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Structural Studies of Synthetic Analgetics. II.

The Crystal and Molecular Structure of the Monoclinic Form of (\pm)- β -Promedol Alcohol

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The crystal structure of the monoclinic form of (\pm)- β -1,2,5-trimethyl-4-phenylpiperidin-4-ol, the alcohol of the most active promedol isomer, has been determined by the direct method, and has been refined by least squares to $R=0.054$ for the 1585 observed reflexions. The piperidine ring has a slightly skewed chair form, with the hydroxyl and three methyl substituents in equatorial positions, and the phenyl group axial. The aromatic ring makes a dihedral angle of 77.0° with the mean plane of the piperidine ring, and its *ortho* hydrogen atoms make short intramolecular contacts $H \cdots H = 1.97$ and $H \cdots O = 2.44$ Å. Intermolecular hydrogen bonds of the type $O-H \cdots N$ link molecules of similar chirality, which are related by the screw symmetry, to form enantiomeric chains along b . The space group is $P2_1/n$, and the unit-cell parameters are $a = 13.298$, $b = 7.721$, $c = 12.776$ Å, $\beta = 90.09^\circ$.

Introduction

As described in the introduction to part I (De Camp & Ahmed, 1972) β -promedol was reported by Casy & McErlane (1971) to be the most analgetically active of the three known promedol isomers and equipotent with betaprodine, and to have the *cis* 2-Me/4-Ph/5-Me configuration. This assignment is in contradiction to the *trans* 2-Me/4-Ph, *cis* 5-Me/4-Ph configuration proposed by Vlasova & Sheinker (1970) for β -promedol alcohol (referred to in their article as the α -isomer). Such an inversion of the substituents at position 2 of the piperidine ring is, however, unlikely to occur under the conditions of esterification.

Crystallization of the β -promedol alcohol from 30 – 60° petroleum spirit produced two crystalline forms in different proportions. The predominant form was of

large rhombohedral crystals, space group $R\bar{3}$, and a very small proportion of well formed small monoclinic crystals, space group $P2_1/n$. The structure of the monoclinic crystals is reported in this paper, and that of the rhombohedral crystals is currently under investigation.

The identity of the β -isomer was verified by both the p.m.r. spectrum and the melting point of its methiodide derivative (m.p. 235 – 236°C ; literature values for the α , β , and γ -isomers respectively are 278 – 280 , 232 – 234 , and 223 – 225°C : Casy & McErlane, 1972).

Crystal data

(\pm)- β -1,2,5-Trimethyl-4-phenylpiperidin-4-ol
 $\text{C}_{14}\text{H}_{21}\text{ON}$; F.W. 219.33

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

Crystal habit: tabular ($10\bar{1}$).

Crystal dimensions: $0.4 \times 0.3 \times 0.2$ mm.

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Unit cell: monoclinic, $P2_1/n$, $h0l$ absent for $h+l=2n+1$, and $0k0$ absent for $k=2n+1$;
 $a=13.298$ (2), $b=7.721$ (2), $c=12.776$ (2) Å,
 $\beta=90.09$ (5)°, $V=1311.8$ Å³, $Z=4$;
 $D_x=1.110$ g.cm⁻³, D_m not measured due to scarcity of crystals.

Radiation: Cu $K\alpha$ 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

Measured on automatic 4-circle diffractometer, crystal mounted along **b**, θ - 2θ scan at 2°.min⁻¹, two background measurements per reflexion, $\sin \theta/\lambda \leq 0.586$; number of reflexions scanned = 2193, number observed = 1585, number unobserved = 608; number of observations per parameter = 6.9.

Corrections

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

Structure determination

By the direct method of symbolic addition; all C, N, O atoms located from *E* map with 267 reflexions; all H atoms from difference map.

Refinement

By block-diagonal least-squares minimizing $\sum w(\Delta F)^2$, where $w=1/\{1+[(|F_o|-50)/40]^4\}$ and $1.5 \leq |F_o| \leq 136.4$, and excluding the unobserved reflexions; anisotropic thermal parameters for C, N, O and isotropic for H; mean and maximum $\Delta/\sigma=0.1$ and 0.4 in final cycle.

