Proton Magnetic Resonance Studies on Compounds with Bridgehead Nitrogen. Part XXXI.[1] Reversible Dimerisation of Perhydropyrido[1,2-*c*]-[1,3]oxazepines; *X*-Ray Analysis of a Fourteen-membered Macrocyclic Dimer; Conformational Analysis of Perhydropyrido[1,2-*c*][1,3]oxazepines

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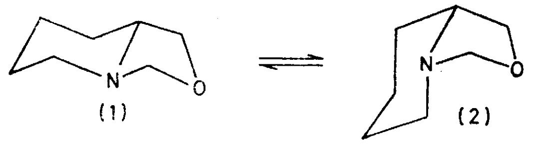
Perhydropyrido[1,2-*c*][1,3]oxazepine, *cis*(9-H, 5a-H)-9-methyl-, *trans*(8-H, 5a-H)-8-ethyl- and 8-methyl-, and *cis*(7-H, 5a-H)-7-methylperhydropyrido[1,2-*c*][1,3]oxazepine (6a, h, d, f, and c) undergo an unusual dimerisation from the liquid state; *X*-ray analysis shows that the crystalline dimer of the 8-ethyl compound contains a 14-membered heterocyclic ring. Epimers of the 8-ethyl and 8-methyl compounds together with *cis*(6-H, 5a-H)-6-methylperhydropyrido[1,2-*c*][1,3]oxazepine do not undergo the dimerisation and exist in solution predominantly in the *cis*-fused ring conformation. Compounds (6c, d, f, and h) prefer the *trans*-fused ring conformation.

PERHYDRO-OXAZOLO[3,4-*a*]PYRIDINE exists in carbon tetrachloride solution as a *cis* ⇌ *trans* equilibrium mixture (2) ⇌ (1) with ΔG^0_{298} *ca.* −0.4 kcal mol^{-1}



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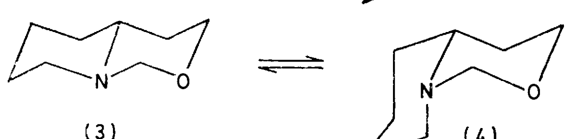

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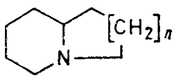

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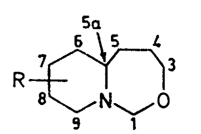


(6)

a; R = H
b; *cis* (6-H, 5a-H), R = 6-Me
c; *cis* (7-H, 5a-H), R = 7-Me
d; *trans* (8-H, 5a-H), R = 8-Et
e; *cis* (8-H, 5a-H), R = 8-Et
f; *trans* (8-H, 5a-H), R = 8-Me
g; *cis* (8-H, 5a-H), R = 8-Me
h; *cis* (9-H, 5a-H), R = 9-Me

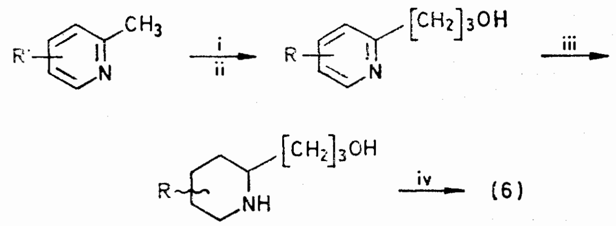
[corresponding to *ca.* 68% (1)][2,3] whereas for the corresponding equilibrium (3) ⇌ (4) for the perhydropyrido[1,2-*c*][1,3]oxazine system ΔG^0_{298} >1.5 kcal mol^{-1} [*ca.* 95% (3)].[1,4] This contrasts with the almost equal ΔG^0 values[5] for the *cis*- ⇌ *trans*-indolizidine (5; $n = 1$) and *cis*- ⇌ *trans*-quinolizidine (5; $n = 2$) equilibria of −2.4 and −2.6 kcal mol^{-1} respectively. To explore further these differences in conformational preferences brought about by the presence of the oxygen atom in the ring, derivatives of the perhydropyrido[1,2-*c*][1,3]oxazepine system (6) were chosen for study especially since perhydropyrido[1,2-*a*]azepine (5; $n = 3$) has been found[6] to exist in a predominantly *trans*-fused ring conformation.

Synthesis of Perhydropyrido[1,2-c][1,3]*oxazepines and Formation, Structure, and Stereochemistry of the Macrocyclic Dimers*.—The perhydropyrido[1,2-*c*][1,3]oxazepines were synthesised according to the route shown in the Scheme. Alkyl-substituted 3-(2-pyridyl)propan-1-ols were prepared by treating the appropriately substituted 2-methylpyridines with phenyl-lithium followed by ethylene oxide. The appropriate pyridyl alcohol was reduced catalytically or by sodium in ethanol, and the resultant mixture of isomeric piperidyl alcohols was cyclised with formaldehyde to give a mixture of the required racemic diastereoisomeric perhydropyrido-[1,2-*c*][1,3]oxazepines (6).

The samples of the octahydro-1*H*-pyrido[1,2-*c*][1,3]-oxazepines, all of which were initially liquids, were stored under nitrogen at −40°. Some of these eventu-

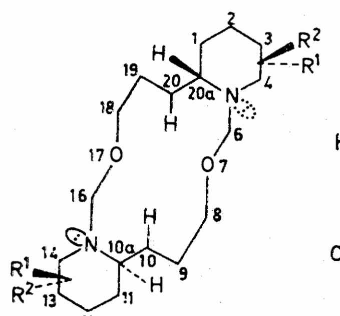
[1] Part XXX, I. D. Blackburne, A. R. Katritzky, D. M. Read, P. J. Chivers, and T. A. Crabb, *J.C.S. Perkin II*, 1976, 418.
[2] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 1997.
[3] T. A. Crabb and M. J. Hall, *J.C.S. Perkin II*, 1974, 1419.
[4] T. A. Crabb and R. F. Newton, *Tetrahedron*, 1968, **24**, 4423.
[5] H. S. Aaron and C. P. Ferguson, *Tetrahedron Letters*, 1968, 6191.
[6] M. N. Aboul-Enein and J. Sam, *J. Heterocyclic Chem.*, 1971, **8**, 7.

ally deposited crystals, which were separated by filtration, washed with light petroleum to remove traces of adhering liquid, and their 60 MHz (CCl_4 or $CDCl_3$ solution) n.m.r. spectra was recorded. In all



SCHEME Reagents: i, PhLi; ii, ethylene oxide; iii, H_2–PtO_2–HOAc or Na–EtOH; iv, 40% aqueous CH_2O

cases, the n.m.r. spectrum corresponded to that of a single pure isomer and was apparently in agreement with structure (6). On re-running the spectrum after 24 h, however, a completely different spectrum, also corresponding to a single, pure isomer of (6), was obtained. In each case when the residual oil obtained on evaporation of the solvent from the n.m.r. sample was allowed to crystallise, the n.m.r. spectra of the crystals (CCl_4 or $CDCl_3$ solution), recorded immediately and after 24 h, were identical to those previously obtained.



