

Structural Studies of Synthetic Analgetics. III.* The Crystal and Molecular Structure of the Rhombohedral form of (\pm)- β -Promedol Alcohol

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The rhombohedral crystals of (\pm)- β -1,2,5-trimethyl-4-phenylpiperidin-4-ol are in space group $R\bar{3}$, with $a=29.754$, $c=7.713$ Å, and $Z=18$. The structure has been determined by the direct method and has been refined to $R=0.054$ for 1410 observed reflexions. The molecular structure is the same as that found for the monoclinic form except for a substantial change in the direction of the O-H bond and small changes in some of the valence angles. The piperidine ring has a skewed chair form, the phenyl ring is axial, and the three methyl groups are equatorial. Each six molecules which are related by the $\bar{3}$ symmetry are linked together by O-H...N' bonds into a hexameric ring of alternating (+) and (-) molecules.

Introduction

A mixture of monoclinic and rhombohedral crystals was produced when β -promedol alcohol, the most active isomer, was crystallized from a 30–60° petroleum spirit solution. The rhombohedral crystals were bigger in size and occurred in larger amounts than the monoclinic. X-ray studies of both forms were undertaken in order to establish whether the difference was in the molecular conformation or just in the packing. Furthermore, there was also the remote possibility of the sample being a mixture of the β isomer and the geometrically possible but hard to isolate δ isomer (Casy & McErlane, 1972; Shvetsov & Kucherov, 1959). The crystal and molecular structure of the monoclinic form was described in part II of this series by De Camp & Ahmed (1972), and that of the rhombohedral crystals is described in this part.

Crystal data

(\pm)- β -1,2,5-Trimethyl-4-phenylpiperidin-4-ol
C₁₄H₂₁ON; F.W. 219.33.

Source: A. F. Casy; recrystallized from 30–60° petroleum spirit.

Crystal habit: Short hexagonal prisms, terminated by {111}, m.p. 104.5–105.0°C.

Crystal dimensions: 0.5 × 0.5 × 0.2 mm.

Unit cell: Rhombohedral, $R\bar{3}$, hkl present only for $-h+k+l=3n$.

Indices and atomic parameters are referred to the hexagonal cell $a=29.754$ (4), $c=7.713$ (1) Å, $V=5913.5$ Å³, $Z=18$, $D_x=1.109$, $D_m=1.110$ g.cm⁻³ (floatation in KI solution, 25°C).

Radiation: Cu K α and Ni filters, $\lambda(K\alpha_1)=1.54050$, $\lambda(K\alpha_2)=1.54434$ Å, $\mu(\text{Cu})=5.51$ cm⁻¹.

Experimental

Intensities

Automatic 4-circle diffractometer, a^* and c^* oriented in equatorial plane, θ - 2θ scan, two background measurements per reflexion, $\sin \theta/\lambda \leq 0.586$. Number of reflexions scanned = 2195, number observed = 1410, number unobserved = 785, number of observations per parameter = 6.2.

Corrections

(1) For crystal decomposition, empirically with the aid of two standard reflexions; (2) 1/Lp.

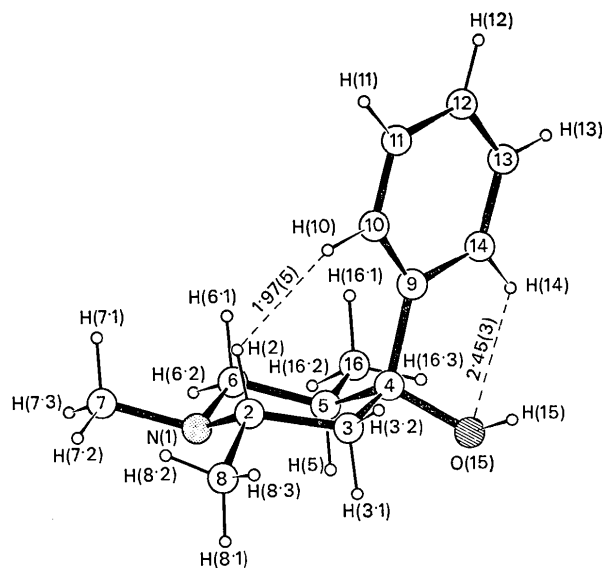


Fig. 1. Molecular structure of β -promedol alcohol in the rhombohedral crystals. The short intramolecular contacts are in Å.