Final agreement

$R=0.054$ for observed reflexions; $|F_c| \leq |F_{th}|$ for 599 unobserved reflexions, and $|F_{th}| < |F_c| \leq 1.5|F_{th}|$ for 9 unobserved.

Residual electron density

$$|\Delta\rho|_{\max} \leq 0.15, \sigma(\rho) = 0.08 \text{ e.Å}^{-3}.$$

f-Curves and computer programs

As in part I (De Camp & Ahmed, 1972).

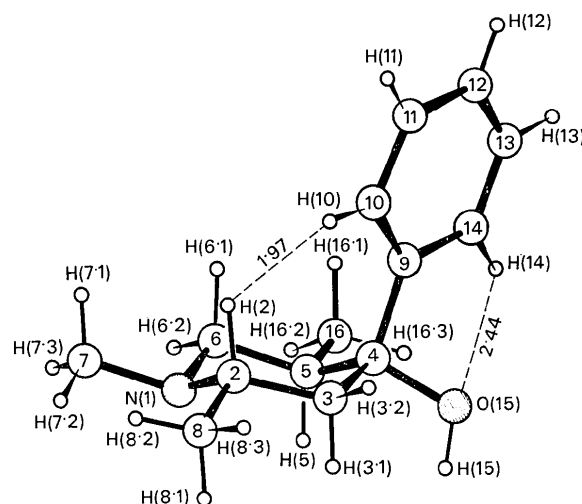


Fig. 1. Molecular structure of the β -promedol alcohol in the monoclinic crystals. The short intramolecular contacts are in Å.

Table 1. Fractional coordinates, vibration tensor components (Å²) 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 $\times 10^4$)

The isotropic temperature factors of the H atoms and their e.s.d.'s are in Å ² .									
	x	y	z	U ₁₁	U ₂₂	U ₃₃	2U ₂₃	2U ₁₃	2U ₁₂
N(1)	3272(2)	-229(3)	3697(2)	646(14)	366(12)	535(13)	-11(22)	-370(22)	-28(23)
C(2)	4016(2)	1183(3)	3783(2)	500(16)	452(16)	561(17)	-123(28)	-227(26)	-53(28)
C(3)	3528(2)	2918(3)	3499(2)	512(17)	425(15)	461(16)	26(26)	23(25)	-165(27)
C(4)	2534(2)	3390(3)	4029(2)	524(16)	421(16)	423(15)	95(25)	-104(25)	65(26)
C(5)	1851(2)	1784(4)	3948(2)	504(16)	541(18)	520(17)	51(28)	-102(27)	-174(29)
C(6)	2390(2)	168(4)	4332(2)	657(19)	483(18)	519(16)	153(29)	-120(27)	-354(30)
C(7)	3698(2)	-1905(4)	4039(2)	975(25)	467(18)	813(23)	35(35)	-697(39)	153(36)
C(8)	4920(2)	867(4)	3085(2)	544(19)	704(22)	984(26)	-403(40)	66(35)	-36(34)
C(9)	2655(2)	4109(5)	5144(2)	610(18)	448(16)	467(15)	75(26)	24(25)	-162(28)
C(10)	3510(2)	3874(4)	5748(2)	765(21)	497(17)	527(17)	-86(30)	-253(30)	-12(33)
C(11)	3593(2)	4648(4)	6737(2)	1029(26)	655(21)	547(18)	-94(34)	-351(34)	-228(40)
C(12)	2831(3)	5648(4)	7123(2)	1112(29)	637(25)	482(13)	-319(35)	253(35)	-521(44)
C(13)	1823(2)	5302(5)	6526(2)	359(25)	1303(28)	729(22)	-567(42)	416(38)	-90(45)
C(14)	1395(2)	5143(4)	5549(2)	662(21)	847(24)	621(19)	-276(38)	216(31)	21(38)
C(15)	2183(1)	4757(2)	2472(1)	773(13)	490(11)	512(11)	69(19)	-162(19)	252(21)
C(16)	810(2)	1968(5)	4463(3)	544(20)	918(27)	1381(28)	-140(46)	165(39)	-357(39)
	x	y	z	B	x	y	z	B	
H(2)	4285(16)	1216(26)	4564(16)	3.7(0.5)	H(8,3)	5363(21)	1902(39)	3061(21)	7.7(0.8)
H(3,1)	3404(16)	2899(30)	2722(17)	3.8(0.6)	H(10)	4059(19)	3190(34)	5508(19)	5.4(0.7)
H(3,2)	4062(16)	3886(30)	3575(16)	3.9(0.6)	H(11)	4200(20)	4472(37)	7150(20)	6.7(0.8)
H(5)	1736(16)	1649(28)	3185(16)	3.5(0.5)	H(12)	2906(20)	6146(37)	7804(20)	7.3(0.8)
H(6,1)	2588(15)	320(29)	5133(16)	3.9(0.6)	H(13)	1420(22)	6620(38)	6841(22)	8.1(0.9)
H(6,2)	1356(18)	-877(33)	4313(18)	5.2(0.7)	H(14)	1224(20)	5330(39)	5124(20)	7.6(0.8)
H(7,1)	3904(20)	-1858(36)	4782(20)	6.4(0.8)	H(15)	2052(22)	4585(41)	2774(22)	8.0(0.9)
H(7,2)	4275(22)	-2178(42)	3537(22)	8.2(0.9)	H(16,1)	867(23)	1978(40)	5285(22)	8.3(0.9)
H(7,3)	3089(24)	-2803(45)	4020(23)	9.7(1.0)	H(16,2)	467(22)	893(38)	4336(21)	7.8(0.8)
H(8,1)	4731(19)	838(34)	2302(19)	6.1(0.7)	H(16,3)	435(23)	3127(41)	4261(24)	9.4(0.9)
H(8,2)	5385(23)	-212(43)	3211(22)	9.5(0.9)					