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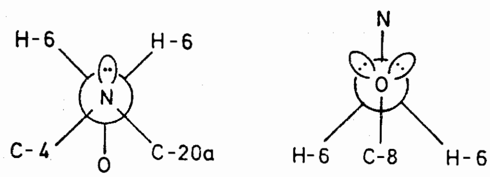


(8)

To examine this phenomenon further an *X*-ray study was undertaken. Crystals were collected from the preparation of (6d), m.p. 86—93°. The relatively wide melting range of the apparently chemically pure substance suggests a certain degree of disorder in the crystal (consistent with rapid formation from a melt). However a suitable crystal was mounted on a four-circle diffractometer; 963 observed intensity data were collected and used in structure determination and refinement. The phases were assigned by a symbolic addition procedure, and an *E* map revealed an asymmetric unit ($C_{11}NO$) clearly not corresponding to any stereochemical modifications of the bicyclic structure (6d). Eventually it was realised that the asymmetric unit comprised half the complete molecule, which was in fact the centrosymmetric dimer (7; $R^1 = H$, $R^2 = Et$), containing a 14-membered heterocyclic ring, *trans*-fused with two perhydropyridine nuclei. Refinement by block-diagonal least squares converged to *R* 0.099 with anisotropic temperature factors for non-hydrogen atoms, and including methine and methylene hydrogens. General views of the molecule, displaying conformations of the rings (and also crystallographic numbering) are shown in Figures 1(a) and (b). Bond lengths and angles, and the arrangement of molecules in the unit cell are shown in Figures 2 and 3, respectively. No surprising intermolecular contacts were noted.

The 220 MHz n.m.r. spectrum of the crystalline dimer obtained from (6d) run before monomerisation occurred supported the *X*-ray structure. Thus the doublet and triplet splitting patterns observed for the signals centred at δ 2.83 and 2.50 arising from the equatorial and axial H-4 (H-14) protons respectively is in accord with a ring A chair conformation in which the ethyl substituent is equatorial rather than axial, since the observed vicinal coupling of 11.5 Hz between H-3 (H-13) and H-4ax (H-14ax) is of the order of magnitude expected for a vicinal coupling constant between axial protons, consistent with the presence of an axial H-3 (H-13)-proton and hence an equatorial 3(13)-ethyl substituent.

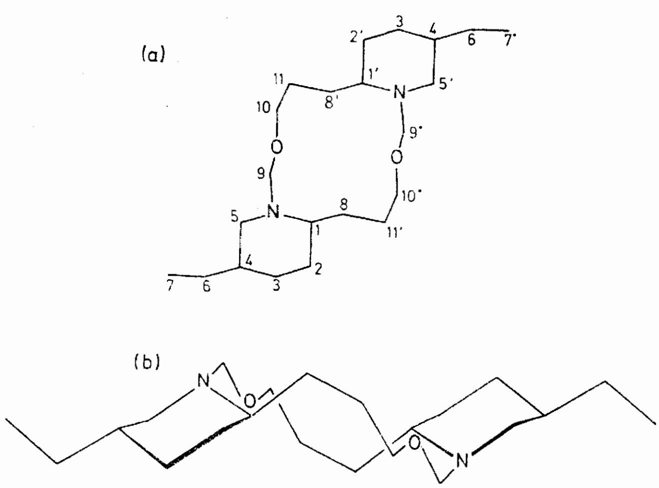


FIGURE 1 (a) General view of the molecule and crystallographic numbering; (b) general view of the molecule

The $\delta_{H\text{-}4eq} - \delta_{H\text{-}4ax}$ ($\delta_{H\text{-}14eq} - \delta_{H\text{-}14ax}$) value of 0.33 p.p.m. is apparently somewhat small for the *trans*-fused conformation in which the ethyl group is equatorial, since H-4ax (H-14 ax) is shielded by the *anti*-lone pair on nitrogen and the 6-methylene (16-methylene) and ethyl groups (by up to 0.47 p.p.m.). However the structure of (7; $R^1 = H$, $R^2 = Et$) shows a near syn-axial relationship between the C(6)–O bond [C(16)–O bond] and H-4ax (H-14ax) which will lead to deshielding of this

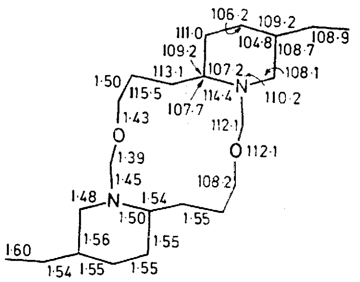


FIGURE 2 Bond lengths (Å; mean σ 0.015 Å) and angles (°; mean σ 0.9°)

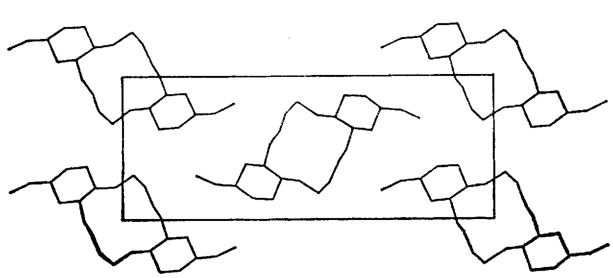
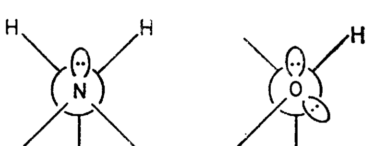


FIGURE 3 Arrangement of molecules in the unit cell projected along the *a* axis

proton with a consequent reduction in the magnitude of the $\delta_{H_{eq}} - \delta_{H_{ax}}$ value.

