Journal of Organometallic Chemistry, 213 (1981) 405—417
Elsevier Sequoia S.A., Lausanne — Printed in The Netherlands

REGIOINTEGRITY OF CARBANIONS DERIVED BY SELECTIVE METALATIONS OF DIMETHYLPYRIDINES AND -QUINOLINES

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(Received November 5th, 1980)

Summary

Metalation of 2,4-dimethylpyridine and -quinolines by strong basic reagents in ethyl ether in the absence of HMPA affords 2-lithiomethyl derivatives regardless of the reaction length. The use of THF in such metalations promotes the formation of the 2-lithiomethyl reagents which isomerize to the more thermodynamically stable 4-lithiomethyl derivatives after relatively long reaction periods or in the presence of amines or an excess of the parent heterocycle. The latter derivatives appear to be formed directly from the heterocycles in ammonia or in the presence of HMPA. The results are discussed in terms of "coordination-only" versus "acid-base" limiting mechanisms for metalations as a function of ion pairing. NMR spectra for certain of the carbanions in ethyl ether and THF are described which support the above concepts. Related metalations of 2,4-dimethylquinoline-*N*-oxide give only the 2-lithiomethyl derivative. Similar reactions of 7-hydroxy-2,4-dimethyl-1,8-naphthyridine lead in synthetically useful yields to derivatization of the 2- and 4-methyl groups via dianions by using n-butyllithium in ethyl ether and sodium amide in liquid ammonia, respectively, followed by the addition of appropriate electrophiles.

Some time ago [1], it was reported that the site of metalation of dimethylated pyridines and quinolines was a function of the metalating agent and the solvent. For example, 2,4-dimethylquinoline could be conveniently and selectively converted to its 2- (II) or 4-alkalimethyl (III) derivatives by n-butyllithium in ether/hexane or alkali metal amides in ammonia, respectively. It was later found that the regiointegrity of such carbanions is dramatically affected by the choice of solvent and time of reaction [2]. For example, lithio salt II isomerizes to III in THF. This paper describes the full details of a study of regiointegrity of carbanions derived by selective metalation of 2,4-dimethyl-

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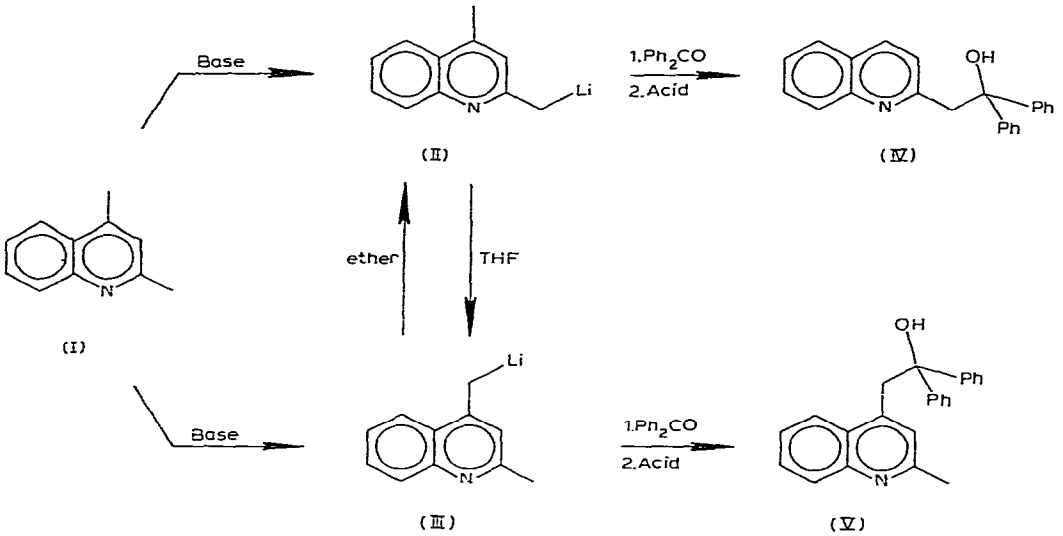
quinoline and -pyridine, and related compounds. It will be shown that such regiochemistry is a function of the solvent and length of reaction but not of the temperature.



Results and discussion

At the onset, it should be stressed that metalations of 2,4-dimethylquinolines and -pyridines afford 2- and 4-metallomethyl derivatives in synthetically useful yields in ether and THF, respectively, though certain precautions must be observed in the latter solvent (vida supra). The synthetic utility of such systems has been discussed previously [1].

