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LATERAL METALLATION OF METHYLATED NITROGENOUS HETEROCYCLES

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Abstract—Me groups on nitrogenous heterocycles can be conveniently metallated by a variety of strongly basic reagents to afford synthetically useful carbanions. The negative charge of such anions resides predominantly on the ring N atoms. The site of lithiation on pyridines and quinolines bearing Me groups in both the 2- and 4-positions depends upon the ability of the ring N atom to complex with the metallating agents. Carbanions derived from methylated pyridines, quinolines, naphthyridines, isoquinolines, pyrido[4,3-b]carbazoles, pteridines, pyrido[3,4-b] indoles and quinoxalines are discussed. References are provided describing condensations of these reagents with a variety of both common and uncommon electrophiles.

Alkylpyridines and related heterocycles are remarkably acidic compared to arenes devoid of ring N atoms. Thus, while the former compounds are routinely and conveniently metallated by organolithiums and relatively "weak" bases such as alkali amides in liquid ammonia, the latter are ionized only by organolithiums complexed with tertiary amines[1] or by stronger bases such as organosodiums and -potassiums.[2] As will be seen later, the lateral metallations of the heterocycles are facilitated by delocalization of negative charge predominately to the ring N atom.

The first interaction of alkylated nitrogenous heterocycles with alkali amides was reported by Chichibabin in 1914 when 2-methylpyridine was treated with sodium amide and methyl iodide; however, no side-chain condensation derivatives were realized.[3] In 1931, Bergstrom disclosed that several alkylpyridines and -quinolines were treated with potassium amide in ammonia to give, in some cases, colors now known to be characteristic of carbanion derivatives of such compounds.[4] Despite this, only alkylations of the salts of 2- and 4-methylquinoline, but not those of 2-methyl-, 2,6-dimethyl- and 2,4,6-trimethylpyridine, were successful.[4,5] Alkylations of 2- and 4-sodiomethylpyridines, prepared from the heterocycles and finely divided sodium amide, were effected using higher molecular weight alkyl chlorides over two day reaction periods.[6-8] Synthetically useful condensations of the Na derivatives of 2-, 4- and even 3-methylpyridines in ammonia were reported in 1951.[9]

Successful metallations by organolithiums of 2-methylpyridine were disclosed in the early 1930s when the 2-lithiomethyl derivative was prepared in ethyl ether using MeLi[10] and PhLi.[11] 4-Methylpyridine was not similarly metallated until 1954 when it was ionized in ethyl ether using PhLi or lithium diethylamide.[12]

Early metallations of methylated quinolines were effected by various metal amides in ammonia,[5,13] n-BuLi in ethyl ether,[10] as well as sodium diisopropylamide,[14] phenylsodium[15] and phenyllithium[16,17] all in benzene.

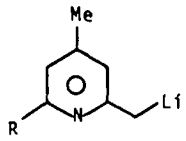
The initial literature describing the site of metallation of hetercycles bearing more than one alkyl side-chain was conflicting and confusing. Thus, despite the fact that the order of acidities of such side-chains in pyridine was found to be 4-Me > 2-Me > -Me,[18] Chichibabin reported the formation of the 2-sodiomethyl derivative from 2,4,6-trimethylpyridine and sodium amide in liquid ammonia.[8] In contrast, the 4-sodiomethyl compound was apparently synthesized from 2,4-dimethylpyridine and sodium amide in liquid ammonia.[19] Compounding the problem was the report that the 2-lithiomethyl derivative was obtained from 2,4-dimethylpyridine and PhLi in ethyl ether.[20] Initial disclosures concerning metallations of 2,4-dimethylquinoline with potassium amide in liquid ammonia were also confusing since alkylations were believed without proof to afford 2-alkylated derivatives in one case[21] and a mixture of 2- and 4-alkylated derivatives in another study.[22] In fact, the authors of the latter paper stated "Since 2,4-dimethylquinoline has two reactive Me groups, its potassium salt is doubtless a mixture...." On the other hand, treatment of 2,4-dimethylquinoline with PhLi in ether reportedly gave the 2-lithiomethyl derivative.[20c]

As we shall describe below, metallations of polymethylated nitrogenous heterocylces seldom yield mixtures of organometallics. Indeed, such acid-base chemistry has been found to be quite regiospecific and thus synthetically useful provided several variables are recognized and controlled. The most important of these variables are solvent and metallic cation.

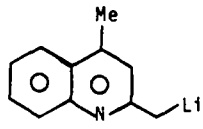
RESULTS

Initially, in an attempt to clarify the confusion about the site of metallation of 2,4-dimethylpyridine, 2,4,6-trimethylpyridine, and 2,4-dimethylquinoline, these heterocycles were treated with n-BuLi in ethyl ether–hexane to afford 2-lithiomethyl derivatives **1**, **2** and **3**, respectively.[23] In contrast, the use of alkali metal amides, usually sodium amide, in liquid ammonia gave 4-alkalimethyl derivatives **4**, **5** and **6**, respectively.[23] That anions **1–6** were indeed obtained was demonstrated by condensations with common electrophiles such as alkyl halides, aldehydes and ketones,[23] and with several uncommon ones illustrated by azobenzene,[24] potassium permanganate,[25] and diphenyldiazomethane.[26] For example, the use of azobenzene and potassium permanganate on carbanion **5** (M=Na) yielded hydrazobenzene **7** and "dimer" **8**, respectively.