The spectrum shows two multiplets at δ 2.56 (2 H) and 2.30 (2 H) respectively. One of these must be due to the angular protons (H-10a and -20a) and the other to a pair of the remaining ring protons, which thus absorb at considerably lower field than the others (δ >1.8). Examination of models of (7; $R^1 = H$, $R^2 = Et$) suggests that such a large deshielding is possible where H-10 and -20 are deshielded by the across-ring C–O bonds (H-10 to 17-O and 7-O distances of 2.8 and 3 Å respectively). The observed $J_{6eq,6ax}$ ($J_{16eq,16ax}$) of −8.9 Hz is in accord with the *X*-ray structure which shows approximate dihedral angles between the C–H



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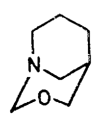


(10)

bonds of these methylene groups and adjacent heteroatom lone pairs as indicated in (8). For the lone pair–CH_2 geometry shown in (9) [*e.g.* in (10) [7]] J_{gem} is observed as −10.5 Hz. Thus for the arrangement in (8) for (7; $R^1 = H$, $R^2 = Et$) in which only the dihedral angles with the oxygen lone pairs [8] is different from that in (9) J_{gem} should be more positive than in (9). The observed ΔJ_{gem} is +1.6 Hz.

60 MHz N.m.r. spectra were obtained on the remaining dimers (7) by running these within 1 min of making up the solution. Only the n.m.r. parameters for the 6(16)-methylene protons were obtained from the spectra and these are shown in Table 1. For the first few entries

TABLE 1

60 MHz N.m.r. spectra (CCl_4 solution) or 14-membered ring dimers (7)

Compound	$J_{6eq'6ax'}$ ($J_{16eq'16ax'}$)/Hz	$\delta_{6eq'(16eq')}$	$\delta_{6ax'(16ax')}$
(7; $R^1 = R^2 = H$)	−8.8	3.87	4.74
(7; R^1 = 2-Me, $R^2 = H$)	−8.8	3.82	4.45
(7; $R^1 = H$, R^2 = 3-Me)	−8.8	3.91	4.61
(7; $R^1 = H$, R^2 = 3-Et) *	−8.9	3.83	4.52
(7; R^1 = 4-Me, $R^2 = H$)	−9.8	4.07	4.32

* 220 MHz Spectrum (CCl_4 solution) gave in addition, $J_{4eq,4ax}$ −11.5, $J_{4eq,3ax}$ 11.5, $J_{4eq,3ax}$ 4.0 Hz; δ 3.33 (8eq′-H), 3.20 (8ax′-H), 2.83 (4eq-H), 2.50 (4ax-H), and 2.56 and 2.30 (10a- and 9-H).

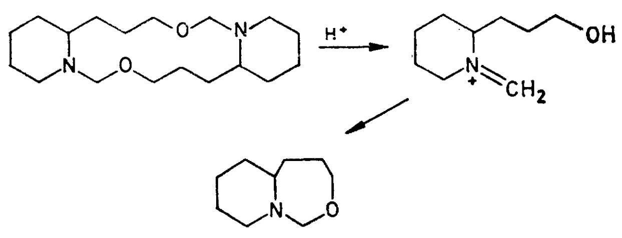
the spectral parameters are very similar, indicating similar structures to (7; $R^1 = H$, $R^2 = Et$) but the 4,14-dimethyl substituted compound showed a much reduced chemical shift difference between the 6(16)-methylene protons (0.25 p.p.m., *cf. ca.* 0.7 p.p.m. in other dimers) and a slightly smaller J_{gem} [−9.8 Hz, *cf.* −8.8 Hz in (7; $R^1 = H$, $R^2 = Et$)] for the 6(16)-methylene protons. The deshielding of H-6eq (H-16eq) must be the result of a '*peri*'-type interaction involving the methyl group [4] and possibly the change in J_{gem} is consequent upon a small change in the average conformation of the seven-membered ring brought about in minimising this interaction.

Thus all the crystalline dimers were assigned *trans*-fused ring junctions with the alkyl substituents in the six-membered rings occupying equatorial positions. A consideration of the stereochemistry of the perhydropyrido[1,2-*c*][1,3]oxazepines described below confirms the correctness of these configurational assignments.

Attempts to measure the molecular weight (366) of (7; $R^1 = H$, $R^2 = Et$) in CCl_4 solution by vapour pressure osmometry gave a value of 283 (±5%) 5 min after making up the solution, which fell to 185 (±5%) (molecular weight of monomer 183) after 1 h. Electron impact mass spectrometry gave no indication of the molecular ion of the dimer but the field desorption technique gave a strong M^+ of 366 with $M^+ + 1$ also present. The ready dissociation in solution of the dimer into monomer was readily followed by n.m.r.

[7] J. M. Lehn and F. G. Riddell, *J. Chem. Soc.* (*B*), 1968, 1224.
[8] G. E. Macial, J. W. McIver, jun., N. S. Ostlund, and J. A. Pople, *J. Amer. Chem. Soc.*, 1970, **92**, 4151.

spectroscopy and was found to be rapidly accelerated by the addition of trace amounts of hydrochloric acid but completely arrested by the addition of a trace of NaOD to the CCl_4 solution contained in a n.m.r. tube. The mechanism (11) ⟶ (12) is therefore suggested.



(12)

Stereochemistry of Perhydropyrido[1,2-c][1,3]*oxazepines*.—Catalytic hydrogenation of ring substituted 3-(2-pyridyl)propan-1-ols is expected [2,9] to result in a predominance of that piperidine derivative resulting from *cis*-addition of hydrogen in the resultant mixture of (14) and (15).† The *O*-outside *cis*-conformer (15) is of higher energy than (13) by *ca.* 2.5 kcal mol^{-1} (*i.e. ca.* 3 *gauche*-butane interactions) and so may be neglected. In (14) one of the *gauche*-butane interactions present in (15) has been replaced by the energetically more favourable methylene–oxygen atom interaction [11] and in

TABLE 2

Configurational assignments to perhydropyrido[1,2-*c*][1,3]-oxazepines based on the method of synthesis [a]

3-(2-Pyridyl)-propan-1-ol	Method of reduction	Major isomer of (6) [b]
3-Me	H_2–PtO_2	6b
4-Me	H_2–PtO_2	6c
5-Me	H_2–PtO_2	6g
	Na–EtOH	6f
5-Et	H_2–PtO_2	6e
	Na–EtOH	6d
6-Me	H_2–PtO_2	6h

[a] See Scheme and Figure 4. [b] Major isomer of (6) obtained by synthetic sequence shown in Scheme utilising reduction method shown in column 2 of this Table.

