

## Sterically Crowded Five-membered Heterocyclic Systems. Part 2.<sup>1</sup> Conformation of 2,2,5,5-Tetramethylpyrrolidin-3-ol from Nuclear Magnetic Resonance Spectroscopy, Crystal Structure, and Molecular Mechanics Calculations

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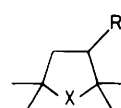
The conformation of 2,2,5,5-tetramethylpyrrolidin-3-ol (**2**) was investigated by <sup>1</sup>H n.m.r. spectroscopy, X-ray diffraction, and molecular mechanics calculations. In solution there is an equilibrium between the forms of the pyrrolidine ring with axial and equatorial orientations of the hydroxy group. The temperature dependence of the <sup>3</sup>J(HH) coupling constants indicates a somewhat lower energy for the axial conformers. The puckering of the CH<sub>2</sub>CHOH part of the ring was estimated from the extended *R* value method, optimized for a five-membered ring, to be 32.9° at 263 K. The crystal structure of (**2**) was solved by direct methods and refined to *R* = 0.045. Two independent molecules in the asymmetric unit adopt nearly identical conformations with the pyrrolidine ring in the <sup>2</sup>T<sub>3</sub> twist form with the hydroxy group and the nitrogen proton in an axial orientation. Molecules are connected by O-H...N hydrogen bonds (O...N = 2.82 Å) into chains along the *z*-axis. There are also weak N-H...O bonds (N...O = 3.40 Å) between molecules in neighbouring chains. The conformational space of (**2**) was explored by molecular mechanics calculations. Several local energy minima were characterized. In all of them the ring is flattened around the fully substituted C-2 or C-5 atoms. The energy difference between these conformations is of the order of 5–7 kJ mol<sup>-1</sup>. The conformation observed in the crystal corresponds very well to the calculated global energy minimum conformation.

Saturated five-membered rings exhibit great conformational mobility. The energy differences between various forms along the pseudorotation pathway are generally small for unsubstituted ring systems.<sup>2</sup> In the presence of substituents, favoured conformations depend on their bulkiness and/or electronegativity.<sup>3</sup> The kind of heteroatom in the ring is also important in establishing a conformational equilibrium.<sup>4,5</sup>

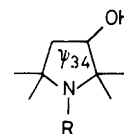
Because of the biological importance of nucleosides and nucleotides, much of the attention directed towards heterocyclic systems has been focused on the conformational behaviour of pentose rings in these compounds. Studies performed in solution and in the solid state, employing a variety of techniques including n.m.r. spectroscopy and X-ray diffraction, led to the recognition of their favoured conformations.<sup>6–8</sup> The availability of experimental data for a large number of nucleosides resulted in the formulation of generalized Karplus-type equations relating vicinal proton–proton coupling constants with H–C–C–H torsion angles and the parametrization of these equations for each pentose ring fragment.<sup>9</sup> Other heterocyclic systems are far less well understood.

Continuing our work on sterically crowded molecules<sup>10,11</sup> we have synthesized a series of 2,2,5,5-tetramethyl-substituted heterocyclic compounds (**1**)<sup>1,12</sup> in order to investigate their conformational preferences. These compounds have one proton at C-3 and two at C-4 and their vicinal spin–spin coupling constants are relatively easy to obtain from <sup>1</sup>H n.m.r. spectra. The application of the Karplus-type formalism permits an estimate of the magnitude of the endocyclic torsion angle  $\psi_{34}$  and thus a gain of some information on the ring conformation in solution.

2,2,5,5-Tetramethylpyrrolidin-3-ol (**2**), the simplest compound of group (**1**) which is solid at room temperature, is a good model for the whole series (**1**). In this paper we present its detailed crystal structure determined by X-ray diffraction,



(1)



- a; X = O, R<sup>1</sup> = OCONHPh, OTs, OH, OMe, NH<sub>2</sub>, Ph (2) R = H  
 b; X = NR<sup>2</sup>, R<sup>1</sup> = OH, R<sup>2</sup> = H, OH, \*O, Me (3) R = \*O  
 c; X = CH<sub>2</sub>, R<sup>1</sup> = OH

compare it with the solution conformation, and report the results of molecular mechanics (MM) calculations.

The oxidation of the amine group of (**2**) yields 2,2,5,5-tetramethylpyrrolidine 1-oxyl radical (**3**). Since the electronic state of the nitrogen atom changes during this reaction it was interesting to compare the crystal structure of (**2**) with the structure of radical (**3**)<sup>13</sup> and determine changes in the conformation of the pyrrolidine ring in both compounds.

### Results and Discussion

**Solution Conformation.**—The conformation of (**2**) in solution was investigated by <sup>1</sup>H n.m.r. spectroscopy. Vicinal spin–spin coupling constants *J*<sup>cis</sup> and *J*<sup>trans</sup> for the CH<sub>2</sub>CHOH fragment within the ring were assigned in agreement with the *syn*-upfield rule.<sup>14</sup> The results are given in Table 1. The <sup>3</sup>J<sub>34</sub><sup>trans</sup> coupling constant increases by 0.7 Hz when the temperature is raised from 263 to 363 K while the <sup>3</sup>J<sub>34</sub><sup>cis</sup> constant is nearly temperature independent. In case of a rapid interconversion between conformers the time-averaged value of *J*<sup>trans</sup> is expressed by equation (1) where *n*<sub>c</sub> is a population fraction of conformers

$$J_{\text{exp}}^{\text{trans}} = n_c J_{\text{cc}} + (1 - n_c) J_{\text{aa}} \quad (1)$$

**Table 1.** Temperature and concentration dependence of coupling constants (Hz) and derived structural parameters for *ca.* 0.4% w/v [<sup>2</sup>H<sub>8</sub>]toluene solutions of (2)

