A STUDY OF THE DISPLACEMENT OF HALOGEN FROM CHLORINATED HETEROAROMATIC AZINES BY DIALKALI SALTS OF BENZOYLACETONE, DISODIO SALTS OF CERTAIN 2-HYDROXY-4-METHYLPYRIMIDINES, AND THE METHYLSULFINYL CARBANION

by

James Carson Greene

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APPROVED:

James F. Wolfe, Chairman

Alan F. Clifford

Michael A. Ogliaruso

John G. Dillard

Thomas C. Ward

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TO BETSY AND POP

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I. INTRODUCTION AND HISTORICAL REVIEW

Halogenated monocyclic and bicyclic heteroaromatic azines, possessing a six or ten π-electron system and one or two ring nitrogens, have been shown to undergo nucleophilic displacement of halide ion with a variety of nucleophiles. A detailed review of the relative reactivity of compounds of these classes, as well as halogenated heteroaromatic azines containing as many as four nitrogen atoms has appeared.[1]

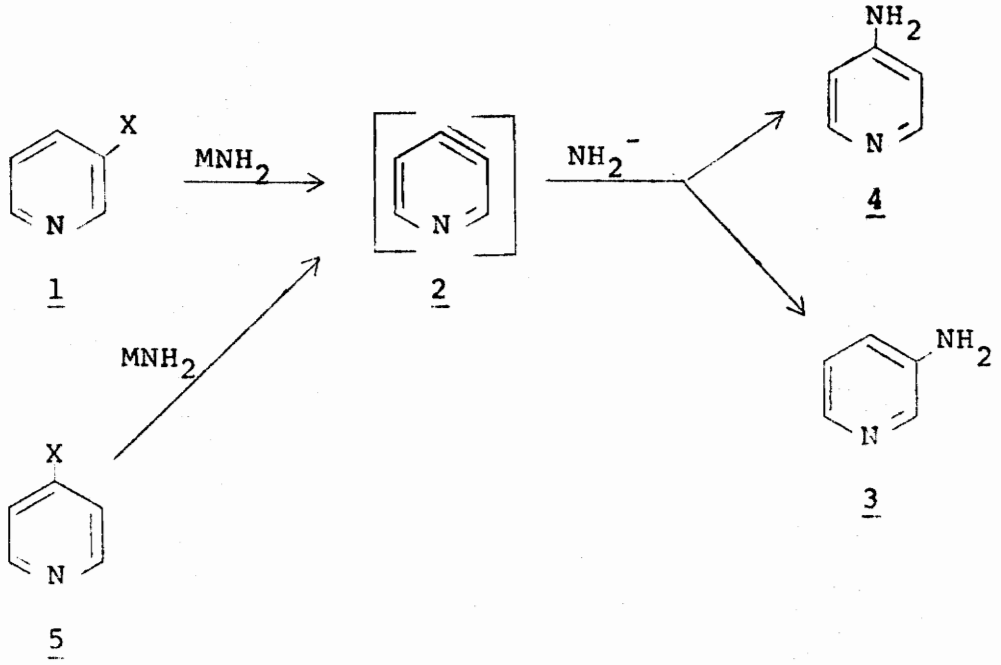
Two mechanisms have been observed for nucleophilic substitution reactions of halogenated heteroaromatic azines and diazines. These mechanisms were classified as the heteroaryne mechanism or elimination-addition and the S_NAr2 mechanism or addition-elimination.

A. The Heteroaryne Mechanism

In these reactions, the key intermediate was a didehydro derivative of the parent heterocycle, analogous to the well-known benzyne formed in certain instances of carboaromatic nucleophilic substitution.[2]

For an aromatic azine to react by way of the heteroaryne mechanism, it must possess a relatively unactivated leaving group, an adjacent hydrogen atom (or ionizable substituent), and involve the presence of a strong base

such as alkali amide (MNH_2).[3] The displacement of halogen from halopyridine (1) has been established as proceeding by such a mechanism (eq 1). The first step involved abstraction of a proton from the 4 position of 3-halopyridine (1) and subsequent loss of halide ion to give the 3,4-pyridyne heteroaryne intermediate 2. Nucleophilic attack by amide ion on 2 gave either the 3- or 4-substituted product (3 and 4 respectively). The product ratio (approximately 1:1) indicated the intermediate was very nearly symmetrical. Had

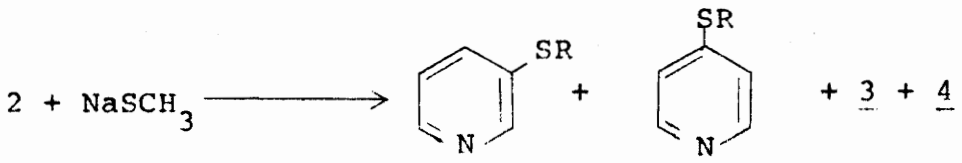


1 2 4 3 5 (1)

X=Cl, Br

direct displacement of the halogen by amide ion occurred, only the 3-amino derivative 3 should have been observed.

Additional experimental evidence for this mechanism was obtained by using 4-halopyridines (5). Thus, 4-bromo- and 4-chloropyridine[1] gave the same product ratio as 1 on treatment with amide ion, which indicated the reaction also proceeded through intermediate 2. Aryne intermediate 2 has been trapped with sodium methanethiolate (6),[4] which reacted with halopyridines 1 or 5 in the presence of sodium amide in liquid ammonia to produce thio ethers 7 and 8 in a 1:1 ratio along with the aminated products 3 and 4. Sodium methanethiolate would not react with chloro- or bromopyridines 1 and 5 in liquid ammonia which indicated that the methylthiopyridines 7 and 8 resulted from the interception of heteroaryne intermediate 2.

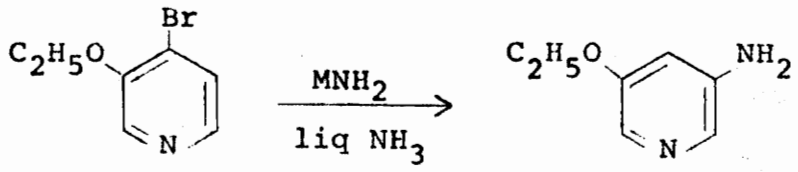


6 7 8

Although the presence and ratio of isomeric products derived from a halogenated azine was often used as indicators of an aryne intermediate, the ratio may be influenced by ring substituents and their positions on the ring. For example, Den Hertog and co-workers[3] found that amination of

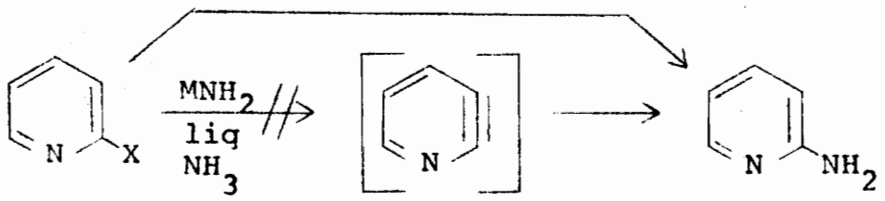
3-ethoxy-4-bromopyridine (9) afforded only the 5-amino derivative 10. This was attributed to the meta-directing influence of the ethoxy group, similar to that observed in 3-methoxybenzyne.

In contrast to the amination reactions of 3- and 4-halogenated pyridines, which involved 3,4-pyridyne (2), there was no evidence that 2,3-pyridyne (12) was involved in similar reactions of 2-halogenated pyridines (11), since treatment of compound 11 (X=F, Cl, Br, or I) with potassium



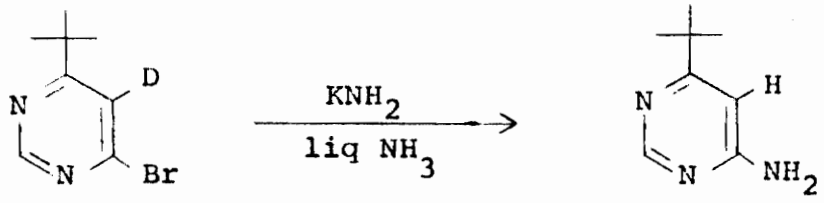
9 10

amide in liquid ammonia afforded only the 2-aminopyridine (13).



11 12 13

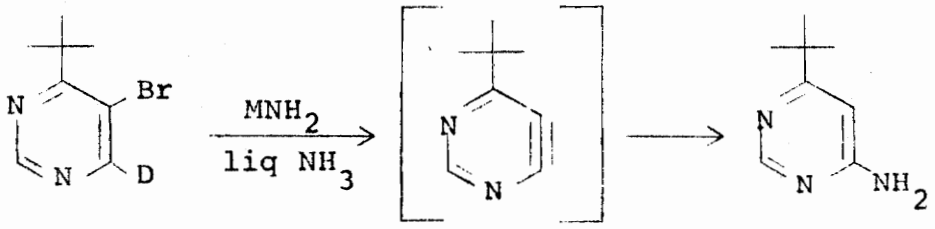
Studies of the reactions of halogenated heteroaromatic diazines with strong bases have revealed the existence of the heteroaryne mechanism in certain cases. In one such study, Vander Plas[5] investigated the amination of deuterated pyrimidines. Reaction of 4-bromo-6-tert-butyl-5-deuteriopyrimidine (14) with potassium amide in liquid ammonia afforded, in 5 minutes, aminopyrimidine 15 in quantitive yield.



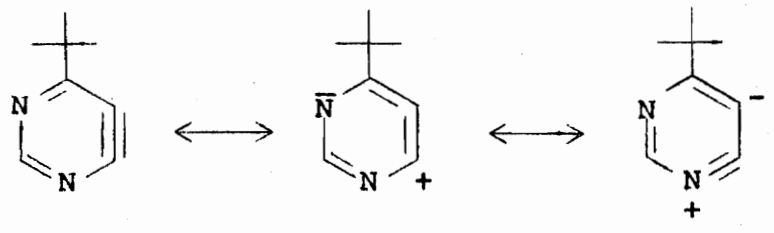
14 15

To determine if deuterium-hydrogen (D/H) exchange was involved, the reaction was allowed to proceed for one-half minute and the mixture analyzed for deuterium. The aminated product 15 contained only hydrogen, and the unreacted bromopyrimidine 14 contained the original percentage of deuterium. This result eliminated the possibility of direct displacement of halogen followed by D/H exchange. Additional information concerned with the intermediate involved in this reaction was obtained by amination of 5-bromo-6-tert-butyl-4-deuteriopyrimidine (16)[6] which resulted in exclusive formation of

nondeuteriated-4-amino compound 17. This pointed very strongly to the existence of heteroaryne intermediate 18. Further support for this pathway was obtained by the isolation of a small amount of 5-aminopyrimidine as well as the 4-amino compound (4-isomer/5-isomer ratio 93:7).[7] The electronic distribution in intermediate 18 has been postulated to explain the predominance of position 4-amination. Deactivation of position 5 and activation of position 4 were illustrated by resonance structures 19 and 20 respectively. Halogenated bicyclic azines have also been found to undergo substitution via heteroaryne intermediate.[8] Thus, reaction of halogenated quinolines 21 (X=Cl, Br, or I) with lithium piperidide and piperidine in boiling ether afforded 3- and 4-piperidinoquinolines (22) and (23) (ratio 49:51), presumably through 3,4-quinolyne (24). However, no evidence

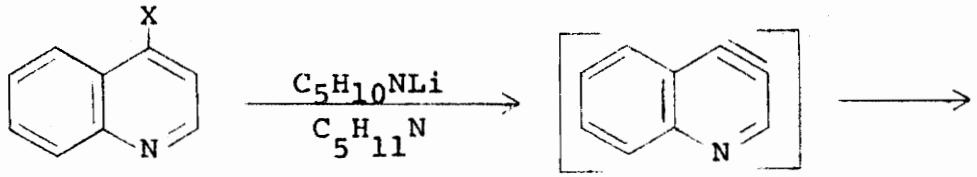


16 18 17

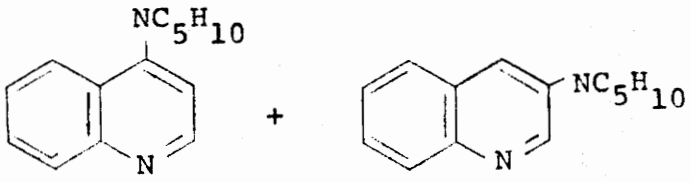


18 19 20

for formation of the analogous 2,3-quinolyne has been obtained from amination reactions of 2-halogenated quinoline, although this intermediate has apparently been generated in



21 24



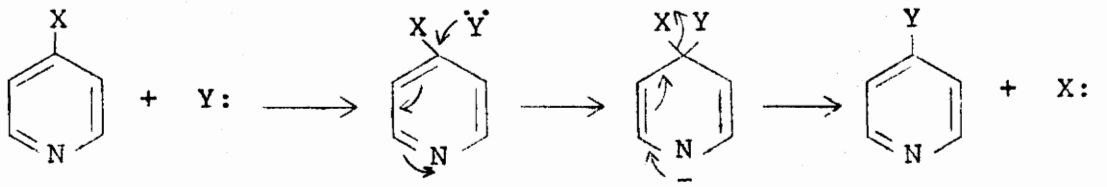
22 23

low yield by reaction of 3-bromo-2-chloroquinoline with lithium amalgam in refluxing furan.[3] 4-Bromoisoquinoline

has been shown to undergo substitution through 3,4-isoquinolyne on treatment with pyridine. However, the possibility that some direct substitution was involved cannot be ruled out completely.

B. The S_NAr2 Mechanism

Many nucleophilic displacement reactions of halogenated heteroaromatic azines and diazines proceeded by way of bimolecular intermediates rather than through heteroarynes. The bimolecular nucleophilic aromatic substitution (S_NAr2) mechanism as applied to 3-substituted pyridines 25 was illustrated by equation 2. The reaction was initiated by attack of the nucleophile Y: on the azine (25). The

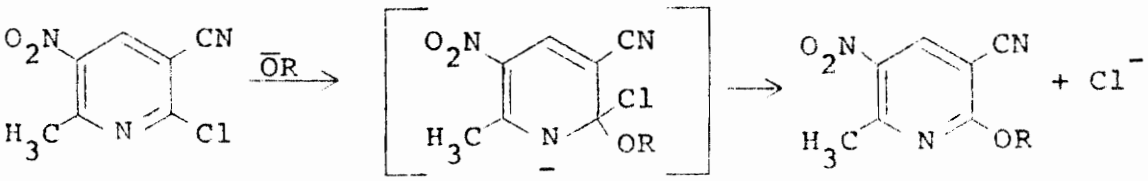


25 26 27 28 (2)

incipient negative charge was spread over several canonical structures, the most stable being 27 because the electronegative nitrogen could accommodate the change better than a ring carbon atom. On loss of the leaving group (X:), the

intermediate rearomatized to give the substituted product 28.

Normally, the first step determined the rate of the overall reaction, and structural features which stabilized intermediates such as 26 and 27 will usually lead to more rapid reactions.[1] There was a great deal of evidence for this type of mechanism, much of which was based on analogies drawn from nucleophilic substitution in carboaromatic systems.[9] Bases too weak for heteroaryne formation gave high yields of substituted products and isomeric substitutions were not usually observed. Meriella and co-workers[10] observed the formation of a colored intermediate in the reaction of halopyridine 29 with alkoxide ion, which disappeared as the alkoxy product 30 was formed. The proposed structure for the intermediate was complex 31.*



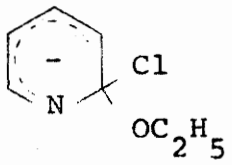
24 31 30

*Intermediates similar to 31 have been detected from the reaction of butyllithium and alkali amide with pyridine.[11,12]

The structure of the halogenated azine was a major factor in its reactivity with nucleophiles by the S_NAr2 pathway (Table I).[13] The relative rates of reaction of the halogenated heterocycles (R-Cl) listed in Table I was based on the displacement of chloride ion by ethoxide (eq 3) or piperidine assuming a bimolecular mechanism (S_NAr2).

$$RCl + MOC_2H_5 \longrightarrow ROC_2H_5 + MCl \qquad (3)$$

The reaction rate for 2-chloropyridine (32) was less than for benzopyridines (33-36); resonance stabilization of the intermediate complex was used to explain the difference. The substituted pyridine complex 37 has a five-atom resonating structure whereas the benzopyridine can form a more highly stabilized nine-atom resonating intermediate 38.



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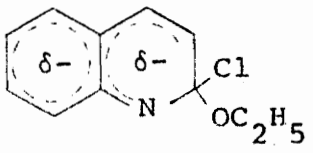

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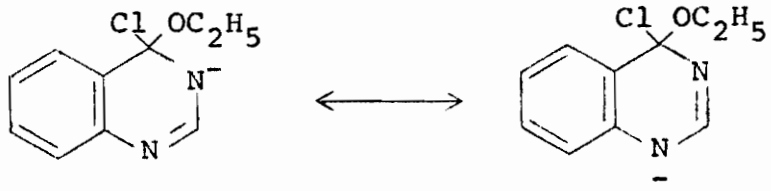
TABLE I

RELATIVE REACTIVITIES OF CERTAIN CHLORINATED HETEROCYCLES

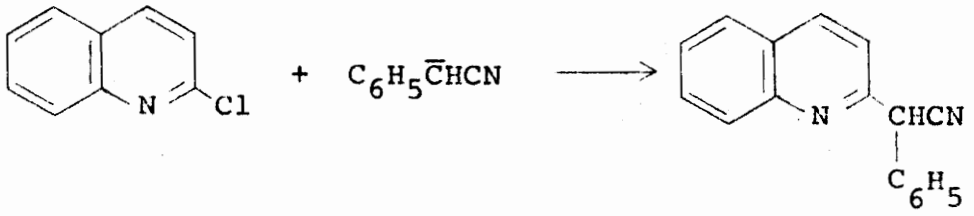
R-Cl		Rate of Reaction 10 + log K	
		with Ethoxide	with Piperidine
2-Chloropyridine	(32)	1.34	0.28
2-Chloroquinoline	(33)	3.80	3.18
4-Chloroquinoline	(34)	3.81	----
2-Chloroquinoxaline	(35)	7.92	5.79
4-Chloroquinazoline	(37)	----	10.49

It has been established that a ring containing two nitrogen atoms, such as 4-chloroquinazoline (36), imparted additional stability to intermediates 39 and 40 in that the negative charge could reside on the more electronegative nitrogen in both resonance forms.



