Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen. Part 34.[1] Stereochemistry of 8,9,10,11,11a,11b,12,13-Octahydro-7a*H*-quino[1,2-*c*][1,3]benzoxazines and 7a,8,9,10,10a,10b,11,12-Octahydrocyclopent[5,6][1,3]oxazino[3,4-*a*]quinolines

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Four diastereoisomeric 8,9,10,11,11a,11b,12,13-octahydro-7a*H*-quino[1,2-*c*][1,3]benzoxazines and two 7a,8,9,10,10a,10b,11,12-octahydrocyclopent[5,6][1,3]oxazino[3,4-*a*]quinolines have been synthesised and their configurations assigned by ^{1}H n.m.r. spectroscopy. In the case of the quinobenzoxazines the *r*-7a,*c*-11a,*c*-11b-compound adopts the *trans*-BC conformation, the *r*-7a,*t*-11a,*c*-11b- and the *r*-7a,*c*-11a,*t*-11b-compounds both exist predominantly in the *trans*-BC conformations, and the *r*-7a,*t*-11a,*t*-11b-compound predominantly adopts the *cis*-BC-O-outside conformation. Similar conformational preferences are exhibited by the *r*-7a,*c*-10a,*c*-10b- and the *r*-7a,*t*-10a,*c*-10b-cyclopenta-analogues. 4,4a,5,6-Tetrahydro-3*H*-[1,3]oxazino[3,4-*a*]quinoline and its 3-methyl derivatives all adopt predominantly the *trans*-fused ring conformations in solution at room temperature.

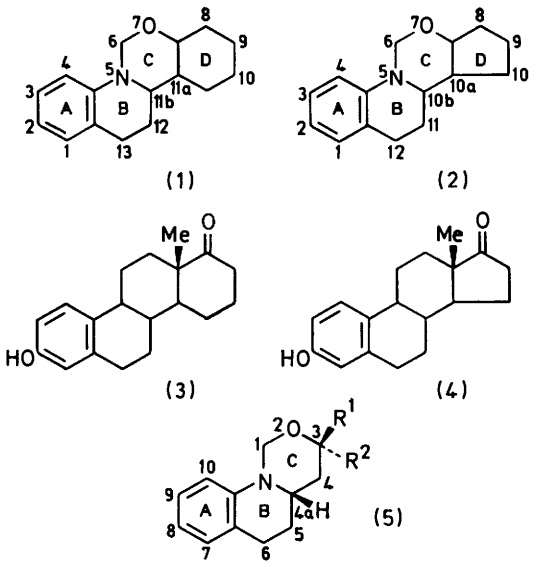
APART from the medicinal interest inherent in heterasteroids, bridgehead nitrogen steroidal systems in particular present some interesting stereochemical features. Accordingly 8,9,10,11,11a,11b,12,13-octahydro-7a*H*-quino[1,2-*c*][1,3]benzoxazines (1) and the corresponding cyclopent[5,6][1,3]oxazino[3,4-*a*]quinolines (2) have been studied, because of their structural resemblance to D-homoestrone (3) and estrone (4). For comparison purposes 4,4a,5,6-tetrahydro-3*H*-[1,3]-oxazino[3,4-*a*]-quinoline (5; $R^1 = R^2 = H$) and the 3-methyl derivatives (R^1 or R^2 = Me) were also synthesised.

Syntheses.—A mixture of the four diastereoisomeric 8,9,10,11,11a,11b,12,13-octahydro-7a*H*-quino[1,2-*c*][1,3]-benzoxazines was prepared as shown in Scheme 1. Three isomers were readily obtained pure by chromatography over grade III Wöelm neutral alumina, but rechromatography over grade I Wöelm neutral alumina was necessary to separate the other isomer.

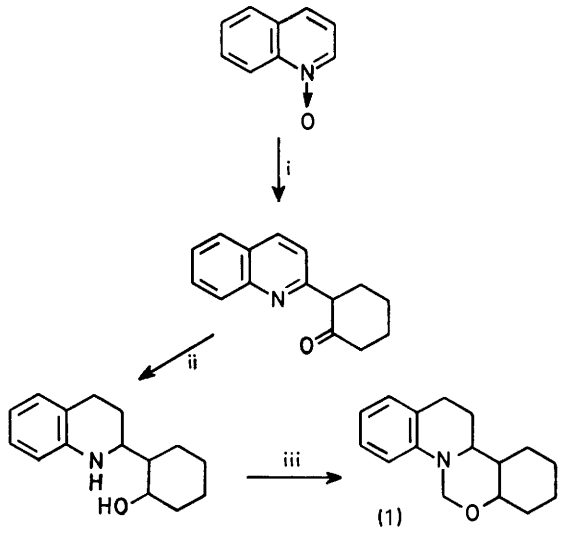
The five-membered ring D compounds were prepared by a similar route from the morpholine enamine of cyclopentanone instead of the cyclohexanone enamine.

[1] Part 33, T. A. Crabb, J. S. Mitchell, and R. F. Newton, *J.C.S. Perkin II*, 1977, 370.

The 2-(2-quinolyl)cyclopentanone was obtained as a black solid which had to be purified before hydrogenation by chromatography over grade H Laporte alumina

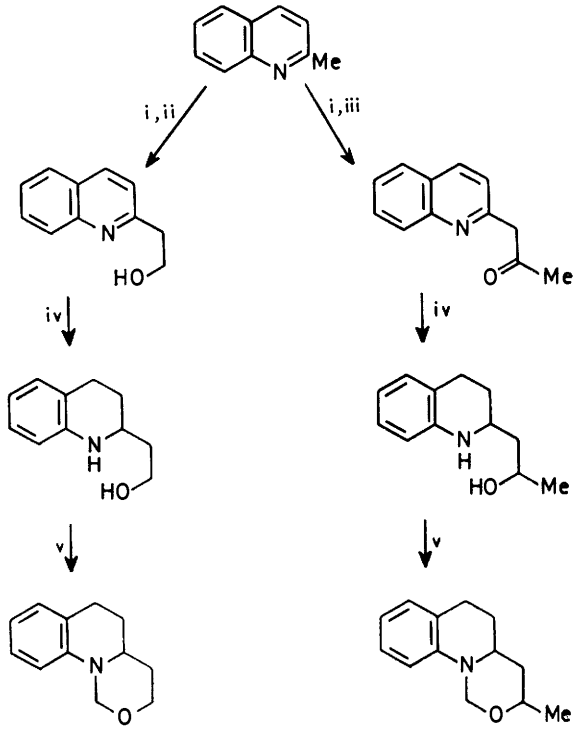


[elution with 30% ether–light petroleum (b.p. 40—60°)], which yielded an orange crystalline solid. After



SCHEME 1 Reagents: i, morpholine enamine of cyclohexanone-BzCl at 0 °C; ii, H_2–PtO_2; iii, aq. 40% CH_2O

catalytic reduction and ring closure as before, the isomeric mixture of tetracyclic products was chromatographed over grade III Wöelm neutral alumina. The isomers when separated were purified by recrystallisation. Only two isomers were obtained out of the possible four. 4,4a,5,6-Tetrahydro-3*H*-[1,3]oxazino-[3,4-*a*]quinoline and the two isomeric 3-methyl derivatives were synthesised as shown in Scheme 2. The isomeric pair were separated by column chromatography over grade III Wöelm neutral alumina and further purified by distillation under high vacuum. The ratio of the first isomer eluted from the column to the second was 3 : 1.



