Proton Magnetic Resonance Studies of Compounds with Bridgehead Nitrogen. Part 33.[1,2] Effect of a Fused Aromatic Ring on the Conformational Preferences of Perhydropyrido[1,2-*c*][1,3]oxazines [2] and Related Compounds

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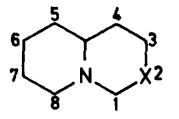
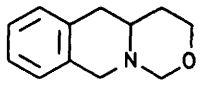
In contrast to 4,4a,5,10-tetrahydro-1*H*,3*H*-[1,3]oxazino[3,4-*b*]isoquinoline which adopts the *trans*-fused ring conformation in solution, 1,6,7,11b-tetrahydro-2*H*,4*H*-[1,3]oxazino[4,3-*a*]isoquinoline predominantly adopts the *cis*-B/C-*O*-inside conformation. The analogous *cis*-fused conformation for 1,6,7,11b-tetrahydro-2*H*,4*H*-[1,3]-thiazino[4,3-*a*]isoquinoline is also preferred. 3-Methyl-1,2,3,4,7,11b-hexahydro-6*H*-pyrimido[6,1-*a*]isoquinoline exists in solution as a conformational equilibrium containing less (*ca.* 54%) of the equatorial *N*Me-*trans*-fused ring conformation than does 2-methylperhydropyrido[1,2-*c*]pyrimidine (*ca.* 75%). These results have been discussed largely in terms of ring fusion strain.

PERHYDROPYRIDO[1,2-*c*][1,3]OXAZINE (1; X = O) [3] and the corresponding thiazine (1; X = S) [4] and pyrimidine (1; X = NMe) [5] exist in solution at ambient temperatures predominantly [6] in the *trans*-fused ring conformation. Alteration in the conformation of the piperidine ring might well affect the conformational balance and to explore this possibility the benzo-derivatives (2) and (3) were chosen for study. Interest in the related system (4; X = O or NR) has been shown [7] and a preliminary discussion on the position of equilibrium in (4; X = O or NMe) has been given.[8]

Synthesis of Compounds.—1,6,7,11b-Tetrahydro-



(1)



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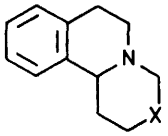

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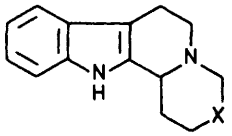
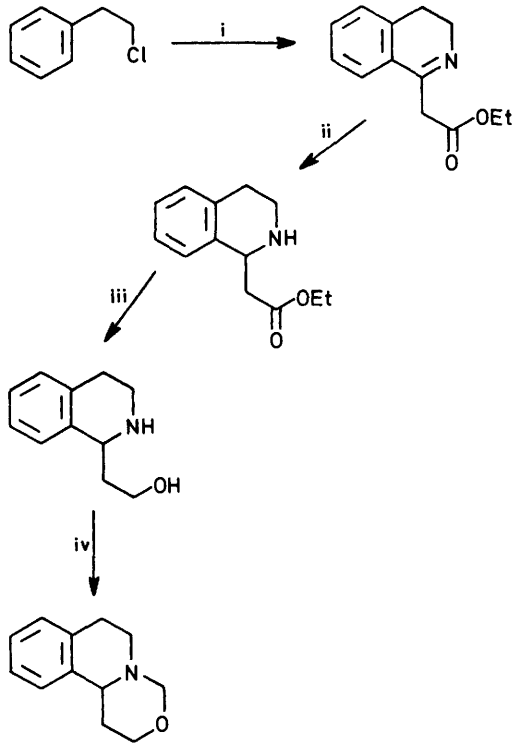


(4)

2*H*,4*H*-[1,3]oxazino[4,3-*a*]isoquinoline and the related 1,2,3,4,4a,9,13b,13c-octahydro-6*H*,8*H*-benzo[5,6][1,3]-oxazino[4,3-*a*]isoquinoline (5) were synthesised as shown in Schemes 1 and 2 respectively. Only one isomer of (5) was obtained.

1,6,7,11b-Tetrahydro-2*H*,4*H*-[1,3]thiazino[4,3-*a*]isoquinoline (3; X = S) was synthesised by ring closure of 1-(β-mercaptoethyl)-1,2,3,4-tetrahydroisoquinoline with formaldehyde. 3-Methyl-1,2,3,4,7,11b-hexahydro-6*H*-pyrimido[6,1-*a*]isoquinoline (3; X = NMe) and 4,4a,5,10-tetrahydro-1*H*,3*H*-[1,3]oxazino[3,4-*b*]isoquinoline (2) were prepared as shown in Schemes 3 and 4 respectively.



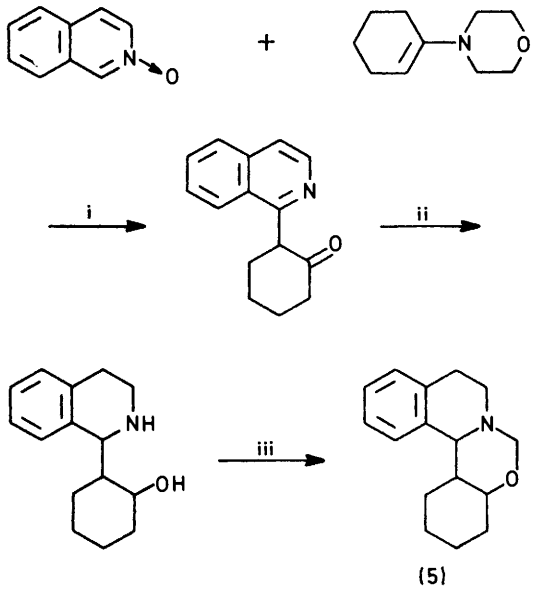
(3; X = O)

SCHEME 1 Reagents: i, $EtOOCCH_2CN$-$SnCl_4$; ii, H_2-PtO_2; iii, $LiAlH_4$; iv, 40% aqueous CH_2O

Assignment of Stereochemistry.—(a) 1,6,7,11b-*Tetrahydro*-2H,4H-[1,3]*oxazino*[4,3-a]*isoquinoline and*