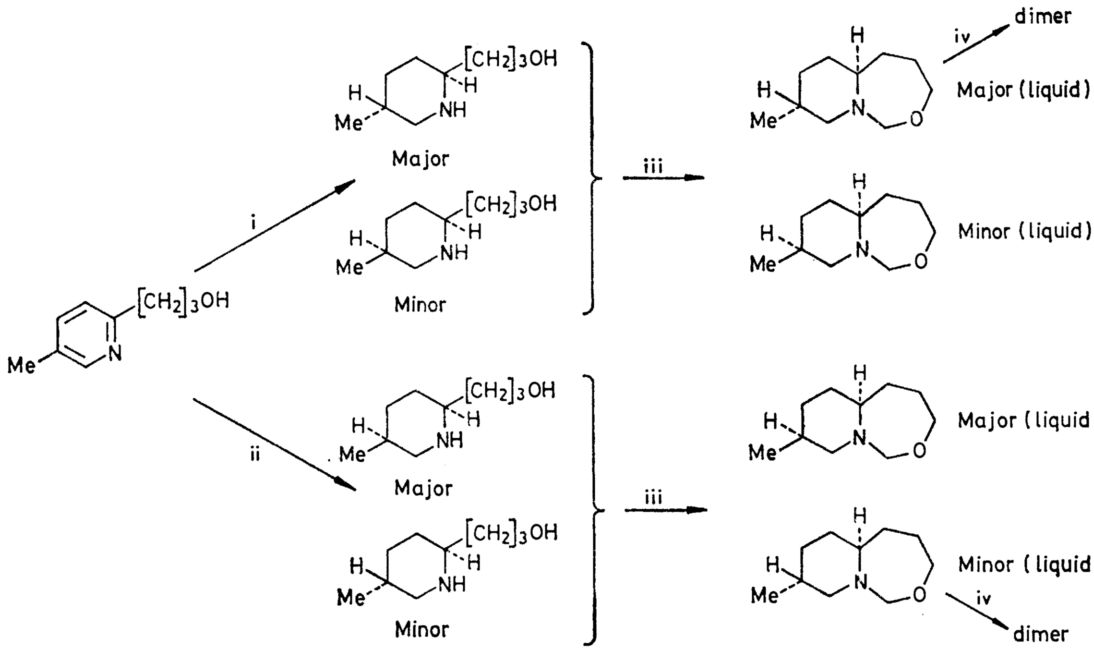


FIGURE 4 Assignment of configurations to *cis*- and *trans*-(8-H, 5a-H)-8-methylperhydro[1,2-*c*][1,3]oxazepines based on the expected stereochemical outcome of reduction methods: reagents i, Na–EtOH; ii, H_2–PtO_2–HOAc; iii CH_2O; iv crystallisation

isomers whereas reduction by sodium and ethanol normally results in a predominance of the diequatorially substituted piperidine.[2,9,10] These expectations are summarised in Figure 4 using the synthesis of (6f and g) as examples. On these grounds, it was possible to make the preliminary assignment of configurations shown in Table 2.

Perhydropyrido[1,2-*c*][1,3]oxazepine (6a) may exist in solution as an equilibrium mixture involving the *trans*-fused conformation (13) and the *cis*-fused conformations

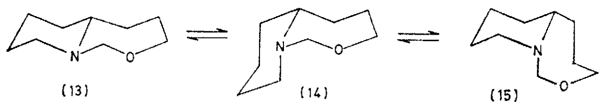
† Examination of Dreiding models suggests the twist-chair conformations shown for the seven-membered rings in (13) and (14) to be energetically most favourable. Rapid partial pseudo-otation will occur about this energy minimised geometry.

addition the generalised anomeric effect [12] favours (14) rather than (13).

With (6c, f, and h), the *trans*-fused conformer should be the most favourable since in the equilibrium [*e.g.* (16) ⇌ (17), shown for (6c)] the *O*-inside *cis*-conformation is disfavoured by interactions involving the axial methyl group. With (6b and g) [see equilibrium

[9] R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985.
[10] T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 1962, 2637.
[11] E. L. Eliel, *Accounts Chem. Res.* 1970, **3**, 1.
[12] S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc.* (*B*), 1971, 136; H. Booth and R. U. Lemieux, *Canad. J. Chem.*, 1971, **49**, 777.

(18) $\rightleftharpoons$ (19) for (6g)] the *trans*-fused conformation is destabilised by the generalised anomeric effect and by interactions arising from the presence of the axial methyl group so that the difference in energy between the axially substituted *trans*-fused conformer and the equatorially substituted *O*-inside *cis*-conformer is (d + CH_3/N − CH_2/O − gb) * which approximates to the difference between the magnitude of the anomeric effect and a *gauche*-butane interaction. Models suggest (almost parallel resultant dipoles for the two groups of C–heteroatom bonds) that the anomeric effect in the *trans*-conformer $\rightleftharpoons$ *O*-inside *cis*-conformer equilibrium will be greater than in (3) $\rightleftharpoons$ (4) so that ΔG^0 for the (18) $\rightleftharpoons$ (19) equilibrium and for the corresponding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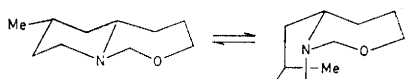
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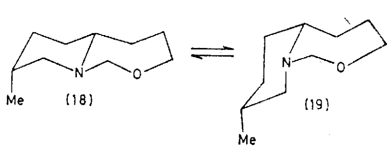
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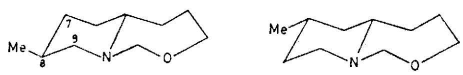
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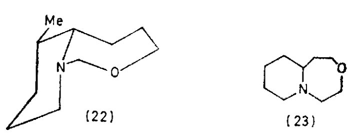
(22) (23)

equilibrium for (6b) should be less than the 0 kcal mol^{-1} observed[1] for *cis*(7-H,4a-H)-7-methylperhydropyrido-[1,2-*c*][1,3]oxazine indicating the preference of (6b and g) for the *cis*-fused ring conformation.

The general trends indicated in this *a priori* discussion of the position of conformational equilibrium in the perhydropyrido[1,2-*c*][1,3]oxazepines are supported by the n.m.r. data for the various isomers with particular reference to the n.m.r. parameters of the 5a-proton and of the 9-methylene protons.

Application of the sequence of reactions shown in Figure 4 to 5-methyl-3-(2-pyridyl)propan-1-ol gave a crystalline dimer and a liquid perhydropyrido[1,2-*c*][1,3]-oxazepine. The dimer was monomerised to an epimer of the liquid product by dissolving it in deuteriochloroform and allowing the solution to stand at room temperature for 1 h. Analysis of the n.m.r. spectra (see Experimental section) of the epimeric † perhydropyrido[1,2-*c*][1,3]oxazepines permitted the assignment of (6g) to the liquid product and of (6f) to that epimer derived from the crystalline dimer. In particular the bridgehead proton (H-5a) in (6f) absorbed to higher field of the corresponding signal in (6g) indicating a greater preference for a *trans*-fused conformation for (6f).[13] This is in general agreement with the conformational argument predicting (6f) to exist preferentially in the *trans*-fused ring conformation (20) and (6g) as a *ca.* 1 : 1 equilibrium mixture of (18) and (19). The vicinal couplings between the 8- and 9-protons permit an estimate of the position of conformational equilibria and support a predominantly *trans*-fused conformation for (6f) and an equilibrium for (6g) in which the *O*-inside *cis*-conformer (19) predominates (for detailed discussion see Experimental section).

