Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen. Part 39.[1] Stereochemistry of Perhydropyrido[3,2,1-*ij*][3,1]-benzoxazines and the Conformational Equilibrium for Perhydropyrido-[1,2-*c*][1,3]oxazine

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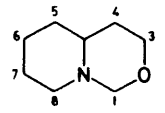
The four diasteroisomeric perhydropyrido[3,2,1-*ij*][3,1]benzoxazines have been synthesised and their configurations assigned by ^{1}H n.m.r. and i.r. spectroscopy and by kinetic studies of *N*-methylation. Comparisons of the ^{1}H n.m.r. chemical shifts of protons α to nitrogen in these isomers suggested an equilibrium ($CDCl_3$, 25°) for perhydropyrido[1,2-*c*][1,3]oxazine containing *ca.* 90% of the *trans*-fused conformer.

PERHYDROPYRIDO[1,2-*c*][1,3]OXAZINE (1) has been shown [2] by ^{1}H n.m.r. and i.r. measurements to exist in solution at room temperature predominantly as the *trans*-fused conformer (2) and dipole moment measure-



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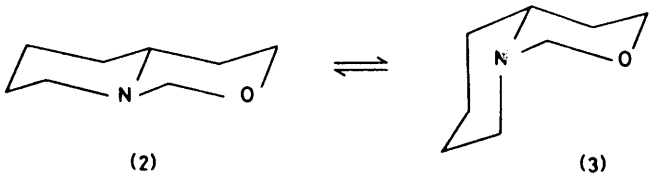


(2) (3)

ments [3] suggest a *trans* ⇌ *cis* equilibrium containing ⩾95% (2) in equilibrium with (3). Since both conformational estimates based on proton–proton geminal coupling constant (J_{gem}) data, as was done in the original qualitative estimate,[2] and those based on dipole moment data [3] are in certain instances open to criticism,[4,5] it seemed appropriate to compare the ^{1}H n.m.r. parameters of (1) with those of the conformationally locked perhydropyrido[3,2,1-*ij*][3,1]benzoxazines (4)—(7) to obtain conformational estimates based on ^{1}H n.m.r. parameters other than J_{gem}.

Syntheses.—The four diastereoisomeric perhydropyrido[3,2,1-*ij*][3.1]benzoxazines (4)—(7) were synthesized by the route shown in the Scheme. Conversion of 5,6,7,8-tetrahydroquinoline, obtained by a sequence of reactions,[6-8] to 8-hydroxymethyl-5,6,7,8-tetrahydroquinoline was accomplished in fair yields by treatment with a slight excess of paraformaldehyde at 110—120° for *ca.* 3 h at atmospheric pressure rather than in a sealed metal tube.[9] Using the same modified procedure but higher temperatures (150—160°) bis-(8-hydroxymethyl-5,6,7,8-tetrahydroquinoline (8) was produced almost exclusively.

Two isomers of 8-hydroxymethyldecahydroquinoline were obtained in a ratio of 4 : 1 by catalytic hydrogenation of 5,6,7,8-tetrahydroquinoline. Treatment of these with aqueous formaldehyde gave *r*-7a,*c*-10a,*c*-10b-perhydrobenzo[3,2,1-*ij*][3,1]benzoxazine (4) from the major isomer and *r*-7a,*t*-10a,*c*-10b-perhydrobenzo-[3,2,1-*ij*][3,1]benzoxazine (5) from the minor isomer.

Reduction of 8-hydroxymethyl-5,6,7,8-tetrahydroquinoline with sodium in ethanol produced a mixture of isomers of 8-hydroxymethyldecahydroquinoline which was converted to a mixture of perhydropyrido[3,2,1-*ij*][3,1]benzoxazines by treatment with aqueous formaldehyde. Chromatographic separation gave approximately equal quantities of *r*-7a,*c*-10a,*t*-10b- and *r*-7a,*t*-10a,*t*-10b-perhydrobenzo[3,2,1-*ij*][3,1]benzoxazine (6) and (7), respectively.