SCHEME 2 Reagents: i, PhLi; ii, CH_2O gas; iii, MeOAc; iv, H_2–PtO_2; v, aq. 40% CH_2O

A priori *Discussion of Conformational Equilibria.*— The conformational analysis of the diastereoisomeric quinobenzoxazines (6)—(9) differs most clearly from

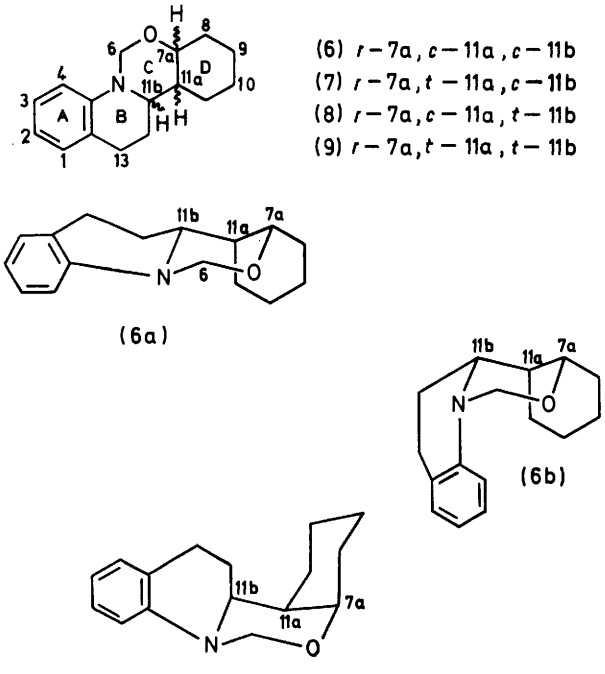


FIGURE 1 Possible conformations of the *r*-7a,*c*-11a,*c*-11b-quinobenzoxazine (6)

that of carbocyclic analogues by the presence of the tertiary bridgehead nitrogen atom, which permits ready interconversion between *cis*-BC and *trans*-BC conformations. The generalised anomeric effect [2] and differences

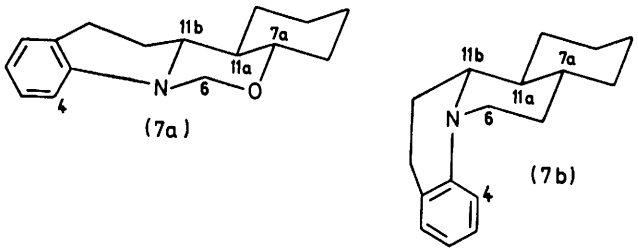


FIGURE 2 Possible conformations of the *r*-7a,*t*-11a,*c*-11b-quinobenzoxazine (7)

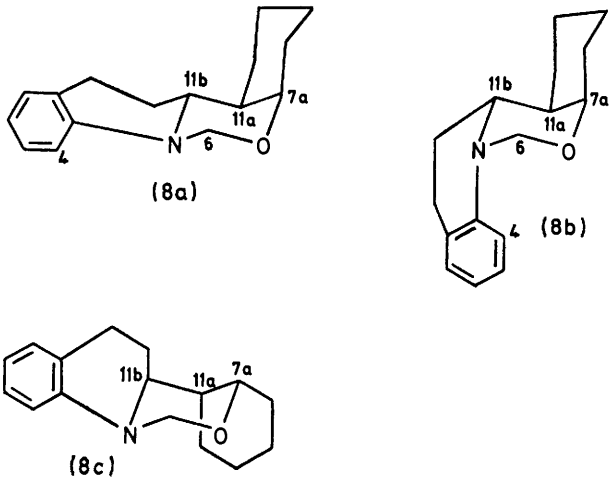


FIGURE 3 Possible conformations of the *r*-7a,*c*-11a,*t*-11b-quinobenzoxazine (8)

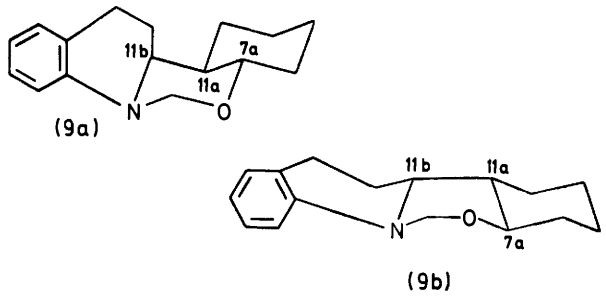


FIGURE 4 Possible conformations of the *r*-7a,*t*-11a,*t*-11b-quinobenzoxazine (9)

in non-bonded interactions between these conformations will determine the position of equilibrium.* In the following discussion ring B is assumed to exist in a half-chair type of conformation and only chair conformations for rings C and D are considered. In addition, in the *trans*-BC and *cis*-BC-O-inside conformations overlap of the nitrogen lone pair and the aromatic ring π orbitals will occur with a resultant flattening of the geometry about the nitrogen atom (*cf.* a pyramidal angle of 39° for aniline [3] with 61° for ammonia).

The three conformations of the *r*-7a,*c*-11a,*c*-11b-compound (6) are depicted in Figure 1,† and the presence of severe *syn*-axial interactions in two of these (6b and c) suggests that (6) will exist almost entirely in the *trans*-BC conformation (6a). Not such a ready decision regarding the position of *cis*-BC ⇌ *trans*-BC equilibria for (7) and (8) is possible, and Table 1 summarises the interactions present in the conformations shown in Figures 2 and 3. Such an analysis shows that for (7) the unfavourable anomeric effect present in the *trans*-BC conformation may be removed only at the expense of introducing a *gauche* butane interaction together with

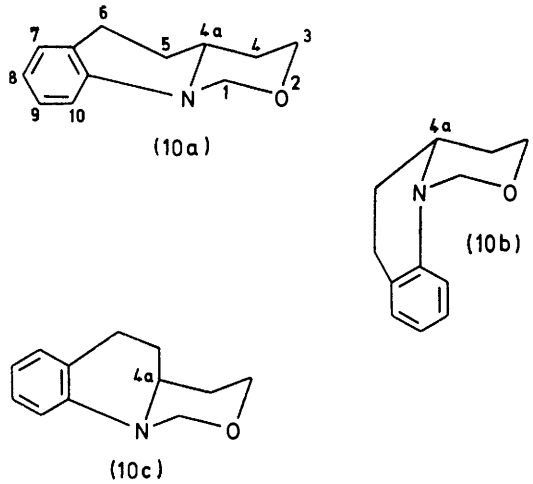


FIGURE 5 Possible conformations of 4,4a,5,6-tetrahydro-3*H*-[1,3]oxazino[3,4-*a*]quinoline

syn axial Ph,C–H and *syn* axial Ph,O interactions.‡ The energy of the Ph,C–H interaction is expected to be *ca.* 1—1.5 kcal mol^{-1} and that of the *gauche* butane interaction *ca.* 0.85 kcal mol^{-1}, so that (7) should exist predominantly in the *trans*-BC-conformation. The situation for (8) is more complex since there are two possible *cis*-BC conformations. The difference in energy between the *trans*-BC (8a) and the *cis*-BC-O-inside conformation (8b) is the same as that between (7a) and (7b), so that of these two the *trans*-BC conformer (8a) might be predicted to predominate.