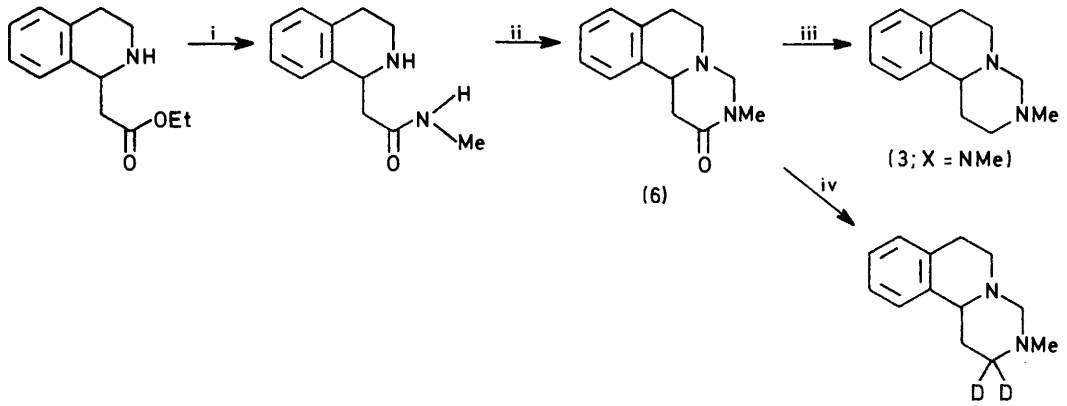
[1] Part 32, T. A. Crabb and J. S. Mitchell, *Org. Magnetic Resonance*, 1976, **8**, 258.
[2] Preliminary communication T. A. Crabb and R. F. Newton, *Tetrahedron Letters*, 1971, 3361.
[3] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 4423.
[4] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1970, **26**, 3941.
[5] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1970, **26**, 701.
[6] I. D. Blackburne, A. R. Katritzky, D. M. Read, P. J. Chivers, and T. A. Crabb, *J.C.S. Perkin II*, 1976, 418.
[7] G. deStevens, H. Lukaszewski, M. Sklar, A. Halamandaris, and H. M. Blatter, *J. Amer. Chem. Soc.*, 1962, **27**, 2457.
[8] T. A. Crabb and J. Mitchell, *J. Heterocyclic Chem.*, 1971, **8**, 721.

1,2,3,4,4a,9,13b,13c-*octahydro*-6H,8H-*benzo*[5,6][1,3]-*oxazino*[4,3-a]*isoquinoline*. 1,6,7,11b-Tetrahydro-2*H*,4*H*-[1,3]oxazino[4,3-*a*]isoquinoline (3; X = O) can exist in three possible conformations (7)—(9) (Figure 1)



SCHEME 2 Reagents: i, C_6H_5COCl at 0 °C; ii, H_2–PtO_2; iii, 40% aqueous CH_2O

which are interconvertable by nitrogen and ring inversion. The predominant conformation adopted by (3; X = O) in solution at room temperature can be identified from an analysis of the n.m.r. data (Table). Thus (9), in which the nitrogen lone pair bisects the C(4) methylene H–H internuclear axis, will exhibit a more negative J_{gem} than will the alternative *cis*- (8) or *trans*-conformation (7) in which the nitrogen lone pair and one oxygen lone pair are parallel to the C(4)–H_{ax} bond. Theoretical reasons have been given [9,10] for a dependency of J_{gem} in methylene groups on the orientation of adjacent hetero-atom lone pairs of electrons. J_{gem} Also varies with ring strain and hybridisation of the carbon atom of the methylene group and the inductive effect of α- and β-substituents.[11] An approach to a linear relationship between J_{gem} and the percentage of axial lone pair in a series of compounds will not then be expected unless the changes in ring strain and substituent effect on J_{gem} are minimised. Indeed, in a series of hexahydropyrimidines, hexahydro-1,3,5-triazines, and tetrahydro-1,3-oxazines no clear relationship was found [12] to exist between J_{gem} and lone pair orientation based on dipole moment measurements. In these series the *N*-alkyl substituent varied from methyl to t-butyl so that the changes in substituent and the related changes in ring strain (models indicate reduced monocyclic heterocyclic systems to be more readily deformable than bicyclic and tricyclic analogues) probably play an important role in determining the magnitude of J_{gem}. For the compounds discussed in this paper lone pair orientation effects on J_{gem} are considered to be dominant [13] so that the estimates of the position of conformational equilibria based on this parameter are justifiable. In addition the conformational assignments are based not only on J_{gem} values but also on the appearance of Bohlmann bands in the i.r. spectra,[14,15] vicinal coupling constant data,



SCHEME 3 Reagents: i, CH_3NH_2; ii, 40% aqueous CH_2O; iii, $LiAlH_4$; iv, $LiAlD_4$

and the difference in chemical shift ($\Delta_{ax,eq}$) between the C(4) methylene protons.[15] In the case of this latter parameter $\Delta_{ax,eq}$ for the C(4) methylene protons will be much smaller for (9) than for (7) and (8) since (9) does not possess the necessary *trans*-diaxial relationship between the nitrogen lone pair and C(4)–H_{ax} [16] together

[9] J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.*, 1965, **42**, 1339.
[10] G. E. Maciel, J. W. McIver, jun., N. S. Ostlund, and J. A. Pople, *J. Amer. Chem. Soc.*, 1970, **92**, 4151.
[11] R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron*, 1966, Supplement 7, 355.
[12] P. J. Halls, R. A. Y. Jones, A. R. Katritzky, M. Snarey, and D. L. Trepanier, *J. Chem. Soc.* (*B*), 1971, 1320.
[13] P. J. Chivers and T. A. Crabb, *Tetrahedron*, 1970, **26**, 3389.
[14] F. Bohlmann, *Chem. Ber.*, 1958, **91**, 2157.
[15] T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, 1971, **71**, 109.
[16] H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Letters*, 1964, 2553; J. B. Lambert, R. S. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, 1967, **89**, 3761.

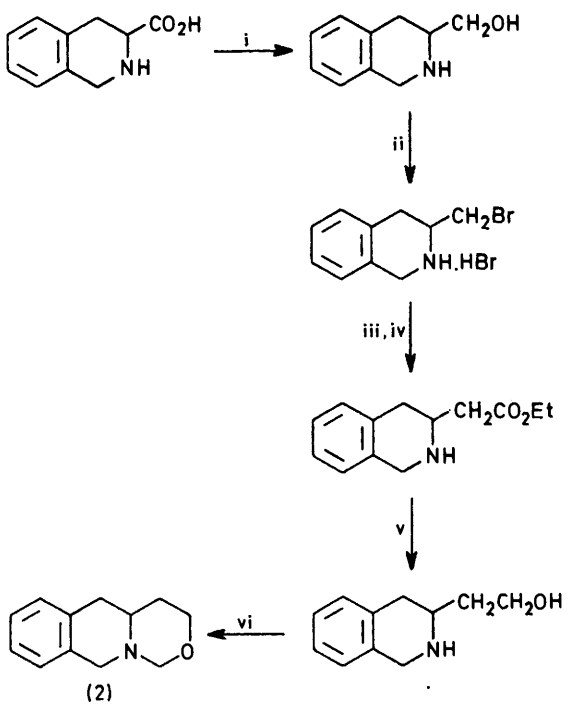
with the C(6) equatorial *N*-methylene group,[17] both necessary for high field absorption by this proton. $\Delta_{ax,eq}$ Values can provide a qualitative indication of the orientation of lone pairs in monocyclic 1,3-heterosystems.[12]