<i>T</i> /K	263	304*	304	363
<sup>3</sup> <i>J</i> <sub>34</sub> <sup>cis</sup>	5.74	5.76	5.86	5.97
<sup>3</sup> <i>J</i> <sub>34</sub> <sup>trans</sup>	5.44	5.80	5.96	6.12
<sup>2</sup> <i>J</i> <sub>44</sub> <sup>gem</sup>	-13.06	-12.94	-12.93	-12.92
<i>R</i> <sub>34</sub>	0.95	1.01	1.02	1.03
ψ <sub>34,av</sub> (°)	32.9	34.5	34.8	35.0

\* For *ca.* 4.0% w/v solution; δ 1.07 (Me), 1.11 (2 × Me), 1.20 (Me), 1.66 and 1.85 (2 H, dq, B and A parts of ABX system, CH<sub>2</sub>), and 3.71 (1 H, m, X part of ABX system, CHOH).

with the carbinol proton of the H-C-OH fragment in an equatorial orientation (*i.e.* the hydroxy group in an axial orientation), *J*<sub>ee</sub> and *J*<sub>aa</sub> are vicinal coupling constants between eq/eq and ax/ax protons, respectively. Basing on a general relationship *J*<sub>aa</sub> ≫ *J*<sub>ee</sub>, the observed dependence of <sup>3</sup>*J*<sub>34</sub><sup>trans</sup> on temperature indicates an increase of the *n*<sub>e</sub> value at low temperatures, *i.e.* an increase of the population of conformers with axial or quasi-axial hydroxy groups (so-called axial conformers). Axial conformers of the ring of (2) are then energetically favoured over equatorial ones. This finding is supported by the observed conformation of (2) in the crystal, where both independent molecules in the asymmetric unit have axially oriented hydroxy groups.

An increase in the concentration of (2) in solution has a similar effect on <sup>3</sup>*J*<sub>34</sub><sup>trans</sup> as a decrease of temperature (Table 1). Since there are more intermolecular hydrogen bonds formed under these conditions, a possible explanation is that hydrogen bonds are more likely to be formed when the hydroxy group is axial thus stabilizing this conformation.

A narrow range of vicinal coupling constants, 5.44 ≤ *J*<sup>vic</sup> ≤ 6.12 Hz, and nearly equal values of *J*<sup>cis</sup> and *J*<sup>trans</sup> for this compound indicate considerable flexibility of the 3,4 fragment of the ring and a rather small energy difference between the axial and equatorial conformers. A similar phenomenon was observed earlier in other five-membered rings.<sup>15</sup>

The <sup>3</sup>*J* coupling constants can be used to estimate the value of the endocyclic torsion angle ψ<sub>34</sub> in the pyrrolidine ring. The presence of an electronegative substituent (hydroxy group) complicates the analysis. Owing to the lack of experimental data on analogous compounds, a reliable determination of the average value of this torsion angle is not straightforward. In practical applications, analysis based on Karplus equation gives reasonable results for systems displaying limited conformational mobility, for which adequate equations related to each molecule fragment can be derived, *e.g.* as in the case of nucleosides.<sup>9</sup>

A more suitable method for the analysis of flexible five-membered rings is the extended *R* value method.<sup>16</sup> The average value of the endocyclic torsion angle ψ<sub>ij</sub> is related to the *R*<sub>ij</sub> = *J*<sub>ij,av</sub><sup>trans</sup>/*J*<sub>ij,av</sub><sup>cis</sup> ratio through relationship (2) where χ is a

$$\operatorname{tg}^2 \psi_{ij,av} = \frac{R_{ij} - K \cos^2 \chi}{K \sin^2 \chi} \quad (2)$$

projection angle of the methylene group in the *i* position on a plane perpendicular to the *ij* bond, and *K* is a constant related to the parameters of the Karplus equation. Lambert<sup>17,18</sup> has suggested the usefulness of the *R* value method in the case of electronegative substituents attached to the ring. He pointed out that, for a rapid interconversion between conformers, the *J*<sup>trans</sup>/*J*<sup>cis</sup> ratio is rather insensitive to the presence of such substituents.

In applications of the *R* value method the assumption χ = 120° was usually made.<sup>16,17</sup> Such an assumption is appropriate

in the case of six-membered rings but not necessarily so for strained five-membered ring systems. Several authors have suggested that in the latter case this angle is greater than 120°.<sup>4,16,19</sup> Cyclopentane is a model compound for five-membered rings. We have analysed the available structural<sup>20</sup> and spectroscopic<sup>21</sup> data and used them to find an estimate of the angle χ. From the <sup>1</sup>*J*(<sup>1</sup>H,<sup>13</sup>C) coupling constant, C-H bond length, C-C-H angle, and with the aid of correlation equations of the iterative maximum overlap approximation (IMOA) method<sup>22</sup> we obtained a value of χ = 124.1°. A similar value for χ was used by Hall *et al.*<sup>19</sup> in their conformational analysis of some D-hexoses. They had selected this value, however, merely as being a few degrees greater than 120°.

Next, the constant *K* was determined from experimental values of the <sup>3</sup>*J*(HH) coupling constants and the average torsion angle in cyclopentane ψ<sub>av</sub> = 26.9° using equation (2). A detailed description of this procedure will be published elsewhere.<sup>23</sup> It led to a simple expression (3) for ψ<sub>av</sub> in terms of a measurable *R*

$$\psi_{av} = \arcsin \operatorname{tg} \sqrt{\frac{R - 0.496}{1.079}} \quad (3)$$

factor.<sup>12</sup> This relation, derived for cyclopentane, may be applied to other saturated five-membered rings satisfying the conditions for the application of the *R* value method.<sup>17</sup> At present it seems to be the only method giving reasonable results from vicinal interproton coupling constants in the case of five-membered rings with heteroatoms and/or electronegative substituents, displaying high flexibility.