That the above regiospecific metallations are even realized is somewhat surprising in light of the reported greater acidities of the 4-Me compared to the 2-Me



1 (R=H)
2 (R=Me)



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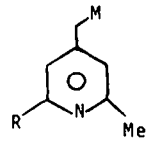
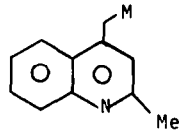


4 (R=H)
5 (R=Me)



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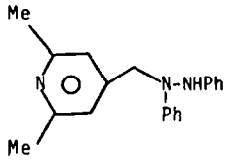

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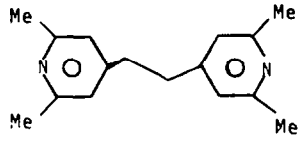

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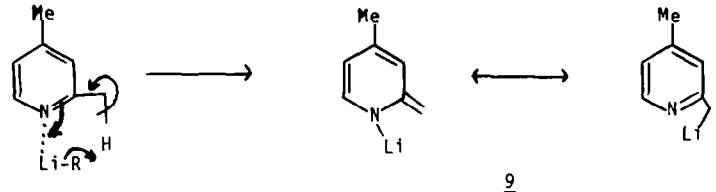

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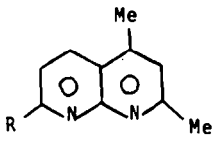
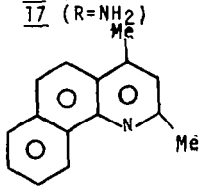
groups.[18] The results with organolithium metallating agents have been justified by complexation of the Li atom with the ring N atom prior to metallation thereby holding the basic reagent in close proximity to the less acidic 2-Me group. Metallation then can proceed by a favorable 6-membered ring process as shown. Other authors have called such a process a "coordination only" limiting mechanism.[27] In contrast, such complexation of the organometallic with the ring N atom should be less when alkali cations other than Li, or basic solvents such as ammonia or other amines are employed. In these cases, the basic reagent is "free" to ionize the more strongly acidic 4-Me group ("acid-base" limiting mechanism.[27])

The problem became even more interesting when it was found that treatment of the above heterocycles with n-BuLi in THF afforded the expected 2-lithiomethyl derivatives **1–3** during short reaction periods. However, upon standing, such organometallics isomerized to the 4-lithiomethyl derivatives **4–6**, respectively.[28] The isomerizations in THF were even faster in the presence of an extra equivalent of the parent heterocycle being complete within a period of 1 hr. In marked contrast, the 2-lithiomethyl derivatives **1**, **2** and **3** were found to be stable in ethyl ether and did not isomerize to **4**, **5** and **6** unless chelating agents such as tetramethylethylenediamine or HMPA were added. Anions **1–3** are tighter ion pairs in ethyl ether than in THF as evidenced by $^{1}H^{28b}$ and $^{7}Li^{29}$ NMR spectroscopy thereby favoring structures such as **9**. Interestingly, although the material balances were low, the opposite isomerization of 4-lithiomethyl derivative **6** (M = Li) to **3** was found to partially occur when THF solvent was replaced by ethyl ether.

There is ample evidence to suggest that the negative charge of carbanions on 2- and 4-Me groups of pyridines and related heterocycles resides nearly exclusively on the ring N atom. Spectral techniques used to reach this conclusion have been based on ^{1}H NMR[18c,28b–c,30a–b], UV[30c], ^{13}C NMR[30d,e] ^{15}N NMR[30f] and ^{7}Li NMR[29] data.



10 (R=OH)
17 (R=NH2)



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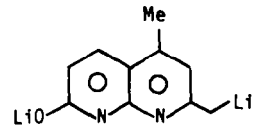

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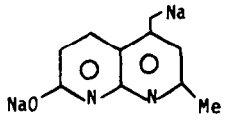

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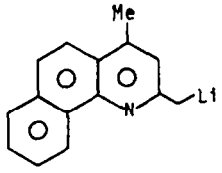

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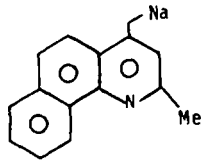

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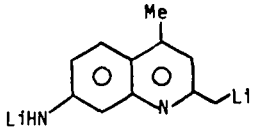

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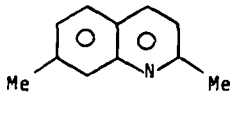
The above selective metallations were further illustrated by the conversions of naphthyridine **10** to **11** or **12**,[28b] and of benzoquinoline **13** to **14** or **15**[31] by n-BuLi in ethyl ether–hexane and sodium amide in ammonia, respectively. Dianion **16** has similarly been prepared from napththyridine **17** and n-BuLi in ethyl ether–hexane.[32b] Not surprisingly, dianions **11**, **12** and **16** underwent condensation with electrophiles such as benzophenone at carbon rather than at O or N.[33]

In contrast to the above, several other dimethylated nitrogenous heterocycles afforded only one of two possible carbanion derivatives regardless of the basic reagents employed. For example, 2,7-dimethylquinoline (**18**)[23] and 2,4-dimethylquinoline-N-oxide (**19**)[28b] yielded only **20** and **21**, respectively, upon treatment with n-BuLi in ether or THF, or lithium dialkylamides in THF. That **18** failed to afford any of the isomeric **22** can be ascribed to the necessity of disrupting the aromaticity of both rings in order to delocalize the negative charge onto the ring N atom. Presumably, the 2-Me group of **18** is also substantially more acidic than the 7-Me group. That the N-oxide **19** gave only **21** can be ascribed to the formation of the stable chelate shown,[28b] and to the enhanced acidity of the 2-Me compared to the 4-Me group of the parent heterocycle.[18a] Incidentally, while some carbanion chemistry is known for the N-oxides of 2- and 4-methylpyridine,[34] 2-[35] and 4-methylquinoline,[36] no other related studies have been reported on the N-oxides of dimethylated nitrogenous heterocycles.

