NMR Proof of the Structure of 4-Aminoquinolines and Pyridines

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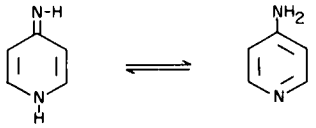
Nmr spectra of a number of 4-*N*-alkylaminoquinolines and 4-*N*-alkylaminopyridines show coupling between hydrogen of the amino group and α-hydrogen on the alkyl group. No such coupling would be observed if the hydrogen were on heterocyclic nitrogen. Other nmr characteristics in the benzenoid region suggest that all simple 4-aminoquinolines and 4-aminopyridines have the amino structure.

INTRODUCTION

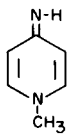
The 2- and 4-aminopyridines and quinolines initially were thought to be abnormal in their chemical behavior when compared with other arylamines or even the 3-isomer. Diazotization, basicity, reaction with methyl iodide, Schiff base formation, Skraup and related syntheses, and hydrolysis either proceed with difficulty or give unexpected products (2).

These reactions and the similarity of the ultraviolet spectra with the hydroxyl derivative, which is known to exist in the keto form, caused some authors to ascribe the imino-tautomer (I) to the structure of 4-aminopyridine, (II) (3).



I II

Anderson and Seeger (4), and later Mason (5) using model compounds such as 1,4-dihydro-4-imino-1-methylpyridine (III), found that there was a low energy transition (*ca.* 270 mμ) characteristic of the imino group which was absent in 4-aminopyridine. Angyal and Werner's infrared studies (6), as well as Angyal and Angyal's calculation of the tautomeric equilibrium constant (7), also give support for the predominance of the amino form (II).



III

More recently, Renault and Cartron (8) made nmr studies with 4-aminoquinoline and some of its alkylated derivatives and found coupling between the 2- and 3-protons on the nucleus to be 5 cps for the amino form and 8 cps for the imino form. They concluded that the imino form is present in neutral media and the amino form is dominant in the presence of alkali amide.

The key to the solution of the problem is the detection of the environment within which the hydrogen atom resides. If the hydrogen resides on the amino nitrogen, certain coupling relationships of it with nearby groups should be found. If it resides on heterocyclic nitrogen, no coupling should be found with the groups near the amino nitrogen. With this *modus operandi* in mind, model compounds were synthesized and their nmr spectral characteristics studied.

EXPERIMENTAL

4-Methylamino-2-methylquinoline (VII).

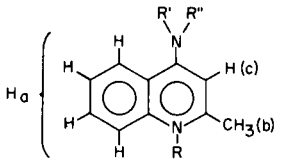
A solution of 4-chloro-2-methylquinoline (5 g., 0.028 mole) and methylamine hydrochloride (2.35 g., 0.035 mole) in 15 g. of phenol was heated at 80° for 3 hours. To the cooled solution was added 10% sodium hydroxide and ether for extraction. A solid residue, which was insoluble in both the base and ether, was filtered and washed with base. From the nmr spectrum the phenoxyl intermediate was suspected. An additional 5 g. of methylamine hydrochloride was heated with the solid at 130° for 1 hour. The cooled mixture was washed with 10% base and the solid sublimed yielding 2 g. (43%) of VII, m.p. 238-239° [Lit. (9) 239°], nmr Table I.

4-Dimethylamino-2-methylquinoline (V).

A mixture of 4-chloro-2-methylquinoline (10 g., 0.056 mole),

TABLE I

NMR Data of Various *N*-Methylated 4-Aminoquinaldines



Compound	R	R′	R″	δ in ppm (c) Ha	Hb	Hc	H_R	$H_{R'}$	$H_{R''}$	cps (a) J_{NH-CH_3}	Solvent
IV	–	H	H	6.9-8.0	2.40	6.39	–	6.10	–	–	DMK-d_6
IV	–	H	H	7.2-8.2	2.46	6.50	–	6.70	–	–	DMSO-d_6
V	–	CH_3	CH_3	7.1-8.1	2.62	6.56	–	2.87	2.87	–	$CDCl_3$
V	–	CH_3	CH_3	7.2-8.1	2.60	6.78	–	2.96	2.96	–	DMSO-d_6
VI	CH_3	–	H	7.0-8.3	2.22	5.79	3.45 (b)	4.82	–	–	DMSO-d_6
VII	–	H	CH_3	7.2-8.2	2.50	6.34	–	2.90	–	5.2 (d)	DMSO-d_6
VII	–	H	CH_3	7.2-8.1	2.58	6.35	–	3.01	–	5.2	DMK-d_6

(a) The methyl hydrogens are split into a doublet which degenerates to a singlet when the hydrogen on the nitrogen is exchanged with deuterium oxide or decoupled. (b) This methyl group exchanged with deuterium oxide. (c) Chemical shifts are relative to the internal standard TMS. (d) Decoupling by irradiation of NH chemical shifts causes collapse to a singlet.