Assignment of Stereochemistry to the Perhydropyrido-[3,2,1-*ij*][3,1]*benzoxazines.*—Examination of Dreiding models of the conformations of the four diastereoisomeric perhydropyrido[3,2,1-*ij*][3,1]benzoxazines shows only one favourable all-chair conformation for each isomer (Figure 1). The assignment of stereochemistry to these diastereoisomers was based on 270 MHz ^{1}H n.m.r. spectra (Table 1), i.r. spectra (Figure 2), and

TABLE 1

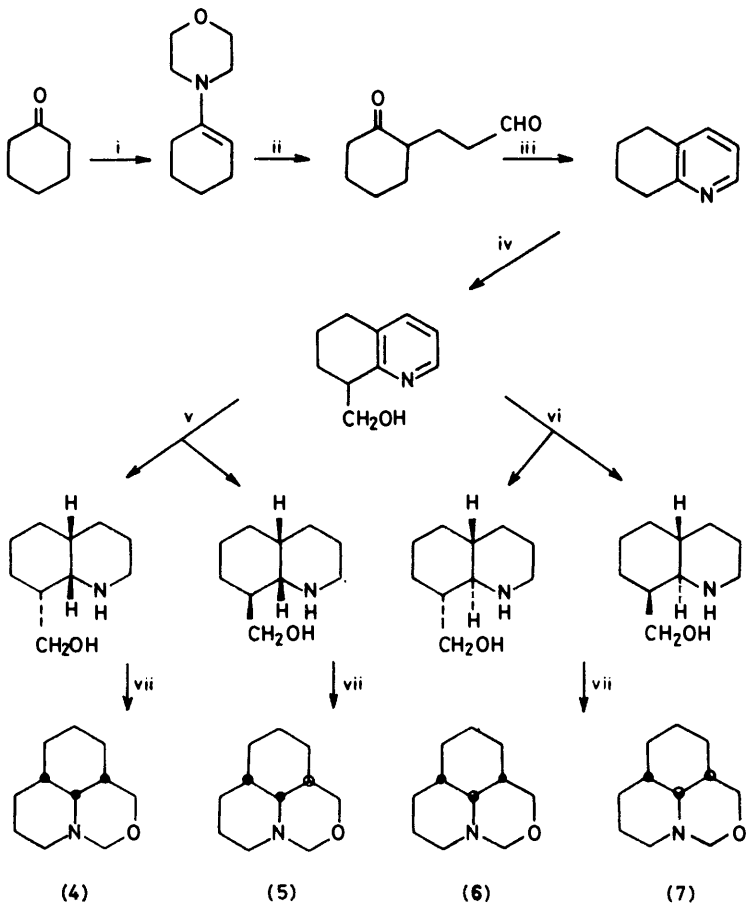
N.m.r. data [δ ($CDCl_3$); J in Hz] for isomeric perhydropyrido[3,2,1-*ij*][3,1]benzoxazines and perhydropyrido-[1,2-*c*][1.3]oxazine

Compound	δ (3eq)	$J_{3eq,3ax}$	δ (5ax)	δ (1eq)	$J_{1eq,1ax}$	δ (1ax)	$J_{1eq,10a}$	$J_{1ax,10a}$	δ (5eq)	$J_{5eq,5ax}$	δ (5ax)	$J_{5ax,6ax}$	$J_{5ax,6eq}$	δ (10a)	$J_{10a,10b}$	δ (10b)	$J_{10b,7a}$
(4)	4.27	−7.67	3.40	3.72	−11.7	3.68	0.0	2.92	2.70	−9.5	1.87				<1	2.20	<1
(5)	4.56	−10.8	4.44	3.85	−10.5	3.22	4.3	10.5	2.60	−10.5	3.17	10.5	3.9	2.21	10.2	2.79	4.5
(6)	4.35	−7.55	3.51	3.86	−11.0	3.11	4.0	11.0	2.67	−10.2	1.84					1.84	
(7)	4.55	−7.55	4.15	3.66	−10.0	3.60			2.85		2.58			2.26	4.2	2.75	10.2