More surprising than the above was the failure of



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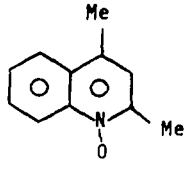

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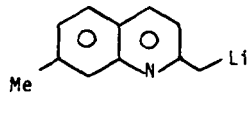

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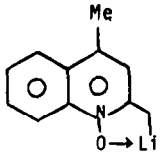

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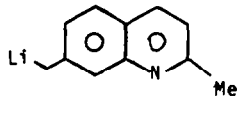
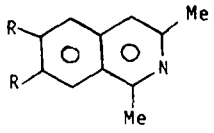
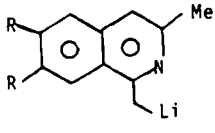


22

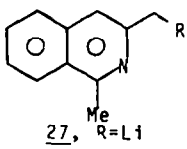
1,3-dimethylisoquinoline (**23**) and its 6,7-dimethoxy derivative **24** to undergo selective metallations.[37] Thus, only **25** and **26** were obtained from **23** and **24**, respectively, regardless of the choice of basic reagent which ranged from n-BuLi or lithium diisopropylamide (LDA) in ethers to sodium amide in liquid ammonia. Interestingly, Li derivative **27**, prepared by reduction of ether **28** using Li metal in THF, did not isomerize to **25** since quenching with D_2O afforded only **29**. Thus, in contrast to anions derived from 2,4-dimethylpyridines and -quinolines (**25**, **26**), those derived from 1,3-dimethyl isoquinolines (**27**) do not equilibrate, at least under the "standard" conditions employed in these studies.



23, R=H
24, R=OCH_3



25, R=H
26, R=OCH_3



27, R=Li
28, R=OMe
29, R=D

A major disappointment to date has been the lack of success in the attempted metallations of the pharmacologically active ellipticine (**30**), a known anti-cancer agent.[38] Thus, treatment of **30** with a variety of strong bases both in the presence and absence of tertiary amines has led to frustration. Small amounts of the N,C-*bis*-n-propyl derivative **31** were obtained in one case when **30** was treated with two equivalents of n-BuLi, followed by n-propyl iodide. This heterocycle thus acts like **18** and the isomeric 2,6-dimethylquinoline where the metallated Me groups must reside on the ring containing the hetero atom. With this in mind, more positive results are anticipated with the isomeric alkaloid olivacene (**32**).

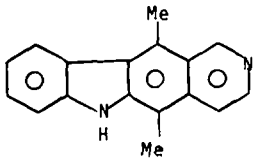
Other lateral carbanion derivatives

A variety of other side-chain derivatives of heterocycles has been synthesized in this research group by means of their organometallic intermediates. For example, 7-methyllumazine (**33**), 2,4-diamino-7-methylpteridine (**34**), and 7-methylpterin (**35**) have been converted to multiple anions **36**, **37** and **38**, respectively, by aqueous–ethanolic sodium hydroxide.[39] Subsequent condensations with aromatic aldehydes conveniently afforded 7-alkylidenepteridines **39**, **40** and **41**, respectively. The aryl groups ranged from phenyl to substituted phenyl to furyl. The only previous carbanion chemistry of pteridines involved the potassium salt **42**[40] and the Li salt **43**.[41]

The first preparation of 3-lithiomethylquinoline (**44**) was accomplished by treatment of the parent heterocycle with LDA in THF–HMPA as evidenced by condensations with aldehydes, ketones and alkyl halides.[42] This same metallating agent was utilized to improve the previously reported synthesis of 3-lithiomethylpyridine (**45**).[9,43] Yields of condensation products using this base were higher, often substantially so, than ones achieved with bases ranging from alkali amides in ammonia to LDA in ethyl ether. It should be realized that, in contrast to all other carbanions described above, **44** and **45** cannot be stabilized by delocalization of the negative charge directly onto the ring N atoms.

The simple 1-lithiomethylisoquinoline (**46**) was first reported in 1957.[44] Surprisingly, the corresponding 6,7-dimethoxy derivative **47** was not disclosed until 1978 when it was obtained from the parent heterocycle and n-BuLi in THF–hexane.[45] Of the variety of condensations of **46** and **47** with electrophiles, the most interesting ones were realized with α,β-unsaturated ketones such as chalcone to afford 1,2-adducts **48** or **49** and 1,4-adducts **50** or **51** depending upon starting carbanion and the reaction conditions.[46] For example, **46** and chalcone in THF gives mostly **48** at −78° and **50** at 25°. That the 1,2-adduct (**48**) is formed under kinetic control was demonstrated by its conversion to the 1,4-adduct (**50**) by a catalytic amount of n-butyllithium. Similar results were realized with other carbanions described in this paper as well as with other α,β-unsaturated ketones.