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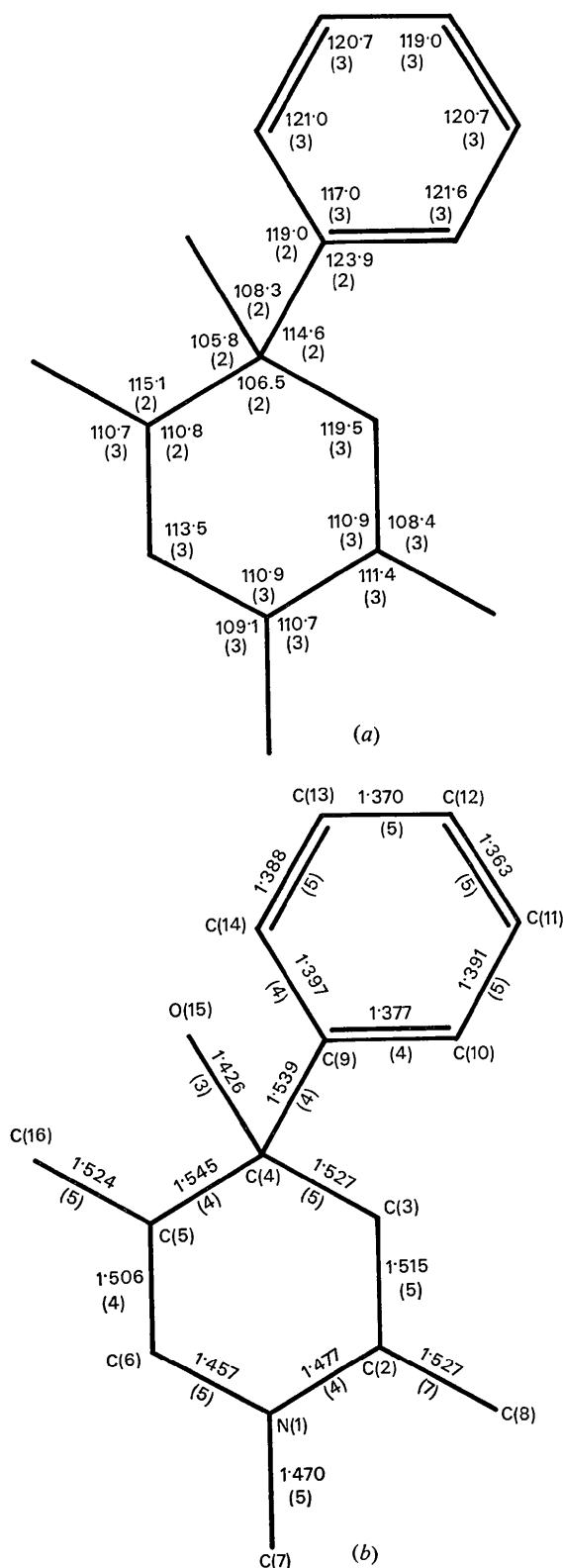


Fig. 2. (a) Bond angles (°) and (b) lengths (Å), not corrected for thermal vibration, and their e.s.d.'s in parentheses referring to the least significant digits. The angles C(5)–C(4)–C(9) and C(3)–C(4)–O(15) are 113.4 (2) and 107.8 (2)° respectively.