	δ (1eq)	$J_{1eq,1ax}$	δ (1ax)	δ (3eq)	$J_{3eq,3ax}$	δ (3ax)	δ (8eq)	$J_{8eq,8ax}$	δ (8ax)	$J_{8ax,7ax}$	δ (4a)
(2) ⇌ (3)	4.30	−8.0	3.60	4.05	−11.8	3.48	2.72	−11.0	1.94	11.0	2.09

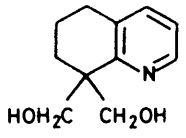
rates of methylation of the bridgehead nitrogen atoms (Table 2). Data on perhydropyrido[1,2-*c*][1,3]oxazine (1) are included for comparative purposes.

The two isomers (4) and (5) obtained *via* the route incorporating the catalytic hydrogenation step were expected to possess the *cis*(7a-H,10b-H) stereochemistry as a consequence of the normally encountered pre-



SCHEME Reagents: i, morpholine; ii, acrolein; iii, hydroxylamine hydrochloride; iv, paraformaldehyde at 110—120°; v, H_2–PtO_2; vi, Na–EtOH; vii, 40% aqueous formaldehyde

dominance of *cis*-addition of hydrogen in such reactions.[10] This *cis*-A–C ring fusion was confirmed by the magnitude of the vicinal coupling constants [11] involving 10b-H [(4) $J_{10b,7a} = J_{10b,10a} \leqslant 1$ Hz; (5) $J_{10b,7a}$ 4.5, $J_{10b,10a}$



(8)

10.2 Hz]. Isomers (4) and (5) were readily distinguished by the zero rate of methylation of (4), since severe non-bonded interactions would arise in the transition state leading to the derived methiodide, and by the presence of strong Bohlmann bands [12] in the i.r. spectrum of (4) (three C–H bonds anticoplanar with the nitrogen lone pair) as compared to weak bands in the spectrum of (5) (one C–H bond anticoplanar with nitrogen lone pair). The *trans*-A–B ring fusion in (4) was shown by $J_{3ax,3eq}$ −7.67 (3ax-H and nitrogen lone pair anticoplanar) [2,13] and the large $\Delta_{3ax,3eq}$ and $\Delta_{5ax,5eq}$ values (0.87 and 0.83 p.p.m., respectively).[14,15] The $J_{3ax,3eq}$ of −10.8 Hz in (5) indicated the *O*-inside *cis*-A–B fusion in which the nitrogen lone pair bisects the 3-methylene.[2,16] Finally the B–C fusions assigned to (4) and (5) were supported

TABLE 2

Rates of methylation [a] of isomeric perhydropyrido[3,2,1-*ij*][3,1]benzoxazines and of perhydropyrido[1,2-*c*][1,3]-oxazine

Compound	Rate constant (pseudo first order)	Interactions in derived methiodide
(4)	0	1 × gb,[b] 2 × Me/CH_2 [c] 1 × gp [d]
(5)	1.20×10^{-3} s^{-1}	2 × gb
(6)	1.07×10^{-3} s^{-1}	3 × gb, 1 × gp
(7)	23.4×10^{-3} s^{-1}	1 × gb, 1 × gp

[a] The rates were measured in CH_3CN solution at 30 °C by following the changes in conductivity of the reaction mixtures and are considered to be accurate to ±2%. [b] gb = *gauche*-butane interaction. [c] Me/CH_2 = interaction between N^+CH_3 and *syn*-axial methylene group. [d] gp = *gauche*-propanol interaction.

by the vicinal coupling constants involving the 1-methylene protons (Table 1).