The results obtained with 2,4-dimethylquinoline are summarized in Table 1. Each entry in the table was obtained by interacting the heterocycle with an appropriate basic reagent in the solvent shown for the indicated time at the designated temperature followed by the addition of benzophenone. In a few of the time studies, aliquots of the organometallic were withdrawn by syringe, then treated with this ketone. The percentages listed in the table are of isolated carbinols IV and V which arise from II and III, respectively. Specifically, it should be noted that metalation of I with n-butyllithium, lithium methylamide, lithium dimethylamide, and lithium diisopropylamide in ether/hexane affords only the 2-lithiomethyl derivative II regardless of the length of the reaction. In contrast, interaction of I with n-butyllithium in THF/hexane gives the 2-lithiomethyl derivative II after short reaction periods, but yields the 4-lithiomethyl derivative III after longer ones. Formation of III is more readily achieved by metalating I with a deficiency of n-butyllithium, n-butyllithium · TMEDA in THF/hexane but not in ether/hexane, or by a variety of lithium amides all in THF/hexane. Of particular interest is the formation of III in only 5 min by the use of lithium dimethylamide in THF/hexane. It should be noted that low temperature (—78°C) did not affect the regiochemistry in these metalations.

TABLE 1

CONDENSATIONS OF LITHIO-2,4-DIMETHYLQUINOLINES WITH BENZOPHENONE

Base	Solvent	Time (h)	Temp. (°C)	Yield (%)	
				IV (II)	V (III)
n-BuLi	ether/hexane	1.0	25	90	—
n-BuLi · TMEDA	ether/hexane	1.0	25	83	—
n-BuLi	ether/hexane	24(96)	25	85(94)	—
n-BuLi	THF/hexane	1.0	25	94	—
n-BuLi · TMEDA	THF/hexane	1.0	25	—	77
n-BuLi	THF/hexane	1.0	—78 or 25	94	—
n-BuLi	THF/hexane	12	—78	65	—
n-BuLi	THF/hexane	24	25	Mixture (75%)	
n-BuLi	THF/hexane	144	25	—	75
1/2 n-BuLi	ether/hexane	1.0(96)	25	94(66)	—
1/2 n-BuLi	THF/hexane	1.0	25	—	94
MeNHLi	ether/hexane	1.0	25	48	—
MeNHLi	ether/THF/hexane	1.0	25	—	58
Me_2NLi	ether/hexane	1.0(120)	25	76(66)	—
Me_2NLi	THF/hexane	5/60(1.0)	25	—	47(81)
Me_2NLi	Me_2NH/ether/hexane	1.0	25	—	47
LDA	ether/hexane	1.0	25	70	—
LDA	THF/hexane	1.0	25	80	—

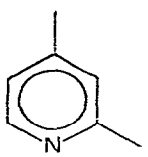
Similar results were realized in metalations of 2,4-dimethylpyridine (VI) to give either VII or VIII which were trapped with benzophenone to yield IX and X, respectively. Thus, as shown in Table 2, metalations of VI by n-butyllithium or LDA in ether/hexane afford only VII regardless of the amount of the base, the time, or the temperature. In contrast, the use of n-butyllithium on VI in THF/hexane gives VII after short reaction periods but yields VIII after only 10 h. This latter time should be compared with the much longer periods required for the related isomerization of quinoline derivative II to III. Equally fast was the preparation of VIII from VI using LDA in THF/hexane after only 1 h although VII was obtained in this solvent provided the reaction mixture

TABLE 2

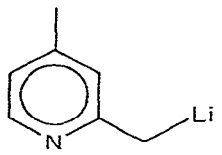
CONDENSATION OF LITHIO-2,4-DIMETHYLPYRIDINES WITH BENZOPHENONE

Base	Solvent	Time (h)	Temp. (°C)	Yields (%)	
				IX (VII)	X (VIII)
n-BuLi	ether/hexane	1.0	25	55	
1/2 n-BuLi	ether/hexane	1.0	0	75	—
n-BuLi	THF/hexane	1.0	—78(0)(25)	24(72)(68)	—
1/2 n-BuLi	THF/hexane	1.0	0	—	60
n-BuLi	THF/hexane	'10(24)	0	—	69(63)
LDA	ether/hexane	0(4)	0	44(52)	—
LDA	THF/hexane	5/60	0	71	—
LDA	THF/hexane	1.0	0	—	72
LDA	THF/hexane/HMPA	1/60(1/2)	0	—	44(64)
LDA	ether/hexane/HMPA	1/60(1/4)	0	—	44(58)

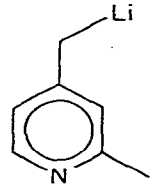
was quenched after 5 min. As before, isomerization of the 2-lithiomethyl to the 4-lithiomethyl derivative in THF/hexane was faster in the presence of a deficiency of n-butyllithium; however, such a deficiency of reagent was without effect in ether. The presence of HMPA in metalations of VI by LDA gave only VIII regardless of the solvent even after reaction periods as short as 1 min.



(VI)



(VII)



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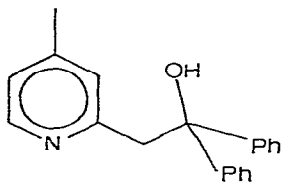
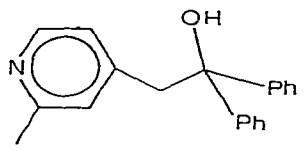


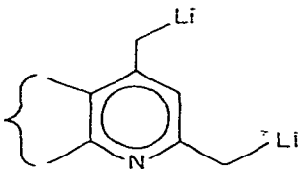
(IX)



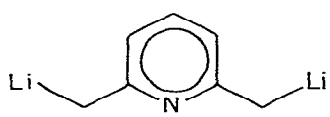
(X)

To summarize the above results, except in the cases of I with lithium dimethylamide in dimethylamine/ethyl ether and VI with LDA/HMPA/ether, it is obvious that the use of ethyl ether in such metalations favors the formation of the 2-lithiomethyl derivatives II and VII. In contrast, the use of THF favors the eventual formation of the 4-lithiomethyl derivatives III and VIII.

