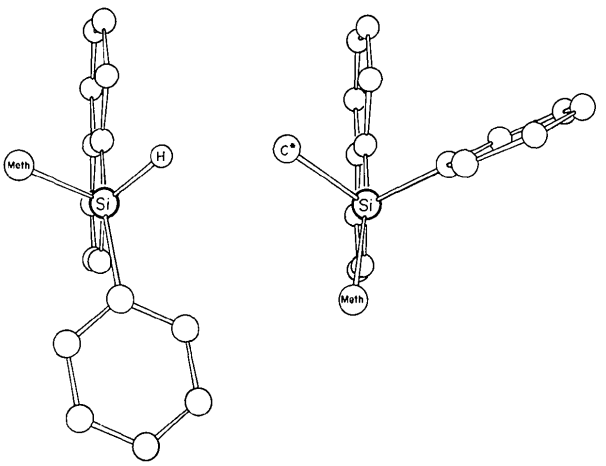
Financial assistance of the National Research Council of Canada is gratefully acknowledged.



(*a*) (*b*)

Fig. 3. (*a*) A view down the Si–αC bond in Okaya & Ashida's (1966) R_3SiH, but for the enantiomorph of opposite hand. The hydrogen position was calculated by assuming sp^3 hybridization on silicon, and an Si–H bond length of 1·48 Å. (*b*) The same view of the present structure. The diagrams show the same distortion of the naphthyl radical, despite the completely different location of neighbouring groups.

References

ABRAHAMS, S. C. & BERNSTEIN, J. L. (1965). *Acta Cryst.* **18**, 926.

ARNDT, U. W. & WILLIS, B. T. M. (1966). *Single Crystal Diffractometry*, p. 174. Cambridge Univ. Press.

BROOK, A. G. & LIMBURG, W. W., (1963). *J. Amer. Chem. Soc.* **85**, 832.

BUSING, W. R., MARTIN, K. O. & LEVY, H. A. (1964). *ORFFE*. Report ORNL-TM-306. Oak Ridge National Laboratory, Oak Ridge, Tennessee.

CRAM, D. J. & ABD ELHAFEZ, F. A. (1952). *J. Amer. Chem. Soc.* **74**, 5828.

CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* A**24**, 321.

CRUICKSHANK, D. W. J. (1957). *Acta Cryst.* **10**, 504.

ELLISON, R. D. (1962). *XFLS*, an extensively modified version of *ORFLS* (Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge 1962), Unpublished.

HAMILTON, W. C. (1965). *Acta Cryst.* **18**, 502.

IBERS, J. A. & HAMILTON, W. C. (1964). *Acta Cryst.* **17**, 781.

International Tables for X-ray Crystallography (1962). Vol. III, p. 214. Birmingham: Kynoch Press.

JOHNSON, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Oak Ridge, Tennessee.

NORTH, A. C. T., PHILLIPS, D. C. & MATHEWS, F. S. (1968). *Acta Cryst.* A**24**, 351.

OKAYA, Y. & ASHIDA, T. (1966). *Acta Cryst.* **20**, 461.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175.

Acta Cryst. (1972). B**28**, 1791

Structural Studies of Synthetic Analgetics. I. The Crystal and Molecular Structure of (±)-γ-Promedol Alcohol

BY WILSON H. DE CAMP* AND F. R. AHMED

Biochemistry Laboratory, National Research Council of Canada, Ottawa, Canada K1A 0R6

(*Received* 4 *January* 1972)

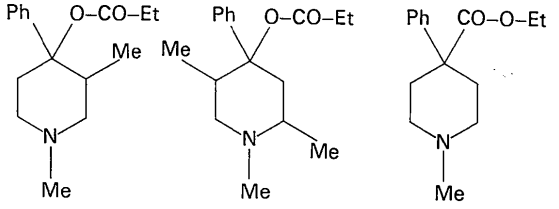
The crystal structure of (±)-γ-1,2,5-trimethyl-4-phenylpiperidin-4-ol, the alcohol of the least active promedol isomer, has been determined by the direct method, and has been refined by least-squares to $R=0{\cdot}048$ for the 1565 observed reflexions. The piperidine ring has the chair form, with the phenyl and three methyl substituents in equatorial positions, and the hydroxyl group axial. The phenyl ring is oriented at 73·7° from the mean plane of the piperidine ring, and its *ortho* hydrogen atoms make rather short intramolecular contacts H···H=2·07 and H···O=2·39 Å. Intermolecular hydrogen bonds of the type O–H···N link molecules of opposite chirality which are related by glide planes to form infinite chains along **c**. The space group is $P2_1/c$, and the unit-cell parameters are $a=10{\cdot}806$, $b=11{\cdot}569$, $c=10{\cdot}460$ Å, $\beta=98{\cdot}75°$.

Introduction

The isomeric prodines (I) and the isomeric promedols, (II) are powerful synthetic analgetics with wide application in medicine, because they combine high potency and relatively low toxicity. The analgetic activity varies widely among the isomers of both the prodines and the promedols. It is important to correlate these variations with the molecular structures in order to establish the rules of these systems and to enhance the understanding of their biological action. The potency of the different isomers of (I) and (II), in terms of

* N.R.C. Postdoctorate Fellow, 1970–1972.

hot plate ED_{50} values, has been reported by Casy & McErlane (1971) to be between 3 and 26 times that of pethidine (III), which is approximately equipotent with morphine. The alcohols are considerably less effective than the corresponding esters, thus the β-promedol alcohol is only one tenth as potent as pethidine, but it still retains its superiority over the γ-promedol alcohol by a factor of 1·6 (Casy, 1971).