Isomers (6) and (7) were obtained by the route involving sodium in ethanol reduction of 8-hydroxymethyl-5,6,7,8-tetrahydroquinoline and so were expected to possess the *trans*-(7a-H,10b-H) configurations since

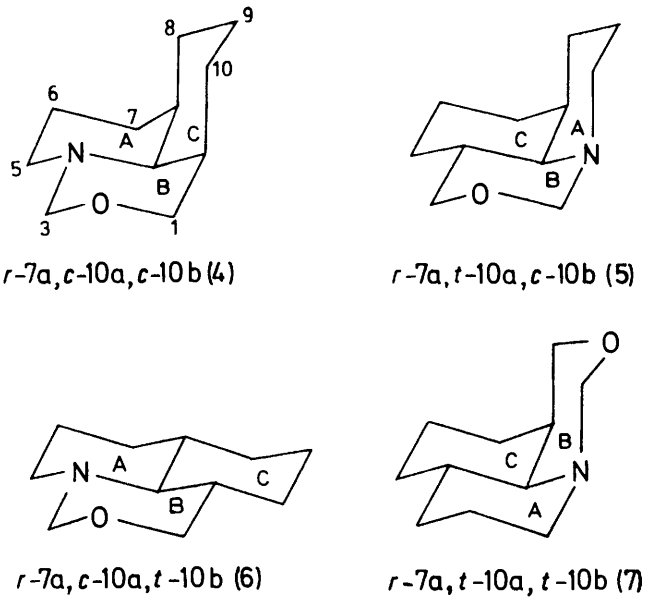


FIGURE 1 Conformations of the perhydropyrido[3,2,1-*ij*][3,1]benzoxazines

trans-decahydroquinolines are thermodynamically more stable than *cis*-decahydroquinolines. Isomer (6) was eluted first from a grade III Wöelm alumina column during a chromatographic separation of (6) and (7) as expected, since the heteroatom lone pairs are more shielded in (6) than in (7).[17] On a firmer basis (6) and (7) were distinguished by the strong Bohlmann absorption in the i.r. spectrum of (6) (three C–H bonds anticoplanar with the nitrogen lone pair) and the weak absorption in (7) (only 3ax-H anticoplanar with nitrogen lone pair).[12] In addition $\Delta_{5ax,5eq}$ and $\Delta_{3ex,3eq}$ values were large for (6) (0.84 and 0.83 p.p.m.) and small for (7) (0.40 and 0.27 p.p.m.) indicating *trans* A/B and *cis* A/B ring fusion respectively.[2,13] The reaction of (7) with methyl iodide showed the highest rate of the four isomers (Table 2) since there is only one *gauche*-butane interaction involving the *N*-methyl group in the derived methiodide. The vicinal coupling constant data (Table 1) confirmed these assignments.

Conformational Analysis of Perhydropyrido[1,2-c][1,3]-*oxazine*.—The four isomeric perhydropyrido[3,2,1-*ij*]-[3,1]benzoxazines provide model systems on which to base estimates of the position of the conformational equilibrium (2) ⇌ (3). Thus *r*-7a,*c*-10a,*t*-10b-perhydropyrido[3,2,1-*ij*][3,1]benzoxazine (6) and *r*-7a,*c*-10a,*c*-10b-perhydropyrido[3,2,1-*ij*][3,1]benzoxazine (4) provide locked *trans*-fused models for (2) and *r*-7a,*t*-10a,*c*-10b-perhydropyrido[3,2,1-*ij*][3,1]benzoxazine (5) provides a locked *cis*-fused model for (3).

