PART A. SYNTHESIS OF NEW 2-SUBSTITUTED-3-ARYL-4(3H)-QUINAZOLINONES AS POTENTIAL CNS AGENTS

PART B. REACTIONS OF β-DIKETONES WITH BENZOPHENONE IN THE PRESENCE OF POTASSIUM HYDRIDE

by

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I. INTRODUCTION

This dissertation deals with two studies involving carbanion chemistry. Since it is more appropriate to consider each investigation separately, the dissertation is divided into two parts.

Part A deals with the synthesis of new 2-substituted-3-aryl-4(3H)-quinazolinones as potential CNS agents. The synthetic approach taken in this study involved metalation at the 2-methyl group of 2-methyl-3-o-tolyl-4(3H)-quinazolinone, methaqualone, followed by condensation of various electrophiles at the resulting carbanionic site. Forty-four new 2,3-disubstituted-4-(3H)-quinazolinones were prepared by such condensations at the 2-methyl group of methaqualone and several related 2-methyl-3-aryl-4(3H)-quinazolinones. The general CNS activity of twenty of these compounds were determined by Pharmakon Laboratories. In addition, twenty-nine of these derivatives were screened specifically for anticonvulsant activity by the National Institute of Neurological and Communicative Disorders and Stroke as part of their Antiepileptic Drug Development Program.

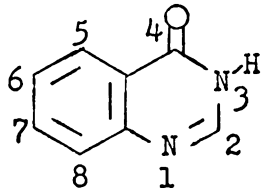
Part B is devoted to a description of an investigation of reactions of acetylacetone and benzoylacetone with benzophenone in the presence of excess potassium hydride. A mechanistic study of these reactions, which led to aldol condensation of benzophenone at the terminal methyl group of the respective diketones, is presented.

PART A:

SYNTHESIS OF NEW 2,3-DISUBSTITUTED-4(3H)-QUINAZOLINONES AS POTENTIAL CNS AGENTS

II. HISTORICAL

Interest in derivatives of 4(3H)-quinazolinones (1) as medicinal agents was stimulated by the elucidation of the structure[1] of febrifugine (2) in 1950. This compound is the active principle of the ancient antimalarial preparation Ch'ang Shan. Consequently, many synthetic derivatives[2] of 2 as well as other compounds containing the 4(3H)-quinazolinone nucleus (1) began appearing in the literature.* The pharmacological properties of these compounds encompass a large variety of activities (Table I).



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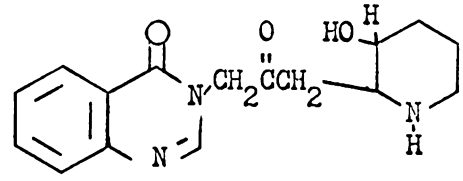

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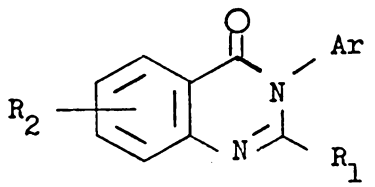
A definite trend toward sedative-hypnotic and anticonvulsant activity has emerged for 4(3H)-quinazolinones possessing both a 2-alkyl and a 3-aryl substitutient.[15] Of this class, 2-methyl-3-o-tolyl-4(3H)-quinazolinone, or methaqualone (3) gained FDA approval in 1962 and is presently marketed by Rorer and Arnar-Stone in the United States under such names as Quaalude and Sopor, respectively.[16] Although

*For a comprehensive discussion of the synthesis and a listing of 4(3H)-quinazolinones, see Ref. 3.

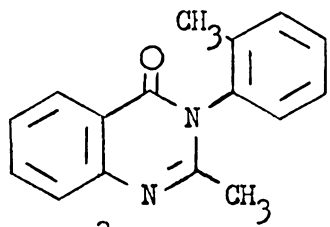
Table I

Pharmacological Activities for Certain 2-Substituted-3-aryl-4(3H)-quinazolinones



Compound #	R_1	Ar	R_2	Activity	Reference(s)
3	methyl	o-tolyl	H	sedative-hypnotic	4,5
4a	methyl	o-chlorophenyl	H	hypnotic-anticonvulsant	6,7
4b	methyl	o-tolyl	6-amino	muscle relaxant	8
4c	methyl	o-tolyl	fluoromethyl	hypnotic-anticonvulsant	9
4e	n-propyl	o-tolyl	6-amino	analgesic	10
4d	methyl	p-allyloxyphenyl	H	NAD inhibitors	11
4f	methyl	o-tolyl	6-fluoro	inhibits pyruvic acid oxidation	12
4g	methyl	4-hydroxy-2-methylphenyl	H	antifertility	13
4h	methyl	o-tolyl	6-Cl	anticonvulsant	14

3 is prescribed as a sedative-hypnotic, originally it was synthesized as a potential analgesic.[17] However, there is only slender evidence that it has such activity[18] or that it potentiates the analgesic effect of codeine.[6]



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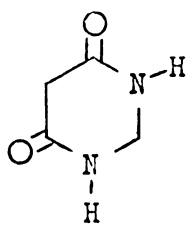

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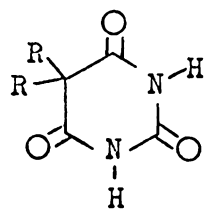


6

Methaqualone is both a cyclic amide and a pyrimidine derivative and as such has a formal structural resemblance to piperidone (5) and barbiturate (6) hypnotics.[19] A comparison of the pharmacologic properties of 3 with compounds 6 reveals that it is comparable to short-acting barbiturates in terms of sedative-hypnotic activity.[4]

Methaqualone is superior to sodium phenobarbitone in preventing pentylenetetrazol (Metrazol) induced convulsive seizures in mice,[5] while phenobarbital is a better[20] protector against maximal electroshock seizures (MES). It should be noted here that compounds which afford protection against Metrazol induced seizures may be useful as anticonvulsants for the treatment of petit mal epilepsy. Protection

against MES induced convulsions is indicative of possible activity as an anticonvulsant for prevent of grand mal epileptic seizures.[21] Additional details concerning these tests are given in chapter IV.

The hypnotic and anticonvulsant properties of 4(3H)-quinazolinones have been demonstrated by many investigators, and several studies of structure-activity relationships have been conducted.[15,22,23] In particular, Boltze and associates,[15] have found that introduction of substituents onto the quinazolinone nucleus of 3 or reduction to the 1,2-dihydro derivative abolishes depressant activity. The lack of hypnotic activity in the 5,6,7,8-tetrahydro derivative[23,24] of 3 indicates that planarity of the entire bicyclic system is essential for such activity. Other integral parts of the quinazolinone ring, which appear to be necessary for sedative-hypnotic activity, include the carbon[23] at position 8, the 3-amide nitrogen, the carbonyl oxygen,[15] and the 2-methyl group.[25] The methyl group of the 3-o-tolyl residue of 3 can be replaced by substituents such as a bromo,[26] chloro, fluoro, methoxy, hydroxy, or amino[15] without much loss of depressant activity.

It has been found that certain substituents on the 3-aryl residue decrease the hypnotic effect while enhancing anticonvulsant activity.[15] This has been observed in the following changes in the 3-o-tolyl group:

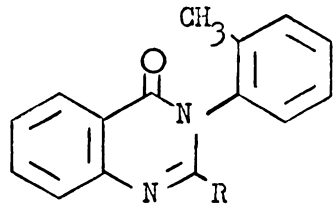
(1) Introduction of an additional 4-amino,[23] 3-chloro or 4-chloro[15] substituent, or

(2) Exchange of the o-methyl group for a 4-bromo[22] or 4-chloro[27] substituent.

Although it appears that the cause for separation of hypnotic and anticonvulsant activity may be a function of ortho vs. para substitution

on the 3-aryl group, it has been observed that 2-methyl-3-o-chlorophenyl-4(3H)-quinazolinone (4a) (mecloqualone)[6] is a better anticonvulsant agent than methaqualone (3) and that 2-methyl-3-(p-diethylaminophenyl)-4(3H)-quinazolinone[23] is of equal hypnotic activity to methaqualone.

Anticonvulsant activity can also be enhanced by adding certain substituents around the perimeter of the quinazolinone ring while keeping the 3-o-tolyl group unchanged. For example, addition of a 6-chloro[14] group or larger alkyl group (7a) at the 2 position increases the anticonvulsant activity at the expense of sedative-hypnotic action.[15] Anticonvulsant activity also emerges when the 2-substituent is a 2-arylethenyl derivative of type 7b. Such compounds have been prepared in low yields by reacting 3 with various aromatic aldehydes in the presence of alkali alkoxides.[15] Boltze, et al., have shown that anticonvulsant activity is greatest,[15] when Ar = 2-pyridyl, 7b.



7a, R = alkyl > CH_3

b, R = CH=CH-Ar

8a, R = CHBrCHBr-2-pyridyl

b, R = CH=CH-3-pyridyl$^+$ CH_3I^-

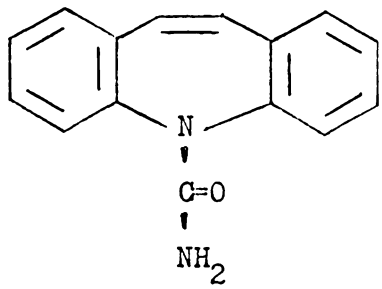
c, R = C≡C-2-pyridyl

d, R = CH_2CH_2-N-piperidinyl

It is interesting to note that compounds 8a-d exhibit a considerable

decrease in anticonvulsant activity or an increase in toxicity when compared to 7a-b.

In early 1974, there were 13 marketed antiepileptic drugs.[28] No new drug had received FDA approval as an antiepileptic since 1960. Although clinicians estimate that the commercial antiepileptic drugs controlled seizures in 70-80% of patients, a National Institute of Neurological and Communicative Diseases and Stroke (NINCDS) survey of the literature in 1970 failed to reveal data that substantiated such efficacy.[29] Such data is not truely documented and may well be below the quoted percentages.[30] In addition there are certain types of seizures for which there are no specific drugs, and others for which controlling therapy is accompanied by significant toxicity.[29] There can be no doubt that new agents with greater specificity and less toxicity would mean significant therapeutic advances in the treatment of epilepsy. Recently, as a result of the clear cut proof of efficacy of carbamazepine (9) and clonazepam (10) in clinical trials[31,32] supported by NINCDS, FDA approved 9 and 10 for marketing as anti-convulsants.



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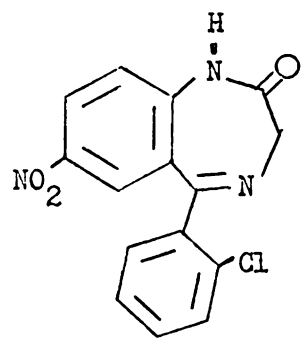

10

In order to stimulate interest in the development of new antiepileptic drugs, NINCDS also expanded its Antiepileptic Drug Development (ADD) Program in January, 1975 by initiating the Anticonvulsant Screening Project, which is designed to determine the potential use of compounds as antiepileptics by measuring anticonvulsant activity and neurotoxicity in appropriate animal models.

The definite trend toward anticonvulsant activity which has been observed in certain 2-substituted-4(3H)-quinazolinones[15] such as (7a) and (7b) coupled with the fact that none of the thirteen commercially available anticonvulsant compounds contain the 4(3H)-quinazolinone,[28] prompted initiation of the present study. This investigation was directed toward the preparation of new, 2-substituted derivatives of the 3-aryl-4(3H)-quinazolinones as potential antiepileptic agents.

2-Substituted-3-aryl-4(3H)-quinazolinones, (12 and 13), are normally prepared by two general methods. The first method involves cyclization of appropriate anthranilic acid derivatives with various other reactants. For instance, N-acylated anthranilic acids 11a may be reacted with aromatic amines in the presence of phosphorous trichloride to give 4(3H)-quinazolinones 12, where R_3 = Ar and R_4 = alkyl.[4,33] This particular method[34] is most extensively employed for preparing compounds of type 12 with $R_4 = CH_3$.* Compounds of class 12 can also be prepared by condensing o-aminobenzanilide derivatives 11b with aliphatic acids.[36]

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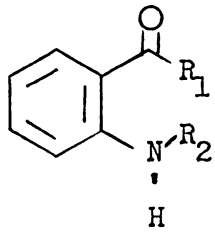
*3,1,4-Benzoazones have also found limited use in the preparation of substituted-3-aryl-4(3H)-quinazolinones.[35]

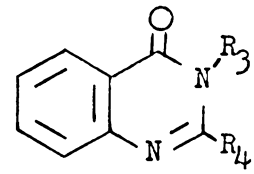


11a, R_1 = OH, R_2 = CO-alkyl

b, R_1 = NH-Ar, R_2 = H

c, R_1 = NH-Ar, R_2 = CO-alkyl

d, R_1 = NH-Ar, R_2 = CO-aryl



12, R_3 = Ar, R_4 = alkyl

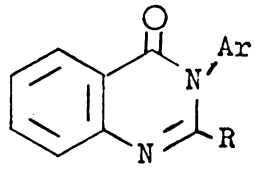
13, R_3 = R_4 = Ar

Direct cyclization of anthranilic acid derivatives 11c has been used to prepare compounds of type 12.[37]

2,3-Diaryl-4(3H)-quinazolinones 13 have been primarily prepared by direct cyclization[38] of the anthranilic acid derivative 11d. These compounds have resulted from the treatment of anthranilic acid with thioarylanilides in the presence of excess methyl anthranilate.[39] Also a modified Willgerodt-Kindler reaction has proven useful for the preparation of such compounds.[38]

2-Halomethyl-3-aryl-4(3H)-quinazolinones, such as 2-chloromethyl derivatives 14a are prepared by direct cyclization of arylamides of N-chloroacetyl anthranilic acid.[37] The 2-bromomethyl-3-aryl derivatives 14b have been prepared by direct bromination of the corresponding 2-methyl-3-aryl derivatives with N-bromosuccinimide.[40]

Treatment of anthranilic acid with aryl isothiocyanates yields the 2-thio-3-aryl derivatives (14c).[41,42]



14a, R = CH_2Cl

b, R = CH_2Br

c, R = SH

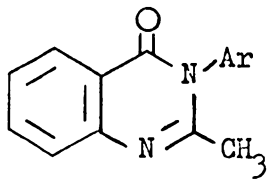
15a, R = CH_2F, CH_2O_2CR, NH_2 NHR, NR_2

b, R = CH_2CN, CH_2O-Alkyl or-Aryl

c, R = S-alkyl, S-allyl, S-benzyl S-phenacyl, S-acetonyl

The second general method for preparing substituted 4(3H)-quinazolinones results from direct chemical modification of quinazolinones originally prepared by cyclization. For instance, the 2-halomethyl derivatives 14a and 14b may be employed as electrophilic reagents in reactions with various nucleophilic species to give the corresponding 2-substituted-3-aryl-derivatives (15a)[43,44,45] and (15b).[40] Another large class of compounds, 15c can be prepared by treating 14c with various alkylating agents in alcoholic sodium hydroxide.[46,47]

Direct functionalization[15] of the 2-methyl group of 2-methyl-3-aryl-4(3H)-quinazolinones (16) has been achieved by base-catalyzed condensations with aromatic aldehydes to give styryl derivatives 17. Similar compounds can be prepared by reactions of 16 with aryl aldehydes in the presence of acetic acid-acetic anhydride.[40] It has also been reported that compounds of type 17 can be prepared in high yields by simply heating a mixture of the appropriate 2-methyl-4(3H)-quinazolinone and an aromatic aldehyde at 150-180°. The success of this reaction is



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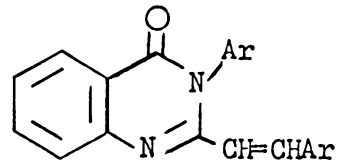
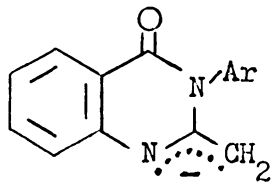


17

not deterred by the presence of a hydrogen, methyl, ethyl, phenyl, p-methoxyphenyl, and α- or β-naphthyl groups on the amide nitrogen.[48]

Condensations with aryl aldehydes are dependent on the liability of the protons of the lateral methyl of the approximate 2-methyl-3-aryl-4(3H)-quinazolinone, which allows formation of a reactive intermediate.[40] In the case of base catalysis the intermediate is the resonance stabilized anion 18. In the acid catalyzed reactions it is thought to be the prototopic tautomer 19. However, owing to the nature of the reaction conditions, the intermediates 18 and 19 are present in only low equilibrium concentration. Undoubtedly the success of these condensations is dependent upon dehydration of the appropriate aldol intermediates to drive the reaction to completion.



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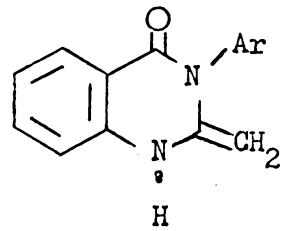
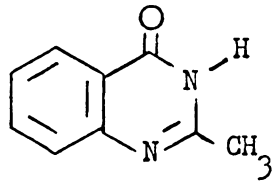


19

The success of aldol type condensations has been shown to be dependent on the nature of the substituents present on the quinazolinone ring and the type of electrophile employed. In the uncatalyzed condensations with aromatic aldehydes, the activating power of the 4-oxo group is demonstrated by the observation that the reactivity of the 2-methyl group of 2-methyl-4(3H)-quinazolinone (20) is greater than that of the 2-methyl group of 2-methylquinazoline (21).[48]



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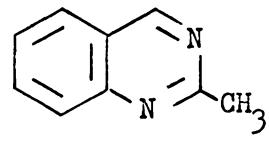
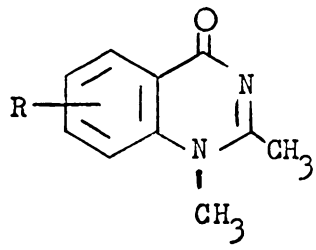
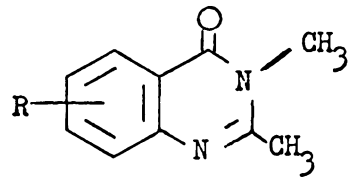


21

Heilbron and collaborators[49] have shown that 1,2-dimethyl-4(1H)-quinazolinones (22a-c), 2,3-dimethyl-4(3H)-quinazolinones (23a) and its 7-methoxy derivative 23c underwent condensation with benzaldehyde in the presence of ethanolic sodium ethoxide. However, 2,3-dimethyl-6-methoxy-4(3H)-quinazolinone (23b) failed to react with benzaldehyde under a variety of conditions, even when anhydrous zinc chloride was added to a melt of the reactants. They also found that the 2-methyl group in 2-methyl-4(1H)-quinazolinone (22a) was more reactive than 2-methyl group of 2-methyl-4(3H)-quinazolinone (20).





22a, R = H

b, R = 6-OCH_3

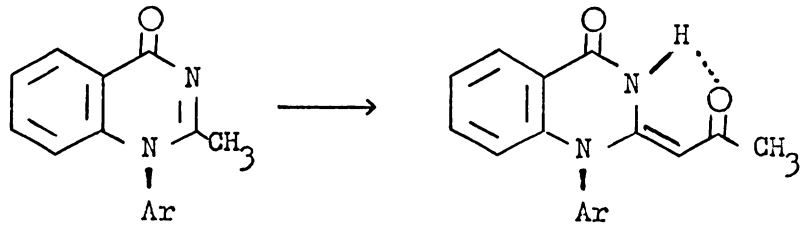
c, R = 7-OCH_3

23a, R = H

b, R = 6-OCH_3

c, R = 7-OCH_3

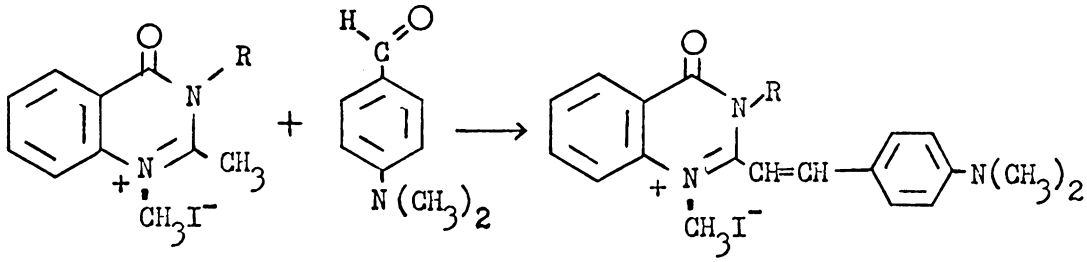
Acetylation of 2-methyl-1-phenyl-4(1H)-quinazolinone (24) in refluxing acetic anhydride lead to acetonyl derivative 25 (Eq. 1).[50] Related acetonyl compounds have not been prepared from compounds of type 20. The only known 2-acetonyl derivative of a 2,3-disubstituted-4(3H)-quinazolinone appears to be 2-acetonyl-3-methyl-4(3H)-quinazolinone, which was prepared by cyclization rather than side-chain acetylation.[51]



(1)

24 25

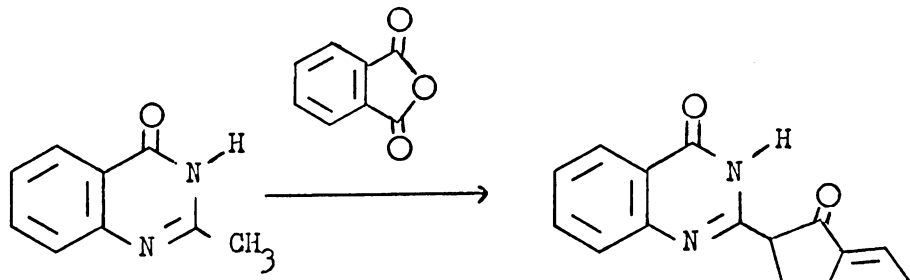
Quaternary salts of 2-methyl-4(3H)-quinazolinones (26) condense more readily with aryl aldehydes than 22a and 23a to give both cis- and trans-2-styryl derivatives 27 (Eq. 2).[52]



(2)

26, R = H, CH_3, C_2H_5 27, R = H, CH_3, C_2H_5

2-Methyl-4(3H)-quinazolinone (20) undergoes condensation with phthalic anhydride at the fusion point of the mixture to give the respective phthalone, (28) (Eq. 3), whereas anhydrous zinc chloride at 200° is necessary to bring about the same condensation with phthalimide.[53]

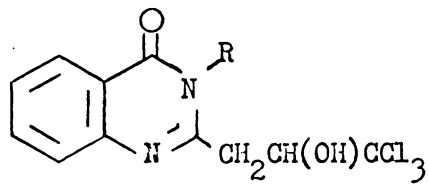


(3)

20 28

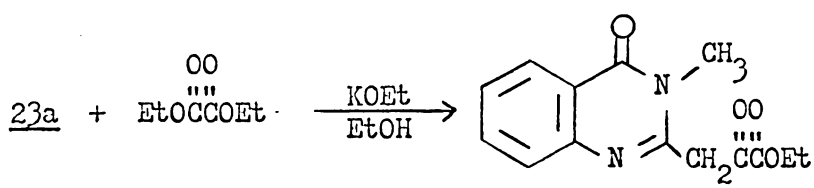
The only aldol type product derived from a 2-methyl-4(3H)-quinazolinone (20) which has been prepared to date involved condensation of chloral with 20 and several 2-methyl-3-substituted-4(3H)-quinazolinones to give the respective 2-(3,3,3-trichloro-2-hydroxy) propyl derivatives 29a-c. Acid catalysis[54] was employed in the preparation of 29a, while

29b and c were prepared by refluxing the reactants in high boiling solvents or by base catalysis using pyridine.[15,40]



29a, R = H
b, R = CH_3
c, R = C_6H_5

The only Claisen type reaction which has been reported for a 2-methyl-3-substituted-4(3H)-quinazolinone involved reactions of 2,3-dimethyl-4(3H)-quinazolinone (23a) with ethyl oxalate in alcoholic potassium ethoxide solution[55] to yield the 2-ethoxalylmethyl derivative 30 (Eq. 4). The same reaction failed with (20).[48] This is a recurring



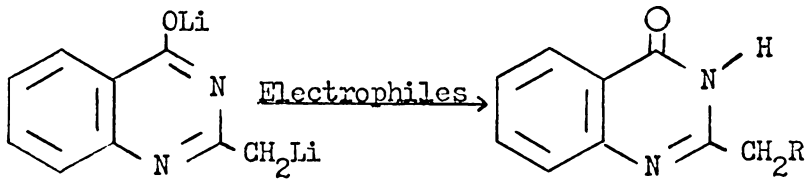
(4)

30

observation for all base catalyzed condensations involving 2-methyl-4(3H)-quinazolinones (20) which do not have a substituent attached to N-3.

Recently the use of stronger bases that can quantitatively metalate "active" methylheteroaromatics has been demonstrated to be a convenient route to direct functionalization of 2-methyl-4(3H)-quinazolinone (20). It was shown that treatment of 20 with 2 equivalents of n-

butyllithium produces dilithio salt 31. Reactions of 31 with electrophiles take place exclusively at the carbanion site to give 2-substituted quinazolinone 32 (Eq. 5).[56]



31 32 (5)

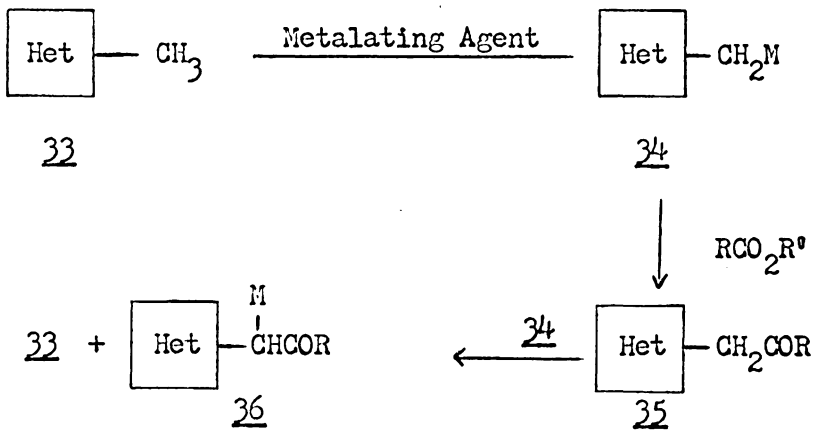
The utility of organolithium reagents as metalating agents has been demonstrated with various methylheteroaromatics;[57,58] however, the generation of 31 appears to be the only reported example of lateral metalation of a 2-alkyl-4(3H)-quinazolinone.

The overall efficiency of the lateral metalation process of alkylated heteroaromatics is sometimes impaired by side reactions, such as heteroaromatic nucleophilic substitution,[59] or addition of the metalating reagent to carbonyl groups present in the heterocyclic substrate. Alkali amides or alkali salts of certain dialkylamines are often more satisfactory metalating agents for methylated heterocycles because they are weaker nucleophiles than organolithium reagents.[60]

Even though many methylated heteroaromatics (33) can be converted into synthetically useful carbanionic intermediates by lateral metalation, reactions of such intermediates with certain electrophilic

reagents are hampered by inherently unfavorable stoichiometry. As a prime example of such a problem, let us consider acylation of a hypothetical carbanion intermediate such as 34 with an ester (Scheme I).[61] In such a reaction the yield of 35 is limited to 50% because intermediates such as 34 usually abstract a methylene proton from the desired product 35 to form the less basic carbanion 36 more rapidly than 34 condenses with the ester.[62] Thus, when a 1:1:1 molar ratio of heterocycle to base to ester is employed, only half of the hetero-

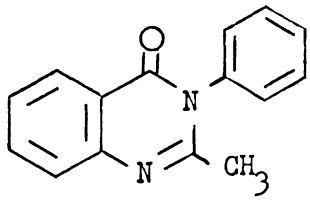
SCHEME I



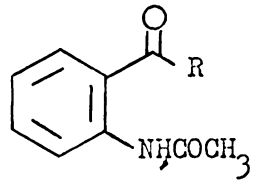
aromatic and ester are consumed. Even when the metalated heteroaromatic is added to the ester (inverse addition), the yield is still limited to 50%.[62] Consumption of the ester is improved by carrying out the condensations with a 2:2:1 molar ratio of heterocycle to base to ester;[63] however, a molecular equivalent of starting heterocyclic remains unchanged, and must be separated from the desired product. Moreover, if the heteroaromatic is expensive, the disadvantage of such a sequence is obvious.

Fortunately, the above problem can be circumvented by employing sodium hydride as the basic reagent with nonenolizable esters.[64] Two equivalents of sodium hydride are required, one for the initial ionization of a lateral methyl proton to form 34 and a second to cause ionization of the methylene proton of the Claisen product 35. Measurement of the hydrogen evolved can be used to determine when acylation is complete.

The use of Grignard reagents, as metalating agents of methylated quinazolinones is unsatisfactory since these organometallics add to the carbonyl group.[65] For example, treatment of 2-methyl-3-phenyl-4(3H)-quinazolinones (37) with one equivalent of ethyl- or phenylmagnesium bromide gave 38a-b on hydrolysis of the reaction mixture, and two equivalents of the same Grignard reagents afforded 39a-b.[66]

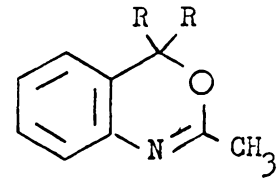


37



38a, R = C_2H_5

b, R = C_6H_5



39a, R = C_2H_5

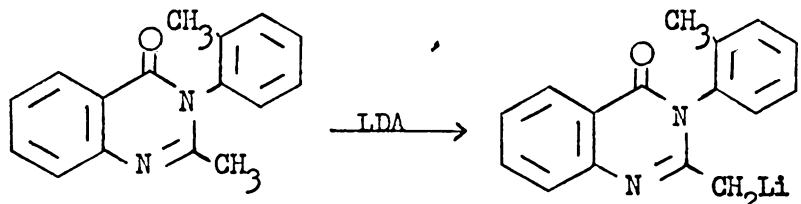
b, R = C_6H_5

In view of the present state of the art of carrying out in functionalization of certain methylated heteroaromatics via intermediate metalation salts,[56,64] it seemed that application of these techniques to a direct route for functionalizing the pharmacologically active 4(3H)-quinazolinones would be of considerable interest as a route to new compounds which might well exhibit interesting CNS activity.

III. RESULTS AND DISCUSSION

As outlined in the historical chapter, 2-methyl-4(3H)-quinazolinone (20) undergoes twofold metalation with n-butyllithium to form dilithio salt 31, which reacts with alkyl halides and carbonyl compounds exclusively at the exocyclic carbanion site to form derivatives of type 32.[56] It, therefore, seemed possible that methaqualone (3) and related 2-methyl-3-substituted-4(3H)-quinazolinones might undergo similar metalation at the 2-methyl group. Generation of a lateral carbanion in these molecules could then provide a site for elaboration of the original 2-methyl substituent to give a variety of new 2,3-disubstituted quinazolinones.

