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Naphthyridines. Part III.[1] Tetrahydro- and Decahydro-1,5-, -1,6-, -1,7-, and -1,8-Naphthyridines

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Decahydro-1,5-, -1,6-, -1,7-, and -1,8-naphthyridines have been prepared by reduction of the respective naphthyridines with sodium and ethanol. Reduction of 1,5-naphthyridine with platinum oxide in acid solution gave a separable mixture of *trans*- and *cis*-decahydro-1,5-naphthyridine. It was possible to distinguish between these isomers, also those of *trans*- and *cis*-decahydroquinolines and decahydroisoquinolines, by proton magnetic resonance spectroscopy. Catalytic reduction of 1,5-, 1,6-, and 1,8-naphthyridine with palladium on charcoal in ethanol gave the corresponding 1,2,3,4-tetrahydro-derivatives, but 1,7-naphthyridine gave a separable mixture 1,2,3,4-tetrahydro- (57%) and 5,6,7,8-tetrahydro-1,7-naphthyridine (43%). The structures of the tetrahydronaphthyridines were established by ionisation measurements and by ultraviolet and proton magnetic resonance spectroscopy.

REDUCTION of 1,2,3,4 tetrahydro-1,5-naphthyridine with sodium and pentyl alcohol was reported to yield a hexahydro-1,5-naphthyridine whereas the 2-methyl and 2,4-dimethyl derivatives gave decahydro-derivatives,[2] and reduction of 4-methyl- and 2,4 dimethyl-1,8-naphthyridine with sodium and ethanol gave the respective decahydronaphthyridines.[3] In no case were the products classified as *trans*- or *cis*-isomers.* I have now reduced 1,5-naphthyridine with sodium in boiling ethanol to decahydro-1,5-naphthyridine in high yield, and shown it to be the *trans*-isomer by comparing it with the *cis*-isomer. *trans*-Decahydro-1,6-, -1,7-, and -1,8-naphthyridine were similarly prepared. Catalytic reduction of 1,5-, 1,6-, and 1,7-naphthyridine was said to form

* *trans* and *cis* refer to the configuration at the two bridgehead hydrogen atoms.

[1] Part II, A. Albert and W. L. F. Armarego, *J. Chem. Soc.*, 1963, 4237.
[2] K. Miyaki, *J. Pharm. Soc. Japan*, 1942, **62**, 257.
[3] E. Ochiai and K. Miyaki, *Ber.*, 1941, **74**, 1115.

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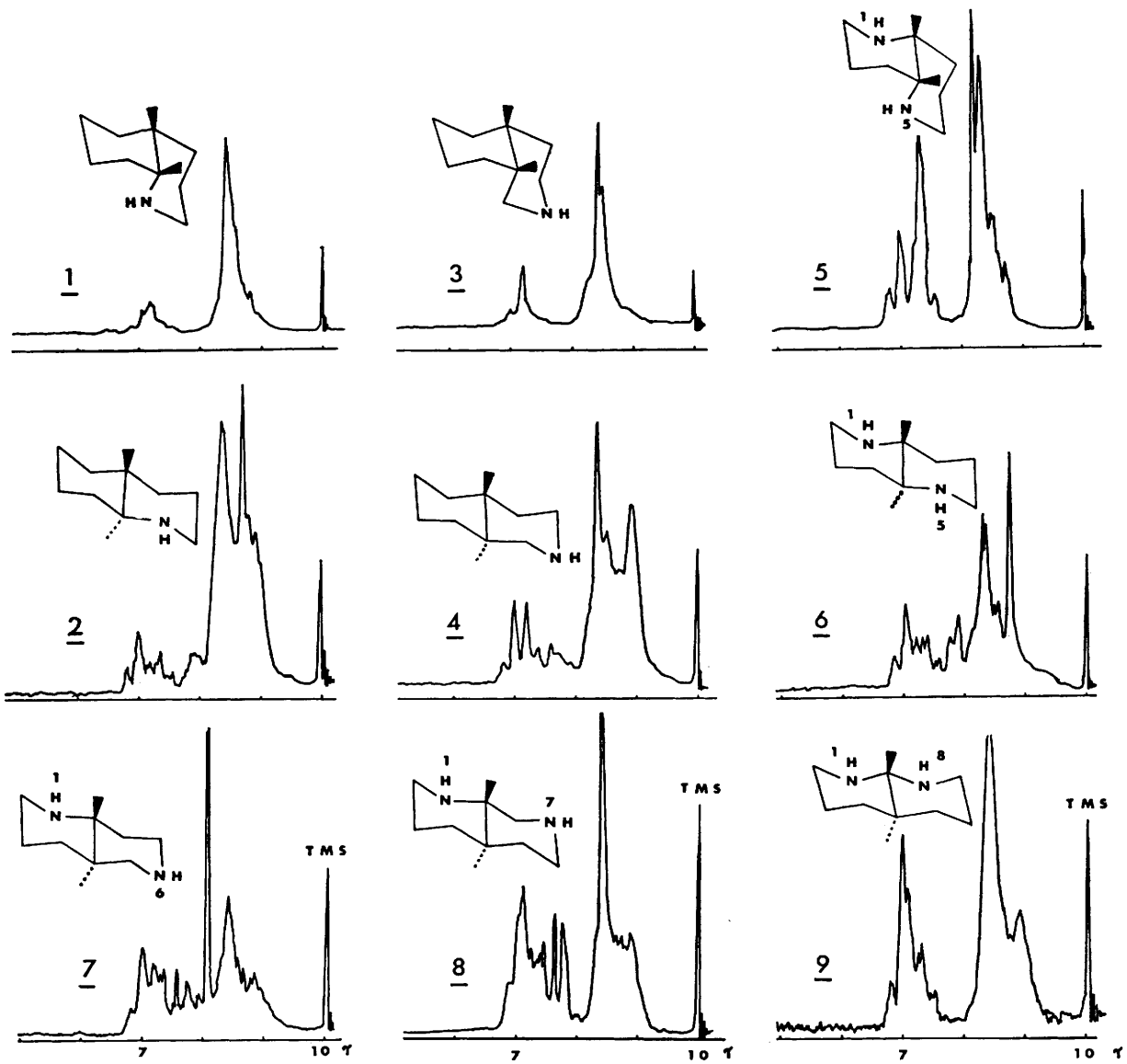
1,2,3,4-tetrahydro-1,5-,[2] 1,2,3,4-tetrahydro-1,6-,[4] and a mixture of 1,2,3,4-tetrahydro-1,7- (98%) and 5,6,7,8-tetrahydro-1,7-naphthyridine (2%).[5] Meagre evidence, however, was presented for the structures of these tetrahydro-derivatives. Thus, the first example rested on analytical data alone, and the other three on spectral