The situation regarding the O-outside conformer (8c) is difficult to assess. This conformer suffers from fewer *gauche* butane interactions than does (8a) and the methylene–heteroatom interactions are expected to be

* For a discussion of the importance of the generalised anomeric effect in tetrahydro-1,3-oxazine derivatives see for example H. Booth and R. U. Lemieux, *Canad. J. Chem.*, 1971, **49**, 776.

† The compounds described in this paper exist as racemates. The conformational structures are drawn in the forms easiest to represent and do not necessarily correspond to the same enantiomer in each case.

‡ For the use of the term *gauche* butane interaction in the conformational analysis of saturated heterocyclic systems see for example P. J. Brignell, K. Brown, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1968, 1462.

[2] S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc.* (*B*), 1971, 136.

[3] D. G. Lister and J. K. Tyler, *Chem. Comm.*, 1966, 6.

small.[4] However (8a and b) are stabilised by conjugation of the nitrogen lone pair with the aryl ring, this stabilisation being lost in (8c). For (9) (Figure 4) only one chair-C,chair-D conformation is possible (9a); an equilibrium mixture of the *trans*-BC conformation (12a) and the *cis*-BC-O-outside conformation (12c).

Assignment of Stereochemistry to the 8,9,10,11,11a,11b,-12,13-*Octahydro*-7a*H*-*quino*[1,2-c][1,3]*benzoxazines*.—The

TABLE 1

Non-bonded interactions in conformations of the *r*-7a, *t*-11a,*c*-11b- (7) and *r*-7a,*c*-11a,*t*-11b- (8) quinobenzoxazines

Compound	*trans*-BC-conformation	*cis*-BC-O-inside conformation [a]	*cis*-BC-O-outside conformation
r-7a,*t*-11a,*c*-11b (7)	(7a) Unfavourable anomeric effect H-4,H-6*eq* 1 × 'gb' [b]	(7b) Favourable anomeric effect H-4,H-6*eq* Ph,H [c] Ph,O [c] 2 × 'gb' [b]	
r-7a,*c*-11a,*t*-11b (8)	(8a) Unfavourable anomeric effect H-4,H-6*eq* 4 × 'gb' [b]	(8b) Favourable anomeric effect H-4,H-6*eq* Ph,H [c] Ph,O [c] 5 × 'gb' [b]	(8c) Unfavourable anomeric effect CH_2, N [d] 2 × CH_2,O [d] Ph,H [c] 2 × 'gb' [b]

[a] In a Dreiding model of the *cis*-BC-O-inside conformation of (7) and (8) with ring B in a half-chair in addition to near 1,3-*syn*-axial interactions between the aryl ring and H-11a and between the aryl ring and the oxygen atom there is a *syn*-axial interaction (H,H distance *ca.* 2 Å) between the C-13 methylene group and H-11a. The latter interaction is included as a 'gb' interaction in the Table since it may be reduced by rotation about the C(12)–C(13) bond only at the expense of introducing torsional interaction between the C-12 and C-13 methylene groups. [b] An approximate *gauche*-butane interaction. Differing bond lengths will result in the energy value of this interaction being different from that (0.85 kcal mol^{-1}) in cyclohexane derivatives. [c] Near *syn*-axial Ph,C–H or Ph,O interaction. Owing to the differing orientations of the phenyl ring with respect to the axial C–H in the O-inside and O-outside conformations, these Ph,O interactions in the two conformers will be of different energies. [d] Near *syn*-axial CH_2, O or CH_2,N interaction.

TABLE 2

Non-bonded interactions in conformations of 4,4a,5,6-tetrahydro-3*H*-[1,3]oxazino[3,4-*a*]quinoline and the isomeric 3-methyl derivatives [a]

Compound	*trans*-BC-conformation	*cis*-BC-O-inside conformation	*cis*-BC-O-outside conformation
(5; $R^1 = R^2 = H$)	(10a) Unfavourable anomeric effect H-10,H-1*eq*	(10b) Favourable anomeric effect H-10,H-1*eq* Ph,H Ph,O gb	(10c) Unfavourable anomeric effect 2 × gb Ph,H
(5; R^2 = Me, $R^1 = H$)	(11a) Unfavourable anomeric effect H-10,H-1*eq*	(11b) Favourable anomeric effect H-10,H-1*eq* Ph,H Ph,O gb	(11c) Unfavourable anomeric effect 3 × gb *syn*-axial Me,CH_2 Ph,H
(5; R^1 = Me, $R^2 = H$)	(12a) Unfavourable anomeric effect H-10,H-1*eq* 2 × gb	(12b) Favourable anomeric effect H-10,H-1*eq* Ph,H Ph,O 3 × gb	(12c) Unfavourable anomeric effect 2 × gb Ph,H

[a] Nature of interactions given in footnotes to Table 1.

alternative conformation (9b) involves a boat ring C. Similar arguments apply to the cyclopenta-compounds (2).

The analysis of interactions present in the conformations of 4,4a,5,6-tetrahydro-3*H*-[1,3]oxazino[3,4-*a*]-quinoline and the isomeric 3-methyl derivatives shown in Figures 5—7 is summarised in Table 2. Both the parent compound and the *cis*(3-H,4a-H)-3-methyl compound might be expected to exist predominantly in the *trans*-BC conformation. The *cis*-BC-O-outside conformation for the latter compound in particular is of high energy as a result of a *syn* axial Me,CH_2 interaction. The *trans*(3-H,4a-H)-3-methyl compound might exist as absence of reduced intensity of bands in the Bohlmann region [5] of the i.r. spectra of bridgehead nitrogen compounds does not necessarily indicate *cis*-fusion. In particular in the diastereoisomers of the quinobenzoxazine (1) overlap of the nitrogen atom lone pair of electrons and the aromatic ring π-electron system may well affect the Bohlmann absorption. To investigate this, the C–H stretching region in the i.r. spectra of *N*-methylpiperidine and *N*-methyl-1,2,3,4-tetrahydroquinoline were recorded. Whereas *N*-methylpiperidine

[4] E. L. Eliel, *Accounts Chem. Res.*, 1970, **3**, 1.
[5] F. Bohlmann, *Chem. Ber.*, 1958, **91**, 2157.

showed marked absorption in the 2 800—2 600 cm^{-1} region with a strong band at 2 780 cm^{-1}, *N*-methyl-1,2,3,4-tetrahydroquinoline showed only slight inflections on the low wavenumber side of the 2 800 cm^{-1}