Compound (6f), existing in the *trans*-fused conformation in solution, readily undergoes crystallisation from the liquid phase to give the dimeric compound whereas (6g) existing predominantly in the liquid phase in the *cis*-fused conformation cannot be induced to crystallise. Exactly analogous results were obtained for the 8-ethylperhydropyrido[1,2-*c*][1,3]oxazepines.

Only one isomer of 7-methylperhydropyrido[1,2-*c*]-[1,3]oxazepine and one of 6-methylperhydropyrido-[1,2-*c*][1,3]oxazepine were obtained by the synthetic sequence shown in Figure 4 and the n.m.r. spectra (see Experimental section) of these were completely in accord with their existence in solution almost exclusively in *trans*-fused conformations carrying equatorial methyl groups [see (20) for the 7-methyl compound]. Both compounds readily crystallised from the liquid state to give the corresponding macrocyclic dimers.

The single isomer of 6-methylperhydropyrido[1,2-*c*]-[1,3]oxazepine obtained was assigned a predominantly *cis*-fused conformation in solution at room temperature on the basis of its 220 MHz spectrum and on conformational grounds must therefore possess the *cis*(6-H,5a-H)-configuration (22). This compound could not be induced to crystallise from the liquid state.

The parent unsubstituted compound (23) readily crystallised from the liquid state to give the macrocyclic dimer (7; $R^1 = R^2 =$ H) and the n.m.r. evidence (Table 1) suggests *trans*-fused ring junctions in the dimer. In solution however (23) appears to exist as an equilibrium mixture containing appreciable amounts of the *cis*-fused ring conformation.

I.r. Spectra of Perhydropyrido[1,2-c][1,3]*oxazepines and of Dimers*.—The Bohlmann i.r. criterion,[14] originally deduced for quinolizidine alkaloids, applies to a variety of heterocyclic systems including (1) $\rightleftharpoons$ (2) [2] and (3) $\rightleftharpoons$ (4) [4] which are closely related to (6). However,

* d Denotes the generalised anomeric effect for the *trans*- $\rightleftharpoons$ *O*-inside *cis*-equilibrium, gb the *gauche*-butane interaction, and CH_2/O and CH_3/N the interactions between the 9-methylene and the oxygen atom in the *O*-inside *cis*-conformation and that between the axial methyl group and the nitrogen atom in the *trans*-conformation.

† All the bi- and tri-cyclic compounds described in this paper exist as racemates.

[13] T. A. Crabb, D. Jackson, and R. F. Newton, *Chem. Rev.*, 1971, **71**, 109.

[14] F. Bohlmann, *Angew. Chem.* 1957, 69; *Chem. Ber.* 1958, **91**, 2157.

examination of the spectra showed that Bohlmann bands are poorly defined in those compounds to which a predominantly *trans*-ring fusion is assigned on the basis of n.m.r. evidence. In contrast, the 1,4-hetero-system (23) showed sharp bands typical of a 'normal' *trans*-fused system. Those compounds adopting the *cis*-conformation are not expected to absorb between 2 800 and 2 600 cm^{-1}, but in fact showed an area of absorption not appreciably smaller than for the *trans*-fused compounds. Because of this anomalous behaviour, conformational assignments in the perhydropyrido[1,2-*c*][1,3]oxazepine series have been based solely upon n.m.r. data. However, the i.r. spectra fall naturally into three categories; the absorption in the 2 800—2 600 cm^{-1} region in *trans*-fused dimer > *trans*-fused monomer > *cis*-fused monomer.

EXPERIMENTAL

Elemental analyses were carried out by Dr. F. Pascher and E. Pascher, Microanalytical Laboratory, Bonn, Germany. N.m.r. spectra were recorded on Varian T60 and HR-220 spectrometers as 10% solutions in $CDCl_3$ and CCl_4 with tetramethylsilane as internal reference. Alkyl-substituted 3-(2-pyridyl)propan-1-ols were prepared from the appropriate alkyl-substituted pyridyl-lithium and ethylene oxide by application of the method of Reinecke and Kray.[15]

TABLE 3

Synthesis of 3-(2-piperidyl)propan-1-ols

Alkyl-substituted 3-(2-piperidyl)-propan-1-ol	B.p. (°C) [*p*/mmHg]	M.p.[a] (°C)	Analysis (%)[a]
6-Methyl	(m.p. 63°)[b]		C, 68.9; H, 12.1; N, 9.0[c]
5-Ethyl	110 [0.5]	(T) 92—94	(T) C, 41.3; H, 5.3; N, 12.3[d]
5-Methyl[e]	98 [0.2]		C, 69.1; H, 12.3; N, 8.2[c]
4-Methyl[f]	100 [0.07]	(T) 158—160	(T) C, 39.9; H, 4.9; N, 12.5[g]
3-Methyl	104 [0.5][h]	(T) 133—135[i]	(T) C, 39.8; H, 4.8; N, 12.1[g]

[a] (T) = 2,4,6-Trinitrobenzenesulphonate. M.p.s are recorded after one recrystallisation of the derivative from EtOH–Et_2O, and probably correspond to the m.p. of an epimeric mixture of the alcohol derivative. [b] M.p. of the pure *cis*-(2-H, 6-H) alcohol recrystallised from ether, δ (CCl_4) 1.04 (Me). The minor *trans*-epimer [δ *ca.* 1.07 (Me)], constituted *ca.* 10% of the mixture obtained by catalytic hydrogenation of 3-(6-methyl-2-pyridyl)propan-1-ol, and only the pure *cis*-isomer was used in the subsequent reaction with formaldehyde. [c] $C_9H_{19}NO$ requires C, 68.7; H, 12.2; N, 8.2%. [d] $C_{16}H_{24}N_4O_{10}S$ requires C, 41.4; H, 5.2; N, 12.1%. [e] δ (CCl_4): 0.98 and 0.80 [Me, major and minor isomers respectively obtained from catalytic hydrogenation of 3-(5-methyl-2-pyridyl)propan-1-ol]. [f] δ (CCl_4) 0.90 (Me). Sole product from catalytic hydrogenation. [g] $C_{15}H_{22}N_4O_{10}S$ requires C, 40.0; H, 4.9; N, 12.4%. [h] Lit.,[15] 112—113° at 2 mmHg. [i] Lit.,[15] 134—135°.