In the present study, lithium diisopropylamide (LDA) was used for effecting metalation of the lateral 2-methyl group of (3) to form monolithio salt 40 (Eq. 6). Reactions of 40 with various electrophiles, which are described in this chapter, provide a detailed description of



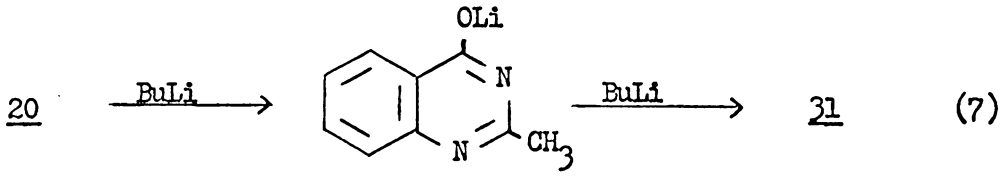
3 40

the chemical nature of this carbanionic intermediate.

In a series of initial attempts to effect formation of lithio salt 40, 3 was treated with one equivalent of n-butyllithium in THF-hexane at 0°. The resulting reaction mixture was then quenched with water, and processed to give a dark oil, which upon analysis by thin

layer chromatography (TLC) revealed five major components, one of which corresponded to 3. Column chromatography afforded 42% of unreacted 3. Preparative TLC of the remaining four fractions showed that each fraction was also a multicomponent mixture, and that certain components decomposed on standing in air. Although further attempts to isolate any of the unidentified components failed, it appears that attack at the carbonyl group of 3 by n-butyllithium seriously competes with side-chain metalation.

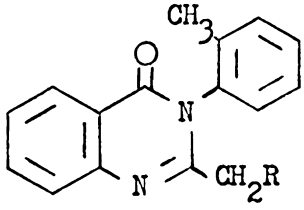
The apparent carbonyl addition involving n-butyllithium and 3 is not in contradiction to the successful side-chain metalation of 20.[56] In the case of 20, the first equivalent of n-butyllithium ionizes the more acidic amide proton (Eq. 7). The resulting monoanion is stabilized by delocalization of the negative charge into the adjacent carbonyl group. This increases the electron density at the carbonyl carbon, which in turn renders it less susceptible to nucleophilic attack by a second equivalent of n-butyllithium and permits lateral proton abstraction to occur to form 31.



The problem of competing carbonyl addition during metalation of 3 was circumvented by employing the less nucleophilic,[60] but strongly basic lithium diisopropylamide (LDA). Reaction of 3 with LDA in THF-

hexane at 0° for one hour, followed by quenching the red-black anion solution* with water resulted in 92% recovery of 3. When lithio derivative 40 was quenched with deuterium oxide, the ^{1}H NMR spectrum of the crude product revealed incorporation of 0.98 deuterium atom at the methyl group of 3.

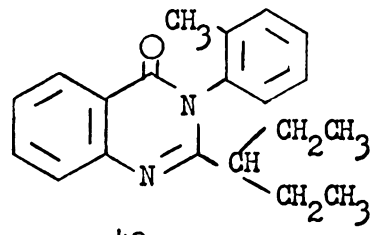
Alkylation of 40 was effected smoothly with methyl iodide to afford 42a in 53% yield. Methylation appeared to be fastest of the alkylation reactions investigated.



42a, R = CH_3

b, R = CH_2-CH=CH

c, R = CH_2CH_3



43

Although 42a had previously been prepared by a standard cyclization method,[17] the success of the methylation reaction encouraged us to investigate the preparation of a series of new compounds by using other alkylating agents. Thus, reaction of allyl bromide with 40 afforded the new quinazolinone 42b in 60% yield.

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*The distinct color of lithio salt 40 allowed qualitative rates of anion consumption to be monitored visually.

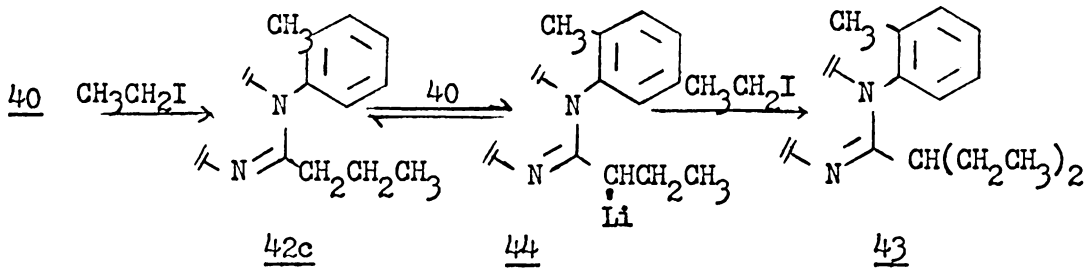
Alkylation of 40 with ethyl bromide or ethyl iodide at 0° proceeded significantly slower than methylation and allylation, as evidenced by the rate at which the color of 40 was discharged. This reaction resulted in formation of monoethylated derivative 42c, diethylated derivative 43, and recovered 3. Column chromatography afforded 42c, 43, and 3 in yields of 25, 5, and 42%, respectively. Elemental analyses and ^{1}H NMR spectra of 43 and 42c were in agreement with the proposed structures. It is interesting to note that the ^{1}H NMR spectrum of the dialkylated product 43 gave evidence for nonequivalent methyl groups of the 2-(3-pentyl) group. Centered at 0.95 ppm, the six-proton signal attributable to the side-chain methyl groups appeared as an overlapping doublet of triplets. This complex signal is apparently caused by restricted rotation about o-tolyl-nitrogen bond. This observation was consistent with the spectra of other compounds which are discussed later.

In order to minimize dialkylation in the preparation of 42c, several variations of the ethylation reaction were investigated. However, significant diethylation still occurred when the temperature was increased to 30°, or when hexamethylphosphoramide (HMPA) was added to the reaction mixture[67] or used alone as the solvent. Other attempts to increase the reactivity of anion 40, such as reacting the corresponding potassium salt of 40 with ethyl bromide in liquid ammonia at -33°, gave the same three component mixture, as did addition of lithio salt to a tenfold excess of ethyl iodide.

Dialkylation undoubtedly results from proton-metal exchange between the original anion, 40, and the monoalkyl derivative 42c to form mono-

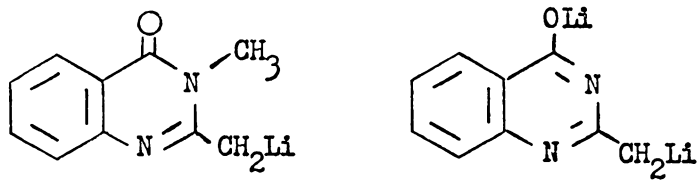
lithio salt 44, which then undergoes further alkylation (Scheme II). With less reactive halides the rate of initial alkylation of 40 is not sufficiently rapid to compete with proton-metal exchange and subsequent alkylation of secondary anion 44. That dialkylation is a

Scheme II



42c 44 43

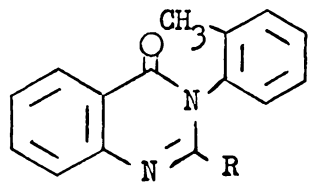
combined function of original anion nucleophilicity and halide electrophilicity rather than the result of steric requirements of 40 toward initial alkylation was supported by the observation that the less hindered lithio salt 45, derived from 2,3-dimethyl-4(3H)-quinazolinone (23a), also underwent considerable dialkylation with ethyl bromide.



45 31

Interestingly, alkylations of dianion 31 with primary halides do not give rise to isolable amounts of dialkylation products.[56] Apparently the higher nucleophility of 31 is responsible for the absence of dialkylation products in reactions of this intermediate with alkyl halides.

Phenylation at the 2-methyl group of 3 to give 2-benzyl derivative 46 was effected in 34% yield through initial formation of the lateral potassium salt 47 by means of potassium amide in liquid ammonia, followed by photostimulated reaction with iodobenzene. This process exhibited mechanistic features characteristic of an $S_{RN}1$ [68,69] reaction in that it proceeded very slowly in the absence of near-ultraviolet irradiation. For instance, no product was formed when the reaction was

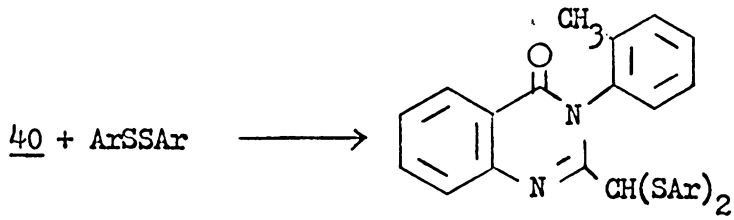


46, R = $CH_2C_6H_5$
47, R = CH_2K
48, R = $CHKC_6H_5$
49, R = $CH(C_6H_5)_2$

conducted in the dark for a period of four hours. However, when the reaction mixture was irradiated at 350 nm, product 46 was formed in five minutes. Because of the intense irradiation produced by the reactor employed in this study, radical scavengers such as p-dinitrobenzene[70] and di-t-butyl nitroxide (0.5 mole%) produced only a short (5-10 min) inhibition period, after which 46 had begun to form as shown by TLC analysis.

Product 46 apparently also undergoes proton-metal exchange with potassio salt 47 to give 48. Potassio salt 48 can then undergo phenylation to form diphenylated product 49. Evidence for such behavior is based on TLC analysis of the crude reaction mixture which showed the presence of 3, 46, and a third product which was isolated by column chromatography and had ^1H NMR spectral properties consistent with structure 49.

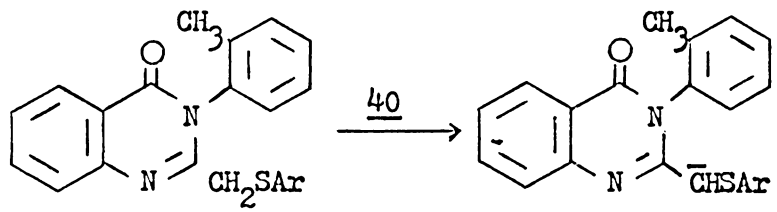
Reaction of 40 with diphenyl disulfide (Eq. 8) afforded only bissulfenylated[71] product 50 (24% based on 40) and recovered 3 (52%). None of the monosulfenylated[72] product 51 could be isolated. It seems



(8)

50

likely that the reaction of 40 with diphenyl disulfide initially yields the monosulfide 51. The acidity of the methylene protons of 51 are



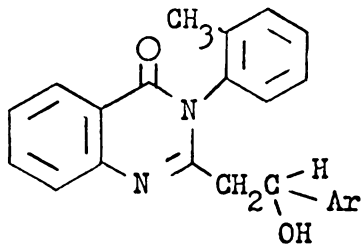
(9)

51 52

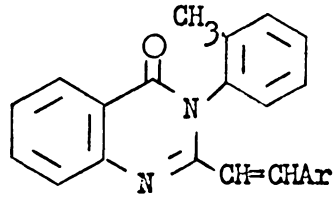
increased to such an extent that the rate of proton-metal exchange between 40 and 51 to form 52 (Eq. 9) is much greater than the initial formation of the monosubstituted 51. These results also imply that diphenyl disulfide apparently reacts faster with 52 than with 40. Assuming that bissulfenylated product 50 undergoes a similar acid-base reaction with 40, the maximum yield for this reaction would be 33%.

Reaction of lithio salt 40 with benzaldehyde proceeded rapidly to afford secondary alcohol 53 in 51% crude yield. This broad melting solid was shown by TLC analysis to contain one major component with

an intermediate R_f value and two other trace components. Attempts to recrystallize the crude material only increased the amounts of the two minor components, which were subsequently identified as 3 and styryl derivative 54. Separation of 53 from 54 and 3 by column chromatography



53



54

was difficult owing to considerable overlap of the bands. Certain fractions did yield pure compounds 54, 53, and 3. The first component to elute was the known styryl derivative 54. The second component to elute was alcohol (53), which was obtained as a solid (mp 136-141°) after allowing evaporation of the solvent at room temperature. Repeated chromatography gave an analytical sample of 53 (mp 137-138°).

The tendency for 53 to undergo dehydration and/or retroaldol condensation upon attempted recrystallization appears to result from severe van der Waals repulsions between the 3-o-tolyl group and the bulky 2-(2-hydroxy-2-phenylethyl) substituent, which are relieved by either of these degradative processes. The steric interactions presents in 53 were strikingly evidenced by the ^{1}H NMR spectrum in that hindered rotation of the o-tolyl group about the C-N bond causes the occurrence of atropisomerism,[73] which in conjunction with the presence of a chiral center in the side chain at the 2-position, results in the existence of

diastereomeric rotational isomers as illustrated in Figure 1. The dotted line in Figure 1 depicts the mirror plane which defines the enantiomeric relationship between the four stereoisomers and at the same time reveals the diastereomeric relation between the pairs of enantiomers (53a-b) and (53c-d). Rotation of the o-tolyl group by 180 degrees about the C-N bond causes interconversion of 53a and 53c, and 53b and 53d. The rate of rotation of the o-tolyl group is slow enough on the ^{1}H NMR time scale at 31° to cause the appearance of two o-tolyl methyl signals at δ 1.87 and 2.11 in DMSO-d_6 (Figure 2). At 140°, the two signals moved closer together, but did not show any significant degree of broadening as might be expected.[74]

Attempts to cause coalescence of the methyl signals of 53 by raising the temperature above 140° caused extensive retroaldol condensation and dehydration was evidenced by the appearance of the characteristic spectrum of 3 and 54, namely the two methyl signals of 3 and the vinyl signal of 54 (Figure 2-c). After heating a deuterochloroform solution of 53 in a sealed nmr tube at 140°, five signals were observed in the region (δ 2.05 - 2.25) which could arise from the methyl resonances of 3, 53, and 54.

In order to see if the hindered rotation about the C-N bond was sufficient to allow separation of the diastereomers,[75] a sample of the rotational isomers was subjected to high performance liquid chromatography.* Although the experimental conditions allowed separation of

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*These experiments were carried out by Dr. P. R. Young of the NASA/ Langley Research Center.

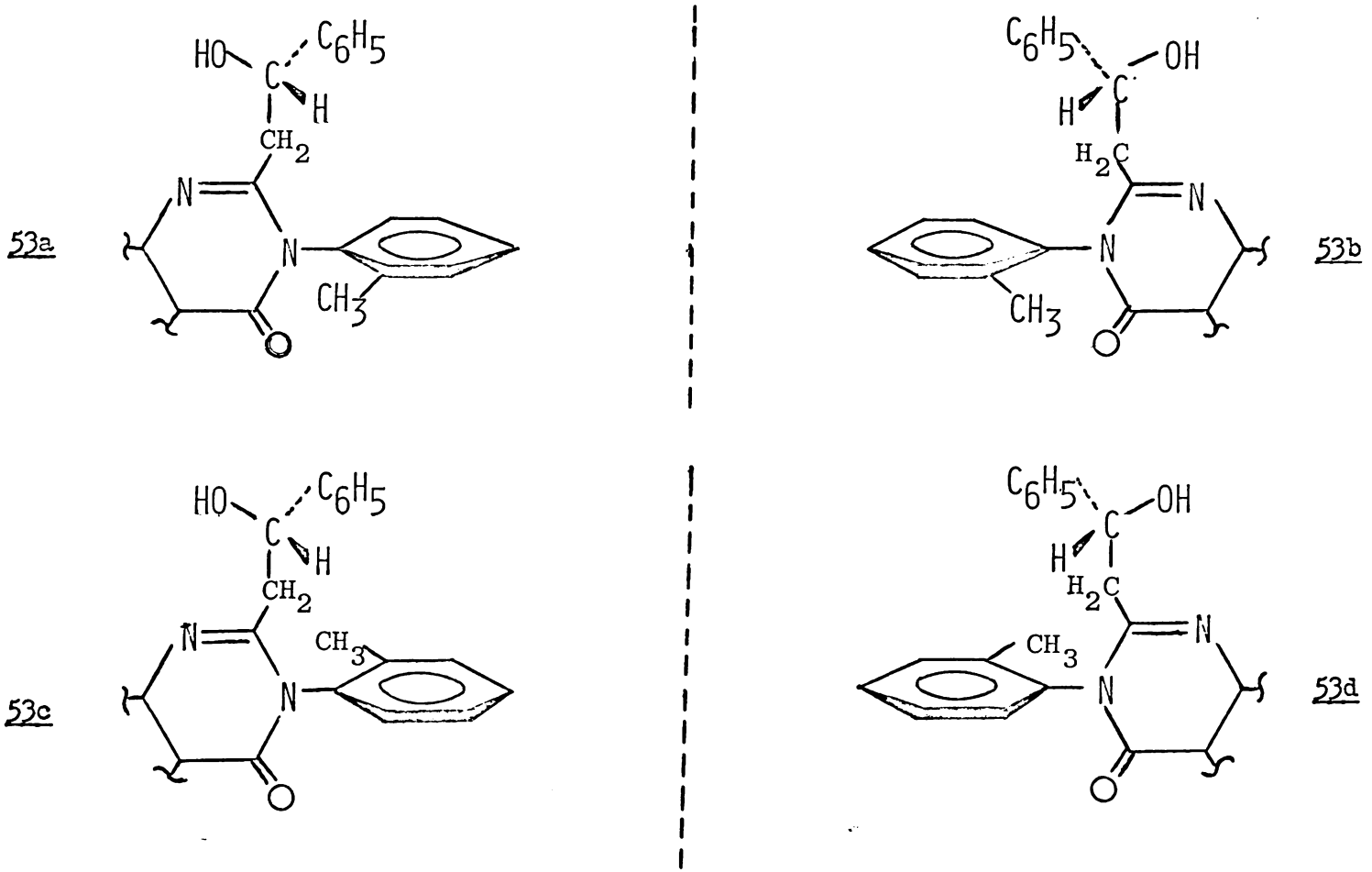


Figure 1. Diastereomeric Rotational Isomers of 2-(2-Hydroxy-2-phenylethyl)-3-o-tolyl-4(3H)-quinazolinone (53).

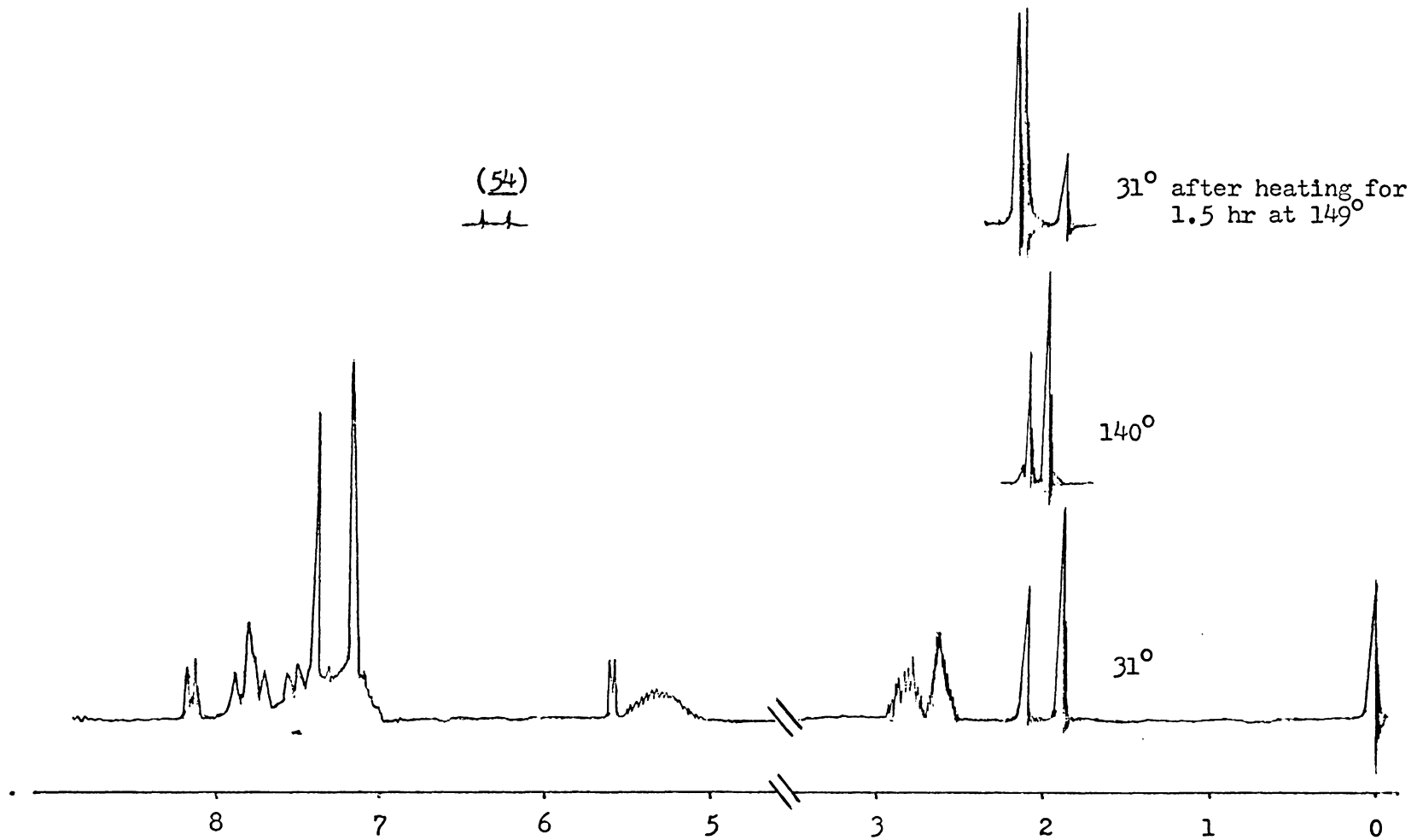
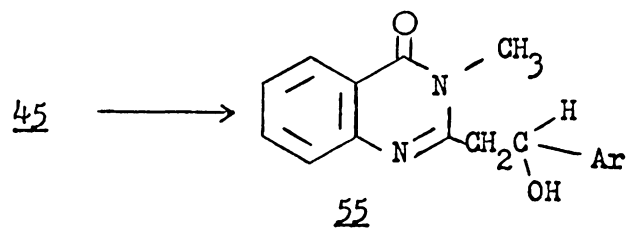


Figure 2. ^{1}H NMR Spectra of 2-(2-Hydroxy-2-phenylethyl)-3-o-tolyl-4(3H)-quinazolinone (53) in DMSO-d_6 at 31°, 140° and at 31° after heating for 1.5 hr at 149°.

3 and 54, the peak, which corresponded to 53, showed no indication of resolution into two components.

Treatment of secondary alcohol 53 at 26° with dilute lithium hydroxide in THF-water afforded styryl derivative 54 in 84% yield.[15] The driving force for this reaction must be due in part to the relief of steric interactions. The ease of dehydration of 53, may explain the presence of the styryl derivative 54 as a persistent part of the reaction mixtures resulting from condensation of 40 with benzaldehyde. Other factors such as the incipient conjugation of 54 may also be influential in provoking dehydration of 53.

In contrast to the difficulties associated with isolation of 53, treatment of the lithio salt 45 with benzaldehyde gave the secondary alcohol 55 in 73% yield (Eq. 10).

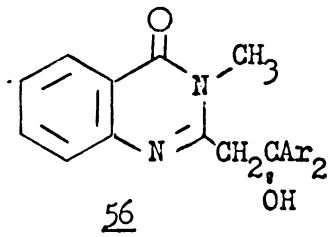


55 (10)

The presence of a methyl group in the 3-position of 55 as opposed to an o-tolyl group in 53 apparently reduced the isolation difficulties by alleviating the steric interactions which led to the facile dehydration and retroaldol reactions of 53.

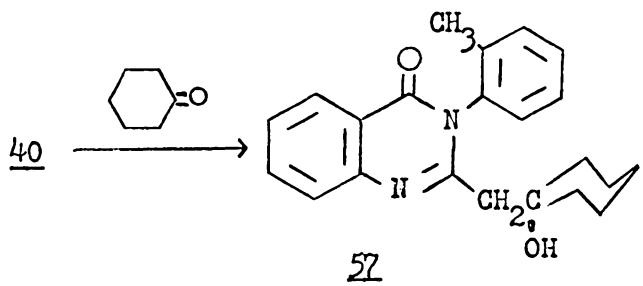
Lithio salt 40 failed to undergo condensation with benzophenone even after a 24 hour reaction period. Persistence of the intense color

of 40 throughout the reaction period was indicative of the severe hindrance to formation of the new carbon-carbon bond rather than a possible rapid retroaldol condensation upon quenching the reaction mixture. Again the importance of steric constraints in the reaction of 40 with benzophenone was demonstrated by the fact that the less hindered lithio salt 45 reacted rapidly with this ketone to give 56 in 69% yield.



56

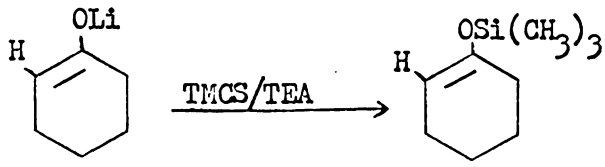
Condensation of 40 with enolizable ketones resulted in appreciable α-proton abstraction. For example, reaction of 40 with cyclohexanone afforded 22% of tertiary alcohol 57 (Eq. 11). The remainder of the



57

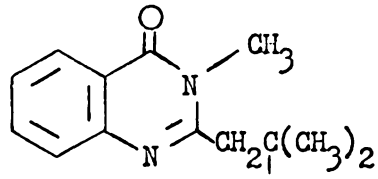
(11)

ketone was converted to its lithium enolate 58. The formation of 58 was demonstrated by quenching the reaction mixture with trimethylchlorosilane/triethylamine (TMCS/TEA) to give cyclohexanone trimethyl silyl enol ether 59 as shown by VPC analysis (Eq. 12).



58 59 (12)

Similar reactions of 40 with acetone and 2-butanone resulted in predominant enolization of the ketones as shown by recovery of 3 in yields of 74 and 68%, respectively. In contrast to this, lithio salt 45 condensed with acetone to give 41% of 60 which was isolated by column chromatography. The behavior of 40 toward aliphatic ketones



60

appears to result from the tendency of this sterically hindered nucleophile to act preferentially as a base.[76]

As in the case of the aldol product 53, alcohol 57 exhibited atropisomerism.[73] The ^{1}H NMR spectrum revealed an AB quartet centered at δ 2.43 for the side-chain methylene protons (Figure 3). Because restricted rotation about the N-o-tolyl bond is slow on the nmr time scale, protons H' and H'' are not magnetically equivalent (Figure 4). Once again, this pattern could not be collapsed, nor was any line broadening observed over a temperature range of 31-140° (Figure 3).

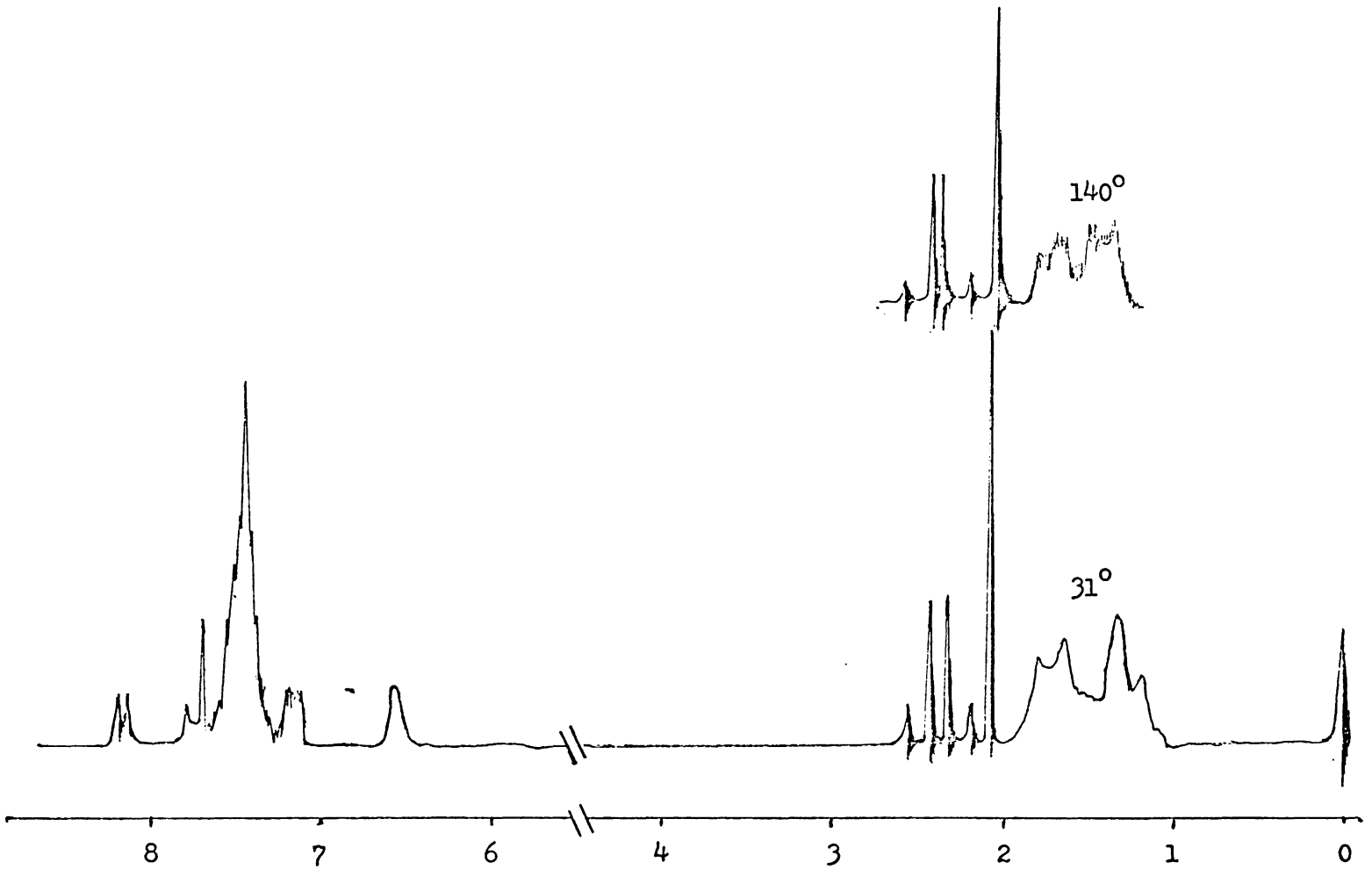


Figure 3. ^{1}H NMR Spectra of 2-[(1-Hydroxy-1-cyclohexyl)methyl]-3-o-tolyl-4(3H)-quinazolinone (57) at 31° and 140°.