The isomerizations of II to III and VII to VIII in the absence of amines probably occur via equilibration of the carbonions with small amounts of unionized parent heterocycle. This hypothesis is supported by the dramatically more rapid isomerizations in the presence of an extra equivalent of the parent heterocycle, that is, in reactions employing a deficiency of the basic reagent. In the slower isomerizations in the presence of equivalent amounts of n-butyllithium, dianions such as XI are certainly possible since the related XII and others have been reported previously [3]. The more rapid isomerization of VII to VIII than of II to III can be attributed to peri-hydrogen steric effects in III.



(XI)

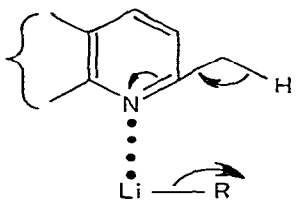


(XII)

The isomerizations of II to III and VII to VIII in the absence of extra I and VI, respectively were more rapid with amide bases than with n-butyllithium. This result is not surprising when it is recalled that amide bases, upon metalation of the heterocycles, are converted to their conjugate acids which should facilitate the equilibration to the more thermodynamically stable carbanions. In the case of lithium dimethylamide and I, at no time has II been observed in

THF even after only 5 min. Thus, it is certainly possible that III is formed directly in this system. The effect of dimethylamine as co-solvent with ether in the metalation of I and of HMPA in the reactions of VI with LDA are especially noteworthy since they represent the only examples where 4-lithiomethyl derivatives II and VIII were obtained in ethyl ether.

The above results may be rationalized by superimposing ion-pairing effects with two recently suggested limiting mechanisms [4] for metalations. As proposed earlier [1], the initial formation of 2-lithiomethyl derivatives II and VII can be ascribed to coordination of the metalating agents with the ring nitrogen atoms of I and VI, as illustrated by XIII ("coordination only" limiting mechanism [4]). In contrast, the apparent direct formation of VIII from VI and LDA/HMPA presumably arises from the "acid-base" limiting mechanism [4] since the 4-methyl hydrogen atoms (pk_a 4-methyl < 2-methyl [5]) are ionized by the coordinately saturated basic reagent which can not be complexed by the ring nitrogen atoms. Such a proposal is also supported by the formation of 2-methyl-4-sodiomethylquinoline and -pyridine by sodium amide in liquid ammonia [1].



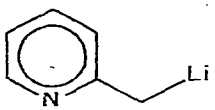
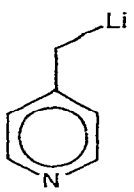
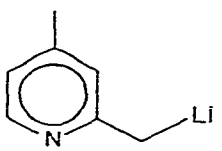
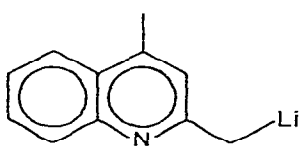
(XIII)

All of the above carbanions are extensively delocalized so the charge lies primarily on nitrogen [6]. Moreover, 2- and 4-picolyl carbanions have been described as tight ion pairs even in monoglyme [6c]. However, none of the earlier extensive NMR studies [6] utilized ethyl ether as solvent. To demonstrate that the currently studied carbanions should be tighter ion pairs in ethyl ether than in THF, the NMR spectra of several of them as well as the related 2- and 4-lithiomethylpyridines in ethyl ether were obtained (Table 3). A comparison of the chemical shifts of the ring protons of 2-lithiomethylpyridine and of 2-lithiomethyl-4-methylpyridine (VII) clearly reveals that more shielding of the ring protons is realized in THF that in ether, presumably a result of more extensive delocalization in THF. Similar results were achieved with 2-lithiomethyl-4-methylquinoline. Of lesser interest are the 4-lithiomethyl derivatives III and VIII which could not be obtained in ether/hexane. However, published chemical shift differences of the ring protons of 2,6-dimethyl-4-lithiomethylpyridine [6b] in DME and THF suggest more delocalization in the former solvent. Thus, it is reasonable to expect less delocalization in III and VIII in ether than in THF.