FIGURES 1—9 Proton magnetic resonance spectra

changes between 0·1N-sodium hydroxide and 0·1N-sulphuric acid, with no elemental analyses for the last two isomers. These reductions have now been re-investigated, extended to include 1,8-naphthyridine, and the ionisation constants and ultraviolet and proton magnetic resonance (p.m.r.) spectra were used to confirm the structures.

Decahydronaphthyridines, like decalin, should be capable of existing in *trans*- and *cis*-forms. It was therefore necessary to find a method to differentiate between the isomers. Musher and Richards [6] examined the p.m.r. spectra of *trans*- and *cis*-decalin and found that the *trans*-form gave a broad resonance signal envelope whereas the *cis*-form gave a much sharper envelope. This was explained by the relatively rigid carbon framework in *trans*-decalin, where the hydrogen atoms were classified as axial or equatorial. In *cis*-decalin a narrow band envelope of the proton signals results from both rapid inversion of the ring system and the near equivalence of axial and equatorial protons.[6]

[4] N. Ikekawa, *Chem. Pharm. Bull.* (*Japan*), 1958, **6**, 263.
[5] N. Ikekawa, *Chem. Pharm. Bull.* (*Japan*), 1958, **6**, 408.
[6] J. Musher and R. E. Richards, *Proc. Chem. Soc.*, 1958, 230, see also J. T. Gerig and J. D. Roberts, *J. Amer. Chem. Soc.*, 1966, **88**, 2791; and F. A. Jensen and B. H. Beck, *Tetrahedron Letters*, 1966, 4523.

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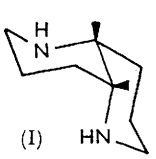
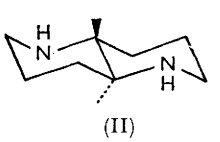
To test this behaviour in azanaphthalenes I have examined the p.m.r. spectra of *trans*- and *cis*-decahydroquinoline and *trans*- and *cis*-decahydroisoquinoline, whose configuration was firmly established by total synthesis [7,8] and dehydrogenation.[9,10] The spectra showed two sets of signals, a downfield set at τ *ca.* 6·5—7 for the protons on the carbon atoms adjacent to the nitrogen atoms, and an upfield set for the other protons (Figures 1—4). As was observed in the decalines, the *trans*-isomers possessed broader signal envelopes than the *cis*-isomers. Although the infrared spectra of the free bases of the isomers, and their hydrochlorides, were different there were no bands which could be ascribed exclusively to the *trans*-isomers (compare Bohlmann bands found in *trans*-quinolizidines [11]). The ionisation constants showed that they were strong bases (see Table 1) but there was little difference between *trans*- and *cis*-isomers.

Reduction of 1,5-naphthyridine with sodium and ethanol gave a solid which on further reduction with platinum oxide in ethanol absorbed ~0·25 mol. of hydrogen without much change in m. p. The product (93% yield) had the analysis required for a decahydronaphthyridine, and gave a dipicrate. It was *trans*-decahydro-1,5-naphthyridine because the p.m.r. spectrum (Figure 6) showed a broad series of signals. Catalytic reduction of 1,5-naphthyridine with platinum oxide in acetic acid containing sulphuric acid (as in the reduction of 1,2,3,4-tetrahydroisoquinoline to a mixture of *trans*- and *cis*-decahydroisoquinoline) gave a mixture of *trans*- (12%) and *cis*-decahydro-1,5-naphthyridine (21%) which were separated by the preferential solubility of the latter in ether. The *trans*-isomer was identical with the above. The *cis*-isomer was a liquid which gave a different dipicrate; its infrared spectrum was different from that of its isomer, and the p.m.r. spectrum had sharper signals (Figure 5). These results agree with the Auwers–Skita rule,[12] which predicts that reductions in neutral or basic media yield predominantly *trans*-isomers whereas reductions in acidic media give high proportions of the *cis*-isomers. The first ionisation constants (Table 1) indicated that they were weaker bases than the decahydroquinolines and decahydroisoquinolines, as would be expected from the presence of a second nitrogen atom. The larger difference between the pK_{a1} and pK_{a2} values in the *cis*-isomer (I) (3·66 pH



(I)



(II)

units) compared with the *trans*-isomer (II) (3·30 pH units) is consistent with the greater difficulty in protonating the mono-cation of the *cis*-isomer.