The n.m.r. spectrum of (3; X = O) showed an AB quartet for the C(4) methylene protons with a J_{gem} (assumed negative) of −10.2 Hz (Table) and δ 4.32 and 4.51 ($\Delta_{ax,eq}$ 0.19 p.p.m.). These values are consistent with the predominant existence of (3; X = O) in the *cis*-fused conformation (9) and are similar to those observed[18] for the C(2) methylene protons in (10) (J_{gem} −10.5 Hz, δ 4.55 and 4.66, $\Delta_{ax,eq}$ 0.11 p.p.m.) in which the nitrogen lone pair also bisects the C(2) methylene. The observed n.m.r. parameters are distinctly different from those in a *trans*-fused compound such as (11)[3,6] (J_{gem} −8.0 Hz, δ 3.65 and 4.35, $\Delta_{ax,eq}$ 0.70 p.p.m.) which possesses the parallel lone pair–CH geometry as in (7). The chemical shift (δ 3.91) of the C(11b) proton, which is to low field of δ 3.8, is also characteristic[19] of the *cis*-B/C ring fusion (9) as are the vicinal coupling constants between the C(11b) proton

N.m.r. spectra

Compound	Solvent	Chemical shift (δ) 4ax	4eq	2ax	2eq	1ax	1eq	11b	6ax	J/Hz $J_{4ax,4eq}$	$J_{3ax,3eq}$	$J_{1ax,1eq}$	$J_{1ax,2ax}$	$J_{1eq,2ax}$	$J_{1ax,2eq}$	$J_{1eq,2eq}$	$J_{11b,1eq}$	$J_{11b,1ax}$	
(3; X = O) [a]	C_6D_6	4.32	4.52	3.45	3.79	1.94	1.16	3.91		−10.2	−11.2	−13.5	12.0	2.6	4.9	*ca.* 1.5	3.8	11.8	
(3; X = S) [a]	$CDCl_3$	4.68	4.04	2.08				3.9	3.52	$J_{4ax,4eq}$ −12.9	$J_{3ax,3eq}$ −14.1	$J_{5ax,5eq}$ −10.5	$J_{1ax,1ax}$ 11.8	$J_{1eq,1ax}$ 3.6	$J_{5ax,7ax}$ 10.5	$J_{5ax,7eq}$ 5.6	$J_{11b,1eq}$ 3.1	$J_{11b,1ax}$ *ca.* 10	$J_{4eq,5eq}$ 2.7
(3; X = NMe) [a]	$CDCl_3$	3.08	3.65					3.48		−9.8									1.8
(6) [b]	$CDCl_3$	4.10	4.20					3.90		−9.8							5.5	11.8	
		1ax	1eq	3ax	3eq	4ax	4eq	10ax	10eq	4a	$J_{1ax,1eq}$	$J_{3ax,3eq}$	$J_{4ax,4eq}$	$10_{ax,10eq}$	$J_{3ax,4ax}$	$J_{4eq,4ax}$	$J_{4ax,5ax}$	$J_{4eq,5ax}$	$J_{4eq,5eq}$	$J_{4a,5eq}$	$J_{4a,5ax}$	$J_{4a,5eq}$
(2) [c]	C_6D_6	3.58	4.48	3.28	3.88	1.62	1.02	3.03	3.66	2.21	−8.2	−11.4	−13.0	−14.0	12.1	2.7	5.0	*ca.* 1.5	3.4	10.2	6.6	6.6
		6ax	6eq	4a	8ax	8eq	9ax	9eq	13b		$J_{8ax,8eq}$	$J_{8ax,9ax}$	$J_{8ax,9eq}$	$J_{8ax,13b}$	$J_{8ax,9ax}$	$J_{9eq,9eq}$						
(13) [a]	$CDCl_3$	3.99	4.59	3.82	2.36	2.91	3.08	2.67	3.52		−8.0	−11.0	−15.5	11.0	4.0	*ca.* 3						

[a] 220 MHz Spectrum. [b] 60 MHz Spectrum. [c] 100 MHz Spectrum.



SCHEME 4 Reagents: i, $LiAlH_4$; ii, HBr–PBr_3; iii, KCN; iv, HCl–C_2H_5OH; v, $LiAlH_4$; vi, 36% aqueous CH_2O

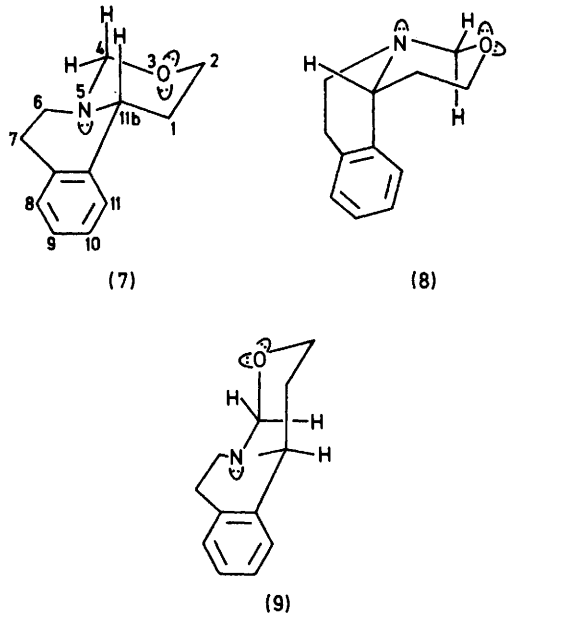


FIGURE 1 Possible conformations of 1,6,7,11b-tetrahydro-2*H*,4*H*-[1,3]oxazino[4,3-*a*]isoquinoline (3; X = O)

[17] H. Booth and J. H. Little, *Tetrahedron*, 1967, **23**, 291; M. J. T. Robinson, *Tetrahedron Letters*, 1968, 1153.

[18] J. M. Lehn and F. Riddell, *J. Chem. Soc.* (*B*), 1968, 1224.

[19] M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.*, 1964, **86**, 3364; H. Bruderer, M. Baumann, M. Uskokovic, and A. Brossi, *Helv. Chim. Acta*, 1964, **47**, 1852.

and C(1) methylene protons: $J_{11b,1ax}$ 11.0, $J_{11b,1eq}$ 4.0 Hz.

An examination of the i.r. spectrum of (3; X = O) in the 2 800—2 600 cm^{-1} region [14] showed a set of weak bands compatible with the presence of a small amount of the *trans*-fused conformer (7). Thus the combined n.m.r. and i.r. spectral evidence demonstrates that (3; X = O) in solution exists as a mixture containing a

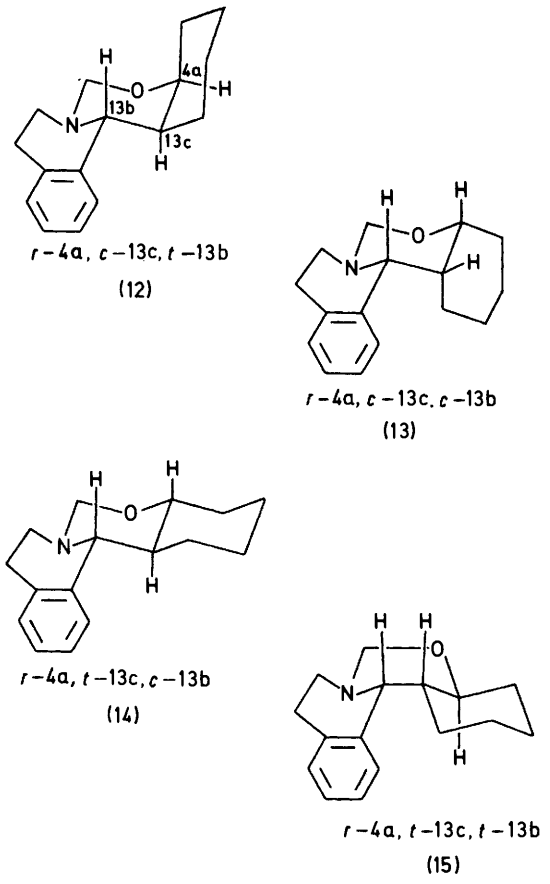


FIGURE 2 Possible *trans*-B/C conformations of 1,2,3,4,4a,9,13b, 13c-octahydro-6*H*,8*H*-benzo[5,6][1,3]oxazino[4,3-*a*]isoquinoline (5)

predominance of the *cis*-fused conformer (9) in equilibrium with a small amount of the *trans*-fused conformer (7).