The NMR data verify more interaction between the carbanions and the cations in ether than in THF, a result not surprising when it is recalled that THF possesses greater coordinating ability towards the cations than does ether. While the presence of a chelate such as XIV [7] has been questioned in THF [6c], it may still be considered a viable contributor to the resonating structures

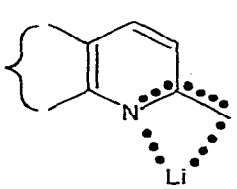
TABLE 3

NMR DATA FOR LITHIUM DERIVATIVES OF CERTAIN METHYLATED PYRIDINES AND QUINOLINES [a]

Compound	Solvent	Chemical shifts (ppm)
	THF/hexane ether/hexane	3 H: 5.63; 4 H: 5.98; 5 H: 4.87; 6 H: 6.90 3 H: 5.84; 4 H: 6.26; 5 H: 5.12; 6 H: 7.00
	THF/hexane ether/hexane	2 H and 6 H: 6.53; 3 H and 5 H: 4.35; 4.10 2 H and 6 H: 6.57; 3 H and 5 H: 4.60; 4.05
	THF/hexane ether/hexane	3 H: 5.37; 5 H: 4.83; 6 H: 6.90 3 H: 5.72; 5 H: 5.12; 6 H: 6.97
	THF/hexane ether/hexane	3 H: 5.87; 5 H—8 H: 5.98—6.88 3 H: 6.03; 5 H—8 H: 6.18—7.22

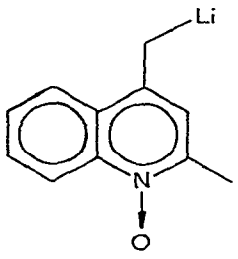
[a] Concentrations in each case were 1.0 *M*. The chemical shifts are relative to internal tetramethylsilane.

for II and VII in ether, where lithium probably uses *p*-orbitals for bonding to both carbon and nitrogen. Whatever the actual structures of II and VII, they can be considered to be kinetically stronger bases in THF than in ether because they are looser ion pairs, so the isomerizations of II to III and VII to VIII occur by the "acid-base" limiting mechanism involving ionization of the most thermodynamic acidic 4-methyl hydrogen atoms. The exact location of the lithium atoms in the above compounds will have to await more sophisticated NMR spectroscopy.

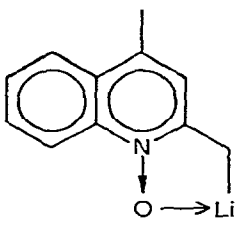


(XIV)

Parenthetically, lithiation of 2,4-dimethylquinoline-*N*-oxide with n-butyllithium or lithium dimethylamide in THF under conditions which should have afforded XV gave only XVI as evidenced by deuteration. Although isomerization of XVI to XV was not realized, the results are consistent with the above conclusions since the 2-methyl hydrogens are the most acidic ones [5a] and especially since XVI should be stabilized by a more favorable five-membered ring chelate as shown.

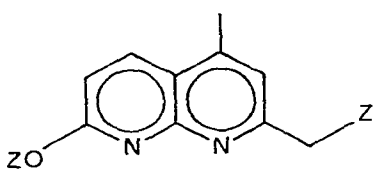


(XV)

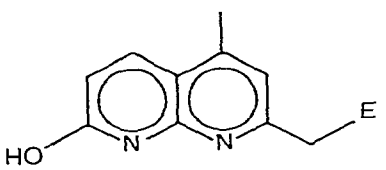


(XVI)

The above work further illustrates the subtle but important differences between ethyl ether and THF. From a synthetic standpoint, it can now be stated that 2-lithiomethyl derivatives of such heterocycles should be prepared using n-butyllithium in ethyl ether regardless of the reaction length or n-butyllithium in THF using short reaction periods. In contrast, the successful formation of the isomeric 4-alkalimethyl derivatives in THF is subject to a suffi-



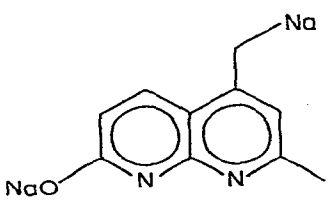
(XVII, Z = H ;
XVIII Z = Li)



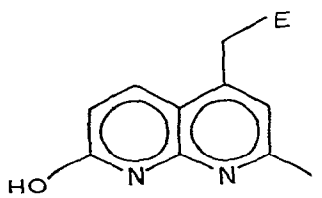
XIX, E = $C(OH)Ph_2$;

XX, E = $\overset{\overset{O}{\|}}{C}Ph$;

XXI, E = $(CH_2)_3CH_3$)



(XXII)



(XXIII, E = $C(OH)Ph_2$;

XXIV, E = $\overset{\overset{O}{\|}}{C}Ph$;

XXV, E = $(CH_2)_3CH_3$)

ciently large number of variables (solvent, time, presence of certain amines, relative amounts of reagents) that optimum conditions will have to be established for each different heterocycle studied. To avoid the latter, it is recommended that such 4-alkalimethyl derivatives be prepared using the simple and convenient system sodium amide in liquid ammonia. These suggestions are supported by the metalations and condensations of 7-hydroxy-2,4-dimethyl-1,8-naphthyridine (XVII). Thus, treatment of XVII with two equivalents of n-butyllithium in ether or THF (1 h) gives XVIII ("coordination only" mechanism) since subsequent condensations with benzophenone, benzonitrile, and n-butyl bromide afford XIX, XX, and XXI, respectively. In contrast, metalation of XVII with two equivalents of sodium amide in liquid ammonia yields XXII ("acid-base" mechanism) as evidenced by reaction with the same three electrophiles to give XXIII, XXIV, and XXV, respectively.