TABLE II

Effect of Temperature on Coupling of 4-Methylamino-2-methylquinoline (a) (VII)

Temperature	J_{NH-CH_3} (b)
35	4.6 cps
60	4.5 cps
80	2.1 cps
90	0 cps
35 (c)	4.5 cps

(a) These spectra were run in DMSO-d_6. (b) The coupling was measured with a sweep width of 50 cps. (c) This is the same sample that was heated to 90°.

dimethylamine (10 g., 0.22 mole), and copper bronze (1 g.) in 30 ml. of methanol was heated in a simple autoclave at 185° for 5 hours. The mixture was poured into water, acidified with hydrochloric acid, filtered, and washed with methylene chloride. The aqueous portion was made basic and extracted with methylene chloride. The organic layer was dried (sodium sulfate), concentrated and distilled, yielding 6.1 g. (59%) of V, b.p. (0.25 mm) 107-108°, nmr Table I. The melting point of the picrate was 228-230°.

Anal. Calcd. for $C_{18}H_{17}N_5O_7$ (picrate): C, 52.04; H, 4.12; N, 16.90. Found: C, 51.84; H, 4.16; N, 16.67.

1,4-Dihydro-4-imino-1,2-dimethylquinoline (VI).

4-Amino-2-methylquinoline methiodide (0.1 g.) was dissolved in a few drops of 20% sodium hydroxide and extracted with chloroform. The chloroform was dried twice (sodium sulfate) and the solution was concentrated under vacuum. The last portion of chloroform was allowed to evaporate in a dry bag which had been flushed with nitrogen. The residue was taken up in dimethylsulfoxide-d_6 and placed directly into the nmr tube. No attempt was made to isolate the compound because of the known instability of this type to air and carbon dioxide (7).

4-*n*-Butylamino-7-chloroquinoline (XIV).

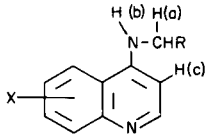
A solution of 4,7-dichloroquinoline (3.4 g., 0.017 mole) and *n*-butylamine (1.6 g., 0.019 mole) in 60 ml. of dimethylsulfoxide was heated at 80° for 4 days. The solution was poured into water and the solid filtered yielding 3.4 g. (89%) of XIV, m.p. 130-131°, [Lit. (10) 130-135°], nmr, Table III.

7-Chloro-4-methylaminoquinoline (XVI).

A solution of 4,7-dichloroquinoline (1 g., 0.005 mole) and methylamine (1 g., 0.032 mole) in 30 ml. of dimethylsulfoxide was heated at 70° for 9 days. The solution was poured into water and the product filtered yielding 0.95 g. (98%) of XVI, m.p. 245-246° [Lit. (11) 247-248°], nmr, Table IV.

TABLE III

NMR Data of Longer Chain 4-Alkylaminoquinolines

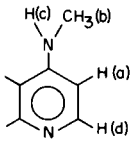


Compound	H_a	J_{ab}	H_c
7-Chloro-4-(3-Dimethylamino-2,2-dimethylpropylamino)quinoline XII	3.17	4.5 (d) (b)	6.24 (5.5)
4-(3-Dimethylaminopropylamino)-2-methylquinoline XIII	3.31	5.0 (q) (c)	6.20
4-Butylamino-7-chloroquinoline XIV	3.28	5.0 (q) (c,d)	6.40 (5.4)
	3.72	7.2 (t)	6.83 (7.8) (e)

(a) All chemical shifts relative to internal standard TMS. (b) Exchange with deuterium oxide causes collapse to a singlet. (c) Exchange with deuterium oxide causes collapse to a triplet. (d) Spin decoupling experiments causes collapse to a triplet. (e) Run in trifluoroacetic acid - all others in deuteriochloroform.