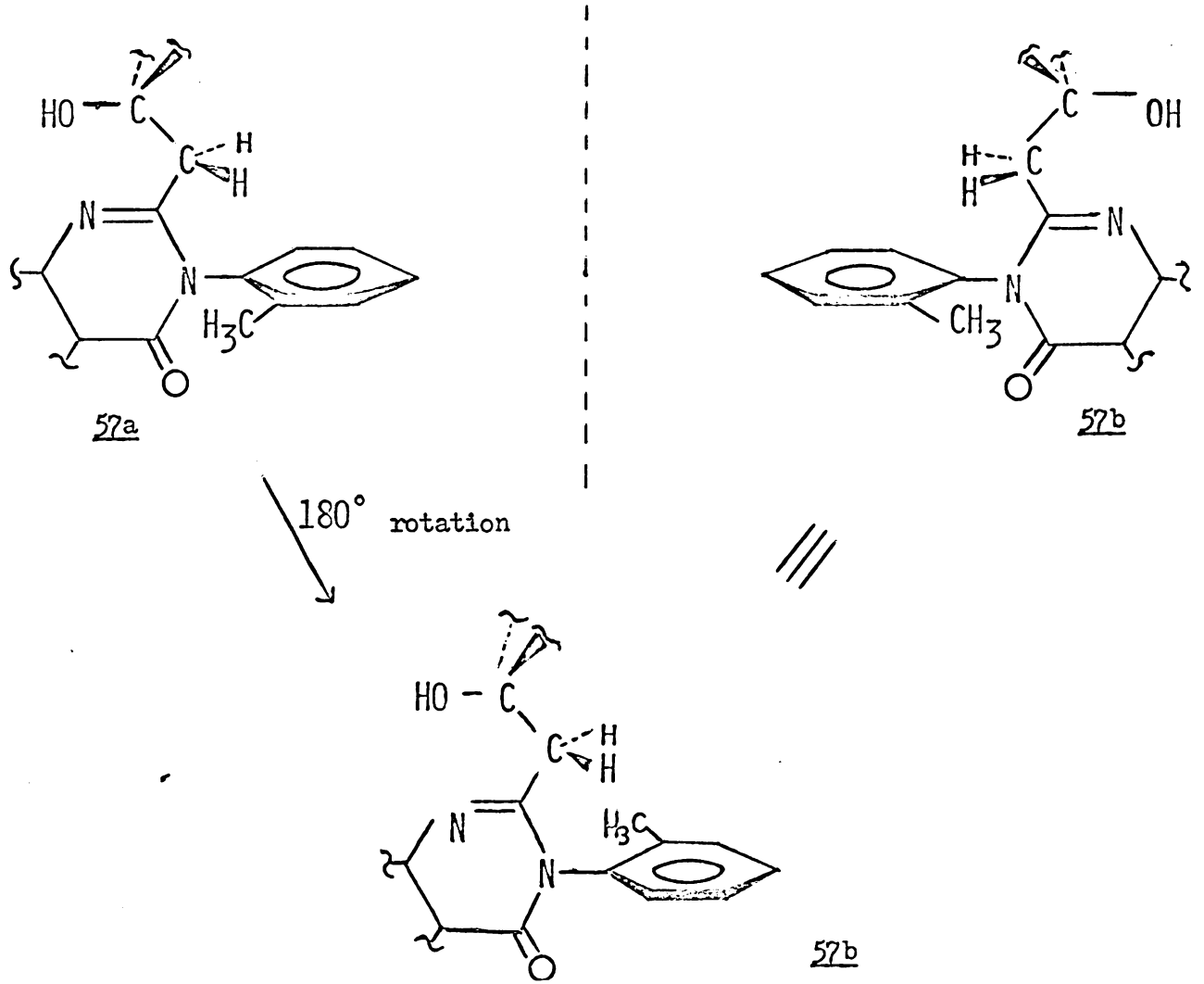
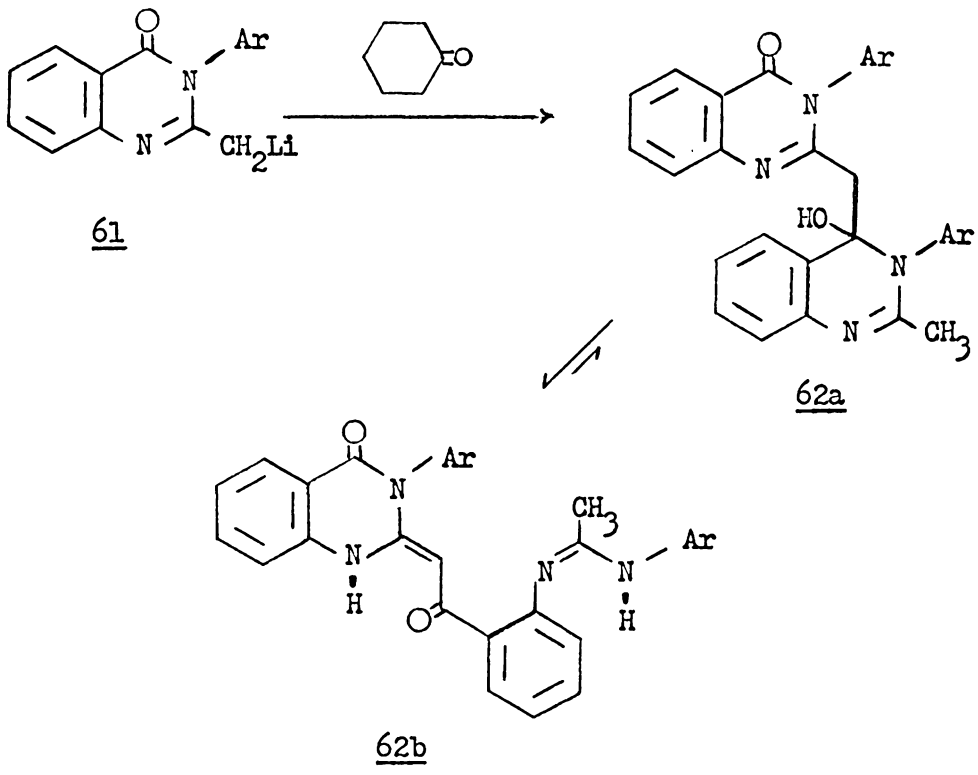


Figure 4. Rotational Isomers of 2-[(1-Hydroxy-1-cyclohexyl)methyl]-3-o-tolyl-4(3H)-quinazolinone (57).

Thus hindrance to rotation in 57 is apparently as severe as that recently observed with a series of 2-benzyl-3-aryl-4(3H)-quinazolinones.[77]

Reaction of the lithio salt, 61, of 2-methyl-3-phenyl-4(3H)-quinazolinone (37) with cyclohexanone led to an unexpected result in that dimer 62a-b was isolated in 36% yield (Eq. 13).



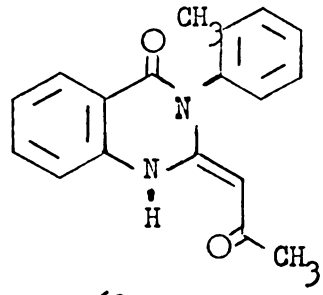
(13)

The ^{1}H NMR spectrum of 62a-b in $CDCl_3$ appeared to indicate that 62a-b exhibited ring-chain tautomerism[78] in which the chain tautomer (62b) was preferred by a factor of ca. 9:1, while in DMSO-d_6, 62b was apparently the only tautomer present.

It seems likely that 62a-b is produced by α-proton abstraction from cyclohexanone to generate neutral 2-methyl-3-phenyl-4(3H)-quinazolinone (37) in the presence of the anion 61. The latter then reacts at the lactam carbonyl function of 37. This mechanism is supported by the observation that addition of quinazolinone 37 to a solution of its conjugate base 61 resulted in formation of 62a-b in 47% yield.

The absence of isolable quantities of a self-condensation product corresponding to 62a-b in the reaction of 40 with cyclohexanone (Eq. 10) may be due to the fact that the carbonyl group of neutral 3 is sufficiently hindered by the 3-o-tolyl group to prevent attack by 40 at a rate competitive with the sum of its rates of neutralization and addition to the carbonyl group of cyclohexanone.

Reaction of 40 with ethyl acetate afforded a low (8%) yield of 63, even when anion 40 was added to the ester. This undoubtedly results from the inherently unfavorable stoichiometry of Claisen condensations of this type[62] and from α-ionization of the ester by 40. Also, 63 could not be isolated after treating 3 with acetic anhydride.[50]

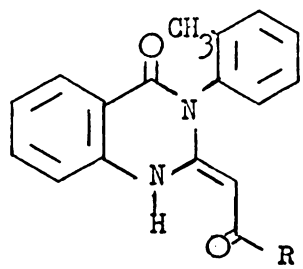


63

In a recent study,[64] successful lateral acylation of various α- and β-methylated heteroaromatic azines and diazines has been accom-

plished with nonenolizable esters using sodium hydride as the condensing agent. However, it was discovered in the present study that attempted acylation of quinaldine failed with ethyl acetate because of self-condensation of the ester to form ethyl acetoacetate. Even though the 2-methyl protons of 3 should be more acidic than the 2-methyl group of quinaldine, it was still somewhat surprising to discover that 3 underwent sodium hydride promoted acylation with ethyl acetate to form 63 in 61% yield.

Similarly, 3 was acylated with ethyl trifluoroacetate, ethyl picolinate, ethyl nicotinate, ethyl isonicotinate, ethyl 1-adamantylcarboxylate, ethyl cinnimate and several esters of substituted benzoic acids to form 64a-j. The general procedure for preparing 64a-j involved



64a, R = CF_3

b, R = 2-pyridyl

c, R = 3-pyridyl

d, R = 4-pyridyl

e, R = 1-adamantyl

f, R = CH=CH-C_6H_5

g, R = C_6H_5

h, R = C_6H_4Cl-p

i, R = $C_6H_4OCH_3$-p

j, R = $C_6H_2(OCH_3)_3$-3,4,5

k, R = $C_6H_4NHCOCH_3$-p

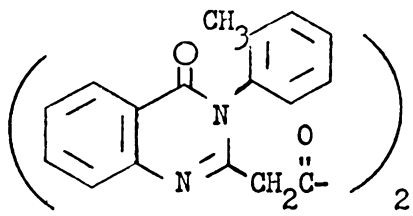
l, R = $C_6H_4NHCOCF_3$-p

m, R = $CO_2C_2H_5$

addition of 3 and the appropriate ester (10% molar excess) to a slurry of excess sodium hydride in refluxing 1,2-dimethoxyethane (DME). The reaction was terminated after evolution of 2 equivalents of hydrogen (based on the amount of 3) had occurred. Reaction periods ranged from one to five hours producing the acylated derivatives 64a-j in yields of 19 to 85%.

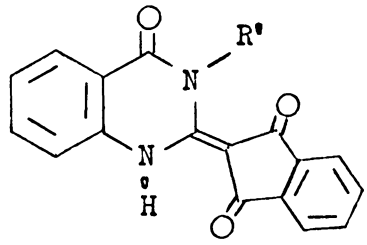
Departing from the general procedures, compounds 64k and 64l were prepared using ethyl p-acetamidobenzoate and ethyl p-trifluoroacetamidobenzoate, which were ionized with sodium hydride prior to the addition of 3.

The yield of 2-ethoxalylmethyl derivative 64m was highest when 3 was added slowly to a mixture of excess sodium hydride and excess diethyl oxalate. In this way, intermolecular condensation was minimized. Such behavior was observed when the general acylation procedure was used for the preparation of 64m. This reaction afforded 51% of 65, the ^{1}H NMR spectrum of which exhibited a vinyl: enol: methyl: aromatic proton ratio of 1:1:3:8; no signals due to an ethyl group were present.



65

1,3-Indandione derivatives 66a and 66b were prepared by sodium hydride promoted acylation of 3 and 23 with dimethyl phthalate.

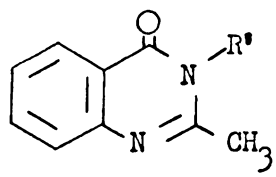


66

66a, R' = o-tolyl

b, R' = methyl

Since 2-(2-ketoalkyl)quinazolinones 64a-m represented a totally new class of 2-substituted-3-o-tolyl-4(3H)-quinazolinones, four other 2-methyl-3-aryl-4(3H)-quinazolinones, where R' = o-chlorophenyl, (4a) R' = phenyl (37), R' = p-tolyl (67), and R' = p-bromophenyl (68), were similarly subjected to acylation by means of sodium hydride in order



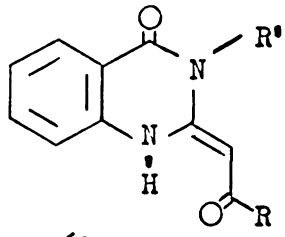
4a, R' = o-chlorophenyl

37, R' = phenyl

67, R' = p-tolyl

68, R' = p-bromophenyl

to obtain a series of compounds which might possibly exhibit CNS activity. Each of these four quinazolinones was acylated with ethyl trifluoroacetate, and the ethyl esters of picolinic, nicotinic, and isonicotinic acid to give 69a-p, respectively.



69

69a, R' = o-chlorophenyl, R = CF_3

b, R' = o-chlorophenyl, R = 2-pyridyl

c, R' = o-chlorophenyl, R = 3-pyridyl

d, R' = o-chlorophenyl, R = 4-pyridyl

e, R' = phenyl, R = CF_3

f, R' = phenyl, R = 2-pyridyl

g, R' = phenyl, R = 3-pyridyl

h, R' = phenyl, R = 4-pyridyl

i, R' = p-tolyl, R = CF_3

j, R' = p-tolyl, R = 2-pyridyl

k, R' = p-tolyl, R = 3-pyridyl

l, R' = p-tolyl, R = 4-pyridyl

m, R' = p-bromophenyl, R = CF_3

n, R' = p-bromophenyl, R = 2-pyridyl

o, R' = p-bromophenyl, R = 3-pyridyl

p, R' = p-bromophenyl, R = 4-pyridyl

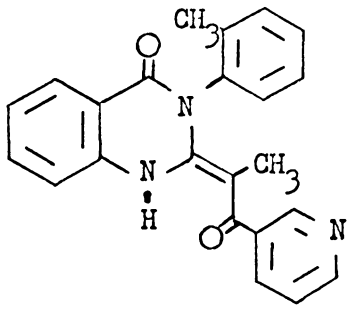
q, R' = p-bromophenyl, R = CH_3

r, R' = methyl, R = C_6H_5

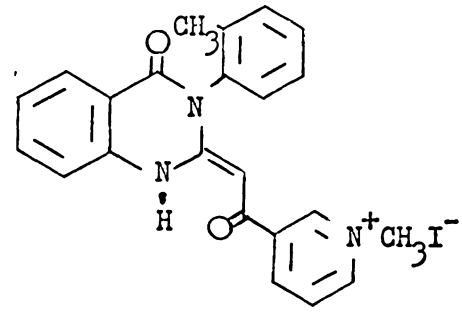
s, R' = methyl, R = 3-pyridyl

In addition, the 2-acetonyl derivative (69q) was prepared from 68, and 69r-s were formed by reacting 2,3-dimethyl-4(3H)-quinazolinone (23a) with methyl benzoate and ethyl nicotinate, respectively.

Attempts to prepare 70 by acylation of 2-ethyl-3-o-tolyl-4(3H)-quinazolinone (42a) with ethyl nicotinate led to a complex mixture of products. Attempted alkylation of the sodium salt of 64c with methyl iodide as a route to 70 gave mostly recovered starting material and a small amount (4.8%) of N-methyl pyridinium salt 71.

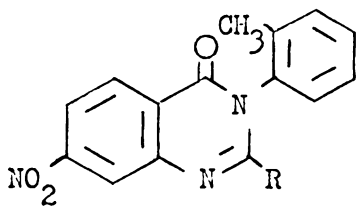


70



71

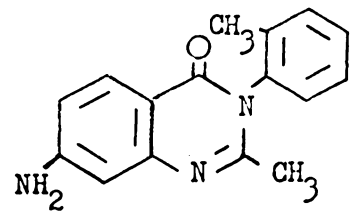
Finally, treatment of 72a with methyl benzoate and sodium hydride as route to the respective 2-phenacyl derivative 72b was shown to be superseded in part by reduction of the nitro group to give 73 as one



72

72a, R = CH_3

b, R = $CH_2COC_6H_5$



73

of the products resulting from this reaction.

As had been observed with other methylated azines, 3 was not significantly metalated by sodium hydride in refluxing DME. Thus, less than 0.2 molecular equivalents of hydrogen were generated upon treatment of 3 with excess sodium hydride after 20 hrs at reflux. However, when 3 (10 mmoles) was allowed to react with excess sodium hydride in the presence of ethyl acetate (13 mmoles), 21.2 mmoles of hydrogen were evolved in 3.5 hours, after which time hydrogen evolution ceased, presumably owing to total consumption of ethyl acetate by formation of the 2-acetonyl derivative 63, and ethyl acetoacetate. If self-condensation of the ester were only reaction, 13 mmoles of hydrogen would evolve. Because two molecules of ethyl acetate are required to form one of ethyl acetoacetate and one molecule of ethyl acetate is needed to form 63, it is possible to calculate the amount of 63 which formed during the 3.5 hr reaction period if the assumption is made that all of the ethyl acetate reacted via these two reaction pathways. Therefore, based on the 21.2 mmoles of hydrogen, 8.2 mmoles of 63 should be present.*

It should be noted that formation of ethyl acetoacetate from ethyl acetate by means of sodium hydride is essentially complete after 1.5 hours in the absence of 3.

In earlier mechanistic considerations concerning the sodium hydride promoted acylations of methylated heteroaromatics the conclusion was

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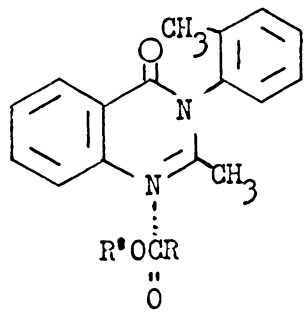
*A simplified equation, which can be used to determine the amount of 63 present after all the ethyl acetate is consumed, is $T = X + Z$, where T is the total mmoles of hydrogen evolved, Z is the mmoles of ethyl acetate used, and X is the amount of ethyl acetate involved in the acylation of 3 (X is also the amount of 63 formed).

drawn that the ester interacted with the ring nitrogen of the heterocycle to form a complex such as 74.[64]



74

Such complexation is thought to increase the acidity of the lateral methyl hydrogens of the heterocycle so that they may then be removed by sodium hydride. This concept was supported by the observation that acylation of 3 with ethyl trifluoroacetate was 82% complete within 1.5 hours at 25°, whereas acylation of 3 with ethyl acetate at reflux required 3.5 hours to form 82% of 63. In the case of ethyl trifluoroacetate, the highly polarized ester carbonyl facilitates complex formation and the accompanying acidification of the lateral methyl protons.

Existence of such a complex, in which α-proton acidity of the participating ester molecules should be less than that of the free ester, may also provide an explanation for the apparent supression of ethyl acetoacetate formation in the reaction of ethyl acetate with 3.

Unfortunately, attempts to detect the existence of complexes such as 74 by ^{1}H NMR and ^{19}F NMR and uv-vis spectroscopy were unsuccessful. This may be due to the fact that such interactions take place largely on the surface of the insoluble hydride base.

The ^{1}H NMR spectra of all the 2-(2-ketoalkyl)-3-aryl-4(3H)-quinazolinones revealed total enolization as evidenced by a broad enol proton singlet located between δ 15.8 and 14.8 and the presence of a vinyl singlet in the range of δ 5.9 to 4.4. This behavior was consistent with tautomerism previously observed in a variety of heterocyclic systems containing exocyclic β-carbonyl substituents.[79] Assignment of the tautomeric enamine structures such as 63, 64a-m and 69a-s to these compounds is arbitrary.

The position of the vinyl proton resonance in the ^{1}H NMR spectra of the twenty 2-(2-ketoalkyl)-3-aryl-4(3H)-quinazolinones (see structural formulas 64a-d, and 69a-p) appears to be a function of the electronegativity of the R group and the ability of the R substituent to deshield the vinyl proton by anisotropy. The R group which shows the greatest ability to deshield the vinyl proton is the 2-pyridyl group. The chemical shift values of this proton for compounds 64b, 69b, 69f 69j, and 69n, all of which contain the 2-pyridyl group, fall in the range of δ 5.96-5.83.

The 3-pyridyl group, regardless of the R' grouping, consistently caused the vinyl proton signal to be further downfield (δ 5.15-5.05) than the vinyl signal observed in compounds containing a 4-pyridyl group. In the latter cases, the vinyl proton resonance occurred at δ 5.08-4.98. The 2-trifluoroacetonyl quinazolinones, 64a, 69a, 69e, 69i, and 69m contain vinyl protons which appear at δ 5.02-4.74. The electronegativity associated with the trifluoromethyl group apparently has a smaller deshielding effect than the pyridyl groupings. In fact, when R' = o-tolyl and R = phenyl (64g), p-chlorophenyl (64h), 3,4,5-

trimethoxyphenyl (64j), p-methoxyphenyl (64i), the vinyl proton signal appears further downfield than the CF_3 derivative 64a. This does not imply that the CF_3 group has no effect since the 2-acetonyl derivatives 63 and 69q exhibit vinyl proton resonances at δ 4.43 and 4.39, respectively.

The extent to which the vinyl proton is shifted downfield is more likely caused by the anisotropic deshielding that the aromatic R groups can impinge on the vinyl proton in question. This is exemplified in the chemical shift of the pyruvate derivative (64m) in which case the vinyl proton appears at δ 5.47 and is probably a consequence of anisotropic effect of the carbonyl group of the R substituent.

In conclusion, it was found that methaqualone could be metalated at the lateral 2-methyl group with lithium diisopropylamide in THF at 0° and subsequent condensation of the resulting lithio salt with various electrophiles met with varying degrees of success. For instance, monoalkylations of the lithio salt were effected with methyl iodide and allyl bromide while the slower reacting electrophile such as ethyl iodide also produced significant dialkylated product. Disubstitution apparently is not a result of steric constraints caused by the methaqualone anion.

The results of aldol condensations involving the lateral lithio salt of methaqualone were revealed by the severe steric requirements imposed upon this nucleophile by the 3-o-tolyl group. For instance, the secondary alcohol resulting from condensation with benzaldehyde underwent facile retroaldol condensation or dehydration. These degradative processes apparently relieve the extreme van der Waals repulsions

between the 3-o-tolyl group and the bulky 2-(2-hydroxy-2-phenylethyl) substituent. These steric interactions were further evidenced by the ^{1}H NMR spectrum of this alcohol which revealed the existence of diastereomeric rotational isomers.

A comparison between aldol condensations involving the less hindered lithio salt of 2,3-dimethyl-4(3H)-quinazolinone and the lithio salt of methaqualone further demonstrated the importance of the steric constraints in the latter anion. For example, the methaqualone anion failed to react with benzophenone, while the less hindered anion underwent smooth condensation with this ketone. Condensation of methaqualone lithio salt with enolizable ketones resulted in appreciable enolate formation.

Sodium hydride promoted acylations at the 2-methyl group of the general class of 2-methyl-3-aryl-4(3H)-quinazolinones can be achieved in refluxing DME with ethyl acetate as well as with various esters such as ethyl trifluoroacetate, ethyl nicotinate, and various substituted benzoate esters to produce the desired 2-(2-ketoalkyl)-3-aryl-4(3H)-quinazolinones in good yield.

The results of the CNS testing for compounds 3, 4a, 42a, 37, 46, 53, 63, 64a-m, 69a-l, 69r-s, 67, 68, 71, 72a and 73 are reported in the following chapter.

IV. PHARMACOLOGICAL TESTING OF NEW 2,3-DISUBSTITUTED-4(3H)-QUINAZOLINONES

Of the forty-four new compounds prepared in this study, twenty were tested for central nervous system activity by Pharmakon Laboratories of Scranton, Pennsylvania. The battery of general observational procedures used by Pharmakon is called a Neuropharmacological Profile (NPP).

Twenty-nine of these compounds were tested in the Anticonvulsant Screening Project of the National Institutes of Neurological and Communicative Diseases and Stroke (NINCDS) at the University of Utah under the direction of Dr. Ewart A. Swinyard.[80]

A. Neuropharmacological Profile (NPP)*

The procedures for the determination of a neuropharmacological profile involved white male mice of the Carworth Farm Strain CF-1 weighing 18 to 22 grams. The test compound, regardless of solubility, was suspended in a 0.25% aqueous methylcellulose solution. Intraperitoneal injections were administered in logarithmic progression and sequentially. The dose levels employed routinely were 10, 30, 100 and 300 mg/kg, using four male mice at each dose level. Since this test was conducted in a sequential manner, the first dose administered was at 300 mg/kg. The mice were injected at this dose level and observed for gross changes produced by the drug, such as behavioral, neurological, autonomic, and toxic effects. Approximately thirty-eight signs and symptoms of pharmacological activity can be identified.

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*Excerpts taken in part from the section of the Pharmakon Laboratories' procedural manual describing CNS primary screening.

The animals were observed continuously for one hour and if no signs of pharmacological or toxicological activity were present at the end of the first hour, they were intermittently checked for activity every fifteen minutes thereafter for two consecutive hours. At the end of the third hour of observation, if no demonstrable change had occurred in the behavior of the mice, the compound was conditionally considered inactive and the animals were checked intermittently for forty-eight hours. Subsequent dose levels below 300 mg/kg were not administered in this case. Alternatively, if demonstrable pharmacological changes occurred within the first three hours after administration of the drug at 300 mg/kg, the subsequent doses were administered and the animals were observed for changes in overt behavior. The observation period began immediately following the injection and the animals were then continuously observed for three hours and intermittently checked thereafter for forty-eight hours. The animals were observed and signs and symptoms of pharmacological activity were recorded continuously until no further symptoms developed and until the symptons that appeared were no longer present. In certain instances, such as with reserpine, the effects of a single dose can exceed the forty-eight hour observation period. In such instances the animals were observed beyond this period until they returned to normal. Routinely, the number of animals alive at the end of the forty-eight hour observation period were recorded and the LD_{50} rapidly estimated.

The animals were observed in a fixed environment consisting of a 15" square in which their movement was not restricted. They were placed on an absorbent paper which detects excretions, expecially

increased urination, which may indicate diuretic activity. It was very important that the animals are free to move about for evaluation of spatial orientation, alertness, and spontaneous motor activity. The animals were systematically observed and manipulated to measure the onset, peak effect, duration and character of drug action.

Since this is a general CNS screening procedure, only peak effects were recorded. Certain measures of behavior and neurological deficit were scored in terms of intensity of effect, while most others were determined on an all or none basis. Thus in scoring measures which were normally present, for example, spontaneous activity and skin color, an increase in score from 4 to 8 was used to denote stimulation or enhancement of skin color, whereas a decrease in score from 4 to 0 indicated depression or cyanosis. For scoring measures normally absent, for example, depression, righting reflex, and ataxia, activity was reflected as an increase in score from 0 to 8. The 0 to 8 scale was condensed so that the actual ratings are only 0, 2, 4, 6, and 8. The compounds were also evaluated for anticonvulsant activity by using the maximal electroshock seizure (MES) test. In the MES study, four mice were dosed intraperitoneally at 100 mg/kg and challenged thirty minutes later with 50 mA, 0.2 second duration of electroshock. A protection ratio, (number of mice protected from tonic extension - number of mice tested) was then established.

At the termination of the test the results were recorded, tabulated, and based on the symptom complex observed and the score values, a suggested pharmacological activity was indicated.

B. NINCDS Identification of Anticonvulsant Activity*

1. Neurological Activity Tests

The biological testing program is designed to evaluate the following four aspects of drug action: (1) the existence and specificity of anticonvulsant activity, (2) the toxicity, particularly of the central nervous system, and if the results of (1) and (2) are favorable, (3) the potency and protective index, a comparison between toxic and effective dose, and (4) the time course of activity. Compounds were evaluated for anticonvulsant activity in two seizure models, the maximal electroshock seizure (MES) test and the subcutaneous pentylenetetrazol (Metrazol) seizure threshold (scMet) test. The Maximal Electroshock Seizure Test was performed according to the method described by Swinyard and coworkers. Maximal electroshock seizures are elicited with a 60 Hz alternating current of 50 mA (5 to 7 times that necessary to elicit minimal electroshock seizures) delivered for 0.2 sec via corneal electrodes. A drop of 0.9% saline is instilled in each eye prior to application of the electrodes. This stimulus will produce a maximal seizure in all normal mice. The maximal seizure typically consists of a short period of initial tonic flexion and a prolonged period of hind limb tonic extension followed by terminal clonus. The seizure lasts about 22 sec. Abolition of the hind limb tonic extensor component of the seizure is defined as protection and indicates anticonvulsant activity in the test compound. Subcutaneous

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*From the first section of the Anticonvulsant Screening Project brochure (DHEW Publication No. (NIH) 76-10903).

Pentylenetetrazol (Metrazol) Seizure Threshold Test (scMet) produces threshold (clonic) seizures. Pentylenetetrazol is administered as a 0.5% solution (in 0.9% sodium chloride) subcutaneously in a loose fold of skin on the back of the neck in a dose of 85 mg/kg. Seizures are produced in at least 97% of the mice. Metrazol is given 10 min. before the beginning of the test to allow for the delay in onset of Metrazol action. The animal is observed for 30 min. Failure to observe even a threshold seizure (a single episode of clonic spasms at least 5 sec in duration) is defined as protection and indicates anticonvulsant activity in the test compound. These two methods of seizure provocation reliably elicit well-characterized seizure phenomena. Together, they have been shown sufficient to identify all compounds known to demonstrate anticonvulsant activity in other tests.

The ability of a compound to prevent maximal electroshock seizures is believed to correlate with its ability to prevent the spread of seizure discharge through neural tissue. Activity against maximal electroshock seizures is thought to indicate potential efficacy in the treatment of major motor (grand mal) seizures. Phenytoin, 5,5-diphenyl-2,4-imidazolidinedione, is the antiepileptic drug best known for its selective action in preventing maximal seizures. The ability of a compound to prevent threshold seizures induced by subcutaneous pentylenetetrazol has been correlated with the ability to raise the threshold for excitation of neural tissue. Selective action in the test is believed to indicate potential efficacy against absence (petit mal) seizures. The benzodiazepines such as diazepam and clonazepam are the most potent

drugs to act selectively in preventing Metrazol-induced threshold seizures.

Central nervous system toxicity was evaluated in the rotorod ataxia test. This test is designed to detect minimal neurotoxicity. The animal is placed on a 1-in diameter knurled plastic rod rotating at 6 rpm. Normal mice can remain indefinitely on a rod rotating at this speed. Neurological deficit is defined as the failure of the animal to remain on the rod for at least 1 min. This test has a clear end-point, is quantifiable, and correlates well with the clinical assessment of minimal toxicity.