Such regiochemistry is currently being applied to the interesting heterocycles olivacene and ellipticene.

Experimental

Melting points 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. 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 tetramethylsilane as an internal standard. n-Butyllithium 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. Tetrahydrofuran was distilled from sodiobenzophenone after prior drying over sodium metal. Ethyl ether was distilled from sodium metal. All reactions involving n-butyllithium were run under argon or helium in 300-ml three-necked flasks fitted with a septum, a pressure-equalized dropping funnel, a reflux condenser equipped with a calcium chloride drying tube, and a magnetic stirrer.

Condensations of lithio-2,4-dimethylquinolines with benzophenone

Table 1 lists the results of a variety of condensations of 2,4-dimethylquinoline with benzophenone effected by several different bases in certain solvents for the indicated times and temperatures. For synthetic purposes, the reader is directed to previously described preparations of IV and V effected by n-butyllithium in ether/hexane and by sodium amide in liquid ammonia, respectively [1]. Other specifics follow.

A. Preparation of 2-lithiomethyl-4-methylquinoline (II); isomerization studies. To 16.0 ml (0.025 mol) of 1.6 *M* n-butyllithium in hexane and 20 ml of anhydrous ethyl ether in the equipment described above was added 3.93 g (0.025 mol) of 2,4-dimethylquinoline in 30 ml of ether. The resulting solution was divided in half using a hypodermic syringe to give parts A and B. Meanwhile, a solution of 4.56 g (0.025 mol) of benzophenone in 80 ml of ether was prepared.

Part A was manipulated as follows. After 24 h, 10 ml of the solution was

removed, cooled to —78° C, and treated with 10 ml of the above benzophenone solution. The cold bath was removed. Upon reaching 25° C, the reaction mixture was poured into water and worked-up as described previously [1] to give 0.9 g (85%) of IV; m.p., m.m.p. 158—159.5° C. After 96 h, 10 ml more of the anion solution was withdrawn and treated at —78° C with 10 ml of the benzophenone solution to give, after work-up, 1.0 g (94%) of IV; m.p., m.m.p. 158—159.5° C.

Part B of the original anion solution was added to 1.96 g (0.013 mol) of 2,4-dimethylquinoline. After 1 h, 10 ml of this solution was withdrawn, cooled to —78° C, and treated as above with 10 ml of the benzophenone solution to give 1.0 g (94%) of IV; m.p., m.m.p. 158—159.5° C. The process was repeated after 24 h and 96 h to give IV, in yields of 75% and 66%, respectively.

The entire sequence described above was repeated using THF instead of ethyl ether. Part A in this series gave 94% of IV after 1 h, 75% of a mixture of IV and V after 24 h, and 75% of pure V (m.p., m.m.p. 170—172° C) after 144 h. Part B in this series gave V in a yield of 94% after only 1 h.

B. Condensations in the presence of TMEDA. Part A was repeated using 2.9 g (0.025 mol) of TMEDA in 30 ml of ether, 16.0 ml (0.025 mol) of 1.6 *M* n-butyllithium in hexane, 3.93 g (0.025 mol) of 2,4-dimethylquinoline in 30 ml of ether, and 4.56 g (0.025 mol) of benzophenone in 25 ml of ether added dropwise during 5 min. The cooling bath was removed and the solution was stirred for 15 min before it was poured into 200 ml of water. Usual work-up afforded 7.0 g (83%) of IV, m.p., m.m.p. 158—159.5° C. Repetition of the experiment employing THF instead of ether gave 6.5 g (80%) of V, m.p., m.m.p. 170.5—172° C.

C. Condensations effected by lithium methylamide. Repetition of Part B using 1.13 ml (0.78 g, 0.025 mol) of methylamine instead of TMEDA in ether and THF afforded 4.1 g (48.4%) of IV and 4.9 g (58%) of V, respectively.

D. Condensations effected by lithium dimethylamide. Part B above was repeated using 1.7 ml (1.13 g, 0.025 mol) of dimethylamine instead of TMEDA to give 6.7 g (79%) of IV and 6.9 g (81%) of V, in ether and THF, respectively. The latter compound (4.0 g, 47%) was also obtained when part B was repeated in the presence of 100 ml of dimethylamine.

E. Condensations effected by lithium diisopropylamide. Part B above was repeated using 2.53 g (0.025 mol) of diisopropylamine instead of TMEDA to yield after 1.0 h, 5.95 g (70%) and 6.8 g (80%) of IV in ether and THF, respectively.