The position of equilibrium (2) ⇌ (3) may be estimated from a comparison of appropriate chemical shifts with corresponding shifts in the model compounds only if the additional ring present in (4)—(6) has

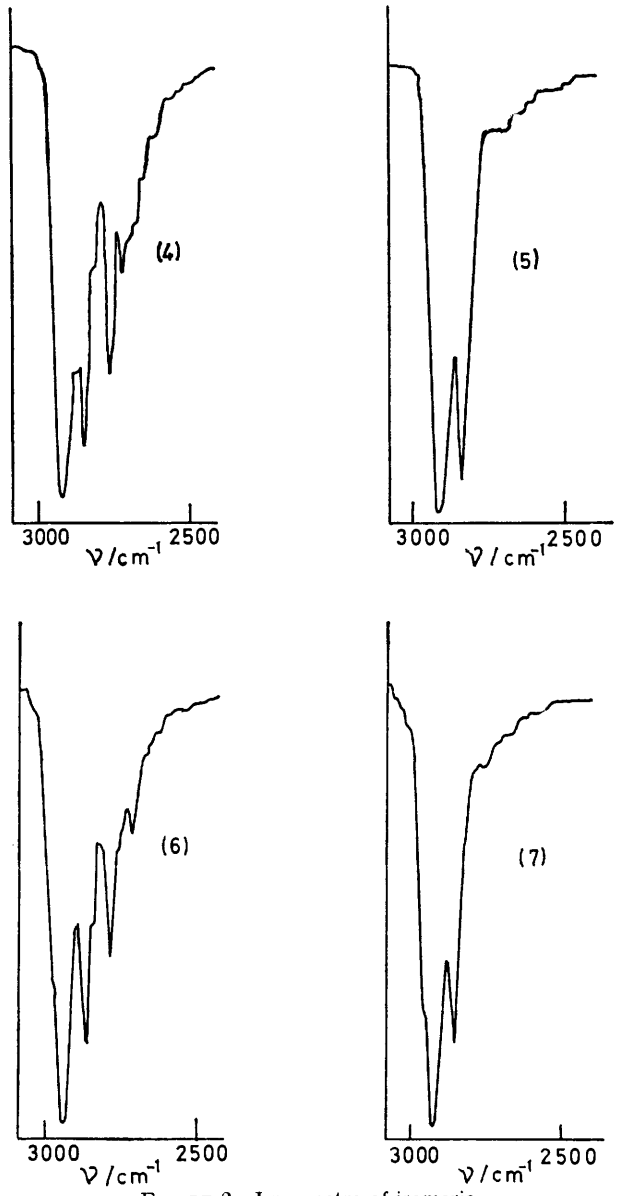


FIGURE 2 I.r. spectra of isomeric perhydropyrido[3,2,1-*ij*][3,1]benzoxazines

no effect on the chemical shifts utilised in the estimation. Since it has been shown [18] that an axial 5-substituent in tetrahydro-1,3-oxazines affects the chemical shifts of the 2-methylene protons the shifts of the 3- and 5-methylene protons in (4) will differ from those in the *trans*-fused conformer (2). A consideration of substituent alkyl effects on the chemical shifts of cyclohexane protons [16] suggests that the shifts of the 1- and 8-methylene protons in (2) ⇌ (3) should not be affected by equatorial substitution at the C(5) and C(4) positions as in (5) and (6) so that the shifts of these protons are appropriate for use in the conformational estimates.

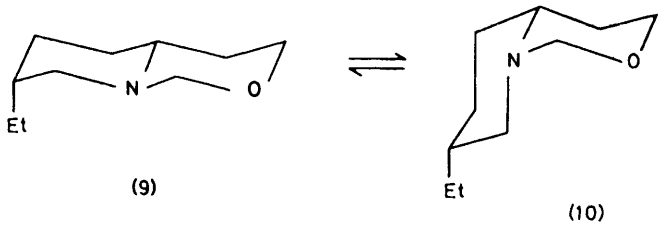
On this assumption the estimates shown in Table 3 were made [19] and although these are obviously only semi-quantitative the figures suggest an equilibrium containing *ca.* 90% (2) ($\Delta G°_{25}$ 1.30 kcal mol^{-1}) rather than ⩾95% ($\Delta G°_{25}$ ⩾ 1.74 kcal mol^{-1}) calculated on dipole moment data (benzene solution).[3] (The positions of equilibria in this system are not affected significantly by solvent changes.[1])