Structure determination

For $R\bar{3}$, the relations $F(hkl) = F(ihl) = F(kil) = F(\bar{h}\bar{k}\bar{l})$ where $i = -h - k$ are to be included in the Σ_2 search, and the origin is to be defined by a single reflexion with l odd (Flippin, Karle & Karle, 1970). Reflexion $89\bar{1}$ ($|E| = 3.82$) was selected for origin definition. Also, since the Σ_2 relations involving equivalent $hk0$ reflexions with large $|E|$ have a high probability of E being +ve, the 850 reflexion with $|E| = 3.11$ was assumed to be +ve, where the corresponding quantity $A = \sigma_3 \sigma_2^{-3/2} |E(hk0) \cdot E(ih0) \cdot E(ki0)| = 1.712$ and the probability $P_+(E_h) = \frac{1}{2} + \frac{1}{2} \tanh A = 0.968$.†

All C, N, O atoms were located from E map with 241 signed independent reflexions for which $|E| \geq 1.50$; and all H atoms from a difference map computed after partial refinement.

Refinement

By block-diagonal least-squares minimizing $\sum w(\Delta F)^2$, where $w = 1/\{1 + [(|F_o| - 40)/30]^4\}$ and $7.5 \leq |F_o| \leq 413.4$, and excluding unobserved reflexions with $|F_c| < |F_{th}|$. Mean and maximum $\Delta/\sigma = 0.2$ and 1.1 in final cycle.

Final agreement

$R = 0.054$ and $R_w = 0.066$ for the 1410 observed reflexions; $|F_c| < |F_{th}|$ for 748 unobserved reflexions, and $|F_{th}| < |F_c| \leq 1.3|F_{th}|$ for 37 unobserved.

Residual electron density

$$|\Delta\rho|_{\max} \leq 0.15, \sigma(\rho) = 0.10 \text{ e.}\text{\AA}^{-3}.$$

f -curves

Hanson, Herman, Lea & Skillman (1964) for C, N, O; Stewart, Davidson & Simpson (1965) for H.

Computer programs

The NRC crystallographic system by Ahmed, Hall, Pippy & Huber (1966) to which three routines by De Camp (1972) have been added to generate the equivalent reflexions for systems higher than orthorhombic and to sort the data as needed; the ORTEP program by Johnson (1965).

Results

The molecular structure, the numbering system, and the short intramolecular contacts are presented in Fig. 1. The atomic parameters and their estimated standard deviations as obtained from the least-squares refinement are listed in Table 1, and the corresponding structure factor data are given in Table 2. The bond lengths and angles, not corrected for thermal vibration, are summarized in Fig. 2. The C–H bond lengths are 0.90–1.03 (e.s.d. = 0.03–0.05) Å, and their mean is 0.99 Å. The O–H bond length is 0.91 (5) Å.

† This idea should be applied with caution. Reflexion 630 with the second highest $|E|$ in the $hk0$ zone turned out to have a -ve sign, where $|E| = 2.75$, $A = 1.189$, and $P_+ = 0.915$.