Preparation of 2-[(2-hydroxy-2,2-diphenyl) ethyl]-4-methylpyridine (IV) and 4-[2-hydroxy-2,2-diphenyl) ethyl]-2-methylpyridine (X) [8]

(A) in ethyl ether with n-butyllithium. To 125 ml of ether in the standard apparatus was added 32 ml (0.05 mol) of 1.6 *M* n-butyllithium in hexane followed immediately by a solution of 5.35 g (0.05 mol) of 2,4-dimethylpyridine in 50 ml of ether added during 5 min. After stirring for 1 h, the mixture was cooled to —78° C and treated with a solution of 9.1 g (0.05 mol) of benzophenone in 50 ml of ether added during 5 min. The reaction mixture was allowed to warm to 25° C, then it was poured into 300 ml of water. Most of the ether was allowed to evaporate from the two phase mixture and the solid was

collected by vacuum filtration. After washing with ether, the crude product was recrystallized from 95% ethanol to afford 8.0 g (55%) of IX m.p. 134—136°C, lit. [9] m.p. 136°C; NMR ($CDCl_3$) δ 8.19 (d, 1, ArH), 7.25 (M, 10, ArH), 6.78 (d, 2, ArH), 3.54 (s, 2, CH_2), 2.20 ppm (s, 3, CH_3); IR (Nujol) 3200 cm^{-1}. Similar results were obtained when the reaction was repeated using 16 ml (0.025 mol) of 1.6 *M* n-butyllithium and 5.35 g (0.05 mol) of 2,4-dimethylpyridine.

B. In THF with n-butyllithium. The above experiment was repeated using 2.68 g (0.025) of 2,4-dimethylpyridine in 75 ml of THF, 16.0 ml (0.025 mol) of 1.6 *M* n-butyllithium in hexane, and 4.56 g (0.025 mol) of benzophenone in 50 ml of THF to give 4.9 g (68%) of IX, m.p., m.m.p. 134—136°C. Repetition of the experiment using 5.35 g (0.05 mol) of 2,4-dimethylpyridine, 16.0 ml (0.025 mol) of 1.6 *M* n-butyllithium in hexane, and 4.56 g (0.025 mol) of benzophenone afforded 4.34 g (60%) of X, m.p., m.m.p. 173—176°C.

C. Using LDA in the absence of HMPA. Part A was repeated using 2.53 g (0.025 mol) of diisopropylamine in 50 ml of ether, 16.0 ml (0.025 mol) of 1.6 *M* n-butyllithium in hexane, 2.68 g (0.025 mol) of 2,4-dimethylpyridine in 25 ml of ether, and 4.56 g (0.025 mol) of benzophenone in 30 ml of ether to yield the following amounts of IX after the indicated times: 3.8 g (52%), 4 h; 3.5 g (48%), 15 min; 3.2 g (44%), 0 min. Repetition of the above in THF rather than in ether gave 5.1 g (71%) of IX (m.p., m.m.p. 132—134°C) and 5.2 g (72%) of X (m.p., m.m.p. 176—178°C) after 5 min and 1 h, respectively.

D. Using LDA in the presence of HMPA. Part C was repeated by adding 4.5 g (0.025 mol) of HMPA to the LDA in ether or THF prior to the addition of 2.68 g (0.025 mol) of 2,4-dimethylpyridine and 4.56 g (0.025 mol) of benzophenone to afford X (44—66%).

Isomerization of 2-lithiomethyl-4-methylpyridine (VII) to 4-lithiomethyl-2-methylpyridine (VIII)

In the standard apparatus, 2.68 g (0.025 mol) of 2,4-dimethylpyridine in 63 ml of THF was treated with 16.0 ml (0.025 mol) of 1.6 *M* n-butyllithium in hexane. This solution was stirred for 45 min then divided into two halves. One half was cooled to —78°C and treated with a solution of 2.28 g (0.0125 mol) of benzophenone in 20 ml of THF. Standard work-up afforded 3.2 g (88%) of IX, m.p. 132—133°C. The second half of the original mixture was treated with 1.34 g (0.0125 mol) of 2,4-lutidine, stirred for 2 h, and treated with benzophenone and worked-up as above to give 3.2 g (88%) of X, m.p. 176.5—178°C.

Metalation and deuteration of 2,4-dimethylquinoline N-oxide

A. Using n-butyllithium in THF-hexane. To 50 ml of THF at 0°C in the standard apparatus was added 2.0 g (0.012 mol) of 2,4-dimethylquinoline *N*-oxide followed by 8.0 ml (0.0125 mol) of 1.6 *M* n-butyllithium in hexane. The red-brown solution was stirred for 40 min, then cooled to —78°C and treated with 11 ml of THF solution containing 3 ml of D_2O. The solution was allowed to warm, then treated with 30 ml of chloroform and filtered to remove LiOD. Evaporation of the solvent gave 1.9 g (95%) of recovered amine oxide containing 0.7 deuterium atoms on the 2-methyl group; m.p. 117—118°C; lit. [10] m.p. 118—120°C; NMR ($CDCl_3$) δ 8.89 (m, 1, ArH), 7.75 (m, 3, ArH), 7.15 (s,

1, ArH), 2.7 (m, 2.3, CH_2), 2.6 ppm (s, 3, CH_3).