General Procedure for Synthesis of Alkyl-substituted 3-(2-*Piperidyl)propan*-1-*ols* (*Table* 3).—(a) *Catalytic hydrogenation of* 3-(2-*pyridyl)propan*-1-*ols*. The appropriate alcohol (20 g), glacial acetic acid (200 ml), and platinum oxide (1 g) were shaken with hydrogen at 60 lb in^{-2} until uptake was complete. The solution was filtered, the acetic acid removed *in vacuo*, and the residue was strongly basified with sodium hydroxide solution and extracted three times with ether. The dried ethereal solution was concentrated and distilled *in vacuo* to give a mixture of *cis*- and *trans*-alkyl substituted 3-(2-piperidyl)propan-1-ols in 96—98% yield.

(b) *Sodium–ethanol reduction of* 3-(2-*pyridyl)propan*-1-*ols*. A solution of the appropriate alcohol (0.1M) in absolute ethanol (250 ml) was boiled under reflux and sodium (40 g) was added. The solution was boiled under reflux for 2 h, acidified with dilute hydrochloric acid, and excess of ethanol removed under reduced pressure. The residue was basified with aqueous sodium hydroxide solution, extracted three times with ether, and the ethereal solution was dried (Na_2SO_4), concentrated, and distilled *in vacuo* to give an epimeric mixture of the required reduced alcohol in *ca.* 40% yield.

Synthesis of Perhydropyrido[1,2-c][1,3]*oxazepines and Dimers*.—The alkyl-substituted piperidylpropanol, obtained by either catalytic or chemical reduction, was shaken with an excess of 36% aqueous formaldehyde solution for 30 min.

TABLE 4

Synthesis of perhydropyrido[1,2-*c*][1,3]oxazepines and dimers

Perhydropyrido-[1,2-*c*][1,3]-oxazepine	Yield (%)	B.p. °C [*p*/mmHg] and analysis of monomer	M.p.[a] (°C) and analysis of dimer
(6a)	87	80—82 [18]	76—86 C, 69.65; H, 10.9; N, 9.1[b]
(6d)	82		86—93[d] C, 72.3; H, 11.6; N, 7.6[g]
(6e)		96 [4][e,f] C, 72.2; H, 11.7; N, 7.7[g]	
(6f)	85		91—96[d] C, 70.7; H, 11.3; N, 8.2[c]
(6g)		66 [1] C, 70.6; H, 11.4; N, 8.2[c]	
(6c)	88		88—95[f] C, 71.1; H, 11.3; N, 8.3[c]
(6b)	86	72 [2] C, 70.7; H, 11.1; N, 8.3[c]	
(6h)	86		66—76[f] C, 70.6; H, 11.35; N, 8.10[c]

[a] M.p.s recorded in this column are not sharp; recrystallisation of the solid products was not possible because of the monomerisation occurring in solution in this series of compounds. [b] $C_9H_{17}NO$ requires C, 69.6; H, 11.0; N, 9.0%. [c] $C_{10}H_{19}NO$ requires C, 71.0; H, 11.3; N, 8.3%. [d] Obtained as the major product from the reaction between formaldehyde and the alcohol obtained by sodium–ethanol reduction. [e] Purification was achieved by standing the mixed product at −40°, filtering to remove crystals (dimer), distilling the filtrate *in vacuo*, and collecting the lowest boiling fraction. [f] Sole reaction product isolated from the reaction between formaldehyde and the alcohol obtained by catalytic hydrogenation. [g] $C_{11}H_{21}NO$ requires C, 72.1; H, 11.55; N, 7.6%.

The mixture was basified with aqueous sodium hydroxide solution and extracted three times with ether. The ethereal solution was dried (Na_2SO_4), concentrated, and distilled *in vacuo* to give the required perhydropyrido[1,2-*c*]oxazepine which was kept under nitrogen at −40°. Details regarding the individual syntheses are recorded in Table 4.

[15] M. G. Reinecke and L. R. Kray, *J. Org. Chem.*, 1964, **29**, 1736.

Detailed Discussion of 220 MHz *N.m.r. Spectra of Perhydropyrido*[1,2-c][1,3]*oxazepines* (*see Table* 5).—In the spectrum of (6f) the 9-methylene signals may be analysed by first-order methods to give $J_{9ax,8ax}$ 11.1, $J_{9eq,8ax}$ 4.0 Hz, values entirely consonant with conformation (20). H-9eq is long range coupled (1.9 Hz), presumably to H-7eq, since in the chair these protons are connected by a planar W pathway. Additional evidence for the chair conformation of the six-membered ring comes from analysis of two multiplets at δ 0.94 (1 H) and 1.40 (1 H). The high field multiplet was assigned to H-7ax, since this proton is shielded by the equatorial 8-methyl group in the chair form, and the vicinal couplings of 12, 12, and 4 Hz are as expected for two ax–ax ($J_{7ax,6ax}$ and $J_{7ax,8ax}$) and one ax–eq ($J_{7ax,6eq}$) coupling. The δ 1.40 multiplet must arise value of 0.7 p.p.m. was observed for the other *trans*-fused compound (6f) but in this compound H-9ax undergoes an additional shielding of up to 0.47 p.p.m.[16] by the equatorial 8-methyl group. The 1- and 3-methylene proton signals are very similar in the 220 MHz spectra of both *trans*-fused compounds, and the absorption of the angular proton at δ 2.33 in the spectrum of the 7-methyl compound is also in accord with a *trans*-fused conformation.

Two multiplets at δ 1.12 (1 H) and 1.24 (1 H) at higher field than the other ring proton signals arise from H-6ax and -8ax which are shielded by the adjacent equatorial methyl; the four-line multiplet at δ 1.12 was assigned to H-6ax since the observed vicinal coupling of 12 Hz is in accord with an ax–ax coupling ($J_{6ax,5a}$). The quartet of doublets at δ 1.24 was assigned to H_{8ax} since analysis gave couplings of 12, 12, 12, and 5 Hz, corresponding to $J_{8eq,8ax}$, $J_{8ax,7ax}$, $J_{8ax,9ax}$, and $J_{8ax,9eq}$, respectively. The broad multiplet at δ 1.48 must arise from the axial 7-proton, which is coupled to four vicinal protons and three protons of the methyl group.