Running the above condensations with α,β-unsaturated ketones in ethyl ether instead of in THF yielded exclusively or nearly so 1,2-adducts. Such 1,2-adducts are even formed with sterically hindered ketones illustrated by **52** and **53**. The fact that, 1,2-adducts are favored in ethyl ether and are the kinetic products in THF, is ascribed to the formation of stable 6-membered ring chelates shown for **54**. The chelates should be less solvated and thus tighter and more stable in ethyl ether than in THF. A fine balance appears to exist between the



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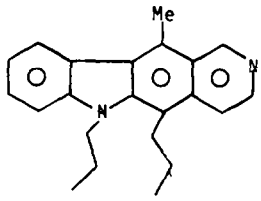

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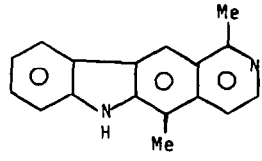

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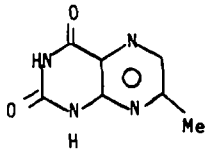

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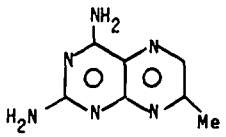

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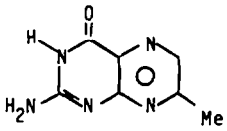

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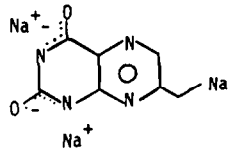

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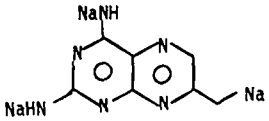

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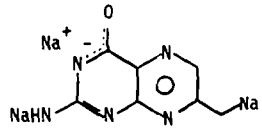

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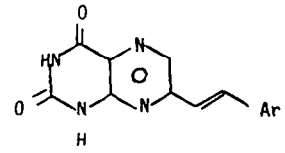

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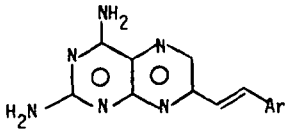

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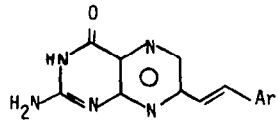

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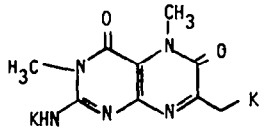

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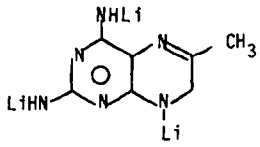

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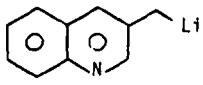

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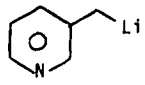

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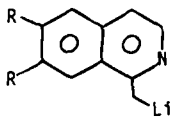
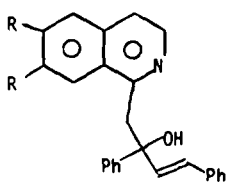


46, R=H
47, R=OCH_3



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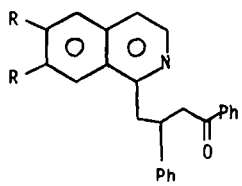

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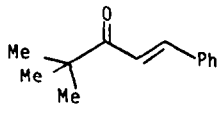

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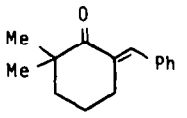

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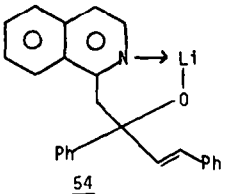

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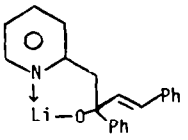

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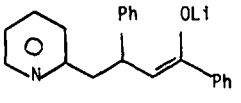

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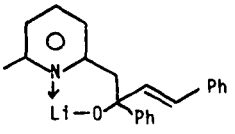
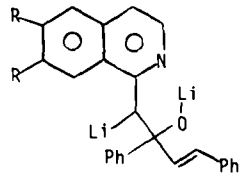


57

relative stabilities of the chelates of the 1,2-adducts and the resonance stabilized enolates of the isomeric 1,4-adducts. While, to date, this fine balance has not been found to be affected by steric hindrance on the α,β-unsaturated ketone, the chelate **55**, derived from 2-lithiomethylpyridine and chalcone, seems especially stable since it is not converted to enolate **56** even upon addition of HMPA. Chelate **55** has less steric interaction around the ring N atom than any others studied and it will be interesting to compare its stability with that of chelate **57**, derived from 6-methyl-2-lithiomethylpyridine.

Interestingly, when **46** was prepared in the presence of an extra equivalent of LDA in THF and chalcone then added at 25°, more **48** was obtained even though the solvent and the temperature favored the formation of **50**. Similar results were realized with **47** and this ketone. Such reactions apparently involve the intermediacy of dianions **58** and **59** since deuteration of the reaction mixture of **47** and chalcone gave **60**. The presence of the α-carbanions in **58** and **59** should preclude isomerization to 1,4-adducts since reversion of **58** and **59** would necessitate the formation of the strongly basic 1,1-dilithio salts **61** and **62**.