The average endocyclic torsion angle ψ<sub>34</sub> calculated from equation (3) is given in Table 1. It indicates considerable puckering of that part of the ring. The ψ<sub>34,av</sub> angle shows some dependence on temperature; it decreases from 35.0° at 363 K to 32.9° at 263 K. Assuming that the puckering of axial and equatorial conformers does not depend on temperature and taking into account the increased population of axial conformers at low temperature, we conclude that the 3,4 fragment of pyrrolidine ring in (2) is less puckered in axial conformers than in equatorial ones. This conclusion is supported by the results of MM calculations (see Table 5). The ψ<sub>34,av</sub> angle calculated at 263 K is in excellent agreement with the data obtained in the crystal. The average value of the C(2)-C(3)-C(4)-C(5) torsion angle in both independent molecules is 32.85°.

**Crystal Structure.**—Preliminary crystallographic data (cell dimensions and space group symmetry) for crystals of a racemate and an enantiomer of (2) obtained from hexane were reported previously by Chion *et al.*<sup>13</sup> Racemic mixture crystallized in the rhombohedral system, space group *Pna*2<sub>1</sub>, with *a*<sub>1</sub> = 5.8, *b*<sub>1</sub> = 10.7, *c*<sub>1</sub> = 14.8 Å, *Z* = 4. Crystals grown in our laboratory from heptane belong to the monoclinic system with *Z* = 8 (see Experimental section). There is an approximate relationship between these two unit cells: 2*a*<sub>1</sub> = *a* + *c*; 2*b*<sub>1</sub> = *a* - *c*; *c*<sub>1</sub> = *b*, with the angle between (*a* + *c*) and (*a* - *c*) being 85.98° and *U*<sub>1</sub> ≈ *U*/2, suggesting the possibility of *B*-type pseudocentring. There was, however, no systematically weak group of reflections in our data set that would indicate a pseudotranslational symmetry and the structure was solved without difficulty. Final atomic parameters are given in Table 2.

To investigate further possible *B*-type pseudocentring we have compared the co-ordinates of two independent molecules, A and B', the latter obtained by a transformation of molecule B by a *c*-glide plane to a position with *y*-co-ordinates similar to those of molecule A. These two molecules have the centres of their pyrrolidine rings translated by the vector (0.520, -0.085,

**Table 2.** Final positional co-ordinates and equivalent isotropic temperature factors (of the non-hydrogen atoms) with e.s.d.s in parentheses

$$B_{eq} = (8\pi^2/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

Atom	Molecule A				Molecule B			
	x	y	z	$B_{eq}/B$	x	y	z	$B_{eq}/B$
N(1)	0.665 5(2)	0.214 8(1)	0.349 7(2)	5.0(1)	0.019 0(2)	0.282 8(1)	0.289 1(1)	4.4(1)
C(2)	0.605 6(2)	0.280 9(1)	0.398 1(2)	5.1(1)	0.078 9(2)	0.210 2(1)	0.383 8(2)	4.7(1)
C(3)	0.584 4(2)	0.231 5(2)	0.505 2(2)	6.4(1)	0.098 9(2)	0.247 0(1)	0.519 8(2)	5.2(1)
C(4)	0.545 6(3)	0.142 4(2)	0.443 1(3)	8.6(2)	0.138 4(2)	0.339 5(2)	0.513 7(2)	6.4(1)
C(5)	0.617 8(2)	0.127 2(1)	0.360 8(2)	6.0(1)	0.066 1(2)	0.366 8(1)	0.363 9(2)	5.4(1)
O(3)	0.697 3(2)	0.227 4(1)	0.628 5(2)	7.6(1)	-0.016 8(1)	0.243 3(1)	0.526 0(1)	6.8(1)
C(21)	0.691 5(3)	0.359 0(2)	0.452 3(3)	7.4(1)	-0.006 3(3)	0.130 9(2)	0.337 2(3)	6.9(1)
C(22)	0.479 2(2)	0.309 3(2)	0.283 1(3)	6.3(2)	0.2071 (2)	0.188 2(2)	0.392 6(3)	6.0(1)
C(51)	0.728 1(3)	0.064 8(2)	0.431 7(4)	8.3(2)	-0.044 9(3)	0.425 5(2)	0.336 9(3)	6.5(1)
C(52)	0.529 0(4)	0.092 1(2)	0.220 4(3)	9.0(2)	0.152 6(3)	0.411 3(2)	0.317 3(3)	8.4(2)
H(N1)	0.745(3)	0.215(1)	0.410(3)	6.3(6)	-0.057(2)	0.275(1)	0.266(2)	3.9(5)
H(O3)	0.677(2)	0.251(2)	0.692(3)	8.0(7)	-0.002(3)	0.231(2)	0.622(4)	11.4(9)
H(31)	0.517(2)	0.261(1)	0.519(2)	5.0(5)	0.162(2)	0.208(1)	0.597(2)	4.7(4)
H(41)	0.566(3)	0.097(2)	0.515(3)	9.5(8)	0.122(2)	0.374(2)	0.568(3)	6.5(6)
H(42)	0.450(3)	0.140(2)	0.382(3)	8.3(8)	0.236(2)	0.344(1)	0.545(2)	6.7(6)
H(211)	0.776(2)	0.335(2)	0.522(2)	6.0(5)	-0.085(3)	0.140(2)	0.334(3)	8.2(8)
H(212)	0.701(3)	0.392(2)	0.373(3)	9.2(8)	-0.017(2)	0.109(2)	0.248(3)	7.6(6)
H(213)	0.655(3)	0.399(2)	0.484(3)	8.8(8)	0.030(2)	0.083(2)	0.403(3)	6.7(6)
H(221)	0.445(2)	0.358(2)	0.314(3)	7.5(7)	0.241(2)	0.135(2)	0.450(2)	6.5(6)
H(222)	0.423(3)	0.259(2)	0.248(3)	8.2(8)	0.265(3)	0.238(2)	0.420(3)	7.8(7)
H(223)	0.489(3)	0.339(2)	0.218(3)	8.2(8)	0.192(2)	0.165(2)	0.305(3)	8.1(7)
H(511)	0.784(3)	0.088(2)	0.527(3)	10.6(10)	-0.101(2)	0.396(2)	0.362(2)	6.1(6)
H(512)	0.696(2)	0.005(2)	0.435(2)	7.3(6)	-0.013(2)	0.483(2)	0.387(3)	8.6(7)
H(513)	0.771(3)	0.053(2)	0.375(4)	10.4(9)	-0.103(3)	0.433(2)	0.237(3)	7.9(7)
H(521)	0.587(3)	0.079(2)	0.193(3)	8.9(9)	0.187(2)	0.458(2)	0.369(3)	6.7(6)
H(522)	0.488(3)	0.039(2)	0.233(3)	8.7(8)	0.226(3)	0.375(2)	0.334(3)	7.7(7)
H(523)	0.458(3)	0.132(2)	0.174(3)	8.9(9)	0.100(3)	0.428(2)	0.220(3)	8.2(7)