[7] F. E. King, T. Henshall, and R. L. St. D. Whitehead, *J. Chem. Soc.*, 1948, 1373.
[8] R. A. Abramovitch and J. M. Muchowski, *Canad. J. Chem.*, 1960, **38**, 557.

The reduction of 1,6- and 1,7-naphthyridine with sodium and ethanol also gave high yields of *trans*-decahydro-1,6- and- 1,7-naphthyridine. *trans*-Decahydro-1,8-naphthyridine was obtained by a similar reduction of 1,2,3,4-tetrahydro-1,8-naphthyridine. The elemental analyses of the free bases and of their dipicrates indicated that they were decahydro-compounds. The broad peaks of their p.m.r. spectra, together with their method of preparation (compare above), is strong evidence for their *trans*-structure (Figures 6—8). The continuous inversion of the nitrogen atoms makes the *trans*-decahydronaphthyridines less rigid than *trans*-decalin, hence the p.m.r. signal envelopes are expected to be relatively narrower (see particularly Figure 9). Their sharp melting and boiling points, analytical figures, and the narrow spreads of their pK_{a1} and pK_{a2} values is good evidence for their purity. The mixture of *trans*- and *cis*-decahydro-1,5-naphthyridine isolated from catalytic reduction of 1,5-naphthyridine melted over a wide range and gave unsatisfactory pK_a values. Attempts to use gas chromatography with columns of polyethylene, Carbowax, silicone, and silicone containing 10% of sodium hydroxide, to purify these perhydro-bases, were unsuccessful. It must be noted that, of the four *trans*-decahydronaphthyridines, the 1,6- and 1,7-isomers are racemates, and they are diastereoisomeric with the respective *cis*-isomers. All attempts to prepare *cis*-decahydro-1,6-, -1,7-, and -1,8-naphthyridine by catalytic reduction in acid media were unsatisfactory.

The ionisation of the *trans*-decahydronaphthyridines can be rationalised by considering the distance between the nitrogen atoms and the application of Coulomb's Law; hence they are all weaker bases than the perhydroquinolines and -isoquinolines.

The pK_{a1} and pK_{a2} values of *trans*-decahydro-1,5- and -1,7-naphthyridine are similar because they are both bicyclic ethylenediamines. *trans*-Decahydro-1,6-naphthyridine is a stronger base because it is essentially a bicyclic propylenediamine, and *trans*-decahydro-1,8-naphthyridine is the weakest base of all because the nitrogen atoms are separated by only one carbon atom. All these decahydroazanaphthalenes were transparent in the ultraviolet spectrum.

Catalytic reduction of naphthyridines with palladium on charcoal in alcoholic solution stops after absorption of 2 mol. of hydrogen, with the formation of tetrahydronaphthyridines. 1,5-Naphthyridine gave 1,2,3,4-tetrahydro-1,5-naphthyridine (III) (90% yield) which melted 8° above the literature [2] value. 1,6-Naphthyridine gave exclusively 1,2,3,4-tetrahydro-1,6-naphthyridine (IV) as shown by p.m.r. spectroscopy. The other isomer, *i.e.*, 5,6,7,8-tetrahydro-1,6-naphthyridine, was never formed in these or in reductions using acetic acid containing sulphuric acid as solvent, or platinum oxide

[9] M. Ehrenstein and W. Bunge, *Ber.*, 1934, **67**, 1715.
[10] B. Witkop, *J. Amer. Chem. Soc.*, 1948, **70**, 2617.
[11] T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 1962, 2637.
[12] K. v. Auwers, *Annalen*, 1920, **420**, 84; A. Skita, *Ber.*, 1920, **53**, 1792.

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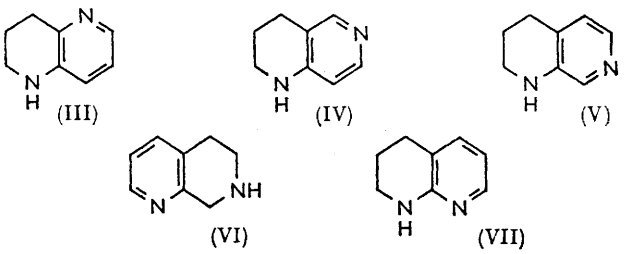
TABLE 1