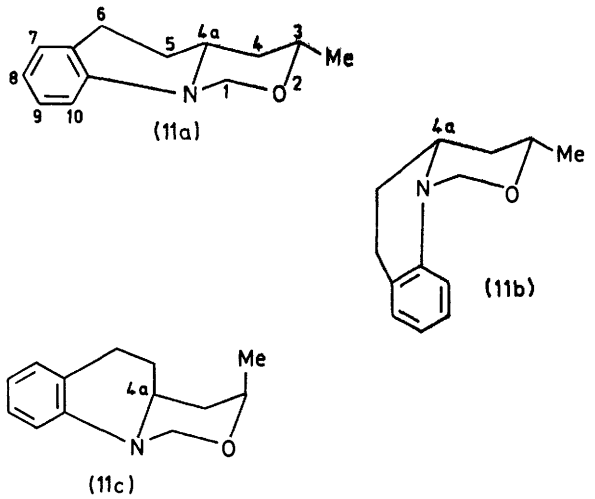


FIGURE 6 Possible conformations of *cis*(3-H,4a-H)-3-methyl-4,4a,5,6-tetrahydro-3*H*-[1,3]oxazino[3,4-*a*]quinoline

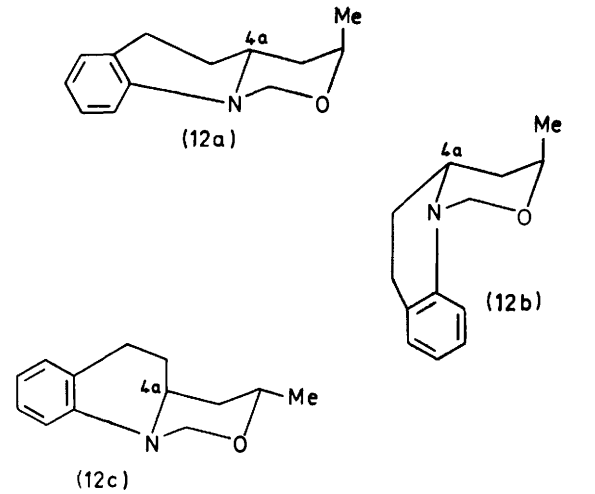


FIGURE 7 Possible conformations of *trans*(3-H,4a-H)-3-methyl-4,4a,5,6-tetrahydro-3*H*-[1,3]oxazino[3,4-*a*]quinoline

band. Thus the presence of an aromatic ring adjacent to the nitrogen atom drastically reduces absorption in the Bohlmann region.

In the light of this it was hardly surprising to find that the four isomers of the quinobenzoxazine (1) showed little absorption in the 2 800—2 600 cm^{-1} region. However, whereas the middle pair of isomers eluted from the chromatography column showed only tailing of the CH stretching vibrations into the Bohlmann region, the remaining two isomers gave recognisable albeit weak peaks in this region.

The u.v. spectra (Table 3) of the four diastereoisomers showed an important difference. The two middle isomers eluted from the chromatography column showed similar u.v. spectra [$\lambda_{max.}$ 248.8 and 291.8 nm (ε 9 590 and 1 780); $\lambda_{max.}$ 250.2 and 293.2 nm (ε 9 570 and 1 710)]. The spectrum of the first eluted isomer was not dissimilar, with shifts to longer wavelengths ($\lambda_{max.}$ 255.5 and 295.5 nm) and an increase in extinction coefficients (ε 11 970 and 2 170). However the last eluted isomer showed a large hypsochromic shift of both peaks ($\lambda_{max.}$ 244.5 and 280 nm) with respect to the other isomers (the higher wavelength peak appeared as a shoulder on the main peak), and the extinction coefficients were greatly reduced (ε 6 180 and 1 008).

TABLE 3

U.v. absorption spectra of compounds (1), (2), and (5) in ethanol

Compound	$\lambda_{max.}$/nm	ε
(6)	255.5, 295.5	11 970, 2 170
(7)	248.8, 291.8	9 590, 1 780
(8)	250.2, 293.2	9 570, 1 710
(9)	244.5, 280sh	6 180, 1 008
(16)	254, 295.4	11 520, 2 075
(17)	249.5, 293	12 190, 2 030
(5; R^2 = Me R^1 = H)	249.8, 293.5	10 600, 2 110
(5; R^2 = H R^1 = Me)	249.5, 293	8 695, 1 720
(5; R^1 = R = H)	250, 292	7 890, 1 500

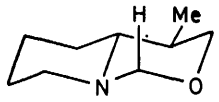
This can be explained in terms of reduced overlap of the nitrogen lone pair with the aromatic ring, indicating a conformation for this diastereoisomer such that the nitrogen lone pair is tipped into the plane of the aromatic ring, preventing transfer of electrons into the aromatic system. These u.v. results imply that the first three eluted isomers exist in conformations where overlap of the nitrogen lone pair and the π orbitals is possible as in the *trans*-BC or *cis*-BC-O-inside conformations, whereas the last eluted isomer exists in a *cis*-BC-O-outside conformation where such overlap is not possible.

In all the conformations of compounds (6)—(9) the conformation of ring B probably approximates to a half-chair. This half-chair is rather flexible so that to minimise changes in non-bonded interactions introduced by changes in CD ring fusion in the various conformers of (6)—(9) ring B may readily deform. This will introduce changes in the geometric relationship between the nitrogen lone pair and the aromatic ring with consequent changes in $\lambda_{max.}$ (Table 3) and in J_{gem} [C(6) methylene] (Table 4). Alterations in ring B geometry will also affect the magnitude of the vicinal couplings of H-11b to H-12*ax*′ and H-12*eq*′. Thus no quantitative estimate of the position of *cis*-BC ⇌ *trans*-BC equilibrium can be based on these parameters (see also note to Table 4). Although changes in ring B may be responsible for the observed variations in the $\lambda_{max.}$ values these may also be due in part to interactions between heteroatom orbitals.[6]

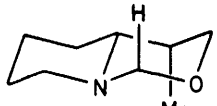
(i) 8,9,10,11,c-11a,c-11b,12,13-*Octahydro*-r-7aH-*quino*-[1,2-c][1,3]*benzoxazine*. The first isomer eluted from the chromatography column was assigned the *r*-7a,*c*-11a,*c*-11b-configuration (6). An important indication of the

[6] R. Hoffmann, *Accounts Chem. Res.*, 1971, **4**, 1; C. C. Levin, R. Hoffmann, W. J. Hehre, and J. Hudec, *J.C.S. Perkin II*, 1973, 210.

stereochemistry of this isomer was the chemical shift (δ 4.40) of H-6*ax*, which was the lowest observed for this proton in all four isomers. A survey of all the conformations in Figures 1—4 reveals that H-6*ax* would be most shielded in conformation (6a). This follows from a consideration of the chemical shifts of H-1*ax* in (13) and (14) (δ 3.55 and 3.27, respectively),[7] illustrating the



(13)