TABLE IV

Effect of Acid and Base on 4-Methylaminoquinoline and 4-Methylaminopyridine

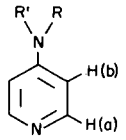


Compound	(ppm) H(a)	(ppm) H(b)	cps J_{bd}	cps J_{ad}	Solvent	Acid or Base
7-Chloro-4-methylaminoquinoline XVI	6.40	2.90	4.7	5.3	DMSO-d_6	None
	6.72	3.14	4.7	7.9	DMSO-d_6	Gaseous HCl
	6.40	2.90	0	5.5	DMSO-d_6	Aqueous KOH (b)
4-Methylaminopyridine XVII	6.49	2.74	5.3	–	DMSO-d_6	None
	–	2.80	0	–	DMSO-d_6	Aqueous KOH (b)
	–	(-)3.86 (a)	0	–	Conc. HCl	–

(a) No internal or external standard was used. The value given is relative to the Ha proton on the nucleus. (b) Catalytic amounts.

TABLE V

NMR Spectra of 4-Amino-, 4-Methylamino-, and 4-Dimethylaminopyridine in DMSO-d_6



Compound	R	R'	δ ppm (a) H(a)	H(b)	H_{CH_3}	H_{N-H}	J_{NH-CH_3}
4-Aminopyridine XVIII	H	H	8.03	6.52	–	6.00	–
4-Methylaminopyridine XVII	H	CH_3	8.03	6.49	2.70	–	5.3 (b)
4-Dimethylaminopyridine XIX	CH_3	CH_3	8.12	6.59	2.95	–	–

(a) All chemical shifts are related to the internal standard TMS. (b) This doublet collapses when deuterium oxide is added.

7-Chloro-4-(2,2-dimethyl-3-dimethylaminopropylamino)quinoline (XII) (12).

A solution of 4-(3-amino-2,2-dimethylpropylamino)-7-chloroquinoline (13), (4 g., 0.015 mole) and aqueous formaldehyde (12 g., 0.15 mole) in 30 ml. of 98% formic acid was brought to reflux. Three additional 12 g. portions of formaldehyde solution were added over a 72 hour period. The solution was concentrated and the residue taken up in 10% hydrochloric acid. The acid was neutralized with aqueous sodium hydroxide and extracted with ether. The ether layer was dried (magnesium sulfate) and concentrated, and the residue recrystallized from hexane yielding 2.4 g. (54%) of colorless crystals of XII, m.p. 73-74°, nmr, Table III.

Anal. Calcd. for $C_{16}H_{22}ClN_3$: C, 65.86; H, 7.60; N, 14.40; Cl, 12.15. Found: C, 66.40; H, 7.73; N, 13.99; Cl, 11.80.

4-(3-Dimethylaminopropylamino)-2-methylquinoline (XIII).

A solution of 4-chloro-2-methylquinoline (10 g., 0.056 mole), phenol (30 g.) and 3-dimethylaminopropylamine (5.8 g., 0.06 mole) was heated at 170° for 4 hours. The phenol was removed by steam distillation. The residue was extracted with ether and washed with 10% sodium hydroxide. The ethereal solution was dried (sodium sulfate) and concentrated to yield 9 g. of a heavy oil. The oil was dissolved in 10% hydrochloric acid, slowly made basic with 10% ammonium hydroxide, and recrystallized from hexane yielding 5.4 g. (40%) of colorless crystals of XIII, m.p. 63-65°. The melting point of the dihydrochloride monohydrate was 232-234°.

Anal. Calcd. for $C_{15}H_{25}Cl_2N_3O$ (dihydrochloride monohydrate): C, 53.90; H, 7.54; N, 12.57. Found: C, 54.17; H, 7.36; N, 12.54. Neutralization equiv. calcd. 167. Found: 169.

4-Methylaminopyridine (XVII).

A solution of 4-chloropyridine hydrochloride (10 g., 0.074 mole) in 40 g. of 40% aqueous methylamine was heated in a simple autoclave at 170° for 9 hours. The cooled solution was extracted several times with methylene chloride which was dried (sodium sulfate) and concentrated. The solid was recrystallized from hexane yielding 3 g. (38%) of colorless crystals of XVII, m.p. 123-124° [Lit. (14) 124°.

Other Compounds.

4-Amino-2-methylquinoline (m.p. 167-168°), 4-aminopyridine (m.p. 161-162°), and 4-dimethylaminopyridine (m.p. 109-110°) were obtained from Aldrich Chemical Co. and sublimed at least twice before spectra were run.

Solvents.

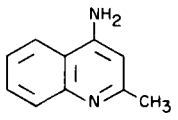
The dimethylsulfoxide-d_6 (99.5% isotopic purity), deuterium oxide (99.8%), acetone-d_6 (99.5%), and chloroform-d (99.8%) were obtained from Diaprep Inc.

Instrument.