Ionisation (H_2O, 20°) *

	pK_a	Spread (±)	Concn. (M)	λ Analyt. (mμ)
	Quinolines			
trans-Decahydro-	11·29	0·04	0·1	—
cis-Decahydro-	11·29	0·03	0·1	—
trans-Decahydroiso-	11·32	0·04	0·1	—
cis-Decahydroiso-	11·35	0·02	0·1	—
	Naphthyridines			
trans-Decahydro-1,5-	10·16	0·02	0·05	—
	6·86	0·04	0·05	—
cis-Decahydro-1,5-	10·31	0·01	0·05	—
	6·65	0·04	0·05	—
trans-Decahydro-1,6-	10·68	0·05	0·1	—
	8·18	0·03	0·1	—
trans-Decahydro-1,7-	10·16	0·02	0·1	—
	7·07	0·01	0·1	—
trans-Decahydro-1,8-	9·36	0·04	0·01	—
	4·82	0·02	0·01	—
1,2,3,4-Tetrahydro-1,5-	6·96	0·04	$0·5 \times 10^{-4}$	350
	−1·35	0·02	$0·5 \times 10^{-4}$	350
1,2,3,4-Tetrahydro-1,6-	10·19	0·02	$0·2 \times 10^{-4}$	280
1,2,3,4-Tetrahydro-1,7-	7·08	0·02	$0·10 \times 10^{-4}$	355
	−1·35	0·05	$0·10 \times 10^{-4}$	355
5,6,7,8-Tetrahydro-1,7-	8·56	0·02	3×10^{-4}	276
	2·48	0·03	3×10^{-4}	270
1,2,3,4-Tetrahydro-1,8-	7·61	0·03	$0·62 \times 10^{-4}$	340

* The decahydro-compounds were measured potentiometrically and the tetrahydro-compounds were measured spectrophotometrically at ionic strength 0·01, as described in "Ionization Constants of Acids and Bases," A. Albert and E. P. Serjeant, Methuen, London, 1962.

preparative gas chromatography. Reduction in acetic acid did not appreciably alter the ratio of these two isomers. 2,4-Dichloro-1,8-naphthyridine gave 1,2,3,4-tetrahydro-1,8-naphthyridine (VII). In none of these



reductions was an intermediate green colour obtained, a colour formerly attributed to the formation of the dihydro-derivatives.[4]

The ionisation constants of the tetrahydronaphthyridines are in Table 1, and their ultraviolet spectra in Table 2. The ionisation data agree with the structures described. The pK_a values of 1,2,3,4-tetrahydro-1,5- (III) and -1,7-naphthyridine (V), and the spectra of the neutral species, mono-cations, and di-cations, are typical of a 3-aminopyridine structure.[13] The high pK_a of 1,2,3,4-tetrahydro-1,6-naphthyridine (10·19) and its ultraviolet data are consistent with its being a 4-aminopyridine (compare 4-methylaminopyridine,[14] pK_a 9·65). The

TABLE 2

Proton magnetic resonance spectra (in deuteriochloroform at 33·5°), and ultraviolet spectra (in water at 20°)

Naphthyridine	Chemical shifts (τ) [a]								Coupling constants (±0·2 c./sec.)					
	2H	3H	4H	5H	6H	7H	8H	NH	$J_{2,3}$	$J_{3,4}$	$J_{5,6}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
1. 1,2,3,4-Tetrahydro-1,5-	6·68(t)	7·93(xq)	7·03(t)	—	2·01(q)	2·99(q)	3·20(q)	5·98(br)	—	—	—	4·2	2·0	8·2
2. 1,2,3,4-Tetrahydro-1,6-	6·66(t)	8·10(xq)	7·31(t)	1·96	—	1·97(d)	3·68(d)	5·13(br)	—	—	—	—	—	6·0
3. 1,2,3,4-Tetrahydro-1,7-	6·64(t)	8·06(xq)	7·24(t)	3·01(d)	2·09(d)	—	2·06	5·81(br)	—	—	5·0	—	—	—
4. 5,6,7,8-Tetrahydro-1,7-	1·48(t)	2·84(q)	2·48(t)	7·11(cq)	6·78(cq)	—	5·84	7·81	5·0	8·5	—	—	—	—
5. 1,2,3,4-Tetrahydro-1,8-	6·57(t)	8·10(xq)	7·29(t)	2·80(d)	3·45(q)	2·07(d)	—	4·38(br)	—	—	7·5	5·0	—	—
6. 1,5-Naphthyridine [d]	—	—	—	—	—	—	—	—	—	—	—	—	—	—

	λ_{max} (mμ) [b]	log ε [b]	Species [c]	pH or H_0
1.	245, 303	3·84, 3·60	0	10·0
	224, 265, 345	4·15, 3·89, 3·65	+	2·8
	208, 267	*3·52*, 3·82	++	−3·6
2.	259·5	4·04	0	13·0
	215·5 + *222*, 281	4·04 + *3·84*, 4·20	+	8·0
3.	247, 297	3·82, 3·35	0	10·0
	222, 268, 341	4·22, 3·87, 3·55	+	3·0
	258 + *264*	3·59 + *3·53*	++	−3·4
4.	267 + *275*	3·63 + *3·56*	0	11·0
	264 + 272	3·61 + 3·51	+	5·0
	269	3·85	++	−0·5
5.	241, 308	3·88, 3·66	0	10·0
	241·5, 318	3·86, 3·83	+	5·0
6.	263 + *270*, *294* + *302* + 304 + 313	3·57 + *3·53*, *3·83* + *4·05* + 4·07 + 4·22	++	−3·7

[a] Tetramethylsilane (τ 10) was used as internal standard; these are parameters from first-order analyses (d = doublet, t = triplet, q = quartet, cq = complex quartet, xq = complex quintet, br = broad signal). [b] Inflexions are in italics. [c] 0 = Neutral species, + = mono-cation, ++ = di-cation. [d] Di-cation, pK_a −1·70 ± 0·05 measured at 1×10^{-4} M and 330 mμ.