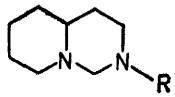
(14)

shift to high field of the axial H-1 signal in compounds containing an axial methyl group at C-4. This has been attributed [8] to conformational distortion arising from non-bonded interactions involving the axial methyl group at such a position. In (6a) there is a methylene group at C-11a in a 1,4-diaxial relationship with H-6*ax* and thus a high field shift of the H-6*ax* signal is expected. This shift is additional to that arising from the *trans*-fusion between rings B and C.[9] The 6*ax*-proton in conformation (8c) although shielded by the axial methylene group at C-11a, will not absorb at notably high field since this shielding is cancelled by the deshielding effect of the axial C-11b methylene group.[10]

Support for the validity of this assignment was supplied by the splitting pattern of the H-7a signal. If (6a) is the correct structure for this isomer then the signals arising from the H-7a might be expected to have a band-width of *ca.* 13 Hz arising from three approximately equal vicinal couplings ($J_{ax,eq}$) of *ca.* 4 Hz. The H-7a signal was in fact a broad singlet, whose width at half-height was 6.5 Hz (*ca.* 12 Hz at the base). This result can only be expected in one other conformation (8c); all the rest require at least one large axial–axial coupling. Analysis of the H-11b multiplet gave values for the vicinal coupling constants involving H-11b as $J_{11b,11a}$ 2.7, $J_{11b,12ax}$ 9.5, and $J_{11b,12eq}$ 5.3 Hz. Ring B in (6a) most probably resembles a half-chair so that the angles between C(11b)–H and the pseudoaxial and pseudoequatorial C-12 methylene bonds will be less than the 180° and 60° present in the perfect chair conformation. The observed vicinal coupling constants therefore are consistent with the *trans*-fused conformation (6a).

The u.v. data for this isomer indicate an overlap of the nitrogen lone pair with the aryl orbitals consistent with the *trans*-BC structure (6a) but not with the *cis*-BC-O-outside conformation (8c).

In the octahydropyrido[1,2-*c*]pyrimidine system (15) [11]



(15)

J_{gem} (assumed negative) for the C-1 methylene protons is −8.5 Hz when R = Bu^t, and this becomes 2.0 Hz more negative (−10.5 Hz) when R = Ph. Thus the observed J_{gem} value of −9.2 Hz for the C-6 methylene protons in (6) is not inconsistent with the proposed stereochemistry (6a). This J_{gem} value is more negative than for the NCH_2O protons in *trans*-fused perhydropyrido[1,2-*c*][1,3]oxazines (−8 Hz),[12] since in (6a) there will be a drift of lone pair electrons away from the nitrogen atom.

TABLE 4

^{1}H N.m.r. spectra [a] of the quinobenzoxazine isomers (6)—(9)

	δ				*J*/Hz [b]						
Isomer	6*eq*	6*ax*	7a	11b	6*ax*,6*eq*	7a,8*ax*	7a,11a	7a,8*eq*	11b,11a	11b,12*ax*	11b,12*eq*
(6)	5.42	4.40	3.70	3.24	−9.2	←	s [c]	→	2.7	9.5	5.3
(7)	5.54	4.60	3.33	3.19	−11.1	10.0	10.0	3.6	6.0	10.0	6.0
(8)	5.10	4.86	3.86	3.59	−10.7	10.0	4.6	4.6	7.0	7.0	7.0
(9)	4.76	4.52	3.28	3.21	−8.7	10.6	10.6	5.0	2.2	11.6	5.0

[a] Values obtained from 220 MHz spectra run in $CDCl_3$. [b] The vicinal coupling constants are in fact splittings extracted by first-order analysis of the spectra and are an approximation of the true vicinal coupling constants. [c] Broad singlet, $W_{\frac{1}{2}}$ 6.5 Hz.

(ii) 8,9,10,11,t-11a,c-11b,12,13-*Octahydro*-r-7aH-*quino*-[1,2-c][1,3]*benzoxazine*. The second isomer eluted from the chromatography column was assigned the *r*-7a,*t*-11a,*c*-11b-stereochemistry (7). Both this isomer and the last isomer eluted showed high field chemical shifts (δ 3.32 and 3.28, respectively) for H-7a as compared with the remaining isomers. This was indicative of a *trans*-CD ring junction in which the axial H-7a is shielded by two equatorial ring methylene groups attached to C-8 and C-11a [10] as in (7a), (7b), and (9a).

A distinction amongst these structures was permitted by the u.v. spectra (Table 3) of the two isomers. The spectrum of the second isomer indicated overlap of the nitrogen lone pair of electrons with the aromatic orbitals, consistent with structures (7a and b) but not with (9a).

Supporting evidence for the assignment of structure (7) to the second isomer was provided by the chemical shift difference ($\Delta_{ax,eq}$) between the C-6 protons. For a parallel arrangement of lone pairs as in (7a) a large $\Delta_{ax,eq}$ value would be expected; for the *cis*-structures (7b) and (9a) (parallel lone pairs but deshielding by the

[7] T. A. Crabb and E. R. Jones, *Tetrahedron*, 1970, **26**, 1217.
[8] T. A. Crabb, P. J. Chivers, E. R. Jones, and R. F. Newton, *J. Heterocyclic Chem.*, 1970, **7**, 635.
[9] H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Letters*, 1964, 2553; H. Booth and J. H. Little, *Tetrahedron*, 1967, **23**, 291; M. J. T. Robinson, *Tetrahedron Letters*, 1968, 1153.
[10] H. Booth, *Tetrahedron*, 1966, **22**, 615.
[11] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1970, **26**, 701.
[12] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 4423.

axial C-11b methylene group) a small $\Delta_{ax,eq}$ value should be observed. Table 4 reveals that the second isomer (7) showed a $\Delta_{ax,eq}$ value of 0.94 p.p.m. and the fourth eluted isomer (9) a much smaller value of 0.24 p.p.m. Thus the second isomer may be assigned the *r*-7a,*t*-11a,*c*-11b-configuration (7) with the large $\Delta_{ax,eq}$ value for the C-6 protons indicating the predominant conformer in solution to be (7a).

The observed values of 10, 6, and 6 Hz for the vicinal couplings involving H-11b, the 12-methylene group, and the angular H-11a support conformation (7a) if the couplings of 10 and 6 Hz are assigned to $J_{11b,12ax}$ and $J_{11b,12eq}$ by analogy with the corresponding values for *trans*-fused (6a) (9.5 and 5.3 Hz, respectively).

(iii) 8,9,10,11,c-11a,t-11b,12,13-*Octahydro*-r-7aH-*quino*[1,2-c][1,3]*benzoxazine*. By elimination, the third isomer eluted from the column was assigned the *r*-7a,*c*-11a,*t*-11b-configuration (8). The three possible conformers interconvertible by nitrogen inversion and ring inversion are shown in Figure 3.