TABLE 5

220 MHz N.m.r. spectra of perhydropyrido[1,2-*c*][1,3]oxazepines *

		δ									*J*/Hz			
Compound	Solvent	1eq	1ax	3eq	3ax	5a	9eq	9ax	Me	Other	1eq, 1ax	9eq, 9ax	CH–Me	Other
(6a)	$CDCl_3$	4.47	4.35	3.95 (m)	3.68 (m)	2.95	2.57 (m)				−11.5			
(6b)	CCl_4	4.40	4.26	3.77 (m)	3.55 (m)	2.65—2.90 (m)			0.90		−11.6			
(6c)	$CDCl_3$	4.47	4.36	3.99	3.62	2.33	2.98 (dq)	2.60	0.96	1.48 (m, 7ax) 1.24 (qd, 8ax) 1.12 (q, 6ax)	−11.2	−12.0	6.8	−12.0 (3eq, 3ax)
(6f)	$CDCl_3$	4.31	4.23	3.88	3.52	2.19	2.83 (dq)	2.13 (t)	0.84	0.94 (7ax) 1.40 (6ax)	−11.1	−11.1	6.5	11.1 (9eq, 8ax) 4.0 (9eq, 8ax) 1.9 (9eq, 7eq) −12.0 (3eq, 3ax)
(6g)	$CDCl_3$	4.52	4.38	3.86 (m)		3.04	2.69	2.58	0.91	1.17 (7ax) 2.17 (6ax)	−11.5	−12.0	6.6	10.0 (9ax, 8ax) 5.0 (9eq, 8ax)
(6h)	$CDCl_3$	4.80	4.45	4.00	3.53	2.57		2.75	1.19		−12.8		6.9	−11.6 (3eq, 3ax)

* For details of assignments see Experimental section.

from H-6ax or -8ax, and since the H-8ax signal will be complicated because of coupling to the 8-methyl group in addition to four vicinal protons, the simple eight line multiplet must arise from H-6ax. Again, the vicinal couplings (12, 11, and 4 Hz) are as expected for two J_{ax-ax} and one J_{ax-eq} couplings.

Analysis of the 9-methylene signals in the spectrum of (6g) gives vicinal coupling constants between H-8 and the 9-methylene protons of 10 and 5 Hz. For (18) approximately equal (*ca.* 4—5 Hz) values of the two vicinal couplings are expected (corresponding to $J_{9ax,8eq}$ and $J_{9eq,8eq}$) whereas for (19) values of 11.1 and 4.0 Hz corresponding to $J_{9ax,8ax}$ and $J_{9eq,8ax}$ are typical [*cf.* (6f)]. The observed values therefore support an equilibrium for (6g) in which the *O*-inside *cis*-conformer (19) predominates.

cis(7-H,5a-H)-7-*Methylperhydropyrido*[1,2-c][1,3]*oxazepine* (6c). The n.m.r. spectrum of (6c) is in accord with its existence in the *trans*-fused ring conformation (21). A doublet of quartets at δ 2.98 was assigned to the equatorial 9-proton, J_{gem} −12, $J_{9eq,8ax}$ 5, $J_{9eq,8eq}$ 2.5 Hz. The corresponding H-9ax signal was a triplet of doublets at δ 2.60 (J_{gem} −12, $J_{9eq,8ax}$ 12, $J_{9ax,8eq}$ 3 Hz) giving $\delta_{eq} - \delta_{ax}$ (9-methylene) 0.38 p.p.m., in accord with *trans*-fused (21) rather than an *O*-outside *cis*-fused conformation for which a very small (or negative) $\delta_{eq} - \delta_{ax}$ is expected. A $\delta_{eq} - \delta_{ax}$

cis(9-H,5a-H)-9-*Methylperhydro*[1,2-c][1,3]*oxazepine* (6h). The 220 MHz n.m.r. spectrum of (6h) is in accord with its existence in the *trans*-fused ring conformation. Two multiplets at δ 2.57 (1 H) and 2.75 (1 H) arise from the 9- and 5a-protons adjacent to nitrogen; the δ 2.75 multiplet was assigned to the 9-proton since it analysed consistently with coupling to the methyl group and two vicinal protons. Thus the triplet at δ 2.57 arises from the angular proton, and this chemical shift is somewhat to lower field of the 5a-proton signals in the other *trans*-fused compounds. The 1-methylene AB quartet gave δ 4.45 and 4.80 and J_{gem} −12.8 Hz. The Δδ of 0.35 p.p.m. is reasonable since deshielding of H-1eq′ by the equatorial 9-methyl group is expected in the *trans*-fused conformation. The J_{gem} value of −12.8 Hz for 1-methylene is smaller than the values observed for (6f and c) (−11.1 and −11.2 Hz respectively). This and the rather atypical δ value of the 5a-proton is most probably a result of distortion of the twist-chair

[16] H. Booth, *Tetrahedron Letters*, 1965, 411.

seven-membered ring in (6h) in order to minimise the *peri*-type interaction involving 9-methyl.

TABLE 6

Fractional atomic co-ordinates with standard deviations in parentheses

Atom no.*	x	y	z
C1	0.247 4(18)	0.102 7(4)	0.015 2(8)
O2	0.090 7(12)	0.079 1(2)	0.100 2(6)
C3	0.758 8(18)	0.402 1(4)	0.130 6(9)
C4	0.588 5(20)	0.348 3(4)	0.141 6(9)
C5	0.795 9(21)	0.303 5(4)	0.228 7(10)
C6	0.257 0(18)	0.058 0(3)	0.238 5(8)
C7	0.640 6(24)	0.248 2(4)	0.243 4(12)
C8	0.088 2(18)	0.476 5(3)	0.270 0(9)
C9	0.901 6(16)	0.426 3(3)	0.285 7(8)
C10	0.859 0(26)	0.198 2(4)	0.301 7(11)
C11	0.073 7(19)	0.028 0(4)	0.314 7(9)
C12	0.913 6(20)	0.329 8(3)	0.384 8(9)
N13	0.081 3(14)	0.380 2(3)	0.370 6(7)
H1a	0.404 (15)	0.076 (3)	0.004 (8)
H1b	0.357 (16)	0.135 (3)	0.084 (8)
H3a	0.895 (15)	0.389 (3)	0.080 (8)
H3b	0.632 (15)	0.430 (3)	0.073 (8)
H4a	0.508 (14)	0.332 (3)	0.035 (7)
H4b	0.423 (17)	0.353 (3)	0.197 (9)
H5a	0.969 (16)	0.275 (3)	0.174 (8)
H6a	0.426 (15)	0.029 (3)	0.214 (8)
H6b	0.378 (15)	0.092 (3)	0.298 (8)
H7a	0.481 (24)	0.260 (5)	0.306 (13)
H7b	0.497 (24)	0.232 (5)	0.144 (13)
H8a	0.271 (15)	0.461 (3)	0.216 (8)
H8b	0.214 (18)	0.491 (4)	0.373 (9)
H9a	0.707 (15)	0.440 (3)	0.332 (8)
H11a	0.262 (19)	0.016 (4)	0.424 (10)
H11b	−0.121 (18)	0.051 (4)	0.329 (10)
H12a	1.037 (22)	0.306 (5)	0.460 (12)
H12b	0.702 (19)	0.334 (4)	0.423 (10)