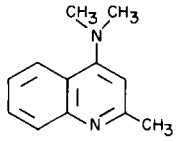
A Varian A60 A nuclear magnetic resonance spectrometer equipped with a model V-6058A spin decoupler and a variable temperature controller was used in this study (15).

RESULTS AND DISCUSSION

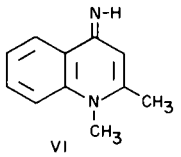
Since most of the solvents in previous nmr studies were aqueous or protonic, a shift to an anhydrous medium seemed more profitable to detect tautomeric differences. With this in mind 4-amino-2-methylquinoline (IV), 4-dimethylamino-2-methylquinoline (V), 1,4-dihydro-4-imino-1,2-dimethylquinoline (VI), and 4-methylamino-2-methylquinoline (VII) were synthesized. Although the synthesis



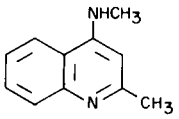
IV



V



VI

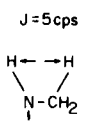


VII

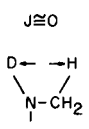
of isomers VI and VII were presented in the Experimental Section, mention should be made here that they can be synthesized unequivocally. The synthesis of VI can be accomplished by allowing IV to react with methyl iodide followed by treatment with base. The condensation of 4-chloro-2-methylquinoline with methylamine gave VII. If the imino form were predominant and if the exchange rate were slow enough, there should be different chemical shifts for the exocyclic and heterocyclic N-H groups. In acetone-d_6 the unsubstituted 4-amino-2-methylquinoline (IV) showed a broad singlet at δ 3.63 and δ 6.11 with each peak integrating for one proton (16).

Compounds V and VI are unique because the only forms possible are the amino- and imino-structures respectively. The 3-H of the quinoline nucleus has a chemical shift of δ 6.56 in V whereas the same hydrogen in VI appears at δ 5.79. This is a shift to higher field of δ 0.77 which is the direction of change of the chemical shift in going from a hydrogen in an aromatic environment to one in an olefinic environment.

The 4-methylamino-2-methylquinoline (VII) spectrum, as anticipated, was most informative in elucidating the structure. The methyl group attached to the nitrogen has a chemical shift of δ 2.90 in DMSO-d_6 and appears as a doublet. When about 0.5 equivalents of deuterium oxide was added, there were three peaks for the methyl peaks. With excess deuterium oxide there was only a single peak, but if excess water was added to the deuterated compound the doublet reappeared. The coupling for hydrogen



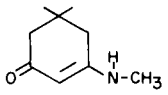
VIII



IX

attached to amine (VIII) was 5.2 cps giving rise to a doublet while the coupling constant for the deuterium attached to amino was essentially zero. When incomplete exchange had occurred, a mixture of VIII and IX was present, and three peaks were observed for the methyl group, the doublet from VIII and the singlet from IX.

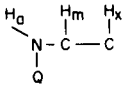
A temperature study of 4-methylamino-2-methylquinoline (VII) over the range 35° to 90° showed a change in the NH-CH_3 coupling constant from 5.2 cps at 35° to 0 cps at 90° (Table II). The coalescence with the temperature increase has been observed with ethanol in which case the hydroxyl triplet became a singlet (17). Also in the enamine (X) -NH-CH_3 coupling was found to vary from 4.6 cps at 15° to 3.4 cps at 50° (18).



X

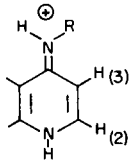
The only aprotic solvents in which the primary and secondary amines of Table I were soluble are acetone and dimethylsulfoxide; however, the longer chain 4-alkylaminoquinolines were soluble in chloroform.

The spectra of these compounds are summarized in Table III. In all three compounds the α-methylene hydrogens were coupled with the hydrogen on amino nitrogen. Another interesting feature of the spectra was that $J_{am} = J_{mx}$ in the compounds that had β-hydrogens. This means a quartet for the α-methylene hydrogens of



XI

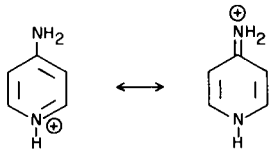
XIII and XIV collapses to a triplet when exchanged with deuterium oxide. Decoupling experiments were run on 4-*n*-butylamino-7-chloroquinoline (XIV) in which both the β-methylene hydrogens and the amino hydrogen were decoupled. In all but one of the systems studied that could exhibit $H_{2,3}$ coupling, the coupling constants were 5 cps which is in agreement with the conclusions of Pople, Schneider, and Bernstein for the quinoline nucleus and consequently the amino form. The lone exception was the constant from the spectra of XIV in trifluoroacetic acid. In this solvent the heterocyclic nitrogen is protonated and contributions from cannonical forms such as XV are possible. The $H_{2,3}$ coupling observed was 7.9 cps.



