Proton Magnetic Resonance Spectra of Some Di- and Tri-azanaphthalenes and Nitroisoquinolines

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The 4-deutero-derivatives of quinazoline and 1,3,5-triazanaphthalene have been prepared and used to show that the signals at lowest field in the proton magnetic resonance spectra of the non-deuterated compounds are due to H-4. Proton magnetic resonance spectra of 5-, 7-, and 8-nitrioisoquinoline, 3-nitro-1,5-, 3-nitro-1,6-, and 8-nitro-1,6-naphthyridine, 1,5-, 1,6-, 1,7-, and 1,8-naphthyridine, and 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-triazanaphthalene have been measured and analysed. Specific shielding effects of ring nitrogen atoms in these series have been calculated and used to predict the chemical shifts of protons in isoquinoline.

THE relative chemical shifts of H-2 and H-4 of quinazoline and its aza-analogues have been the subject of a number of recent investigations.[1-5] Black and Heffernan [6] suggested that H-2 of quinazoline absorbs at lower field than H-4, whereas Katritzky *et al.*,[7] from a study of substituted quinazolines, reached the opposite conclusion. We have now settled this question by preparing 4-deuteroquinazoline, and we find that H-4 of the undeuterated compound absorbs at lower field than H-2.

Proton magnetic resonance (p.m.r.) spectra of quinazoline in several solvents have been reported,[6-8] and separation of the broad singlets assigned to H-2 and H-4 increases with increase in the polarity of the solvent (Table 1). Comparison of the spectra of quinazoline and its 4-deutero-derivative in the listed solvents showed

TABLE 1

Solvent effects on the signals from H-2 and H-4 of quinazoline

Solvent	Chemical shifts (τ) H-2 *	H-4	Separation	Ref.
Cyclohexane			0·0	8
Carbon tetrachloride ...	0·77 (0·78)	0·71	0·06	6
Deuterochloroform ...	0·62 (0·62)	0·55	0·07	
Acetone	0·73 (0·72)	0·48	0·25	6
Dimethyl sulphoxide ...	0·59 (0·58)	0·30	0·29	7

* Values in parentheses are for the 4-deutero-derivative.

that, in every case, the signal at lowest field was due to H-4. Black and Heffernan [6] postulated that solute–solvent interactions in polyazanaphthalene solutions are strongest at α-nitrogen atoms (counteracting normal solvation effects on adjacent protons). Hence, the signal from H-4 of quinazoline undergoes the normal downfield shift as the polarity of the solvent increases, but that from H-2 is much less affected and sometimes moves in the opposite direction, presumably owing to the counterbalancing influence of the adjacent solvated nitrogen atom (N-1). This selective solvation hypothesis is further supported by the absence of the expected solvent effects in the spectra of 1,3,5-triazanaphthalene (Table 2), where all protons except H-7 are either adjacent or *peri* to an α-nitrogen atom. The spectra of 1,3,6-triazanaphthalene show solvent effects very similar to those observed in quinazoline spectra.

Complete analyses of the spectra of four triazanaphthalenes are given in Table 2. First-order parameters have been checked by computation which showed that the errors involved are less than those incurred in the measurements of line positions. In all cases, the signal from H-4 was either coincident with or downfield from that of H-2. In the spectra of 1,3,5-, 1,3,6-, and 1,3,7-triazanaphthalene and quinazoline, reported here, the signal from H-4 normally exhibited observable splitting ($J_{4,8} = 0{\cdot}8$ c./sec.) but that from H-2 was always considerably broader owing to coupling with the adjacent nitrogen atoms. The signals from H-2 and H-4 of 1,3,6-, 1,3,7-, and 1,3,8-triazanaphthalene (in deuterochloroform) are close together, but those from 1,3,5-triazanaphthalene, in which H-4 is *peri* to N-5, are more widely separated (0·25 p.p.m.) and have been unequivocally assigned by comparison with the spectrum of the 4-deutero-derivative.

P.m.r. parameters for 1,5-, 1,6-, 1,7-, and 1,8-naphthyridine are in Table 2. Gawer and Dailey [8] published a partial analysis of the spectrum of 1,5-naphthyridine (in cyclohexane) which is in qualitative agreement with our results (in deuterochloroform). The spectra of 5-, 7-, and 8-nitroisoquinoline and 3-nitro-1,5-, 3-nitro-1,6-, and 8-nitro-1,6-naphthyridine have been measured, and relevant data are in Table 2.