Only one of the possible four diastereoisomers of 1,2,3,4,4a,9,13b,13c-octahydro-6*H*,8*H*-benzo[5,6][1,3]-oxazino[4,3-*a*]isoquinoline was obtained from the synthesis shown in Scheme 2 and this was readily assigned a predominantly *trans*-fused B/C conformation on the basis of strong Bohlmann bands [14] in the i.r. spectrum, the J_{gem} of −8.0 Hz for the N-CH_2O proton,[3] and the chemical shift of the angular C(13b) proton (δ 3.52, Table) which is to high field of δ 3.8.[19] The *trans*-fused B/C conformations of the four possible isomers are shown in Figure 2.

Since these differ about the C/D ring junction, the splitting patterns of the C(4a), C(13b), and C(13c) protons should provide the means with which to distinguish between them. Unfortunately the signals for the C(13c) proton are not visible in the n.m.r. spectrum of (5). However, those signals corresponding to the C(4a) and C(13b) protons are clearly visible at δ 3.82 and 3.52 respectively. Both protons absorb as broad singlets which implies only small vicinal couplings (*ca.* 2—4 Hz) indicating $J_{ax,eq}$ or $J_{eq,eq}$ couplings (dihedral angle *ca.* 60°). Of the structures shown in Figure 2, only (13) has all dihedral angles between C(13b)–H and C(13c)–H and between C(4a)–H and C(4)–H_{eq} and C(4)–H_{ax} of 60°. For (13) a large chemical shift difference between the C(6) protons is expected due to the extra shielding experienced by the C(6ax) proton from both the *trans* and axial nitrogen lone pair,[16] and the equatorial C(8) methylene group.[17] The actual chemical shift difference between the C(6) protons is 0.60 p.p.m. which is a reasonable value for this geometry [*cf.* (11), $\Delta_{ax,eq}$ 0.7 p.p.m. as opposed to the *cis*-compound (10), $\Delta_{ax,eq}$ 0.11 p.p.m.].

Thus (5) possesses the *r*-4a, *c*-13c, *c*-13b configuration (13) and in solution at ambient temperatures exists predominantly in the *trans*-B/C conformation.

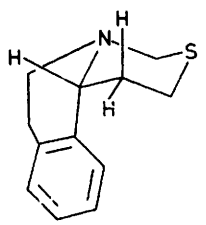
(b) 1,6,7,11b-*Tetrahydro*-2H,4H-[1,3]*thiazino*[4,3-a]*isoquinoline*. Differences in the stereochemistry of thiazino-compounds relative to that of the related oxazino-compounds would be expected to arise chiefly because of the long C–S bond (1.82 Å) compared with the C–O bond (1.43 Å).

In compound (3; X = S) the C(4) methylene protons gave rise to an AB quartet (n.m.r. data in Table). The high field half of the quartet was further split into two doublets (*J* 2.7 Hz) due to long range coupling. Since four bond coupling is usually observed when the protons involved are linked by a planar W pathway,[20] the high field signal was assigned to the C(4eq) proton and the observed coupling to $J_{2eq,4eq}$. The higher field absorption of the C(4eq) proton is in contrast to the oxazino-compound (3; X = O) and to most cyclohexane derivatives in which the C(4eq) proton signal is at lower field than the C(4ax) proton. This is in agreement with previous chemical shift data on methylene protons adjacent to sulphur in a six-membered ring and has been interpreted [21] in terms of the differences between C–S and C–C bond anisotropies. The C(11b) proton signal appeared as two doublets, one of which was hidden under the C(4eq) proton signals. Thus the chemical shift of the C(11b) proton could not be accurately determined, but since it was to lower field of δ 3.9 the *cis*-fused ring stereochemistry was indicated.[19] The virtual absence of any absorbance in the 2 800—2 600 cm^{-1} region of the i.r. spectrum provided further evidence for a *cis*-B/C ring junction.[14]

As with the oxazino-compounds, two *cis*-conformations are possible as depicted in (16) and (17). These conformations can be distinguished by consideration of

[20] M. Barfield and B. Chakrabarti, *Chem. Rev.*, 1969, **69**, 757.
[21] E. Campaigne, N. F. Chamberlain, and B. E. Edwards, *J. Org. Chem.*, 1962, **27**, 135.

the splitting pattern of the C(11b) proton. For structure (16) two small couplings ($J_{11beq,1ax} = J_{11beq,1eq}$) would be expected, while for (17) one large ($J_{11bax,1ax}$) and one



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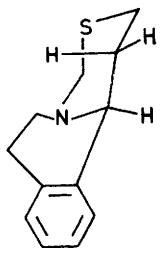
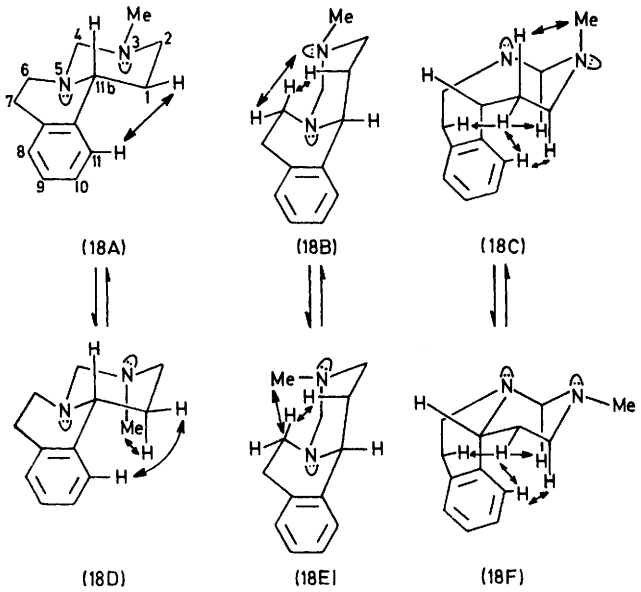


(17)

small ($J_{11bax,1eq}$) coupling should result. Only one splitting is accurately measurable ($J_{11b,1eq}$ 3.1 Hz), since one-half of the 11b-proton signal is obscured by the 4eq-H signal, but the distance from the mid-point of the visible doublet to the mid-point of the overlapping 4eq- and 11b-H signals is *ca.* 10 Hz which is of the order of a



(18A) (18B) (18C)

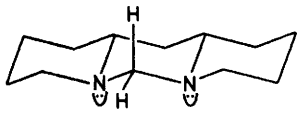
(18D) (18E) (18F)

FIGURE 3 Possible conformations of 3-methyl-1,2,3,4,7,11b-hexahydro-6*H*-pyrimido[6,1-*a*]isoquinoline (3; X = NMe)

$J_{ax,ax}$ vicinal coupling. Thus it would appear that the thiazino-compound predominantly adopts conformation (17) in solution at ambient temperatures. This conformation is favoured by the generalised anomeric effect.