**Table 3.** Bond lengths (Å), valence and torsion angles (°)

	Bonds		Angles			
	Molecule A	Molecule B	Molecule A	Molecule B		
N(1)-C(2)	1.488(3)	1.477(2)	C(3)-C(4)	1.510(4)	1.511(3)	
N(1)-C(5)	1.493(3)	1.501(2)	C(3)-O(3)	1.411(2)	1.422(3)	
C(2)-C(3)	1.545(4)	1.542(3)	C(4)-C(5)	1.553(5)	1.547(3)	
C(2)-C(21)	1.512(3)	1.516(3)	C(5)-C(51)	1.521(4)	1.516(4)	
C(2)-C(22)	1.521(3)	1.529(4)	C(5)-C(52)	1.529(3)	1.528(5)	
average C-H		0.99				
			Torsion angles*			
			Molecule A	Molecule B	Molecule A	Molecule B
C(2)-N(1)-C(5)	108.4(2)	108.7(1)	C(4)-C(3)-O(3)	111.0(2)	111.9(2)	
N(1)-C(2)-C(3)	103.6(2)	103.6(2)	C(3)-C(4)-C(5)	106.1(2)	106.2(2)	
N(1)-C(2)-C(21)	109.7(2)	109.8(1)	N(1)-C(5)-C(4)	104.9(2)	104.3(2)	
N(1)-C(2)-C(22)	110.1(2)	110.2(2)	N(1)-C(5)-C(51)	110.0(2)	109.8(2)	
C(3)-C(2)-C(21)	114.0(2)	113.8(2)	N(1)-C(5)-C(52)	109.8(2)	109.3(2)	
C(3)-C(2)-C(22)	110.0(2)	109.6(2)	C(4)-C(5)-C(51)	111.8(2)	111.6(2)	
C(21)-C(2)-C(22)	109.3(2)	109.7(2)	C(4)-C(5)-C(52)	111.0(2)	112.0(2)	
C(2)-C(3)-C(4)	102.3(2)	101.9(2)	C(51)-C(5)-C(52)	109.2(2)	109.7(2)	
C(2)-C(3)-O(3)	110.9(2)	109.6(1)				
C(5)-N(1)-C(2)-C(3)	30.5	30.9	C(3)-C(4)-C(5)-N(1)	-14.5	-15.3	
C(5)-N(1)-C(2)-C(21)	152.6	152.8	C(3)-C(4)-C(5)-C(51)	104.7	103.2	
C(5)-N(1)-C(2)-C(22)	-87.1	-86.3	C(3)-C(4)-C(5)-C(52)	-133.1	-133.4	
N(1)-C(2)-C(3)-C(4)	-38.4	-39.1	C(4)-C(5)-N(1)-C(2)	-10.2	-10.0	
N(1)-C(2)-C(3)-O(3)	80.0	79.5	C(51)-C(5)-N(1)-C(2)	-130.7	-129.7	
C(21)-C(2)-C(3)-C(4)	-157.6	-158.4	C(52)-C(5)-N(1)-C(2)	109.1	109.9	
C(22)-C(2)-C(3)-C(4)	79.2	78.5	C(21)-C(2)-C(3)-O(3)	-39.2	-39.7	
C(2)-C(3)-C(4)-C(5)	32.4	33.3	C(22)-C(2)-C(3)-O(3)	-162.4	-162.8	
O(3)-C(3)-C(4)-C(5)	-85.9	-83.7				

\* Standard deviation for torsion angles is 0.4°.

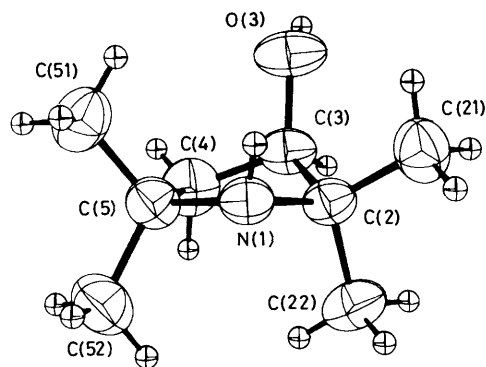


Figure 1. An ORTEP view of the molecule B in the *R* configuration with thermal ellipsoids at the 50% probability level

0.497). They form, however, an enantiomeric pair and are not parallel (see Figure 2).

Both independent molecules adopt nearly identical conformations. Bond lengths, valence, and torsion angles are given in Table 3 and a view of molecule B (*R* configuration) with the numbering scheme is shown in Figure 1. The pyrrolidine ring is described by puckering parameters<sup>24</sup>  $q_A = 0.374 \text{ \AA}$ ,  $\phi_A = 238.0^\circ$  (or  $58.0^\circ$  for the *S* enantiomer) and  $q_B = 0.380 \text{ \AA}$ ,  $\phi_B = 238.8^\circ$  (or  $58.8^\circ$  for the *S* enantiomer) for molecules A and B, respectively, where the sequence of atoms N(1), C(2)–C(5) was taken. The ring is flattened around C(5) and is best described as a  ${}^2T_3$  twist form (ideal  $\phi = 234^\circ$ ) with approximate two-fold symmetry about the axis passing through C(5) and the midpoint of C(2)–C(3) bond. The asymmetry parameter<sup>25</sup> is  $C_2^{2-3} = 3.33$  and  $4.10^\circ$  for molecule A and B respectively. The hydroxy group and the amine hydrogen are in a *cis* relationship and both assume an axial orientation to the ring. The shortest distance between the methyl groups at C(2) and C(5) is  $3.524 \text{ \AA}$  in both molecules. There is a close contact between the hydroxy group and one of the methyl groups at the C(2) atom [ $O(3) \cdots C(21) = 2.813(4)$  and  $2.789(4) \text{ \AA}$  in molecules A and B, respectively].