Dilithioharman (**63**), first reported in 1957[47] but only condensed with diethyl oxalate, has also been combined with α,β-unsaturated ketones.[46] For example, **63** and chalcone in THF afford mostly 1,2-adduct **64** at −78° and 1,4-adduct **65** at 25°. When **63** and this ketone were heated to 60°, **64** was again obtained but without an extra equivalent of base. In the latter case , one is tempted to speculate on the presence of the rather unconventional dianion **66** arising from an internal proton transfer though efforts to trap this species have not been successful. Dianion **63** has also been combined with a variety of aldehydes to yield simple alcohols **67** (Ar = Ph, 4-$CH_3OC_6H_4$, 3,4-$OCH_2OC_6H_3$).[48]



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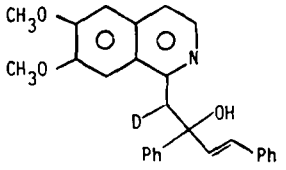

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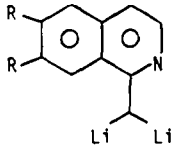

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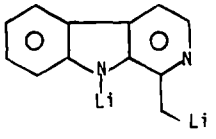

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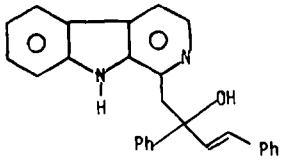

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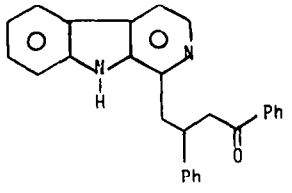

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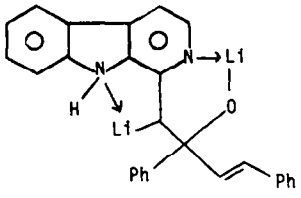

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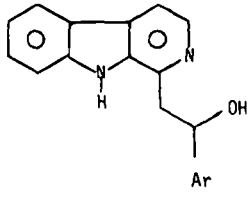

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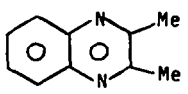

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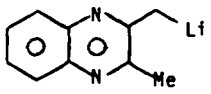

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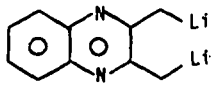

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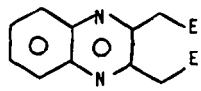

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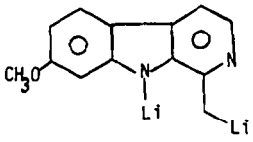

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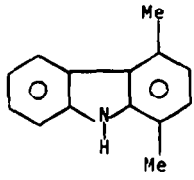

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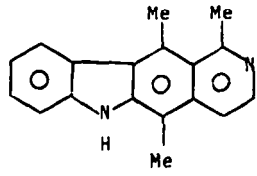

74

In another study, 2,3-dimethylquinoxaline (**68**) was converted to its monolithio derivative **69** and its dilithio derivative **70** by one and two equivalents of LDA in THF/HMPA, respectively.[49] Both **69** and **70** were combined with electrophiles in fair to good yields. In contrast to most multiple anions,[32] **70** entered into two-fold condensations with the electrophiles to afford products represented by **71**. The dipotassio and disodio derivatives corresponding to **68** had each been reported once,[13,50] but little study was performed on either species.

Some of the work currently in progress in this laboratory is concerned with systems such as dilithioharmine (**72**), directed lithiations of certain substituted carbazoles illustrated by **73**, and metalations of more complex systems like **74**. This area should continue to be a fruitful one.

EXPERIMENTAL

Representative examples of the reactions cited above are presented. M.ps were taken in capillary tubes on a Thomas–Hoover Uni-melt apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc. of Knoxville, Tennessee; correct elemental analyses (±0.3%) were obtained for all compounds described below. Infrared spectra were recorded on a Perkin–Elmer 237B spectrophotometer and NMR spectra were obtained at 60 MHz on a Varian A-60 or a Varian EM-360 spectrometer using TMS, as an internal standard. n-BuLi was purchased from Apache Chemicals of Rockford, Illinois and from Aldrich Chemical Company of Milwaukee, Wisconsin. Unless otherwise indicated, organic chemicals were purchased from Aldrich Chemical Company. THF was distilled from sodiobenzophenone after prior drying over Na metal. Ethyl ether was distilled from Na metal unless otherwise specified. All reactions involving n-BuLi were run under argon or helium in 300-ml 3-necked flasks fitted with a septum, a pressure-equalized dropping funnel, a reflux condenser equipped with a $CaCl_2$ drying tube, and a magnetic stirrer.

Preparation of 2 - *(diphenylhydroxymethyl)methyl* - 4 - *methyl* - *quinoline via anion* **3**.[23] Ethyl ether (125 ml) was treated via a syringe with 32.0 ml (0.05 mol) 1.6 M n-BuLi in hexane followed immediately with a soln 7.85 g (0.05 mol) 2,4-dimethylquinoline in 50 ml ether added during 5 min. After 1 hr, the mixture was cooled to −78° by a dry-ice–acetone bath, then treated during 5 min with a soln of 9.1 g (0.05 mol) benzophenone in 50 ml ether. After 5 min, the mixture was poured into 300 ml water and extracted into ether. The extracts were dried over $CaSO_4$ and concentrated to afford, after recrystallization from 95% EtOH, 12.0 g (75%) of product, m.p. 158–159.5°.

Preparation of hydrazine **7** *via anion* **5**.[24] To 0.05 mol sodium amide in 250 ml anhyd liquid ammonia contained in a 3-necked round-bottomed flask fiitted with a glass stirrer, a dry-ice condenser, and a pressure equalized addition funnel was added during 5 min 6.05 g (0.05 mol) 2,4,6-trimethylpyridine in 25 ml ethyl ether. After 1 hr, the soln was treated with 9.1 g (0.05 mol) azobenzene in 30 ml ether added during 5 min. After an additional 5 min reaction period, the mixture was poured into 250 ml liquid ammonia containing excess NH_4Cl. The solvents were allowed to evaporate over night and the residue was treated with 100 ml water. The organic material was extracted into ether, dried ($CaSO_4$), and concentrated to give, after recrystallization from aqueous EtOH, 4.2 g (28%) of **7**, m.p. 168–171°. This hydrazine was prepared in 77% yield by using a 2:1 excess of **5** (M = Li), prepared from the heterocycle and LDA in THF, and azobenzene.[24]