(c) 3-*Methyl*-1,2,3,4,7,11b-*hexahydro*-6H-*pyrimido*[6,1-a]*isoquinoline*. Six conformations (Figure 3) of the parent compound (3; X = NMe) require consideration. Dreiding models of these showed a severe interaction in (18E) between C(6) methylene and axial 3-*N*-methyl and an interaction between the C(1) methylene group and 6_{ax}-H. In addition (18C and F) suffer from a number of non-bonded interactions indicated on the structures. Accordingly structures (18E, C, and F) were disregarded.

In the n.m.r. spectrum of (3; X = NMe) the C(4) protons gave rise to a quartet, the low field half of which was further split into two doublets by long range coupling (J 1.8 Hz). It is therefore reasonable [20] to assign the low field part of the quartet to 4eq-H and the coupling to $J_{4eq,2eq}$. The J_{gem} of the C(4) protons (−9.8 Hz) is intermediate between that in (19) [13] (−8.5 Hz) in which both lone pairs are axial and that in (20) [13] (−11.3 Hz) in which one of the lone pairs bisects the N–CH_2–N methylene group. This shows an equilibrium between *ca.* 54% of a conformation in which both nitrogen lone pairs are axial [(18A)] and 46% of conformations in which one of the nitrogen lone pairs



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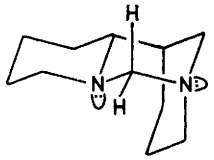


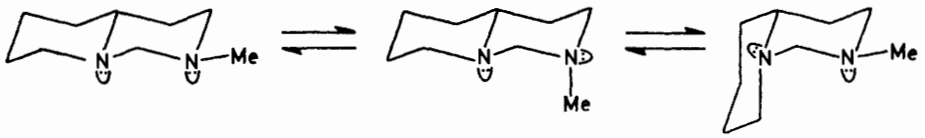
(20)

bisects the CH_2 [(18B and D)]. Dipole moment studies [6] have shown 3-methylperhydropyrido[1 2-*c*]pyrimidine to exist as an equilibrium mixture of 75% (21A), 20% (21B), and 5% (21C). Attempts to 'freeze' out the individual conformations of (3; X = NMe) by running the n.m.r. spectrum at low temperature were unsuccessful. The application of the Bohlmann criterion to this system is complicated both by the presence of two nitrogen atoms and by the hydrogen atoms of the methyl group which contribute to Bohlmann bands when the methyl group is equatorially orientated.

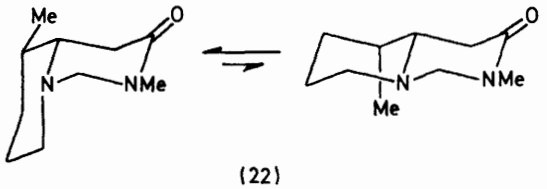
The $J_{4ax,4eq}$ for the 2-oxo-derivative (6) is −9.8 Hz (Table), intermediate between the values observed [22] for the predominantly *cis*-fused (22) (−11.7 Hz) and the *trans*-fused (23) (−8.7 Hz) indicating that the position of equilibrium in this amide is not too far different from that in (3; X = NMe). Examination of the i.r. spectrum of (6) shows medium intensity Bohlmann bands which must arise from the bridgehead nitrogen atom in the *trans*-fused ring conformation since C–H bonds adjacent to N–C=O groups do not give rise to such i.r. absorption.[14]

(d) 4,4a,5,10-*Tetrahydro*-1H,3H-[1,3]*oxazino*[3,4-b]*isoquinoline*. 4,4a,5,10-Tetrahydro-1*H*,3*H*-[1,3]oxazino-[3,4-*b*]isoquinoline (2) may exist as an equilibrium mixture of (24)—(26). The presence of strong Bohlmann bands [14] in the 2 800—2 600 cm^{-1} region of the i.r. spectrum of (2) indicated a predominance of the *trans*-B/C conformer (24) and the n.m.r. spectrum (Table) was consistent with this. The value of $J_{1ax,1eq}$ was large (−8.2 Hz) suggesting a parallel lone pairs–C(1)–H_{ax} geometry as in conformers (24) and (26) [*cf.* (11), J_{gem} −8.0 Hz]. The large chemical shift difference of 0.90 p.p.m. between the C(1) protons ruled out conformation (25) in which the nitrogen lone pair bisects the C(1) methylene group [*cf.* (10), Δ_{ae} 0.11 p.p.m.]. In addition

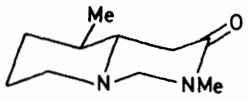
[22] T. A. Crabb and R. F. Newton, *J.C.S. Perkin II*, 1972, 1920.



(21A) (21B) (21C)

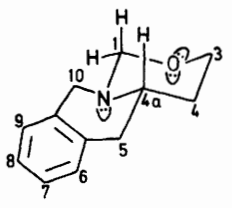


(22)

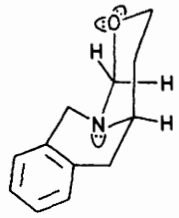


(23)

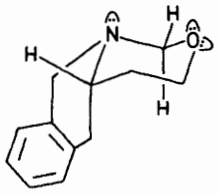
conformation (26) can be ruled out since although the parallel lone pairs–C(1)–H_{ax} geometry is present the $C(1_{ax})$ proton is deshielded by the *syn*-axial C(5) methylene group [*cf.* (27) for which $\Delta_{1ax,1eq} = 0.00$ p.p.m.].[3] The splitting pattern of the C(4a) proton is also in agreement with the predominant existence of (2) in the *trans*-B/C conformation (24).



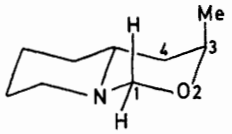
(24)



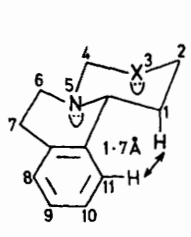
(25)



(26)



(27)



(28)

(29)

DISCUSSION

All the bicyclic systems (1; X = O, S, or NMe) [3-6] exist predominantly in *trans*-fused conformations whereas in the tricyclic derivatives (3; X = O, S, or NMe), fusion of the benzo-ring at the 5,6-positions of the perhydropyridine ring in (1) moves the position of conformational equilibria towards the *cis*-fused ring conformations. In contrast, fusion of the benzo-ring onto the 6,7-position of the perhydropyridine nucleus in (1) to give (2) largely unaffects the position of conformational equilibria, both (2) and (1; X = O) preferring their respective *trans*-fused conformations.