39 40

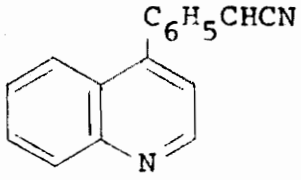
Among the many examples of nucleophilic displacements involving halogenated heteroaromatic azines which appeared to proceed by the S_NAr2 mechanism, the reactions of bicyclic azines and diazines with carbanions derived from active hydrogen compounds have received little attention, from a mechanistic viewpoint, although such reactions were of definite synthetic value. For example, reaction of 2-chloroquinoline (33) with the carbanion derived from phenylacetonitrile in refluxing benzene afforded the 2-quinolylnitrile 41 in quantitative yield (eq 4).[14] A similar reaction of this anion with 4-chloroquinoline gave the corresponding 4-quinolylnitrile 42.[15] Elderfield and Serlin[16] observed

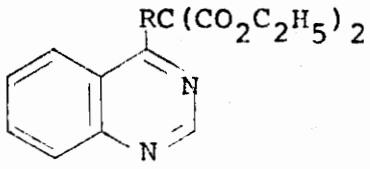


(4)

33 41

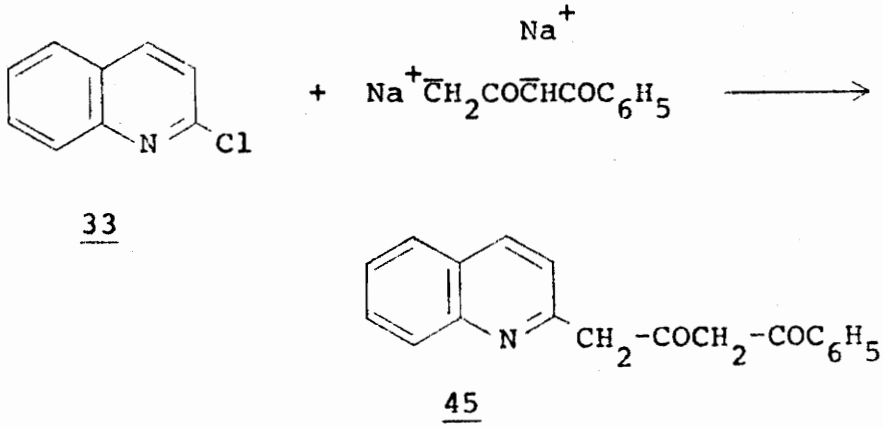
that 4-chloroquinazoline reacted with anions of substituted malonic esters to give compounds of type 43.





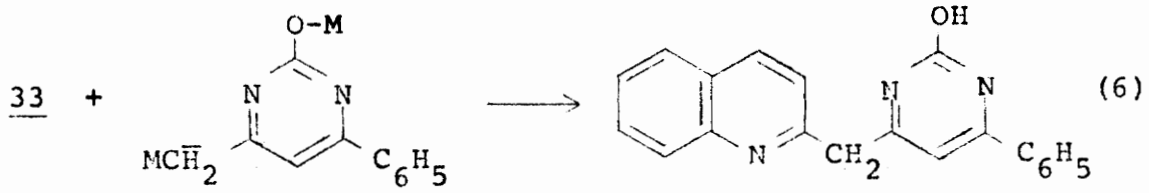
42 43

Recently, the first examples of reactions of a halogenated bicyclic azine with organic dianions have been reported. Wolfe and Murray[17] have demonstrated the displacement of chlorine from 2-chloroquinoline (33) using the disodio salt of benzoylacetone (44) in liquid ammonia to produce 1-phenyl-4-(2-quinolyl)-1,3-butanedione (45) in 17% yield (eq 5). In the same study, these workers reported



33 45 (5)

that the dianion 46 derived from 2-hydroxy-4-methyl-6-phenylpyrimidine by means of sodium amide in liquid ammonia reacted with 2-chloroquinoline (33) to give the substituted pyrimidine 47 in low yield (eq 6).



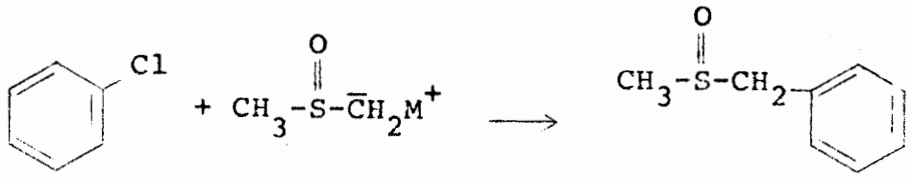
46 47 (6)

Further attempts by Wolfe and Murray to facilitate the preparation of diketone 45 by allowing 2-chloroquinoline to react with the disodio salt 44 in aprotic solvents having a higher boiling point than liquid ammonia resulted in no significant improvement in the yield.

These results were somewhat surprising since disodiobenzoylacetone (44) and the pyrimidine dianion 46 were highly nucleophilic and tended to react quite rapidly with

electrophilic reagents such as alkyl halides and carbonyl compounds at liquid ammonia temperature.[18]

In spite of the variety of carbanionic species which have been allowed to react with halogenated azines and diazines, there appeared to be no examples of the reaction of the anion of dimethyl sulfoxide (methylsulfinyl carbanion or dimsyl anion) with such compounds since its discovery in 1962.[19] In studies related to such reactions, this synthetically useful anion has been shown to react with halogenated carboaromatics and certain non-halogenated azines.[20] For example, reaction of chlorobenzene (48) with excess dimsyl anion 49 in dimethyl sulfoxide yielded 41% of methylbenzylsulfoxide (50) (eq 7). A benzyne intermediate



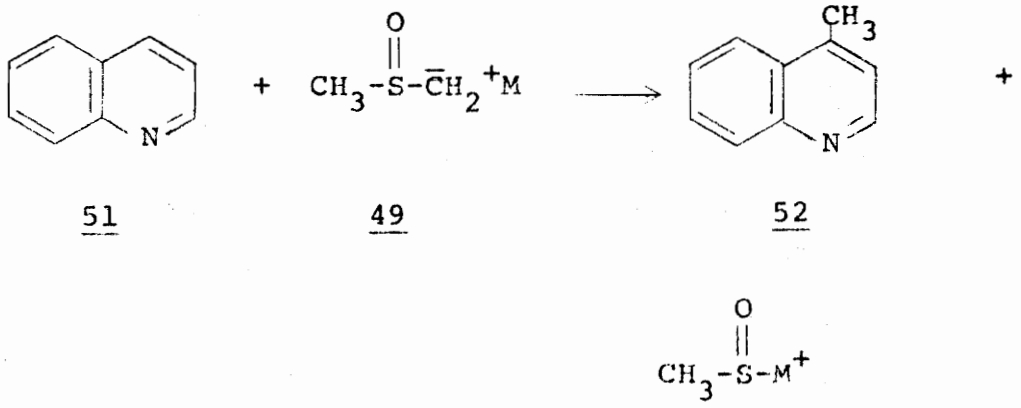
(7)

48 49 50

which subsequently underwent attack by the dimsyl anion (49) was thought to be involved; however, more recently dimethyl sulfoxide itself has been shown to react with benzynes.[21,22] Little information has been reported about the mechanism of methylsulfinyl carbanion reactions with aliphatic organic

halides, for example, the reaction with benzylchloride has been reported to afford 42% of trans-stilbene and a mixture of unidentified sulfones.[23] The mechanism was also obscure for the reaction of sodio or lithio carbanion 48, at 50°, with n-pentyl bromide to yield a mixture of methylpentylsulfoxide and methylhexylsulfoxide, whereas potassio carbanion 49 (M=K) at 0° affords only methylpentylsulfoxide.[24]

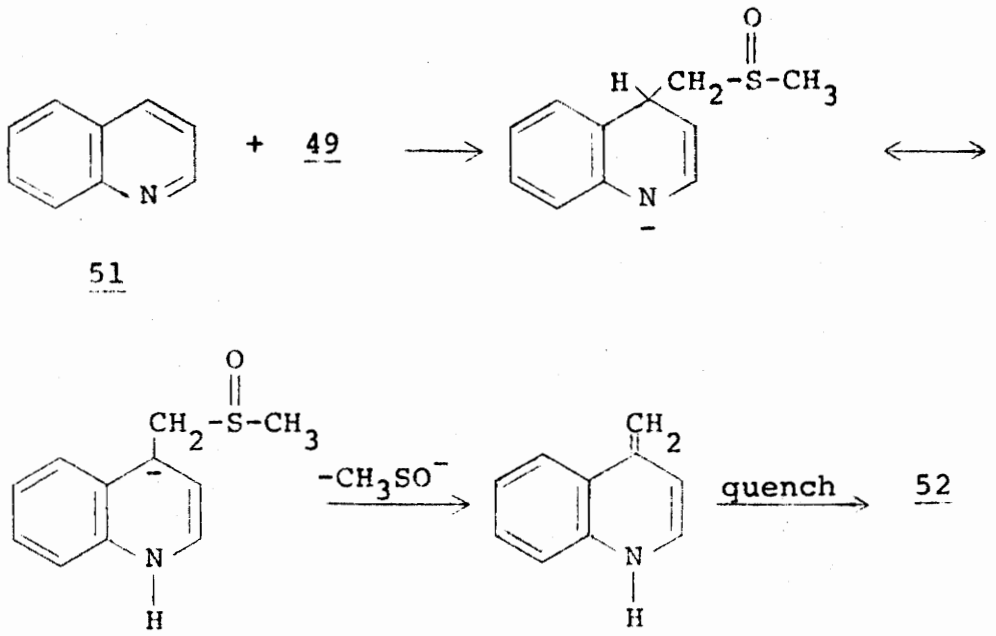
Russell and Weiner [20] found that heteroaromatic compounds such as quinoline (51) underwent methylation when treated with methylsulfinyl carbanion (eq 8). The 4-substituted product 52 was in agreement with the calculated



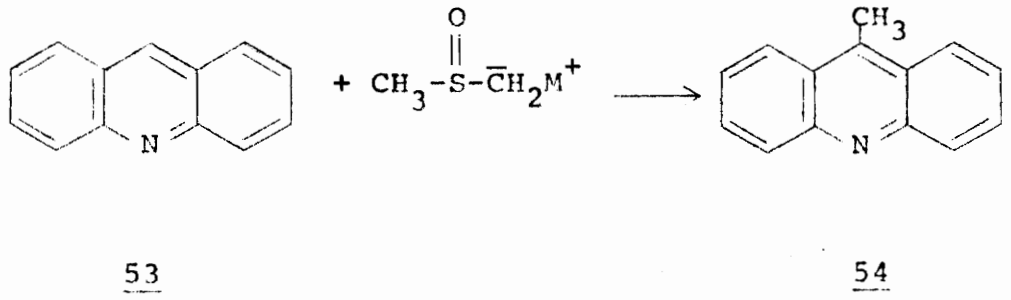
51 49 52

charge density of quinoline (51).[25] The proposed mechanism for the methylation of quinoline (Scheme I) was in agreement with the products obtained although no intermediates were detected or isolated. They also found that several other aromatic azines such as acridine 53 and isoquinoline formed the corresponding 9-methylacridine (54) (eq 9) and

Scheme I



l-methyl-isoquinoline, respectively, in good yields.



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As shown in the foregoing review, most halogenated heteroaromatic azines underwent nucleophilic displacement reactions with a variety of anions. However, in many of

these reactions, such as those involving treatment of 2-chloroquinoline with dianions in liquid ammonia, the mechanism has not been established. In view of this, a study was undertaken to examine the mechanism of chloride ion displacement from several halogenated heteroaromatic azines by dialkali salts of benzoylacetone, disodio salts of certain 2-hydroxy-4-methylpyrimidines, and the methylsulfinyl carbanion.

II. DISCUSSION OF RESULTS

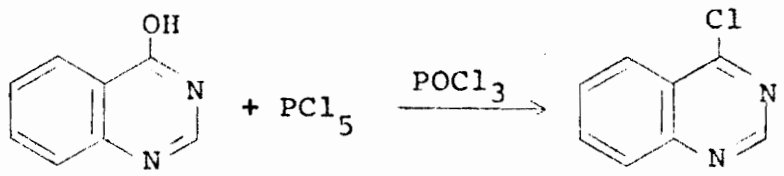
A. Displacement Reactions of 4-Chloroquinazoline with Alkali Dianions.

The choice of reactants for these experiments was based on several prime considerations. First of all, comparison of the relative reactivities of a series of halogenated heterocycles toward the negative nucleophile, ethoxide ion (Table I), indicated that 4-chloroquinazoline (36) might be reactive toward disodiobenzoylacetone. Secondly, the method of formation and reactions of disodiobenzoylacetone (44) with various other electrophilic reagents has been well established. Finally, displacement of halogen from quinazoline 36 has been demonstrated on numerous occasions. Therefore, it seemed likely that dianion 44 which has been shown to react rapidly and selectively at its terminal carbanion site with numerous electrophilic reagents[17,26,27] would take part in the desired displacement reaction.

In order to obtain 4-chloroquinazoline (36), it was necessary to chlorinate 4-(3H)-quinazolinone (55). Initial efforts were directed toward use of established procedures[28] involving treatment of 4-(3H)-quinazolinone with a mixture of phosphorus pentachloride and phosphorus oxychloride. The

yield of chlorinated product was 62% when the reaction mixture was refluxed for 2 hours.

It was found that the yield of 36 could be increased to 73-75% by allowing the reaction to proceed under ultraviolet radiation (see Experimental), which indicated radical character may be involved in the reaction intermediate. However, when the reaction was conducted with a

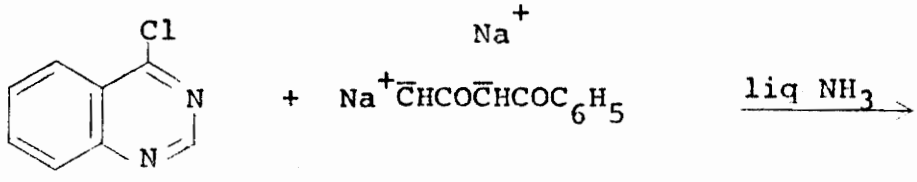


55 36

known radical initiator, benzoyl peroxide, the yield was not increased (60%). It was observed that halogenated quinazoline 36 decomposed autocatalytically within 4-7 days on exposure to moisture. However, if a freshly prepared sample was stored in a desiccator over potassium hydroxide pellets shielded from light, it could be kept indefinitely. One such sample was stored under these conditions for over two years without decomposition, as was indicated by the melting point.

Benzoylacetone was converted into its disodio salt 44 by two molecular equivalents of sodium amide in liquid ammonia. Treatment of dianion 44 in this medium with an

ethereal solution of 4-chloroquinazoline (36) produced 1-phenyl-4(4-quinazolinyl)-1,3-butanedione (56) in 52% yield (eq 10).



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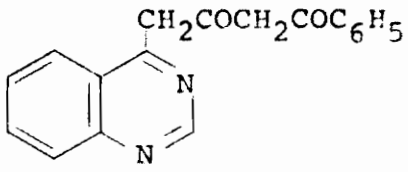


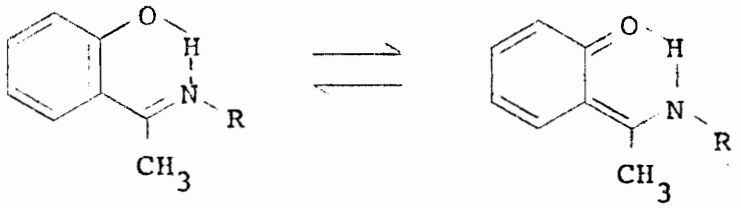
56

The structure of diketone 56 was established by elemental analysis and spectral data. The mass spectrum showed a molecular ion peak at m/e 290 (see Experimental). The infrared (ir) spectrum showed a strong, broad absorption at 1600 cm^{-1}, which was characteristic of enolized β-diketones.[29,30] The nuclear magnetic resonance (nmr) spectrum of 56 lent further support to the existence of this compound as a mixture of enol forms. The spectrum in deuteriochloroform had singlets at 19.12, 14.68, 6.68, 6.58, 6.36, and 4.50 ppm, and a multiplet centered at 8.28 ppm. Previous nmr studies on related compounds aided in peak assignments.

Dudek and Dudek[31] were able to make a detailed assignment of proton resonances in the nmr spectrum of o-(acetoacetyl) phenol (57) and o-hydroxy(β-methylamino)acrylophenone (58) using N^{15} labeling in the latter case (Table II). The nmr spectrum of a freshly prepared deuteriochloroform solution of phenol 57 showed the presence of only the doubly hydrogen-bonded enol form, but on standing several hours, extraneous peaks appeared due to equilibration involving keto form 57a.

The structure of o-hydroxy(β-methylamino)acrylophenone (58) was confirmed by synthesizing the N^{15} analog and observing the coupling constants of N^{15} with H, CH_3, and vinyl protons, respectively. When compared with the resonance of normal, single hydrogen bonds, the NH signal of the Schiff base 58 with double hydrogen bridges was shifted upfield and the phenolic hydrogen resonance was shifted downfield.

Dudek and Dudek[32] also found the imine-amine equilibrium (eq 11) of o-hydroxyacetophenone imines 59a,b was



(11)

59a 59b

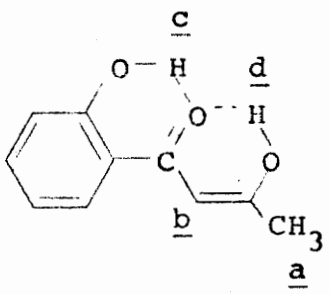
TABLE II

NMR SPECTRAL DATA FOR TAUTOMERS OF

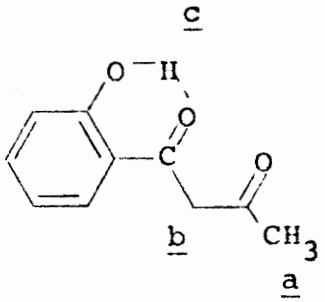
o-ACETOACETYLPHENOL AND

o-HYDROXY(β-METHYLAMINO)-

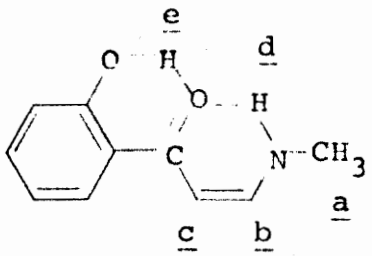
ACRYLOPHENONE-N[15]



57



57a

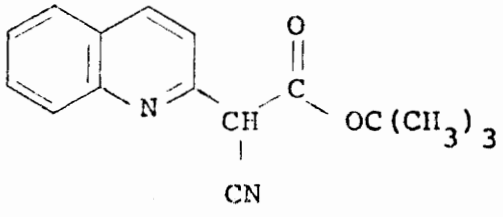


58

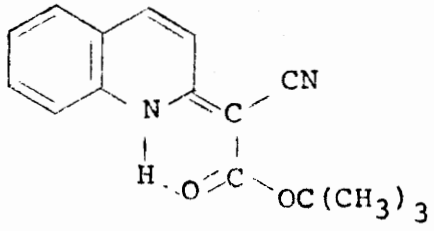
Proton	Peak,ppm	Proton	Peak,ppm	Proton	Peak,ppm
a.	2.12	a.	2.29	a.	3.02
b.	6.16	b.	4.09	b.	5.61
c.	13.65	c.	13.65	c.	Aromatic
d.	14.95				Region
				d.	9.61
				e.	13.52

shifted toward the non-aromatic tautomer 59b in deuteriochloroform. It was also found that the OH peak of 59a was 2 to 3 ppm downfield from the NH proton of 59b.