catalyst, or by catalytic reduction of 4-chloro-1,6-naphthyridine. Catalytic reduction of 1,7-naphthyridine in ethanol gave a mixture of 1,2,3,4-tetrahydro-1,7-naphthyridine (V) (57%) and 5,6,7,8-tetrahydro-1,7-naphthyridine (VI) (43%) as shown by p.m.r. spectroscopy. These two bases were liquids and were separated by preparative thin-layer chromatography or better by

ultraviolet spectra of 5,6,7,8-tetrahydro-1,7-naphthyridine (VI) and its cation are very similar to those of pyridine and its cation. Its first pK_a value (8·56) is for the protonation of N-7 and is like that of an aliphatic amine. Although N-7 is one and two carbon

[13] A. Albert, *J. Chem. Soc.*, 1960, 1020.
[14] J. M. Essery and K. Schofield, *J. Chem. Soc.*, 1961, 3939.

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atoms removed from the pyridine ring, its protonation alters the pyridine chromophore to the extent that it is possible to measure the ionisation of its conjugate acid spectrophotometrically. The pK_a value for the second protonation (2·48) is much lower than that for 2,3-dimethylpyridine [15] (6·60) but is consistent with the base-weakening effect of a protonated aminomethyl group on the pyridine ring (compare 2-aminomethylpyridine pK_{a_1} 8·62, pK_{a_2} 1·85).[7,16] 1,2,3,4-Tetrahydro-1,8-naphthyridine (VII) (pK_a 7·61) is a typical 2-aminopyridine (pK_a 6·86),[13] and the increased basic strength is attributed to the presence of the alkyl side-chain and an alkyl substituent on the amino group.

The p.m.r. data of the tetrahydronaphthyridines are in Table 2, and all the protons are assigned by inspection. 1,2,3,4-Tetrahydro-1,5- (III) and -1,8-naphthyridine (VII) give typical ABX patterns, at low field, which can be assigned to the protons of the unreduced ring, and $A_2B_2C_2$ patterns further upfield, from the protons of the reduced ring. Small long-range couplings between the 2- and 4-protons with 5-H are also observed. 1,2,3,4-Tetrahydro-1,6-naphthyridine (IV) shows a typical upfield $A_2B_2C_2$ pattern, a downfield AB system, and a signal from 6-H which coincides with one of the peaks from the 7-H doublet. Compound (V) has essentially the same pattern of signals as compound (IV). 5,6,7,8-Tetrahydro-1,7-naphthyridine (VI) gives a downfield ABX pattern, and upfield A_2B_2 pattern, and a signal at τ 5·84 for the C-8 protons, which integrates for two protons.

EXPERIMENTAL

Analyses, by Dr. J. E. Fildes and her staff, are in Table 3. Evaporations were carried out in a rotary evaporator at 50°/15 mm. 1,5-,[17] 1,6-,[18] 1,7-,[18] and 1,8-naphthyridine [17] were prepared as in the references cited.

Ultraviolet spectra were measured on a Perkin-Elmer Spectracord model 4000 recording spectrophotometer, and the peaks were checked on an Optica CF4 manual instrument. Infrared spectra were measured on a Perkin-Elmer 21 spectrometer. A Perkin-Elmer R10 spectrometer operating at 60 Mc./sec. and 33·5° was used for p.m.r. spectra.

trans- *and* cis-*Decahydroquinoline*.—A commercially available mixture of *trans*- and *cis*-decahydroquinoline (Eastman) was fractionated in a spinning-band column (type E, Hagge after Dr. Koch) at 708·2—708·5 mm. The fraction of b. p. 205—206° was *trans*-decahydroquinoline; it crystallised on cooling, m. p. 48° (lit.,[19] 48°), $\nu_{max.}$ (film) 2905, 2840, 2780, 1447, 1335, 1305, 1240, 1177, 1125, 987, 900, 835 cm.$^{-1}$. The hydrochloride, formed by bubbling dry hydrogen chloride through an ethereal solution, had m. p. 285—286° (from ethanol–ethyl acetate) (lit.,[20] 286—287·5°), $\nu_{max.}$ (KBr) 2920, 2760, 2578, 2520, 1580, 1455, 1070, 1050, 975, 950, 833 cm.$^{-1}$. The higher-boiling fraction, b. p. 207—208°, remained liquid on cooling, and was converted into *N*-benzoyl-*cis*-decahydroquinoline which crystallised from light petroleum (b. p. 80—100°) (6 parts), m. p. 95° (lit.,[19] 96°). The benzoyl derivative was hydrolysed with 20% hydrochloric acid, and the hydrochloride was isolated (73%) as before,[21] m. p. 222—224° (lit.,[21] 222—224°), $\nu_{max.}$ (KBr) 2900, 2780, 2560, 1580, 1445, 1432, 1403, 1165, 1080, 1036, 990, 867 cm.$^{-1}$. The free bases were isolated from their hydrochlorides, and distilled before use. *cis*-Decahydroquinoline had $\nu_{max.}$ (film) 2900, 2840, 2770, 1445, 1357, 1330, 1305, 1140, 1125, 1109, 1068, 844 cm.$^{-1}$.

trans- *and* cis-*Decahydroisoquinoline*.—*trans*-Decahydroisoquinoline, $\nu_{max.}$ (film) 2880, 2820, 2700, 1445, 1315, 1136, 970, 840 cm.$^{-1}$, was prepared by reduction of 1,2,3,4-tetrahydroisoquinoline with lithium and ethylenediamine, as before;[22] picrate, m. p. 175—176° (lit.,[22] 173—174°); hydrochloride, $\nu_{max.}$ (KBr) 2930, 3800, 1587, 1450, 1400, 1070, 952, 837 cm.$^{-1}$, prepared as for the *cis*-isomer (below), m. p. 221—222° (lit.,[22] 222—223°).