Results

The molecular structure is shown in Fig. 1. The atomic parameters and their estimated standard deviations,

as obtained from the least-squares refinement, are given in Table 1, and the corresponding structure factor data are listed in Table 2. The bond lengths and valence angles for the non-hydrogen atoms, not cor-

Table 2. Observed and calculated structure factor data ($\times 10$)

* Indicates an unobserved reflexion and $|F_{th}|$ in place of $|F_o|$.

Table with multiple columns of numerical data representing structure factor data. The columns are organized in groups, likely corresponding to different reflections or data sets. The data includes observed values (F_o) and calculated values (F_th) for various hkl indices. Some values are marked with an asterisk to indicate unobserved reflexions.

rected for thermal vibration, are presented on the schematic drawing in Fig. 2. The C–H bond lengths are between 0.95 and 1.08 Å and their mean is 1.023 Å. The O–H bond length is 0.91 Å. The e.s.d. for these bonds is 0.03 Å.

Discussion

The conformation of (\pm)- β -promedol alcohol in the monoclinic crystals is 1,2*e*,5*e*-trimethyl-4*a*-phenylpiperidin-4*e*-ol, where *e* stands for equatorial and *a* for axial. The substituents on the piperidine ring have the configuration *trans* 2-Me/4-Ph, *cis* 5-Me/4-Ph as proposed by Vlasova & Sheinker (1970). Although Casy & McErlane (1971) gave the configuration as *cis* 2-Me/4-Ph/5-Me, their argument regarding the superiority of the *cis* 5-Me/4-Ph geometry over the *trans* arrangement in 4-phenylpiperidine analgetics is not altered by

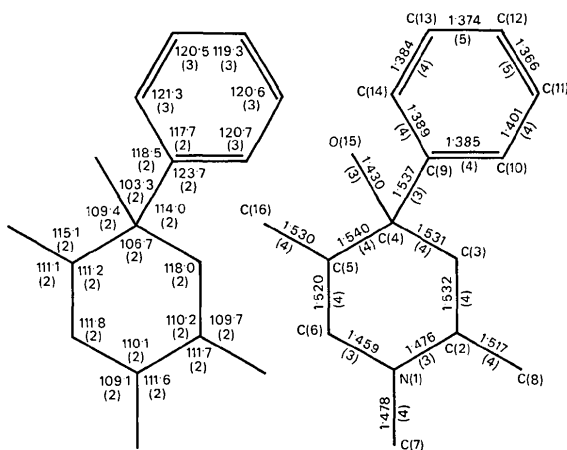


Fig. 2. Schematic drawing showing the bond angles ($^{\circ}$) and lengths (Å), not corrected for thermal vibration, and their e.s.d.'s in parentheses referring to the least significant digits. The angles C(5)–C(4)–C(9) and C(3)–C(4)–O(15) are 114.5 (2) and 108.8 (2) $^{\circ}$, respectively.