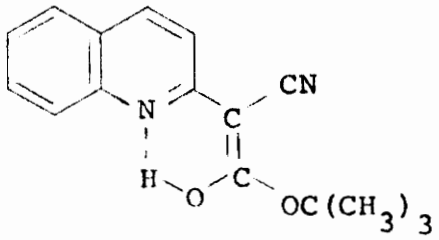
Borror and Haebere[33] demonstrated that 2-substituted quinolines would form tautomeric structures involving the ring nitrogen when the 2-substituents contained electron-withdrawing groups. On the basis of the nmr spectrum of t-butylcyane-2(1H)-quinolylideneacetate (60a), it was established that this compound did not exist in deuteriochloroform as the aromatic structure 60a but in tautomeric structures 60b and/or 60c. The 2-substituted quinoline showed a nmr signal (nine protons) attributed to the methyl groups at 1.60 ppm, a complex set of signals from 7.1 to



60a



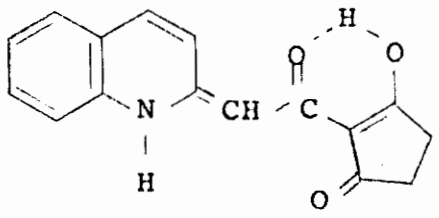
60b



60c

7.8 due to six protons attached to the unsaturated carbons of the ring, and a broad peak at 13.3 ppm due to a single proton which could not be assigned to a proton in structure 60a. However, this nmr spectrum was consistent with tautomeric structures 60b,c.

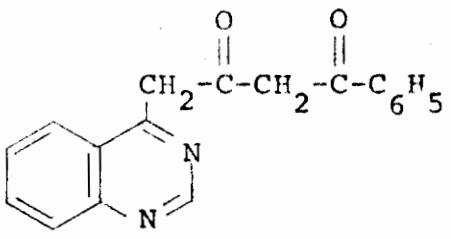
Similarly, Baty, Jones, and Moore[34] have shown that 2-(2-quinolyl)cyclopentanediones such as 61 exist predominantly as the non-aromatic tautomers.



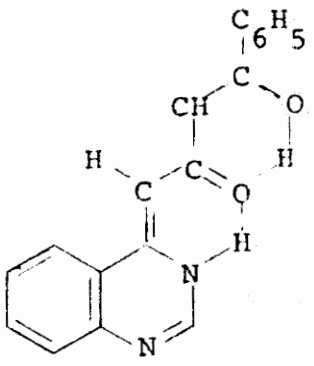
61

By applying the results of the above studies, the proton resonances of 1-phenyl-4(4-quinazolinyl)-1,3-butanedione (56a) were assigned as follows: the singlets at 19.12 and 14.68 ppm were assigned to OH and NH respectively, since they disappear rapidly on addition of D_2O to the nmr sample. Singlets at 6.68, 6.58, and 6.36 ppm were attributed to vinyl protons. Methylene proton absorption was assigned to the singlet at 4.50 ppm, which was also shown to exchange (peak area decreased by 50%) with D_2O. The ratio of the integrated intensity of the aromatic absorption, which was

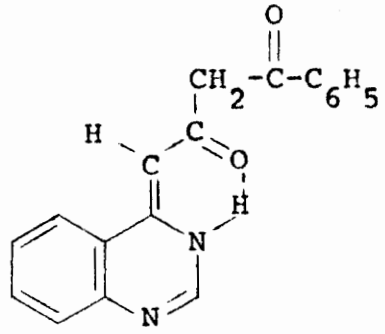
centered at 8.28 ppm to the total intensities of all other peaks indicated that absorption for a vinyl proton, possibly the one nearest the aromatic ring system,[32] was also located in this region. These peak assignments were attributed to tautomeric structures such as doubly hydrogen-bonded 56b and 56c. The ratio of the area of methylene protons expected (4H) for the totally ketonic tautomer 56a to the area obtained (0.5H) indicated that diketone 56 existed largely as a mixture of the two enol forms 56a and 56b in deuteriochloroform. The appearance of only one type of the methylene proton absorption at 4.50 ppm, which was characteristic of the methylene protons of simple β-diketones, indicated that this absorption arose from 56c and did not arise from methylene protons adjacent to the heterocyclic ring in tautomer 56b.



56a

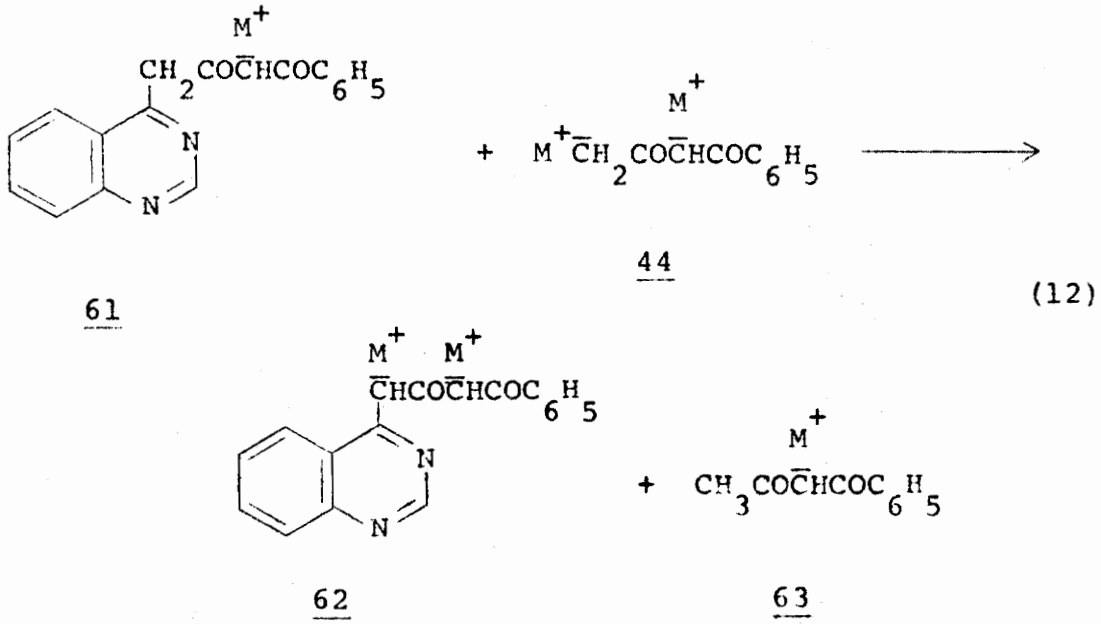


56b



56c

Under the conditions initially used in the reaction of disodiobenzoylacetone (44) with 4-chloroquinazoline (36) (1:1 molar ratio) a methylene proton of initially formed intermediate 61 could be abstracted by the benzoylacetone dianion 44 remaining in solution to form a new dianion 62 and a monoanion 63 (eq 12).[35] Since monoanion 63 would not

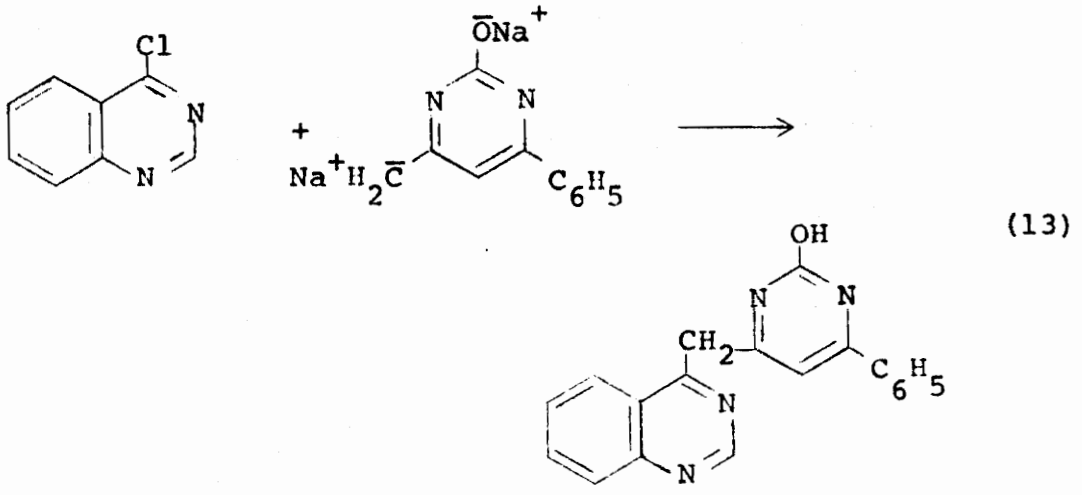


61 44 62 63 (12)

be expected to react with 4-chloroquinazoline, it seemed possible that the yield of diketone 56 could be increased by using a 2:1 molar ratio of dianion to halogen heterocycle. In this instance, the excess dianion could effect ionization of 63.

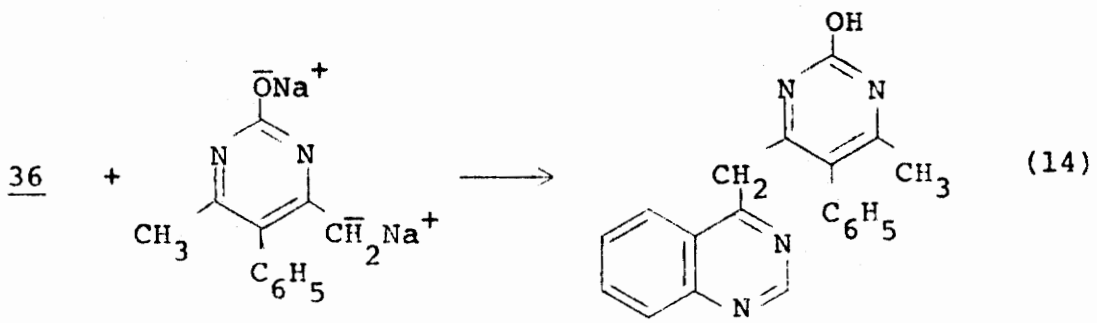
When a 2:1 ratio of disodiobenzoylacetone (44) to 4-chloroquinazoline (36) was used, the overall yield of diketone 56 was increased to 60%. On the other hand, a molar ratio of dilithiobenzoylacetone 49 to 36 in a 2:1 ratio gave a slightly lower yield of diketone 56 (51%) than the disodio salt even under a nitrogen atmosphere.

Since the dianion (46) of 2-hydroxy-4-methyl-6-phenylpyrimidine (64) has been shown to displace halogen from 2-chloroquinoline (33) in low yield,[18] it was of interest to examine the reaction of this dianion with 4-chloroquinazoline (36). Addition of pyrimidine 64 to a solution of sodium amide in liquid ammonia formed the disodio salt 46,[18] which was treated with 4-chloroquinazoline (36) in a 1:1 molar ratio to give 2-hydroxy-4(4-quinazolinylmethyl)-6-phenylpyrimidine (65) in 45% yield (eq 13). Similarly, disodio salt 66 which was prepared from 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine (67) by means of sodium amide in liquid ammonia[18] reacted with 4-chloroquinazoline (36) to give 2-hydroxy-4(4-quinazolinylmethyl)-6-methyl-5-phenylpyrimidine



(13)

(68) in 36% yield (eq 14).

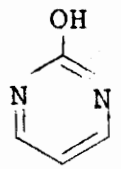


(14)

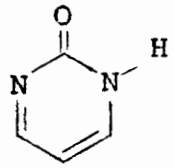
66 68

Structural assignments for 65 and 68 were based on elemental analyses and spectral evidence. Molecular ion peaks at m/e were 314 and 328 for 65 and 68 respectively (see Experimental). The ir spectra of both 65 and 68 showed absorption at 1640 cm^{-1} attributable to the carbonyl group of the amide-like tautomers of 2-hydroxypyrimidines.

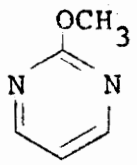
Published nmr data for certain simple 2-hydroxypyrimidines assisted in making structural and nmr spectral assignments for pyrimidines 65 and 68. In the nmr spectrum of 2-hydroxypyrimidine (69) resonance for the proton at the 5-position occurred 0.67 ppm toward higher field than that of fully aromatic 2-methoxypyrimidine (71) (6.40 vs. 7.07 δ), which indicated that hydroxypyrimidine 69 was actually 1,2-dihydro-2-oxopyrimidine (70).[36] It has also been shown[37] that if an unsymmetrical pyrimidine such as 4-ethoxy-1-hydro-2-oxopyrimidine existed in two tautomeric forms a and b, in



69

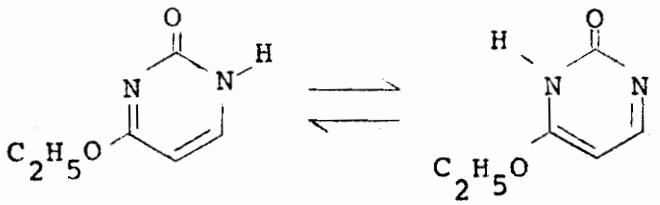


70



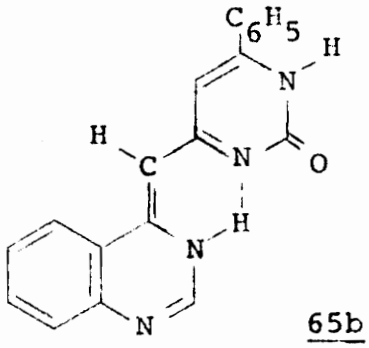
71

non-aqueous solution, the major structure appeared to be a.



a b

The nmr spectrum of quinazolinylpyrimidine 65 in trifluoroacetic acid had singlets at 6.60 (1H), 6.90 (1H), and 8.90 (1H) ppm along with an aromatic multiplet centered at 7.96 ppm (9H). On the basis of the nmr spectrum of 2-hydroxy-4-methyl-6-phenylpyrimidine (CF_3COOH) in which the 5-proton appeared at 6.8 ppm, and the spectrum of 4-chloroquinazoline (DMSO-d_6) where resonance for the 2-proton was found at 8.8 ppm, the peaks at 6.90 and 8.90 were assigned to the hydrogens at carbon-5 of the pyrimidine and carbon-2 of the quinazoline ring, respectively. The multiplet at 8.90 ppm was attributed to the remaining aromatic protons of the phenyl substituent and the carboaromatic ring of the quinazoline nucleus. The absence of a 2-proton absorption for the methylene group bridging the connecting heterocyclic rings (cf. structure 65a) and the presence of vinyl absorption at 6.60 ppm presented compelling evidence that the true structure for this compound was that illustrated by structural formula 65b. The absence of NH absorption from the spectrum was due to rapid exchange with the solvent.

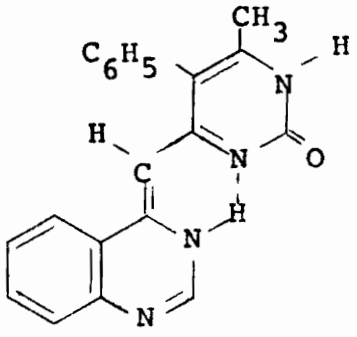


65b

The nmr spectrum of pyrimidine 68a, which had singlets at 2.39 (3H), 6.31 (1H), and 9.24 (1H), accompanied by a multiplet at 7.63 ppm (9H), indicated that this compound existed entirely in tautomeric form 68b. The peak at 2.39 ppm was assigned to the 6-methyl group of the pyrimidine ring, the absorption at 6.31 ppm to the vinyl proton on the carbon bridging the rings, the singlet at 9.24 ppm to the 2-proton of the quinazoline ring, and the multiplet at 7.63 ppm to the remaining aromatic protons of the 5-phenyl substituent and the quinazoline ring. The absence of methylene proton absorption was consistent with structural assignment 68b rather than the alternate tautomer 68a.

Having established the structures of pyrimidines 65 and 68, the possibility of increasing the yields was studied. Reaction of the disodio salt of pyrimidine 64 in a 2:1 molar ratio with 4-chloroquinazoline (36), under a nitrogen atmosphere, afforded pyrimidine 65 in 55% yield. Similarly, dianion 66 displaced halogen from 4-chloroquinazoline (36) to afford pyrimidine 68 in only 30% yield. The fact that the yield of 68 was not increased may be due to the low solubility of the disodio salt in liquid ammonia.