Table 1. Fractional coordinates, vibration tensor components (\AA^2) for the expression $T = \exp[-2\pi^2(U_{11}a^{*2}h^2 + \dots + 2U_{23}b^*c^*kl + \dots)]$, and their e.s.d.'s (all quantities $\times 10^4$)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	2 <i>U</i> ₂₃	2 <i>U</i> ₁₃	2 <i>U</i> ₁₂
N(1)	5729 (1)	4382 (1)	5874 (3)	439 (13)	715 (17)	458 (13)	-113 (24)	-21 (22)	150 (24)
C(2)	5575 (1)	3828 (1)	6020 (4)	426 (17)	724 (20)	656 (20)	467 (35)	-249 (31)	-54 (30)
C(3)	5420 (1)	3563 (1)	4269 (4)	376 (13)	479 (17)	785 (21)	344 (29)	42 (28)	354 (27)
C(4)	5051 (1)	3646 (1)	3111 (3)	364 (13)	420 (13)	454 (15)	11 (23)	-38 (23)	364 (24)
C(5)	5252 (1)	4236 (1)	3108 (3)	341 (13)	408 (13)	516 (16)	87 (24)	103 (24)	324 (24)
C(6)	5340 (1)	4445 (1)	4931 (4)	418 (17)	517 (17)	672 (19)	-222 (29)	177 (28)	253 (27)
C(7)	5802 (2)	4618 (2)	7599 (5)	766 (27)	1477 (40)	588 (22)	-604 (48)	129 (39)	205 (54)
C(8)	6015 (2)	3761 (2)	6745 (7)	719 (27)	1030 (34)	1523 (43)	1194 (61)	-1000 (55)	51 (47)
C(9)	4474 (1)	3317 (1)	3601 (3)	394 (13)	356 (13)	498 (15)	-106 (23)	-99 (23)	388 (24)
C(10)	4301 (1)	3108 (1)	5223 (4)	388 (13)	423 (13)	612 (18)	131 (26)	16 (26)	320 (24)
C(11)	3774 (1)	2799 (1)	5582 (4)	470 (17)	527 (17)	759 (22)	212 (31)	159 (30)	362 (30)
C(12)	3412 (1)	2700 (1)	4334 (5)	372 (17)	498 (17)	919 (24)	-44 (32)	27 (30)	263 (27)
C(13)	3573 (1)	2899 (1)	2705 (4)	398 (17)	608 (20)	830 (23)	-324 (33)	-389 (30)	434 (30)
C(14)	4098 (1)	3202 (1)	2329 (4)	447 (17)	522 (17)	590 (18)	-122 (28)	-163 (27)	424 (27)
O(15)	5114 (1)	3519 (1)	1378 (2)	582 (13)	566 (10)	533 (11)	-156 (18)	143 (19)	534 (20)
C(16)	4920 (1)	4402 (1)	2092 (5)	532 (20)	475 (17)	965 (26)	293 (33)	-126 (34)	472 (30)

Table 1 (cont.)

The isotropic temperature factors of the H atoms and their e.s.d.'s are in \AA^2 .

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
H(2)	5265 (12)	3660 (12)	6865 (38)	6.1 (0.7)
H(3,1)	5746 (10)	3691 (10)	3556 (31)	3.9 (0.6)
H(3,2)	5290 (11)	3192 (11)	4507 (36)	5.2 (0.7)
H(5)	5586 (9)	4377 (9)	2512 (27)	2.5 (0.5)
H(6,1)	5022 (13)	4277 (12)	5650 (39)	5.9 (0.8)
H(6,2)	5461 (12)	4826 (12)	4876 (38)	6.0 (0.8)
H(7,1)	5478 (17)	4447 (16)	8332 (50)	9.2 (1.1)
H(7,2)	6061 (17)	4586 (16)	8185 (51)	9.9 (1.2)
H(7,3)	5895 (15)	4999 (15)	7409 (44)	8.9 (1.0)
H(8,1)	6341 (16)	3954 (16)	6029 (48)	9.1 (1.1)
H(8,2)	6055 (19)	3861 (19)	7863 (59)	12.6 (1.4)
H(8,3)	5972 (18)	3431 (18)	6792 (58)	11.5 (1.3)
H(10)	4546 (12)	3160 (12)	6196 (35)	5.2 (0.7)
H(11)	3678 (12)	2691 (12)	6800 (37)	5.4 (0.7)
H(12)	3033 (12)	2493 (12)	4582 (36)	5.3 (0.7)
H(13)	3330 (13)	2844 (13)	1835 (42)	6.8 (0.9)
H(14)	4217 (11)	3341 (11)	1144 (36)	4.6 (0.7)
H(15)	4980 (19)	3171 (19)	1253 (57)	11.1 (1.4)
H(16,1)	4570 (14)	4274 (15)	2705 (45)	7.6 (0.9)
H(16,2)	5094 (13)	4788 (13)	2071 (42)	7.0 (0.9)
H(16,3)	4845 (15)	4244 (15)	861 (47)	8.9 (1.0)