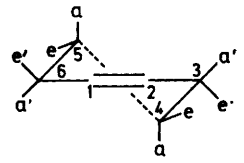
Consideration of the *trans*- and *cis*-fused conformations (28) and (29) of (3) suggest the following factors to be influential in determining the position of conformational equilibria: (*a*) the generalised anomeric effect,[23] (*b*) close approach (*ca.* 1.7 Å) of the C(1ax) and C(11) hydrogen atoms, (*c*) ring fusion strain in the *trans*-B/C ring fused conformation (28).

The conformation of the B ring of (28) may be compared with cyclohexene. In cyclohexene (30) true axial and equatorial bonds are found only at C(4) and C(5), those at C(3) and C(6) being differently disposed (pseudo-axial, a′ and pseudoequatorial, e′) by their proximity to the double bond. Some evidence exists [24] to suggest that the e′,a (or a′,e) bonds can approach each other more readily than ordinary e,a bonds, while the e′,e

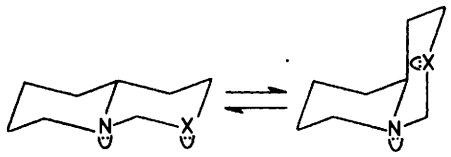
[23] S. Wolf, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc.* (*B*), 1971, 136.

[24] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, Conformational Analysis,' Interscience, London, 1965, p. 111.

bonds cannot approach each other as readily as in cyclohexane. In the *trans*-conformation (28) of the isoquinoline systems (3) studied the C ring is fused onto the



(30)



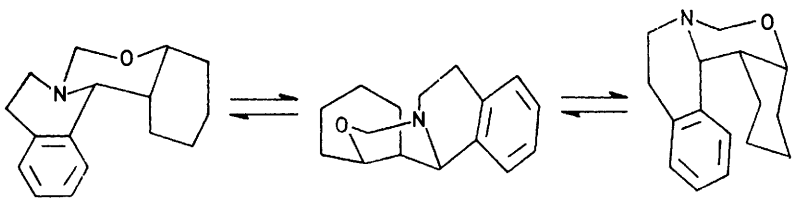
(31) (32)

B ring by utilisation of the e',e bonds of the B ring and this increases the strain in the fused system. However in the *cis*-conformation (29) fusion of the C ring can readily occur without extra strain since fusion involves the e',a (or a',e) bonds.

The unfavourable C(1)–H_{ax}–C(11)–H interaction present in (28) cannot be responsible for the shift towards (29) since this is relieved in (29) only at the expense of introducing a *gauche* butane interaction [C(6)–H_{ax} and C(1)–H_{ax} *ca.* 1.7 Å apart] and a *syn*-axial interaction between C(6)–H_{ax} and 3-X (X = O, S, or NMe). The generalised anomeric effect also cannot be responsible since its magnitude for the (28) ⇌ (29) equilibrium should not be greatly different from that in the (31) ⇌ (32) equilibrium. Thus the *trans*-ring fusion strain must be the predominant influence on the shift in conformational equilibrium.

The conformational analysis of *r*-4a,*c*-13c,*c*-13b-1,2,3,4,4a,9,13b,13c-octahydro-6*H*,8*H*-benzo[5,6][1,3]-oxazino[4,3-*a*]isoquinoline (5) shown to exist in the *trans*-fused conformation (13) is slightly different. The conformational equilibrium for (5) is between the *trans*-fused (13) and the two *cis*-fused conformers (33) and (34) and although (13) is disfavoured by *trans*-ring fusion strain, the generalised anomeric effect and the close approach (*ca.* 1.6 Å) of C(13)–H and C(13c)–H, (33) and (34) are disfavoured by much more serious non-bonded interactions.

In the case of the *trans*-fused ring conformer of 4,4a,5,10-tetrahydro-1*H*,3*H*-[1,3]oxazino[3,4-*b*]isoquinoline *trans*-fusion between the C ring involves the true e,e bonds of the B ring and there should accordingly be no *trans*-fusion strain. This is reflected in the position of conformational equilibrium for (2) which like (1; X = O) lies predominantly on the side of the *trans*-fused ring conformation.



(13) (33) (34)

EXPERIMENTAL

Elemental analyses were carried out by the Analytical Section, Department of Chemistry, Portsmouth Polytechnic. I.r. spectra were recorded on a Perkin-Elmer 457 grating instrument as 0.2M solutions in deuteriated chloroform using 0.2 mm matched cells. The n.m.r. spectra were determined on Varian T60, HA 100, and HR 220 spectrometers as 10% solutions in deuteriated chloroform with tetramethylsilane as internal reference, unless otherwise stated. M.p.s are uncorrected.

Ethyl (3,4-*Dihydro*-1-*isoquinolyl*)*acetate*.—Following the procedure of Agbalyan *et al.*,[25] β-chloroethylbenzene (80.0 g) was added to the white crystalline complex, formed by the addition of stannic chloride (130.25 g) to ethyl cyanoacetate (56.5 g), and the mixture heated for 2.5 h at 110—115°. While still hot the dark yellow viscous mass formed was poured in small portions into 20% sodium hydroxide solution (1 l) and left to stand overnight. The resultant mixture was repeatedly extracted with ether, and the combined ether extracts then extracted with dilute hydrochloric acid (*ca.* 2N) to remove the required base. The hydrochloric acid extracts were washed with ether then basified by addition of 30% sodium hydroxide solution. The base separated out as a yellow oil and was repeatedly extracted with ether. The combined ether extracts were dried ($MgSO_4$) and evaporated leaving an oil which was distilled under vacuum to yield ethyl (3,4-dihydro-1-isoquinolyl)acetate as a viscous yellow oil (39 g, 36%), b.p. 138—140° at 0.13 mmHg (lit.,[25] 156—158° at 1 mmHg, 32%).

Ethyl (1,2,3,4-*Tetrahydro*-1-*isoquinolyl*)*acetate*.—A solution of ethyl (3,4-dihydro-1-isoquinolyl)acetate (21.7 g) in glacial acetic acid (200 ml) was hydrogenated in the presence of Adams platinum oxide catalyst (0.5 g) under a pressure of 60 lb in^{-2}. The catalyst was filtered off, the filtrate evaporated to small bulk, and basified with 30% sodium hydroxide solution. The mixture was ether extracted several times, the combined extracts dried (Na_2SO_4), and evaporated leaving a yellow oil. Distillation of this oil under vacuum yielded ethyl (1,2,3,4-tetrahydro-1-isoquinolyl)acetate as a mobile liquid (17.2 g, 78.5%), b.p. 112—114° at 0.05 mmHg (lit.,[25] 145—150° at 3—4 mmHg, 68.5%).