A large chemical shift difference between the C-6 protons in (8c) would be expected because of the parallel lone pair geometry. This $\Delta_{ax,eq}$ value should not be as large as that for the isomer (6), since the shift to high field of the H-6*ax* signal resulting from the presence of the C-11a axial methylene group [7] would be cancelled by the deshielding effect of the axial C-11b methylene group.[10] A smaller chemical shift difference between the C-6 protons would arise in (8a), since although the parallel lone pair arrangement is present, H-6*ax* would be deshielded [10] by the C-7a methylene group. The *cis*-BC structure (8b) would exhibit a very small $\Delta_{ax,eq}$ value for the C-6 protons, since not only is the parallel arrangement of lone pairs lost but H-6*ax* would be deshielded by the C-7a methylene group. The value observed was 0.24 p.p.m. (Table 4), which was not in accord with a predominance of (8c). One large axial–axial and two small axial–equatorial vicinal couplings involving H-7a were expected for structures (8a and b), as compared with three small axial–equatorial couplings in (8c). Couplings of 10.0, 4.6, and 4.6 Hz were observed, again not in accord with conformation (8c).

The values of $J_{6ax,6eq}$ in (7) and (8) of −11.1 and −10.7 Hz, respectively, are more negative than that in (6a) (−9.6 Hz), but this may be a result of changes in nitrogen lone pair–aryl π-orbital overlap consequent upon changes in ring B conformation rather than of changes in the position of a *trans*-BC ⇌ *cis*-BC equilibrium.

The similar conformational analysis (Table 1) and u.v. spectra (Table 3) for (7) and (8) suggests a similar position of *trans*-BC ⇌ *cis*-BC equilibrium for both and hence the predominant existence of (8) in solution as (8a). The n.m.r. data are consistent with this.

(iv) 8,9,10,11,t-11a,t-11b,12,13-*Octahydro*-r-7aH-*quino*[1,2-c][1,3]*benzoxazine*. The last isomer eluted from the column was assigned the *r*-7a,*t*-11a,*t*-11b-stereochemistry (9). This isomer would be expected to exist in the most favourable all-chair conformation (9a), since the alternative conformation (9b) involves a boat ring B. The u.v. spectrum of this isomer resembles that of *NN*-dimethyl-*o*-toluidine, implying a structure in which the nitrogen lone pair is tilted into the plane of the aromatic ring, preventing transfer of electrons to the π orbitals. The only conformation under consideration able to fit this latter requirement is (9a).

The J_{gem} value of the C-6 protons for this isomer (−8.7 Hz) was the largest of all the four isomers, in agreement with conformation (9a) since this possessed parallel nitrogen lone pair–C(6)–H_{ax} geometry and a nitrogen lone pair not involved in overlap with aromatic ring orbitals.

TABLE 5

^{1}H N.m.r.[a] spectra of the cyclopentoxazinoquinolines

	δ				*J*/Hz						
Isomer	6*ax*	6*eq*	7a	10b	6*ax*,6*eq*	7a,8*eq*	7a,8*eq*	7a,10a	10b,10a	10b,11*ax*	10b,11*eq*
(16)	4.43	5.39	4.04	3.62	−10.0	←	s[b]	→	6.0	10.0	2.0
(17)	4.51	5.62	3.38	3.27	−11.1						

[a] 60 MHz Spectra run in $CDCl_3$. [b] Broad singlet, $W_{\frac{1}{2}}$ 5 Hz.

The chemical shift difference between the C-6 protons was expected to be small in (9a) owing to deshielding of H-6*ax* by the *syn*-axial C-11b methylene group, and was in fact so (0.24 p.p.m.). The high field chemical shift of H-7a (δ 3.28) was in accord with a *trans*-CD ring fusion in which this proton would be shielded by the equatorial C-8 and C-11a methylene groups.

Since delocalisation of the nitrogen lone pair over the aromatic system was prevented in this conformation, the Bohlmann region of the i.r. spectrum of this isomer would be expected to represent the true situation. Thus the weak absorption found in this region was indicative of a *cis*-BC ring fusion.

Assignment of Configurations and Preferred Conformations to the 7a,8,9,10,10a,10b,11,12-*Octahydrocyclopent*-[5,6][1,3]*oxazino*[3,4-a]*quinolines*.—Only two of the four possible stereoisomers of the cyclopentoxazinoquinoline (2) were obtained. Configurational assignments were made by comparing the spectral data with those of the corresponding benzo-compounds (1). Stereochemically related isomers would be expected to give rise to similar spectra, since the 5-membered ring D should not influence the position of conformational equilibrium drastically.

Both isomers had large chemical shift differences between the C-6 protons (Table 5) and comparison with the results for the benzo-analogues indicated that only two configurations (*r*-7a,*c*-10a,*c*-10b and the *r*-7a,*t*-10a,*c*-10b) were compatible with this observation.

The spectral data for the first isomer eluted from the column were in accord with the *trans*-BC conformation [*cf.* (6a)] of the *r*-7a,*c*-10a,*c*-10b-isomer, the other two possible conformations being neglected due to severe *syn*-axial interactions as in the benzo-compounds. The chemical shift of H-6*ax* was only 0.03 p.p.m. to lower field, and that of the H-6*eq* proton 0.03 p.p.m. to higher field than in (6). The H-7a signal appeared as a broad singlet, consistent with the expected three small axial–equatorial couplings, although the signal was 0.34 p.p.m. to lower field than in (6). The deshielding of H-7a with respect to the six-membered analogue could be partly attributed to the distortion of ring C caused by fusion to a five-membered ring. This distortion would be expected to be similar to that encountered in *cis*-perhydroindane, in which the torsional strain caused by *cis*-fusion of cyclopentane onto a six-membered ring is relieved by a slight flattening of the latter so that the adjacent axial and equatorial bonds are bent towards each other.[13] Such a distortion in (16) would be expected to result in slightly different lone pair–C–H bond orientations, which should be reflected in the value of $J_{6ax,6eq}$. In support of this the $J_{6ax,6eq}$ value for (16) was −10.0 Hz, smaller than in (6) (J_{gem} −9.2 Hz).

Derivatives.— 4,4a,5,6-Tetrahydro-3*H*-[1,3]oxazino-[3,4-*a*]quinoline (5; $R^1 = R^2 = H$) can exist in three conformations interconvertible by nitrogen inversion and ring inversion (Figure 5). The non-bonded interactions present in each conformation are summarised in Table 2.

The *trans*-BC conformation (10a) would be expected to exhibit a large chemical shift difference between the C-1 protons and a $J_{1ax,1eq}$ value of *ca.* −9.2 Hz [as observed for (6a)]. The *cis*-BC-O-inside conformation (10c) would result in a small chemical shift difference and a more negative $J_{1ax,1eq}$ value. The last conformation should also give rise to a small chemical shift difference [parallel arrangement of nitrogen lone pair and C(1)–H*ax*, but deshielding of H-1*ax* by the axial C-4a methylene group], and a $J_{1ax,1eq}$ value of *ca.* −8.7 Hz [*cf.* (9)]. The actual values (Table 5: $\Delta_{ax,eq}$ 1.05 p.p.m.; J_{gem} −10.4 Hz) were in accord with a predominance of the *trans*-BC conformation (10a).

Comparison of the n.m.r. data (Table 6) relating to the parent and the isomeric 3-methyl compounds permitted the assignment of the *cis*(3-H,4a-H)-configuration to the first 3-methyl isomer eluted from the column. This isomer would be expected to most resemble the parent since in two conformations (11a and b) the methyl group is equatorial.