The effects of replacing a ring carbon atom by a nitrogen atom, or of inserting a nitro substituent, on the chemical shifts of the remaining protons have been calculated from these spectra and those of quinoline [9] and the diazanaphthalenes [6] reported by Black and Heffernan. These effects are presented in terms of the "interactions" used by Wells and Alcorn [10] to classify similar effects in the spectra of nitronaphthalenes. The terminology is summarised on the formulæ (I) and (II).

Table 3 lists the "interactions" observed when a

[1] S. Matsuura and T. Goto, *J. Chem. Soc.*, 1963, 1773.
[2] S. Matsuura and T. Goto, *J. Chem. Soc.*, 1965, 623.
[3] S. Matsuura and T. Goto, *Tetrahedron Letters*, 1963, 1499.
[4] C. D. Jardetsky and O. Jardetsky, *J. Amer. Chem. Soc.*, 1960, **82**, 222.
[5] G. S. Reddy, L. Mandell, and J. H. Goldstein, *J. Chem. Soc.*, 1963, 1414.
[6] P. J. Black and M. L. Heffernan, *Austral. J. Chem.*, 1965, **18**, 707.
[7] A. R. Katritzky, R. E. Reavill, and F. J. Swinbourne, *J. Chem. Soc.*(*B*), 1966, 351.
[8] A. H. Gawer and B. P. Dailey, *J. Chem. Phys.*, 1965, **42**, 2658.
[9] P. J. Black and M. L. Heffernan, *Austral. J. Chem.*, 1964, **17**, 558.
[10] P. R. Wells and P. G. E. Alcorn, *Austral. J. Chem.*, 1963, **16**, 1108.

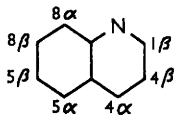
TABLE 2

Proton magnetic resonance spectra

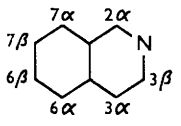
	Chemical shifts (τ)								Coupling constants (c./sec.)												
	H-1	H-2	H-3	H-4	H-5	H-6	H-7	H-8	$J_{1,4}$	$J_{1,5}$	$J_{2,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,8}$	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
Naphthyridines																					
1,5-	—	1·11	2·50	1·69	—	1·11	2·50	1·69	—	—	4·2	1·8	8·5	—	0·8	—	—	—	4·2	1·8	8·5
1,6-	—	1·00	2·64	1·87	0·88	—	1·32	2·19	—	—	4·2	1·8	8·4	—	0·9	—	—	Br	—	—	5·8
1,7-	—	1·10	2·49	1·93	2·52	1·51	—	0·58	—	—	4·1	1·8	8·3	—	0·8	5·8	—	Br	—	—	—
1,8-	—	0·99	2·65	1·93	1·93	2·65	0·99	—	—	—	4·1	1·8	8·3	—	—	8·3	1·8	—	4·1	—	—
3-NO_2-1,5-	—	0·12	—	0·65	—	0·71	2·18	1·35	—	—	—	2·7	—	—	0·8	—	—	—	4·2	1·8	8·5
3-NO_2-1,6-	—	0·19	—	0·70	0·37	—	0·90	1·81	—	—	—	2·6	—	—	0·9	—	—	0·8	—	—	5·9
8-NO_2-1,6-	—	0·57	2·16	1·44	0·40	—	0·70	—	—	—	4·2	1·9	8·5	—	—	—	—	—	—	—	—
Triazanaphthalenes																					
1,3,5-	—	0·55	—	0·30	—	0·88	2·15	1·60	—	—	—	—	—	—	0·8	—	—	—	4·1	1·7	8·3
*	—	0·61	—	0·37	—	0·84	1·99	1·58	—	—	—	—	—	—	0·8	—	—	—	4·2	1·8	8·3
†	—	0·60	—	0·35	—	0·86	1·94	1·54	—	—	—	—	—	—	0·8	—	—	—	4·1	1·8	8·4
1,3,6-	—	0·46	—	0·38	0·53	—	1·00	2·08	—	—	—	—	—	—	0·7	—	—	0·8	—	—	5·8
*	—	0·49	—	0·19	0·40	—	1·00	2·12	—	—	—	—	—	—	0·7	—	—	0·8	—	—	5·8
1,3,7-	—	0·43	—	0·42	2·21	1·15	—	0·45	—	—	—	—	—	—	0·8	5·8	—	Br	—	—	—
1,3,8-	—	0·43	—	0·43	1·56	2·28	0·67	—	—	—	—	—	—	—	—	8·3	1·9	—	4·2	—	—
Isoquinolines																					
5-NO_2	0·61	—	1·25	1·54	—	1·41	2·28	1·64	—	—	—	—	5·8	—	0·8	—	—	—	8·5	1·8	8·5
7-NO_2	0·38	—	1·12	2·17	1·87	1·43	—	0·93	0·8	0·7	—	—	5·8	—	0·9	8·8	—	0·8	—	2·4	—
8-NO_2	—0·40	—	1·26	2·20	1·85	2·23	1·65	—	0·8	—	—	—	5·7	0·7	—	8·3	1·5	—	7·4	—	—