Preparation of 1,2-*di*[4-(2,6-*dimethyl*)*pyridyl*]*ethane* (**8**).[24] To 0.05 mol of **5** (M = K), prepared as above from 6.1 g (0.05 mol) 2,4,6-trimethylpyridine and 0.05 mol potassium amide in 250 ml liquid ammonia, was added in small portions, 7.9 g (0.05 mol) solid $KMnO_4$. The resulting blue–green mixture was stirred for 1 hr and neutralized by the addition of excess NH_4Cl. The solvents were allowed to evaporate and the residue was extracted with benzene in a solvent extractor. Concentration yielded, after recrystallization from EtOH, 2.3 g (38%) of **8**, m.p. 90–92°.

Isomerization of 2 - *lithiomethyl* - 4 - *methylpyridine* (**1**) *to* 4 - *lithiomethyl* - 2 - *methylpyridine* (**4**).[28] In the standard apparatus, 2.68 g (0.025 mol) 2,4-dimethylpyridine in 63 ml THF was treated with 16.0 ml (0.025 mol) 1.6 M n-BuLi in hexane. This soln was stirred for 45 min then divided into two halves. One half was cooled to −78° and treated with a soln 2.28 g (0.0125 mol) benzophenone in 20 ml THF. Standard work-up afforded 3.2 g (88%) 2 - (diphenyldroxymethyl)methyl - 4 - methylpyridine, m.p. 132–133°. The second half of the original mixture was treated with 1.34 g (0.0125 mol) 2,4-lutidine, stirred for 2 hr and treated with benzophenone and worked-up as above to give 3.2 g (88%) 4 - (diphenylhydroxymethyl)methyl - 2 - methylpyridine, m.p. 176.5–178°.

Preparation of 2 - [(2 - *oxo* - 2 - *phenyl*)*ethyl* - 7 - *hydroxy* - 4 - *methyl* - 1,8 - *naphthyridine via anion* **11**.[28a] To a suspension of 4.35 g (0.025 mol) 7 - hydroxy - 2,4 - dimethyl - 1,8 - naphthyridine in 60 ml THF was added 32 ml (0.05 mol) 1.6 M n-BuLi in hexane. The solid dissolved and the soln turned deep red. After stirring for 1 hr, the soln was cooled to −78° and treated with a soln 2.6 g (0.025 mol) benzonitrile in 20 ml THF. The mixture was stirred overnight at 25°, then refluxed for 0.5 hr. At the end of this time, it was treated with 75 ml water containing

10 ml conc. HCl and heated for 1 hr. The soln was then neutralized with 10% $NaHCO_3$ and extracted with THF. The THF was removed *in vacuo* and the residue treated with MeOH to yield 1.9 g of solid. The MeOH was evaporated and the residue was chromatographed on silica gel with 10% acetone/chloroform to yield 1.1 g of solid identical to the one above. These were combined to yield 2.0 g of product; m.p. 216–218° ($CHCl_3$).

Preparation of 4 - [(2 - *oxo* - 2 - *phenyl)ethyl*] - 7 - *hydroxy* - 2 - *methyl* - 1,8 - *naphthyridine via anion* **12**.[28b] To 0.05 mol of **12**, prepared from 4.35 g (0.025 mol) of **10** and 0.055 mol sodium amide in 250 ml liquid ammonia, was added a soln of 2.6 g (0.025 mol) benzonitrile in 30 ml ether. The mixture was allowed to stand overnight then neutralized with NH_4Cl. The ammonia was evaporated and the residue was heated with 100 ml of 10% HCl soln for 1 hr. The soln was then made basic with 10% $NaHCO_3$ aq and product (3.4 g, 49%) was removed by vacuum filtration: m.p. 235–238° (2/10 methanol/acetone).

Metallation and deuteration of 2,4-*dimethylquinoline* N-*oxide using n-butyllithium in THF–hexane.*[28b] To 50 ml of THF at 0° in the standard apparatus was added 2.0 g (0.012 mol) 2,4-dimethylquinoline N-oxide followed by 8.0 ml (0.0125 mol) 1.6 M n-BuLi in hexane. The red–brown soln was stirred for 40 min, then cooled to −78° and treated with 11 ml THF soln containing 3 ml D_2O. The soln was allowed to warm, then treated with 30 ml of $CHCl_3$ and filtered to remove LiOD. Evaporation of the solvent gave 1.9 g (95%) of recovered amine oxide containing 0.7 D atoms on the 2-Me group; m.p. 117–118°.

Preparation of 1 - *lithiomethyl* - 3 - *methylisoquinoline* (**25**) *using n-butyllithium*; *condensation with benzophenone.*[37] To a 100 ml 3-necked flask equipped with a septum, reflux condenser and stirrer were added under an argon atmosphere at room temp 25 ml dry THF, 1.00 g (0064 mol) 1,3-dimethylisoquinoline, and 4.1 ml (0.0064 mol) 15% n-BuLi in hexane. After stirring for 30 min, the red–brown soln was assumed to contain 0.0064 mol 1 - lithithiomethyl - 3 - methylisoquinoline. To this soln was added 1.15 g (0.0064 mol) benzophenone in 25 ml THF and the soln was stirred for 1 hr. The mixture was then quenched with water, filtered and concentrated under vacuum to give a yellow semi-solid. This material was dissolved in 30 ml ether to give, upon standing, 1.61 g (75%) 1,1 - diphenyl - 2 - (3 - methyl - 1 - isoquinolyl)ethanol, m.p. 149–151°. Similar results were obtained using LDA in THF–hexane and in ethyl ether–hexane, and sodium amide in liquid ammonia.