Discussion

It is evident from the analysis that the molecules in the rhombohedral and monoclinic crystals have the same configuration and conformation, namely, (\pm)- β -1,2*e*,5*e*-trimethyl-4*a*-phenylpiperidin-4*e*-ol, where *e* and *a* stand for equatorial and axial respectively. Their molecular structures show a substantial difference in the direction of the O-H bond accompanied by much smaller changes in some of the valence angles. The intermolecular hydrogen bonding scheme is completely different in the two forms. In the monoclinic crystals, O-H...N' hydrogen bonds link molecules of identical chirality to form infinite chains, while in the rhombohedral crystals they link molecules of alternating chirality to form hexameric rings. As shown in Fig. 3, the six molecules of each cyclic

hexamer are related by the $\bar{3}$ symmetry and there are no linkages between the different hexamers. In order to achieve these two different hydrogen bond schemes, the direction of the O-H bond is changed substantially from being nearly antiplanar to the C(4)-C(9) bond in the monoclinic crystals to being synclinal to C(4)-C(9) [or antiplanar to C(4)-C(5)] in the rhombohedral crystals. Thus, the torsion angle H(15)-O(15)-C(4)-C(9) is 172.0° in the former and 53.6° in the latter. This illustrates the wide range through which the O-H bond is free to rotate to form an intermolecular hydrogen bond wherever possible.

In this case, the change in the O-H direction is accompanied by significant changes in the valence angles C(5)-C(4)-O(15) and C(9)-C(4)-O(15) which are 105.8 (2)° and 108.3 (2)° in the rhombohedral crystals, and 109.4 (2)° and 103.3 (2)° in the monoclinic crystals respectively. Thus, in the rhombohedral crystals, O(15) is shifted away from C(9) and closer to C(5), relative to the monoclinic polymorph. In addition, H(15) becomes less subject to *syn*-axial interactions with H(3,1) and H(5,1) in the rhombohedral form. There are smaller but significant changes of about 1.0-1.7° in the four angles C(3)-C(4)-O(15), C(8)-C(2)-C(3), C(5)-C(6)-N(1), and C(2)-C(3)-C(4). The other angles and all the bond lengths are very similar in the two crystal forms.

As shown from the projection of the molecule in Fig. 4, the plane of the axial phenyl ring is intermediate between the parallel and perpendicular conformations relative to the C(7), N(1), C(4), C(9), O(15) plane. The dihedral angle between the two planes is 37.6° for the rhombohedral form and 40.9° for the monoclinic. The stability of this conformation appears to be due to the steric requirements of atom H(16,1), of the equatorial methyl substituent on C(5), which prevents the phenyl ring from taking the perpendicular orientation. Thus, the *ortho* hydrogen atoms of the phenyl ring are brought into short intramolecular contacts H(14)...O(15)=2.45 and H(10)...H(2)=1.97 Å as previously found in the monoclinic crystals.

Table 2. Observed and calculated structure factor data (x 10)

* indicates an unobserved reflexion and |F₀| in place of |F_h|.

Table with multiple columns for h, k, l, F_o, F_c, and phase information. The table is organized into a grid of 10 columns, each representing a different set of Miller indices (h, k, l). Each cell contains numerical values for observed (F_o) and calculated (F_c) structure factors, along with phase angles in degrees. Asterisks indicate unobserved reflexions.

The piperidine ring has a slightly skewed chair form. Mean planes calculated through atoms N(1), C(3), C(4), C(6) and atoms C(2), C(3), C(5), C(6) show that the four atoms of each group are not coplanar. However, atoms N(1), C(2), C(4) and C(5) are found to be coplanar within experimental error, and atoms C(3) and C(6) are on opposite sides of the plane at distances 0.530 (4) and 0.664 (4) Å. This, along with the large interior angles at C(3) and C(6), suggests that the distortion of the ring occurs primarily along the C(3)···C(6) diagonal.