TABLE 3

Estimate of % *trans*-conformer (2) in the *trans* ⇌ *cis* equilibrium (2) ⇌ (3) of perhydropyrido[1,2-*c*][1,3]-oxazine (1) estimated from a comparison of the chemical shifts of protons adjacent to nitrogen and the geminal coupling constants of the interheteroatom methylene protons in (1) and in *trans* (6) and *cis* (5) locked isomers of perhydropyrido[3,2,1-*ij*][3.1]benzoxazines

^{1}H N.m.r. parameter	Compound (6) (*trans*)	(2) ⇌ (3)	(5) (*cis*)	% *trans* (2)
δ NCH_{ax}H$_{eq}$CH$_2$	1.84	1.94	3.17	92
δ NCH$_{ax}$$H_{eq}CH_2$	2.67	2.72	2.60	
δ NCH$_{ax}$O	3.51	3.60	4.44	90
δ NCH$_{eq}$O	4.35	4.30	4.56	
J_{NCH_2O}	−7.55	−8.0	−10.8	86

This estimate is in better agreement with the conformational preferences of alkyl substituted perhydropyrido[1,2-*c*][1,3]oxazines. Thus accepting a value of $\Delta G°_{25}$ of 1.30 kcal mol^{-1} for the *trans* (2) ⇌ *cis* (3) equilibrium, and taking the conformational free energy of a 3-methyl substituent in piperidine as 1.51 kcal mol^{-1},[20] then to a first approximation the $\Delta G°_{25}$ for (9) ⇌ (10) may be estimated as −0.21 kcal mol^{-1}, *i.e.* favouring *ca.* 58% *cis*-conformer (10). This is in accord with the low temperature spectrum (−90°) of (9) ⇌ (10) in which signals were observed [3] for both



(9) (10)

conformers in the ratio 70% *cis* (10) to 30% *trans* (9). Assuming a small entropy difference between the conformers then a $\Delta G°_{25}$ of −0.34 kcal mol^{-1} may be estimated (corresponding to 63% *cis*-conformer). This is in agreement with an estimate of 63% *cis*-conformer in the (9) ⇌ (10) equilibrium based on the J_{gem} value of the NCH$_2$O protons of −9.6 Hz compared with the values of −7.55 and −10.8 Hz in the locked *trans*- and *cis*-fused compounds (6) and (5) (Table 2). [The values from the J_{gem} of the locked compounds were taken rather than those from the spectra of (9) and (10) at −90° since broadening of the signals rendered the measurement of J_{gem} to a greater accuracy than ±0.3 Hz impossible.]

Taking the higher value of $\Delta G°_{25}$ *trans* (2) ⇌ *cis* (3) of 1.74 kcal mol^{-1} (from dipole moment data) [3] leads to the expectation of a (9) ⇌ (10) equilibrium containing *ca.* 60% *trans*-fused conformation ($\Delta G°_{25}$ + 0.23 kcal mol^{-1}). Thus the estimate for $\Delta G°_{25}$ for perhydropyrido[1,2-*c*][1,3]oxazine based on ^{1}H n.m.r. chemical shifts of 1.30 kcal mol^{-1} corresponding to *ca.* 90% *trans*-fused conformer (2) is preferable to that based on dipole moment data.

EXPERIMENTAL

The ^{1}H n.m.r. spectra were determined on Varian T60 and Brüker 270 MHz spectrometers normally as 10% solutions with tetramethylsilane as internal reference where appropriate. The error in chemical shift measurement was ±0.02 p.p.m. and for the coupling constants measured on the Varian T60 ±0.05 Hz, whereas that from the Brüker 270 MHz spectrometer was ±0.1 Hz. I.r. spectra were recorded on Perkin-Elmer 237 and 297 grating instruments as 0.2M solutions in $CDCl_3$ using 0.2 mm matched cells. Elemental analyses were carried out by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic.