A summary of the results of halogen displacement from 4-chloroquinazoline (36) with disodiobenzoylacetone (44) and the disodiopyrimidine salts 46 and 66 is given in



68

Table III. The nucleophilic displacement reactions with these dianions were believed, as no evidence was found to the contrary, to proceed by way of the sequence shown in Scheme II. The first step involved attack by the dianion at the halogenated carbon to form complex 72. The negative charge was stabilized by several resonance structures such as 72a and 72b. In the next step, the molecule rearomatized on loss of chloride ion to give 4-substituted quinazoline which then underwent a prototropic rearrangement to give the observed compound 65.*

An alternate mechanism involving a heteroaryne intermediate can be eliminated by theoretical evidence based on

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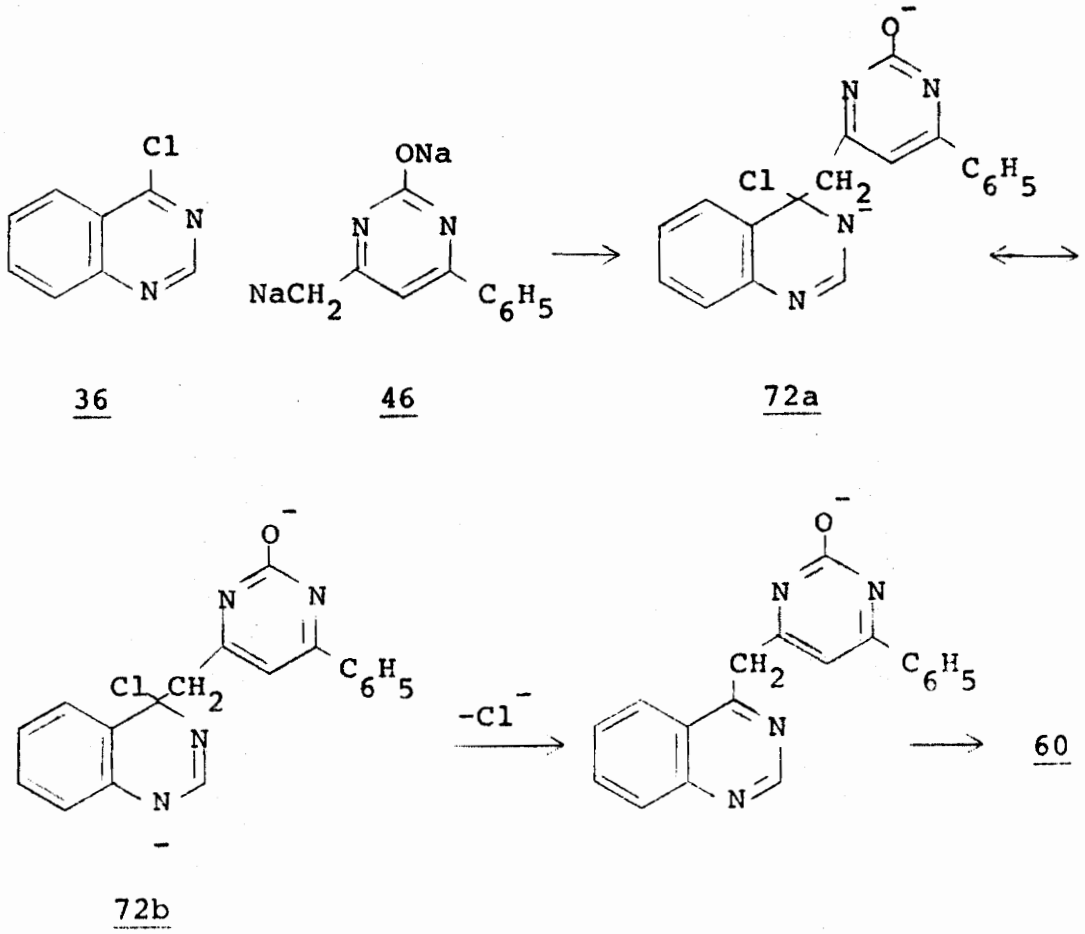
*It is also possible that the intermediate 72a could undergo the shift of a proton from the methylene group to the negative ring nitrogen to give a carbanionic species, elimination of chloride from which could give compound 65b directly.

TABLE III

SUMMARY OF DISPLACEMENT REACTIONS OF 4-CHLOROQUINAZOLINE (36) WITH DIANIONS

Dianion	Ratio, Dianion to 36	Atmosphere	Product	Yield, %
44	1:1	Air	diketone 56	52
44	2:1	N_2	diketone 56	60
57	2:1	N_2	diketone 56	51
46	1:1	Air	pyrimidine 65	45
46	2:1	N_2	pyrimidine 65	55
66	1:1	Air	pyrimidine 68	36
66	2:1	N_2	pyrimidine 68	30

Scheme II



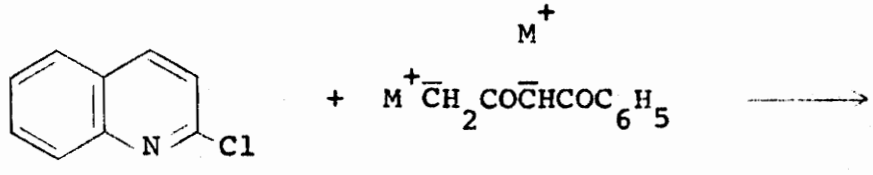
36 46 72a 72b 60

the work of Hoffmann and co-workers.[38] They carried out EHT calculations for several heteroaryne intermediates which indicated that an aryne produced from 4-chloroquinazoline (36) would be unstable and unlikely to form.

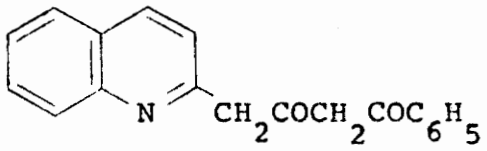
B. Displacement Reactions of 2-Chloroquinoline with Alkali Dianions.

Having found that displacement reactions of 4-chloroquinazoline (36) with disodiobenzoylacetone (44) and the pyrimidine dianions 46 and 66 proceeded relatively well, then attention was next focused on the reaction of 44 with 2-chloroquinoline. As stated previously, displacement of chlorine from 2-chloroquinoline (33) with disodiobenzoylacetone (44) has been demonstrated; however, the yield of the expected quinolyldiketone 45 was quite low and no attempts had been made to assay the total reaction mixture for other products or to determine the major fate of the starting materials.

Treatment of a suspension of disodiobenzoylacetone in liquid ammonia with an ethereal solution of 2-chloroquinoline (33) (using a 1:1 molar ratio of dianion to 2-chloroquinoline) for 1 hour, followed by neutralization and isolation afforded only 3.75% of 1-phenyl-4-(2-quinolyl)-1,3-butanedione (45) (eq 15). The melting point and spectral data of this compound were consistent with those reported in the literature.[17] Analysis of the total crude product mixture by thin layer chromatography (tlc) and gas liquid partition chromatography (glpc) showed the presence of unreacted benzoylacetone, 2-chloroquinoline, and diketone 45; no other products could be detected. Repeated attempts



33 44 (15)

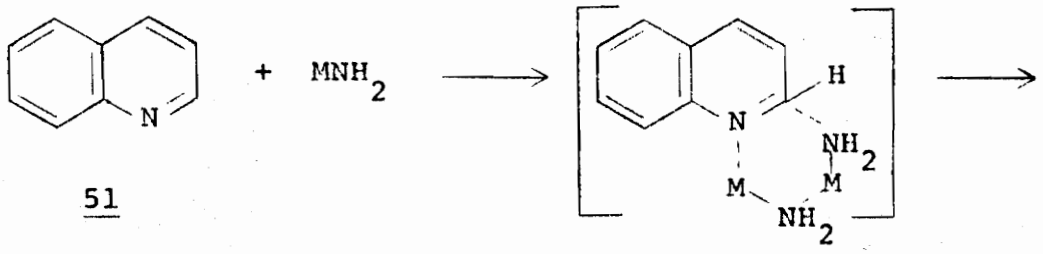


45

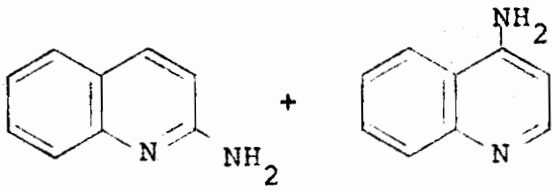
to increase the yield of 45 using the same procedure failed. Since it might be expected, on the basis of previous studies,[13] that 2-chloroquinoline would be less reactive toward nucleophilic substitution than 4-chloroquinazoline it appeared, therefore, that disodiobenzoylacetone was insufficiently reactive at liquid ammonia temperature (-33°) to effect the desired substitution in the case of 2-chloroquinoline.

It has been shown that coordination of the ring nitrogen of aromatic azines with certain metal cations can increase the susceptibility of the heterocyclic ring toward nucleophilic displacement reactions.[1] The effect of cationization is to delocalize the π-electron cloud, thereby making the molecule more susceptible to nucleophilic attack. This

increased reactivity has been attributed to simultaneous or prior coordination of the cationic portion of the nucleophile with the ring nitrogen (cationization) resulting in a cyclic transition state. Such a cyclic transition state has been used to explain the results obtained from the amination of quinoline (51) with metal amides in liquid ammonia[30] (eq 16). Treatment of quinoline with potassium



51 75 (16)



73 74

amide (M=K) in liquid ammonia produced a mixture of 2- and 4-substituted products 73 and 74. Barium amide, on the other hand, was thought to react exclusively by way of cyclic transition state 75 (M=1/2Ba) since it afforded only 2-amino quinoline (73); experimental evidence indicated a heteroaryne was not involved.[39] It has also been observed

that in the reaction of lithium alkyls and aryls with pyridines and quinolines, 2-substitution occurred without detectable 4-substitution.[40]

From the above examples of the reactions of quinoline with metal amide, which showed the influence of cationization of the ring nitrogen with a metal ion in heteroaromatic nucleophilic substitution, it seemed possible that the superior coordinating power of lithium compared to sodium[41] could enable dilithiobenzoylacetone to cationize with 2-chloroquinoline to a larger extent than the disodio salt, thereby facilitating halogen displacement.

Treatment of benzoylacetone with two molecular equivalents of lithium amide in liquid ammonia to produce dilithiobenzoylacetone (49)[18] followed by addition of 2-chloroquinoline (33) gave the expected diketone 45 in 14.2% yield, after 1 hour, along with unreacted starting materials. Even though this yield was low, it represented a four-fold increase over the yield obtained with disodio salt 44.

In view of the increased product yield with dilithiobenzoylacetone (49), it was of interest to determine if the yields could be further increased by using very anhydrous conditions. To this end, the reaction vessel was flame dried and purged with dry nitrogen for 12 hours. The dilithio salt 49 was then prepared, under a nitrogen atmosphere, and an ether solution containing a molecular

equivalent of 2-chloroquinoline (33) was added. The reaction mixture was stirred for 1 hour under nitrogen atmosphere before being quenched with solid ammonium chloride. From this reaction, the expected diketone 45 was obtained in 43% yield. Increasing the reaction time under these same conditions from 1 hour to 6.75 hours did not improve the yield. However, using the same reaction conditions with a 2:1 molar ratio of dilithio salt 45 to 2-chloroquinoline (33) gave a 71.5% yield of diketone 45 (based on 2-chloroquinoline) after a 1 hour reaction period. These experiments with dilithiobenzoylacetone were quite interesting since they illustrated that lithium indeed could increase the ease of substitution and also showed an unusual dependence of the success of the reaction on exclusion of atmospheric oxygen.* This second point raised the possibility that reactions of dilithiobenzoylacetone with 2-chloroquinoline might involve radical intermediates, a pathway which is rarely observed with 1,3-dianions of this type.[42]

While this work was in progress, Bunnett and Kim[43,44] demonstrated the existence of radicals in nucleophilic substitution involving halogenated carboaromatics. They

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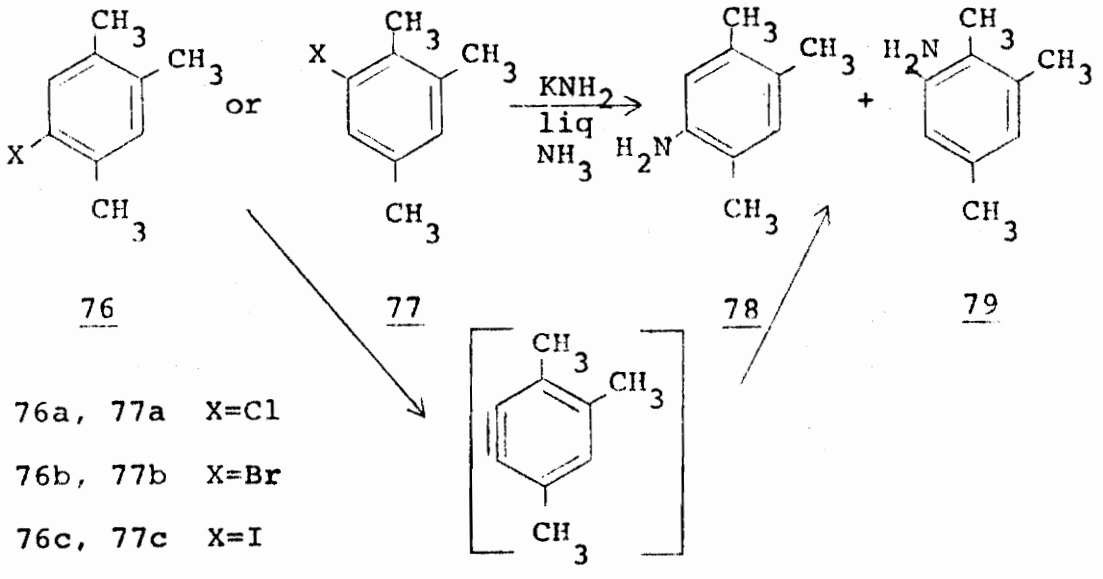
*This precaution was hardly ever necessary in other reactions of the benzoylacetone dianion; we have shown that the reaction of dilithiobenzoylacetone with 4-chloroquinazoline does not proceed any more satisfactorily under nitrogen than the reaction of the disodio salt when an inert atmosphere was not employed.

found that the amination of chloro- and bromopseudocumenes 76a,b and 77a,b with potassium amide in liquid ammonia produced 6- and 5-aminopseudocumene (79 and 78 respectively) in a 1.5:1 ratio. Neither the identity of the halogen nor its location affected the product ratio, which would be expected if the intermediate in each case were the same aryne 80. However, when the reaction was performed using iodo compounds 76c and 77c, the ratios of 79:78 were 0.63 and 5.86 respectively, and pseudocumene, a by-product, was produced in 5 to 10% yields. This deviation from the expected aryne ratio and the increase in the amount of direct



substituted product indicated another mechanism was operating and that it was of a non-rearranging type.

Evidence obtained from additional reactions indicated the non-rearranging mechanism to be radical in character. When the reaction of 5- and 6-iodopseudocumene (76c and 77c) with potassium amide was carried out in the presence of tetraphenylhydrazine, a radical trapping agent, the ratio of 6- and 5-aminopseudocumene reverted to that expected if an aryne intermediate were involved. Having shown the product ratio was changed by a radical-trapping agent, Kim and Bunnett turned their attention to the effect of an added electron donor. When potassium metal, as a source of solvated electrons, was used along with potassium amide, the aryne mechanism was often totally eclipsed and substitution occurred with very little rearrangement. Thus, reaction of 76c with potassium amide plus potassium metal in liquid ammonia afforded a 50% yield of 5-aminopseudocumene (78), and a 40% yield of pseudocumene, but in contrast to the reaction in the absence of potassium metal, no 6-aminopseudocumene (79) was detected. Similarly, 6-iodopseudocumene (77c) afforded 6-aminopseudocumene (54% yield), pseudocumene (30% yield) and only a trace of 5-aminopseudocumene. Based on these results, Kim and Bunnett proposed the mechanism given in Scheme III.

Scheme III

$$e^{-}NH_3 + ArX \longrightarrow [ArX]^{\cdot-} \quad (1)$$

$$[ArX]^{\cdot-} \longrightarrow Ar^{\cdot} + X^{-} \quad (2)$$

$$Ar^{\cdot} + NH_2^{-} \longrightarrow [ArNH_2]^{\cdot-} \quad (3)$$

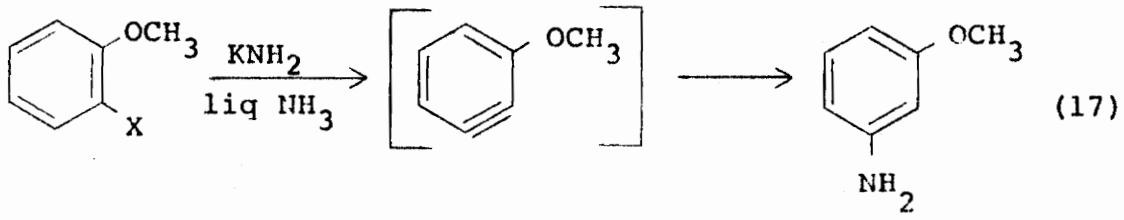
$$[ArNH_2]^{\cdot-} + ArX \longrightarrow [ArX]^{\cdot-} + ArNH_2 \quad (4)$$

$$Ar^{\cdot} + NH_3 \longrightarrow ArH + NH_2 \quad (5)$$

termination steps (6)

In the first step, a radical anion was formed by electron donation from a solvated electron to the aryl halide, which quickly formed an aryl radical and halide ion (Step 2). The aryl radical then reacts with amide ion to form an arylamine radical anion (Step 3) which transfers an electron to the aryl halide (Step 4) to generate the radical anion of the halide and the aminated product. Another reaction path for the aryl radical generated in Step 2 was abstraction of a proton from the solvent to generate ArH (Step 5). The radical formed may continue the cycle, Steps 2-4, or become involved in termination, Step 6. These steps have been demonstrated elsewhere.[45-49]

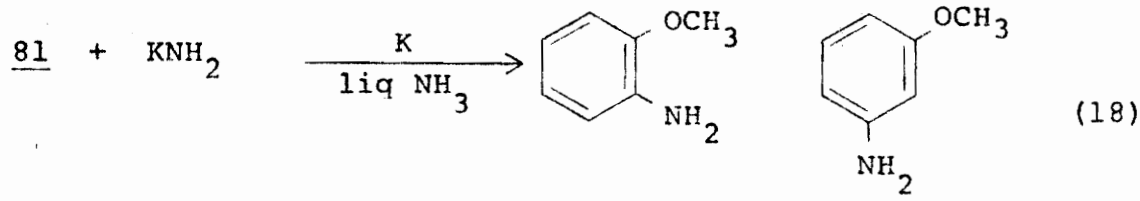
Further support for this mechanism was obtained from the reaction of o-haloanisoles 81 with potassium amide



(17)

81 82

(eq 17). The reaction afforded the products predicted from an aryne intermediate, m-anisidine (82). However, when a catalytic amount of potassium metal per mole of 81 was used, o-anisidine 83 (eq 18) was formed in preference to or in amounts equivalent to m-anisidine. The yields of o-anisidine



(18)

83 82

(83), based on the amount of potassium used, ranged from 175 to 340%, which indicated a definite catalytic effect.

Based on the above work of Kim and Bunnett, it was suspected that the reaction of dilithiobenzoylacetone (49) with 2-chloroquinoline (33) might be taking place through a similar radical chain process, although this type of

reaction has not been observed in azine nucleophilic substitution. This hypothesis was supported by the adverse affect of oxygen, which could be trapping one of the radical intermediates necessary for propagation of the chain.