Solvents: * acetone; † dimethyl sulphoxide (D6); others deuterochloroform.

ring carbon atom of quinoline is replaced by a nitrogen atom. The 4β and 8α " interactions " of N-2 in cinnoline and the 1β " interaction " of N-3 in quinazoline have not been used in the calculation of these values because



(I)



(II)

the " proximity " contributions (from adjacent or *peri* nitrogen atoms, cf. refs. 9 and 10) to those interactions apparently involve both nitrogen atoms and give values

TABLE 3

Effects of a second ring-nitrogen atom on the chemical shifts of quinoline protons

Inter-action *	Shift (p.p.m.)	Inter-action *	Shift (p.p.m.)
2α	−1·36 ± 0·06	1β	−1·44 ± 0·04
3α	+0·22 ± 0·03	3β	−1·06
4α	−0·31	4β	+0·10 ± 0·02
5α	−0·04	5β	−0·08 ± 0·00
6α	−0·04	6β	−0·23 ± 0·06
7α	−0·14	7β	−0·11 ± 0·03
8α	−0·35	8β	−0·23 ± 0·03

* See formulæ (I) and (II).

differing greatly from those in Table 3. When such " proximity " effects are absent, as in the naphthyridines, the interactions are remarkably constant, and when three or more values were obtainable standard deviations are quoted. Qualitatively, most of these values are similar to those exhibited by the nitrogen atom of quinoline [6] but interactions 2α, 1β, and 3β, which involve normal " proximity " contributions, are substantially larger. Also, the 3α and 4β " interactions," with protons *meta* to the nitrogen atom, are positive. We have used these " interactions " to predict the chemical shifts of the isoquinoline protons by removal of a nitrogen atom from 1,6- and 1,7-naphthyridine and cinnoline (Table 4). Comparison of the observed and computed spectra of isoquinoline in the Figure shows the validity

TABLE 4

Predicted chemical shifts (τ) of isoquinoline protons

Proton	From 1,6-naphthyridine Shift	From 1,7-naphthyridine Shift	From cinnoline Shift	Average *
1	0·92	0·93	—	0·92
3	1·55	1·59	†	1·57
4	2·54	2·56	2·56	2·55
5	—	2·24	2·24	2·24
6	2·44	2·39	2·38	2·41
7	2·54	2·54	2·53	2·54
8	2·18	—	†	2·18

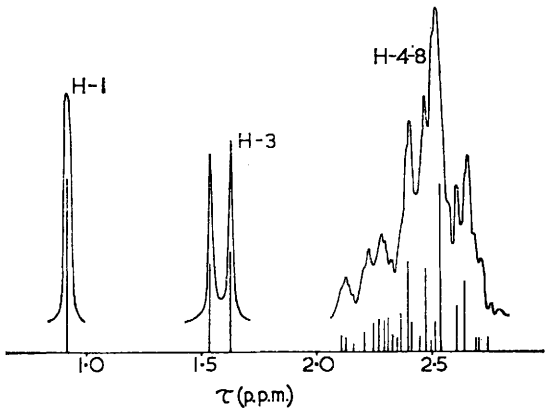
* To nearest 0·01 p.p.m. † " Double proximity " effects present.

of this approach. Similar " interactions " are observed for the nitrogen atoms in the triazanaphthalenes, but values vary greatly from compound to compound, probably owing to the presence of three nitrogen atoms and the associated " proximity " effects. The spectra of 5-, 7-, and 8-nitroisoquinoline were measured, and the nitro group " interactions " (Table 5) are qualitatively similar to those obtained by Black and Heffernan [9] for nitroquinolines. However, the shifts to lower field are consistently greater (by 0·1—0·3 p.p.m.), suggesting a more effective withdrawal of electrons by the nitro group in the isoquinoline than in the quinoline molecules.