2. Formulation and Administration of Test Compound

All compounds to be tested were solubilized in either 0.9% sodium chloride or 30% polyethylene glycol 400. Studies of the anticonvulsant and toxic effects of these solvents in the above tests were performed early in the course of the Screening Project. Except for a specific interaction between certain drugs and polyethylene glycol in only the Metrazol test, resulting in increased activity of the drug, the solvents introduce no significant bias into the testing of anticonvulsant activity. The compounds are administered intraperitoneally in a volume of 0.01 ml/gm to Carworth Farms #1 mice weighing about 20 gm. The mice are the same type used by Pharmakon Laboratories for the NPP.

3. Testing Protocol

All compounds undergo a Primary Evaluation and those which demonstrate activity are tested in a Secondary Evaluation. The results from this testing protocol provide a profile of each compound's anti-

convulsant activity, toxicity, potency, and pharmacokinetics, which together with structural and physicochemical data, are used to identify those compounds with significant antiepileptic potential.

The object of the Primary Evaluation is to gain a maximum amount of information about a compound's activity from as few animals and as little drug as possible. The compounds were tested at doses of 30, 100, and 300 mg/kg. Four animals were injected with each dose. Thirty minutes later, each animal was examined for toxicity in the rotorod test. Immediately thereafter, anticonvulsant activity was evaluated by subjecting one mouse to the MES test and another to the subcutaneous Metrazol test. The same tests were repeated 4 hr later on the two remaining mice.

Testing in the dose range 30-300 mg/kg provides information on the potency of the compound and allows an estimate of the protective index. Testing at both 30 min and 4 hr yields elementary information about the compound's pharmacokinetics and minimizes the likelihood of failing to identify slowly absorbed compounds or those with anticonvulsant activity in a metabolite.

Based on the results of the Primary Evaluation, each compound is placed in one of three categories. Those failing to demonstrate anticonvulsant activity at doses up to at least 300 mg/kg were considered inactive and were placed in Class III. Those that demonstrated anticonvulsant activity in either the MES test or the scMet test at doses of 100 mg/kg or less and had an estimated protective index greater than 1 were placed in Class I. These were considered the most promising as anticonvulsants and were scheduled for the Secondary Evaluation, the

compounds in Class II are those with anticonvulsant activity at doses greater than 100 mg/kg or with narrow protective indices. These were considered potentially useful but are either toxic or not very potent agents. Of the currently marketed antiepileptic drugs, ethosuximide would be included in this last class of compounds. In order that similarly useful compounds would not be disregarded, those in Class II are reevaluated. This reevaluation focuses on the estimation of the compound's protective index; those with a satisfactory protective index undergo a Secondary Evaluation.

During the Secondary Evaluation, the compound's time of peak effect upon seizure tests and its time of peak neurotoxicity are determined. The median effective dose is then determined in the rotorod, the MES, and the scMet tests at the appropriate times.

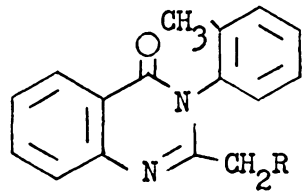
At the time of the writing of this thesis, compounds that were placed in Class II were being reevaluated, and those categorized into Class I were scheduled for Secondary Evaluation. Therefore, the results of NINCDS which follow are preliminary and reflect the initial classifications assigned to the compounds that were submitted for anticonvulsant screening and neurotoxicity evaluation.

C. Results of the Pharmakon Neuropharmacological Profiles

The results of the Pharmakon Neuropharmacological Profiles of twenty new compounds along with the profiles of methaqualone (3), 37 and 67 are reported in Tables II and III. Table II contains results of compounds prepared from 3, while Table III presents the findings for other 4(3H)-quinazolinones which contain 3-substituents other than an o-tolyl group. Scores for behavioral symptoms, including depression,

Table II

NPP Results for 2-Substituted-3-o-tolyl-4(3H)-quinazolinones

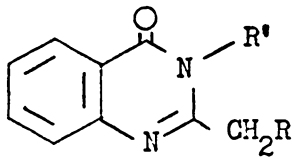


Compound No.	R	CNS Depression @ 100 mg/kg and (30 mg/kg)	% MES Protection @ 100 mg/kg	LD_{50} mg/kg
3	H(methaqualone)	(8)[a,b,c]	0[d]	>562
64g	COC_6H_5	4(4)	0	>562
64h	COC_6H_4Cl-p	0[e]	0	316
64j	$COC_6H_2(OCH_3)_3$-3,4,5	2[e]	0	>562
64i	$COC_6H_4OCH_3$-p	2[e]	0	>562
64m	$COCO_2C_2H_5$	4	0	>562
64f	$COCH{=}CHC_6H_5$	4(2)	25	>562
64a	$COCF_3$	(4)[c,f]	50	>562
63	$COCH_3$	8(4)	0	>562
64b	CO-2-pyridyl	2	0	>562
64c	CO-3-pyridyl	6(4)[b]	100	562
64d	CO-4-pyridyl	0[e]	0	>562

a. Righting Reflex = 8 @ 100 mg/kg.
b. Ataxia = 8 @ 100 mg/kg.
c. Depression not determined at 100 mg/kg.
d. MES protection at 30 mg/kg.
e. Depression = 4 @ 300 mg/kg.
f. Ataxia = 2 @ 100 mg/kg.

Table III

NPP Results for 2,3-Disubstituted-4(3H)-quinazolinones



Compound No.	R'	R	CNS Depression @ 100 mg/kg and (30 mg/kg)	% MES Protection @ 100 mg/kg	LD_{50} mg/kg
69a	o-chlorophenyl	$COCF_3$	8(6)	0[a]	178
69b	o-chlorophenyl	CO-2-pyridyl	0[b]	0	562
69c	o-chlorophenyl	CO-3-pyridyl	4	25	562
69d	o-chlorophenyl	CO-4-pyridyl	6(2)[c,d,e]	50[a]	237
67	p-tolyl	H	8(4)[f]	100	>562
69i	p-tolyl	$COCF_3$	4[g]	100	562
69k	p-tolyl	CO-3-pyridyl	4	0	562
37	phenyl	H	8(4)[c,f]	0[a]	562
69e	phenyl	$COCF_3$	2	0	562

Table III (Continued)

Compound No.	R'	R	CNS Depression @ 100 mg/kg and (30 mg/kg)	% MES Protection @ 100 mg/kg	LD_{50} mg/kg
69g	phenyl	CO-3-pyridyl	2	0	562
69s	CH_3	CO-3-pyridyl	4	0	422

a. Conducted @ 30 mg/kg.
b. Depression = 2 @ 300 mg/kg.
c. Righting reflex = 8 @ 100 mg/kg.
d. Ataxia = 6 @ 100 mg/kg.
e. Depression = 2 @ 10 mg/kg.
f. Ataxia = 8 @ 100 mg/kg.
g. Ataxia = 2 @ 100 mg/kg.

righting reflex, and ataxia are the actual numbers reported by Pharmakon. Protection against MES is reported as a percentage. Since four animals were involved in this test, the findings are 0% for none protected, 25% for one out of four, etc. An LD_{50} of 562 or greater means that no deaths occurred during the observation period. In order to maintain reasonable uniformity in the reporting of results, each entry corresponds to a dosage level of 100 mg/kg. Any variations from that dosage are indicated.

Recalling that a value of 0 for a compound means that no signs of depression, ataxia, or loss of righting reflex were observed, and a value of 8 represents maximum manifestations of these symptoms, it may be noted that all but two of the compounds (64d and 64h)* tested by Pharmakon elicited some measure of depression at 100 mg/kg. The most active compound was the acetonyl derivative 63, which scored a measure of 2 for depression at dosage levels as low as 10 and 3 mg/kg. The potency of 63 is noteworthy in that it is comparable to its active parent 3, which exhibited depression scores of 6 and 0 at the same dosage levels. In addition, 63 also displayed activity equal to 3 in its ability to effect righting reflex and cause ataxia at 100 mg/kg, (Table II). One other new compound that displayed activity in all three of these behavioral areas was the isonicotinoyl derivative 69d. The scores of 69d were essentially equal to those of 3 at 100 mg/kg (Table III).

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*Both of these compounds had depression scores of 4 @ 300 mg/kg.

Of the remaining new derivatives, which exhibited depression, 64a, 64c (Table II) and 69i (Table III) also exhibited ataxia scores of 2, 8, and 2 respectively at 100 mg/kg. In terms of admittedly preliminary structure activity relationships, the results of the Neuropharmacoligal Profiles imply that 2,3-disubstituted quinazalinones with R = $COCH_3$, $COCF_3$, CO-3-pyridyl, and CO-4-pyridyl, cause depression and in most cases, ataxia, and loss of righting reflex, if the 3-aryl grouping is ortho substituted with either a chloro or methyl moiety.

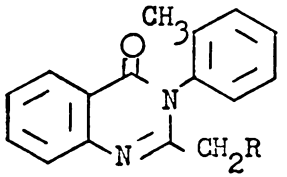
Since the MES protection of 3 was determined at 30 mg/kg rather than at 100 mg/kg, as were its derivatives, it is difficult to draw direct comparisons in the area of anticonvulsant activity between 3 and the compounds listed in Table II. However, certain chemical modifications at the 2-methyl group of 3 do appear to enhance its anticonvulsant activity. For example, methaqualone derivatives, 64f, 64a and 64c, where R = $COCH{=}CHC_6H_5$, $COCF_3$ and CO-3-pyridyl respectively, exhibited 25, 50 and 100% MES protection. Similar chemical elaborations at the 2-methyl group of mecloqualone (4a) to give derivatives, with R = CO-3-pyridyl (69c) and CO-4-pyridyl (69d), imparted MES protection of 25 and 50%, respectively. The occurrence of anticonvulsant activity in 64c, 69c and 69d, all of which contain a pyridyl moiety, is consistent with earlier findings that 2-substituents containing pyridyl groups give rise to anticonvulsant activity in certain 2,3,-disubstituted-4(3H)-quinazolinones.[15,81]

D. NINCDS Primary Evaluation Results

Specific anticonvulsant evaluations, performed by NINCDS using MES, scMet, and Rotorod assays are presented in Tables IV and V for

Table IV

Results of Primary Evaluation of 2-Substituted-3-o-tolyl-4(3H)-quinazolinones in the NINCDS Anticonvulsant Screening Project

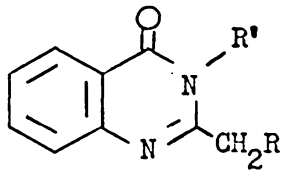


Compound No.	R	MES, mg/kg after 0.5 hr	MES, mg/kg after (4 hr)	scMet, mg/kg after 0.5 hr	scMet, mg/kg after (4 hr)	Rotorod mg/kg after 0.5 hr	Rotorod mg/kg after (4 hr)	NINCDS Classification
3	H	100	(300)	100	(300)	100	(300)	II
53	$CHOHC_6H_5$			300			(300)	II
42[a]	CH_3	100	(300)	100	(300)	100	(300)	II
63	$COCH_3$				(300)			II
64b	CO-2-pyridyl			300				II
64c	CO-3-pyridyl				(300)			II
64d	CO-4-pyridyl	100		30	(300)			I
64l	COC_6H_4-NHCOCF$_3$-p			300		300		II
46	$CH_2C_6H_5$			300	(300)			II
71	CO-3-$C_5H_4N^+CH_3I^-$		(100)		(30)	100		I[a]
73	H and 7-amino	100	(100)	100	(100)	100	(300)	II[a]

a. Extremely toxic

Table V

Results of Primary Evaluation of 2,3-Disubstituted-4(3H)-quinazolinones in the NINCDS Anticonvulsant Screening Project



Compound No.	R'	R	MES, mg/kg after 0.5 hr or (4 hr)		scMet, mg/kg after 0.5 hr or (4 hr)		Rotorod, mg/kg after 0.5 hr or (4 hr)		NINCDS Classification
4a	o-chlorophenyl	H		(300)	30	(100)	30	(100)	I[a]
69a	o-chlorophenyl	$COCF_3$					300	(300)	III
69c	o-chlorophenyl	CO-3-pyridyl			300	(300)		(300)	II
69d	o-chlorophenyl	CO-4-pyridyl	300	(100)	30	(100)			I
69l	p-tolyl	CO-4-pyridyl				(300)			II
69g	phenyl	CO-3-pyridyl	100		100				I
69h	phenyl	CO-4-pyridyl			100				II
69r	methyl	COC_6H_5				(300)			II

a. Extremely toxic

fourteen new compounds as well as several known compounds. Table IV centers attention on 2-substituted-3-o-tolyl-4-(3H)-quinazolinones while Table V includes the findings for various other 2,3-disubstituted-4(3H)-quinazolinones. As described earlier, the MES, scMet, and Rotorod tests were performed one-half hour and four hours after administration of each compound. The tables identify the dosage level that elicited a positive result, such as protection against MES and scMet induced seizures, or loss of balance on the rotorod. Compounds which did not exhibit activity in any of the 3 categories at dose levels of 300 mg/kg were placed in Class III by NINCDS and are not listed. Excluded from Table IV for this reason are the 3-o-tolyl derivatives in which R = $COCF_3$ (64a), COC_6H_5 (64g), COC_6H_4-Cl-p (64h), $COC_6H_4OCH_3$-p (64i), $COC_6H_2(OCH_3)$-3,4,5 (64j), $COCOC_2H_5$ (64m), COC_6H_4-$NHCOCH_3$-p (64k) and with R = H and a nitro group at position 7 of the quinazolinone ring (72a). Excluded from Table V because of their lack of activity are derivatives with R = $COCF_3$, R' = phenyl (69e) or p-tolyl (69i); R = CO-2-pyridyl, R' = o-chlorophenyl (69b), or phenyl (69f); R = CO-2-pyridyl (69j), CO-3-pyridyl (69k), or H (67), R' = p-tolyl.

The anticonvulsant activity and neurotoxicity of the model compounds methaqualone (3) and mecloqualone (4a) are apparent from the results presented in Tables IV and V. Mecloqualone is more effective in protection against scMet induced seizures, while 3 is more active in the MES test. This illustrates the need for having two tests that apparently are selective for convulsive seizures which are aroused by different physiological mechanisms.

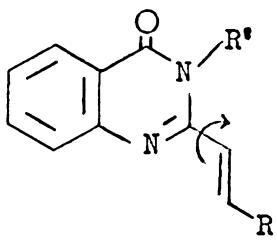
In the present series, the majority of activity observed was in the scMet test. Positive scMet results, were elicited by thirteen of the new compounds, of which only four, 64d, 71 (Table IV), 69d and 69g (Table V), gave indications of MES protection. Interestingly, all four had an R group which contained a 3-pyridyl or 4-pyridyl substituent. The most active derivative of 3 in the scMet test was compound (64d) which had an R = CO-4-pyridyl. After one-half hour and after four hours, 64d gave positive results at 30 mg/kg and 30 mg/kg, respectively. Another new compound, 69d, with R = CO-4-pyridyl and R' = o-chlorophenyl, afforded protection against scMet seizures at 30 mg/kg after one-half hour and at 100 mg/kg after four hours.

Unlike the active parent compounds 3 and 4a, which displayed measurable neurotoxicity in the rotorod test, the respective new derivatives, 64d and 69d were void of such characteristics. Because of the absence of neurotoxicity and the scMet activity at 30 mg/kg, 64d and 69d were classified by NINCDS as Class I compounds and have been submitted for Secondary Evaluation.

It should be noted that compounds 64d and 69d also displayed MES protection. Based on the NINCDS Primary Evaluation of the new compounds that have been synthesized in this investigation, 64d and 69d offer the most promise of becoming effective anticonvulsive agents. Since the results are indeed preliminary, an attempt to predict which of these two compounds is the better anticonvulsant would be pure conjecture at this time; however, these results do imply that in order for maximum anticonvulsant activity (scMet) to occur in our series of

new compounds, the 3-aryl position must be ortho substituted and R = CO-4-pyridyl.

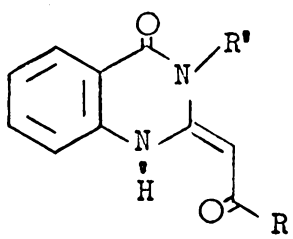
As mentioned in the historical chapter, II, the significance of an ortho substituted 3-aryl group and a pyridyl moiety as part of a 2-substitutent was also observed in the extensive work on 2,3-disubstituted-4-(3H)-quinazolinone anticonvulsants performed by Boltze, et al.[15] Of 103 such compounds -- most of which contained 3-aryl groups -- they found the 2-[2-(2-pyridyl)ethenyl] - and the 2-[2-(3-pyridyl)-ethenyl]-3-o-tolyl-4(3H)-quinazolinones (75a and 75b) to be the most active in the MES test. In the area of scMet protection, the most active compounds were 75b and the 2-[2-(3-pyridyl)ethenyl] derivative 75c.



75a, R = 2-pyridyl, R' = o-tolyl

b, R = 3-pyridyl, R' = o-tolyl

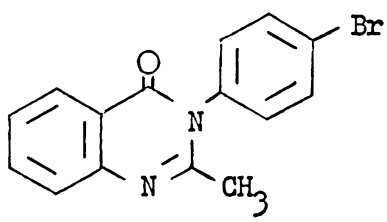
c, R = 3-pyridyl, R' = o-chlorophenyl



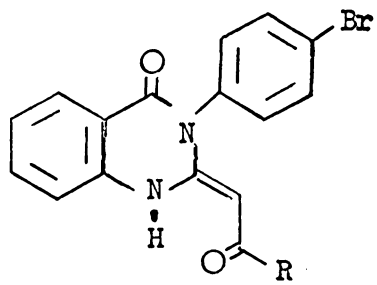
64d, R = 4-pyridyl, R' = o-tolyl

69d, R = 4-pyridyl, R' = o-chlorophenyl

It is interesting to note the structural relationship between our active acylated derivatives 64d and 69d and compounds 75a-c. Based on the proton magnetic resonance of 64d and 69d both carbon atoms of the side chain are coplanar with the quinazolinone ring as a result of sp^2 hydridization. Likewise, the trans configuration of the ethenyl derivatives 75a-c can assume a similar spatial orientation. Although the degree of free rotation about the bond joining C-1 of the ethenyl substituent to C-2 of the quinazolinone ring in 75a-c is not known, a planar two carbon side chain terminating in a pyridyl residue is a structural feature which the two classes of compounds, 64d, 69d and 75a-c have in common.



68



69m, R = CF_3
n, R = 2-pyridyl
o, R = 3-pyridyl
p, R = 4-pyridyl
q, R = CH_3

As a continuation of our investigation we have prepared, from 2-methyl-3-p-bromophenyl-4(3H)-quinazolinone (68), several acylated derivatives 69m-q. Quinazolinone 68, designated as B.D.H. 1880, has been shown to offer the best scMet protection out of forty 2,3-disubstituted-4(3H)-quinazolinones tested by Bianchi and David.[22]

The choice of preparing derivatives 69m-q based on the overall activity displayed by compounds containing the corresponding R groups in tests conducted by Pharmakon and NINCDS. Because of the activity associated with 68 and the particular R grouping, it is possible that the anticonvulsant test results 69m-q will aid in determining the validity of the present structure-activity relationship, which correlates maximum scMet protection with R = CO-4-pyridyl and R' = ortho-substituted phenyl.

In conclusion the results of the Neuropharmacological Profiles of Pharmakon indicated:

(1) that depression was exhibited by eighteen of twenty new compounds at 100 mg/kg or less.

(2) that 2,3-disubstituted quinazolinones with R = $COCH_3$, $COCF_3$, CO-3-pyridyl and CO-4-pyridyl cause depression - and in most instances ataxia, and loss of righting reflex - if the 3-aryl grouping is ortho-substituted with either a chloro or methyl moiety.

(3) the derivative of methaqualone, 3, where R = $COCH_3$ 63, is equal to methaqualone in affecting behavioral activity, and displayed possible muscle relaxant properties not exhibited by methaqualone itself.

(4) that the behavioral activity elicited by the derivative of mecloqualone (4a), where R = CO-4-pyridyl, approaches, that of methaqualone.

The results of the Primary Anticonvulsant Evaluation of NINCDS showed:

(1) that of twenty-nine new compounds submitted, thirteen displayed anticonvulsant activity.

(2) that the anticonvulsant activity of these thirteen compounds was most prominent in the area of scMet protection, but four also gave positive results in the MES test.

(3) a structure-activity correlation in which scMet activity was associated with R = CO-4-pyridyl and a 3-aryl group containing either an ortho methyl (64d) or ortho chloro (69d) substituent.

(4) a lack of neurotoxicity for 64d and 69d.

V. EXPERIMENTAL

A. General

Melting points were taken on either a Thomas-Hoover or Mel Temp apparatus in open capillaries and are uncorrected. Boiling points were also uncorrected. Temperature is reported in degrees Celsius.

Elemental analyses were performed in this laboratory under the direction of Thomas W. Glass, using a Perkin-Elmer 240 C, H, and N analyzer.

Infrared (ir) measurements were made with potassium bromide pellets, or dilute solutions in carbontetrachloride. Spectra were recorded using a Beckman IR-20 AX spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}).

Ultra-violet (uv) and visible (vis) spectra were taken on a Cary 14 spectrophotometer.

Proton and magnetic nuclear resonance (^{1}H NMR) spectra were recorded on a JEOL JMN-PS-100 instrument. Chemical shifts are reported in δ, parts per million (ppm), downfield from tetramethylsilane (TMS) as an internal standard. The splitting patterns are reported as m = multiplet, q = quartet, t = triplet, d = doublet, and s = singlet. Fluorine magnetic resonance (^{19}F NMR) spectra were recorded on the same instrument with proper probe and radio frequency of 94 megaherz. Chemical shifts of fluorine are reported in ppm downfield from hexafluorobenzene (HFB) and are, therefore, negative.

Certain units of measure have been abbreviated as follows: millimeters of mercury (mm), grams (g), moles (mol), millimoles (mmol),

liters (l), milliliters (ml), hours (hr), minutes (min), molar (M), and normal (N).

Mass spectra were taken with a Varian MAT 112 Double Focusing Version Mass Spectrometer with a pressure of less than 10^{-6} mm maintained in the analyzer tube.

Analytical thin layer chromatography (TLC) was carried out using Eastman Chromagram sheets (silica gel) Type 6060 or EM Merck sheets (silica gel) both of which contained fluorescent indicator. Developing solvents are designated and spots were detected with ultraviolet light or iodine. The amount of silica gel employed in column chromatography was based on the ratio of 1 g sample to 50 g silica gel.

Vapor phase chromatography (VPC) was conducted using a Varian Aerograph Model 90- instrument. The conditions are described with the appropriate experiment.

Tetrahydrofuran (THF) was distilled immediately before use from lithium aluminum hydride. Diisopropylamine was distilled from barium oxide and stored over 3A molecular seives in a dessicator charged with Drierite. 1,2-Dimethoxyethane (DME) was refluxed first over sodium metal then oil-free sodium hydride, and distilled immediately prior to use. Unless otherwise specified, all other chemicals were commercial reagent grade and were used without further purification.

Sodium hydride, as an 50% or 57% mineral oil dispersion, potassium hydride as a 24% oil suspension, and n-butyl lithium as 1.6 M, 1.9 M, and 2.4 M solutions in hexane were obtained from Ventron Corporation, Inc., Beverly, Massachusetts. A 1.6 M solution of n-butyllithium in hexane was also obtained from Aldrich Chemical Company.

Photostimulated reactions were conducted in a Raynet RPR-208 photochemical reactor equipped with four 24-W 3500 Å lamps.

B. Preparation of 2-Methyl-3-aryl-4(3H)-quinazolinones.

The following procedure, which is described in detail for the synthesis of 2-methyl-3-o-tolyl-4(3H)-quinazolinone, methaqualone, (3) is essentially that of Grimmel, Guenther, and Morgan[33] and was used to prepare all 2-methyl-3-aryl-4(3H)-quinazolinones employed in this study.

Preparation of N-Acetylanthranilic Acid.

To a magnetically stirred solution of 41.1 g (0.3 mol) of anthranilic acid in 300 ml of glacial acetic acid contained in a 500 ml erlenmeyer flask was added 33 ml (0.35 mol) of acetic anhydride. After heating on a hot plate for 3 hr, 150 ml of hot water was added and the solution was allowed to stand at room temperature. The resulting crystals were filtered, washed with cold water, and recrystallized from 50% ethanol to yield 41.6 g (77.7%) of N-acetylanthranilic acid, mp 182-184° (lit.[82] mp 184-184.5°).

Cyclization of N-Acetylanthranilic Acid with o-Toluidine to form (3).

To 24.8 g (0.139 mol) of N-acetylanthranilic acid, 14.8 g (0.139 mol) of freshly distilled o-toluidine and 450 ml of toluene in a one l three-necked flask fitted with a mechanical stirrer, reflux condenser, addition funnel, and heating mantle, was added dropwise 9.2 g (69 mmol) of phosphorous trichloride (PTC) in 25 ml of toluene over a period of 15 min. Heat was then applied and the solution allowed to reflux for 3 hr and then cooled to room temperature. The toluene was removed by

decantation and 50 ml of water was added to the remaining residue. Solid sodium bicarbonate was added until evolution of gas ceased, then an additional 300 ml of water was added. The resulting solution was stirred vigorously and then extracted twice with 200 ml portions of chloroform, which were combined, dried ($MgSO_4$) and concentrated to give a viscous red oil which crystallized upon standing. The crude product was recrystallized twice from isopropyl alcohol to yield 22.8 g (66%) of 3, mp 114-115° (lit.[17] 115-116°): ^{1}H NMR ($CDCl_3$) δ 8.37 (d, J=8Hz, 1H, 5-H),[83] 7.98-7.18 (m, 7H, aromatic), 2.22 (s, 3H, CH_3), and 2.16 ppm (s, 3H, CH_3): ir (KBr) 1670 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.67; H, 5.64; N, 11.19.
Found : C, 76.61; H, 5.71; N, 11.28.

2-Methyl-3-o-chlorophenyl-4(3H)-quinazolinone (4a)

Reaction of 21 g (0.12 mol) of N-acetylanthranilic acid and 16.4 g (0.13 mol) of o-chloroaniline with 7.5 g (0.055 mol) of phosphorous trichloride in 500 ml of refluxing toluene gave 20 g (62%) of 4a, mp 126-127° (lit.[15] mp 126-127°): ^{1}H NMR ($CDCl_3$) δ 8.35 (d, J=8Hz, 1H, 5-H), 7.96-7.12 (m, 7H, aromatic), and 2.20 ppm (s, 3H, CH_3).

2-Methyl-3-p-tolyl-4(3H)-quinazolinone (67)

Reaction of 27 g (0.15 mol) of N-acetylanthranilic acid with 16 g (0.15 mol) of p-toluidine and 9.6 g (0.07 mol) of phosphorous trichloride in 500 ml of refluxing toluene gave 29 g (77%) of 67, mp 147-148° (lit.[33] mp 147-149°).

2-Methyl-3-phenyl-4(3H)-quinazolinone (37)

Treatment of 27 g (0.15 mol) of N-acetylanthranilic acid and 14 g

(0.15 mol) of aniline with 9.6 g (0.07 mol) of phosphorous trichloride in 500 ml of refluxing toluene yielded 25 g (71%) of 37, mp 143-144° (lit.[33] mp 145-147°): ^{1}H NMR ($CDCl_3$) δ 8.46 (d, J=8Hz, 1H, 5-H), 8.05-7.35 (m, 8H, aromatic), and 2.31 ppm (s, 3H, CH_3); ir (KBr) 1670 cm^{-1} (C=O).

2-Methyl-3-p-bromophenyl-4(3H)-quinazolinone (68)

Treatment of 26 g (0.15 mol) of p-bromoaniline and 27 g (0.15 mol) of N-acetylanthranilic acid with 10.3 g (0.075 mol) of phosphorous trichloride in 500 ml of refluxing toluene gave 42 g (88%) of 68, mp 168-169° (lit.[15] mp 171-172°): ^{1}H NMR ($CDCl_3$) δ 8.28 (d, J=8Hz, 1H, 5-H), 7.87 (m, 7H, aromatic), and 2.26 ppm (s, 3H, CH_3).

C. Preparation and Reactions of Metalated 2-Methyl-3-aryl-4(3H)-quinazolinones.

Lateral Metalation of Methaqualone (3) to Form Lithio Salt 40.

The apparatus used in the metalation experiments consisted of a 100 ml three-necked flask equipped with magnetic stirring bar, rubber septum, ice bath, and nitrogen inlet with a back pressure bubble valve. Solutions were added via a 25 ml pressure-equalizing addition funnel.

Attempted Metalation of 3 with n-Butyllithium.

To a solution of 1.25 g (5 mmol) of 3 in 60 ml of dry THF, was added 3.1 ml (5 mmol) of a 1.6 M solution of n-butyllithium in hexane. A red color appeared immediately, and when addition was complete the solution was red-black in color. After 20 min, the solution was poured into 100 ml of cold water. The orange organic layer was separated and

the aqueous layer was extracted twice with 100 ml portions of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated to yield a red oil.

Analysis of this material by TLC (benzene-ether, 3:1) showed the presence of four components, one of which was unreacted 3. Attempted separation of the reaction products by column chromatography on silica gel using gradient elution with hexane-ether-chloroform afforded 0.52 g (42%) of recovered 3, mp 110-113°. The ^1H NMR spectrum was identical with that of authentic 3. No other pure products could be isolated.

Metalation of 3 by Means of Lithium Diisopropylamide (LDA) to Form Lithio Salt (40).

To 0.7 g (5 mmol) of diisopropylamine in 40 ml of dry THF, was added 3.1 ml (5 mmol) of a 1.6 M solution of n-butyllithium in hexane. After 15 min, lithium diisopropylamide (LDA) was assumed to have formed, and a solution of 1.25 g (5 mmol) of 3 in 10 ml of dry THF was added dropwise to the LDA solution. The dark red anion color appeared immediately and metalation to form lithio salt (40) was assumed to be complete after 20 min. The solution was then poured into 100 ml of cold water, which contained 10 ml of 1 N HCl. The organic phase was separated and the aqueous layer was extracted twice with 100 ml of ether. The organic layers were combined, dried ($MgSO_4$), filtered and concentrated. TLC analysis of the concentrate showed only one spot whose R_f corresponded to that of 3. The crude solid was recrystallized from isopropanol to yield 1.15 g (86%) of 3, mp 113-115°. The ^1H NMR spectrum was identical with that of an authentic sample.

Deuteration of Lithio Salt (40).

To 5 mmol of 40, prepared as described above, was added 3 drops of deuterium oxide via syringe and the reaction mixture was stirred until the color of 40 disappeared (10 sec). The reaction solution was immediately transferred to a one-necked flask and concentrated. The light yellow sticky solid was placed in a vacuum oven over-night. The ^{1}H NMR spectrum ($CDCl_3$) of the resulting solid revealed that 98% of one deuteron was incorporated into the 2-methyl group.