Preparation of 3 - (*lithiomethyl*) - 1 - *methylisoquinoline* (**27**).[37] A 100-ml 3-necked flask equipped with dropping funnel, reflux condenser and stirrer was charged with 0.75 g (0.011 g-atom) of a Li dispersion in 25 ml dry THF, and cooled to 0°. To this stirred suspension was added dropwise under an argon atmosphere a soln of 2.00 g (0.011 mol) 3 - methoxymethyl - 1 - methylisoquinoline in 10 ml dry THF and the resulting light brown soln stirred at 0° for 60 min. The mixture was then quenched with D_2O, filtered and concentrated under vacuum to give a light yellow oil. The oil was vacuum distilled at 82–84°/1.0 mm Hg to give 1.05 g (71%) 3 - deuteriomethyl - 1 - methylisoquinoline; NMR ($CHCl_3$) δ 2.6 (s,3,CH_3), 2.70 (s,2,CH_2), 6.75–7.85 (m,5,ArH) ppm.

Preparation of 7-*styryllumazine* (**39**, Ar = Ph) *via multiple anion* **36**.[39] To a 100 ml round bottom flask equipped with a magnetic stirrer and reflux condenser was added 1.8 g (0.01 mol) of **33**, 20 ml water and 1.4 g (0.036 mol) NaOH. The suspension was gently warmed until the pteridine dissolved, then it was treated with a soln of 1.6 g (0.015 mol) benzaldehyde in 10 ml 95% EtOH. The soln was warmed to reflux for 3 hr and the salt of the product was filtered, washed with EtOH and then ethyl ether. After drying, the yellow solid was dissolved in boiling water and acidified with conc. HCl. The resulting solid was collected and washed with EtOH and ether to afford 1.45 g (53%) of **39**, m.p. >300°; NMR(CH_3CO_2H) δ 8.92 (s,1,ArH), 7.92 (d,1,vinyl, J = 15 Hz), 7.27 (m.5,ArH), 7.13 (d,1,vinyl, J = 15 Hz); UV (0.1 N NaOH) λ_{max} (log e) 260 (4.18), 320 (3.98), 348 (3.87), 390 (4.11).

General procedure for the preparation of 3-*substituted quinolines.*[42] To 0.71 g (0.007 mol) diisopropylamine in 10 ml THF at 0° under an argon atmosphere was added 4.4 ml (0.007 mol) of 1.6 M n-BuLi in hexane followed, after 30 min, by 1.26 g (0.007 mol) of HMPA. Upon cooling to −78° with a dry-ice–acetone bath, the soln was treated during 10 min with 1.0 g (0.007 mol) 3-methylquinoline to afford a red soln which was stirred for 30 min. This soln was then treated during 5 min with 0.007 mol of an electrophile in 10 ml THF at −78°. After 1 hr at −78°, the mixture was poured into 100 ml 10% HCl, treated with 30 ml ether and made basic with KOH pellets, and the product was extracted with three 20-ml portions of ethyl ether. The combined extracts were washed with water, dried ($CaCl_2$) and concentrated. For example, 1.27 g (0.007 mol) benzophenone gave 1.4 g (61%) (aqueous EtOH) of 1,1 - diphenyl - 2 - (3 - quinolyl)ethanol, m.p. 178–180°.

General procedure for the preparation of 3-*substituted pyridines.*[43] To a soln of diisopropylamine (2.53 g, 0.025 mol) in THF (10 ml) at 0° contained in a 300 ml, 3-necked flask, equipped with a magnetic stirrer, constant pressure addition funnel and a rubber septum, was added 1.6 M n-BuLi (16 ml, 0.025 mol) in hexane via a syringe. The resulting pale yellow soln was maintained at 0° for 30 min, then treated with HMPA (4.5 g, 0.025 mol). The bright yellow soln was stirred at 0° for 15 min, then treated during 5 min with a soln of 3-methylpyridine (2.3 g, 0.025 mol) in THF (10 ml). After 30 min at 0°, the mixture containing **45** was treated during 5 min with an electrophile (0.025 mol) in THF (15 ml). The resulting soln was stirred for 1 hr at 25° and poured into 10% HCl (100 ml). In the case of condensations with carbonyl compounds, the solid was removed by filtration, washed with diethyl ether and subsequently suspended in water (100 ml). The suspension was made basic with KOH pellets and the soln was extracted with three 20-ml portions diethyl ether. The combined organic extracts were washed with two 25-ml portions water, dried over $CaCl_2$ and concentrated to afford a white solid. The crude product was recrystallized from an appropriate solvent to give pure product.

In the case of the alkylations with ethyl and n-propyl bromides and the acylation with methyl benzoate, neutralization with 10% HCl gave a two-layered system. The layers were separated and the aqueous layer was made basic with solid KOH pellets. The basic soln was extracted with three 20-ml portions of diethyl ether and the combined extracts were worked-up as above. Distillation of the crude product gave pure material. For example, n-propyl bromide on **45** yielded 3-n-butylpyridine (77%), b.p. 74–76°/7.0 mm.