* Hydrogens are allocated the number of their attached carbon

Perhydropyrido[1,2-c][1,3]*oxazepine* (6a) *and its* cis-(6-H,5a-H)-6-*methyl derivative* (6b). In the 220 MHz spectrum of (6a) the low field absorption of the angular proton (δ 2.95) and the occurrence of the 9-methylene signals as a multiplet centred at δ 2.57 are in accord with a *cis*-fused conformation, in which H-9ax is deshielded by the C(5)–C(5a) axial bond. The n.m.r. parameters for the 1-methylene protons, δ 4.47 and 4.35 (J_{gem} −11.5 Hz), are very similar to those of *cis*(8-H,5a-H)-8-methylperhydropyrido[1,2-*c*][1,3]oxazepine. The 220 MHz spectrum of (6b) resembled that of the parent compound very closely. Consistent with the *cis*-conformation (22), the angular and 9-methylene protons absorbed as a three-proton multiplet between δ 2.65 and 2.90. J_{gem} for the N–CH_2–O protons (−11.6 Hz) was similar to that of the other compounds adopting a similar *cis*-conformation.

Crystallography.—Crystals of (7; R^1 = H, R^2 = Et) formed long thin needles, m.p. 86—93°. Oscillation and Weissenberg photographs were taken about the *a* and *b* axes to establish the space group and approximate unit cell dimensions. For intensity measurements a crystal was mounted about the *b* axis on a Hilger and Watts four-circle diffractometer. The unit cell dimensions were refined by a least squares fit on the positions of 17 peaks found on the diffractometer. Data for *hkl*, $\bar{h}kl$ were collected with Mo-K_α radiation scanning reflections in the Cu sphere. 963 Independent observed reflections with net count $>3\sigma$ were used in structure solution and refinement. All crystallographic calculations used the National Research Council (Ottawa) programs of Ahmed, Hall, Pippy, and Saunders. Atomic scattering factors were taken from ref. 17.

Crystal Data.—$C_{22}H_{42}N_2O_2$, $M = 366$. Monoclinic, $a = 5.08 \pm 0.01$, $b = 23.47 \pm 0.05$, $c = 9.43 \pm 0.03$ Å, $\beta = 106.17 \pm 0.05°$, $U = 1\,078$ Å^3, $D_m = 1.13$ g cm^{-3}, $Z = 2$, $D_c = 1.14$ g cm^{-3}. Space group $P2_1/c$ from systematic absences $h0l$ when $l = 2n + 1$, $0k0$ when $k = 2n + 1$. Mo-K_α radiation, $\lambda = 0.710\,7$ Å.

The structure was solved by use of a symbolic addition procedure using the programs above. After calculation of overall temperature and scale factors from a Wilson plot, normalised structure factors were computed and phase relationships for 369 reflections with $E > 1.5$ set up using the sigma 2 expression. Analysis *via* symbolic addition required only two symbols; the correct phases of 361 reflections were determined. An E map with these reflections revealed the positions of all unique non-hydrogen atoms. Structure factor calculation and four cycles of block-diagonal least-squares refinement, with isotropic temperature factors, reduced R to 0.195. Two more cycles with anisotropic temperature factors lowered R to 0.133. The positions of 18 methine and methylene hydrogens were then computed, using standard C–H bond lengths and angles, and included in a structure factor calculation with temperature factors set at 0.5 above the isotropic temperature factor of attached carbon. The resulting R factor was 0.11, decreased to 0.099 on one cycle of refinement. No significant improvement in R was obtained on further least-squares refinement; all parameter shifts were less than the standard deviation, and as no significant peaks

TABLE 7

Anisotropic temperature factors * for non-hydrogen atoms

Atom no.	B_{11}	B_{22}	B_{33}	B_{23}	B_{13}	B_{12}
C1	0.044 4(45)	0.002 0(2)	0.009 0(10)	0.001 1(7)	−0.005 9(33)	−0.004 6(16)
C2	0.057 4(34)	0.001 9(1)	0.008 7(7)	0.000 8(5)	−0.002 7(24)	0.000 7(11)
C3	0.054 2(52)	0.001 9(2)	0.009 7(10)	−0.000 1(7)	−0.009 6(37)	0.000 1(16)
C4	0.061 0(57)	0.001 8(2)	0.011 9(12)	−0.001 0(7)	−0.006 7(41)	−0.002 6(16)
C5	0.088 0(73)	0.001 4(2)	0.012 4(13)	0.000 6(7)	−0.015 0(47)	−0.005 8(18)
C6	0.052 5(47)	0.001 6(2)	0.008 9(10)	0.001 3(6)	−0.009 0(35)	−0.003 7(15)
C7	0.084 5(79)	0.002 3(2)	0.021 5(19)	−0.000 5(10)	−0.008 9(60)	−0.010 1(22)
C8	0.049 1(51)	0.001 7(2)	0.011 8(11)	0.000 8(7)	0.005 0(37)	−0.003 5(15)
C9	0.037 0(41)	0.001 4(2)	0.009 6(10)	−0.000 0(6)	−0.000 9(31)	−0.000 3(13)
C10	0.118 4(92)	0.001 4(2)	0.017 6(17)	0.000 1(8)	−0.009 6(60)	+0.002 8(21)
C11	0.063 1(58)	0.001 7(2)	0.009 5(10)	−0.000 1(7)	−0.005 0(38)	+0.004 4(16)
C12	0.075 7(62)	0.001 5(2)	0.009 9(10)	0.000 6(7)	−0.011 0(40)	−0.003 7(17)
N13	0.053 0(41)	0.001 6(1)	0.009 0(8)	−0.000 3(6)	−0.007 9(29)	0.001 6(12)

* In the form: $\exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{23}kl + B_{13}hl + B_{12}hk)]$

17 'International Tables for Crystallography', Kynoch Press, Birmingham, 1962.

were found on a difference-Fourier map, refinement was terminated. Unit weights were used throughout. Final atomic co-ordinates are listed in Table 6. Thermal parameters (Table 7) and observed and calculated structure factors are listed in Supplementary Publication No. SUP 21756 (3 pp.).*

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue. Items less than 10 pp. are supplied as full size copies.

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