2-Ethyl-3-o-tolyl-4(3H)-quinazolinone (42a).

To a solution of 5 mmol of lithio salt 40 in 75 ml of THF-hexane was added 0.71 g (5 mmol) of methyl iodide via syringe. The anion color was discharged within 2 min. After 30 min, the reaction mixture was poured into 50 ml of cold water containing 10 ml of 1 N HCl. The resulting two phase mixture was extracted twice with 100 ml portions of ether. The ethereal layers were combined, dried ($MgSO_4$) and concentrated. The resulting light yellow solid was recrystallized from isopropanol-hexane to afford 0.69 g (53%) of 42a, mp 93-94° (lit.[15] 91-92°): ^{1}H NMR ($CDCl_3$) δ 8.33 (d, J=8Hz, 5-H), 7.89-7.09 (m, 7H, aromatic), 2.39 (q, J=7Hz, 2H, CH), 2.14 (s, 3H, CH_3), and 1.23 ppm (t, J=7Hz, 3H, CH_3); ir (KBr) 1670 cm^{-1} (C=O).

2-[bis(Phenylithio)methyl]-3-o-tolyl-4(3H)-quinazolinone (50).

To a solution of 5 mmol of lithio derivative 40 prepared as described previously, in 60 ml of THF-hexane-diisopropylamine, was added 1.24 g (5.7 mmol) of diphenyl disulfide in 15 ml of dry THF. The anion color disappeared gradually over a period of 45 min. After

a total reaction time of 1.5 hr, the yellow orange solution was poured into 100 ml of saturated solution of sodium carbonate. The organic layer was separated and the aqueous layer was extracted twice with 100 ml portions of chloroform. The organic layers were combined and extracted once with 50 ml of water containing 7 ml of 1 N HCl. The organic layer was then dried ($MgSO_4$), filtered, and concentrated. The resulting orange oil was chromatographed on silica gel. Elution with hexane-ether (98:2) afforded 0.38 g (31%) of recovered diphenyl disulfide, mp 60°, mmp with an authentic sample 59-60°. The ir (KBr) spectrum was identical with that of an authentic sample.

Elution with hexane-ether (85:15) afforded 0.56 g (24%) of 50, mp 139-142°. Recrystallization from hexane-ether raised the mp to 142-143°: ^{1}H NMR ($CDCl_3$) δ 8.34 (d, J=8Hz, 1H, 5H) and 7.93-6.87 (m, 17H, aromatic), 4.97 (s, 1H, CH), and 2.08 ppm (s, 3H, CH_3): mass spectrum (m/e) 467 (m^+); ir (KBr) 1670 cm^{-1} (C=O).

Anal. Calcd for $C_{28}H_{22}N_2OS_2$: C, 72.07; H, 4.75; N, 6.00.

Found : C, 72.35; H, 5.08; N, 6.28.

Final elution of the column with hexane-ether (1:1) yielded 0.65 g (52%) of recovered 3, mp 112.5-114°. The ^{1}H NMR spectrum was identical with that of an authentic sample of 3. No monosulfenylated derivative 51 of 3 could be isolated.

2-(3-Butenyl)-3-o-tolyl-4-(3H)-quinazolinone (42b).

To a solution of 5 mmol of 40, in 75 ml of THF-hexane was added 0.72 (6 mmol) of allyl bromide via syringe. After 30 min, no further change in the color of the yellow orange reaction solution was observed.

The solution was then poured into 100 ml of cold water, containing 10 ml of 1 N HCl. The resulting solution was extracted twice with 150 ml portions of chloroform. The chloroform extracts were combined, dried ($MgSO_4$) and concentrated. The light orange oil yielded a yellow solid on trituration with hexane. The crude product was recrystallized from isopropanol to afford 0.87 g (60%) of 42b, as white rhombic crystals, mp 269-270°: ^1H NMR ($CDCl_3$) δ 8.28 (d, J=8Hz, 1H, 5-H), 7.78-7.08 (m, 7H, aromatic), 6.00-5.54 (m, 1H, vinyl), 5.03-4.85 (m, 2H, vinyl), 2.62-2.16 (m, 4H, CH_2CH_2), and 2.07 ppm (s, 3H, CH_3); ir (KBr) 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65.
Found : C, 78.83; H, 6.63; N, 9.56.

2-Propyl-3-o-tolyl-4(3H)-quinazolinone (42c) and 2-(3-Pentyl)-3-o-tolyl-4(3H)-quinazolinone (43).

To a solution of 5 mmol of 40 in 60 ml of THF-hexane-diisopropylamine, was added 0.78 g (5 mmol) of ethyl iodide via syringe. After 45 min, the reaction solution still retained a clear orange color. After a total reaction time of 1 hr, the reaction solution was poured into 100 ml of water, containing 10 ml of 1 N HCl. The resulting yellow solution was extracted twice with 150 ml portions of chloroform. The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated. TLC (benzene-ether, 98:2) analysis revealed the presence of three spots. The component having the lowest R_f value was identified as 3. The spot with the greatest R_f value was noticeably the least intense of the three. Column chromatography of the red oil on silica gel achieved only

partial separation of the components regardless of the elution system employed. The following represents the best separation achieved: Elution with hexane-ether (95:5) afforded 0.08 g (5%) of the diethylated derivative 43 as white crystals, mp 98-99°: ^{1}H NMR ($CDCl_3$) δ 8.47 (d, J=8Hz, 1H, 5-H), 7.95-7.27 (m, 7H, aromatic), 2.59-2.13 (m, 1H, CH), 2.27 (s, 3H, CH_3), 2.13-1.55 (m, 4H, CH_2), and 1.11-0.89 ppm (d of t, 6H, CH_3).

Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.39; H, 6.96; N, 8.80.
Found : C, 78.36; H, 6.71; N, 8.78.

Elution with hexane-ether (90:10) yielded 0.35 g (25%) of monoethylated derivative. An analytical sample was prepared by recrystallization from isopropanol-hexane. The resulting white crystals had mp 69-70° (lit.[17] as the HCl salt 199-200°): ^{1}H NMR ($CDCl_3$) δ 8.43 (d, J=8Hz, 1H, 5-H), 7.96-7.24 (m, 7H, aromatic), 2.44 (t, J=8Hz, 2H, CH_2), 2.23 (s, 3H, CH_3), 2.03-1.64 (m, 2H, CH_2), and 0.99 ppm (t, J=7Hz, 3H, CH_3).

Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06.
Found : C, 77.44; H, 6.60; N, 10.06.

Elution with hexane-ether (75:25) yielded 0.53 g (42%) of recovered 3, mp 110-113°. The ^{1}H NMR spectrum was identical to authentic sample of 3 and showed possible traces of monoethyl derivative 42c.

In order to investigate the possibility of favoring formation of monoalkyl derivative 42c, the above reaction was repeated by adding 0.91 g (5 mmol) or excess of hexamethylphosphoramide (HMPA) to the THF-hexane solution of anion 40. TLC analysis (benzene-ether, 98:2) revealed the presence of three spots with R_f values corresponding to

3, 42c and 43. Similar results were obtained when the reaction was conducted in liquid ammonia using potassium amide as the ionizing base and ethyl iodide as the alkylating agent.

Using the procedure described above 5 mmol of 40 was prepared in 42 ml of dry THF. The resulting solution was added dropwise via a 50 ml syringe to a stirred solution of 7.8 g (50 mmol) of ethyl iodide in 40 ml of dry THF at 0° under nitrogen. Assuming the disappearance of anion color to be an indication of reaction, the rate of addition was adjusted to allow the color of each drop of anion to be consumed before adding another drop. After addition of the first 17 ml of anion solution, the reaction appeared to be noticeably slower, and after addition of a total of 20 ml, the ethyl iodide-THF solution maintained an orange color with no apparent change in intensity within 15 min. The remaining 16 ml of anion 40 was added over a period of 40 min. Total addition time was 1 hr, 40 min. The orange solution was then processed as previously described to give a dark red oil. TLC analysis again revealed the presence of 3 spots having identical R_f values to the three products isolated in the ethylation described above.

Attempted Ethylation of Lithio Salt (45).

In order to investigate the possible steric influence that the 3-o-tolyl group of 40 plays in alkylation with ethyl bromide, the lithio salt (45) of 2,3-dimethyl-4(3H)-quinazolinone (23a) was similarily prepared. To anion 45 was added ethyl bromide and TLC analysis of the concentrate revealed the same behavior as 40 by exhibiting a 3 component

mixture. No attempt to isolate the alkylated products of 23a was carried out.

Phenylation of Potassio Salt (47) to Give 2-Benzyl-3-o-tolyl-4(3H)-quinazolinone (46).

The reaction was performed in a cylindrical pyrex vessel, having an inside diameter of 4.2 cm and a height of 43 cm. This flask was equipped with a magnetic stirrer, and a three-necked adapter to which a solid carbon dioxide-isopropanol condenser fitted with a nitrogen inlet was attached. To a stirred suspension of (10 mmol) of potassium amide, prepared from 0.40 g (10 mg-atom) of potassium in 300 ml of anhydrous liquid ammonia and a catalytic amount of ferric nitrate, was added 2.50 g (10 mmol) of 3 as a solid through a long-stemmed funnel. The deep red anion color of 3 appeared immediately and a dissolution period of 1 hr was then allowed. To the resulting solution was added 3.06 g (15 mmol) of iodobenzene in 30 ml of dry ether, and the reaction flask was lowered into the photoreactor and irradiated for 1 hr. The red solution was then quenched by carefully adding 1 g of solid ammonium chloride. The condenser was removed and the ammonia was evaporated while 150 ml of ether was added. Water (150 ml) was added to the resulting suspension. The organic phase was separated and the aqueous phase was extracted twice with 100 ml portions of chloroform. The organic phases were combined, dried ($MgSO_4$), and concentrated. TLC analysis (chloroform) of the crude product showed the presence of four components. By comparison of R_f values, the broad leading spot and slowest moving spot were identified as iodobenzene

and 3, respectively. The yellow oil was chromatographed on silica gel. After the residual iodobenzene had been washed off the column with hexane, elution with hexane-ether (9:1) afforded ca. 15 mg of a clear nonviscous oil: ^{1}H NMR ($CDCl_3$) 8.28 (d, J=8, 1H, 5-H), 7.73-6.83 (m, 17H, aromatic), 5.08 (s, 1H, CH), and 2.93 ppm (s, 3H, CH_3). Attempts to cause crystallization failed and no further characterization was carried out. Elution with hexane-ether (80:20) yielded 0.55 g (34%) of 46, which as white platelets, mp 113-114° (lit.[77] mp 113°): ^{1}H NMR ($CDCl_3$) δ 8.27 (d, J=8Hz, 1H, 5-H), 7.80-6.77 (m, 12H, aromatic), 3.84 (s, 2H, CH_2)* and 1.67 ppm (s, 3H, CH_3); ir (KBr) 1660 cm^{-1} (C=O).

Continued elution with hexane-ether (80:20) afforded 0.51 g (41%) of 3, mp 112-113°, mmp 112-113°.

2. "Dark" Reaction Followed by Photostimulation.

The above reaction procedure was repeated except that the reaction vessel was enclosed in aluminum foil prior to the addition of iodobenzene, and the reaction was allowed to proceed without external illumination. After 1 hr, a 1 ml aliquot was removed by means of a dip tube and was quenched with solid ammonium chloride. To the resulting mixture, 5 ml of water was added. The resulting solution was extracted with 5 ml of chloroform. TLC (chloroform) analysis of the organic phase revealed that no 46 was present. After 4 hr an aliquot treated as described above revealed only unreacted 3 and iodobenzene. The aluminum foil was

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*This signal sometimes appears as a doublet, J=2Hz, otherwise it appears as a singlet.

then removed and the reaction solution was irradiated. After 5 min of irradiation, TLC analysis of an aliquot revealed two spots of equal intensity which corresponded to unreacted 3 and to phenylated product 46. No attempt was made to isolate any of the products of the reaction.

3. Photostimulation of the Reaction of (47) with Iodobenzene in the Presence of p-Dinitrobenzene (DNB).

To (10 mmol) of 47, prepared as before, in 300 ml of anhydrous liquid ammonia, was added 0.084 g (0.5 mmol) of solid DNB, which caused the dark red solution to become dark green in color. After 3.06 g (15 mmol) of iodobenzene in 30 ml of dry ether was added, the resulting solution was irradiated for 1 hr. TLC analysis (chloroform) of an aliquot after 15 min revealed the presence of a spot having an R_f identical to phenylated product 46 while after 5 min no 46 had formed. The above experiment was repeated using 0.072 g (0.5 mmol) of di-t-butyl nitroxide as an inhibitor; similar results were obtained.

4. Dark Reaction of (47) and Iodobenzene in the Presence of One Equivalent of Potassium Amide.

To a suspension of 20 mmol of potassium amide in 300 ml of liquid ammonia was added 2.50 g (10 mmol) of solid 3. The reaction vessel was enclosed in aluminum foil. After 1 hr, 3.06 g (25 mmol) of iodobenzene in 30 ml of dry ether were added. Hourly aliquots from the reaction solution were taken. After 4 hr, TLC analysis (chloroform) revealed by comparison of R_f that 46 was present. No attempt to isolate the product (46) ensued.

2-(2-Hydroxy-2-phenylethyl)-3-o-tolyl-4(3H)-quinazolinone (53).

To a solution of 5 mmol of 40, prepared as described previously, in 60 ml of THF-hexane-diisopropylamine, was added 0.53 g (5 mmol) of freshly distilled benzaldehyde via syringe. The intensity of the anion color rapidly lessened upon the addition of each drop of benzaldehyde. After 3 min, the resulting clear yellow solution was poured into 100 ml of cold water, containing 10 ml of 1 N HCl. The aqueous-THF solution was extracted three times with 100 ml portions of ether. The ethereal extracts were combined, dried ($MgSO_4$), and concentrated at room temperature. TLC analysis (hexane-ether-acetone, 70:25:5) of the yellow oil revealed a three-component mixture. The major component, 53, was located between the two minor components corresponding to 54 (greatest R_f) and 3 (smallest R_f).

Trituration of the oil with hexane afforded 0.91 g (51%) of crude 53, which as a yellow solid, mp 119-128°. Further purification by recrystallization of the yellow amorphous solid from solvents such as isopropanol, ethyl acetate, ether, benzene, hexane and combinations of these solvents were unsuccessful. TLC analysis revealed that recrystallization caused decomposition of 53 to 54 and/or 3.

The reaction was repeated and the similarly-obtained oil was column chromatographed on silica gel. Various mixtures of benzene-ether and benzene-hexane solvent systems were unsatisfactory for achieving separation. The styryl derivative 54 could always be isolated, since it was the first component to elute from the column. Yields of 54 ranged from 2 to 16%, mp 160-161° (lit.[15] 162-163°): ^1H NMR ($CDCl_3$)

δ 8.44 (d, J=8Hz, 1H, 5-H), 8.12 (d, J=16Hz, 1H, vinyl), 7.98-7.22 (m, 12H, aromatic), 6.41 (d, J=16Hz, 1H, vinyl), and 2.16 ppm (s, 3H, CH_3).

Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.29.
Found : C, 81.32; H, 5.18; N, 8.24.

Hexane-ether solvent systems provided the best separation. On elution with hexane-ether (95:5), 0.25 g (14%) of 54 were obtained. Elution with (90:10) gave 0.030 g of 53, as a white solid, mp 136-141°: ^1H NMR ($CDCl_3$) δ 8.43 (d, J=8Hz, 1H, 5-H), 8.00-7.00 (m, 12H, aromatic), 5.82, and 5.68 (s, 1H, OH), 5.36 and 5.26 (m, 1H, CH), 2.96-2.32 (m, 2H, CH_2), and 2.74 and 2.06 ppm (s, 3H, CH_3). The spectrum shows a consequence of rotational diastereomers, as is also the case for the following spectrum in DMSO: ^1H NMR (DMSO-d_6) δ 8.18-7.05 (m, 12H, aromatic), 5.50 and 5.54 (s, 1H, OH), 5.40-5.03 (m, 1H, CH), 2.77-2.59 (m, 2H, CH_2), and 2.09 and 1.85 ppm (s, 3H, CH_3); ir (KBr) 1670 cm^{-1} (C=O).

An analytical sample was obtained from a fraction which gave a solid, mp 137-138°.

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.61; N, 7.86.
Found : C, 77.31; H, 5.54; N, 7.90.

Continued elution hexane-ether (80:20) afforded 0.1 g (8%) of recovered 3, mp 114-115°, mmp 114-115°. The ^1H NMR spectrum was identical with an authentic sample of 3.

In an attempt to prevent the apparent dehydration of 53, the reaction mixture was quenched with trimethylchlorosilane-triethylamine after benzaldehyde and 40 had reacted. This apparently only increased

the amount of 54 as evidenced by TLC analysis. No further isolation was carried out on the reaction mixture.

The ease of formation of 54 became apparent when a reaction mixture was quenched with 10 ml of water, and after a reaction period of 2 hr at room temperature, 1.4 g (84%) of 54 were isolated following similar processing of the reaction mixture. The mp and ^{1}H NMR spectrum were the same as those previously described for 54.

The HPLC analysis of 53 employed the following conditions: column, Zorbax-SIL; solvent, chloroform-methanol-cyclohexane (19.5:0.5:80); flow rate, 0.5 ml/min @ 1800 psi.

Synthesis of 55, 56 and 60 via the Lithio Salt of 2,3-Dimethyl-4(3H)-quinazolinone (23a).

2,3-Dimethyl-4(3H)-quinazolinone (23a).

A stirred solution of 6.36 g (40 mmol) of 2-methyl-4(3H)-quinazolinone, 3.2 g (56 mmol) of potassium hydroxide, and 5.6 g (45 mmol) of dimethyl sulfate in 140 ml of THF-water was heated for 18 hrs at 50-60°. The brown solution was cooled to room temperature, poured into 100 ml of water and extracted three times with 100 ml portions of chloroform. The chloroform extracts were combined, dried ($MgSO_4$), and concentrated to give a yellow oil which solidified on standing. The yellow crude product was recrystallized twice from isopropanol-hexane to give 4.4 g (63%) of 23a, as light yellow needles, mp 108-110° (lit.[84] mp 108-109°): ^{1}H NMR ($CDCl_3$) δ 8.18 (d, J=8Hz, 1H, 5-H), 7.76-7.18 (m, 3H, aromatic), 3.69 (s, 3H, CH_3) and 2.60 ppm (s, 3H, CH_3); ir (KBr) 1660 cm^{-1} (C=O).

The same apparatus was used in the preparations of 55, 56 and 60 as was employed in the formation of the anion 40. The following preparation of 56 describes in detail the standard preparation of lithio salt, 45.

2-(2-Hydroxy-2,2-diphenylethyl)-3-methyl-4(3H)-quinazolinone (56).

To a solution of 0.71 g (7 mmol) of diisopropylamine in 60 ml of dry THF at 0° under nitrogen, was added 2.4 ml (5 mmol) of a 2.1 M solution of n-butyllithium in hexane via syringe. After 15 min, 0.87 g (5 mmol) of 2,3-dimethyl-4(3H)-quinazolinone (23a) was added as a solid to the stirred solution of 5 mmol of LDA. The red anion color appeared immediately and formation of lithio salt 45 was assumed to be complete after 30 min. To the slightly insoluble salt was added 0.91 g (5 mmol) of solid benzophenone. After 3 min, the solution became light orange; however, the reaction was continued until the traces of precipitated salt 45 on the walls of the reaction flask had reacted (0.5 hr). The resulting light orange solution was poured into 100 ml of water containing 12 ml of 1 N HCl. The resulting solution was extracted three times with 100 ml portions of ether. The ethereal extracts were combined, dried ($MgSO_4$), and concentrated. Trituration of the yellow concentrate with hexane yielded a light yellow solid, which was recrystallized from isopropanolacetone to yield 1.23 g (69%) of 56, mp 159-161°. A second recrystallization produced an analytical sample as white crystals, mp 161-162°: ^1H NMR ($CDCl_3$) δ 8.15 (d, J=8Hz, 1H, 5-H), 7.70-7.04 (m, 14H, 13 aromatics and one OH), 3.66 (s, 2H, CH_2), and 3.60 ppm (s, 3H, CH_3); ir (KBr) 3330 (OH) 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86.
Found : C, 77.16; H, 5.39; N, 7.53.

2-(2-Hydroxy-2-phenylethyl)-3-methyl-4(3H)-quinazolinone (55).

To a solution of 5 mmol of lithio salt 45, prepared as described above in 60 ml of dry THF, was added via syringe a solution of 0.53 g (5 mmol) of benzaldehyde in 5 ml of dry THF. The dark-red anion solution immediately turned clear yellow and the reaction was allowed to continue until all visible traces of anion 45 had reacted. The clear yellow reaction solution was worked up as described in the preparation of 56 to give a solid upon concentration of the ethereal extract. The yellow solid was recrystallized from isopropanol-ether to yield 1.0 g (73%) of 55 as white crystals, mp 132-133°: ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J=8Hz, 1H, 5-H), 7.80-7.12 (m, 8H, aromatic), 5.50 (d, J=2Hz, 1H, OH), 5.38 (overlapping triplets, J=6Hz, 1H, C-H), 3.50 (s, 3H, CH_3), and 3.05 ppm (d, J=6Hz, 2H, CH_2); ir (KBr) 3460 (OH) 1650 cm^{-1} (C=O).
Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99.
Found : C, 73.08; H, 5.46; N, 10.33.

2-(2-Hydroxy-2,2-dimethylethyl)-3-methyl-4(3H)-quinazolinones (60).

To a solution of 5 mmol of the lithio salt 45, in 60 ml of dry THF, was added via syringe 0.29 g (5 mmol) of acetone, which had been stored over 4A molecular sieves. After 30 min, the yellow reaction solution was processed as described previously in the preparation of 56. TLC analysis (chloroform) revealed by comparison of R_f's the presence of 23a and 60. The yellow oil was chromatographed on silica gel with hexane-ether-chloroform (80:10:10) afford 0.45 g (41%) of 60.

An analytical sample was prepared by recrystallization from isopropanol. The resulting white crystals melted at 123-124°: ^{1}H NMR ($CDCl_3$) δ 8.28 (d, J=8Hz, 1H, 5-H), 7.84-7.40 (m, 3H, aromatic), 6.15 (s, 1H, OH), 3.62 (s, 3H, CH_3), 2.92 (s, 2H, CH_2), and 1.42 ppm (s, 6H, CH_3); ir (KBr) 3480 (OH) 1640 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06.

Found : C, 66.92; H, 6.99; N, 11.91.

2-[(1-Hydroxy-1-cyclohexyl)methyl]-3-o-tolyl-4(3H)-quinazolinone (57).

To a stirred solution of (5 mmol) of 40 in THF-hexane-diisopropylamine at 0° was added 0.49 g (5 mmol) of cyclohexanone via syringe. After 20 min, the reaction solution was a clear red-orange color. After 1 hr the solution was yellow-orange in color and remained so for an additional hr. The reaction solution was then poured into 100 ml of cold water containing 10 mmol of 1 N HCl. The organic and aqueous layers were separated and the aqueous layer was extracted twice with 100 ml portions of chloroform. The organic layers were combined, dried ($MgSO_4$), and concentrated to yield a clear oil. Column chromatography on silica gel, upon elution with hexane-ether (85:15) yielded a clear viscous oil which could not be crystallized by trituration. The oil was vacuum dried for three days during which time the sample was heated periodically with a hot air gun. This treatment afforded 0.38 g (22%) of 57 which remained a very viscous syrup: ^{1}H NMR ($CDCl_3$) δ 8.46 (d, J=8Hz, 1H, 5-H), 8.04-7.17 (m, 7H, aromatic), 6.48 (s, 1H, OH), 2.43 (d, J=16Hz, 2H, CH_2), 2.18 (s, 3H, CH_3), and 2.01-1.05 ppm (broad m, 10H, cyclohexyl); mass spectrum (m/e) 348 (m^+); ir (CCl_4) 3375 (OH) 1690 cm^{-1}

(C=O). No melting point is reported since 57 failed to crystallize. After standing in the air at room temperature for over 8 months, the material became glass-like.

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04.

Found : C, 75.89; H, 7.25; N, 7.94.

Elution with hexane-ether (60:40) afforded 0.7 (56%) of recovered 3, mp 113-114°: ^{1}H NMR ($CDCl_3$) was identical with an authentic sample of 3.

Independent Preparation of the Trimethylsilyl Enol Ether (59) of Cyclohexanone.

In a 250 ml three-necked flask, 5.83 g (35 mmol) of potassium hydride, as a 24% mineral oil suspension, was washed twice with 100 ml portions of dry hexane. After this washing, 100 ml of dry THF was immediately added. To the resulting magnetically stirred suspension was then added a solution of 3.43 g (35 mmol) of cyclohexanone in 10 ml of dry THF, and after a slight induction period hydrogen gas was evolved. The theoretical volume of hydrogen had evolved within 3 min. The reaction vessel was then placed in a Dry Ice-acetone bath. To the cooled reaction mixture was added a solution of 52 mmol of triethylamine and 52 moles of freshly distilled[85] trimethylchlorosilane in 30 ml of dry THF through a pressure equalizing funnel.

After ca. 15 min the solution was diluted with 100 ml of hexane. The resulting solution was washed successively with 5% HCl (100 ml) and 5% $NaHCO_3$ (100 ml) solutions,[86] concentrated, and vacuum distilled to give 59 (lit.[87] bp 74-75°/20 mm): ^{1}H NMR (neat-signals are reported

downfield from [$OSi(CH_3)_3$] δ 4.66 (m, 1H, vinyl), 1.94-1.29 (m, 8H, CH_2), and 0.00 ppm [s, 9H, $OSi(CH_3)_3$].

Trapping of Cyclohexanone Enolate Ion (58) with Trimethylchlorosilane/Triethylamine (TMCS/TEA).

The previous description for the preparation of 57 was repeated to the point of allowing cyclohexanone to react with 40 for 1 hr. After this time, a solution of 0.87 g (8 mmol) of TMCS and 0.81 g (8 mmol) of TEA in 30 ml of THF was added rapidly *via* a pressure-equalizing addition funnel. Flocculent solid material formed in the addition funnel but did not hinder addition. The reaction solution, which also contained small amounts of solid, became light yellow. After addition was complete the ice-bath was removed, and the solution was concentrated. Analysis* of the residual oil by VPC (6 ft, 6.3% Carbowax on Chromosorb Z 60/80 mesh at 120°) revealed the presence of trimethylsilyl enol ether of cyclohexanone (59) as determined by comparison of retention time with that of an authentic sample.

In order to determine if the silyl enol ether (59) formed in the presence of diisopropylamine, TMCS, TEA, and cyclohexanone, these reactants (7, 8, 8, and 5 mmol, respectively) were mixed together in 50 ml of THF at 0° under nitrogen. The ice bath was removed and the stirring was continued for 4 hr. The reaction solution was concentrated and VPC analysis showed that 59 had not formed.

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*Detector cell current, 150 ma; injector port temperature 164°; helium flow at exit, 100 cm^3/min; sample size, 10-30 μl.

Attempted Condensation of Lithio Salt of 2-Methyl-3-phenyl-4(3H)-quinazolinone (37) with Cyclohexanone.

To a solution of 10 mmol of LDA (prepared by mixing 1.2 g (12 mmol) of diisopropylamine and 4.2 ml (10 mmol) of n-butyllithium (2.4 M) in 70 ml of dry THF at 0° under nitrogen) was added 2.36 g (10 mmol) of 37. The corresponding anion formed rapidly as evidenced by the immediate dark red coloration. After 30 min, 0.98 g (10 mmol) of cyclohexanone was added to the dark red solution via syringe. The anion color disappeared slowly and after 1 hr the resulting clear orange-yellow solution was poured into 100 ml of cold water containing 22 ml of 1 N HCl. The organic and aqueous layers were separated and the aqueous layer was extracted twice with 100 ml portions of chloroform. The chloroform layers were combined, dried ($MgSO_4$), and concentrated to give a yellow oil. TLC analysis (chloroform) of the concentrate, revealed two major components. The less mobile component had an R_f identical with 37. The other component was 62a-b. Trituration with hexane-ether afforded 0.81 g (36%) of 62a-b as a white solid, mp 176-180°. Recrystallization from isopropanol-chloroform elevated mp 193-194°: ^1H NMR ($CDCl_3$) δ 13.08 (s, 0.9H, enol), 8.37 (s, 0.9H, NH), 8.28-7.01 (m, 18H, aromatic), 4.52 (s, 0.9H, vinyl), 3.83 (s, < 1H, OH), 1.90 (s, 2.7H, CH_3-chain), 1.74 (s, CH_2), and 1.64 ppm (s, 0.3H, CH_3-ring); (DMSO-d_6) δ 13.00 (s, 1H, enol), 10.63 (s, 1H, NH), 8.20-7.00 (m, 18H, aromatic), 4.32 (s, 1H, vinyl), and 1.98 ppm (s, 3H, CH_3). The signals at 13.00 and 10.63 exchanged with deuterium oxide; mass spectrum (m/e) 472 (m+); ir (KBr) 3380 (NH) 1670 cm^{-1} (C=O).

Anal. Calcd. for $C_{30}H_{24}N_4O_2$: C, 76.25; H, 5.12; N, 11.85.
Found : C, 76.34; H, 5.08; N, 12.01.

A second crop of solid obtained by the trituration of the mother liquors consisted of 37 and traces of 62a-b.

Preparation of 62a-b was also achieved by reacting 0.69 g (2.9 mmol) of 37 with 1.5 mmol of LDA for a period of 1.5 hr. Normal processing of the reaction solution previously afforded three crops of solid. The second of these crops yielded 0.32 g (47%) of 62a-b as a white solid, mp 190-192°. The ^{1}H NMR and ir spectra were identical with 62a-b obtained from the reaction of the lithio salt of 37 and cyclohexanone, as described above. The first and third crops (total 0.3 g) were subsequently identified as 37 by ^{1}H NMR.

Formation of 63 by Condensation of Lithio Salt 40 with Excess Ethyl Acetate.