Although Bunnett and Kim have observed that the reaction of pseudocumene with alkali amides via the radical nucleophilic substitution (SRN1) pathway could be facilitated by addition of alkali metal, it was found that in the reaction of 2-chloroquinoline with dilithiobenzoylacetone, the yield of diketone 45 was slightly decreased on addition of excess lithium to the reaction mixture. When 2-chloroquinoline (33) was added to dilithiobenzoylacetone (49) in a 1:2 molar ratio, immediately followed by 0.25 equivalent (based on 2-chloroquinoline) of lithium metal, a 56% yield of diketone (45) was isolated along with 30% of recovered starting benzoylacetone. Varying the reaction conditions by using 1.0 equivalent of lithium metal based on 2-chloroquinoline in addition to dilithio salt 49, afforded diketone 45 in 36.2% yield; 43.3% of benzoylacetone was recovered. When the reaction was carried out using 1.0 equivalent of lithium metal and the stirred reaction mixture irradiated with ultraviolet light for 1 hour, a 27.8% yield of diketone 45 was isolated from the reaction mixture as well as considerable uncharacterized decomposed material.

The reaction was next carried out using dilithio salt 49 and 2-chloroquinoline (33) in a 2:1 molar ratio, along with tetraphenylhydrazine (0.08:1 molar ratio with 2-chloroquinoline) under a nitrogen atmosphere. After 1 hour, the reaction was quenched and the total ether soluble mixture analyzed by glpc to reveal the presence of quinoline (17% yield, based on 2-chloroquinoline), benzoylacetone (29% recovery), 2-chloroquinoline (10% recovery), and tetraphenylhydrazine (20% recovery). From the reaction mixture was isolated only a 3.5% yield of diketone 45. Although the reaction pathway leading to the formation of quinoline was not clear, there could be no doubt that tetraphenylhydrazine markedly inhibited the substitution reaction.

It was also observed that when the reaction of 2-chloroquinoline with dilithiobenzoylacetone was carried out in the cavity of an ESR spectromater at -70°. a poorly resolved signal was observed, which indicated the formation of a paramagnetic intermediate or intermediates.

Since high yields of diketone 45 had been obtained using dilithiobenzoylacetone and low yields with the disodio salt, it was of interest to investigate the reaction of 2-chloroquinoline with the dipotassio salt of benzoylacetone.

Reaction of a molecular equivalent of 2-chloroquinoline (33) with 2 molecular equivalents of dipotassiobenzoylacetone prepared by reaction of potassium amide in liquid ammonia

under a nitrogen atmosphere for 1 hour, gave the expected substituted product, diketone 45 in 2.2% yield. Unreacted benzoylacetone and 2-chloroquinoline were shown to be present in the crude reaction mixture along with some quinoline. Treatment of a molecular equivalent of 2-chloroquinoline (33) with 2 molecular equivalents of dipotassiobenzoylacetone in the presence of 0.25 molecular equivalent of added potassium metal increased the yield of diketone 45 to 16.3%. Interestingly, the yield of quinoline produced also increased to 26%, based on 2-chloroquinoline. In a similar reaction, addition of 2.5 molecular equivalents of potassium metal lowered the isolated yield of diketone 45 to 3.2% and the yield of quinoline to 3.2%. Apparently in this reaction the large excess of added metal served to decompose the products as a considerable amount of intractable solid was obtained, along with 45% recovered benzoylacetone. The results of these three experiments and the other reactions of 2-chloroquinoline with benzoylacetone dianions are summarized in Table IV.

It appeared from the evidence presented above that the reaction of 2-chloroquinoline (33) with dilithiobenzoylacetone (49) proceeded by way of radical intermediates as was indicated by the increase in yield of diketone 45 when oxygen was excluded from the reaction mixture, the decrease in yield of diketone 45 when the radical trapping agent

TABLE IV

SUMMARY OF DISPLACEMENT REACTIONS ON 2-CHLOROQUINOLINE (33) WITH DIANIONS

Ratio (33) to Dianion	Metal, g-atom eq	Atmosphere	Product	Yield, %
1:1 (Na)	---	Air	diketone 45	3.75
1:2 (Li)	---	N_2	diketone 45	14.2
1:2 (Li)	---	N_2	diketone 45	71.5
1:2 (Li)	0.25	N_2	diketone 45	56
1:2 (Li)	1.0	N_2	diketone 45	36.2
1:2 (Li)[a]	1.0	N_2	diketone 45	27.8
1:2 (Li)[b]	---	N_2	diketone 45	3.5
			quinoline 51	17
1:2 (K)	---	N_2	diketone 45	2.2
			quinoline 51	0.5
1:2 (K)	0.25	N_2	diketone 45	16.3
			quinoline 51	26.5
1:2 (K)	2.5	N_2	diketone 45	3.2
			quinoline 51	3.2

[a]with ultraviolet irradiation

[b]with tetraphenylhydrazine

tetraphenylhydrazine was introduced in the reaction mixture, (Table IV), and the appearance of an ESR signal.

This information becomes intelligible in terms of a radical process (Scheme IV). The reaction sequence was analogous to that proposed by Bunnett for the SRN1 reaction and was similar to the mechanism advanced by Russell[47] and Kormblume[48] involving nucleophilic substitution involving p-nitrobenzyl halides.

Scheme IV

$$BenzoAc^{=} + ClQuin \longrightarrow [ClQuin]^{\cdot -} + [BenzoAc]^{\cdot -} \quad (1)$$

$$[ClQuin]^{\cdot -} \longrightarrow Quin^{\cdot} + Cl^{-} \quad (2)$$

$$Quin^{\cdot} + BenzoAc^{=} \longrightarrow [QuinBenzoAc]^{\cdot =} \quad (3)$$

$$[QuinBenzoAc]^{\cdot =} + ClQuin \longrightarrow QuinBenzoAc + [ClQuin]^{\cdot -} \quad (4)$$

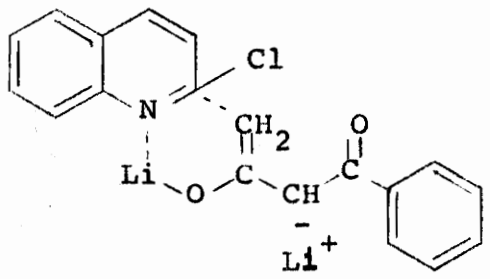
$$Quin^{\cdot} + NH_3 \longrightarrow Quinoline + {}^{\cdot}NH_2 \quad (5)$$

termination steps (6)

The initiation step involved electron transfer from benzoylacetone dianion to 2-chloroquinoline to form the radical anion of each. The chloroquinoline radical anion underwent carbon-chlorine bond cleavage to form a quinoline radical and chloride ion (Step 2). The quinoline radical combines with benzoylacetone dianion (Step 3) to form

quinolylbenzoylacetone radical dianion which then transferred an electron to chloroquinoline (Step 4) generating the chloroquinoline radical anion and quinolylbenzoylacetone. The quinoline radical generated in Step 2 can abstract a proton from ammonia or from another hydrogen atom donor to form quinoline and a radical. Benzoylacetone radical anion formed in Step 1 can become involved in termination steps or be neutralized when the reaction is quenched. Radical trapping agents such as oxygen or tetraphenylhydrazine can interupt the chain process by combining with one of several of the radical intermediates formed in the proposed propagating Steps 2-4.

The striking metallic cation effect observed on going from dipotassio- or disodiobenzoylacetone to the dilithio salt can also be rationalized in terms of this mechanism. In such a case, the better coordinating lithium could result in formation of a cyclic transition state such as 84 for initial transfer of an electron from dilithio salt[41] to 2-chloroquinoline, thereby facilitating the overall chain process. Coordination of lithium with the ring nitrogen and formation of a cyclic transition state should facilitate the electron transfer reaction, shown as Step 1 in Scheme IV, by making the ring system more positive, thus more receptive to addition of an electron and by bringing the electron donor into close proximity of the heterocyclic ring



84

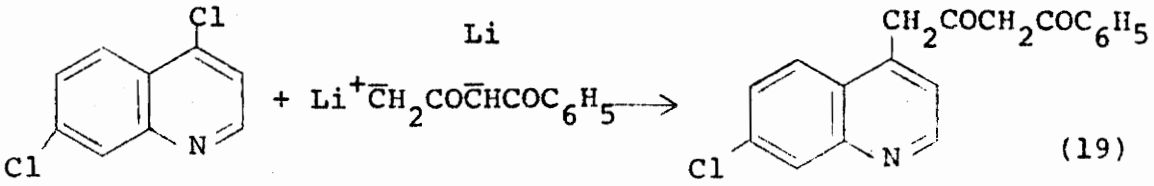
at the 2-position, a site of low electron density.

In contrast to the reaction of 4-chloroquinazoline with dialkali salts of benzoylacetone, which showed no significant evidence of a radical mechanism, the reaction of dilithiobenzoylacetone with 2-chloroquinoline appeared to be largely radical in character. Such a mechanism has not previously been reported for heteroaromatic nucleophilic substitution.

In order to obtain further information on the effect of the structure of the heterocycle on displacement reactions involving dialkali salts of benzoylacetone, three other chlorinated heterocycles were examined as substrates for these reactions.

Reaction of 4,7-dichloroquinoline (85) with dilithiobenzoylacetone (49) in a 2:1 molar ratio under nitrogen

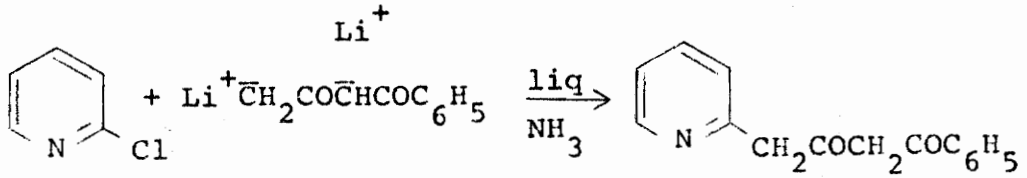
atmosphere for 1 hour failed to give any isolable amount of the expected diketone 86 (eq 19). Benzoylacetone and 4,7-dichloroquinoline were recovered in yields of 75% and 85% respectively.



(19)

85 49 86

Treatment of 2-chloropyridine (32) under various reaction conditions with dilithiobenzoylacetone alone (eq 20) or in the presence of added lithium metal (1.0 and 2.5 molecular equivalents) resulted in recovery of benzoylacetone and no detectable amount of 87.



(20)

32 87

Reaction of 2-chloroquinoxaline (35) with both disodio- and dilithiobenzoylacetone afforded an insoluble solid with a wide melting point range. All attempts to purify the solid by crystallization failed.

The results obtained on treating 4,7-dichloroquinoline (85) with dilithiobenzoylacetone (49) indicated that simple coordination or cationization alone cannot be used to explain the good yields obtained from the reaction of 2-chloroquinoline (33) with the dilithio salt (49) and a cyclic transition state seemed to be required. For in the case of 4,7-dichloroquinoline, cationization of the ring nitrogen should proceed as well as in the 2-position; however, a cyclic transition state such as 84 would certainly be prevented by the relative positions of nitrogen and chlorine.

The failure of 2-chloropyridine (32) to undergo appreciable nucleophilic substitution with dilithiobenzoylacetone under a variety of conditions (see Experimental) could be due to its reluctance to accept an electron from the dilithio salt 49 even though a cyclic transition state such as 84 would be possible. It has been shown that pyridine underwent electrochemical reduction at a much more negative potential than quinoline[50] in the absence of cationizing reagents, and it would be expected that the order of ease of

reduction would not be reversed in the presence of coordinating metal ions. The detection of pyridine in these reactions indicated that the pyridine radical underwent hydrogen abstraction from the solvent at a rate comparable to or greater than reaction with dilithiobenzoylacetone, thereby limiting the yield of substituted product. Although 2-chloroquinoxaline could yield the required cyclic transition state and should be a better electron acceptor than quinoline,[50] when the compound was treated with dilithio- or disodiobenzoylacetone a product was obtained which appeared to be polymeric in nature, based on its insolubility and wide melting point range. Since the product was not characterized, little can be said about the reaction involved.

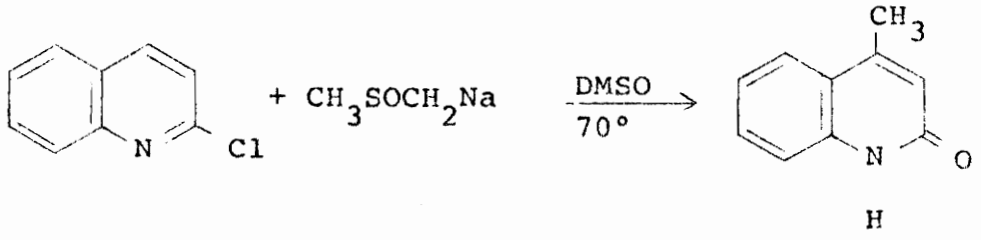
C. Displacement Reactions of 2-Chloroquinoline with Methylsulfinyl Carbanion.

In the preceding sections, the reactions of halogenated heterocycles with dianions in liquid ammonia was studied extensively. It seemed that a similar study with the monoanion of dimethylsulfoxide (methylsulfinyl carbanion) would be of interest since it has not been investigated and the methylsulfinyl carbanion can be generated in both dimethylsulfoxide (DMSO)[19] and in liquid ammonia.[51] To this end, the following experiments were carried out.

Methylsulfinyl carbanion was generated in DMSO with sodium hydride by treating 0.11 mol sodium hydride, under nitrogen atmosphere, with 100 ml of freshly distilled DMSO. The mixture was stirred at 70° until it became a pale yellow; this suspension was then treated with an ethereal solution of 0.02 mol of 2-chloroquinoline (33). After 4 hours, the reaction mixture was cooled to room temperature and quenched with water. Extraction of the water layer by methylene chloride and removal of the last traces of DMSO from the concentrated extracts under vacuum afforded, as the major product, 4-methylcarbostyryl (88) in 35.4% yield (based on 2-chloroquinoline). Comparison of the nmr and ir spectra and melting point with a known sample established the identity of this compound.

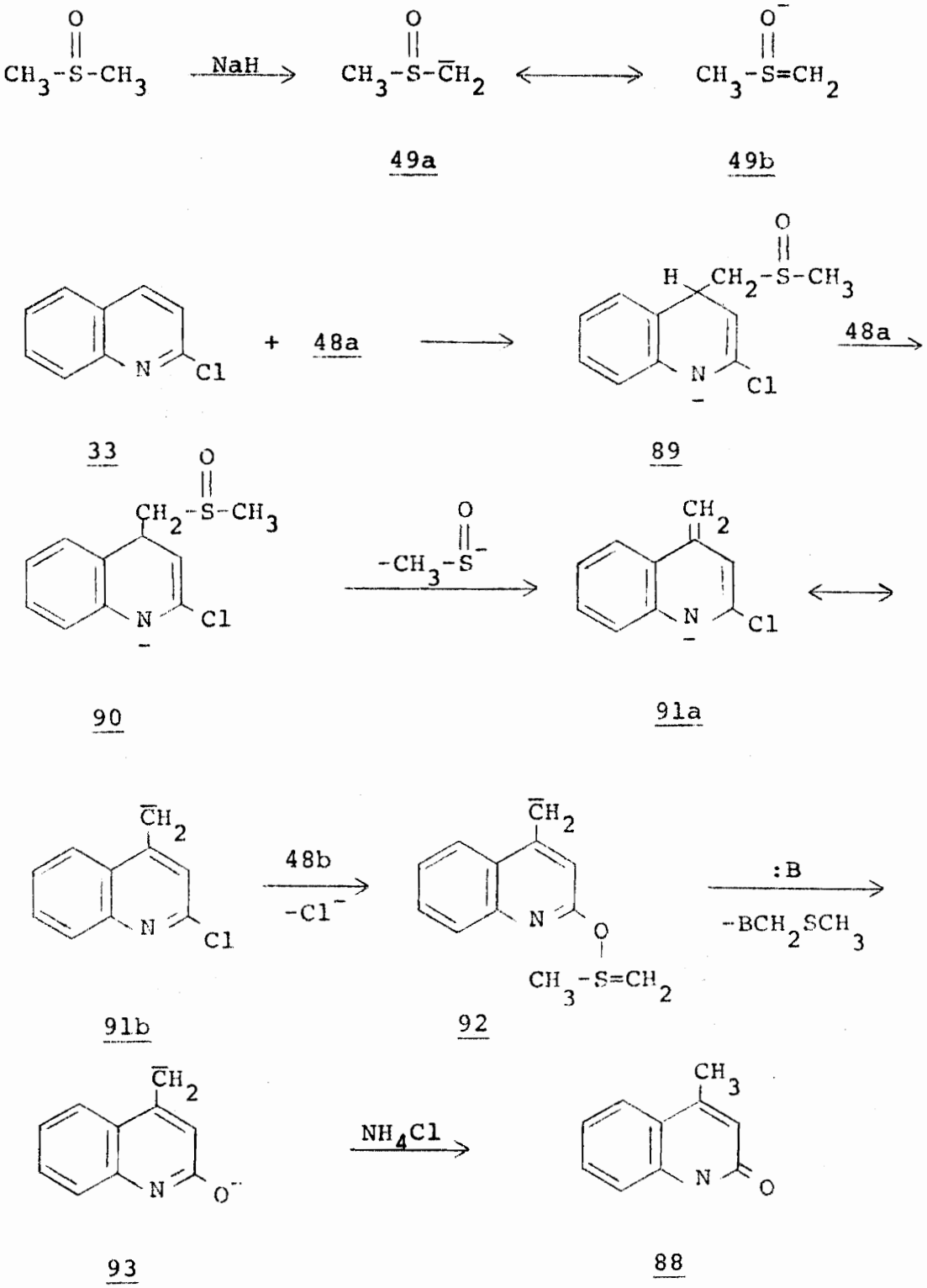
Methylation in the four position of quinoline by

methylsulfinyl carbanion (49) has been shown to occur in good yields.[20] But, the source of oxygen at the 2-position of product 88 was not clear from this first reaction. To determine if chloride ion was displaced by solvolysis in DMSO or basic hydrolysis after quenching, DMSO was added to 2-chloroquinoline (33), in the same ratio as before, without sodium hydride. The mixture was stirred for 4 hours at 70°, cooled to room temperature and a 4.4% aqueous solution of sodium hydroxide added. Extraction of the water layer by methylene chloride and removal of the DMSO from the concentrated extracts afforded a red oil which was shown by tlc to consist only of the starting material, 2-chloroquinoline. Column chromatography of the oil afforded 2-chloroquinoline in 48% recovery. From this experiment, it was concluded that displacement of chloride ion occurred while 2-chloroquinoline was in contact with anion 49. A mechanism that is consistent with the experimental facts is presented in Scheme V.



