(3)	59(2)
C(5)	2186(4)	5048(11)	3375(3)	49(2)
C(6)	2550(3)	3151(9)	4093(2)	36(1)
C(7)	3620(3)	1780(11)	4446(3)	42(1)
C(8)	3615(3)	374(10)	5380(3)	39(1)
C(9)	2463(3)	-59(10)	5345(3)	38(1)
C(10)	2430(3)	984(12)	6297(3)	48(2)
C(11)	4041(3)	2404(11)	6203(3)	41(1)
N(1)	3335(3)	2483(10)	6721(2)	50(1)
O(1)	4840(2)	3786(9)	6399(2)	60(1)
O(2)	1719(2)	621(11)	6634(2)	73(2)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor


O(2)
N(1)
C(14)
O(1)
C(11)
C(13)
C(12)
N(2)
C(8)
C(7)
C(1)
C(2)
C(6)
C(3)
C(5)
C(4)

STRUCTURE DETERMINATION SUMMARY

Crystal Data

Empirical Formula	$C_{12} H_8 N_2 O_2$
Color; Habit	Amber rectangular prism
Crystal Size (mm)	0.8 x 0.5 x 0.2
Crystal System	Monoclinic
Space Group	$P2_1/m$
Unit Cell Dimensions	a = 16.408(3) A
	b = 7.5226(12) A
	c = 17.106(3) A
	β = 92.508(13)°
Volume	2109.4(6) A^3
Z	8
Formula weight	212.2
Density(calc.)	1.336 Mg/m^3
Absorption Coefficient	0.088 mm^{-1}
F(000)	880

Data Collection

Diffractometer Used	Siemens R3m/V
Radiation	MoKα (λ = 0.71073 A)
Temperature (K)	0
Monochromator	Highly oriented graphite crystal
2θ Range	3.5 to 55.0^{o}
Scan Type	2θ-θ
Scan Speed	Variable; 1.50 to 15.00^{o}/min. in ω
Scan Range (ω)	1.20^{o} plus Kα-separation
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 25.0% of total scan time
Standard Reflections	3 measured every 200 reflections
Index Ranges	$-10 \leq h \leq 0$, $-9 \leq k \leq 0$ $-22 \leq \ell \leq 22$
Reflections Collected	3676
Independent Reflections	3297 (R_{int} = 1.05%)
Observed Reflections	2748 ($F > 3.0\sigma(F)$)
Absorption Correction	N/A

Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w(F_o-F_c)^2$
Absolute Structure	N/A
Extinction Correction	χ = 0.0033(4), where $F^* = F [1 + 0.002\chi F^2/\sin(2\theta)]^{-1/4}$
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0008F^2$
Number of Parameters refined	290
Final R indices (obs. data)	R = 4.36 %, wR = 5.95 %
R Indices (all data)	R = 5.13 %, wR = 6.16 %
Goodness-of-Fit	1.69
Largest and Mean Δ/σ	0.018, 0.001
Data-to-Parameter Ratio	9.5:1
Largest Difference Peak	0.22 eA^{-3}
Largest Difference Hole	-0.15 eA^{-3}

Table 1. Atomic coordinates ($x10^4$) and equivalent isotropic displacement coefficients (A^2x10^3)

	x	y	z	U(eq)
C(1)	7560(1)	722(2)	7946(1)	41(1)
C(2)	8203(2)	1111(2)	7463(1)	50(1)
C(3)	9001(2)	979(3)	7739(1)	63(1)
C(4)	9178(1)	445(3)	8507(1)	66(1)
C(5)	8555(2)	38(3)	8986(1)	62(1)
C(6)	7760(1)	181(2)	8717(1)	50(1)
C(7)	6697(1)	935(2)	7685(1)	41(1)
C(8)	6153(1)	1326(3)	8309(1)	57(1)
C(11)	5494(1)	992(2)	6741(1)	46(1)
C(12)	6371(1)	755(2)	6949(1)	39(1)
C(13)	6775(1)	156(2)	6222(1)	46(1)
C(14)	6068(1)	-118(2)	5643(1)	48(1)
O(1)	4954(1)	1529(2)	7142(1)	62(1)
O(2)	6098(1)	-722(2)	4985(1)	68(1)
N(1)	5373(1)	462(2)	5973(1)	52(1)
N(2)	5782(1)	1572(3)	8847(1)	89(1)
C(1A)	2172(1)	3176(2)	-2572(1)	45(1)
C(2A)	2718(1)	2778(2)	-3143(1)	50(1)
C(3A)	2482(2)	2958(3)	-3931(1)	64(1)
C(4A)	1715(2)	3534(3)	-4150(1)	68(1)
C(5A)	1167(2)	3953(2)	-3589(1)	65(1)
C(6A)	1390(1)	3755(2)	-2801(1)	55(1)
C(7A)	2392(1)	2972(2)	-1720(1)	42(1)
C(8A)	1727(2)	2415(3)	-1255(1)	56(1)
C(11A)	3307(1)	3234(2)	-509(1)	45(1)
C(12A)	3125(1)	3327(2)	-1378(1)	39(1)
C(13A)	3871(1)	4052(2)	-1732(1)	44(1)
C(14A)	4405(1)	4622(2)	-1035(1)	46(1)
O(1A)	2883(1)	2624(2)	-11(1)	62(1)
O(2A)	5034(1)	5462(2)	-1047(1)	61(1)
N(1A)	4053(1)	4014(2)	-373(1)	51(1)
N(2A)	1158(1)	1979(3)	-942(1)	86(1)

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

X. VITA

Sushama Ashok Dandekar (nee Gadre) was born in Pune, India on June 1, 1956, to Vimal and Ramakrishna Gadre. In August 1975 she received her B.S. degree in chemistry from University of Bombay, India, where she graduated with honors and distinction. In August 1977 she received her M.S. degree in chemistry from the University of Bombay where she graduated with honors. In September of 1984 she began her graduate studies in chemistry at Virginia Polytechnic Institute and State University under the guidance of Dr. James F. Wolfe. For the past two years she has been teaching at William Rainey Harper College in Palatine, Illinois.