To a magnetically stirred solution of 5 mmol of LDA, prepared by mixing 2.1 ml (5 mmol) of n-butyllithium (2.4 M) and 0.71 g (7 mmol) of diisopropylamine in 25 ml of dry THF at 0° under nitrogen, was added 1.25 g (5 mmol) of 3. After 30 min the entire solution of lithio salt 40 was transferred via syringe (50 ml) to an addition funnel which was attached to a three-necked 100 ml flask. The bottom half of the addition funnel was loosely enclosed in aluminum foil which formed a cup that held several small pieces of dry ice. To a solution of 4.40 g (50 mmol) of ethyl acetate in 60 ml of dry THF at 0°, was added dropwise the 5 mmol solution of lithio salt 40 over a 65 min period. After addition was complete, the clear yellow solution was poured into 100 ml

of water containing 10 ml of 1 N HCl. The resulting solution was extracted twice with 200 ml portions of ether, which were combined, dried and concentrated. TLC analysis (ether-acetone, 98:2) revealed two spots, with 3 as the major component. Column chromatography afforded, on elution with hexane-ether (9:1), 0.14 g (8%) of 2-acetonyl-3-o-tolyl-4(3H)-quinazolinone (63) as white crystals, mp 164-165.5°. The ^{1}H NMR spectrum was identical with 63, prepared by the general sodium hydride acylation procedure described subsequently.

The above reaction was repeated but in the presence of 0.48 g (10 mmol) of sodium hydride so that any hydrogen that might be evolved from the reaction of 63 with sodium hydride could be monitored manometrically. Evolution of hydrogen was not observed during the addition of the 5 mmol solution of the lithio salt of 3, nor for 30 min after addition was complete. TLC of a concentrate of this solution appeared to be similar to that of the concentrate obtained in the reaction. No further attempt at isolation of the reaction components was carried out.

D. Sodium Hydride Promoted Acylations of 2-Methyl-3-aryl-4(3H)-quinazolinones.

Attempted Acylation of Quinaldine with Ethyl Acetate in the Presence of Excess Sodium Hydride.*

To a refluxing slurry of 2.5 g (52 mmol) of 50% sodium hydride in 150 ml of DME was added 1.14 g (13 mmol) of ethyl acetate and 1.43 g (10 mmol) of quinaldine in 20 ml of dry DME. After a reaction period

*See general acylation procedure for apparatus description.

of 2.5 hr, hydrogen evolution ceased (290 ml at STP, 12.9 mmol). The cooled reaction mixture was quenched with 50 ml of cold water containing 9 ml of 6 M HCl. The solution was diluted with 100 ml of water, made basic with 5% sodium bicarbonate solution, and then extracted three times with 100 ml portions of ether which were combined, dried ($MgSO_4$), and concentrated at room temperature. VPC analysis of the yellow concentrate on 1% SE-52 on Chromasorb W (High performance) at 120° revealed the presence of ethyl acetoacetate and unreacted quinaldine. The presence of a trace amount of 2-acetonyl-quinoline was verified by TLC analysis (hexane-ether, 1:1).

Preparation of Ethyl Acetoacetate using Ethyl Acetate and Excess Sodium Hydride.

To a refluxing slurry of 2.5 g (52 mmol) of 50% sodium hydride in 150 ml of DME was added 1.14 g (13 mmol) of ethyl acetate in 20 ml of DME. After a reaction period of 1.5 hr, hydrogen evolution ceased (285 ml at STP, 12.7 mmol) and the reaction mixture was worked up as described above to give a 0.47 g (62%) of crude ethyl acetoacetate, which was identified by VPC.

2-Acetonyl-3-o-tolyl-4(3H)-quinazolinone (63).*

To a refluxing slurry of 2.5 g (52 mmol) of 50% sodium hydride in 140 ml of DME was added 2.5 g (10 mmol) of 3 and 1.14 g (13 mmol) of ethyl acetate in 20 ml of dry DME. After a reaction period of 3.5 hr, 475 ml (21.2 mmol) at STP of hydrogen had evolved. Since no

*See the general acylation procedure for description of the apparatus.

further hydrogen evolution occured during an additional half-hour, the reaction was processed as described above except that chloroform was used in the extractions in place of ether. TLC analysis (ether hexane, 2:1) revealed the presence of 3, ethyl acetoacetate, and 63. Trituration of the concentrate with hexane-ether afforded a solid which was recrystallized from isopropanol to yield 1.78 g (61%) of 63 as yellow tinted crystals, mp 161-163°. An analytical sample was prepared by a second recrystallization from isopropanol, which raised the mp to 163-164°: ^{1}H NMR ($CDCl_3$) δ 14.98 (broad s, 1H, enol), 8.11 (d, J=8Hz, 1H, 5-H), 7.76-7.06 (m, 7H, aromatic), 4.39 (s, 1H, vinyl), 2.18 (s, 3H, CH_3), and 1.98 ppm (s, 3H, CH_3); ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58.

Found : C, 74,13; H, 5.60; N, 9.48.

General Acylation Procedure

The apparatus used in these reactions consisted of a 250 ml three-necked flask equipped with a magnetic stirring bar, a 60 ml pressure-equalizing addition funnel, and an efficient condenser. The reflux condenser was connected at its upper end to a U-shaped drying tube charged with Drierite and moisture indicator. The drying tube was in turn connected to a Precision Scientific wet-test meter, or a 1000 ml gas buret. Both measurement devices were filled with water.

The following general method was employed for the preparation of all acylated compounds except for 64k-m, 66a-b, 69q and 71.

Yields of acylated products are based on the starting 2-methyl-3-aryl-4(3H)-quinazolinone and represent amounts obtained after one

recrystallization of the crude product resulting from Methods A or B described below. In many instances no further treatment was required to produce an analytical sample. Melting points are those of analytical samples.

A 2.50 g (52 mmol) sample of 50% sodium hydride-mineral oil dispersion was washed with 30 ml of hexane and filtered, and the oil-free sodium hydride was quickly added to the reaction flask along with 150 ml of dry DME. The resulting gray slurry was brought to reflux and a solution of 10 mmol of the appropriate 2-methyl-3-aryl-4(3H)-quinazolinone and 11 mmol of the appropriate ester was added dropwise over a period of 15 min. When addition was completed, the stirred reaction mixture was allowed to reflux until the theoretical amount of hydrogen was evolved. The volume of hydrogen expected in each experiment was calculated using the following equation:

$$V_m = \frac{T_m}{T_s} \times \frac{P_s}{P_m - P^o_{H_2O}} \times n \times 10^3 \times 22.4$$

where subscript s represents conditions at STP, subscript m represents the conditions of the meter, and n equals the theoretical number of moles of hydrogen. When hydrogen evolution ceased (2-10 hr), the heating mantle was removed and the flask was allowed to cool to room temperature. To the thick reaction mixture was added dropwise 3.12 g (52 mmol) of acetic acid (Caution!), followed by 50 ml of cold water. The resulting mixture was transferred to a 500 ml separatory funnel, and an additional 100 ml of water was added. The pH of the resulting aqueous solution or suspension was then tested. If the aqueous layer

was acidic, 5% sodium bicarbonate solution was added until the aqueous layer became basic to pH paper. Chloroform (100 ml) was added to the basic solution, and from this point on the reaction mixtures were processed according to either Method A or Method B described below.

Method A: If no solid was present at the chloroform-water interface, the organic phase was separated and the remaining aqueous phase was extracted twice with 100 ml portions of chloroform. The organic extracts were combined, dried, ($MgSO_4$), filtered, concentrated, and the crude products were recrystallized from appropriate solvents.

Method B: If a solid was present at the interface, it was collected by suction filtration. Method A was then followed, except that the initially collected solid was combined with the material obtained by concentration of the chloroform extracts before recrystallization.

Acylations of 2-Methyl-3-aryl-4(3H)-quinazolinones

2-(3,3,3-Trifluoroacetonyl)-3-o-tolyl-4(3H)-quinazolinone (64a).

Preparation of 64a required 2.50 g (10 mmol) of 3 and 1.56 g (11 mmol) of ethyl trifluoroacetate with a reaction period of 2 hr, followed by workup Method A to afford a crude solid, which on recrystallization from isopropanol-chloroform yielded 3.02 g (87%) of 64a as white crystals, mp 194-195°; ^{1}H NMR ($CDCl_3$) δ 14.87 (broad s, 1H, enol), 8.41 (d, J=8Hz, 1H, 5-H), 8.07-7.26 (m, 7H, aromatic), 4.92 (s, 1H, vinyl), and 2.23 ppm (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ-94.3 ppm (s); ir (KBr) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{13}F_3N_2O_2$: C, 62.43; H, 3.78; N, 8.09.
Found : C, 62.50; H, 3.81; N, 7.98.

2-[2-Oxo-2-(2-pyridyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (64b).

Treatment of 2.50 g (10 mmol) of 3 with 1.66 g (11 mmol) of ethyl picolinate for a period of 2 hr, followed by workup method A, afforded a yellow-brown crude solid which was recrystallized from isopropanol-chloroform to give 2.84 g (80%) of 64b. An analytical sample was prepared by one recrystallization from chloroform-hexane. The resulting light yellow crystals had mp 254-255°: ^{1}H NMR ($CDCl_3$) δ 15.48 (broad s, 1H, enol), 8.52-7.20 (m, 12H, aromatic), 6.01 (s, 1H, vinyl), and 2.25 ppm (s, 3H, CH_3); ir (KBr) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82.
Found : C, 74.24; H, 4.98; N, 11.91.

2-[2-Oxo-2-(3-pyridyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (64c).

Reaction of 2.50 g (10 mmol) of 3 and 1.66 g (11 mmol) of ethyl nicotinate for a period of 3 hr, followed by workup method A afforded a yellow crude product which was recrystallized from isopropanol to give 2.48 g (70%) of 64c. An analytical sample was prepared by one recrystallization from chloroform-hexane. The resulting yellow microcrystals had mp 234-235°: ^{1}H NMR ($CDCl_3$) δ 15.29 (broad s, 1H, enol), 8.78-7.25 (m, 12H, aromatic), 5.15 (s, 1H, vinyl), and 2.23 ppm (s, 3H, CH_3); ir (KBr) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82.
Found : C, 73.98; H, 4.72; N, 11.66.

2-[2-Oxo-2-(4-pyridyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (64d).

Preparation of 64d required 2.50 g (10 mmol) of 3 and 1.66 g (11 mmol) of ethyl isonicotinate. After a reaction period of 2 hr and using workup method B, the crude product was recrystallized from isopropanol-chloroform to give 3.02 g (85%) of 64d, as yellow crystals, mp 219-220°: ^{1}H NMR ($CDCl_3$) δ 15.40 (broad s, 1H, enol), 8.62-7.12 (m, 12H, aromatic), 5.08 (s, 1H, vinyl), and 2.20 ppm (s, 3H, CH_3); ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82.
Found : C, 74.42; H, 5.12; N, 11.62.

2-[2-Oxo-2-(1-adamantyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (64e).

Treatment of 2.50 g (10 mmol) of 3 with 2.3 g (11 mmol) of ethyl 1-adamantylcarboxylate[88]-prepared from the acid chloride and excess absolute ethanol-for a reaction period of 3.5 hr and using workup Method A afforded a brown oil which solidified on standing. The crude product was recrystallized from isopropanol-chloroform-hexane to yield 3.3 g (81%) of 64e. An analytical sample was prepared by one recrystallization from isopropanol-hexane. The resulting white crystals had mp 221-222°: ^{1}H NMR ($CDCl_3$) δ 15.82 (broad s, 1H, enol), 8.20 (d, J=8Hz, 1H, 5-H), 7.72-7.16 (m, 7H, aromatic), 4.56 (s, 1H, vinyl), 2.18 (s, 3H, CH_3), and 2.06-1.48 ppm (m, 15H, CH and CH_2); ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79.
Found : C, 78.23; H, 6.69; N, 6.64.

2-(2-Oxo-4-phenylbut-3-enyl)-3-o-tolyl-4(3H)-quinazolinone (64f).

Reaction of 2.50 g (10 mmol) of 3 and 1.94 g (11 mmol) of ethyl cinnamate for a period of 2.5 hr, followed by workup method A, afforded a brown oil, which on trituration with hexane-ether gave a yellow solid that was recrystallized from isopropanol-ether to yield 0.64 g (19%) of 64f. An analytical sample was prepared by two recrystallization from the same solvents. The resulting yellow crystals had mp 190-191°; ^{1}H NMR ($CDCl_3$) δ 16.18 (broad s, 1H, enol), 8.35 (d, J=8Hz, 1H, 5-H), 7.97-7.23 (m, 13H, vinyl and aromatic), 6.55 (d, J=17Hz, 1H, vinyl), 4.73 (s, 1H, vinyl) and 2.25 ppm (s, 3H, CH_3); ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{25}H_{20}N_2O_2$: C, 78.98; H, 5.30; N, 7.37.
Found : C, 78.99; H, 5.22; N, 7.10.

2-(2-Oxo-2-phenylethyl)-3-o-tolyl-4(3H)-quinazolinone (64g).

Treatment of 2.50 g (10 mmol) of 3 with 1.5 g (11 mmol) of methyl benzoate for a period of 5 hr, followed by workup method A afforded a crude product that was recrystallized from isopropanol to yield 2.84 g (80%) of 64g as light yellow flakes, mp 216-217°: ^{1}H NMR (DMSO-d_6) δ 15.50 (broad s, 1H, enol), 8.18 (d, J=8Hz, 1H, 5-H), 7.98-7.32 (m, 12H, aromatic), 5.07 (s, 1H, vinyl), and 2.19 ppm (s, 3H, CH_3); ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{18}N_2O_2$: C, 77.13; H, 5.12; N, 8.17.
Found : C, 77.41; H, 5.04; N, 8.27.

2-[2-Oxo-2-(4-chlorophenyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (64h).

Reaction of 2.50 g (10 mmol) of 3 and 1.88 g (11 mmol) of methyl p-chlorobenzoate for a period of 4 hr, followed by workup method A,

afforded a crude product that was recrystallized from chloroform-isopropanol to give 2.88 g (74%) of 64h, mp 227-227.5°: ^{1}H NMR ($CDCl_3$) δ 15.83 (broad s, 1H, enol), 8.36 (d, J=8Hz, 1H, 5-H), 7.98-7.29 (m, 11H, aromatic), 5.15 (s, 1H, vinyl), and 2.25 ppm (s, 3H, CH_3); ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{17}ClN_2O_2$: C, 71.04; H, 4.41; N, 7.20.
Found : C, 70.90; H, 4.37; N, 7.17.

2-[2-Oxo-2-(4-methoxyphenyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (64i).

Reaction of 2.50 g (10 mmol) of 3 with 1.83 g (11 mmol) of methyl anisate for a period of 3 hr, followed by workup method A, afforded a crude solid that was recrystallized from isopropanol to give 2.76 g (72%) of 64i, as yellow crystals, mp 169-170°; ^{1}H NMR ($CDCl_3$) δ 15.79 (broad s, 1H, enol), 8.38 (d, J=8Hz, 1H, 5-H), 7.98-6.94 (m, 11H, aromatic), 5.20 (s, 1H, vinyl), 3.92 (s, 3H, OCH_3), and 2.28 ppm (s, 3H, CH_3); ir (KBr) 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29.
Found : C, 75.16; H, 5.24; N, 7.59.

2-[2-Oxo-2-(3,4,5-trimethoxyphenyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (64j).

Preparation of 64j required 2.50 g (10 mmol) of 3 and 2.49 g (11 mmol) of methyl 3,4,5-trimethoxybenzoate. After a reaction period of 4 hr and using workup method A, the crude product was recrystallized from chloroform-hexane to yield 2.98 g (67%) of 64j. An analytical sample was prepared by a second recrystallization from the same solvents,

mp 200-201°: ^{1}H NMR ($CDCl_3$) δ 15.54 (broad s, 1H, enol), 8.31 (d, J=8Hz, 1H, 5-H), 7.93-7.30 (m, 7H, aromatic), 6.96 (s, 2H, phenyl), 5.08 (s, 1H, vinyl), 3.91 and 3.86 (two s, 9H, OCH_3), and 2.22 ppm (s, 3H, CH_3); ir (KBr) 1675 cm^{-1} (C=O).

Anal. Calcd for $C_{26}H_{24}N_2O_5$: C, 70.26; H, 5.44; N, 6.30.
Found : C, 70.39; H, 5.61; N, 6.06.

Ethyl p-Acetamidobenzoate

To a stirred solution of 8.25 g (50 mmol) of ethyl p-aminobenzoate in 100 ml of acetic acid was added 6.12 g (60 mmol) of acetic anhydride. The resulting solution was allowed to react for 3 hr at reflux. The hot reaction solution was then poured into a 250 ml beaker containing 100 ml of water and the resulting solution was concentrated to half its volume on a hot plate. An additional 100 ml of hot water was added to the concentrate, which was then removed from the heat. On standing, the solution deposited white platlets which were collected by suction filtration and washed with 300 ml of water. A second crop of crystals developed in the filtrate and were also collected. The two crops of crude product were combined and air dried to give 8.9 g (86%) of title compound, mp 98-100° (lit.[89] mp 103-104°). Recrystallization from ethanol-hexane followed by drying in a vacuum oven raised the mp to 101-102°: ^{1}H NMR ($CDCl_3$) δ 8.43 (broad s, 1H, N-H), 7.96-7.48 (m, 4H, aromatic), 4.31 (q, J=7Hz, 2H, CH_2), 2.21 (s, 3H, CH_3), and 1.37 ppm (t, J=7Hz, 3H, CH_3).

Ethyl p-Trifluoroacetamidobenzoate

The same procedure as described above was followed, except that

12.6 g (60 mmol) of trifluoroacetic anhydride, and a reaction time of 1 hr were employed. Hot water (50 ml) was added to the concentrate. Two crops of crude product were obtained to yield 9.2 g (70%) of the titled compound, mp 120-124° (lit.[90] mp 127.5-128.5°). Recrystallization from ethanol-hexane followed by vacuum drying raised the mp to 125-126°: ^{1}H NMR ($CDCl_3$) δ 8.27 (broad s, 1H, NH), 8.06-7.56 (m, 4H, aromatic), 4.36 (q, J=7Hz, 2H, CH_2), and 1.40 ppm (t, J=7Hz, 3H, CH_3); the ^{19}F NMR spectrum of the same sample revealed the presence of fluorine.

2-[2-Oxo-2-(p-trifluoroacetamidophenyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (641).

To a stirred gray slurry of 1.26 g (30 mmol) of sodium hydride as a 57% mineral oil dispersion in 100 ml of dry THF, was added a solution of 1.30 g (5 mmol) of ethyl p-trifluoroacetamidobenzoate in 30 ml of dry THF. After the evolution of hydrogen ceased, the resulting solution was brought to reflux and a solution of 1.25 g (5 mmol) of 3 in 30 ml of dry THF was added over a period of 15-20 min. After a reaction period of 5 hr, during which evolution of the theoretical volume of hydrogen occurred, the thick brown reaction-mixture was cooled to room temperature and 1.8 g of acetic acid in 50 ml of cold water was added dropwise (Caution!) to the reaction solution. The resulting solution was poured into 200 ml of water and the aqueous layer was made basic with 5% sodium bicarbonate solution. The organic layer was separated and the aqueous phase was extracted twice with 200 ml portions of chloroform. The organic phases were combined, dried ($MgSO_4$), and concentrated to give a brown solid. The brown solid was recrystallized

from chloroform to give 1.09 g (47%) of 64l. An analytical sample was prepared by two additional recrystallizations from chloroform. The resulting yellow microcrystals melted at 278-280°: ^{1}H NMR ($CDCl_3$-50% by vol CF_3COOH) δ 8.85 (s, 1H, NH), 8.37-7.12 (m, 12H, aromatic) and 2.18 ppm (s, 3H, CH_3); ir (KBr) 3290 (NH) 1690 cm^{-1} (C=O).

The signals due to vinyl and melthylene hydrogens are not reported since these protons appeared to be severely affected by the presence of the trifluoroacetic acid, and only a broad peak centered at 4.76 ppm gave possible evidence for their presence.

Anal. Calcd for $C_{25}H_{18}F_3N_3O_3$: C, 64.51; H, 3.90; N, 9.03.
Found : C, 64.35; H, 3.71; N, 9.24.

2-[2-Oxo-2-(p-acetamidophenyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (64k).

To a stirred gray slurry of 1.26 g (30 mmol) of sodium hydride as a 57% mineral oil dispersion in 100 ml of dry THF, was added a solution of 1.04 g (5 mmol) of ethyl p-acetamidobenzoate in 30 ml of dry THF. After the evolution of hydrogen ceased, the resulting solution was brought to reflux and a solution of 1.25 g (5 mmol) of 3 in 30 ml of dry THF was added over a period of 15-20 min. After evolution of the theoretical amount of hydrogen (4 hr) the reaction mixture was cooled to room temperature and a solution of 1.8 g of acetic acid in 50 ml of cold water was added dropwise (Caution!) to the reaction solution. The brown reaction mixture was poured into 200 ml of water and the resulting solution was extracted twice with 200 ml portions of chloroform. The chloroform extracts were combined, dried ($MgSO_4$), and concentrated to afford a yellow solid, which was recrystallized from chloro-

form to give 0.86 g (42%) of crude 64k. An analytical sample was prepared by three recrystallizations to give yellow microcrystals, mp 272-275° (dec): ^{1}H NMR ($CDCl_3$ 50% by vol CF_3CO_2H) δ 8.86 (m, 13H, NH and aromatics), 2.30 (s, 3H, CH_3), and 2.15 ppm (s, 3H, CH_3). The ^{1}H NMR signals corresponding to the methylene and vinyl protons of the proposed formula showed the same behavior as those of 64k; ir (KBr) 3310 (NH) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.14; N, 10.21.
Found : C, 73.17; H, 5.32; N, 9.91.

2-Ethoxalylmethyl-3-o-tolyl-4(3H)-quinazolinone (64m).

Compound 64m was prepared by inverse addition and not by the general acylation procedure. To a refluxing slurry of 1.05 g (25 mmol) of sodium hydride (57%) and 3.2 g (22 mmol) of diethyl oxalate in 140 ml of dry DME, was added dropwise 1.25 g (5 mmol) of 3 in 40 ml of DME over a period of 4.5 hr. When addition was complete, the reaction was allowed to continue at reflux for an additional 45 min. The resulting yellow reaction mixture was processed as described in the general acylation procedures, followed by workup Method A. The resulting concentrate upon trituration with hexane-ether afforded a yellow solid that was recrystallized from isopropanol to give 1.08 g (62%) of 64m, mp 187-190°. A second recrystallization was required to produce the analytical sample, as yellow crystals, mp 191-191.5°: ^{1}H NMR ($CDCl_3$) δ 15.51 (broad s, 1H, enol), 8.35 (d, J=8Hz, 1H, 5-H), 8.00-7.24 (m, 7H, aromatic), 5.47 (s, 1H, vinyl), 4.30 (q, J=7Hz, 2H, CH_2), 2.21 (s, 3H, CH_3), and 1.35 ppm (t, J=7Hz, 3H, CH_3); ir (KBr) 1710 and 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00.
Found : C, 68.42; H, 5.03; N, 7.88.

2-(3,3,3-Trifluoroacetonyl)-3-o-chlorophenyl-4(3H)-quinazolinone (69a).

The preparation of 69a was carried out with 2.7 g (10 mmol) of 4a and 1.56 g (11 mmol) of ethyl trifluoroacetate for a reaction period of 1.5 hr. After using workup method B, the resulting solid was recrystallized from isopropanol-chloroform to give 3.19 g (87%) of 69a, as light yellow crystals, mp 158-159°: ^{1}H NMR ($CDCl_3$) δ 14.33 (broad s, 1H, enol), 8.19-7.20 (m, 8H, aromatic), and 4.74 ppm (s, 1H, vinyl); ir (KBr) 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{10}ClF_3N_2O_2$: C, 55.68; H, 2.75; N, 7.63.
Found : C, 55.78; H, 2.82; N, 7.80.

2-[2-Oxo-2-(2-pyridyl)ethyl]-3-o-chlorophenyl-4(3H)-quinazolinone (69b).

Preparation of 69b required 2.70 g (10 mmol) of 4a and 1.66 g (11 mmol) of ethyl picolinate. After a reaction time of 2 hr, followed by workup Method B, a yellow solid was obtained which was recrystallized from chloroform-isopropanol to yield 3.08 g (82%) of 69b as yellow crystals, mp 240-241°: ^{1}H NMR ($CDCl_3$-DMSO-d_6) δ 15.44 (broad s, 1H, enol), 8.40-7.20 (m, 12H, aromatic), and 5.85 ppm (s, 1H, vinyl); ir (KBr) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.76; N, 11.18.
Found : C, 67.25; H, 3.88; N, 11.24.

2-[2-Oxo-2-(3-pyridyl)ethyl]-3-o-chlorophenyl-4(3H)-quinazolinone (69c).

The reaction of 2.70 g (10 mmol) of 4a and 1.66 g (11 mmol) of ethyl nicotinate was carried out for a period of 1.5 hr. After using

workup method A, the crude product which solidified on standing was recrystallized from chloroform-hexane to give 2.97 g (79%) of 69c. An analytical sample was prepared by an additional recrystallization from the same solvents. The resulting crystals had mp 235-237°: ^{1}H NMR ($CDCl_3$) δ 15.19 (broad s, 1H, enol), 8.72-7.18 (m, 12H, aromatic), and 5.05 ppm (s, 1H, vinyl); ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.76; N, 11.18.
Found : C, 66.83; H, 3.44; N, 11.19.

2-[2-Oxo-2-(4-pyridyl)ethyl]-3-o-chlorophenyl-4(3H)-quinazolinone (69d).

Treatment of 2.70 g (10 mmol) of 4a and 1.66 g (11 mmol) of ethyl isonicotinate for a reaction period of 2 hr followed by workup method B, yielded a crude product which was recrystallized from chloroform-isopropanol to give 3.46 g (92%) of 69d. An analytical sample was prepared by a recrystallization from chloroform. The resulting yellow crystals had mp 214-215°: ^{1}H NMR ($CDCl_3$) δ 15.36 (broad s, 1H, enol), 8.65-7.16 (m, 12H, aromatic), and 4.98 ppm (s, 1H, vinyl); ir (KBr) 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.76; N, 11.18.
Found : C, 67.43; H, 4.01; N, 11.28.

2-(3,3,3-Trifluoroacetonyl)-3-phenyl-4(3H)-quinazolinone (69e).

Reaction of 1.18 g (5 mmol) of 37 and 0.78 g (5.5 mmol) of ethyl trifluoroacetate with 1.05 g (25 mmol) of sodium hydride (57%) for a period of 2 hr, followed by workup Method A, afforded a crude product which was recrystallized from chloroform-hexane to give 1.34 g (81%)

of 69e as a white solid, mp 199-200°: ^{1}H NMR ($CDCl_3$) δ 14.88 (broad s, 1H, enol), 8.36 (d, J=8Hz, 1H, 5-H), 8.05-7.34 (m, 8H, aromatic), and 4.94 ppm (s, 1H, vinyl); ^{19}F NMR ($CDCl_3$) δ-94.3 ppm (s); ir (KBr) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{11}F_3N_2O_2$: C, 61.45; H, 3.34; N, 8.43.
Found : C, 61.31; H, 3.30; N, 8.62.

2-[2-Oxo-2-(2-pyridyl)ethyl]-3-phenyl-4(3H)-quinazolinone (69f).

Treatment of 2.36 g (10 mmol) of 37 and 1.66 g (11 mmol) of ethyl picolinate in 160 ml of THF for a reaction period of 2.5 hr, followed by workup Method A, afforded a yellow crude product which was recrystallized from chloroform-hexane to give 2.6 g (76%) of 69f as yellow crystals, mp 272-273° (dec): ^{1}H NMR ($CDCl_3$) δ 15.31 (broad s, 1H, enol), 8.27-7.02 (m, 13H, aromatic), and 5.90 ppm (s, 1H, vinyl); ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31.
Found : C, 73.87; H, 4.13; N, 12.69.

2-[2-Oxo-2-(3-pyridyl)ethyl]-3-phenyl-4(3H)-quinazolinone (69g).

The preparation of 69g required 2.36 g (10 mmol) of 37 and 1.66 g (11 mmol) of ethyl nicotinate. After a reaction period of 3.5 hr, and using workup Method A, the crude product was recrystallized from isopropanol-chloroform to yield 2.45 g (72%) of 69g as yellow crystals, mp 248-249°: ^{1}H NMR ($CDCl_3$) δ 15.38 (broad s, 1H, enol), 8.79-7.15 (m, 13H, aromatic), and 5.10 ppm (s, 1H, vinyl); ir (KBr) 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31.
Found : C, 74.02; H, 4.79; N, 12.46.

2-[2-Oxo-2-(4-pyridyl)ethyl]-3-phenyl-4(3H)-quinazolinone (69h).

Treatment of 2.36 g (10 mmol) of 37 and 1.66 g (11 mmol) of ethyl isonicotinate in 160 ml of THF for a reaction period of 3.5 hr, followed by workup Method B, afforded a crude product which was recrystallized from chloroform-hexane to give 2.1 g (62%) of 69h. An analytical sample was prepared by a recrystallization from the same solvent system. The resulting yellow crystals had mp 241-242°: ^{1}H NMR ($CDCl_3$) δ 15.12 (broad s, 1H, enol), 8.48-7.02 (m, 13H, aromatic), and 5.02 ppm (s, 1H, vinyl); ir (KBr) 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31.
Found : C, 73.71; H, 4.40; N, 12.16.

2-(3,3,3-Trifluoroacetonyl)-3-p-tolyl-4(3H)-quinazolinone (69i).

Treatment of 1.25 g (5 mmol) of 67 and 0.78 g (5.5 mmol) of ethyl trifluoroacetate with 1.05 g (25 mmol) of sodium hydride (57%) for a reaction period of 1.5 hr, followed by workup Method A, afforded a crude product which was recrystallized from isopropanol-chloroform to give 1.25 g (72%) of 69i as white crystals, mp 215-216°: ^{1}H NMR ($CDCl_3$) δ 14.89 (broad s, 1H, enol), 8.36 (d, J=8Hz, 1H, 5-H), 8.04-7.20 (m, 7H, aromatic), 5.02 (s, 1H, vinyl), and 2.54 ppm (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$) δ-94.3 ppm (s); ir (KBr) 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{13}F_3N_2O_2$: C, 62.43; H, 3.78; N, 8.09.
Found : C, 62.17; H, 3.73; N, 8.16.

2-[2-(Oxo-2-(2-pyridyl)ethyl]-3-p-tolyl-4(3H)-quinazolinone (69j).

The preparation of 69j required 2.50 g (10 mmol) of 67 and 1.66 g (11 mmol) of ethyl picolinate. After a reaction period of 2.5 hr,

followed by workup Method A, the crude produced was recrystallized from chloroform-hexane to yield 2.7 g (76%) of 69j. An analytical sample was prepared by one recrystallization from chloroform-hexane. The resulting yellow microcrystals had mp 268-269°: ^{1}H NMR ($CDCl_3$) δ 15.30 (broad s, 1H, enol), 8.29-7.20 (m, 12H, aromatic), 5.96 (s, 1H, vinyl), and 2.48 (s, 3H, CH_3); ir (KBr) 168 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82.
Found : C, 74.01; H, 4.83; N, 11.91.