B. Using n-butyllithium-TMEDA in THF. A n-butyllithium-TMEDA complex (0.0125 mol) was prepared from 8.0 ml (0.0125 mol) of 1.6 *M* n-butyllithium and 1.45 g (0.0125 mol) of TMEDA in 10 ml of THF and then treated with 2.0 g (0.012 mol) of 2,4-dimethylquinoline *N*-oxide in 50 ml of THF. This solution was then treated with D_2O as described above to give 1.9 g (95%) of product; m.p. 117—118°C; NMR ($CDCl_3$) δ 8.9 (m, 1, ArH), 7.75 (m, 3, ArH), 7.15 (s, 1, ArH), 2.7 (m, 2.0, CH_2), 2.6 ppm (s, 3, CH_3). Thus, the product contained 1.0 deuterium atoms on the 2-methyl group.

C. Using lithium dimethylamide in THF. To a solution of 0.0125 mol of lithium dimethylamide, prepared from 1.7 ml (0.025 mol) of dimethylamine and 8.0 ml (0.0125 mol) of 1.6 *M* n-butyllithium in hexane all in 20 ml of THF was added 2.0 g (0.012 mol) of 2,4-dimethylquinoline *N*-oxide in 50 ml of THF. Helium was bubbled into the anionic solution for 1.5 h to remove the excess dimethylamine, then the solution was cooled to —78°C and treated with D_2O as described above to give 1.9 g (95%) of product; m.p. 117—118°C; NMR δ 8.89 (m, 1, ArH), 7.75 (m, 3, ArH), 7.15 (s, 1, ArH), 2.7 (m, 2.4, CH_2), 2.6 ppm (s, 3, CH_3). The product thus possessed 0.6 deuterium atoms on the 2-methyl group.

Preparation of 7-hydroxy-2,4-dimethyl-1,8-naphthyridine

An acidic solution was prepared from 40 ml of sulfuric acid and 300 ml of water and cooled to —3°C. A solution of 40 g (0.23 mol) of 7-amino-2,4-dimethyl-1,8-naphthyridine [11] in 300 ml of water containing 40 ml of sulfuric acid and a solution of 17 g of sodium nitrite in 40 ml of water were prepared. The latter solutions were added simultaneously to the initial cooled acid solution. The temperature during the addition was held below 0°C and the solution was stirred for 15 min after addition was complete. The temperature was gradually raised to 80°C and the mixture then allowed to cool. The pH of the solution was adjusted to 8—9 using 330 ml of 7.5 *M* NaOH and finally 60 ml of 10% $NaHCO_3$. Filtration of the suspension gave 38.4 g (95%) of yellow solid. This solid was dissolved in 3 l of boiling methanol and the solution was concentrated to a volume of about 500 ml. After cooling, 34.7 g (86%) of the title compound (XVII) as a yellow solid was removed; m.p. 252.5—254°C (lit. [12] 251—252°C); NMR (CF_3COOH) δ 8.53 (d, 1, ArH), 7.45 (m, 2, ArH), 2.95 ppm (s, 6, CH_3).

Preparation of 2-[(2-hydroxy-2,2-diphenyl)ethyl]-7-hydroxy-4-methyl-1,8-naphthyridine (XIX)

To 175 ml of ether and 32 ml (0.05 mol) of 1.6 *M* n-butyllithium in hexane was added portion-wise during 1 h, 4.35 g (0.025 mol) of 7-hydroxy-2,4-dimethyl-1,8-naphthyridine. The solution was stirred for 1 h, then cooled to —78°C and treated with 4.56 g (0.025 mol) of benzophenone in 30 ml of ether. The solution was stirred for 10 min then poured into 100 ml of 5% $NaHCO_3$ solution. The solid which formed was filtered and recrystallized from 95% ethanol to yield 4.0 g (45%) of XIX; m.p. 243—244°C; IR (Nujol) 3300 cm^{-1} (OH). Anal.: Found: C, 77.30; H, 5.76; N, 7.68. $C_{23}H_{20}N_2O_2$ calcd.: C, 77.50; H, 5.66; N, 7.86%.

Preparation of 2-[(2-oxo-2-phenyl)ethyl]-7-hydroxy-4-methyl-1,8-naphthyridine (XX)

To a suspension of 4.35 g (0.025 mol) of 7-hydroxy-2,4-dimethyl-1,8-naphthyridine in 60 ml of THF was added 32 ml (0.05 mol) of 1.6 *M* n-butyllithium in hexane. The solid dissolved and the solution turned deep red. After stirring for 1 h, the solution was cooled to —78° C and treated with a solution of 2.6 g (0.025 mol) of benzonitrile in 20 ml of THF. The mixture was stirred overnight at 25° C, then refluxed for 0.5 h. At the end of this time, it was treated with 75 ml of water containing 10 ml of concentrated HCl and heated for 1 h. The solution was then neutralized with 10% $NaHCO_3$ and extracted with THF. The THF was removed in vacuo and the residue treated with methanol to yield 1.9 g of solid. The methanol 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 and recrystallized from chloroform to yield 2.0 g of XX; m.p. 216—218° C; NMR (CF_3COOH) δ 7.93 (m, 10, ArH), 5.14 (s, 2, CH_2), 3.0 ppm (s, 3, CH_3); IR (Nujol) 1650 cm^{-1} (C=O), 1590 and 750 cm^{-1} (aromatic). Anal.: Found: C, 73.50; H, 5.04. $C_{17}H_{14}N_2O_2$ calcd.: C, 73.36; H.07%.