Among all possible conformations of a five-membered ring the  ${}^2T_3$  (or  ${}^3T_2$ ) conformer has the largest C(2)–C(3) endocyclic torsion angle and maintains the substituents at C(2) and C(3) atoms in the most staggered position. Similar conformations of both molecules despite differences in their surrounding would indicate that such a conformation corresponds to the lowest energy state of the molecule of (2). The same form of pyrrolidine ring was observed in 2,2,5,5-tetramethyl-3-phenylethynylpyrrolidin-3-ol<sup>11</sup> ( $q = 0.41 \text{ \AA}$ ,  $\phi = 55.9^\circ$ ) and in spiro-[6-ethyl-1,5-dimethyl-2-oxa-6-azabicyclo[3.3.0]nona-3,2'-(1'-ethyl-3'-methylpyrrolidin-3'-ol)]<sup>26</sup> ( $q = 0.42 \text{ \AA}$ ,  $\phi = 51.0^\circ$ ), where C(2) and C(3) are fully substituted. Also, a change of the heteroatom in the five-membered ring from nitrogen to oxygen seems to have little effect on the most stable conformation since the molecule of 3-dimethoxyphosphoryl-2,2,5,5-tetramethyloxolan-3-ol<sup>27</sup> maintains a  ${}^2T_3$  pucker with  $q = 0.39 \text{ \AA}$  and  $\phi = 240.3^\circ$  (or  $60.3^\circ$ ) in the crystal.

Compound (3), the *N*-oxyl derivative of (2), adopts a different conformation in the solid state. The puckering parameters for the pyrrolidine ring are:  $q = 0.35 \text{ \AA}$ ,  $\phi = 80.7^\circ$ . The ring is flattened around the N atom and forms a  ${}^3T_4$  twist with the two-fold axis passing through the N atom rather than C(5) as in the case of amine (2). Such a conformation has also been observed in other pyrrolidine *N*-oxyl radicals<sup>28</sup> and seems to be their energetically preferred form. A change in the hybridization of the N atom towards  $sp^2$  results in an opening of the CNC angle by  $6.7^\circ$ . Similar effect has also been observed in six- and seven-

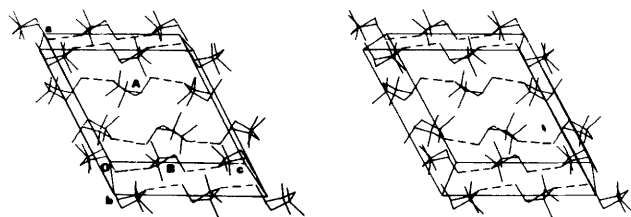
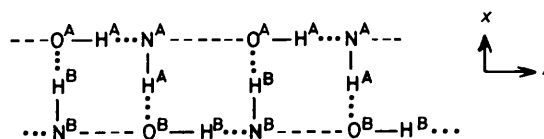


Figure 2. A stereoscopic view (PLUTO) showing the packing of molecules. Hydrogen bonds are marked with dashed lines



Scheme.

membered rings containing the *N*-oxyl moiety.<sup>29,30</sup> An opening of the CNC angle may constitute one of the main factors in a change of conformation of the five-membered ring from a  ${}^3T_2$  form observed in (2) to a  ${}^3T_4$  twist form in (3) since this angle attains its largest value in such a conformation along the pseudorotation pathway, thus reducing the strain in the ring. Another difference between amine (2) and radical (3) is the orientation of the hydroxy group. In a molecule of (3) this group is equatorial, most probably because in an axial orientation it would clash with axial methyl group at C(5). The methyl groups at C(2) and C(5) are further away in (3) than they are in (2), the shortest distance between them in (3) being  $4.008(8) \text{ \AA}$ .

**Crystal Packing.**—Packing of molecules in the crystal is shown in Figure 2. The hydrogen bonds are shown in the Scheme. Their geometry is given in Table 4. Each molecule forms four intermolecular hydrogen bonds of which two are relatively strong ( $O \cdots N = 2.82 \text{ \AA}$ ) and two are weak ( $N \cdots O = 3.40 \text{ \AA}$ ). Hydrogen bonds between molecules related by a *c*-glide plane join them into chains along the *z*-axis. Neighbouring chains of molecules A and B are connected by weak hydrogen bonds into pairs (along the *x*-axis). A closer approach of molecules A and B that would permit the formation of stronger hydrogen bonds between them is prevented by steric repulsion between the methyl groups C(21) and C(51) of both molecules. The shortest, important, intermolecular  $H \cdots H$  distances in these interactions are  $2.39(7)$  and  $2.44(7) \text{ \AA}$ . There is another close contact between molecules A and B of  $2.13(8) \text{ \AA}$  but it is not altered significantly on approach of molecules A and B along the direction of the hydrogen bond between them.

**Molecular Mechanics Calculations.**—To explore the conformational space of the pyrrolidine ring in (2) we employed the methods of molecular mechanics. There are several sets of force field parameters available in the literature.<sup>31</sup> One of the most advanced and widely applied is the force field developed by Allinger and his co-workers.<sup>32</sup> In our calculations we have used their MM2 parametrization.\* Since the parameters for torsion energy of the N–C–C–O angle were not defined in the MM2 set, we assigned them the same values as for the O–C–C–O angle.