2-[2-Oxo-2-(3-pyridyl)ethyl]-3-p-tolyl-4(3H)-quinazolinone (69k).

The preparation of 69k required 2.50 g (10 mmol) of 67 and 1.66 g (11 mmol) of ethyl nicotinate. After a reaction period of 4 hrs, and using workup Method A, the yellow crude product was recrystallized from chloroform-isopropanol to give 2.87 g (81%) of 69k as yellow crystals, mp 267-268°: ^{1}H NMR ($CDCl_3$) δ 15.32 (broad s, 1H, enol), 8.64-7.05 (m, 12H, aromatic), 5.14 (s, 1H, vinyl), and 2.48 ppm (s, 3H, CH_3); ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82.
Found : C, 74.27; H, 4.59; N, 11.71.

2-[2-Oxo-2-(4-pyridyl)ethyl]-3-p-tolyl-4(3H)-quinazolinone(69l).

Reaction of 2.50 g (10 mmol) of 67 and 1.66 g (11 mmol) of ethyl isonicotinate for a period of 3 hr, followed by workup Method B, afforded a yellow solid which was recrystallized from dimethyl sulfoxide to give 3.0 g (84%) of 69l. An analytical sample was prepared by one recrystallization from dimethyl sulfoxide-chloroform. The resulting yellow microcrystals had mp 262-263°: ^{1}H NMR (DMSO-d_6 @ 90°) δ 15.1

(very broad s, 1H, enol), 8.44-6.80 (m, 12H, aromatic), 5.05 (s, 1H, vinyl), and 2.40 ppm (s, CH_3). The methyl signal at δ 2.40 could not be integrated owing to the presence of an impurity in the DMSO-d_6; ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82.
Found : C, 74.01; H, 4.47; N, 12.07.

2-(3,3,3-Trifluoroacetonyl)-3-p-bromophenyl-4(3H)-quinazolinone (69m).

Treatment of 3.15 g (10 mmol) of 68 and 1.7 g (12 mmol) of ethyl trifluoroacetate with 1.2 g (25 mmol) of sodium hydride for a reaction period of 2 hr, followed by workup Method A which afforded a pink solid. The solid was recrystallized from chloroform-hexane to give 3.44 g (84%) of 69m as off-white crystals, mp 238-239°: ^1H NMR ($CDCl_3$) δ 14.53 (broad s, 1H, enol), 8.24-7.14 (m, 8H, aromatic), and 4.86 ppm (s, 1H, vinyl); ir (KBr) 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{10}BrF_3N_2O_2$: C, 49.66; H, 2.45; N, 6.81.
Found : C, 49.87; H, 2.27; N, 6.76.

2-[2-Oxo-2-(2-pyridyl)ethyl]-3-p-bromophenyl-4(3H)-quinazolinone (69n).

Upon treatment of 3.15 g (10 mmol) of 68 and 1.81 g (12 mmol) of ethyl picolinate with 1.92 g (40 mmol) of sodium hydride (50%) in 160 ml of THF for a reaction period of 2.5 hr, resulted in a yellow-brown reaction slurry which was processed using Method B. The crude yellow product was recrystallized from dimethyl sulfoxide-acetone to yield 4.06 g (96%) of 69n which as yellow microcrystals, mp 312-313° (dec): ^1H NMR ($CDCl_3$ with 3 drops CF_3CO_2H) δ 8.96-7.11 (m, 12H, aromatic, and 5.50 ppm (s, 1H, vinyl); ir (KBr) 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{14}BrN_3O_2$: C, 60.02; H, 3.36; N, 10.00.
Found : C, 60.18; H, 3.40; N, 9.75.

2-[2-Oxo-2-(3-pyridyl)ethyl]-3-p-bromophenyl-4(3H)-quinazolinone (69o).

The reaction of 2.0 g (6.3 mmol) of 68 and 1.2 g (8 mmol) of ethyl nicotinate with 0.8 g (17 mmol) of 50% sodium hydride was carried out for a period of 2 hr. After using workup Method A, the crude product was recrystallized from isopropanol-chloroform-hexane to give 2.43 g (92%) of 69o as a yellow solid, mp 269-270°; ^{1}H NMR ($CDCl_3$) δ 15.50 (broad s, 1H, enol), 8.88-7.20 (m, 12H, aromatic), and 5.14 ppm (s, 1H, vinyl); ir (KBr) 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{14}BrN_3O_2$: C, 60.02; H, 3.36; N, 10.00.
Found : C, 60.20; H, 3.59; N, 9.85.

2-[2-Oxo-2-(4-pyridyl)ethyl]-3-p-bromophenyl-4(3H)-quinazolinone (69p).

The preparation of 69p employed 3.15 g (10 mmol) of 68 and 1.81 g (12 mmol) of ethyl isonicotinate in the presence of 1.92 g (40 mmol) of sodium hydride in 160 ml of THF. After a reaction period of 2.5 hr, followed by workup Method B, a yellow solid which was recrystallized from dimethyl sulfoxide to give 3.8 g (90%) of 69p. An analytical sample was prepared by recrystallization from chloroform-dimethyl sulfoxide. The resulting yellow microcrystals had a mp 307-308°(dec): ^{1}H NMR ($CDCl_3$ with 3 drops of CF_3CO_2H) δ 8.96-7.02 (m, 12H, aromatic), and 5.35 ppm (s, 1H, vinyl).

Anal. Calcd for $C_{21}H_{14}BrN_3O_2$: C, 60.02; H, 3.36; N, 10.00.
Found : C, 59.73; H, 3.57; N, 9.68.

2-Acetonyl-3-p-bromophenyl-4(3H)-quinazolinone (69q).*

To a refluxing slurry of 1.5 g (31 mmol) of 50% sodium hydride in 140 ml of THF was added 2.0 g (6.3 mmol) of 68 and 0.88 g (10 mmol) of ethyl acetate in 15 ml of dry THF. After a reaction period of 3 hr, the reaction mixture was processed by using workup Method A. TLC analysis of the concentrate showed the presence of 68, 69q, and ethyl acetacetate. Trituration of the concentrate with ether gave a solid, which was recrystallized from isopropanol-chloroform to afford 1.72 g (48%) of 69q as a yellow solid, mp 217-219°: ^{1}H NMR ($CDCl_3$) δ 15.07 (broad s, 1H, enol) 8.18 (d, J=8Hz, 1H, 5-H), 7.86-7.14 (m, 7H, aromatic) 4.49 (s, 1H, vinyl), and 2.04 ppm (s, 3H, CH_3); ir (KBr) 1685 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{13}BrN_2O_2$: C, 57.16; H, 3.67; N, 7.84.
Found : C, 57.05; H, 3.80; N, 7.99.

Preparation of Acylated Derivatives of 2,3-Dimethyl-4(3H)-quinazolinone (69r-s) Employing the General Acylation Method.

2-(2-Oxo-2-phenylethyl)-3-methyl-4(3H)-quinazolinone (69r).

In the preparation of 69r, 1.20 g (25 mmol) of sodium hydride as a 50% mineral oil dispersion, 0.87 g (5 mmol) of 23a, and 0.75 g (5.5 mmol) of methyl benzoate were used. After a reaction period of 9.5 hr, and using workup Method A, the crude product was recrystallized from isopropanol-chloroform to yield 1.07 g (77%) of 69r as white crystals, mp 175°: ^{1}H NMR ($CDCl_3$) δ (15.44 broad s, 1H, enol), 8.14

*Because of the competing reaction involving formation of ethyl acetoacetate from ethyl acetate, the reaction time indicates the period required for complete hydrogen evolution.

(d, J=8Hz, 1H, 5-H), 8.00-7.13 (m, 8H, aromatic), 5.91 (s, 1H, vinyl), and 3.53 ppm (s, 3H, CH_3); ir (KBr) 1670 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07.
Found : C, 73.22; H, 5.19; N, 9.74.

2-[2-Oxo-2-(3-pyridyl)ethyl]-3-methyl-4(3H)-quinazolinone (69s).

In this preparation, 2.6 g (54 mmols) of sodium hydride as a 50% mineral oil dispersion, 1.81 g (12 mmol) of ethyl nicotinate, and 1.74 g (10 mmol) of 23a were employed. After a reaction period of 2.5-3 hr, following workup Method A, the crude product was recrystallized from chloroform-hexane to yield two crops of yellow amorphous solid for a total of 1.73 g (62%) of 69s. An analytical sample was prepared by recrystallization from chloroform, which produced yellow microcrystals, mp 244-245° (dec): ^1H NMR ($CDCl_3$-DMSO-d_6 with 2 drops of CF_3CO_2H) δ 9.34 (broad s, 1H, aromatic), 9.06-8.74 (m, 2H, aromatic), 8.18-7.20 (m, 5H, aromatic), 5.99 (s, 1H, vinyl), and 3.58 ppm (s, 3H, CH_3).

Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.04.
Found : C, 68.78; H, 4.46; N, 15.32.

2-(1,3-Dioxo-2-indanyl)-3-o-tolyl-4(3H)-quinazolinone (66a).

To a refluxing slurry of 1.05 g (25 mmol) of sodium hydride (57%) and 3.88 g (20 mmol) of dimethyl phthalate in 140 ml of DME, was added dropwise 1.25 g (5 mmol) of 3 in 40 ml of DME over a period of 6 hr. After addition was complete, the reaction was allowed to continue for an additional 1 hr. The orange reaction mixture was worked up as described in the general acylation procedure using Method A. TLC analysis (ether) of the red concentrate revealed several colored (red)

and yellow) spots trailing a component whose R_f corresponded to that of 3. Column chromatography afforded, on elution with ether-chloroform (98:2), 0.43 g (22%) of 66a as yellow crystals, mp 268-270°: ^{1}H NMR ($CDCl_3$) δ 14.66 (broad s, 1H, enol), 8.22 (d, J=8Hz, 1H, 5-H), 7.90-7.07 (m, 11H, aromatic) and 2.39 ppm (s, 3H, CH_3); ir (KBr) 1710 and 1690 cm^{-1} (C=O).

Anal. Calcd for $C_{24}H_{16}N_2O_3$: C, 75.78; H, 4.24; N, 7.36.
Found : C, 75.71; H, 4.33; N, 7.00.

No attempt was made to identify any of the other components.

2-(1,3-Dioxo-2-indanyl)-3-methyl-4(3H)-quinazolinone (66b).

To a refluxing slurry of 1.05 g (25 mmol) of sodium hydride as a 57% mineral oil dispersion and 1.94 g (10 mmol) of dimethyl phthalate in 150 ml of dry DME, was added dropwise over a period of 21 hrs a solution of 0.87 (5 mmol) of 23a. After a total reaction time of 23 hr, the resulting yellow-red slurry was quenched with 4 ml of 6 N HCl in 150 ml of water. A yellow solid, which formed at the interface of the aqueous layer and organic layer, was filtered. The organic layer was separated and the aqueous layer was extracted twice with 150 ml portions of chloroform. The chloroform layers were combined, dried ($MgSO_4$), and concentrated. TLC analysis (benzene-acetone, 10:1) revealed that the solid collected at the interface was 66b and that the chloroform concentrate also contained 66b, along with several other components. No further attempt to isolate 66b from the chloroform extract was carried out; however, recrystallization of the filtered solid from chloroform-isopropanol yielded a 0.43 g (28%) of 66b in two

crops. An analytical sample was prepared by one recrystallization from chloroform-hexane to afford yellow needles, mp 194-195°: ^{1}H NMR ($CDCl_3$) δ 13.95 (broad s, 1H, enol), 8.27 (d, 1H, 5-H), 7.90-7.30 (m, 7H, aromatic), and 3.91 ppm (s, 3H, CH_3).

Anal. Calcd for $C_{18}H_{12}N_2O_3$: C, 71.05; H, 3.97; N, 9.21.
Found : C, 71.09; H, 4.21; N, 8.93.

Attempted Preparation of 2-[1-Methyl-2-oxo-2-(3-pyridyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (70).

By Acylation of 2-Ethyl-3-o-tolyl-4(3H)-quinazolinone (42a).

Using the general acylation procedure, 0.92 g (3.5 mmol) of 42a, 0.6 g (4 mmol) of ethyl nicotinate and 1.1 g (23 mmol) of sodium hydride (50%) were allowed to react for a period of 3 hr. Following the workup Method A, TLC analysis (chloroform-ether, 9:1) revealed four components, which included 42a. No further isolation of reaction components was carried out.

The above reaction was repeated with 2.9 g (18 mmol) of potassium hydride (24%) instead of sodium hydride. TLC analysis of the reaction concentrate also revealed a multicomponent reaction mixture.

By Alkylation of 2-[2-Oxo-2-(3-pyridyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (64c).

The general acylation procedure as described for the preparation of 64c was followed up to evolution of the theoretical volume of hydrogen. At this point, it was assumed that 10 mmol of the sodium salt of 64c had formed in situ. To the refluxing, yellow reaction

mixture, was added 1.7 g (12 mmol) of methyl iodide in 20 ml of dry DME. After 8 hr, 70 ml (3.1 mmol) of hydrogen (STP) had been evolved. TLC analysis (chloroform-ether, 9:1) of the resulting crude product revealed several spots, of which two could be identified as 64c and a trace of 3. The reaction mixture was processed using Method B except the yellow solid that was collected at the interface was not combined with the concentrate.

The yellow solid collected from the interface was recrystallized from acetone to give 0.24 g (4.8%) of the methiodide of 2-[2-oxo-2-(3-pyridyl)ethyl]-3-o-tolyl-4(3H)-quinazolinone (71) as yellow needles, mp 260-261° (dec): ^{1}H NMR ($CDCl_3$-3 dps of CF_3CO_2H) δ 9.09-7.21 (m, 12H, aromatic) 5.24 (broad s, 1H, vinyl), 4.47 (s, 3H, CH_3), and 2.20 ppm (s, 3H, CH_3); ir (KBr) 1690 cm^{-1} (C=O).

A methanolic solution of 71 gave a precipitate on addition of 3-5 drops of an aqueous-methanol solution of silver nitrate.

Anal. Calcd for $C_{23}H_{19}N_3O_2I$: C, 55.66; H, 3.86; N, 8.47.
Found : C, 55.30; H, 4.07; N, 8.30.

The above alkylation was attempted again in refluxing THF, using 1.07 g (3 mmol) of 64c, 0.43 g (3 mmol) of methyl iodide, and 2.0 g (4.2 mmol) of sodium hydride (50%). Normal workup procedures afforded only recovered 64c, mp 234-235° (dec), mmp 234-235° (dec).

4-Nitro-N-acetylanthranilic Acid.

The procedure was essentially that used for the preparation of N-acetylanthranilic acid. Treatment of 18.1 g (0.1 mol) of 4-nitro-

anthranilic acid* and 15 g (0.15 mol) of acetic anhydride in refluxing glacial acetic acid gave 18.5 g (82%) of title compound as yellow flakes, mp 212-214° (lit.[91] mp 214-215°).

7-Nitro-2-methyl-3-o-tolyl-4(3H)-quinazolinone (72a).

Treatment of 13.5 g (60 mmol) of 4-nitro-N-acetylanthranilic acid and 7.41 g (69 mmol) of o-toluidine with 4.1 g (30 mmol) of phosphorous trichloride in 500 ml of refluxing toluene yielded 15.6 g (88%) of 72a, yellow crystals, mp 188-190° (lit.[92] mp 183-186°).

7-Amino-2-methyl-3-o-tolyl-4(3H)-quinazolinone (73).

To a solution of 2.95 g (10 mmol) of 7-nitro-2-methyl-3-o-tolyl-4(3H)-quinazolinone in 100 ml of benzene in a three-necked 250 ml flask fitted with a reflux condenser and overhead stirrer, was added 5.58 g (0.1 g-atm) of iron powder and 80 ml of 6 N HCl. The resulting two layer system was allowed to reflux for 16 hr. The remaining iron powder was separated from the cooled reaction solution by suction filtration. The aqueous layer was separated from the benzene layer and diluted with 150 ml of water. The yellow aqueous layer was then slowly added to solid $NaHCO_3$. After the evolution of gas ceased, the aqueous layer was extracted three times with 150 ml portions of chloroform. The chloroform extracts were combined, dried ($MgSO_4$), and concentrated. The resulting yellow solid was recrystallized from isopropanol to give 2.4 g (91%) of (73) as light yellow crystals, mp 204-206° (lit.[93] mp 206-208°).

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*Obtained from Aldrich Chemical Company.

Attempted Acylation of 7-Nitro-2-methyl-3-o-tolyl-4(3H)-quinazolinones (72a).

Acylation of 2.95 g (10 mmol) of 72a was attempted with 1.5 g (11 mmol) of methyl benzoate and 2.5 g (52 mmol) of sodium hydride as described in the general acylation procedure. After 3 hr the reaction solution became dark brown and 95 ml (4.2 mmol) of hydrogen at STP (21% of the theoretical volume) had been evolved. TLC analysis (chloroform) of an aliquot revealed the presence of 72a and 73 in addition to several other components. No further attempt to isolate any of the reaction products was carried out.

Evolution of Hydrogen Resulting from the Acylation of Methaqualone (3) with Ethyl Trifluoroacetate at Room Temperature in the Presence of Excess NaH.

To a stirred solution of 1.0 g (7 mmol) of ethyl trifluoroacetate and 1.05 g (25 mmol) of sodium hydride (57%) in 130 ml of dry DME at 26°, was added 1.25 g (5 mmol) of 3 in 20 ml of DME. After 1.5 hr 186 ml (8.3 mmol) of hydrogen at STP was evolved from the gray reaction slurry. After a total reaction period of 2.5 hr, no additional hydrogen was generated. TLC analysis (ether) of a reaction mixture aliquot quenched with acetic acid, revealed the presence of 64a and 3. The reaction was brought to reflux and the reaction was allowed to continue for 1 more hr. The resulting mixture was worked up as described for the preparation of 64a to afford 1.4 g (81%) of 64 mp 193-194°. The ^{1}H NMR spectrum of this material was identical with that of 64a.

When the experiment described above was repeated in the absence of ethyl trifluoroacetate no hydrogen was evolved. In order to investigate the reason for the apparent increased acidity of 3 in the presence of ethyl trifluoroacetate uv and ^{1}H NMR studies were carried out to detect a possible complex between the ester and 3. A comparison of the uv spectrum of an equimolar solution ($5x10^{-4}M$) of 3 and ethyltrifluoroacetate, and the spectra of individual compounds at the same concentrations ($5x10^{-4}M$) revealed them to be essentially identical with regard to peak shape and wavelength of absorption.

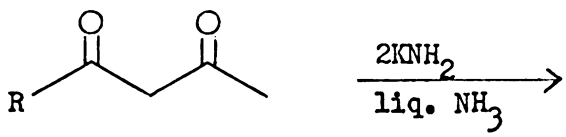
The chemical shift differences (0.07-0.08 ppm) of the ^{1}H NMR signals arising from the 2-methyl group and the o-tolyl methyl substituent of 3 in $CDCl_3$ remained essentially unchanged regardless of the amount of ethyl trifluoroacetate present. The chemical shift difference of the same methyl groups of 3 was 0.31 ppm when 2 drops of trifluoroacetic acid was added to a $CDCl_3$ solution of 3. The ^{19}F NMR signal of the trifluoromethyl group of ethyl trifluoroacetate was unsatisfactory for monitoring possible interaction between the ester and 3 since the fluorine resonance of the ester showed solvent ($CDCl_3$) dependency.

PART B:

REACTIONS OF β-DIKETONES WITH BENZOPHENONE IN THE PRESENCE OF POTASSIUM HYDRIDE

VI. HISTORICAL

Alkylations and other carbon-carbon condensations at the terminal methyl group of β-diketones[94,95] such as acetylacetone (1a) and benzoylacetone (1b) and β-ketoesters such as ethyl acetoacetate[96] (1c) have been achieved through dianions, 2a-c, which were prepared with 2-equivalents of potassium amide in liquid ammonia. Aldol type condensations of 2a-c with benzophenone afforded tertiary alcohols 3a-c.



1a, R = CH_3

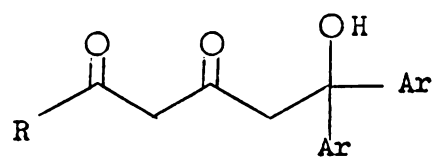
b, R = Ar

c, R = EtO

2a, R = CH_3

b, R = Ar

c, R = EtO



3a, R = CH_3

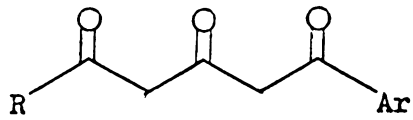
b, R = Ar

c, R = EtO

1,3-Dianions of 1b[97] and certain β-ketoesters[98] have also been generated by using 2-equivalents of lithium diisopropylamide in tetrahydrofuran (THF). In addition, the dianions of β-ketoesters are readily

formed in THF upon sequential treatment of the ester with sodium hydride followed by n-butyllithium.[99]

Aroylations at the methyl group of 1a-c with aromatic esters have been accomplished using sodium hydride as the condensing agent.[100] For example, reactions of 1a-b with methyl benzoate gave 1,3,5-triketones 4a-b. A similar reaction of ethyl benzoate with 1c gave the acid (4c).



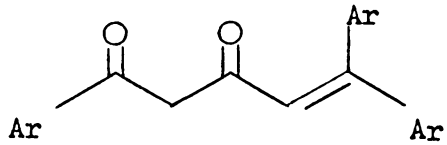
4a, R = CH_3

b, R = Ar

c, R = HO

The mechanism of these aroylations does not involve formation of the intermediate dianions, since the dicarbonyl compounds form only monoanions with excess sodium hydride in refluxing 1,2-dimethoxyethane (DME), the solvent employed in these condensations.[100]

The use of sodium hydride in the condensation of 1b with benzophenone did not give rise to 3b, but rather unsaturated β-diketone 5 was isolated in moderate yield.[100] The mechanism of this reaction was

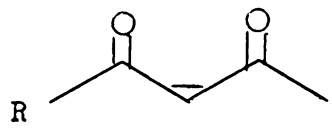


5

not investigated, but on the basis of the sodium hydride promoted acylations of 1b, it seems unlikely that a dianion intermediate was involved in this reaction.

In contrast to lithium and sodium hydrides, potassium hydride rapidly metalates ketones,[101] esters,[102] amines and other feeble organic acids such as dimethyl sulfoxide[103] and tertiary alcohols.[104] Various ketones such as acetone, 3-methyl-2-butanone, 2,4-dimethyl-3-pentanone, 2-methylcyclohexanones, and mesityl oxide are rapidly metalated in THF at 25° with no accompanying reduction or self-condensation. By controlling the rate of addition of certain esters and nitriles to a suspension of potassium hydride, self-condensation products were realized in good yields.[102] Kaliation* of amines, such as pyrrolidine and bis(trimethylsilyl) amines, and hindered alcohols such as triethylmethanol, and 2,6-di-t-butyl-phenol with potassium hydride has produced a convenient route to preparing their respective potassio salts, which are synthetically useful bases.[104]

Because of the remarkable basic properties of potassium hydride[105] we were prompted to investigate the reaction of this base with β-diketones (1a-b) and β-ketoesters, 1c. Certainly the methylene proton of these compounds would be rapidly ionized by potassium hydride to form monanions 6a-c, but to what extent and under what conditions would the formation of dianions 3a-c be achieved? These were the questions for which answers were sought to the present study.



6a, R = CH_3

b, R = Ar

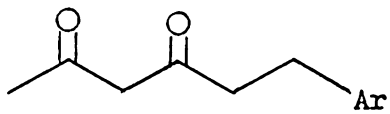
c, R = EtO

*This term has been coined by Brown[101] to indicate replacement of active hydrogens by potassium.

VII. RESULTS AND DISCUSSION

Addition of acetylacetone (1a) to a four-fold molar excess of potassium hydride in THF at 25° resulted in immediate evolution of 1.1 to 1.2 equivalents of hydrogen. Essentially no additional hydrogen was evolved under these conditions over a period of 18 hours, indicating that the predominant species formed was the monoanion 6a. The origin of the extra 0.1 to 0.2 equivalents of hydrogen is not known. However, the most likely reason for excess hydrogen is the reaction of potassium hydride with traces of water present in the THF and apparatus. Slow dianion formation seems unlikely, since this should lead to gradual release of hydrogen during 18 hours.

Initial formation of 6a at 25° followed by increasing the temperature of the reaction mixture to 64° for four hours, produced an additional 0.4 equivalents of hydrogen, indicating partial formation of dianion 2a. The presence of 2a was demonstrated by adding benzyl chloride to the reaction mixture at 25° to form the terminal benzylated derivative, (7).[94] Thus, benzylation at the terminal methyl group of



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1a is strong evidence for the presence of a carbanion site at this position.

When this experiment was carried out using benzophenone to trap dianion 2a, terminal condensation product 3a was isolated in 64% yield. This latter trapping experiment was characterized by two unusual features. First, the yield of 3a was higher than anticipated from total hydrogen (1.5-1.6 equivalents) generated prior to addition of benzophenone. Secondly, introduction of benzophenone was accompanied by rapid (30 min) evolution of an additional 0.7 equivalents of hydrogen. Thus, benzophenone obviously promotes ionization of a terminal methyl proton of the β-diketone substrate.

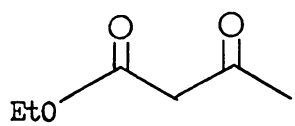
The striking influence of benzophenone on hydrogen evolution was clearly demonstrated by first preparing monoanion 6a with excess KH and then adding an equivalent of benzophenone at 25°. This resulted in evolution of an additional 0.9 equivalents of hydrogen within 30 minutes and carbinol 3a was isolated in 81% yield.

Benzoylacetone (1b) behaved analogously to 1a in that only monoanion 6b was formed with excess KH at 25°, as evidenced by evolution of 1.2 equivalents of hydrogen. Addition of benzophenone resulted in liberation of an additional equivalent (0.9) of hydrogen after 2 hours, and carbinol 3b was isolated from the reaction in 66% yield.

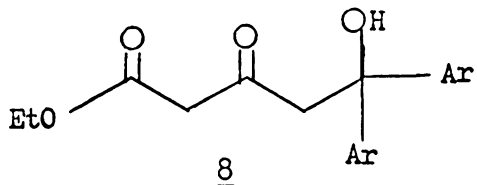
The present observations are apparently unique for potassium hydride, since sodium hydride, even in the presence of the powerful ionizing solvent hexamethylphosphoramide (HMPA),[67] failed to effect reaction of benzophenone at the terminal methyl group of monosodium salts of 6a-b over a period of 48 hours at 25°.

When the monoenolate of ethyl acetoacetate (6c) was treated with benzophenone, 0.55 equivalents of additional hydrogen had evolved in

1 hour. However, none of the expected product could be detected, instead triphenylcarbinol and benzoic acid were isolated in yields of 55 and 30%, respectively. TLC analysis of the crude reaction mixture



6c



8

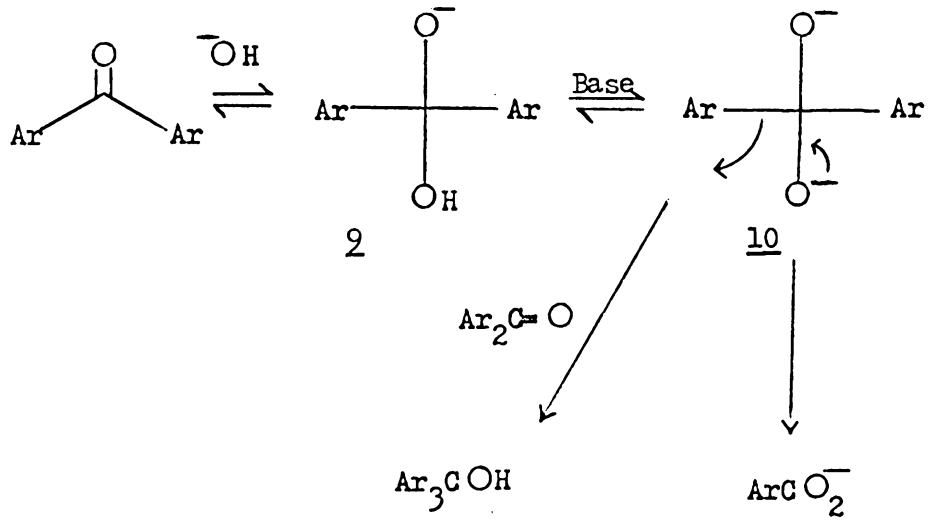
also revealed the presence of benzhydrol, ethyl acetoacetate and benzophenone.

The benzhydrol could perhaps result from the reduction of benzophenone with excess KH. However, benzophenone (10 mmol) and excess potassium hydride (40 mmol) did not produce either benzhydrol or triphenylcarbinol even after 13 hours at 25° in the absence of ethyl acetoacetate.

In contrast to monopotassio salt 6c, the potassium salts of benzhydrol and t-butanol gave trace amounts of triphenylcarbinol and benzoic acid when these alcohols were added to reaction mixtures containing benzophenone and excess potassium hydride.

Cleavage of nonenolizable ketones such as benzophenone to form benzoic acid has been observed to occur with potassium t-butoxide in ether. Although the reactions were conducted in the presence of varying amounts of water, trace amounts of triphenylcarbinol were still detected.[106] Gassman[107] has shown the formation of benzoic acid to occur by attack of hydroxide ion at the carbonyl of benzophenone to form

Scheme I



adduct 9. The adduct 9 of hydroxide ion and the ketone then reacts with t-butoxide to form dianion 10, which would have significant driving force to cleave in forming the phenyl anion and a potassium benzoate (Scheme I).

Cleavage of benzophenone was observed to occur when water (0.5 equivalents) was added to a slurry of benzophenone (1 equivalent) and excess potassium hydride as evidenced by formation of benzoic acid and triphenylcarbinol.* Potassium hydride apparently is involved in the formation of the unstable dianion, 10 since the reaction is accompanied by hydrogen evolution. Potassium hydride could participate directly as

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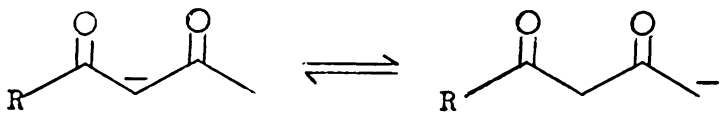
*In addition, benzhydrol was present in the reaction mixture.

a base or indirectly by causing the regeneration of a base that is soluble and actively involved in Scheme I. Such may be the case in the reaction involving potassium t-butoxide.