1-(β-*Hydroxyethyl*)-1,2,3,4-*tetrahydroisoquinoline*.—A solu-

[25] S. G. Agbalyan, A. O. Nshanyan, and L. A. Nersesyan, *Izvest. Akad. Nauk Armanskoi S.S.R.*, 1963, **16**, 77.

tion of ethyl (1,2,3,4-tetrahydro-1-isoquinolyl)acetate (11.0 g) in dry ether (100 ml) was added dropwise with stirring to a mixture of lithium aluminium hydride (2.5 g) and dry ether (200 ml). The mixture was refluxed overnight, cooled, and ethanol (10 ml) added dropwise followed by 15% sodium hydroxide solution (10 ml). The precipitated inorganic salts were filtered off, the filtrate dried ($MgSO_4$), and evaporated under vacuum to leave a viscous residue. Distillation of the residue under vacuum yielded 1-(β-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline as a viscous liquid (7.1 g, 80%), b.p. 112—114° at 0.09 mmHg which solidified on standing and was recrystallised from cyclohexane as crystals, m.p. 64—66° (lit.,[26] 65—66°, 94%).

1,6,7,11b-*Tetrahydro*-2H,4H-[1,3]*oxazino*[4,3-a]*isoquinoline*.—40% Aqueous formaldehyde (1 ml) was added to 1-(β-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (1.0 g). An exothermic reaction ensued and the mixture was shaken for 0.5 h. The mixture was made strongly basic by the addition of 30% sodium hydroxide solution, and extracted several times with ether. The combined ether extracts were dried ($MgSO_4$) and the solvent evaporated, leaving a liquid which was distilled under vacuum to yield 1,6,7,11b-*tetrahydro*-2H,4H-[1,3]*oxazino*[4,3-a]*isoquinoline* as a mobile liquid, b.p. 114—116° at 0.1 mmHg (Found: C, 75.7; H, 8.0; N, 7.7. $C_{12}H_{15}NO$ requires C, 76.15; H, 8.0; N, 7.4%).

2-(1-*Isoquinolyl*)*cyclohexanone*.—Benzoyl chloride (5.06 g) was added dropwise with stirring to a solution of the morpholine enamine of cyclohexanone (10.0 g) and isoquinoline *N*-oxide (4.34 g) in chloroform (30 ml) cooled to 0 °C. The rate of addition of the benzoyl chloride was such that the temperature did not rise above 0 °C. The solution was then allowed to attain room temperature and left overnight. The orange-red mixture was poured into hydrochloric acid (20%, 60 ml). The acidic solution was separated, washed with benzene and ether, then basified with solid potassium carbonate and extracted with chloroform several times. The combined chloroform extracts were dried (Na_2SO_4) and evaporated to dryness leaving a solid residue. Recrystallisation of the solid residue from ethanol yielded 2-(1-isoquinolyl)cyclohexanone as white felted needles (4.0 g, 59.7%), m.p. 139—140° (Found: C, 80.1; H, 6.6; N, 5.9. Calc. for $C_{13}H_{15}NO$: C, 80.0; H, 6.7; N, 6.2%) (lit.,[27] 141.5—143.5°, 73.3%).

2-(1,2,3,4-*Tetrahydro*-1-*isoquinolyl*)*cyclohexanol*.—(A) A solution of 2-(1-isoquinolyl)cyclohexanone (8.0 g) in glacial acetic acid (180 ml) was hydrogenated under a pressure of *ca.* 60 lb in^{-2} in the presence of Adams platinum oxide catalyst (1.0 g). 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 30% sodium hydroxide solution and extracted with chloroform several times. The combined chloroform extracts were dried (Na_2SO_4) and evaporated to yield the 2-(1,2,3,4-tetrahydro-1-isoquinolyl)cyclohexanol as a viscous liquid (7.5 g), which was not purified but used directly in the next preparation.

(B) A mixture of 2-(1-isoquinolyl)cyclohexanone (6.0 g) and sodium borohydride (0.45 g) in dry ether (150 ml) and ethanol (15 ml) was boiled under reflux for 4 h. The solvents were removed *in vacuo* and water and ether were added to the residue. The ether layer was separated and the water layer extracted several times with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated leaving 2-(1-isoquinolyl)cyclohexanol as a viscous liquid (5.4 g). A solution of the alcohol in glacial acetic acid (100 ml) was hydrogenated under a pressure of 40 lb in^{-2} in the presence of Adams platinum oxide catalyst (0.5 g). The reaction mixture was worked up as in sequence (A).

1,2,3,4,4a,9,13b,13c-*Octahydro*-6H,8H-*benzo*[5,6][1,3]*oxazino*[4,3-a]*isoquinoline*.— 2-(1,2,3,4-Tetrahydro-1-isoquinolyl)cyclohexanol (3.5 g) from sequence (A) was shaken with 40% aqueous formaldehyde (4.0 ml) for 0.5 h, then warmed on a water-bath for 3 h, and finally left overnight at room temperature. The mixture was basified with 30% sodium hydroxide solution and ether-extracted several times. The combined extracts were dried (Na_2SO_4) and evaporated leaving a viscous residue (3.5 g). The residue was chromatographed over Grade III Wöelm neutral alumina (140 g), eluting with light petroleum (b.p. 40—60°) and collecting 200 ml fractions. Only one isomer of 1,2,3,4,4a,9,13b,13c-octahydro-6*H*,8*H*-benzo[5,6][1,3]oxazino[4,3-*a*]isoquinoline was isolated, which was then recrystallised from light petroleum (b.p. 40—60°) to yield the *product* as crystals, m.p. 110—111° (Found: C, 79.1; H, 9.0; N, 5.3. $C_{16}H_{21}NO$ requires C, 79.0; H, 8.7; N, 5.8%).

2-(1,2,3,4-Tetrahydro-1-isoquinolyl)cyclohexanol obtained from reaction sequence (B) was treated as above but only the isomer of 1,2,3,4,4a,9,13b,13c-octahydro-6*H*,8*H*-benzo[5,6][1,3]oxazino[4,3-*a*]isoquinoline previously obtained was isolated.

1-(β-*Mercaptoethyl*)-1,2,3,4-*tetrahydroisoquinoline*.— A solution of 1-(β-hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline (5.0 g) in carbon tetrachloride (50 ml) was cooled in ice and saturated with hydrogen bromide gas. The solvent was removed *in vacuo* leaving the hydrobromide as a viscous mass. Phosphorus tribromide (15.0 g) was added directly to the crude hydrobromide, and the mixture heated on a water-bath for 4 h. On cooling the residue solidified to a mass, which was washed several times with dry ether, then recrystallised from absolute alcohol once, yielding the bromide hydrobromide (7.3 g). A solution of the bromide hydrobromide (16.3 g) and thiourea (3.9 g) in absolute ethanol (250 ml) was boiled under reflux for 5 h. The isothiouronium salt so obtained was not isolated but reacted *in situ* with 3,6,9-triazaundecane-1,11-diamine (9.0 g) which was added to the solution followed by boiling of the mixture under reflux for a further 1 h. The ethanol was removed *in vacuo* and the resultant very viscous residue distilled under high vacuum to yield the 1-(β-mercaptoethyl)-1,2,3,4-tetrahydroisoquinoline as a pale yellow mobile *liquid* (5.2 g, 53%), b.p. 135—140° at 0.5 mmHg (Found: C, 68.3; H, 7.6; N, 7.1. $C_{11}H_{15}NS$ requires C, 68.4; H, 7.8; N, 7.25%).