\* The stretch-bend terms were not included in our calculations. That part of the energy accounts for *ca.* 10% of the bending energy and may be neglected without introducing any significant effects to the minimized conformation.

**Table 4.** Geometry of hydrogen bonds

	O-H or N-H (Å)	O...N (Å)	H...O or H...N (Å)	O...H...N (°)
O <sup>A</sup> (3)-H <sup>A</sup> (O3)...N <sup>A</sup> (1)	0.93(4)	2.834(2)	1.92(4)	168(2)
O <sup>B</sup> (3)-H <sup>B</sup> (O3)...N <sup>B</sup> (1)	1.03(4)	2.814(2)	1.79(4)	176(2)
N <sup>A</sup> (1)-H <sup>A</sup> (N1)...O <sup>B</sup> (3)	0.87(3)	3.391(2)	2.56(3)	164(2)
N <sup>B</sup> (1)-H <sup>B</sup> (N1)...O <sup>A</sup> (3)	0.83(3)	3.404(2)	2.60(3)	163(2)

**Table 5.** Results of energy minimization of 2,2,5,5-tetramethylpyrrolidin-3-ol (*R* configuration)

Starting conformation	<sup>1</sup> T <sub>2</sub>	<sup>3</sup> T <sub>2</sub>	<sup>3</sup> T <sub>4</sub>	<sup>5</sup> T <sub>4</sub>	<sup>5</sup> T <sub>1</sub>	<sup>2</sup> T <sub>1</sub>	<sup>2</sup> T <sub>3</sub>	<sup>4</sup> T <sub>3</sub>	<sup>4</sup> T <sub>5</sub>	<sup>1</sup> T <sub>5</sub>
Ideal φ (°)	18	54	90	126	162	198	234	270	306	342
<i>cis</i> isomer*										
Final conformation	<sup>3</sup> T <sub>2</sub>	<sup>3</sup> T <sub>2</sub>	<sup>3</sup> T <sub>2</sub>	E <sub>4</sub>	E <sub>4</sub>	<sup>2</sup> T <sub>3</sub>	<sup>2</sup> T <sub>3</sub>	<sup>2</sup> T <sub>3</sub>	<sup>4</sup> T <sub>5</sub>	<sup>4</sup> T <sub>5</sub>
φ (°)	58.6	58.8	59.2	112.6	112.9	239.6	243.5	240.5	307.5	309.4
q (Å)	0.391	0.390	0.390	0.376	0.375	0.356	0.361	0.356	0.346	0.346
E <sub>tot</sub> /kJ mol <sup>-1</sup>	76.01	76.01	76.01	78.82	78.83	76.59	76.49	76.59	77.88	77.85
ψ <sub>34</sub> (°)	33.5	33.5	33.7	34.9	34.8	31.0	32.4	31.2	27.9	27.0
Hydroxy	eq	eq	eq	eq	eq	ax	ax	ax	ax	ax
<i>trans</i> isomer*										
Final conformation	<sup>3</sup> E	<sup>3</sup> E	<sup>5</sup> T <sub>4</sub>	<sup>5</sup> T <sub>4</sub>	<sup>5</sup> T <sub>4</sub>	<sup>2</sup> T <sub>3</sub>	<sup>2</sup> T <sub>3</sub>	<sup>2</sup> T <sub>3</sub>	<sup>4</sup> T <sub>5</sub>	<sup>4</sup> T <sub>5</sub>
φ (°)	66.4	67.2	117.4	119.7	120.7	233.8	236.1	234.1	297.7	300.1
q (Å)	0.379	0.380	0.386	0.385	0.385	0.369	0.373	0.368	0.329	0.329
E <sub>tot</sub> /kJ mol <sup>-1</sup>	78.38	78.37	76.13	76.09	76.10	73.88	73.90	73.88	80.77	80.77
ψ <sub>34</sub> (°)	34.9	35.2	34.4	33.6	33.3	30.0	31.1	30.0	29.4	28.8
Hydroxy	eq	eq	eq	eq	eq	ax	ax	ax	ax	ax

\* Relation with respect to the hydroxy group and the nitrogen proton.

All calculations have been performed with the EMIN program<sup>33</sup> written by one of us (M. C.). Atomic co-ordinates for ten twist conformers along the pseudorotation pathway have been calculated with the ring puckering parameters  $q = 0.374$  Å and  $\varphi \approx (18 + n \cdot 36)^\circ$ . Such puckering corresponded to the conformation observed in the crystal. Each model was then submitted to energy minimization and the resulting co-ordinates were used to calculate molecular geometry. The lone electron pairs on oxygen and nitrogen atoms were explicitly included in the calculations. In such case a possible inversion of configuration on the nitrogen atom of the amine group, which leads to a lower energy of the molecule, could not be reproduced automatically in the process of energy minimization. To overcome this problem we have carried out the calculations for both configurations of the hydrogen and the lone pair on the nitrogen atom, that is for *cis* and *trans* relations of the nitrogen proton and the hydroxy group. Envelope conformers were not used as starting points in our calculations. When such a conformation corresponded to a local energy minimum, as e.g. E<sub>4</sub>, it could be reached from a neighbouring starting twist conformer.

To detect the influence of N-C-C-O torsion energy parameters on the results, we have repeated the calculations for two starting conformations using parameters as for the N-C-C-N angle, significantly different from O-C-C-O angle parameters in the MM2 force field. The minimized geometry was nearly identical in both calculations but the difference in energy between axial and equatorial conformer increased in favour of the former. In further discussion we comment on relative rather than absolute values of energy differences.