The mechanistic role of benzophenone in the formation of aldol products 3a-b would appear to involve either 1) an increase in the basicity of potassium hydride brought about by benzophenone 2) the presence of equilibrating monoanions (Eq. 1) producing anion 11a-b which could react with benzophenone to form the observed aldol product and



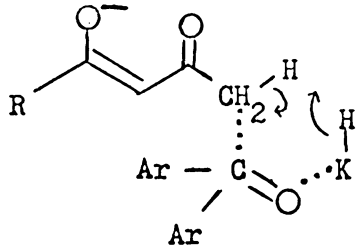
(1)

6a, R = CH_3 11a, R = CH_3

b, R = Ar b, R = Ar

simultaneously deplete 6a-b, or 3) an increase in the acidity of the methyl hydrogens of monoenolates 6a-b via interaction of these intermediates with benzophenone.

The first of these premises now seems unlikely, since the rate of hydrogen evolution from triphenylmethane in the presence of excess potassium hydride at 25° in THF was not increased when a molar equivalent of benzophenone was present in the reaction mixture. If benzophenone were simply potentiating the basicity of the hydride, the rate



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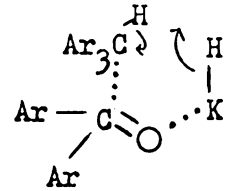


13

of trityl carbanion formation should certainly have increased. This would also appear to argue against the proposed termolecular mechanism for aldol condensation involving an intermediate such as 12[100] formed on the surface of KH, since proton abstraction from triphenylmethane should be favored by similar interactions (13).

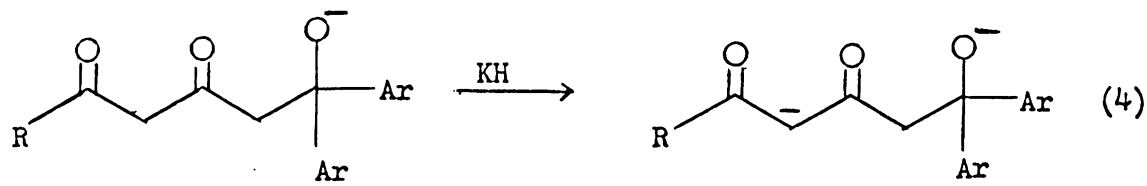
It should be noted that the hydrogen evolution in this three-component mixture (Eq. 2) involving potassium hydride, triphenylmethane and benzophenone was reproducible, 3.7 mmol (average) in 16 hours. This average was in one instance greater than the amount of hydrogen that was generated when the reaction shown in Eq. 3 was performed in the absence

$$Ar_3CH + Ar_2C{=}O \xrightarrow{KH} H_2 + ArCO_2H + Ar_3COH + Ar_2CHOH \qquad (2)$$

$$Ar_3CH \xrightarrow{KH} H_2 \qquad (3)$$

of benzophenone (3 mmol in 16 hours). However, when the reaction without benzophenone was repeated, 5.2 mmol of hydrogen were produced in 16 hours. These results identified two major problems associated with making the comparisons between reactions 2 and 3. First, reaction 2 is also accompanied by the production of triphenylcarbinol and benzoic acid which would provide an additional source of hydrogen if cleavage is occurring via Scheme I. Secondly, the fluctuation in the extent of hydrogen evolution is an indication of the difficulty in preparing samples of potassium hydride of equal reactivity.

The formation of 3a-b occuring through an equilibrium (Eq. 1) between the monoenolates 6a-b and 11a-b can be ruled out by several experimental facts. Admittedly the equilibrium should lie to the left; however, once the terminal monoanion 11 is formed it could condense with benzophenone to form 14a-b. The reaction would eventually be driven to completion by ionization of 14a-b to give 15a-b (Eq. 4). This ionization would aid in the prevention of a retroaldol condensation and could be the source of the second equivalent of hydrogen which evolves during the potassium hydride promoted condensation. It would then seem likely that sodium hydride could also perform the irreversible



(4)

14a, R = CH_3

b, R = Ar

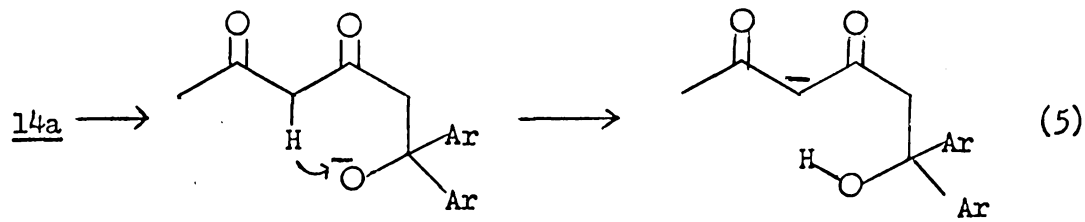
15a, R = CH_3

b, R = Ar

abstraction of the methylene proton of 14a-b to form 15a-b, since this reagent readily ionizes β-dicarbonyl compounds.[99] However, addition of excess sodium hydride to a mixture of benzophenone and monopotassio salt 6a failed to form aldol product 3a; only traces of triphenylcarbinol and benzoic acid were detected. The formation of the latter two compounds was also observed in the reaction involving 1a and benzophenone in the presence of excess sodium hydride.

It is also plausible that if the equilibrium shown in Eq. 1 were operating, the tertiary alkoxide function of intermediate 14a could intramolecularly remove the methylene proton in question and effectively

drive the reaction to completion by forming stabilized anion 16 (Eq. 5).* Subsequent reaction of 16 with potassium hydride would then account for the second equivalent of hydrogen. This sequence of reactions would require only monoanion 11 and benzophenone. However, when monoanion was treated with benzophenone in the absence of potassium hydride product 3a was not formed.



(5)

16

The accelerating influence of benzophenone on the rate of hydrogen production and formation of alcohols 3a-b could reside in the ability of this ketone to increase the acidity of the methyl hydrogens of 6a-b by a complex such as 17, which may also be represented by separate structures 18 and 19. In any case, the effect is the same in that the negative charge of the original monoanion would be transferred to the carbonyl function of benzophenone. The methyl protons of the complex would then possess acidity similar to the α-hydrogen of a monoketone, thereby allowing facile removal by potassium hydride.[101]

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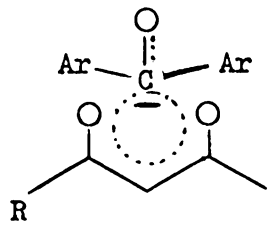
*An intermolecular process is also possible. In such a case the overall result would be the same.



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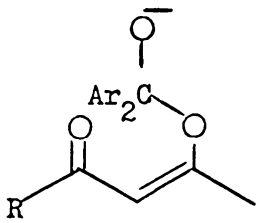

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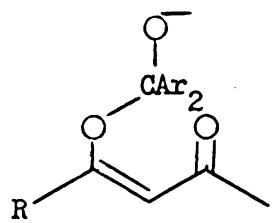


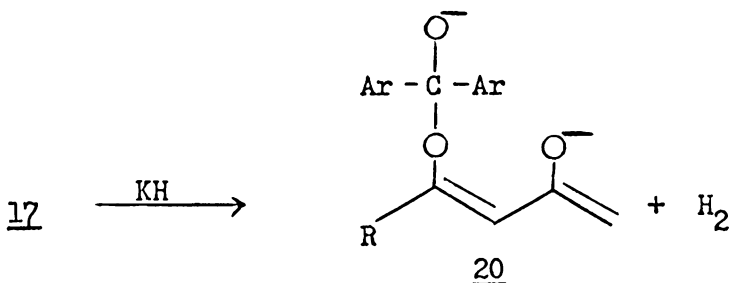
19

17-19a, R = CH_3

b, R = Ar

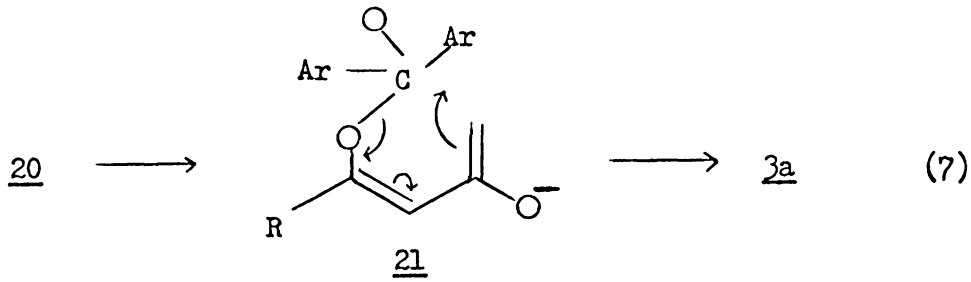
c, R = EtO

For instance, as potassium hydride begins to initiate proton abstraction of the terminal methyl group of 17, the complex responds by increasing its interaction with the carbonyl oxygen that lies farther away from the site of secondary ionization (Eq. 6), thereby freeing the closer carbonyl for subsequent stabilization of the incipient dianion 20. It should be noted that in the case of acetylacetone (6a),



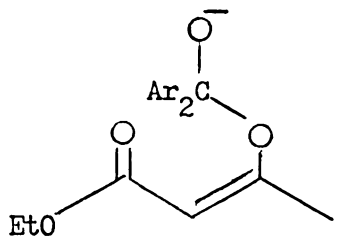
17 —KH→ 20 + H_2 (6)

17 is symmetrical. This might imply that the reaction of 6a with benzophenone and potassium hydride should be faster than the reaction of 6b with this ketone. Indeed this proved to be the case. Once the dianion (20) is formed from 17, 18 or 19, condensation of 20 can occur either with a free molecule of benzophenone or possibly by an intramolecular transfer thru cyclic intermediate 21 (Eq. 7).

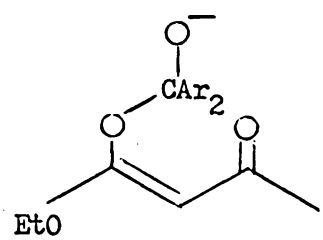


(7)

If complexes such as 17-19 are formed from monoanions 6a-c and benzophenone, the monoanion of ethyl acetoacetate should prefer the configuration represented by 18c since most of the negative charge will reside on the oxygen of the ketone carbonyl. This seems likely because electron delocalization into the carbonyl of the ester function is unfavorable.



18c



19c

If 19c is actually present, it would appear that it is not as effective in increasing the acidity of the terminal methyl group of the monoanion of ethyl acetoacetate as proposed for the monenolates of 6a-b. Therefore, because of the inability of potassium hydride to cause ionization of the methyl group of the monoenolate complex of ethyl acetoacetate, potassium hydride probably then participates in the reduction and cleavage of benzophenone. If the cleavage of benzophenone is via the proposed Gassman mechanism (Scheme I), the evolution of hydrogen that is observed during the reaction is due, in part, to the direct or indirect ionization of adduct 9 by potassium hydride.

In conclusion, the unusual behavior of benzophenone and excess potassium hydride to form aldol products 3a-b, triphenylcarbinol and benzoic acid, or benzhydrol in the presence of various potassio anionic species, such as 6a-c, hydroxide, and alkoxides is perhaps consistent with one fact. In all these reactions, the potassium hydride was initially ionized in situ before the various products were formed. This might indicate that the removal of hydride from the surface is perhaps a necessary step in leading to formation of the isolated products. Also in view of the evidence for adduct 9 which is formed from hydroxide ion and benzophenone,[107] a similar complex involving monoanions 6a-c and the ketone seems possible since these interactions 17-19 aid the explaination of the present results.

VIII. EXPERIMENTAL

The reaction apparatus for the reactions involving potassium hydride (KH) was the same as that described in the general acylation procedure in Chapter V of Part A.

Because of the extreme sensitivity of that KH toward traces of water, care must be taken to avoid contact of this reagent with air, especially after the KH has been washed of the oil vehicle.

All hydrogen evolutions are reported in mmol which were calculated using the gas law after adjusting the pressure to account for the vapor pressure of water.

Preparation of KH

To a three-necked 250 ml flask, was added 6.66 g (40 mmol) of KH as a 24% oil dispersion via a 25 ml pipet (wide stem) equipped with a rubber bulb. Immediately 80 ml of dry hexane and a magnetic stirring bar were added and the resulting slurry was stirred for a few seconds. After the solid KH settled out, the hexane was decanted off leaving approximately 25 ml of hexane in the flask to which a second portion of 75 ml of dry hexane was added. The decanted hexane wash was quenched with isopropanol. After decanting the second portion of hexane (100 ml). The reaction flask was attached to the 1000 ml gas buret, and fitted with a pressure-equalizing addition funnel containing 140 ml of dry THF. The system was purged once with nitrogen via the third neck of the reaction flask. The THF was then added and the solution was stirred for 15 min.

Reaction of Acetylacetone (1a) and KH at Reflux Followed by Addition of Benzophenone.

To a slurry of 40 mmol of KH prepared as described above, was added dropwise a solution of 1.0 g (10 mmol) of 1a in 20 ml of THF. After addition of 1a was initiated, a short induction period (5 sec) was observed before hydrogen began to evolve. Once the evolution of hydrogen began, the gas was liberated rapidly. After addition was complete, the reaction was allowed to continue for an additional 20 min, after which time monoanion 6a was assumed to have formed as indicated by the generation of 11-12 mmol of hydrogen. The reaction mixture was then brought to reflux. After 4 hr additional 4 mmol of hydrogen had evolved (total 15-16 mmol).

To the resulting reaction mixture maintained at room temperature, was added 1.82 g (10 mmol) of solid benzophenone, the reaction was allowed to proceed for 1.2 hr. Hydrogen (7 mmol) evolved during the first 30 minutes following addition of benzophenone (total 22-23 mmol). The brown solution was quenched (Caution) with 40 mmol of aqueous HCl (50 ml) and poured into 100 ml of water. The aqueous THF solution was extracted three times with 150 ml portions of ether. The ethereal layers were combined, dried ($MgSO_4$), and concentrated. TLC analysis (hexane-benzene, 1:1) revealed one major component along with a trace of benzophenone. After addition of hexane and ether to the concentrate, a seed crystal of 3a was added and on standing, 2.1 g (75%) of crude 1,1-diphenyl-1-hydroxy-3,5-hexanedione- (3a), was formed as a light yellow solid, mp 127-132°. Recrystallization from methanol gave 1.84 (64%) of 3a, mp 131-132° (lit.[95] mp 133-135°): ^{1}H NMR ($CDCl_3$) δ 14.98 (s, 0.8H,

enol), 7.66-7.40 (m, 10H, aromatic), 5.55 (s, 0.8H, vinyl), 5.29 (s, 1H, OH), 3.57 (s, 0.4H, CH_2), 3.32 (s, 2H, CH_2), 2.16 (s, 0.6H, CH_2-keto), and 2.05 ppm (s, 2.4H, CH_3-enol).

Reaction Between 1a and Benzophenone at Room Temperature in Presence of KH.

In order to investigate the influence that benzophenone had on the hydrogen evolution, the above reaction was repeated excluding the reflux step. Again (12 mmol) of hydrogen were evolved initially. After benzophenone (10 mmol) was added to the reaction solution, 9 mmol of hydrogen were generated in 30 min. The reaction solution was processed as described above to give a white solid, which on recrystallization from methanol, afforded 2.28 g (81%) of 3a as a white solid mp 131-132°. The ^1H NMR was identical with that of 3a obtained previously.

The above experiment was repeated in the absence of benzophenone in order to observe the evolution of hydrogen which might be a result of slow formation of dianion 2a. No hydrogen was evolved in 18 hr at 25°.

Blank reactions conducted with 140 ml of THF and 40 mmol of potassium hydride revealed evolution of no more than 1 mmol of hydrogen over a period of 48 hr regardless of whether the THF was maintained at reflux or at room temperature.

Detection of the Dipotassio Salt of Acetylacetone (2a) by Alkylation with Benzyl Chloride.

Independent Preparation of 6-Phenyl-2,4-hexandione (7) by the Method of Huckin and Weiler.[99]

To a solution of 10 mmol of the monosodium salt of acetylacetone-prepared by reaction of 0.63 g (13 mmol) of sodium hydride (50%) with 1a - in 70 ml of THF at 0° under nitrogen, was added 6.25 ml (10 mmol) of n-butyllithium (1.6 M). This caused most of the voluminous solid present in the reaction mixture to disappear. After 30 min, 1.26 g (10 mmol) of benzyl chloride was added to the light gray solution via syringe. The benzylation was allowed to continue for 15 min after which time the solution was quenched (Caution) with 15 ml of cold water containing 4 ml of 6 M HCl. The organic layer was separated from the aqueous layer, which was extracted twice with 100 ml portions of ether. The organic phases were combined, dried, and concentrated. VPC analysis revealed several components, the major peak being 7. Using the same column and conditions, a sample of 7 was collected by preparative VPC: ^{1}H NMR ($CDCl_3$) δ 15.18 (s, 0.85H, enol), 7.21-6.81 (m, 5H, aromatic), 5.17 (s, 0.85H, vinyl), 3.47 (s, 0.3H, CH_2), 2.85 (m, 2H, CH_2), 2.53 (m, 2H, CH_2), 2.13 (s, 0.4H, CH_3-keto), and 1.98 ppm (s, 2.6H, CH_3-enol).

Trapping Dianion 2a with Benzyl Chloride.

To a stirred slurry of 40 mmol of KH in 140 ml of THF, was added dropwise 1.05 (10 mmol) of acetylacetone (1a) in 20 ml of THF. After the evolution of hydrogen (11.5 mmol) ceased, the reaction was allowed to continue for 4 hrs at reflux. After this time an additional 4 mmol of hydrogen had been generated. The resulting orange-brown solution was cooled to room temperature. The middle stopper on the reaction flask

was replaced with an adapter fitted with a rubber septum. Benzyl chloride 1.26 g (10 mmol) was added via syringe. After a reaction period of 20 min, the reaction solution was processed in the usual manner (HCl quench) to give a concentrate which showed by VPC analysis that 7 was present. No attempt to isolate 7 was made. The VPC analysis and preparative isolation of 7 was carried out on a column of 6.3% Carbowax 20 M on Gas Chrom Z at 150°.

1-Hydroxy-1,1,5-triphenyl-3,5-pentanedione-3,5 (3b).

To a stirred slurry of 40 mmol of KH in 140 ml of THF, was added dropwise a solution of 1.62 g (10 mmol) of benzoylacetone (1b) in 20 ml of THF. After addition was complete, the solution was stirred for 20 min at 25° (12 mmol of hydrogen) after which time the solution was brought to reflux. After 2.5 hr, the heat was removed (4.5 mmol of hydrogen, total 16.5 mmol). To the brown reaction solution, which contained some green solid, was added 1.82 g (10 mmol) of benzophenone as a solid. After 2 hr, the reaction mixture was quenched (Caution) with 50 ml of cold water containing 4 ml of conc. HCl. The resulting brown solution was diluted with 100 ml of water and extracted three times with 150 ml portions of ether. The ethereal layers were combined, dried ($MgSO_4$), and concentrated. TLC analysis (benzene) revealed the presence of 3b and traces of benzoylacetone and benzophenone. Column chromatography of the crude product on silica gel gave on elution with hexane-benzene (80:20) 1.86 (54%) of 3b as a yellow tinted solid, mp 113-114 (lit.[95] 115-116°); ^{1}H NMR ($CDCl_3$) δ 15.90 (s, 0.9H, enol), 8.04-7.20 (m, 15H, aromatic), 6.26 (s, 0.9H, vinyl), 5.33 (s, 1H, OH), 4.11

(s, 0.2H, CH_2), 3.67 (s, 0.2H, CH_2-keto), and 3.52 ppm (s, 1.8H, CH_2-enol).

No attempt was made to isolate benzophenone and benzoylacetone which eluted before 3b during chromatographic processing.

The preparation of 3b was repeated; however, benzoylacetone (10 mmol) was not refluxed in the presence of KH (40 mmol) before addition of benzophenone (10 mmol). The reaction between benzoylacetone and KH initially produced 12 mmols of hydrogen, and after addition solid benzophenone an additional 9 mmols of hydrogen had evolved in 2 hr. The reaction mixture was processed as described above to give a concentrate which partially solidified. The solid was collected and recrystallized from 95% ethanol to give 2.27 g (66%) of 3b, mp 115-116°. The ^1H NMR spectrum was identical with that of 3b obtained earlier.

Reaction Between 1a and Excess Sodium Hydride in the Presence of Benzophenone.

To a slurry of 1.92 g (40 mmol) of sodium hydride (50%) previously washed with hexane in 140 ml of THF, was added 1.05 (10 mmol) of 1a in 20 ml of THF over a period of 15 min. After an additional 20 min, the sodium salt of 1a was assumed to have formed as indicated by the evolution of 11 mmol of hydrogen. To the resulting white slurry 1.82 g (10 mmol) of benzophenone was added as a solid. After a reaction time of 48 hr, only 30 ml (1.2 mmol) of additional hydrogen had evolved. The reaction mixture was then quenched (Caution) with 40 ml of 1 M HCl. The resulting solution was added to 100 ml of water and extracted three times with 100 ml portions of ether. TLC analysis (hexane-ether, 10:3) revealed the presence of benzophenone and the absence of 3a.

The above reaction was repeated in the presence of HMPA (20 mmol), which appeared to aid in dissolution of sodium salt 6a, by decreasing the amount of white solid present in the reaction mixture. The reaction mixture was then quenched with 40 ml of 1 M HCl and processed as described above to give a condentrate that showed no evidence of 3a.

In both of the above reactions triphenylcarbinal and benzoic acid were present in the reaction concentrates as evidenced by TLC analysis.

Attempted Formation of Ethyl 3-Oxo-5-hydroxy-5,5-diphenylpentanoate (3c).

To a slurry of 40 mmol of KH in 140 ml of THF was added dropwise a solution of 1.30 g (10 mmol) of freshly distilled ethyl acetoacetate in 20 ml of THF. This caused the evolution of 11 mmol of hydrogen. After 30 min, 1.82 g (10 mmol) of benzophenone was added as a solid, which was accompanied by the evolution of an additional 5.4 mmol of hydrogen in 1 hr. After 24 hr and no further hydrogen evolution had occurred, the reaction mixture was quenched with 50 ml of cold water containing 40 mmol of HCl. The solution was made basic with 5% sodium bicarbonate and extracted twice with ether (100 ml portions). The ethereal layers were combined, dried, and concentrated to give 0.72 g (55%) of triphenylcarbinol in two crops, as white crystals, mp 160-161° (lit.[108] 164.2°) mmp 160-161°: ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 15H, aromatic), and 2.73 ppm (s, 1H, OH).

Concentrated HCl (2 ml) was added to the basic aqueous layer which was then extracted twice with 100 ml portions of ether. The ethereal layers were combined, dried, concentrated and combined with the mother liquor from which the triphenylcarbinol was obtained.

TLC analysis revealed the presence of ethyl acetoacetate, benzoic acid, triphenylcarbinol, and benzhydrol. On complete evaporation of solvent, the remaining solid was vacuum sublimed to give a mixture (0.17 g) of benzhydrol, and benzoic acid. Comparison of ir spectra (CCl_4) of this sample with an authentic 1:1 mixture of benzhydrol-benzoic acid showed them to be essentially identical. In repeating this reaction, the best yield (32%) of benzoic acid recrystallized from hot water was 0.2 g, which was isolated from the basic aqueous layer as before. The mp 120-121° (lit[108] 122.4°) mmp 120-121° and ^{1}H NMR were consistent with benzoic acid. The benzhydrol was never isolated pure for a yield from the reaction mixture; however, ^{1}H NMR, ir, and TLC analysis (hexane-ether, 10:3) certainly account for its presence in the crude products isolated during the processing of reaction mixtures.

Reaction Between Benzophenone and Excess Potassium Hydride.

To a slurry of 6.68 g (40 mmol) of potassium hydride (24%) in 140 ml of THF at 25°C was added 1.82 g (10 mmol) of benzophenone. TLC analysis (hexane-ether, 10:3) of an aliquot taken after 13 hr revealed the presence of only benzophenone.

To the gray reaction slurry was added 10 mmol of benzhydrol in 20 ml of THF. After 2 hr, TLC analysis revealed the presence of starting materials plus benzoic acid and triphenylcarbinol.

The above reactions were repeated using 10 mmol of t-butanol (9 hr) or 5 mmol of water (2 hr) instead of benzhydrol with similar results in that triphenylcarbinol and benzoic acid were present.

The reaction involving t-butanol showed only traces of benzhydrol, while the reaction doped with water appeared to have more benzhydrol. In all reactions benzophenone was still a major component as evidenced by TLC analysis.

The reaction between benzophenone and potassium hydride was repeated except with 40 mmol of benzophenone. In which case, triphenylcarbinol, benzoic acid and benzhydrol were formed.

Comparison of the Extent of Hydrogen* Evolution Resulting from the Reaction Between Excess Potassium Hydride and Triphenylmethane in the Presence and Absence of Benzophenone.

To a gray slurry of 40 mmol of potassium hydride in 130 ml of THF, was added a solution of 2.44 g (10 mmol) of triphenylmethane and 1.82 g (10 mmol) of benzophenone in 30 ml of THF. After a total reaction period of 16 hr, 91 ml of hydrogen (4.1 mmol) had evolved from the resulting maroon solution. When this reaction was repeated, 76 ml of hydrogen (3.4 mmol) were generated. The reaction was repeated twice more for 16 hr but in the absence of benzophenone. In these reactions 67 ml (3 mmol) and 116 ml (5.2 mmol) of hydrogen resulted in 16 hours.

All the reactions were quenched with aq HCl (Caution), added to 75 ml of water, extracted twice with 100 ml portions of ether, which were then combined and concentrated. The concentrate resulting from the reaction of potassium hydride and triphenylmethane showed by TLC analysis (hexane-ether, 10:3) that starting material remained. Analysis (TLC) of the reactions performed in the presence of benzophenone revealed a com-

*Hydrogen is reported in milliliters (ml) corrected to STP conditions.

plex mixture consisting of triphenylmethane, benzophenone, benzoic acid, triphenylcarbinol and benzhydrol. No attempt was made to isolate these compounds.

Reactions of the Potassio Salt of 1a with Benzophenone in the Absence and Presence of Excess Sodium Hydride.

To a slurry of 1.67 g (10 mmol) of potassium hydride (24%) in 130 ml of THF, was added dropwise 1.05 g (10.5 mmol) of acetylacetone (1a) in 20 ml of THF. Addition was accompanied by the evolution of 10 mmol of hydrogen.* After a reaction period of 2 hr no additional hydrogen was evolved. Then 1.44 g (30 mmol) of sodium hydride (50%) was quickly added to the reaction mixture. A slight effervescence was observed on the addition of the sodium hydride. The resulting slurry was stirred for an additional 1 hr after which time 1.82 g (10 mmol) of benzophenone was added to the reaction mixture. After 3 hr, 1.1 mmol of additional hydrogen had evolved. The solution was processed in the usual manner, and TLC analysis (hexane-benzene, 1:1) of the reaction mixture indicated that 3a had not formed. The concentrate was then adsorbed onto 5 g of silica gel and stored. Since it was later learned from experiments involving ethyl acetoacetate that triphenylcarbinol and benzoic acid were being formed in preference to 3c. The sample was then subjected to TLC analysis (hexane-ether, 10:3)

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*Since it was critical that all of the potassium hydride be initially consumed and because of the uncertainty of the actual amount of potassium hydride used in these experiments, a 5% excess of acetylacetone was reacted with the potassium hydride in order to prevent the formation of condensation product (3a) resulting from traces of potassium hydride.

and revealed that traces of benzoic acid and triphenylcarbinol were present and benzhydrol was not.

The above experiment was repeated in the absence of excess sodium hydride. After a reaction period of 10 hr between 6a and benzophenone, the solution was processed in the normal manner to reveal that no aldol product 3a had formed. At a later date, TLC analysis (hexane-ether, 10:3) of the reaction concentrate which had been stored on silica gel revealed that benzoic acid and triphenylcarbinol were present.

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PART A. SYNTHESIS OF NEW 2-SUBSTITUTED-3-ARYL-4(3H)-QUINAZOLINONES AS POTENTIAL CNS AGENTS

PART B. REACTIONS OF β-DIKETONES WITH BENZOPHENONE IN THE PRESENCE OF POTASSIUM HYDRIDE

by

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(ABSTRACT)

Part A

2-Methyl-3-o-tolyl-4(3H)-quinazolinone (Methaqualone) and various other 2-methyl-3-aryl-4(3H)-quinazolinones were functionalized by active hydrogen condensations at the 2-methyl position. For example, methaqualone was metalated at the lateral 2-methyl group with lithium diisopropylamide at 0° in tetrahydrofuran (THF) and the resulting lithio salt was condensed with various electrophiles including alkyl halides and carbonyl compounds.

Results of aldol condensations involving the lateral lithio salt of methaqualone revealed the severe steric requirements imposed upon this nucleophile by the 3-o-tolyl group. For instance, the secondary alcohol resulting from condensation with benzaldehyde underwent facile retroaldol condensation or dehydration. These degradative processes apparently relieve the extreme van der Waals repulsions between the 3-o-tolyl group and the bulky 2-(2-hydroxy-2-phenylethyl) substituent. These steric interactions were further evidenced by the ^{1}H NMR spectrum

of this alcohol which revealed the existence of diastereomeric rotational isomers.

A comparison between aldol condensations involving the less hindered lithio salt of 2,3-dimethyl-4(3H)-quinazolinone and the lithio salt of methaqualone further demonstrated the importance of the steric constraints in the latter anion.

Sodium hydride promoted acylations at the 2-methyl group of methaqualone were achieved in refluxing 1,2-dimethoxyethane (DME) with ethyl acetate as well as with various nonenolizable esters, such as ethyl trifluoroacetate and substituted benzoate esters. Since these acylations afforded the desired 2-(2-ketoalkyl)-3-o-tolyl-4(3H)-quinazolinones in good yield, and since these products represented a totally new class of 2-substituted-3-aryl-4(3H)-quinazolinones, various other esters were employed in this synthetic scheme to prepare a representative group of derivatives of this pharmacologically active parent molecule. Likewise, other 2-methyl-3-aryl-4(3H)-quinazolinones were similarly acylated and a preliminary structure-activity correlation with respect to CNS depression and anticonvulsant activity was derived.

Part B

The use of potassium hydride to achieve possible twofold kaliation of acetylacetone and benzoylacetone was investigated. As expected, the hydride readily ionized the methylene proton of these diketones at room temperature in THF to form the expected monoanions. After refluxing the monoanion of acetylacetone in the presence of excess potassium hydride for 4 hours, evidence for formation of the 1,3-

dianion was obtained by measurement of hydrogen evolution and trapping experiments using benzyl chloride and benzophenone to form the corresponding terminal derivative of the diketone. Addition of benzophenone to a THF solution of the monopotassio salts of acetylacetone and benzoylacetone at room temperature resulted in rapid evolution of a second equivalent of hydrogen and formation of the tertiary alcohols derived from condensation of benzophenone at the terminal methyl group of the diketone. A detailed study of the mechanism of this reaction was carried out. Several possible mechanisms were discarded. A proposed sequence of steps involving complexation of benzophenone with the diketone monoanions prior to ionization of a terminal methyl proton of the monoanion is presented.