The intermolecular hydrogen bond is approximately linear with $O(15)-H(15)=0.910$, $H(15)\cdots N(1')=2.045$, $O(15)\cdots N(1')=2.953$ Å, and $O(15)-H(15)\cdots N(1')=176.1^\circ$ (e.s.d. = 4.7°). The angles $H(15)\cdots N(1')-C(2')=113.5^\circ$, $H(15)\cdots N(1')-C(6')=121.3^\circ$, and $H(15)\cdots N(1')-C(7')=88.9^\circ$ (e.s.d. = 1.5° in each case) show considerable deviations from the 109.4° value for ideal tetrahedral coordination at the N atom. Atom H(15) makes a somewhat short intermolecular contact of 2.50 (5) Å to C(7') of the molecule to which the hydrogen bond is formed. There are no other short intermolecular contacts within a given hexamer or between the separate hexamers.

Despite the difference in packing, the monoclinic and rhombohedral crystals have almost the same density. However, the melting points are $90.5-91.0^\circ\text{C}$ for the monoclinic, and $104.5-105.0^\circ\text{C}$ for the rhombohedral. These were measured on a hot place micro-

scope using crushed single crystals after having identified them from zero-level precession photographs. The difference in melting points could not be related to the

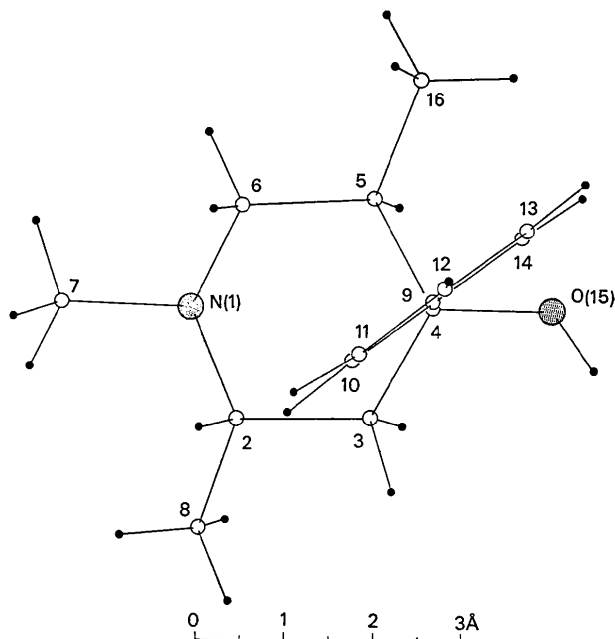


Fig. 4. Projection of the molecule onto the mean plane of atoms C(2), C(3), C(5), and C(6), showing the orientation of the phenyl ring.