Preparation of 7-hydroxy-4-methyl-2-n-pentyl-1,8-naphthyridine (XXI)

To 0.02 mol of XVIII prepared as above in THF was added a solution of 3.42 g (0.025 mol) of n-butyl bromide in 50 ml of THF. After stirring for 1 h at —78° C, the solution was refluxed for 5 h then allowed to stand for 60 h. The mixture was neutralized with aqueous ammonia chloride and the aqueous mixture was extracted with THF. Removal of the THF in vacuo followed by treatment of the oily residue with 200 ml of an ether/petroleum ether mixture (1/3) gave a tan solid which was recrystallized from acetone to yield 2.8 g (40%) of XXI; m.p. 171—173° C; NMR ($CDCl_3$) δ 7.93 (d, 1, ArH), 6.8 (m, 2, ArH), 2.8 (m, 5, CH_2, CH_3, benzylic), 1.35 ppm (m, 9, CH_2, CH_3, aliphatic). Anal.: Found: C, 73.17; H, 7.99. $C_{14}H_{18}N_2O$ calcd.: C, 73.01; H, 7.88%.

Preparation of 4-[(2-hydroxy-2,2-diphenyl)ethyl]-7-hydroxy-2-methyl-1,8-naphthyridine (XXIII)

To a sodium amide solution in liquid ammonia, prepared from 1.27 g (0.055 g atom) of sodium in 250 ml of ammonia, was added portionwise 4.35 g (0.025 mol) of 7-hydroxy-2,4-dimethyl-1,8-naphthyridine over a 35 min period. The solution was stirred for 45 min, then treated with a solution of 4.56 g (0.025 mol) of benzophenone in 40 ml of ether over 5 min. After stirring for 10 min more, the solution was poured into a flask containing 10 g of NH_4Cl and the ammonia was allowed to evaporate. The residue was hydrolyzed by the addition of 100 ml of water and the crude product was collected by filtration and recrystallized from 95% ethanol to afford 3.8 g (43%) of XXIII; m.p. 231—232° C; NMR (CF_3COOH) δ 7.98 (d, 1, ArH), 6.7 (m, 14, ArH, vinyl, OH), 1.95 ppm (s, 3, CH_3); IR (Nujol) 3300 cm^{-1} (OH), 1610 and 700 cm^{-1} (aromatic). Anal.: Found: C, 76.11; H, 5.54. $C_{23}H_{20}N_2O_2$ calcd.: C, 77.50; H, 5.66%.

Preparation of 4-[(2-oxo-2-phenyl) ethyl]-7-hydroxy-2-methyl-1,8-naphthyridine (XXIV)

To 0.055 mol of sodio salt XXII, prepared as above, was added a solution of 2.6 g (0.025 mol) of benzonitrile in 30 ml of ether. The mixture was allowed to stand overnight then neutralized with NH_4Cl. The ammonia was evaporated and the residue heated with 100 ml of 10% HCl solution for 1 h. The solution was then made basic with 10% $NaHCO_3$ solution and XXIV (3.4 g, 49%) was removed by vacuum filtration: m.p. 235—238°C (2/10 methanol/acetone); NMR (CF_3COOH) δ 7.84 (m, 9, ArH), 5.2 (s, 2, CH_2), 3.0 ppm (s, 3, CH_3); IR 1660 cm^{-1} (C=O), 1610 cm^{-1} (aromatic). Anal.: Found: C, 73.20; H, 5.06. $C_{17}H_{14}N_2O_2$ calc.: C, 73.36; H, 5.07%.

Preparation of 7-hydroxy-2-methyl-4-n-pentyl-1,8-naphthyridine (XXV)

To 0.055 mol of sodio salt XXII was added a solution of 2.4 g (0.0175 mol) of n-butyl bromide in 30 ml of ether over a 30 min period. After stirring overnight, the solution was poured onto 10 g of NH_4Cl and the ammonia allowed to evaporate. The residue was slurried with water and filtered (vacuum) to give 5.0 g of tan solid. This was recrystallized from acetone to yield 3.3 g (57%) of XXV as light yellow flakes; m.p. 158—161°C (acetone), NMR ($CDCl_3$) δ 7.9 (d, 1, ArH), 6.75 (m, 2, ArH), 2.7 (m, 5.3, CH_2, CH_3, benzylic), 1.3 (m, 8.4, CH_2, CH_3, aliphatic). Anal.: Found: C, 72.83; H, 7.78. $C_{14}H_{18}N_2O$ calc.: C, 73.01; H, 7.88%.

Acknowledgement

A portion of this work was supported by the National Institute of General Medical Sciences, National Institutes of Health on grant R01GM21500 and by the Petroleum Research Fund, administered by the American Chemical Society, on grant 11703-AC4.

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