In agreement with the findings of Reddy *et al.*[11] with pyrimidine, coupling between H-2 and H-4 of

[11] G. S. Reddy, R. T. Hobgood, and J. H. Goldstein, *J. Amer. Chem. Soc.*, 1962, **84**, 336.

quinazoline or of the triazanaphthalenes is very small and could not be resolved. The major couplings in these systems originate from either a quinoline or an isoquinoline ring system, and do not vary with the



Comparison of computed and observed spectra of isoquinoline (20% CCl_4). The computed spectrum has been simplified by omission of weak lines and summation of peaks with similar frequencies.

Parameters used were: τ_1 0·92; τ_3 1·57; τ_4 2·55; τ_5 2·27; τ_6 2·41; τ_7 2·54; τ_8 2·18
$J_{3,4}=6·0$; $J_{5,6}=8·4$; $J_{5,7}=1·6$; $J_{5,8}=0·5$; $J_{6,7}=7·0$; $J_{6,8}=1·6$; $J_{7,8}=8·4$ c./sec.
Only τ_5 varies from the predicted chemical shifts

number or position of nitrogen atoms in the second ring. Thus, for quinoline-type rings, $J_{2,3} = 4·1$, $J_{2,4} = 1·8$, $J_{3,4} = 8·4$ c./sec. (all $\pm 0·1$ c./sec.), while for isoquinoline type rings, $J_{3,4} = 5·8$, $J_{1,4} = 0·5$—$0·8$ c./sec. Coupling between H-4 and H-8 of 1,3,5-, 1,3,6-, and 1,3,7-triazanaphthalene was observed as splitting of signals from both protons ($J_{4,8} = 0·8$ c./sec.).

4-Deuteroquinazoline and 4-deutero-1,3,5-triazanaphthalenes were prepared by decomposition of the hydrochlorides of the corresponding 4-*N'*-toluene-*p*-sulphonylhydrazino-compounds with sodium deuteroxide in deuterium oxide. P.m.r. spectra showed the 4-position to be almost completely deuterated. Good yields of

TABLE 5

Nitro group " interactions " in nitroisoquinolines

Interaction *	Shift (p.p.m.)	Interaction *	Shift (p.p.m.)
2α	−1·21	1β	−0·95
3α	−0·37	3β	−0·98
4α	−0·54	4β	−0·22
5α	−0·33	5β	−0·31
6α	−0·38	6β	−0·45
7α	−0·54	8β	−0·32
8α	−0·98		

* See formulæ (I) and (II).

1,6-naphthyridine were obtained from the reaction of 4-hydrazino-1,6-naphthyridine with copper sulphate on a one-gram scale,[12] but the yields dropped considerably if larger quantities were used. 4-Chloro-1,6-naphthyridine rapidly absorbed one mol. of hydrogen to give good yields of 1,6-naphthyridine. 1,7-Naphthyridine was most conveniently prepared by the following synthesis: 2-hydroxy-3-nitropyridine ⟶ 3-amino-2-hydroxypyridine ⟶ 8-hydroxy-1,7-naphthyridine ⟶ 8-chloro-1,7-naphthyridine ⟶ 8-*N'*-toluene-*p*-sulphonylhydrazino-1,7-naphthyridine hydrochloride ⟶ 1,7-naphthyridine, which involved fewer steps than that previously described.[12] Decomposition of 8-hydrazino-1,7-naphthyridine with copper sulphate and catalytic dechlorination of 8-chloro-1,7-naphthyridine gave *ca.* 6% yields of 1,7-naphthyridine.

EXPERIMENTAL

P.m.r. spectra were measured at 60 Mc./sec. and 33·5° on a Perkin-Elmer R10 spectrometer. Tetramethylsilane was used as internal standard (τ 10), and chemical shifts were measured accurately from the 400 c./sec. calibrating side-band. Values quoted in the Tables are for 10% solutions and are the average of at least six determinations. To confirm the assignments of protons with 4-deuteroquinazoline and 4-deutero-1,3,5-naphthyridine, the deuterated compound was mixed with undeuterated material and the results checked by inspection and integration.

Microanalyses were by Dr. J. E. Fildes and her staff. 1,5- and 1,8-Naphthyridine,[12] 3-nitro-1,5-, 3-nitro-1,6-, and 8-nitro-1,6-naphthyridine,[13] and 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-triazanaphthalene [14] were prepared as before.