1,2,3,4-Tetrahydroisoquinoline (3·0 g.) in glacial acetic acid (30 ml.) containing concentrated sulphuric acid (15 drops) was hydrogenated at 20° and atmospheric pressure in the presence of platinum oxide (3·0 g.), as described for the reduction of isoquinoline.[10] The catalyst was filtered off, and the filtrate evaporated, diluted with water (30 ml.), adjusted to pH 11, and extracted with ether. The ether was evaporated, and the residue treated with excess of aqueous picric acid. The picrate, washed with cold methanol (6 ml.) to remove most of the *trans*-isomer, had m. p. 149—150° (from methanol) (3·89 g.) (lit.,[10] 150°). Reduction did not occur when 5% palladium–charcoal [23] was the catalyst. The hydrochloride was isolated as follows because the earlier method [10] was unsatisfactory. The picrate (3·0 g.) in 5N sodium hydroxide (40 ml.) was shaken with ether, and enough water was added to the mixture to dissolve the sodium picrate formed, the ethanol extract was washed with 10N-sodium hydroxide and dried over a mixture of anhydrous sodium carbonate and aluminium oxide (B.D.H. for chromatography, to remove the yellow colour). The ether solution was filtered and evaporated to 50 ml., and dry hydrogen chloride was bubbled through the solution until crystallisation was complete. *cis*-Decahydroisoquinoline hydrochloride (0·88 g., 63%) was dried at 100°, m. p. 182—183° (from ethanol–ether) (lit.,[10] 183°) $\nu_{max.}$ (KBr) 2920, 2820, 1582, 1470, 1445, 1410, 1395, 1315, 1135, 1080, 990, 870 cm.$^{-1}$. The free base was isolated as above, $\nu_{max.}$ (film) 2920, 2820, 2720, 2560, 1584, 1470, 1445, 1415, 1395, 1315, 1300, 1135, 1080, 1020, 990, 873 cm.$^{-1}$.

trans-*Decahydro*-1,5-*naphthyridine*.— 1,5-Naphthyridine (1·30 g.) in ethanol (30 ml.) was treated with sodium (3·9 g.) and refluxed for 5 hr. The solution was cautiously diluted with water and acidified, the ethanol distilled off, and the residue basified, and extracted with chloroform. The extract was dried (Na_2CO_3) and evaporated, to give a solid, m. p. 171—174°. This could not be crystallised easily so it was dissolved in ethanol (50 ml.) containing platinum oxide (200 mg.) and hydrogenated at 20°/714 mm. whereby 0·25 mol. of hydrogen was absorbed. The catalyst was filtered off, and the residue, which had no ultraviolet

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absorption, was sublimed at 110°/0·3 mm. and recrystallised from light petroleum (b. p. 60—80°), to yield the *product*, m. p. 177—178°, glistening plates (1·3 g., 93%), $\nu_{max.}$ (KBr) 3200, 2905, 2840, 2770, 1470, 1468, 1437, 1338, 1274, 1180, 1125, 1110, 1000, 910, 860, 842 cm.$^{-1}$. The *dipicrate*, recrystallised from ethanol, darkened at 288° and decomposed explosively at 295°.

trans-*Decahydro*-1,6-*naphthyridine*.— 1,6-Naphthyridine was reduced as in the previous case, and, after three distillations, the *product*, b. p. 74°/1·0 mm., 64°/0·4 mm., was obtained as a colourless oil (65%), $\nu_{max.}$ (KBr) 3260, 2920, 2850, 2795, 1442, 1365, 1338, 1317, 1304, 1245, 1145, 1105, 987, 860, 790 cm.$^{-1}$. Sometimes a solid was also formed which crystallised from methanol to give trans-*decahydro*-1,6-*naphthyridine carbonate*, m. p. 348—350° effervescence with slight sublimation at ~300°. This salt liberated carbon dioxide when treated with dilute hydrochloric acid. The free base obtained by treating this salt with aqueous sodium hydroxide was identical with the above. The *dipicrate* (from acetic acid) had m. p. 283—285° (decomp.) with darkening above 270°.

trans-*Decahydro*-1,7-*naphthyridine*.—Reduction of 1,7-naphthyridine as in the previous case gave the *product*, b. p. 76°/1·3 mm., m. p. 76—77° (67%), $\nu_{max.}$ (film) 3225, 2900, 2820, 2780, 1440, 1333, 1285, 1233, 1180, 1130, 1095, 992, 855 cm.$^{-1}$. The *dipicrate* (from acetic acid) had m. p. 269—270° (decomp.).