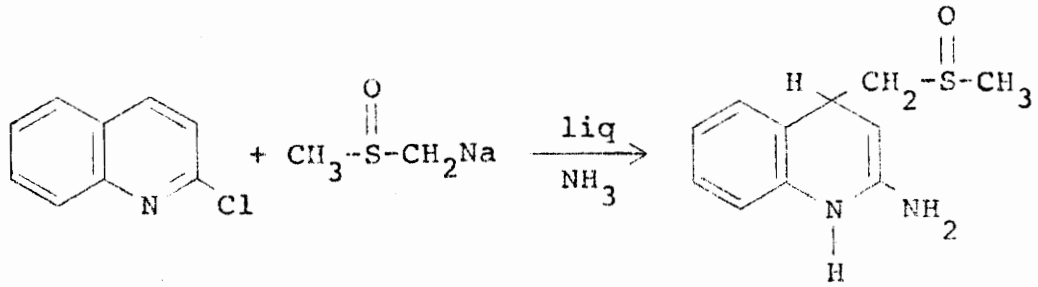
33 44 88

Scheme V


NaH
49a
49b
+ 48a
33
89
48a
90
91a
48b
-Cl⁻
91b
92
:B
-BCH2SCH3
NH4Cl
93
88

Methylsulfinyl carbanion can exist in two resonance forms[23] (49a and 49b). Initial reaction involves addition of anion 49a to the 4-position of 2-chloroquinoline to give salt 89 in which the negative charge resides on nitrogen. A second equivalent of anion 49a could then abstract a proton from the 4-position of 89 to give dianion 90, which on loss of methylsulfenate ion gave the resonance stabilized anion 91a. The oxygen of the "enolate" tautometer of dimysl anion (49b) then displaced chloride ion from 91a to form anion 92, a type of intermediate which has been proposed in reactions of acid chlorides and anhydrides with dimethylsulfoxide.[52] Intermediate 92 could then undergo attack by base (DMSO anion, Cl^- or OH^- produced in the work-up) to form the dianion 4-methylcarbostyryl 93 and the corresponding substituted sulfide or sulfides 88. Neutralization of dianion 93 would then afford the observed product 88. It should be noted that intermediates 92 and 93 in Scheme V could be formed before intermediates 89-91. Formation of 89-91 appeared to have ample precedent and has been used to explain the introduction of a methyl group at carbon-4 of the quinoline nucleus.[20] This mechanism was consistent with the experimental finding that introduction of oxygen function at the 2-position required the DMSO anion, and that neither DMSO itself or water was the source of oxygen found in the final product.

Having demonstrated that 2-chloroquinoline (33) reacts with anion 49 in DMSO, it was of interest to determine the effect of a different solvent, liquid ammonia, on the same reaction. An ethereal solution of DMSO was added to sodium amide in liquid ammonia under a nitrogen atmosphere. After 45 minutes, the gray anion of DMSO was treated with one-half of a molecular equivalent of 2-chloroquinoline (33). The reaction mixture was stirred 1 hour, quenched with solid ammonium chloride, and the ammonia replaced with ether. Separation and concentration of the ether layer afforded 34.5% of a compound to which has been assigned structure 94 (eq 21). This structural formulation was based on elemental



(21)

33 49 94

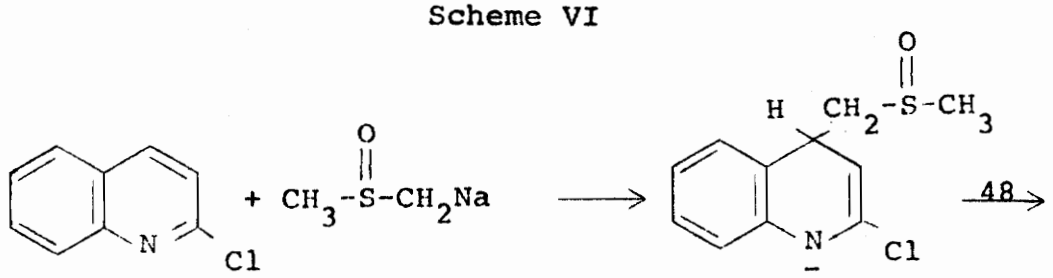
analysis and mass spectral data (molecular ion peak at m/e 222, see Experimental) which were consistent with a molecular formula of $C_{11}H_{14}N_2OS$. The ir spectrum of 94 had two broad bands at 3440 and 3120 cm^{-1} attributed to NH and NH_2, and a medium intensity band at 1640 cm^{-1} attributed to the

enamine system and a peak at 1020 cm^{-1} for the $R_2S=O$ function. The nmr spectrum had a singlet (3H) at 2.66 which arose from the CH_3SO protons, a multiplet at 2.94 ppm for the non-equivalent methylene protons adjacent to the sulfoxide group, a multiplet at 3.70 ppm attributed to the methylene proton at the 4-position of the heterocyclic ring and an aromatic multiplet at 7.10 ppm arising from the vinyl proton of the heterocyclic ring and the remaining protons of the carbocyclic ring. The integrated intensity (4H) of the multiplet at 2.94 indicated that the NH_2 protons of 94 were also appearing in this region and the intensity of the aromatic peaks at 7.10 ppm indicated that NH of the heterocyclic ring which may also be located in this region.

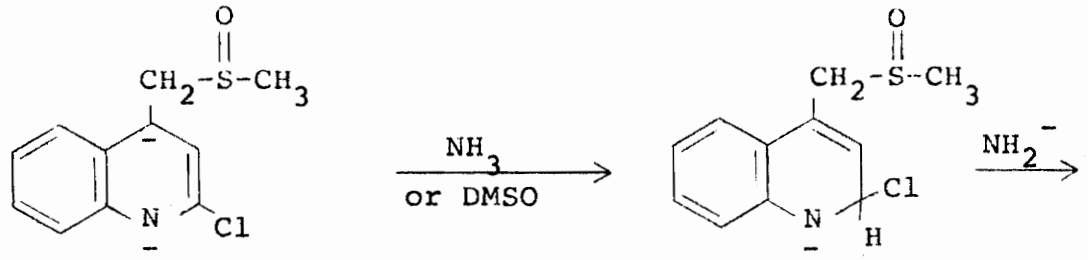
To determine if the NH_2 group of 94 was incorporated by reaction of 2-chloroquinoline with ammonia, the reaction was carried out as above but without sodium amide. Analysis of the mixture by tlc gave a chromatogram with one spot which was identified, by comparison of R_f values, as starting 2-chloroquinoline. This indicated that replacement of chloride by ammonia was not responsible for introduction of NH_2 function. A mechanism was proposed in Scheme VI.

Intermediates 89 and 90 were analogous to those discussed for Scheme V; however, loss of methylsulfenate from 90 does not occur, which may be due to its stability at this low temperature (-33°). The methylsulfenate underwent

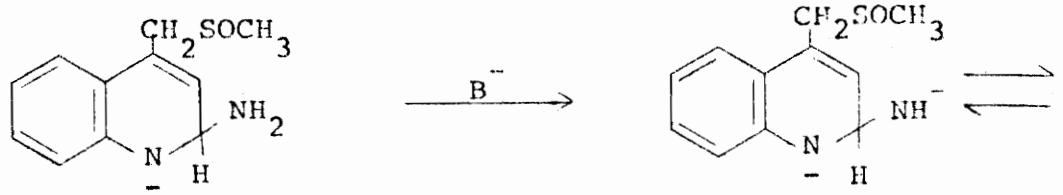
Scheme VI



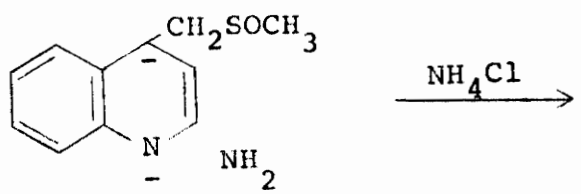
33 89



90 95



96 97a



97b 94

reprotination at the 2-position by abstracting a proton from the solvent or from DMSO to give an allylic chlorine 95 which readily underwent nucleophilic displacement with amide ion to give 96. The presence of amide could be explained by an equilibrium reaction of ammonia with methylsulfinyl carbanion (eq 22).

$$CH_3S\bar{O}CH_2 + NH_3 \rightleftharpoons CH_3SOCH_3 + \bar{N}H_2 \qquad (22)$$

A proton was abstracted from the amino group of 96 by base to give 97 which can exist in one of two forms, 97a and 97b. Quenching 97b with ammonium chloride, at liquid ammonia temperature, afforded the product 94. Intermediates 89 and 90 must be formed before displacement of chloride ion by amide since we have shown that 2-chloroquinoline does not react with sodium amide in the 1 hour reaction time.

The reactions of 2-chloroquinoline with methylsulfinyl carbanion in DMSO and in liquid ammonia are more complex than they appeared to be at first glance; therefore, further studies along these lines might be fruitful.

III. EXPERIMENTAL

A. General

Melting points were taken on a Thomas-Hoover melting point apparatus or a Mel-Temp melting point apparatus in capillary tubes and were uncorrected. Boiling points were also uncorrected. Temperature was reported in degrees centigrade.

Elemental analyses were performed in this laboratory by Miss Q. H. Tan, using an F & M Model 185 or a Perkin-Elmer Model 240 C, H, and N analyzer.

Infrared (ir) spectra were taken on Beckman IR-5A and Beckman IR-5 infrared spectrophotomers using potassium bromide pellets, dilute solutions in chloroform, or Nujol mulls.

Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Associates A-60 spectrometer. Chemical shifts, relative to tetramethylsilane as the internal standard, were measured to the center of a singlet or multiplet. The following designations were used in describing multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer at 50 ev. Pressures in the analyzer

tube were maintained at less than $1x10^{-6}$ mm.

The esr spectra were recorded in flat quartz cells using a Varian E-3 EPR spectrometer.

Gas-liquid partition chromatography (glpc) was conducted using a Varian Aerograph Model 90-P, equipped with a 6-ft column, packed with 20% SE-30 on Chromosorb W; operating conditions were as follows: column temperature, 200°; detector cell current, 150 ma; injector port temperature, 240°; helium flow at exit, 60 cm^3/min; sample size, 2.0 μl.

Thin layer chromatography (tlc) was conducted with an Eastman Chromagram apparatus on Chromagram sheets type 6060 (silica gel) with fluorescent indicator using the designated developing solvents. Spots were detected with ultraviolet light.

Unless otherwise specified, chemicals were commercial reagent grade and were used without further purification. The sodium hydride was an approximately 50% dispersion in mineral oil obtained from Metal Hydrides, Inc., Beverly, Massachusetts.

B. Displacement of Halogens from Heterocycles with Dianions

Cyclization of Anthranilic Acid with Foramide to form 4(3H)-Quinazolinone. To a stirred solution of 151.2 g (2.80 mol) of foramide in a 1000 ml three-necked flask was added 274.28 g (2.00 mol) of anthranilic acid (98). After heating for 4 hr at 120°-130°, the white product was removed by breaking it into small lumps. Crystallization of this material from 95% ethanol yielded 267.55 g (91.5%) of 4(3H)-quinazolinone (55): mp 213°-214° (lit[53] mp 215.5°-216.5°); nmr (DMSO-d_6) δ 8.40 (m, aromatic); ir (KBr) 6.03 (C=O).

Chlorination of 4-(3H)-Quinazolinone to form 4-Chloroquinazoline. To 3.6 g (0.025 mol) of 4-(3H)-quinazolinone (55) was added 7.5 g (0.042 mol) of phosphorus pentachloride and 30 ml of phosphorus oxychloride. The mixture was refluxed and irradiated with an ultraviolet lamp, (BLE spectroline model B-100, 2 amps) for 4 hr. Removal of the excess chlorinating agent under reduced pressure left a yellow solid. After addition of this material to a stirred solution of 1000 ml of ice and water, the resulting solid was extracted with ether, dried (Na_2SO_4), and the solvent was removed to give 4-chloroquinazoline (36) as a white solid. Crystallization from hexane gave 3.06 g (74.5%) of the halogenated product: mp 95°-96° (lit[53] mp 96.5°-97.5°); nmr ($CDCl_3$) δ 9.10 (s, 1H, aromatic); 8.06 (m, 4H, aromatic); ir (KBr) 1562 cm^{-1} (aromatic C-H) and 760 cm^{-1} (aromatic C-H).

Displacement of Halogen from 4-Chloroquinazoline by Dianions. (A). With Disodiobenzoylacetone. To a stirred suspension of 0.05 moles of sodium amide, prepared from 1.15 g-atom of sodium in 300 ml of liquid ammonia, containing a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ was added to 4.06 g (0.025 mol) of benzoylacetone as a 4% w/v solution in dry ether. After 30 min, the green solution was assumed to contain 0.025 mol of disodiobenzoylacetone (44). A 4.06 g (0.025 mol) sample of 4-chloroquinazoline (36) was then added as 4% w/v solution in dry ether and the mixture was stirred for 1 hr. The reaction was quenched by addition of excess solid ammonium chloride. The ammonia was evaporated (steam bath) as 100 ml of dry ether was added. Cold water (100 ml) was added to the ethereal solution and the mixture filtered. The resulting insoluble brown solid was crystallized from 95% ethanol to give 3.80 g (52%) of red diketone 56, mp 140°-142°. Recrystallization raised the melting point to 141.5°-142°: nmr ($CDCl_3$) δ 19.12 (s), 14.68 (s), 8.28 (m), 6.68 (s), 6.58 (s), 6.36 (s), and 4.50 (s); ir (KBr) 1600 cm^{-1} (C=O); mass spectrum (50 ev), molecular ion peak at m/e 290, with abundant fragment peaks at m/e 129 (quinazoline nucleus) and 77 (phenyl ring).

Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.87; N, 9.62. Found: C, 74.64; H, 4.73; N, 9.65.

In a second experiment, the above procedure was varied by using a 2:1 molar ratio of disodiobenzoylacetone (0.05 mol) to 4-chloroquinazoline (0.025 mol). A 60% yield (based on 4-chloroquinazoline) of the diketone was obtained.

(B). With Dilithiobenzoylacetone. To a stirred suspension of 0.025 moles of lithium amide, prepared from 0.17 g (0.025 g-atom) of lithium in 300 ml of liquid ammonia, containing a catalytic amount of $Fe(NO_3)_3 \cdot 9H_2O$ was added 1.94 g (0.012 mol) of benzoylacetone. The entire reaction was carried out under nitrogen atmosphere and after 30 min the green solution was assumed to contain 0.012 mol of dilithiobenzoylacetone. A 2.03 g (0.012 mol) sample of 4-chloroquinazoline (36) was then added as a 4% w/v solution in dry ether and the mixture was stirred for 1 hr. The reaction was quenched by addition of excess solid ammonium chloride. The ammonia was evaporated (steam bath) as 100 ml of dry ether was added. Cold water (100 ml) was added to the ethereal solution and the mixture filtered. The resulting insoluble brown solid was crystallized from 95% ethanol to give 0.92 g (51%) of diketone (56).

(C). With the Dilithio Salt of 2-Hydroxy-4-Phenyl-6-Methylpyrimidine. To a stirred suspension of 0.056 mol of sodium amide prepared from 1.29 g of sodium in 700 ml of liquid ammonia contained in a 1000 ml three-necked flask, was added 5.2 g (0.028 mol) of pyrimidine. After 30 min,

the dark red solution was assumed to contain 0.028 mol of disodio salt 46. A 4.2 g (0.028 mol) sample of 4-chloroquinazoline (36) was then added as a 4% w/v solution in dry ether and the mixture was stirred for 1 hr. The reaction was quenched by addition of excess solid ammonium chloride. The ammonia was evaporated (steam bath) as 100 ml of dry ether was added. Cold water (100 ml) was added to the ethereal solution and the mixture was filtered. The resulting insoluble dark brown solid was crystallized from N,N-dimethylformamide to give 3.6 g (45% yield based on 4-chloroquinazoline (36)) of 2-hydroxy-4-(4-quinazolinylmethyl)-6-phenylpyrimidine (65), mp 324°-325°. Recrystallization raised the melting point to 326°-327°: nmr (trifluoroacetic acid) δ 8.90 (s, 1), 7.96 (m, 9, aromatic), 6.90 (s, 1), and 6.60 (s, 1); ir (KBr) 3340 cm^{-1} (NH) and 1640 cm^{-1} (C=O); mass spectrum (50 ev), molecular ion peak at m/e 314; with abundant fragment peaks at m/e 185 (pyrimidine nucleus) and 129 (quinazoline nucleus).

Anal. Calcd for $C_{19}H_{14}N_4O$: C, 72.61; H, 4.46; N, 17.83. Found: C, 72.81; H, 4.16; N, 17.92.

The above procedure was varied by using a 2:1 molar ratio of dianion 46 to 4-chloroquinazoline (36) under nitrogen atmosphere. To a stirred suspension of 0.024 mol of sodium amide prepared from 0.552 g (0.024 g-atom) of sodium in 400 ml of liquid ammonia, was added 2.23 g (0.012 mol) of

pyrimidine. After 30 min, the dark red solution was assumed to contain 0.012 mol of disodio anion 45. A 0.987 g (0.006 mol) sample of 4-chloroquinazoline (36) was then added as a 4% w/v solution in dry ether and the mixture was stirred for 1 hr. The reaction was quenched by addition of excess solid ammonium chloride. From the reaction mixture, following the usual work-up, was isolated a brown solid. Crystallization of the material from N,N-dimethylformamide gave 1.03 g (55% yield based on 4-chloroquinazoline (36)) of pyrimidine 65, mp 322°-325°.

(D). With the Disodio Salt of 2-Hydroxy-4,6-Dimethyl-5-Phenylpyrimidine. To a stirred suspension of 0.07 mol of sodium amide prepared from 0.161 g (0.07 g-atom) of sodium in 300 ml of liquid ammonia contained in a 500 ml three-necked flask, was added 7.00 g (0.035 mol) of pyrimidine. After 30 min, the solution was assumed to contain 0.035 mol of disodio anion 66. A 5.75 g (0.035 mol) sample of 4-chloroquinazoline (36) was then added as a 4% w/v solution in dry ether and the mixture was stirred for 1 hr. The reaction was quenched by addition of excess solid ammonium chloride. The ammonia was evaporated (steam bath) as 100 ml of dry ether was added. Cold water (100 ml) was added to the ethereal solution and the mixture was filtered. The resulting insoluble brown solid was crystallized from 95%

ethanol to produce 2-hydroxy-4-(4-quinazolinylmethyl)-5-phenylpyrimidine (68) in 36% yield (based on 4-chloroquinazoline (36)). The brown needles had a melting point of 342°-343°: nmr (trifluoroacetic acid) δ 9.24 (s, 1), 7.63 (m, 9, aromatic), 6.31 (s, 1), and 2.39 (s, 3, methyl); ir (KBr) 3330 cm^{-1} (NH) and 1640 cm^{-1} (C=O); mass spectrum (50 ev), molecular ion peak at m/e 328; with abundant fragment peaks at 198 (pyrimidine nucleus) and 129 (quinazoline nucleus).

Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.17; H, 4.84; N, 17.07. Found: C, 73.43; H, 4.95; N, 17.02.

The above procedure was varied by using a 2:1 molar ratio of disodiopyrimidine 66 to 4-chloroquinazoline. To a stirred suspension of 0.024 mol of sodium amide prepared from 0.552 g (0.024 g-atom) of sodium in 300 ml of liquid ammonia was added 2.40 g (0.012 mol) of pyrimidine under nitrogen atmosphere. After 30 min, the dark red solution was assumed to contain 0.012 mol of disodio anion 66. A 0.987 g (0.006 mol) sample of 4-chloroquinazoline (36) was then added and the mixture was stirred for 1 hr. The reaction was quenched by addition of excess solid ammonium chloride. Following the usual work-up, 0.28 g (30%) of the substituted pyrimidine 68 was obtained.

Displacement of Halogen from 2-Chloroquinoline. (A). With Disodiobenzoylacetone. To a suspension of 0.05 mol of

sodium, prepared from 1.15 g (0.05 mol) sodium metal in 400 ml of commercial, anhydrous liquid ammonia, contained in a 500 ml three-necked flask equipped with an air condenser and mechanical stirrer, was added 4.06 g (0.025 mol) of benzoylacetone. After 30 min, the resulting green solution was assumed to contain 0.025 mol of disodio salt 44. To 0.025 mol of disodiobenzoylacetone in 400 ml of liquid ammonia was added 4.06 g (0.025 mol) of 2-chloroquinoline (33). After 1 hr, 13.25 g (0.25 mol) of ammonium chloride was added and the ammonia replaced with ether. Cold water (100 ml) was added to the ethereal solution and the layers were separated. The water layer was extracted with three 100 ml portions of ether. The original ether layer and the extracts were combined, dried (Na_2SO_4), and concentrated to give a red liquid which was purified by column chromatography on silica gel with benzene as the eluting solvent to give 0.13 g (3.75%) of 1-phenyl-4-(2-quinolyl)-1,3-butanedione (45): mp 133°-136° (lit[17] 138°-139.5°); nmr ($CDCl_3$) δ 8.05 (m, 11, aromatic), 7.06 (s), 6.90 (s), 6.66 (s), 6.24 (s), 5.72 (s), 5.44 (s), and 4.30 ppm (d) (methylene and vinyl); ir ($CHCl_3$) 1610 cm^{-1} (C=O).

(B). With Dilithiobenzoylacetone. To 0.024 mol of dilithiobenzoylacetone (49) prepared from 0.168 g (0.024 mol) of lithium metal in 400 ml of liquid ammonia was added 1.97 g (0.012 mol) of 2-chloroquinoline (33). After 1 hr, the

reaction was quenched by addition of excess solid ammonium chloride. The usual work-up gave a red oil. Analysis by tlc gave a chromatogram containing two spots. One spot, by comparison of R_f values was identified as benzoylacetone. The other spot had an R_f value the same as the diketone 45. Column chromatography on silica gel with benzene as the eluting solvent afforded 0.50 g (14.2% based on 2-chloroquinoline (33)), mp 133°-136°.

(C). With Dilithiobenzoylacetone Under Nitrogen Atmosphere. To a stirred solution of 400 ml of anhydrous liquid ammonia under nitrogen atmosphere was added 0.175 g (0.025 g-atom) of lithium. After 10-15 min, 2.02 g (0.012 mol) of benzoylacetone was added to the light gray amide suspension. The resulting green reaction mixture was allowed to stir for 30 min. A solution of 2.02 g (0.012 mol) of 2-chloroquinoline in 100 ml of dry ether was added. After 1 hr, the reaction was neutralized with excess ammonium chloride. The ammonia was distilled as 100 ml of anhydrous ether was added. The ether was separated and the aqueous layer extracted three times with 75 ml portions of ether. The combined ethereal fractions were dried (Na_2SO_4) and concentrated to give a red oil. Analysis by tlc gave a chromatogram containing two spots. One spot, by comparison of R_f values, was identified as benzoylacetone. The other spot had an R_f value the same as diketone 45. Column chromatography (benzene afforded 1.50 g (43%) of the diketone 45.

The above procedure was varied by using a 2:1 molar ratio of dilithio anion 49 to 2-chloroquinoline (33). To a stirred suspension of 0.012 mol of dilithio anion under nitrogen atmosphere, was added 0.985 g (0.006 mol) of 2-chloroquinoline (33). After 1 hr, the reaction mixture was neutralized with excess ammonium chloride. The ammonia was distilled as 100 ml of anhydrous ether was added. The ether was separated and the aqueous layer extracted three times with 75 ml portions of ether. The combined ethereal fractions were dried (Na_2SO_4) and concentrated to give a red oil. Analysis by tlc gave a chromatogram containing two spots. By comparison of R_f values, one spot was identified as benzoylacetone and the other as diketone 45. Column chromatography afforded 1.25 g (71.5% based on 2-chloroquinoline (32)) of diketone 45, mp 132°-135°. Reaction times up to 6.75 hr did not increase the yield.

(D). With Dilithiobenzoylacetone and Added Lithium Metal. To 0.048 mol of lithium amide under nitrogen atmosphere, prepared from 0.336 g (0.048 g-atom) of lithium in 400 ml of liquid ammonia, was added 3.89 g (0.24 mol) of benzoylacetone. The resulting green reaction mixture was allowed to stir 30 min. To the stirred solution of dilithio salt was then added 1.97 g (0.012 mol) of 2-chloroquinoline (33), immediately followed by the addition of 0.21 g (0.003 g-atom) of lithium metal. The dark red mixture was stirred

1 hr, then quenched with excess ammonium chloride. As the ammonia was removed, 100 ml of dry ether was added followed by 100 ml of water. Analysis of the dried, concentrated ethereal extracts by tlc gave a chromatogram containing two spots. By comparison of R_f values, one spot was identified as benzoylacetone and the other as diketone 45. Column chromatography afforded 1.89 g (55%) of diketone, mp 134°-136°.

The above procedure was varied by using 1 eq (0.012 mol) of lithium metal. To 0.048 mol of lithium amide under nitrogen atmosphere, prepared from 0.336 g (0.048 g-atom) of lithium in 400 ml of liquid ammonia, was added 3.89 g (0.024 mol) of benzoylacetone. The resulting green reaction mixture was allowed to stir 30 min. To the stirred solution of dilithio salt was then added 1.97 g (0.012 mol) of 2-chloroquinoline (33), immediately followed by the addition of 0.084 g (0.012 g-atom) of lithium metal. The dark red mixture was stirred for 1 hr, then quenched with excess ammonium chloride. As the ammonia was removed, 100 ml of dry ether was added followed by 100 ml of water. Analysis of the dried, concentrated ethereal extracts by tlc gave a chromatogram containing two spots. By comparison of R_f values, one spot was identified as benzoylacetone and the other as diketone 45. Column chromatography afforded 1.26 g (36%) of diketone 45, mp 133°-135°.

The procedure for preparation of dianion was the same as that given in the preceding paragraph. After addition of 2-chloroquinoline (1.97 g, 0.012 mol) and lithium metal (0.021 g, 0.003 mol), the mixture was irradiated with a light source for 1 hr. As the ammonia was removed, 100 ml of dry ether was added, followed by 100 ml of water. The dried ethereal extracts were concentrated and purified by column chromatography (benzene) to yield 0.96 g (27.8%) of diketone 45, mp 135°-137°.

(E). With Dipotassiobenzoylacetone. This procedure is representative of the displacements using dipotassio salt. Potassium amide (0.048 mol) was prepared by addition of 1.88 g (0.096 g-atom) of potassium to 400 ml of liquid ammonia under a nitrogen atmosphere. The gray suspension was treated with 3.89 g (0.024 mol) of benzoylacetone and stirred for 30 min to form dipotassiobenzoylacetone. 2-Chloroquinoline (1.97 g, 0.012 mol) was added as the solid and the resulting red solution was stirred for 1 hr before being neutralized with 13.25 g (0.25 mol) of ammonium chloride. The ammonia was removed as 100 ml of ether was added. To the resulting suspension was added 100 ml of 10% w/v hydrochloric acid. The ethereal layer was separated and the aqueous layer extracted with three 100 ml portions of ether. The combined ether layers were washed twice with 100 ml of 5% $NaHCO_3$, dried (Na_2SO_4), concentrated to give 6.37 g of red oil.

From glpc analysis of the oil (using acetylacetone as internal standard) was found 1.49 g benzoylacetone; 0.03 g, 2-chloroquinoline; and 0.008 g quinoline (starting material contained 0.041 g of quinoline). Column chromatography afforded 0.07 g (2.2% based on 2-chloroquinoline (33)) of diketone 45.

(F). With Dipotassiobenzoylacetone and Added Potassium Metal. To 0.024 mol of dipotassiobenzoylacetone, under nitrogen atmosphere, prepared from 3.89 g (0.024 mol) of benzoylacetone and 1.88 g (0.048 g-atom) of potassium, was added 1.97 g (0.012 mol) of 2-chloroquinoline (33). This was immediately followed by 0.117 g (0.003 g-atom) of potassium metal. The reaction was quenched after 1 hr and the usual work-up afforded 8.34 g of crude product. Analysis of this material by glpc showed the presence of 1.28 g of benzoylacetone, only a trace of 2-chloroquinoline and 0.41 g of quinoline. Column Chromatography afforded 0.568 g (16.3%) of the desired quinoline (45), mp 135°-136°.

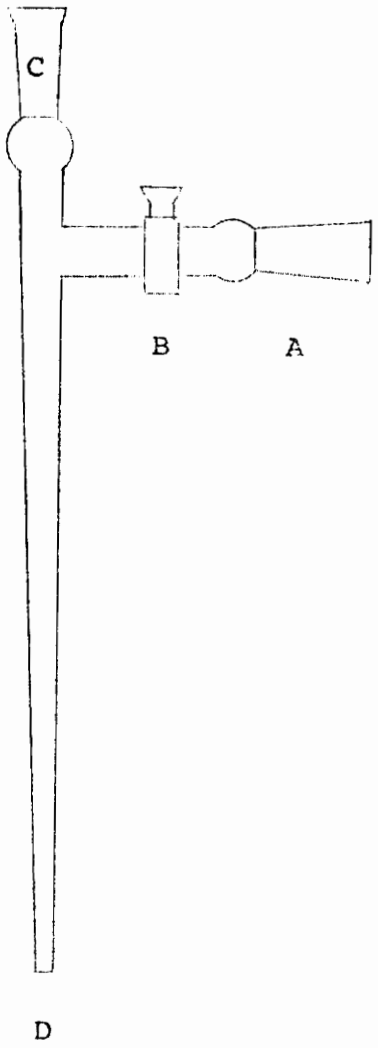
In a subsequent experiment, the amount of added potassium metal was increased to 2.5 eq. To a stirred suspension of 0.024 mol of dipotassiobenzoylacetone prepared as described previously, 0.012 mol of 2-chloroquinoline was added 1.88 g (0.048 mol) of potassium, and the mixture was stirred for 1 hr. From the reaction mixture was obtained 4.39 g of a red-black oil. Analysis of this material by glpc showed the

presence of 1.75 g of benzoylacetone; a trace of 2-chloroquinoline; and 0.05 g of quinoline. Column chromatography afforded 0.111 g (3.2%) of 1-phenyl-4-(2-quinolyl)-1,3-butanedione (45), mp 133°-135°.

(G). With Dilithiobenzoylacetone in the Presence of Tetraphenylhydrazine. To a stirred solution of 0.024 mol of dilithiobenzoylacetone in 400 ml of liquid ammonia was added 0.322 g (0.00095 mol) of tetraphenylhydrazine followed by 1.97 g (0.012 mol) of 2-chloroquinoline; 10 ml of dry ether was used to rinse the solids into the reaction mixture. After 1 hr, the reaction was neutralized with 13.25 g (0.25 mol) of ammonium chloride. The ammonia was removed as 100 ml of ether was added. The mixture was treated with 100 ml of cold water and the layers were separated. The aqueous phase was extracted three times with ether. The combined ethereal solutions were dried (Na_2SO_4) and concentrated to give 3.77 g of a red oil. Analysis of the oil by glpc indicated the presence of 1.0 g of benzoylacetone; 0.20 g of 2-chloroquinoline; 0.27 g of quinoline; 0.064 g of tetraphenylhydrazine. Column chromatography of the mixture afforded 0.125 g (3.5%) of diketone 45, mp 134°-136°.

ESR Study of the Reaction of Dilithiobenzoylacetone with 2-Chloroquinoline. The sample to be examined in the esr spectrophotometer was prepared as follows: to a stirred suspension of 0.048 mol of lithium amide, prepared from

FIGURE 1. SAMPLE CELL FOR STUDYING DIANION RADICAL



A. Side arm for introducing dianion solution

B. Stopcock for sealing sample tube

C. Septum for introduction of dry nitrogen and ethereal solution

D. Esr probe

0.336 g (0.048 g-atom) of lithium in 400 ml of liquid ammonia under a nitrogen atmosphere, was added 3.89 g (0.024 mol) of benzoylacetone. After 30 min, the green solution was assumed to contain 0.024 mol of dilithiobenzoylacetone (49). The sample was examined in a 4-mm quartz flat cell which was connected with a graded seal to an open ended tube, equipped with a rubber septum. Connected to the tube was a side arm with a stopcock and a ground glass joint for attaching the sample tube, by way of an adaptor, to a reaction flask (Figure 1). The dilithio salt solution was poured through the side arm (A) filling the esr probe (D) to a height of about 50 mm. The stopcock (B) was closed to seal off the tube. A stream of dry nitrogen was introduced through the septum (C) by a hypodermic needle. A second needle was placed in the septum (C) to allow the nitrogen to escape. The tube was immediately inserted into the variable-temperature probe of the spectrometer which was cooled to about -70°. To the dilithiobenzoylacetone (55) solution in the esr tube was added, by hypodermic syringe, 0.5 ml of a solution containing 1.97 g (0.012 mol) of 2-chloroquinoline (32) dissolved in 150 ml of dry ether. The esr spectrum of the reaction mixture was recorded. A poorly resolved signal was obtained.

Attempted Displacement of Halogen from the 4-Position of 4,7-Dichloroquinoline. To a stirred suspension of 0.048

mol of lithium amide, prepared from 0.048 g-atom of lithium in 400 ml of liquid ammonia under a nitrogen atmosphere, was added 3.89 g (0.024 mol) of benzoylacetone. After 30 min, the green solution was assumed to contain 0.024 mol of dilithiobenzoylacetone (49). A 2.38 g (0.012 mol) sample of 4,7-dichloroquinoline (85) was then added and the mixture was stirred for 1 hr. The reaction was quenched by addition of excess solid ammonium chloride. The ammonia was evaporated (steam bath) as an equal volume of ether was added. Cold water (100 ml) was added to the ethereal solution and the layers separated. The water layer was extracted with three 100 ml portions of ether. The original ether layer and the extracts were combined, dried (Na_2SO_4), and concentrated to give 5.44 g of an oil. Analysis of the material by glpc indicated the presence of 2.01 g of 4,7-dichloroquinoline (85) and 2.89 g of benzoylacetone.

Attempted Displacement of Halogen from 2-Chloroquinoxaline. (A). With Disodiobenzoylacetone. To a suspension of 0.05 mol of sodium amide prepared from 1.15 g (0.05 g-atom) of sodium metal in 400 ml of anhydrous liquid ammonia was added 4.06 g (0.025 mol) benzoylacetone as a 4% w/v ethereal solution of benzoylacetone. The resulting green suspension was allowed to stir for 30 min to form disodiobenzoylacetone (44). A solution of 4.06 g (0.025 mol) of 2-chloroquinoxaline purified by sublimation of 37°/0.01 mm

in 100 ml of anhydrous ether was added during a period of 2 min and the dark red reaction mixture was allowed to stir for 1 hr before being neutralized with excess ammonium chloride. The ammonia was distilled (steam bath) as 100 ml of ether was added. Cold water (100 ml) was added to the ethereal solution and the suspension filtered. Analysis of the resulting brown solid by tlc gave a chromatogram containing two spots. One spot was identified, by comparison of R_f values, to be benzoylacetone; the other spot had a value less than benzoylacetone. All attempts to crystallize the solid, 3.3 g, failed.

(B). With Dilithiobenzoylacetone. To a suspension of 0.05 mol of sodium amide prepared under nitrogen atmosphere from 0.35 g (0.05 g-atom) lithium metal in 400 ml of anhydrous liquid ammonia was added 4.06 g (0.025 mol) of 4% w/v ethereal solution of benzoylacetone. The resulting green suspension was allowed to stir for 30 min to form dilithiobenzoylacetone (49). A solution of 4.06 g (0.025 mol) of 2-chloroquinoxaline purified by sublimation at 37°/0.01 mm, in 100 ml of anhydrous ether was added over a period of 2 min and the dark red reaction mixture was allowed to stir for 1 hr before being neutralized with excess ammonium chloride. The ammonia was distilled (steam bath) as 100 ml of ether was added. Cold water (100 ml) was added to the ethereal solution and the suspension filtered. A brown solid (5.9 g) was isolated. Analysis of this material by

tlc (benzene-acetone (12:1)) of the solid gave a chromatogram with spots having a R_f value less than that of the benzoylacetone. Repeated attempts to crystallize the crude product failed.

Attempted Displacement of Halogen from 2-Chloropyridine. (A). With Dilithiobenzoylacetone. To a stirred suspension of 0.10 mol of lithium amide in 400 ml of anhydrous liquid ammonia under nitrogen atmosphere was added 8.10 g (0.05 mol) of solid benzoylacetone. The resulting green suspension was stirred for 30 min and then 5.65 g (0.05 mol) of neat 2-chloropyridine (32) was added. The red reaction mixture was then stirred for 1 hr. Excess ammonium chloride was added to neutralize the reaction. The liquid ammonia was distilled (steam bath) from the reaction mixture and replaced with 300 ml of ether. Cold water was added and the ethereal layer separated. The aqueous solution was extracted with three 100 ml aliquots of ether and the combined ethereal fractions were dried (Na_2SO_4), and concentrated to give a red oil. Analysis by tlc of the red liquid gave a chromatogram containing one spot with a R_f value equal to that of the benzoylacetone. Column chromatography afforded 4.22 g of recovered benzoylacetone.