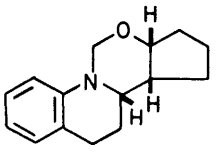
TABLE 6

220 MHz ^{1}H N.m.r.[a] spectra of 4,4a,5,6-tetrahydro-3*H*-[1,3]oxazino[3,4-*a*]quinoline and the isomeric 3-methyl derivatives

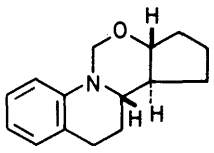
	δ							*J*/Hz								
Compound	1*ax*	1*eq*	3*ax*	3*eq*	4a	5*ax*	Me	CH, Me[b]	1*ax*, 1*eq*	3*ax*, 3*eq*	3*ax*, 4*ax*	3*ax*, 3*eq*	3*eq*, 4*ax*	4a, 4*ax*	4a, 5*ax*	4a, 5*eq*	4a, 4*eq*
(5; $R^2 = R^1 = H$)	4.45	5.50	3.77	4.08	3.48	2.12			−10.4	−12.0	12.0	2.4	5	8	8	3	6
(5; R^2 = Me, R^1 = H)	4.48	5.47		3.80	3.45	2.12	1.23	6.4	−10.7		10.0	3.0					
(5; R^2 = H, R^1 = Me)	4.80	5.07		4.13	3.61		1.39	6.8	−10.0								

[a] Spectra run in $CDCl_3$. [b] Apparent coupling constant.

The couplings measured for H-10b (10.0, 6.0, and 2.0 Hz) were in accord with the *r*-7a,*c*-10a,*c*-10b-configuration. The 10b-proton was deshielded by 0.38 p.p.m. relative to the corresponding 11b-proton in (6), presumably owing to the ring C distortion. The i.r. spectrum showed only weak absorption in the Bohlmann region, though as previously discussed for the benzo-analogues this does not necessarily indicate *cis*-BC ring fusion. The u.v. spectrum of (16) was very similar to that of (6).



(16)



(17)

The second isomer was assigned the *r*-7a,*t*-10a,*c*-10b-stereochemistry (17). The n.m.r. data were almost identical with those of (7). The distortion of ring C evident in (16) did not manifest itself in this isomer.

Conformational Analysis of 4,4a,5,6-*Tetrahydro*-3H-[1,3]*oxazino*[3,4-a]*quinoline and of the Isomeric* 3-*Methyl*

[13] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, London, 1965.

The chemical shift difference between the C-1 protons (0.99 p.p.m.), the $J_{1ax,1eq}$ value of −10.7 Hz, and the remainder of the spectral data were consistent with a predominance of the *trans*-conformation (11a).

The spectral data for *trans*(3-H,4a-H)-3-methyl-4,4a,5,6-tetrahydro-3*H*-[1,3]oxazino[3,4-*a*]quinoline suggested its existence in solution predominantly in the *trans*-BC conformation (12a) (see Figure 7). The u.v. spectrum of (5; $R^2 = H$, $R^1 = Me$) did not differ markedly from that of its epimer and the values of $J_{1ax,1eq}$ (−10.0 Hz) and $\Delta_{1ax,1eq}$ (0.27 p.p.m.) were close to those for the tetracyclic analogue (8a) (−10.7 Hz and 0.24 p.p.m., respectively).

EXPERIMENTAL

Elemental analyses were carried out by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic. I.r. spectra were recorded with a Perkin-Elmer 457 grating instrument for 0.2M-solutions in deuteriochloroform in 0.2-mm matched cells. The n.m.r. spectra were determined with Varian T60 and HR-220 spectrometers for solutions in deuteriochloroform (Me_4Si as internal reference). U.v. spectra were recorded with a Unicam SP 800A instrument for solutions in ethanol.

2-(2-*Quinolyl*)*cyclopentanone*.—Benzoyl chloride (40.48 g) was added to a stirred ice-cooled solution of quinoline *N*-oxide (34.80 g) and the morpholine enamine of cyclopentanone (75 g) in chloroform (200 ml) at such a rate that the temperature of the mixture did not rise above 0 °C. The resultant deep red solution was left overnight at room temperature, then poured into 20% hydrochloric acid (400 ml) and shaken. The aqueous acidic layer was separated, washed with ether and benzene, basified with solid potassium carbonate, and extracted several times with chloroform. The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to yield 2-(2-quinolyl)-cyclopentanone as a black crystalline solid, which could not be purified by recrystallisation. Column chromatography over grade H Laporte alumina (500 g) with 30% ether–light petroleum (b.p. 40—60 °C) as eluant, followed by recrystallisation from ether, yielded 2-(2-*quinolyl*)*cyclopentanone* as orange crystals (13.2 g, 32%), m.p. 109—110° (Found: C, 80.0; H, 6.3; N, 6.4. $C_{14}H_{13}NO$ requires C, 79.6; H, 6.2; N, 6.6%). The yield of product fell markedly when smaller quantities of reactants were used.

2-(1,2,3,4-*Tetrahydro*-2-*quinolyl*)*cyclohexanols*.—A solution of 2-(2-quinolyl)cyclohexanone [14] (10 g) in glacial acetic acid (200 ml) was hydrogenated (*ca.* 60 lb in^{-2}) over Adams platinum oxide (1 g) in a Parr hydrogenator. When the theoretical amount of hydrogen had been taken up (40 min), the catalyst was filtered off and the filtrate evaporated to small bulk *in vacuo*. The residue was basified with aqueous sodium hydroxide (30%) and extracted with chloroform several times. The combined extracts were dried (Na_2SO_4) and evaporated under vacuum to yield the isomeric 2-(1,2,3,4-tetrahydro-2-quinolyl)cyclohexanols as a viscous residue (9.3 g). The alcohols were not purified or separated but used directly in the next stage.

2-(1,2,3,4-*Tetrahydro*-2-*quinolyl*)*cyclopentanols*.—A solution of 2-(2-quinolyl)cyclopentanone (8 g) in glacial acetic acid (100 ml) was hydrogenated as described above. The isomeric 2-(1,2,3,4-tetrahydro-2-quinolyl)cyclopentanols were obtained as a viscous residue (6.2 g) and were not further purified or separated but used directly in the next stage.

8,9,10,11,11a,11b,12,13-*Octahydro*-7aH-*quino*[1,2-c][1,3]-*benzoxazines*.—The crude mixture of (2-(1,2,3,4-tetrahydro-2-quinolyl)cyclohexanols (3 g) was shaken with aqueous 40% formaldehyde (3 ml) for 0.5 h. The mixture was then heated on a water-bath for 3 h, left overnight at room temperature, basified with sodium hydroxide solution (30%), and extracted with ether several times. The combined extracts were dried (Na_2SO_4) and evaporated. The n.m.r. spectrum of the viscous residue showed the presence of several products, and so the residue was chromatographed over grade III Wöelm neutral alumina (120 g) [eluant light petroleum (b.p. 40—60 °C) with increasing amounts of ether; 120 ml fractions]. Only three of the four isomers were separated on this initial column (Table 7); rechromatography over grade I Wöelm alumina (14.4 g) was necessary to separate isomer (7) from isomer (8), and yielded 0.10 g of the latter. The separated isomers were purified by vacuum sublimation followed by recrystallisation from light petroleum (b.p. 30—40 °C). Table 8 gives the m.p.s and analytical results for the four isomers.