trans-*Decahydro*-1,8-*naphthyridine*.— 1,2,3,4-Tetrahydro-1,8-naphthyridine was reduced as in the previous example, to give the *product* (50%), m. p. 119—120° [from light petroleum (b. p. 40—60°)] $\nu_{max.}$ (KBr) 3165, 3020, 2900, 2780, 2720, 2680, 1475, 1463, 1450, 1440, 1320, 1254, 1172, 1154, 1134, 1123, 1012, 957, 892, 877, 810, 800 cm.$^{-1}$. The *dipicrate* (from acetic acid) had m. p. 216—217° (decomp.).

cis-*Decahydro*-1,5-*naphthydridine*.— 1,5-Naphthyridine (2·0 g.) was reduced with platinum oxide in acetic acid–sulphuric acid, as described above for the preparation of *cis*-decahydroisoquinoline. When the solution had absorbed 10 mol. of hydrogen (5 hr.), the crude base was dissolved in light petroleum (b. p. 40—60°) and passed through a magnesium oxide column (5 × 0·5 in.). The fractions that gave an oil were collected and the oil distilled, to give the *product*, b. p. 55°/0·1 mm. (450 mg., 21%), which did not crystallise on cooling, $\nu_{max.}$ (film) 3200w, 2910, 2835, 2760, 1450, 1435, 1350, 1325, 1300, 1160, 1130, 1120, 1064, 953, 875, 795 cm.$^{-1}$. The *dipicrate* (from ethanol) decomposed at 270° with effervescence after darkening at above 218°. Further elution gave a small amount of solid, m. p. 173—175° undepressed with the above *trans*-isomer. The aqueous liquors from the above ether extraction were extracted further with chloroform (6 × 50 ml.), the extract was dried (Na_2CO_3) and evaporated, and the residue sublimed at 170°/0·1 mm. and recrystallised from light petroleum (b. p. 60—80°), to give *trans*-decahydro-1,5-naphthyridine (220 mg., 12%), m. p. 175—177° undepressed with the above *trans*-isomer from the sodium and ethanol reduction.

TABLE 3

Analyses

	Found (%)				Required (%)		
	C	H	N	Formula	C	H	N
trans-Decahydroquinoline (HCl)	61·7	10·3	8·0	$C_9H_{18}ClN$	61·5	10·3	8·0
cis-Decahydroquinoline (HCl)	61·7	10·1	8·0	$C_9H_{18}ClN$	61·5	10·3	8·0
trans-Decahydroisoquinoline (HCl)	61·5	10·4	8·0	$C_9H_{18}ClN$	61·5	10·3	8·0
cis-Decahydroisoquinoline (HCl)	61·2	10·0	7·9	$C_9H_{18}ClN$	61·5	10·3	8·0
Naphthyridine							
trans-Decahydro-1,5-	68·6	11·4	20·0	$C_8H_{16}N_2$	68·5	11·5	20·0
picrate	40·0	3·7	18·7	$C_8H_{16}N_2,2C_6H_3N_3O_7$	40·15	3·7	18·7
cis-Decahydro-1,5-	68·7	11·5	20·1	$C_8H_{16}N_2$	68·5	11·5	20·0
picrate	40·3	3·8	18·6	$C_8H_{16}N_2,2C_6H_3N_3O_7$	40·15	3·7	18·7
trans-Decahydro-1,6-	68·7	11·7	20·6	$C_8H_{16}N_2$	68·5	11·5	20·0
picrate	40·1	3·5	18·95	$C_8H_{16}N_2,2C_6H_3N_3O_7$	40·15	3·7	18·7
carbonate	—	—	13·6	$C_8H_{16}N_2,H_2CO_3$	—	—	13·85
trans-Decahydro-1,7-	68·7	11·2	20·1	$C_8H_{16}N_2$	68·5	11·5	20·0
picrate	40·4	3·5	18·9	$C_8H_{16}N_2,2C_6H_3N_3O_7$	40·15	3·7	18·7
trans-Decahydro-1,8-	68·6	11·4	19·9	$C_8H_{16}N_2$	68·5	11·5	20·0
picrate	40·05	3·7	18·9	$C_8H_{16}N_2,2C_6H_3N_3O_7$	40·15	3·7	18·7
1,2,3,4-Tetrahydro-1,5-	71·9	7·6	20·8	$C_8H_{10}N_2$	71·6	7·5	20·9
picrate	46·1	3·5	19·1	$C_8H_{10}N_2,C_6H_3N_3O_7$	46·3	3·6	19·3
1,2,3,4-Tetrahydro-1,6-	71·9	7·4	21·1	$C_8H_{10}N_2$	71·6	7·5	20·9
picrate	46·4	3·3	19·5	$C_8H_{10}N_2,C_6H_3N_3O_7$	46·3	3·6	19·3
1,2,3,4-Tetrahydro-1,7-	69·5	7·5	20·1	$C_8H_{10}N_2,\frac{1}{4}H_2O$	69·2	7·6	20·3
picrate	46·4	3·6	19·0	$C_8H_{10}N_2,C_6H_3N_3O_7$	46·3	3·6	19·3
5,6,7,8-Tetrahydro-1,7-	69·3	7·5	20·2	$C_8H_{10}N_2,\frac{1}{4}H_2O$	69·2	7·6	20·3
picrate	40·3	2·6	18·7	$C_8H_{10}N_2,2C_6H_3O_7$	50·55	2·7	18·9
1,2,3,4-Tetrahydro-1,8-	71·9	7·6	20·8	$C_8H_{10}N_2$	71·6	7·5	20·9
picrate	46·4	3·5	19·1	$C_8H_{10}N_2,C_6H_3N_3O_7$	46·3	3·6	19·3