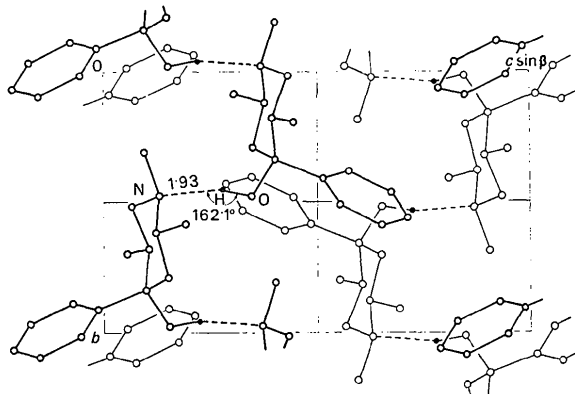


Fig. 3. Projection of the unit-cell contents down the *a* axis. The intermolecular hydrogen bonds are identified by broken lines.

the present findings. Both the most active prodine (betaprodine), and the most active promedol alcohol (β -isomer), have a *cis* relationship between the phenyl ring and the adjacent methyl group, as in morphine, while both alphaprodine and γ -promedol alcohol have a *trans* relationship.

The plane of the phenyl ring in this case is oriented at 40.8 $^{\circ}$ from the plane through atoms O(15), C(4), and C(9). This is intermediate between the parallel and perpendicular conformations of an axial phenyl ring, (Allinger & Tribble, 1971). The *ortho* hydrogen atoms of the phenyl ring make short intramolecular contacts with O(15) and the axial H atom on C(2) so that, as shown in Fig. 1, H(14)···O(15) = 2.44 (3) Å and H(10)···H(2) = 1.97 (3) Å. The corresponding normal van der Waals contacts should be 2.6 and 2.4 Å, respectively. The overcrowding caused by having the bulky phenyl ring in an axial position, seems to have resulted in skewing the piperidine ring from the regular chair form. Thus, atoms C(2), C(3), C(5), and C(6) which form the seat of the chair are no longer coplanar but are at distances ± 0.040 ($\sigma = 0.003$) Å from their mean plane, compared to only ± 0.004 ($\sigma = 0.002$) Å for the γ -isomer. The end atoms N(1) and C(4) are at distances 0.67 and -0.63 Å from the seat of the chair in the β -isomer, compared to 0.66 and -0.68 Å in the γ -isomer, thus indicating a small shift of 0.05 Å of atom C(4) towards the seat of the chair. The strain on the piperidine rings of the β - and γ -isomers can also be observed on examination of the torsion angles listed in Table 3 and their deviations from the corresponding values for an ideal chair. These deviations are largest for the bonds C(2)–C(3), C(3)–C(4), and C(4)–C(5) of the β -isomer.

Table 3. Torsion angles of the piperidine rings in the β - and γ -promedol alcohols and their deviations from the ideal chair values

	Ideal chair	β -Isomer Angle	$ d $	γ -Isomer Angle	$ d $
C(6)–N(1)–C(2)–C(3)	–60	–54.6 $^{\circ}$	5.4 $^{\circ}$	–56.6 $^{\circ}$	3.4 $^{\circ}$
N(1)–C(2)–C(3)–C(4)	60	50.0	10.0	58.5	1.5
C(2)–C(3)–C(4)–C(5)	–60	–47.3	12.7	–55.7	4.3
C(3)–C(4)–C(5)–C(6)	60	50.9	9.1	52.6	7.4
C(4)–C(5)–C(6)–N(1)	–60	–62.3	2.3	–57.0	3.0
C(5)–C(6)–N(1)–C(2)	60	63.1	3.1	58.3	1.7