(B). With Dilithiobenzoylacetone and Added Lithium Metal. To 0.05 mol of dilithio salt (55), prepared from (0.10 mol) of lithium amide, was added 5.65 g (0.05 mol) of

neat 2-chloropyridine followed by 0.84 g (0.012 mol) of lithium metal. After 1 hr, 21.3 g of ammonium chloride was added and the ammonia replaced with ether. Water (100 ml) was added to the ethereal solution and the layers were separated. The water layer was extracted with three 100 ml portions of ether. The combined ethereal aliquots were dried (Na_2SO_4) and concentrated to give a red oil. A tlc (benzene) of the liquid gave a chromatogram with one spot having a R_f value the same as benzoylacetone, indicating only starting materials being present. Column chromatography (benzene) afforded 6.17 g of recovered benzoylacetone.

Another reaction was run as above using 1 eq of added lithium metal. To 0.012 mol of dilithio salt 49, prepared from (0.24 mol) of lithium amide, was added 0.678 g (0.006 mol) of neat chloropyridine (32) followed by 0.042 g (0.006 mol) of lithium metal. After 1 hr, 21.3 g of ammonium chloride was added and the ammonia replaced with ether. Water (100 ml) was added to the ethereal solution and the layers were separated. The water layer was extracted with three 100 ml portions of ether. The combined ethereal aliquots were dried (Na_2SO_4) and concentrated to give a red oil. After processing, the resulting oily product was analyzed by tlc (benzene) and it contained spots corresponding to starting material along with a light spot with R_f value less than that of the recovered benzoylacetone. Attempts

to isolate other products were unsuccessful. Column chromatography (benzene) gave 1.46 g of recovered benzoylacetone along with an oil which was not characterized.

The above procedure was varied by using 2.5 eq (0.437 g, 0.0625 g-atoms) of lithium. Thin layer chromatography of the crude product indicated the presence of mainly starting materials. Analysis by glpc showed the presence of 1.40 g benzoylacetone, 0.27 g 2-chloropyridine, and 0.58 g of pyridine. Column chromatography afforded 0.68 g of a white solid which was not characterized.

(C). Reaction of 2-Chloroquinoline with the Methylsulfinyl Carbanion in Dimethyl Sulfoxide. To a 1000 ml three-necked flask was added 0.11 mol of sodium hydride as a 50% dispersion in mineral oil. The dispersion was washed with three 50 ml portions of light petroleum ether. The flask was immediately fitted with a mechanical stirrer, a pressure-equalizing addition funnel, and a reflux condenser, connected at its upper end to a water aspirator and a source of dry nitrogen by a three-way stopcock. The system was evacuated until all the petroleum ether was removed and then filled with nitrogen under a slight positive pressure. To the reaction flask was added 100 ml of dimethyl sulfoxide (DMSO) distilled from calcium hydride via a dropping funnel and the mixture was heated with stirring to 70°-75°. After

2 hr, the pale yellow-gray solution was assumed to contain 0.11 mol of the methylsulfinyl carbanion (49). To this mixture was added 3.09 g (0.019 mol) of 2-chloroquinoline (33) as a 3% w/v solution in dimethyl sulfoxide and the red suspension was stirred for 4 hr at 70°. The reaction was quenched with 100 ml of water and then the mixture poured into 1500 ml of water. The water solution was extracted with four 500 ml portions of benzene. The organic layers were combined, dried (Na_2SO_4) and concentrated to give a red oil. The last traces of dimethyl sulfoxide were removed by heating under vacuum. The resulting crude product was washed with ethanol and the remaining solid collected by filtration to give 1.38 g (35.4%) of 4-methylcarbostyryl (88), mp 217°-218° (lit[54] 222°-224°); nmr ($CDCl_3$) 12.66 (s, NH), 7.38 (m, aromatic), 6.58 (s, vinyl), and 2.44 ppm (s, methyl); ir (KBr) 6.10 μ (C=O). Comparison of these spectra with those of an authentic sample of 88 demonstrated their identity.

In order to determine if 2-chloroquinoline would react with DMSO, 100 ml of freshly distilled DMSO, in a 500 ml three-necked flask, condenser and pressure-equalizing funnel was added 3.09 g (0.019 mol) of 2-chloroquinoline (33). The reactants were heated to 70° and stirred under nitrogen atmosphere. After 4 hr, the mixture was allowed to cool to room temperature and 100 ml of 4.4% solution w/v of sodium

hydroxide was added. Then the mixture was extracted with four 100 ml portions of methylene chloride. The organic extracts were dried (Na_2SO_4) and concentrated to give an oil. Analysis by tlc of the product gave a chromatogram with one spot which was identified as 2-chloroquinoline by comparison of R_f values.

In order to determine if 2-chloroquinoline would react with base, a solution of 3.09 g (0.019 mol) of 2-chloroquinoline and 100 ml of a 4.4% w/v solution of sodium hydroxide. After stirring for 15 min, the mixture was poured into 1500 ml of water and extracted with four 100 ml aliquots of methylene chloride. The extracts were combined, dried (Na_2SO_4) and concentrated to yield a colorless oil. A tlc (benzene) of the product gave a chromatogram with one spot having a R_f value equal to that of the starting material 2-chloroquinoline and no evidence of 4-methylcarbostyryl. Column chromatography (benzene) afforded 1.48 g of 2-chloroquinoline.

In Liquid Ammonia. To a stirred suspension of 0.08 g-atom of sodium in 600 ml of liquid ammonia contained in a 1000 ml three-necked flask, under nitrogen atmosphere, was added 6.24 g (0.08 mol) of dimethyl sulfoxide in a 6% w/v solution of dry ether. After 45 min, the gray mixture was treated with 6.52 g (0.04 mol) of 2-chloroquinoline (33) dissolved in 100 ml of ether. After 1 hr, the reaction was

quenched by addition of 15.6 g (0.30 mol) of ammonium chloride. The ammonia was evaporated (steam bath) as 100 ml of ether was added. The ethereal suspension was filtered to give a red solution, which was concentrated to yield a semi-solid. The crude product was crystallized from 95% ethanol to give 2.93 g (34.5%) of 94. The analytical sample had mp 217°-218°; nmr $(CCl_3)_2CO$ δ 7.10 (m), 3.70 (m), 2.94 (m), and 2.66 ppm (m); ir (KBr) 3440 cm^{-1} (NH), 3120 cm^{-1} (NH_2) and 1020 cm^{-1} (S=O). Mass spectrum (50 ev) molecular ion peak at m/e 222; with abundant fragment peaks at m/e 145 (dihydroaminoquinoline) and 77 (methylmethylenesulfoxide).

Anal. Calcd for $C_{11}H_{14}N_2OS$: C, 59.19; H, 6.73; N, 12.56. Found: C, 59.21; H, 6.63; N, 12.24.

In order to see if 2-chloroquinoline would react with DMSO in liquid ammonia, the reaction was carried out by the above procedure, but without lithium amide. Analysis of the product by tlc gave a chromatogram with one spot, which was identified, by comparison of R_f values, as starting 2-chloroquinoline.

IV. SUMMARY

1. Treatment of 4-chloroquinazoline (36) with disodiobenzoylacetone (44) in liquid ammonia in 1:1 and 1:2 molar equivalent ratios afforded 1-phenyl-4(4-quinazolinyl)-1,3-butanedione (56) in 52% and 60% yield, respectively. Use of dilithiobenzoylacetone (49), under a nitrogen atmosphere, did not increase the yield. On the basis of the nmr spectrum, the diketone 56 was found to exist in several tautomeric forms (56b and 56c). Displacement of chloride ion from 4-chloroquinazoline (36) in liquid ammonia with dianions of 2-hydroxy-4-methyl-6-phenylpyrimidine (64) and 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine (67) gave 2-hydroxy-4(4-quinazolinylmethyl)-6-phenylpyrimidine (65) and 2-hydroxy-4(4-quinazolinylmethyl)-6-methyl-5-phenylpyrimidine (68) in 45% and 36% yield, respectively. From the nmr spectra, both quinazolinylpyrimidines 65 and 68 were found to exist as a mixture of tautomeric forms. Having found no evidence to the contrary, displacement reactions of 4-chloroquinazoline (36) with dianions 44, 46, and 66 was assumed to proceed by an S_NAr2 pathway.

2. Attention was next focused on the reaction of 2-chloroquinoline (33) with alkali salts of benzoylacetone. Treatment of 2-chloroquinoline (33) with disodiobenzoylacetone (44) in liquid ammonia in a 1:1 molar ratio afforded

1-phenyl-4(2-quinolyl)-1,3-butanedione (45) in 3% yield. When the dilithio salt 49, in a 2:1 molar ratio, was used the yield of diketone 45 increased to 14%; however, using a 1:1 molar ratio of reactants, under nitrogen atmosphere, afforded diketone 45 in 4% yield. Using a 2:1 molar ratio of dilithio salt 49 to 2-chloroquinoline (33), under nitrogen atmosphere, afforded a 71% yield of diketone 45. The increase in yield of diketone 45 when lithium salt 49 and nitrogen atmosphere were used, were thought to be the result of a radical process. Further support for such a radical process was obtained by isolating only a 3% yield of diketone 45, when the reaction of dilithiobenzoylacetone (49) and 2-chloroquinoline (33) (2:1 molar ratio, nitrogen atmosphere) were carried out in the presence of a radical trapping agent, tetraphenylhydrazine, and the appearance of an esr signal from the reaction mixture. The first step of a proposed radical mechanism involved electron transfer from benzoylacetone dianion 49 to 2-chloroquinoline (33) to form the radical anion of each. The chloroquinoline radical then underwent carbon-chlorine bond cleavage to form quinoline radical and chloride ion. Next, the quinoline radical combined with benzoylacetone dianion to form quinolylbenzoylacetone radical dianion and the final product, diketone 45. The quinoline radical can abstract a proton from a hydrogen donor to form quinoline (51). A cyclic electron transfer

complex 84 was thought to be involved, based on the failure of 4,7-dichloroquinoline (85) to undergo 4-substitution under the same reaction conditions as 2-chloroquinoline (33) with dilithiobenzoylacetone (49). Additional support for the radical mechanism was obtained on treatment of dipotassiobenzoylacetone with 2-chloroquinoline (33) and potassium metal under a nitrogen atmosphere which afforded low yield of diketone 45 (2-16%) along with quinoline (51) in as much as 26% yield. The expected diketones were not isolated from the reaction of 2-chloroquinoxaline (35) and 2-chloropyridine (32) with dialkalibenzoylacetone 44 and 49.

3. Treatment of 2-chloroquinoline (33) with methylsulfinyl carbanion (44), prepared from sodium hydride in dimethylsulfoxide at 70°, afforded, as the major product, 4-methylcarbostyryl (88) in 35% yield. Based on experimental evidence that oxygen in the 2-position of carbostyryl 88 did not come from the solvent or from hydrolysis of the final reaction mixture, a mechanism was proposed to explain the formation of product 88. The first step of the mechanism involved addition of methylsulfinyl carbanion (49) to 2-chloroquinoline (33) to form a charged complex 89, on loss of a proton formed 1,4-dianion 90. The dianion 90, on loss of methylsulfenate ion, formed a negatively charged methylene intermediate 91 which can exist with the negative charge either in the 1-position 91a or on the methyl group 91b.

Oxygen of the methylsulfinyl carbanion 49 displaced chloride ion from the 4-methyl-2-chloroquinoline anion 91b to form substituted intermediate 92. The dimethyl sulfoxide moiety of 92 then underwent attack by base, followed by loss of substituted sulfide to give dianion 93, which on neutralization formed 4-methylcarbostyryl (88). If 2-chloroquinoline (33) is treated with methylsulfinyl carbanion (49) in liquid ammonia, an aminomethylmethylenesulfoxide derivative 94 is isolated. A possible mechanism was proposed.

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VI. VITA

Name: James Carson Greene

Born: July 25, 1941, West Jefferson, North Carolina

Education:

Primary School: Cove Creek Elementary School
Sugar Grove, North Carolina, 1955

High School: Cove Creek High School
Sugar Grove, North Carolina, 1959

College: Appalachian State University
Boone, North Carolina
B. S. in Chemistry and Science, 1963

College: Appalachian State University
Boone, North Carolina
M. A. in Chemistry, 1965

College: Virginia Polytechnic Institute and
State University, Blacksburg, Virginia
Candidate for Ph. D. degree, 1972

Honorary and Professional Societies:

American Chemical Society
Phi Lambda Upsilon
Sigma Xi

Positions:

Teaching Assistant, Appalachian State University, Boone, North Carolina, 1963-1965.

Instructor of Chemistry, Virginia Polytechnic Institute, Danville Division, Danville, Virginia, 1966-1968.

Teaching Assistant, Virginia Polytechnic Institute and State University, 1968-1969, 1970-1971.

Research Assistant, Virginia Polytechnic Institute and State University, 1968-1969.

Publications and Presentations:

"Reactions of Certain Halogenated Heterocycles with 1,3-Dicarbanions." (with J. F. Wolfe), presented before the Virginia Academy of Science, Richmond, Virginia, May, 1970.

"Reaction of 2-Chloroquinoline with Dialkali Salts of Benzoylacetone." (with J. F. Wolfe), presented at the 1971 Southeastern Regional Meeting of the American Chemical Society, Nashville, Tennessee, November, 1971.

James Carson Greene

A STUDY OF THE DISPLACEMENT OF HALOGEN FROM CHLORINATED HETEROAROMATIC AZINES BY DIALKALI SALTS OF BENZOYLACETONE, DISODIO SALTS OF CERTAIN 2-HYDROXY-4-METHYLPYRIMIDINES, AND THE METHYLSULFINYL CARBANION

by

James Carson Greene

(ABSTRACT)

Treatment of 4-chloroquinazoline with disodiobenzoylacetone in liquid ammonia in 1:1 and 1:2 molar equivalent ratios afforded 1-phenyl-4(4-quinazolinyl)-1,3-butanedione in 52% and 60% yield, respectively. Use of dilithiobenzoylacetone, under a nitrogen atmosphere, did not increase the yield. On the basis of the nmr spectrum, the diketone product was found to exist in several tautomeric forms. Displacement of chloride ion from 4-chloroquinazoline in liquid ammonia with dianions of 2-hydroxy-4-methyl-6-phenylpyrimidine and 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine gave 2-hydroxy-4(4-quinazolinylmethyl)-6-phenylpyrimidine (45%) and 2-hydroxy-4(4-quinazolinylmethyl)-6-methyl-5-phenylpyrimidine (36%) respectively. From the nmr spectra, both quinazolinyl pyrimidines were found to exist as a mixture

of tautomeric forms. Having found no evidence to the contrary, displacement reactions of 4-chloroquinazoline with dianions were assumed to proceed by an S_NAr2 pathway.

Attention was next focused on the reaction of 2-chloroquinoline with alkali salts of benzoylacetone. Treatment of 2-chloroquinoline with disodiobenzoylacetone in liquid ammonia in a 1:1 molar ratio afforded 1-phenyl-4(2-quinolyl)-1,3-butanedione in 3% yield. When the dilithio salt, in a 2:1 molar ratio, was used the yield of diketone increased to 14%; however, using a 1:1 molar ratio of reactants under nitrogen atmosphere afforded the diketone product in 43% yield. Using a 2:1 molar ratio of dilithio salt to 2-chloroquinoline under a nitrogen atmosphere afforded 71% yield of the diketone. The increase in yield of product when lithium salt and a nitrogen atmosphere were used was thought to be the result of a radical process. Further support for such a radical process was obtained by isolating only a 3% yield of diketone when the reaction of dilithiobenzoylacetone and 2-chloroquinoline (2:1 ratio, nitrogen atmosphere) was carried out in the presence of a radical trapping agent, tetraphenylhydrazine, and the appearance of an esr signal from the reaction mixture. The first step of a proposed radical mechanism involved electron transfer from benzoylacetone dianion to 2-chloroquinoline to form the radical anion of each. The chloroquinoline radical then underwent carbon-

chlorine bond cleavage to form quinoline radical and chloride ion. Next, the quinoline radical combined with benzoylacetone dianion to form quinolylbenzoylacetone radical dianion which then transferred an electron to chloroquinoline generating chloroquinoline radical anion and the final product, quinolylbenzoylacetone. The quinoline radical can abstract a proton from a hydrogen donor to form quinoline. A cyclic electron transfer complex was thought to be involved, based on the failure of 4,7-dichloroquinoline to undergo 4-substituion under the same reaction conditions as 2-chloroquinoline with dilithiobenzoylacetone. Additional support for the radical mechanism was obtained on treatment of dipotassiobenzoylacetone with 2-chloroquinoline and potassium metal under a nitrogen atmosphere which afforded low yields of the expected diketone (2-16%) along with quinoline up to 26% yield. Attempts to displace chlorine ion from 2-chloroquinoxaline and 2-chloropyridine with dialkali benzoylacetone resulted in isolation of none of the expected diketones.

Treatment of 2-chloroquinoline with methylsulfinyl carbanion, prepared from sodium hydride in dimethyl sulfoxide at 70°, afforded as the major product, 4-methylcarbostyryl in 35% yield. Based on the experimental evidence that oxygen in the 2-position did not come from the solvent or from hydrolysis, a mechanism was proposed to explain the formation

of product. The first step of the mechanism involved addition of methylsulfinyl carbanion to 2-chloroquinoline to form a charged complex, which lost a proton from the 4-position to give a 1,4 dianion. The dianion, on loss of methylsulfenate icn, formed a negatively charged 4 methylene substituted intermediate which can exist with the negative charge either in the 1-position or on the methyl group. Oxygen of the enolate tautomer of methylsulfinyl carbanion displaced chloride ion from the 4-methyl-2-chloroquinoline amine to form a substitution intermediate. The dimethyl sulfoxide moiety of this intermediate then underwent attack by base followed by loss of substituted sulfide to give the dianion of 4-methylcarbostyryl, which on neutralization forms 4-methylcarbostyryl. If 2-chloroquinoline is treated with methylsulfinyl carbanion in liquid ammonia, a compound which analyzes for $C_{11}H_{14}N_2OS$ is formed. A structure and mechanism for its formation was proposed.