7a,8,9,10,10a,10b,11,12-*Octahydrocyclopent*[5,6][1,3]-*oxazino*[3,4-a]*quinolines*.—The crude mixture of isomeric 2-(1,2,3,4-tetrahydro-2-quinolyl)cyclopentanols (5 g) was shaken with aqueous 40% formaldehyde (5 ml) for 0.5 h and then set aside at room temperature overnight. After basification with sodium hydroxide solution (30%), the mixture was extracted with ether several times. The combined extracts were dried (Na_2SO_4) and evaporated to leave a viscous syrup (5 g). The n.m.r. spectrum indicated the presence of more than one product, so the residue was chromatographed over grade III Woelm neutral alumina (200 g) [elution with light petroleum (b.p. 40—60 °C); 200 ml fractions]. Only two isomers of 7a,8,9,10,10a,10b,11,12-octahydrocyclopent[5,6][1,3]oxazino[3,4-*a*]quinoline were separated, together with two isomers of the fully hydrogenated product. Recrystallisation from light petroleum (b.p. as in Table 9) yielded white crystalline solids (m.p.s and analytical results in Table 9).

TABLE 7

Results of chromatographic separation of the isomeric quinobenzoxazines over grade III Woelm neutral alumina

Eluant	No. of fractions (120 ml)	Isomers	Weight (g)
Light petroleum (b.p. 40—60 °C)	12	(6)	0.56
Light petroleum (b.p. 40—60 °C) + 0.5% ether	7	(7) + (8)	0.36
Light petroleum (b.p. 40—60 °C) +1% ether	5	(8)	0.14
Light petroleum (b.p. 40—60 °C) +2% ether	7	(9)	0.21
Light petroleum (b.p. 40—60 °C) +4% ether	12	(9)	0.01

TABLE 8

M.p.s and analysis [a] of the quinobenzoxazine isomers

Isomer	M.p. (°C)	% C	% H	% N
(6)	78.5—79.5	79.0	8.6	5.5
(7)	67—68	78.9	8.9	5.9
(8)	56—60	79.1	8.7	5.6
(9)	96—97	79.0	8.4	5.7

[a] $C_{16}H_{21}NO$ requires C, 79.0, H, 8.7, N, 5.8%.

TABLE 9

Experimental results relating to the isomeric cyclopentoxazinoquinolines

Isomer	Weight (g)	Recryst. solvent	M.p. (°C)	%C [a]	%H [a]	%N [a]
(16)	0.84	Light petroleum (b.p. 40—60 °C)	71—72	78.7	8.6	5.9
(17)	0.30	Light petroleum (b.p. 30—40 °C)	62—63	78.7	8.4	6.1

[a] $C_{15}H_{19}NO$ requires C, 78.6; H, 8.4; N, 6.1%.

2-(1,2,3,4-*Tetrahydro*-2-*quinolyl*)*ethanol*.— 2-(2-Quinolyl)-ethanol (8.7 g) in glacial acetic acid (100 ml) was hydrogenated at *ca.* 60 lb in^{-2} over Adams platinum oxide (1 g) until the theoretical amount of hydrogen had been absorbed. The catalyst was filtered off, the acetic acid removed *in vacuo*, and the residue basified with sodium carbonate solution. The mixture was then extracted with ether, and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was distilled under vacuum to yield 2-(1,2,3,4-*tetrahydro*-2-*quinolyl*)*ethanol* as a pale yellow viscous liquid (4.7 g, 53%), b.p. 140—143° at 0.3 mmHg (Found: C, 74.0; H, 8.3; N, 7.6. $C_{11}H_{15}NO$ requires C, 74.5; H, 8.5; N, 7.9%).

[14] M. Hamana and H. Noda, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 918.

4,4a,5,6-*Tetrahydro*-3H-[1,3]*oxazino*[3,4-a]*quinoline*.— 2-(1,2,3,4-Tetrahydro-2-quinolyl)ethanol (3 g) and aqueous 40% formaldehyde (3 ml) were shaken together for 0.5 h and kept at room temperature for a further 0.5 h. The mixture was basified with sodium hydroxide solution (30%) and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated to yield a viscous liquid, which was distilled under high vacuum to give 4,4a,5,6-*tetrahydro*-3H-[1,3]*oxazino*[3,4-a]*quinoline* as an oil (2.6 g, 87%), b.p. 108—110° at 0.175 mmHg (Found: C, 75.9; H, 8.2; N, 7.3. $C_{12}H_{15}NO$ requires C, 76.2; H, 8.0; N, 7.4%).

1-(1,2,3,4-*Tetrahydro*-2-*quinolyl*)*propan*-2-*ol*.—A solution of methyl 2-quinolylmethyl ketone [15] (10 g) in glacial acetic acid (100 ml) was partially hydrogenated (*ca.* 60 lb in^{-2}) over Adams platinum oxide (0.5 g). When the theoretical amount of hydrogen had been absorbed (*ca.* 2 h), the catalyst was filtered off and the acetic acid removed *in vacuo*. The residue was basified with sodium hydroxide solution (30%) and then extracted with chloroform. The combined extracts were dried (Na_2SO_4) and concentrated to yield 1-(1,2,3,4-tetrahydro-2-quinolyl)propan-2-ol as a viscous liquid (9 g), which was not further purified.

3-*Methyl*-4,4a,5,6-*tetrahydro*-3H-[1,3]*oxazino*[3,4-a]*quinolines*.—1-(1,2,3,4-Tetrahydro-2-quinolyl)propan-2-ol (2 g) was shaken with aqueous 40% formaldehyde (2 ml) for 0.5 h, then heated on a water-bath for 4 h. The mixture was basified with sodium hydroxide solution (30%) and extracted with chloroform. The combined extracts were dried (Na_2SO_4) and concentrated leaving a viscous residue (2 g). The n.m.r. spectrum showed the presence of two products; column chromatography over grade III Wöelm neutral alumina (80 g) (light petroleum as eluant; 80 ml fractions) separated the isomers, which were purified by distillation under high vacuum. Table 10 gives the results of this separation and purification procedure.

TABLE 10

Experimental results pertaining to the isomeric 3-methyl-4,4a,5,6-tetrahydro-3*H*-[1,3]oxazino[3,4-*a*]quinolines

Fraction no.	Weight (g)	Product	B.p. (°C)	%C[a]	%H[a]	%N[a]
4—12	0.6	(5; R^1 = H, R^2 = Me)	82—86 at 0.03 mmHg	77.2	8.9	7.0
15—32	0.2	5; R^1 = Me, R^2 = H)	86—88 at 0.035 mmHg	77.0	8.7	6.7

[a] $C_{13}H_{17}NO$ requires C, 76.8, H, 8.4, N, 6.9%.

[6/2254 *Received*, 10*th December*, 1977]

[15] N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Amer. Chem. Soc.*, 1951, **73**, 4301; N. N. Goldberg and R. Levine, *ibid.*, 1952, **74**, 5217.