3-(2-Oxocyclohexyl)propanal.—Acrolein (56 g) dissolved in ether (50 ml) was added dropwise over 2 h to a stirred solution of 1-morpholinocyclohexene [21] (167 g) in ether (150 ml) under a blanket of nitrogen. After a further 1 h of stirring, 2N-hydrochloric acid (550 ml) was added with continuous stirring. The ether layer was washed with saturated sodium hydrogencarbonate solution and dried (Na_2SO_4). After removing the ether *in vacuo* the residue was distilled giving 3-(2-oxocyclohexyl)propanal (51 g, 33%), b.p. 99° at 1.0 mmHg (lit.,[6] 83—85° at 0.7 mmHg).

5,6,7,8-Tetrahydroquinoline.— 3-(2-Oxocyclohexyl)propanal (51 g) and hydroxylamine hydrochloride (23 g) were boiled under reflux in ethanol (100 ml) for 2 h. After removal of the ethanol *in vacuo*, the dark residue was neutralised with sodium carbonate and extracted with ether. The ether was removed *in vacuo* and the residue distilled giving 5,6,7,8-tetrahydroquinoline (19 g, 43%). b.p. 60° at 0.2 mmHg (lit.,[22] 92—93° at 12 mmHg).

8-Hydroxymethyl-5,6,7,8-tetrahydroquinoline.— 5,6,7,8-Tetrahydroquinoline (50 g) and paraformaldehyde (30 g) were heated for 3 h in a lightly sealed flask with the temperature controlled between 110 and 120°. After cooling, hydrochloric acid (200 ml; 20%) was added and the solution filtered. The filtrate was basified with aqueous sodium hydroxide solution and then extracted with benzene. After removal of the benzene *in vacuo* the remaining liquid was distilled giving 8-hydroxymethyl-5,6,7,8-tetrahydroquinoline (12.0 g, 21%) as a liquid, b.p. 108—112° at 0.1 mmHg (lit.[9] 80—82° at 0.07 mmHg). Because of the contamination of the product with bis-(8-hydroxymethyl)-5,6,7,8-tetrahydroquinoline the reaction was repeated at slightly lower temperatures. It was found that yields of up to 35% could be obtained by heating the same materials on a boiling-water-bath for periods between 40 and 100 h.

8-Hydroxymethyldecahydroquinoline (Isomeric Mixture).—A solution of 8-hydroxymethyl-5,6,7,8-tetrahydroquinoline (7.5 g) in glacial acetic acid (100 ml), to which Adams catalyst (PtO_2; 1 g) had been added, was shaken with hydrogen in a Parr hydrogenator until the calculated uptake of hydrogen had been accomplished. The catalyst was removed by filtration and acetic acid in the filtrate was evaporated *in vacuo* and the residue just basified with a solution of sodium hydroxide. The solution was extracted

with ether; the ether layer was separated and dried (Na_2SO_4). After removing the ether, the remaining crude whitish solid (6.8 g, 88%) was fractionally recrystallised from a solution of 1 : 1 ether–light petroleum (b.p. 40—60°) to give r-4a,c-8,c-8a-8-*hydroxymethyldecahydroquinoline* (2.5 g) as long needles, m.p. 125° (Found: C, 71.0; H, 11.2; N, 8.3. $C_{10}H_{19}NO$ requires C, 71.0; H, 11.3; N, 8.3%), and r-4a,t-8,c-8a-8-*hydroxymethyldecahydroquinoline*, m.p. 84—85° (Found: C, 71.2; H, 11.3; N, 8.2%), in the ratio of 4 : 1.