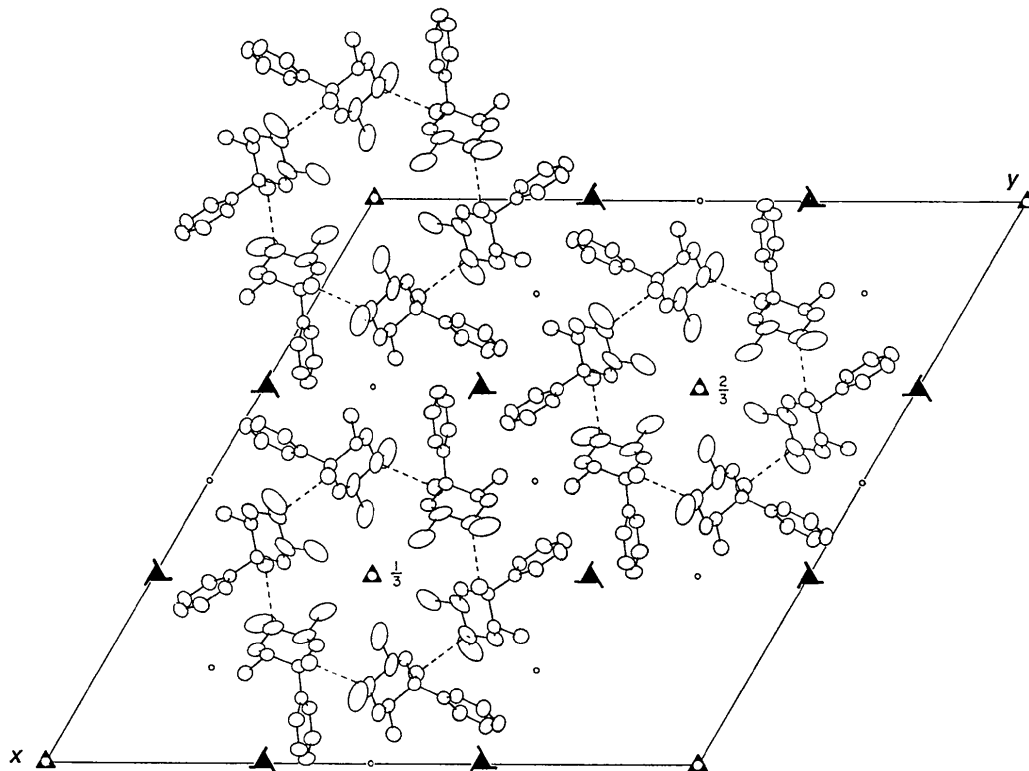


Fig. 3. Projection of the unit-cell contents down the c axis. The hydrogen bonds are identified by broken lines.

strength of the hydrogen bond since the O...N' and H...N' distances are about 0.1 Å shorter in the former than the latter, unless it is assumed that the strength increases with the linearity of the O-H...N' bond. A more plausible explanation is that higher energy is required to separate the molecules which are linked into a hexameric ring, than those linked into a chain. An alternative hypothesis is that the difference in melting points is due to the difference in the entropy of mixing of each of the two forms. Each hexamer contains (+) and (-) molecules, while each chain in the monoclinic crystals contains molecules of identical chirality and thus may be considered to be more ordered. As discussed by Krigbaum & Wildman (1971), the entropy of mixing results in a lower melting point for an ordered than for a disordered crystal structure.

The linking together of (+) and (-) molecules is statistically more favourable than the linking of molecules of identical chirality; this may explain why the rhombohedral crystals are bigger in size and occur in larger quantities than the monoclinic.

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Structural Studies of Synthetic Analgetics. IV. The Crystal and Molecular Structure of (\pm)- α -Promedol Alcohol

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The conformation in the solid state of α -promedol alcohol, whose propionate ester has intermediate analgetic potency between β - and γ -promedol, has been determined as (\pm)- α -1,2*a*,5*e*-trimethyl-4*e*-phenylpiperidin-4*a*-ol, where *a*=axial and *e*=equatorial. The unit cell is monoclinic, $P2_1/c$, $a=8.311$, $b=15.970$, $c=10.434$ Å, and $\beta=109.62^\circ$. The *R* index of the refined structure is 0.049 for 1227 observed reflexions. The piperidine ring has a slightly distorted chair form, and the phenyl ring is more nearly perpendicular to it than in the least active γ -isomer. Molecules of alternating chirality are linked through hydrogen bonds, O-H...N', into infinite chains. Analgetic potency of the prodines and promedols appears to be enhanced if the methyl substituent on the 3- or 5-position of the piperidine ring is *cis* to the 4-phenyl substituent, or if the 2-methyl substituent is *trans* to the 4-phenyl.

Introduction

Among the isomeric promedols, the α -isomer has intermediate analgetic potency between the γ - and β -promedols (Casy & McErlane, 1971). The p.m.r. spectrum of its alcohol (De Camp & Ahmed, 1972*a*) gives an aromatic signal identical to that of the γ -isomer. From studies of the infrared and p.m.r. spectra by Prostavok,

Yagodovskaya & Mikheeva (1964), and by Vlasova & Sheinker (1970), α -promedol was assigned the configuration *t*-2-CH₃, *t*-5-CH₃, *r*-4-C₆H₅.† However, a study of the p.m.r. spectrum by Casy & McErlane (1971, 1972) led to a different configuration assignment, namely *t*-2-CH₃, *c*-5-CH₃, *r*-4-C₆H₅. The present X-ray analysis, as described in a brief report by De Camp & Ahmed (1972*b*), has substantiated the former assign-

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† *t*=*trans*, *c*=*cis*, *r*=reference substituent.