General experimental procedure for the preparation and condensations of 1-*lithiomethylisoquinolines* **46** *and* **47**.[45] To a 100 ml, 3-necked flask equipped with a septum, reflux condenser, pressure equalized addition funnel, and magnetic stirrer was added under an argon atmosphere dry THF (25 ml), 1-methylisoquinoline (1.43 g, 0.01 mol), and, via a syringe, 15% n-BuLi (6.4 ml, 0.01 mol) in hexane. After stirring for 25 min, the red–brown soln was treated during 1–2 min with the electrophile (0.01 mol) in dry THF (25 ml) and the mixture stirred for 30 min. At the end of this time, the mixture was hydrolyzed by the addition of wet THF, filtered, and concentrated *in vacuo* to afford either an oil or a solid which was purified by crystallization or recrystallization, respectively.

An identical procedure was employed to effect condensations of 6,7 - dimethoxy - 1 - methylisoquinoline (1.015 g, 0.005 mol) using 15% n-BuLi (3.2 ml, 0.005 mol) in hexane and appropriate electrophiles (0.005 mol). Thus, benzaldehyde on **46** and **47** afforded the corresponding quinolylethanols in 80% (m.p. 109–112°) and 74% (m.p. 153–155°), respectively.

Preparation of **50** *from* **46** *and chalcone.*[51] To a 0.02 mol soln of **46**, prepared as above, was added 5 ml dry HMPA followed by the addition of 4.16 g (0.020 mol) chalcone in 30 ml dry THF and the yellow soln was stirred for 30 min. The mixture was then quenched with wet THF, filtered and concentrated under vacuum to give a red oil. This oil was dissolved in 100 ml ethyl ether and was added to a separatory funnel containing 150 ml 10% HCl. After standing for 1 hr, the solid which had formed was filtered off and was recrystallized from acetone to give 2.30 g (60%) of 1 - (2,4 - diphenyl - 4 - oxobutyl)isoquinoline hydrochloride; white solid, m.p. 151–153°. A portion of this material was converted to the free base with NaOH to give **50**, m.p. 112–116°.

Preparation of **48** *from* **46** *and chalcone.*[52] Repetition of the above in ethyl ether gave only **48** (69.4%), m.p. 106–107°.

Metallation of harman.[51] To a 100-ml 3-necked flask equipped with a septum, reflux condenser and stirrer were added under an argon atmosphere 0.91 g (0.005 mol) harman, 30 ml dry THF and 6.5 ml (0.010 mol) 15% n-BuLi in hexane. A yellow ppt formed rapidly and, after stirring for 30 min, the suspension was assumed to contain 0.005 mol of **63**.

Addition of **63** *to chalcone.*[51] To a 0.005 mol soln of **63**, prepared as above, was added 1.04 g (0.005 mol) chalcone in 25 ml dry THF and the orange soln was stirred for 60 min. The mixture was then quenched with wet THF, filtered and concentrated under vacuum to give a yellow solid. This solid was dissolved in a minimum amount of ethyl ether and placed on a silical gel column and eluted with ethyl ether, collecting the yellow band (R_f 0.6–0.7). The solvent was removed from this fraction leaving a pale yellow solid which was recrystallized from ethyl ether to yield 1.56 g (80%) of **65**; white needles, m.p. 135–138°.

Addition of **63** *to benzaldehyde.*[51] To a 0.005 mol soln of **63**, prepared as above, was added 0.53 g (0.005 mol) benzaldehyde in 25 ml dry THF and the yellow soln was stirred for 30 min. The mixture was then quenched with wet THF, filtered and concentrated under vacuum to yield a yellow oil. This oil was dissolved in a minimum amount of acetone and placed on a silica gel column and eluted with acetone, collecting the yellow band (R_f 0.7). The solvent was removed from this fraction leaving a yellow oil which was dissolved in ethyl ether. Upon scratching and cooling, the soln yielded 1.15 g (80%) of **67** (Ar = Ph) m.p. 146–148°. An analytical sample was obtained from two further recrystallizations from ethyl ether to give light yellow prisms, m.p. 166–168°.

Preparation and reactions of 2 - *lithiomethyl* - 3 - *methylquinoxaline* (**69**).[49] To a soln of 2.53 g (0.025 mol) diisopropylamine in 10 ml THF contained in a 300-ml, 3-necked flask, equipped with a magnetic stirrer constant pressure addition funnel and a rubber spectrum, was added 16 ml (0.025 mol) commercial 1.6 M n-BuLi in hexane via a syringe. The resulting pale yellow soln was maintained at 0° for 30 min, then treated with 4.5 g (0.025 mol) HMPA via a syringe. The resulting bright yellow soln was stirred at 0° for 15 min, then cooled to −78°. This solution was then treated during 5 min with 3.9 g (0.025 mol) 2,3-dimethylquinoxaline in 15 ml THF. After 30 min, this mixture was reacted with electrophiles. For example, 4.6 g (0.025 mol) benzophenone in 15 ml THF for 1 hr afforded 6.4 g (74%) of 1,1 - diphenyl - 2 - (3 - methyl - 2 - quinoxalinyl)ethanol, m.p. 144–145°.

Preparation and reactions of the dilithio salt of 2,3-*dimethylquinoxaline.*[49] The title compound was prepared as described above for the corresponding monoanion using LDA and 2,3-dimethylquinoxaline in a 2:1 ratio. Condensations were effected by adding the electrophile at −78° during 5 min followed by stirring at 25° for 1 hr. Benzophenone in this case gave 49% of **71** (E = $C(OH)Ph_2$), m.p. 182–184°.

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