8-*Hydroxymethyldecahydroquinoline* (*Isomeric Mixture*).—8-Hydroxymethyl-5,6,7,8-tetrahydroquinoline (7.5 g) was boiled under reflux for 2 h in absolute ethanol (125 ml) together with finely cut pieces of sodium (25 g). After cooling, water (50 ml) was added and the solution neutralised with hydrochloric acid and then just basified with sodium hydroxide. The solution was extracted with chloroform. The combined dried organic layers were evaporated to remove chloroform and ethanol and the residue distilled producing a mixture of isomeric *trans*(4a-H,8a-H)-8-hydroxymethyldecahydroquinolines (4 g, 53%), b.p. 74—104° at 0.5 mmHg. The mixture partly solidified but efforts at fractional recrystallisation were unsuccessful. The mixture of isomers was therefore used in the next stage without further purification.

Perhydropyrido[3,2,1-ij][3,1]*benzoxazine* (4).—*r*-4a,*c*-8,*c*-8a-8-Hydroxymethyldecahydroquinoline (6.5 g) was shaken with 40% aqueous formaldehyde (20 ml) for 30 min. The reaction mixture was basified with 30% aqueous sodium hydroxide and extracted with ether several times. The dried ethereal extracts were combined and distilled to give r-7a,c-10a,c-10b-*perhydropyrido*[3,2,1-ij][3,1]*benzoxazine* (4) (5 g, 76%) as a mobile liquid, b.p. 92° at 0.1 mmHg (Found: C, 73.1; H, 10.7; N, 7.6. $C_{11}H_{19}NO$ requires C, 72.9; H, 10.6; N, 7.7%).

Perhydropyrido[3,2,1-ij][3,1]*benzoxazine* (5).—*r*-4a,*t*-8,*c*-8a-8-Hydroxymethyldecahydroquinoline (4.5 g) was shaken with 40% aqueous sodium hydroxide solution and extracted with ether several times. The dried ethereal extracts were combined and distilled to give a mobile liquid (3.5 g, 77%), b.p. 120—132° at 0.5 mmHg, which was chromatographed over grade III Wöelm neutral alumina (250 g) to give r-7a,t-10a,c-10b-*perhydropyrido*[3,2,1-ij][3,1]*benzoxazine* (5) (1.5 g), b.p. 130—132° at 0.5 mmHg (Found: C, 72.6; H, 10.5; N. 7.8%).

Perhydropyrido[3,2,1-ij][3,1]*benzoxazines* (6) *and* (7).—The isomeric mixture of *trans*(4a-H,8a-H)-8-hydroxymethyldecahydroquinolines from Na–EtOH reduction of 8-hydroxymethyl-5,6,7,8-tetrahydroquinoline (2.5 g) was shaken with 40% aqueous formaldehyde (10 ml) for 30 min, basified with 30% aqueous sodium hydroxide, and ether-extracted several times. The dried ether extracts were distilled to give a mobile liquid consisting of a mixture of isomers of perhydropyrido[3,2,1-*ij*]benzoxazine (1.9 g, 76%), b.p. 101—110° at 760 mmHg. The product was chromatographed over grade III Wöelm neutral alumina (250 g) eluting with ether–light petroleum (b.p. 30—40°) containing increasing percentages of ether from 0 to 50%. Forty fractions (50 ml) were taken. Fractions 8—14 produced r-7a,c-10a,t-10b-*perhydropyrido*[3,2,1-ij][3,1]*benzoxazine* (6) (*ca.* 0.4 g), b.p. 98° at 760 mmHg (Found: C, 72.9; H, 10.7; N, 7.6%). Fractions 22—26 produced r-7a,t-10a,t-10b-*perhydropyrido*[3,2,1-ij][3,1]*benzoxazine* (7) (*ca.* 0.35 g), b.p. 115° at 760 mmHg (Found: C, 72.7; H, 10.6; N, 7.6%).

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