4-Deuteroquinazoline.— Toluene-*p*-sulphonylhydrazine (1·0 g.) in chloroform (30 ml.) was shaken with deuterium oxide (5 ml., 99%) for 30 min., separated, dried, and recovered. The deuterated reagent (611 mg.) in chloroform (6 ml.) was added to 4-chloroquinazoline (544 mg.) in chloroform (3 ml.). The solution was heated to boiling, set aside for 10 min., the insoluble hydrochloride filtered off, dried, and added to 1N-sodium deuteroxide in deuterium oxide (10 ml.). The salt dissolved and a yellow solid separated after a few minutes. The mixture was boiled gently until clear (N_2 evolved), cooled, and extracted with ether. The dried extract (Na_2SO_4) was decolourised (charcoal), evaporated, and the residue in benzene was passed through an alumina column. Evaporation of eluates followed by distillation of the residue at 0·5 mm. gave 4-deuteroquinazoline (90 mg., 21%), m. p. 45°, *M*, 131 (mass spectrum). This had ultraviolet spectra and chromatographic behaviour identical with those of quinazoline.

4-Deutero-1,3,5-triazanaphthalene.— 4-*N'*-Toluene-*p*-sulphonylhydrazino-1,3,5-triazanaphthalene hydrochloride (702 mg.) [14] in deuterium oxide (20 ml.) containing 2 mol. of sodium deuteroxide was heated at 100° until nitrogen evolution ceased (2 hr.). Work-up as above gave 4-deutero-1,3,5-triazanaphthalene (26 mg., 10%), m. p. 97—97·5°, *M*, 132 (mass spectrum), with ultraviolet spectra and R_F values identical with those of 1,3,5-triazanaphthalene.

1,6-Naphthyridine.—4-Chloro-1,6-naphthyridine [12] (14 g.) and anhydrous sodium acetate (7·7 g., 1·1 mol.) in ethanol (300 ml.) containing 5% palladium–charcoal (4 g.) were shaken with hydrogen at 20°/720 mm. After the initial rapid absorption of hydrogen (2230 ml., 1 mol., in 30 min.), the reduction was stopped, the solution filtered, and the filtrate evaporated, and worked up in the usual manner. 1,6-Naphthyridine distilled at 80°/0·5 mm. The hygro-

[12] A. Albert, *J. Chem. Soc.*, 1960, 1790.
[13] A. Albert and W. L. F. Armarego, *J. Chem. Soc.*, 1963, 4237.
[14] W. L. F. Armarego, *J. Chem. Soc.*, 1962, 4094.

scopic distillate (60%) solidified, m. p. 30° (lit.,[12] 31·5°) (Found: C, 71·4; H, 5·1; N, 20·5. Calc. for $C_8H_6N_2,0{\cdot}25H_2O$: C, 71·4; H, 4·9; N, 20·8%).

1,7-*Naphthyridine*.—8-Hydroxy-1,7-naphthyridine was prepared in 26% yield as before,[15] but the liquid–liquid extraction procedure was not used. Instead, the final solution was evaporated to dryness and the residue extracted (Soxhlet) with chloroform. The hydroxy-compound (7·0 g.) and phosphoryl chloride (100 ml.) were refluxed for 1½ hr., evaporated under reduced pressure, the residue treated with ice-cold water, basified with saturated sodium hydrogen carbonate solution, and extracted with chloroform. The dried extract (Na_2SO_4) was evaporated and the residue recrystallised from light petroleum (b. p. 60—80°) or sublimed at 60—80°/0·5 mm., to yield 8-*chloro*-1,7-*naphthyridine* (5·7 g., 72%), m. p. 91—92° (Found: C, 58·4; H, 2·9; N, 17·0. $C_8H_5ClN_2$ requires C, 58·4; H, 3·1; N, 17·0%).

The chloronaphthyridine (5·6 g.) in chloroform (10 ml.) and toluene-*p*-sulphonylhydrazine (6·3 g., 1 mol.) in chloroform (60 ml.) were refluxed overnight, and the tosylhydrazino-derivative filtered off (10·2 g., 84%). This derivative (40·6 g.) and sodium carbonate (26·8 g., 2·2 mol.) in water (930 ml.) were heated at 100° with shaking, until nitrogen evolution ceased (3 hr.). The solution was cooled and extracted with chloroform. The dried extract (Na_2SO_4) was decolourised (charcoal), evaporated, and the residue passed through an alumina column as above. Pure 1,7-naphthyridine (9·9 g., 66%), obtained by sublimation at 50°/0·3 mm. had m. p. 65—66° (lit.,[12] 64°) (Found: C, 73·5; H, 4·65; N, 21·4. Calc. for $C_8H_6N_2$: C, 73·8; H, 4·65; N, 21·5%).

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[15] A. Albert and A. Hampton, *J. Chem. Soc.*, 1952, 4985.