The results of our calculations are summarized in Table 5. Along the pseudorotation pathway of (2) there are eight conformations corresponding to local energy minima. Ordered

increasingly in energy they are <sup>3</sup>T<sub>2</sub> (e), <sup>2</sup>T<sub>3</sub> (a), <sup>4</sup>T<sub>5</sub> (a), and E<sub>4</sub> (e) for the *cis*-isomer and <sup>2</sup>T<sub>3</sub> (a), <sup>5</sup>T<sub>4</sub> (e), <sup>3</sup>E (e), and <sup>4</sup>T<sub>5</sub> (a) for the *trans*-isomer, where (a) and (e) stands for the axial and equatorial hydroxy group, respectively. When the N-C-C-N angle parameters are used (see above) the <sup>2</sup>T<sub>3</sub><sup>cis</sup> (a) conformer has lower energy than the <sup>3</sup>T<sub>2</sub><sup>cis</sup> (e) one. A global energy minimum corresponds to the <sup>2</sup>T<sub>3</sub> (a) *trans*-conformer. The energy difference between conformers is rather low; the greatest difference is of the order of 4.5–7.5 kJ mol<sup>-1</sup>, depending on the parametrization of the N-C-C-O torsion energy. Two of the lowest energy conformers are axial and two are equatorial. There is a good correlation with the solution studies which indicated the coexistence of axial and equatorial conformers, with the former having somewhat lower energy. The comparison of the ψ<sub>34</sub> angle in the low energy forms of the ring shows that its average value is 3° lower in the axial than in the equatorial conformers (30.4° versus 33.5°). This is also in agreement with the n.m.r. studies. A change of configuration on nitrogen atom from *trans* to *cis* (relative to the hydroxy group) in the lowest energy <sup>2</sup>T<sub>3</sub> (a) conformer increases the energy of the molecule by 2.5 kJ mol<sup>-1</sup> (independent of N-C-C-O parametrization since this angle is nearly identical in both conformers). The <sup>3</sup>T<sub>2</sub> (e) form has, on the other hand, lower energy for the *cis* isomer. In all conformers corresponding to the local energy minima, the ring is least puckered around fully substituted C-2 or C-5. The twist forms <sup>3</sup>T<sub>2</sub> and <sup>2</sup>T<sub>3</sub> have the methyl groups on C-5 nearly eclipsed with hydrogens on the neighbouring N-1 and C-4. In <sup>4</sup>T<sub>5</sub> and <sup>5</sup>T<sub>4</sub> forms the hydroxy group and one of the methyl groups on C-2 are nearly eclipsed.

As Table 5 shows, conformations obtained by energy minimization from different starting conformers, although very similar, are not identical. The partition of energy between various types of interactions, and endocyclic torsion angles in

**Table 6.** Partition of energy (kJ mol<sup>-1</sup>) among stretching ( $E_s$ ), bending ( $E_b$ ), torsion ( $E_t$ ), and van der Waals interactions ( $E_w$ ) for local minimum energy conformations of (2),\* and endocyclic torsion angles (°)†

Conformation	$E_s$	$E_b$	$E_t$	$E_w$	$E_{tot}$	$\psi_{12}$	$\psi_{23}$	$\psi_{34}$	$\psi_{45}$	$\psi_{15}$
Crystal ‡						30.7	-38.8	32.85	-14.9	-10.1
<sup>2</sup> T <sub>3</sub> <sup>trans</sup> (a)	4.67	14.04	40.56	14.61	73.88	32.3	-38.1	30.0	-11.2	-13.3
	4.66	13.98	40.65	14.60	73.88	32.1	-38.0	30.0	-11.4	-13.1
	4.71	14.31	40.37	14.51	73.90	31.6	-38.5	31.1	-12.8	-11.9
<sup>3</sup> T <sub>2</sub> <sup>cis</sup> (e)	4.47	15.36	42.57	13.60	76.01	-31.6	40.1	-33.5	15.0	10.5
<sup>5</sup> T <sub>4</sub> <sup>trans</sup> (e)	4.65	15.17	41.59	14.71	76.09	9.3	15.9	-33.6	39.5	-30.7
<sup>2</sup> T <sub>3</sub> <sup>cis</sup> (a)	5.03	12.86	42.11	16.50	76.49	27.1	-36.8	32.4	-16.9	-6.5
	5.02	12.48	42.32	16.77	76.59	28.2	-36.6	31.2	-14.9	-8.4
	5.02	12.54	42.21	16.83	76.59	28.7	-36.7	31.0	-14.4	-9.0
<sup>4</sup> T <sub>5</sub> <sup>cis</sup> (a)	4.92	14.06	42.81	16.06	77.85	-14.5	-8.5	27.0	-35.9	31.6
<sup>3</sup> E <sup>trans</sup> (e)	4.75	13.90	44.30	15.42	78.37	-26.4	38.3	-35.2	19.9	4.2
$E_4^{cis}$ (e)	5.00	13.66	43.25	16.91	78.82	4.0	19.8	-34.9	37.8	-26.3
<sup>4</sup> T <sub>5</sub> <sup>trans</sup> (a)	5.21	12.63	44.84	18.09	80.77	-8.2	-13.4	28.8	-34.2	26.4
	5.18	12.65	44.96	17.98	80.77	-6.7	-14.7	29.4	-34.0	25.4

\* Results obtained from various starting conformations are given for some conformers. †  $\psi_{ij}$  is the endocyclic torsion angle along the  $i$ - $j$  bond in the ring. ‡ Average values for molecule A and B are given.

the ring are given in Table 6. Despite very small differences in the total energy some torsion angles differ by 1–2°. A small change in one part of the molecule is accompanied by a concerted change in another part, compensating each other in total energy. The largest changes in energy are usually in torsion and van der Waals terms.