In the β -isomer, the axial C(4)–C(9) bond is tilted 17.3 $^{\circ}$ away from the normal to the mean plane of the piperidine ring, while in the less-crowded γ -isomer the axial C(4)–O(15) bond is at 1.8 $^{\circ}$ from the normal. The tilt of the axial bond has resulted in reducing the exocyclic angle C(9)–C(4)–O(15) to 103.3 $^{\circ}$ in the β -isomer from 110.3 $^{\circ}$ in the γ . Also, the equatorial substituent on C(4) has been shifted away from the mean plane of the piperidine ring. Thus, in the β -isomer the C(4)–O(15) bond makes 30.5 $^{\circ}$ with the mean plane of the ring, whereas in the γ -isomer the C(4)–C(9) bond is at an

angle of 21.1° . There is, however, no noticeable change in the interior angle C(3)–C(4)–C(5) which is $106.7(2)$ and $107.2(1)^\circ$ in the β - and γ -isomers, respectively. The changes in the ring angles are largest at atoms C(3) and C(6), suggesting that the ring strain is taken up at these atoms.

Equivalent bond lengths are approximately the same in the two structures, except for the three bonds C(2)–C(3), C(4)–C(9), and C(10)–C(11) where significant differences of 0.02 \AA are observed. The C–N bond lengths have a mean value of 1.471 \AA in both structures.

As shown in Fig. 3, intermolecular hydrogen bonds of the type O–H \cdots N link molecules which are related by the screw axis to form infinite chains along b , with all molecules of each chain having identical chirality. The geometry of these hydrogen bonds is as follows: O–H = 0.91 \AA , H \cdots N = 1.93 \AA , O \cdots N = 2.811 \AA , and O–H \cdots N = 162.1° . It is important to note that the two hydrogen bonds of each molecule are *cis* relative to the piperidine ring, while they are *trans* in the γ -isomer. It is possible, therefore, that the analgetic activity is

enhanced when the molecule can assume a geometry such that the hydrogen donor and the hydrogen acceptor of the same molecule are *cis* relative to the piperidine ring. This particular point will be examined further in the subsequent parts of this series.

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The Crystal and Molecular Structure of a Non-Alternant Hydrocarbon: Heptafulvalene*

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Heptafulvalene, $C_{11}H_{12}$, crystallizes in $P2_1/c$ with $Z=2$, $a=9.688(4)$, $b=7.730(2)$, $c=6.971(2) \text{ \AA}$ and $\beta=98.03(2)^\circ$ [$\cos \beta = -0.1399(2)$]. 630 reflections were accessible using Ni filtered $Cu K\alpha$ radiation ($\lambda=1.5418 \text{ \AA}$) and each of these was measured using a computer-controlled, four-circle diffractometer; $d_{\min}=0.98 \text{ \AA}$. The crystal structure of heptafulvalene has been solved using the symbolic addition procedure. The molecule is approximately S shaped; largest deviations from the best molecular plane are 0.35 \AA . There is an alternation of almost single and almost double bonds in the seven-membered ring in fair agreement with the results of earlier π -electron molecular orbital calculations on a planar idealized molecule. It is shown that there is a strong correlation between bond length and bond torsion, the strain in the seven-membered ring being relieved almost exclusively in the longer bonds.

Introduction

Though the molecular structure of non-alternant hydrocarbons is of considerable importance for comparison with theoretical predictions, few precise structure determinations of unsubstituted molecules are available. For example, the determination of the mole-

cular structure of azulene has been hampered by disorder (Robertson, Shearer, Sim & Watson, 1962; Pawley, 1965), but a complex with trinitrobenzene (Hanson, 1965) and a dipropionic acid derivative (Ammon & Sundaralingam, 1966) have been analyzed. Other derivatives for which the structures have been described include dicyanoheptafulvene (Shimanouchi, Ashida, Sasada & Kakudo, 1966) and dimethylfulvene (Norman & Post, 1961).

The work described in the present paper was

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