XV

The fact that the exchange rate was slow enough for -NH-CH_2- coupling to be observed was unusual. The mean life-time between exchange events must be at least 0.21 seconds for hydroxyl proton coupling to be observed in ethanol and concentrations of acid as low as 10^{-1} *N* will cause collapse of the triplet (19). A study of the effect of acid and base on an aminoquinoline and pyridine was made and summarized in Table IV.

7-Chloro-4-methylquinoline (XVI) showed a doublet for the *N*-methyl protons with coupling constants of 4.7 cps. When gaseous hydrogen chloride was passed through the solution, there was no change in the NH-CH_3 coupling. A shift of all peaks to lower field does occur as well as a change in $H_{2,3}$ coupling from 5.3 cps to 7.9 cps, indicative of ring protonation to the exclusion of exocyclic nitrogen protonation, an unusual feature; nevertheless, an examination of the *p*Ka's of 4-aminopyridine and aniline gives a reasonable rationale (2). Aniline (*p*Ka = 4.19) is much less basic than 4-aminopyridine (*p*Ka = 9.17) which can be explained in terms of the stability of the cations (20). When aniline is protonated, loss of all π interaction occurs between the amino group and the phenyl ring. When 4-aminopyridine is protonated, gain in resonance stabilization of the cation, XVIII a and b, occurs if the ring nitrogen is protonated.

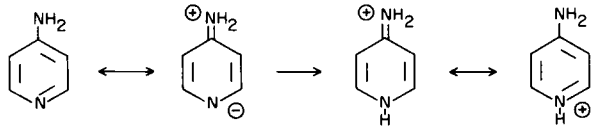


XVIIIa XVIIIb

When one equivalent or less of acid is present, most of the protonation is on the ring nitrogen and therefore does not effect the coupling at the exocyclic site. However, when a large excess is present, rapid exchange does occur and alkyl-amino coupling is no longer observed. The effect of small amounts of base on the exchange does lead to the rapid exchange of the amino-hydrogen and to the disappearance of any multiplicity arising from coupling with that hydrogen. With the quinoline derivative (XVI) in Table IV, $J_{2,3}$ = 5.5 before and after catalytic amounts of base were added. The chemical shifts of the neutral and basic solution were also identical.

The nmr spectra of 4-aminopyridine and 4-dimethylaminopyridine were examined by Brugel in aqueous DMSO, but he did not study 4-methylaminopyridine (21). The spectra of the three aminopyridines are summarized in Table V. The expected NH-CH_3 coupling is present in 4-methylaminopyridine (XVII), $J_{NH\text{-}CH_3}$ = 5.3 cps, the same coupling constant observed for the quinoline series. On this basis the 4-aminopyridines seem to be structurally similar to their quinoline benzologs. As shown in Table IV base catalyzes the rapid exchange of 4-methylaminopyridine and causes the methyl hydrogens to coalesce to a singlet.

In our opinion, the nmr spectra offers conclusive evidence that the hydrogen in 4-aminoquinolines and pyridines resides on the amino nitrogen (22). The chemical behavior of these compounds cannot be attributed to abnormal structure but rather to relatively greater contributions from cannonical forms involving heterocyclic nitrogen in the free base and cation:



EXPERIMENTAL

(1) Taken in part from the Ph.D. thesis of J. C. C., 1968. This work was supported by the U. S. Army Medical Research and Development Command, Contract DA-49-193-MD-2752, Contribution No. 439.

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(11) J. Gage, *J. Chem. Soc.*, 1458 (1949).

(12) We are indebted to Mr. Taylor Barbee for the preparation of this compound.

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(15) We are indebted to the National Science Foundation for a grant which enabled the department to purchase this intrument.

(16) Initially, the two peaks were thought to be caused by two different N-H absorptions; however, an exchangeable deuterium

impurity in the solvent was found to be responsible. The peak at δ 6.11 was the NHD and at δ 3.63 was the HOD absorption. This impurity was found also in DMSO-d_6.

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(22) Although the evidence is unequivocal for 4-alkylaminoquinolines and 4-alkylaminopyridines, the evidence for primary aminoquinolines and aminopyridines is equivocal insofar that judgment is based on similarity in the aromatic portion of the nmr spectra (see Table I and contrast amino spectrum of IV and imino spectrum of VI).

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