An interesting example of the important role played by van der Waals interactions is the <sup>4</sup>T<sub>5</sub><sup>trans</sup> (a) conformer. It has the highest energy of all local minima. The neighbouring <sup>4</sup>T<sub>3</sub> twist form refines to the lowest energy <sup>2</sup>T<sub>3</sub> form. What makes an energy barrier between these conformations? The greatest difference between <sup>2</sup>T<sub>3</sub><sup>trans</sup> and <sup>4</sup>T<sub>5</sub><sup>trans</sup> forms is in torsion and van der Waals interactions (see Table 6). The largest energy terms in van der Waals interactions in the latter form arise from close contacts between the axial H(N) atom and the methyl groups. From a Dreiding model it is obvious that in order to change the conformation towards <sup>2</sup>T<sub>3</sub>, this hydrogen atom would have to cross both NCC<sub>Me</sub> planes, what corresponds to a maximum of van der Waals energy [the shortest Me...H(N) distance]. To check if the interactions of this hydrogen atom with methyl groups are responsible for the build-up of an energy barrier, we repeated the energy minimization for the <sup>4</sup>T<sub>5</sub> conformer with the H(N) atom removed. As was expected, this time the molecule converged to a <sup>2</sup>T<sub>3</sub> form.

A comparison of conformation of (2) observed in the crystal with the results of molecular mechanics calculations shows good agreement. Both molecules exist in the crystal in a *cis* configuration with H(N) atoms involved in strong N–H...O hydrogen bonds. The observed conformation is intermediate between <sup>2</sup>T<sub>3</sub> conformation calculated for *cis*- and *trans*-isomers, but somewhat closer to the latter ( $\varphi^{trans} = 236^\circ$ ,  $\varphi_{exp} = 238^\circ$ ,  $\varphi^{cis} = 240$ – $243^\circ$ ; see also data in Table 6). One could speculate that molecules of (2) enter the crystal in their lowest energy <sup>2</sup>T<sub>3</sub> conformation and are then locked in a *cis* configuration by the formation of hydrogen bonds. A shift of electron density of the hydrogen atom towards nitrogen, amplified by the interaction with the oxygen atom, decreases the van der Waals radius of the hydrogen atom and results in moving the conformation towards the <sup>2</sup>T<sub>3</sub><sup>trans</sup> form.

**Conclusions.**—Despite the four methyl groups attached to the ring, the molecule of (2) is very flexible. In solution there is a mixture of conformers with axial and equatorial hydroxy groups. N.m.r. data analysis, MM calculations, and the conformation adopted in the crystal indicate that the axial conformers are energetically favoured over the equatorial ones.

The energy difference is, however, small (*ca.* 2 kJ mol<sup>-1</sup> from MM calculations). Both n.m.r. investigations and the MM approach show that the puckering of the 3,4 fragment of the pyrrolidine ring in (2) is smaller in axial conformers than in equatorial ones. The value of  $\psi_{34}$  angle calculated from n.m.r. data by the optimized *R* value method agree very well with the crystal structure and MM calculations.

The <sup>2</sup>T<sub>3</sub> (a) conformation observed in the crystal is well reproduced by MM calculations. The conformation corresponding to the global energy minimum differs from that observed by the inverted configuration on the nitrogen atom. An inversion of configuration could be compensated energetically in the crystal by the formation of convenient hydrogen bonds. In all conformers corresponding to local energy minima the ring is flattened around the fully substituted C-5 or C-2.

For other compounds of series (1), having larger R<sup>1</sup> groups, conformers <sup>5</sup>T<sub>4</sub> and <sup>4</sup>T<sub>5</sub> with the ring flattened around C-2 may be less significant. A nearly eclipsed orientation of R<sup>1</sup> with respect to one of the methyl groups on C-2 would result in severe steric repulsion.

## Experimental

**N.m.r. Data.**—<sup>1</sup>H N.m.r. spectra were recorded in the continuous wave mode at 100.1 MHz using a Varian XL-100 spectrometer equipped with a variable-temperature accessory. Samples were prepared as *ca.* 0.4 and 4.0% w/v solutions in [<sup>2</sup>H<sub>8</sub>]toluene with tetramethylsilane as an internal reference standard. The temperature dependence of coupling constants was investigated at 263–363 K. Measurements at lower temperature were impossible due to solubility problems. Interproton coupling constants were obtained by a second-order analysis<sup>34</sup> of the three-spin slightly perturbed ABX system from spectra recorded at sweep width of 100 Hz; they are considered accurate to within  $\pm 0.10$  Hz.

**Crystal Data.**—C<sub>8</sub>H<sub>17</sub>NO, *M* = 143.23, m.p. 341.7–342.2 K, monoclinic, *a* = 11.98(3), *b* = 15.39(4), *c* = 11.26(3) Å,  $\beta$  = 118.10(6)°, *U* = 1 831.3 Å<sup>3</sup>, *Z* = 8, *D<sub>c</sub>* = 1.039 g cm<sup>-3</sup>, *F*(000) = 640, space group *P*2<sub>1</sub>/*c*, monochromated Cu-K<sub>α</sub> radiation. Prismatic crystals were obtained from heptane. A crystal with the dimensions 0.22 × 0.20 × 0.43 mm was mounted on a Syntex P2<sub>1</sub> diffractometer and was used to collect 2 469 independent reflections in the 2θ range of 3–120°, with the ω–2θ scan mode. Cell dimensions were refined from setting angles of 15 high-angle reflections. There were 2 000

reflections with  $I > 3\sigma(I)$  used in the refinement. The structure was solved by direct methods (SHELX<sup>35</sup>) and refined with the full-matrix least-squares algorithm. There are two molecules in the asymmetric unit. All atoms, except hydrogens, were refined with anisotropic temperature factors. There were 318 refined parameters; the average and maximum shift/e.s.d. ratio in the last cycle of refinement was 0.18 and 0.71, respectively. At the convergence the agreement factors were:  $R = 0.045$  and  $R_w (= \sum w^{\frac{1}{2}} \Delta / \sum w^{\frac{1}{2}} |F_o|) = 0.052$  with the weights  $w^{-1} = \sigma^2(F_o) + 0.0007 F_o^2$ .

Anisotropic thermal parameters are listed in Supplementary Publication No. SUP 56284 (3 pp.).\*

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\* For details of Supplementary Publications, see Instructions for Authors in *J. Chem. Soc., Perkin Trans. 2*, 1985, Issue 1.

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