1,2,3,4-*Tetrahydro*-1,5-*naphthyridine*.—1,5-Naphthyridine (524 mg.) in ethanol (40 ml.) and 5% palladium–charcoal [23] (524 mg.) were shaken with hydrogen at 20°/715 mm. After 6 hr., 2 mol. of hydrogen had been absorbed and reduction ceased. The solution was filtered, evaporated, and the residue sublimed at 100°/0·5 mm., then recrystallised from light petroleum (b. p. 60—80°), to give the product (488 mg., 90%), m. p. 113—114° (Miyaki,[2] using platinum oxide in acetic acid, gave m. p. 105°). The picrate (from acetic acid) had m. p. 215—216° (lit.,[2] 210°).

1,2,3,4-*Tetrahydro*-1,6-*naphthyridine*.—1,6-Naphthyridine was reduced (3·5 hr.) as above. After sublimation at 130°/0·2 mm. and recrystallisation from light petroleum (b. p. 80—100°) (3000 parts) or benzene (8 parts), the product, m. p. 162—163° (75%), was obtained (Ikekawa,[4] using palladium on calcium carbonate in methanol, gave m. p.

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155—158°). The p.m.r. spectrum of a concentrated solution in deuteriochloroform showed no 5,6,7,8-tetrahydro-1,6-naphthyridine. The *picrate* (from ethanol) had m. p. 177—178°. The same compound was obtained (43%) by hydrogenation of 4-chloro-1,6-naphthyridine with 5% palladium–charcoal in ethanol containing 1 mol. of anhydrous sodium acetate.

1,2,3,4- *and* 5,6,7,8-*Tetrahydro*-1,7-*naphthyridine*.— 1,7-Naphthyridine (2·6 g.) was reduced with 5% palladium–charcoal in ethanol, as in the previous case, and 2 mol. of hydrogen were absorbed in 8 hr. The residue distilled at 96—100°/0·4 mm. (1·17 g.), and the p.m.r. spectrum showed only a mixture of the products (57 : 43). These were separated by preparative gas chromatography (Loenco Inc., model 160 series, prep-matic) using a column of 20% SE30 on Chromosorb W (60—80 mesh) with temperature-programming at 130—220° (10°/min.) and nitrogen as carrier gas (70—130 mm./min.). The mixed bases were diluted with one third their volume of chloroform, and 0·07 ml. was injected at a time. The product from the faster peak was converted into a *dipicrate* (750 mg.) (from acetic acid), m. p. 210—212° (decomp.), which gave 5,6,7,8-tetrahydro-1,7-naphthyridine, b. p. 78—79°/1·0 mm. (100 mg.), which was pure as shown by gas chromatography (retention time relative to $CHCl_3$, 6·75 min.). The slower peak gave a *monopicrate* (600 mg.) (from ethanol), m. p. 158—159°, which was decomposed with sodium hydroxide in the usual way (see above) and gave 1,2,3,4-*tetrahydro*-1,7-*naphthyridine*, b. p. 110°/1·0 mm. (190 mg.), which was shown to be pure by gas chromatography (retention time relative to $CHCl_3$, 12·8 min.). The separation was also effected by preparative thin-layer chromatography on Kieselgel G, with chloroform–methanol (20 : 1) as solvent. The bands were examined under a mercury lamp with a filter for 254 mμ light and then with a filter for 365 mμ light. The faster band (R_F ~0·8) was eluted with methanol and gave pure 1,2,3,4-tetrahydro-1,7-naphthyridine. The slower band (R_F ~0·1) was impure and was re-run on aluminium oxide plates with chloroform–methanol (20 : 1·75), and the band with R_F ~0·8 was eluted with methanol and gave pure 5,6,7,8-tetrahydro-1,7-naphthyridine.

1,2,3,4-*Tetrahydro*-1,8-*naphthyridine*.— 2,4-Dichloro-1,8-naphthyridine [24] (13·5 g.), anhydrous sodium acetate (22 g., 4 mol.), and 5% palladium–charcoal (14 g.) in ethanol (300 ml.) were hydrogenated at 20°/715 mm. After 5½ hr., 4 mol. of hydrogen had been absorbed. The catalyst was filtered off, the filtrate evaporated, and the residue basified with 5N-sodium hydroxide and extracted with chloroform. The dried extract (Na_2CO_3) was evaporated, and the residue distilled to give the *product*, b. p. 96°/0·6 mm., 100°/0·8 mm. (3·0 g., 35%), which solidified on cooling. The yields were 15—50% depending on the quality of the dichloro-compound used. 1,8-Naphthyridine gave the same product. The *picrate* (from acetic acid) had m. p. 226—227°.

I thank Professor A. Albert and Dr. T. J. Batterham for helpful discussion, and Mr. F. Seselja, Mr. I. Pavelic, and Mr. S. Brown for technical assistance.

[6/1252 *Received, October 5th*, 1966]

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Published on 01 January 1967 on http://pubs.rsc.org | doi:10.1039/J39670000377
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