1,6,7,11b-*Tetrahydro*-2H,4H-[1,3]*thiazino*[4,3-a]*isoquinoline*.—40% Aqueous formaldehyde (1.5 ml) was added dropwise to the foregoing thiol (1.5 g) when an exothermic reaction ensued. The mixture was shaken for 5 min, basified with 30% sodium hydroxide, and ether-extracted. The combined ether extracts were dried ($MgSO_4$) and evaporated. The residue was distilled under vacuum to yield 1,6,7,11b-tetrahydro-2*H*,4*H*-[1,3]thiazino[4,3-*b*]iso-

[26] G. Van Binst and J. C. Nouls, *J. Chem. Soc.* (*C*), 1970, 150.

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

quinoline as a yellow viscous *liquid* (1.3 g, 87%), b.p. 112—114° at 0.08 mmHg which eventually solidified, m.p. 43—44° (Found: C, 70.4; H, 7.5; N, 6.6. $C_{12}H_{15}NS$ requires C, 70.2; H, 7.4; N, 6.8%).

1-(N-*Methylacetamido*)-1,2,3,4-*tetrahydroisoquinoline*.—An ice-cooled solution of ethyl (1,2,3,4-tetrahydro-1-isoquinolyl)acetate [25] in absolute ethanol was saturated with dry methylamine gas. The solution was left to stand overnight at room temperature and the ethanol then removed under vacuum, leaving a viscous residue which solidified on cooling. Recrystallisation of the solid from ether yielded 1-(*N*-methylacetamido)-1,2,3,4-tetrahydroisoquinoline as felted *needles* (6.5 g, 92%), m.p. 109—109.5° (Found: C, 70.7; H, 8.1; N, 13.7. $C_{12}H_{16}N_2O$ requires C, 70.6; H, 7.9; N, 13.7%).

2-*Methyl*-1,3,4,6,7,11b-*hexahydropyrimido*[6,1-a]*isoquinolin*-2-*one*.—A mixture of 1-(*N*-methylacetamido)-1,2,3,4-tetrahydroisoquinoline (1.5 g) and aqueous 40% formaldehyde (2 ml) was heated on a water-bath for 0.5 h. The solution was cooled, then shaken with a small amount of ether, and the ether decanted off. A second addition of ether with scratching of the walls of the flask gave a solid which was filtered off and recrystallised from ether to yield the required *product* as crystals, m.p. 116—117° (Found: C, 72.2; H, 7.6; N, 12.9. $C_{13}H_{16}N_2O$ requires C, 72.2; H, 7.4; N, 13.0%).

3-*Methyl*-1,2,3,4,7,11b-*hexahydro*-6H-*pyrimido*[6,1-a]*isoquinoline*.—A solution of 2-methyl-1,3,4,6,7,11b-hexahydropyrimido[6,1-*a*]isoquinolin-2-one (4.0 g) in dry tetrahydrofuran (60 ml) was added dropwise with stirring to a mixture of lithium aluminium hydride (1.3 g) and dry tetrahydrofuran (100 ml). The mixture was boiled under reflux overnight, cooled, and the excess of lithium aluminium hydride decomposed by the dropwise addition of ice–water. The insoluble inorganic salts were filtered off and washed with tetrahydrofuran. The combined tetrahydrofuran filtrate was dried ($MgSO_4$) and the solvent removed *in vacuo* leaving a viscous residue. The residue was dissolved in a small amount of benzene and filtered through alumina in an effort to purify it. The benzene was removed and the residue stored at −40° when after many months it eventually solidified. Recrystallisation from light petroleum (b.p. 30—40°) yielded 3-methyl-1,2,3,4,7,11b-hexahydro-6*H*-pyrimido[6,1-*a*]isoquinoline as granular *crystals*, m.p. 38—39° (Found: C, 77.3; H, 9.3; N, 13.9. $C_{13}H_{18}N_2$ requires C, 77.2; H, 9.0; N, 13.85%). The picrate was made in the usual way and recrystallised from ethanol as a yellow crystalline *solid*, m.p. 155° (decomp.) (Found: C, 53.0; H, 5.0; N, 16.1. $C_{19}H_{21}N_5O_7$ requires C, 52.9; H, 4.9; N, 16.2%).

4,4a,5,10-*Tetrahydro*-1H,3H-[1,3]*oxazino*[3,4-b]*isoquinoline*.—1,3,4,5-Tetrahydro-3-isoquinolylmethanol (12 g) in dry CCl_4 (100 ml) was saturated with dry HBr gas. The solution was evaporated to dryness and PBr_3 (25 g) was added to the residue. A vigorous exothermic reaction ensued and HBr was evolved. The mixture was heated on a steam-bath (30 min), volatile products removed *in vacuo*, and the residues triturated with ether to give 1,2,3,4-tetrahydro-3-isoquinolylmethyl bromide hydrobromide (18 g), as a light brown crystalline solid. The bromide hydrobromide (18 g) was added without further purification to a solution of KCN (16 g) and KI (2 g) in 60% EtOH (150 ml). The mixture boiled under reflux for 3 h and stood overnight after which it was concentrated *in vacuo* and the residue basified (K_2CO_3) and extracted with $CHCl_3$. The extracts were dried (Na_2SO_4), concentrated and distilled to give 3-cyanomethyl-1,2,3,4-tetrahydroisoquinoline (5.2 g) as a viscous oil, b.p. 142—147° at 0.25 mmHg, which later solidified to a crystalline solid. The nitrile (5.2 g) in absolute EtOH (50 ml) was saturated with dry HCl gas and heated under reflux for 1 h. The mixture was concentrated *in vacuo*, basified (Na_2CO_3), and ether extracted. The extracts were dried (Na_2SO_4), concentrated and distilled to give 3-ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (4.1 g) as an oil, b.p. 131—134° at 0.15 mmHg. The ester (4.1 g) in dry ether (50 ml) was added dropwise with stirring to a suspension of lithium aluminium hydride (0.75 g) in dry ether (50 ml). When addition was complete the mixture was boiled under reflux for 1 h, excess of lithium aluminium hydride was destroyed with wet ether, the reaction mixture was acidified (dilute HCl), basified (NaOH), and ether-extracted. The extracts were dried (Na_2SO_4), concentrated and distilled to give 2-(1,2,3,4-tetrahydro-3-isoquinolyl)ethyl alcohol (2.2 g) as a viscous oil, b.p. 142—144° at 0.2 mmHg. The alcohol (2.2 g) was shaken with 36% formaldehyde solution (4 ml) for 30 min, basified (NaOH) and ether extracted. The extracts were dried (Na_2SO_4), concentrated and the crude product recrystallised from petrol to give 4,4a,5,10-tetrahydro-1*H*,3*H*-[1,3]oxazino[3,4-*b*]isoquinoline (2.0 g), as a crystalline *solid*, m.p. 49—51° (Found: C, 76.2; H, 7.9; N, 7.5. $C_{12}H_{15}NO$ requires C, 76.15; H, 8.0; N, 7.4%).

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