X-ray structural studies of the α- and β-prodine HCl and HBr by Kartha, Ahmed & Barnes (1960), Ahmed, Barnes & Masironi (1963) and Ahmed & Barnes (1963) have established that alphaprodine has the *trans* 3-Me/4-Ph configuration, while the more active betaprodine has the *cis* 3-Me/4-Ph configuration. Thus, at least in the case of the prodines, the more active isomer has a similar configuration to the piperidine portion of the morphine molecule as determined by Mackay & Hodgkin (1955), although the conformation of the substituents on the piperidine ring is different.

The promedols have three known isomers which have been arbitrarily designated α, β, and γ. The γ-isomer, also known as trimeperidine or simply promedol, is the principal isomer formed and the least analgetically active. The designations of the other two isomers appear to be sometimes interchanged in the literature. Thus, the most active is referred to as α-promedol by Vlasova & Sheinker (1970), and as β-promedol by Casy & McErlane (1971). Since the samples were supplied to us by Dr Casy, his designations have been adopted for the present X-ray studies, so that as suggested by Prostakov & Mikheeva (1962) the most active promedol which also has identical physiological activity to β-prodine is designated the β-promedol. Also, for proper identification of the three promedol alcohols used in the X-ray analyses, their p.m.r. spectra are given in Fig. 1. It should be noted that according to our designation, the α-promedol alcohol has a nearly identical aromatic signal to that of the γ-isomer, while the β-isomer is different.

The conformations of the isomeric promedols have been investigated by different workers, from studies of their p.m.r. and infrared spectra, but the latest determinations have led to contradictory *cis*/*trans* assign-

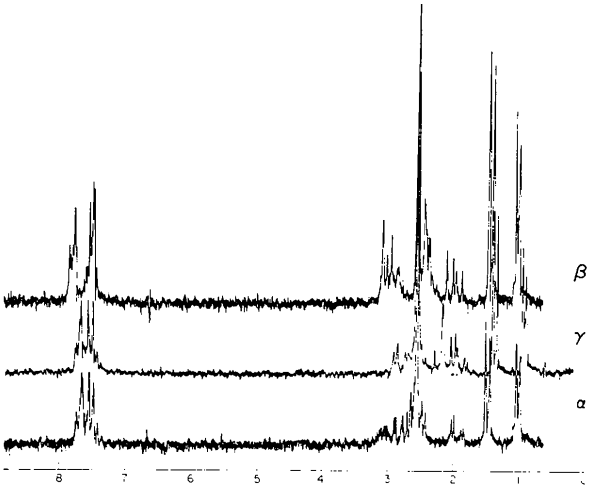


Fig. 1. The p.m.r. spectra of the isomeric promedol alcohols, as obtained with CCl_4 solvent at 30 °C, 100 MHz, chemical shifts are given as ppm from HMDS as an internal standard.

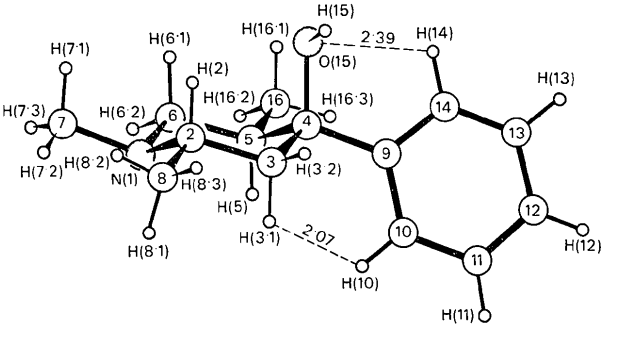


Fig. 2. Molecular structure of the γ-promedol alcohol showing the short intramolecular contacts (Å).

Table 1. *Analgetic potency and proposed configurations of the isomeric promedols*

Isomer	Analgetic potency* Propionate ester	Alcohol	Substituents	Configuration assignments Vlasova *et al.* (1970).	Casy *et al.* (1971).
α	0·58	–	2-Me/4-Ph	*trans*	*trans*
			5-Me/4-Ph	*trans*	*cis*
β	0·18	35·4	2-Me/4-Ph	*trans*	*cis*
			5-Me/4-Ph	*cis*	*cis*
γ	1·6	56·3	2-Me/4-Ph	*cis*	*cis*
			5-Me/4-Ph	*trans*	*trans*

* Expressed as ED_{50} values (mg/kg) measured by the hot-plate test in mice. Values for the esters by Casy & McErlane (1971), and for the alcohols by Casy (1971).

ments for the substituents. The results of Vlasova & Sheinker (1970) on the promedol alcohols, and of Casy & McErlane (1971) on the corresponding propionate esters are summarized in Table 1. The earlier studies by Prostakov, Yagodovskaya & Mikheeva (1964) of the infrared spectra of the promedols, gave identical results to those by Vlasova & Sheinker (1970) for the alcohols.

The crystal structure of the γ-promedol alcohol is reported in part I of this series. The X-ray results of the β- and γ-promedol alcohols have been described in a preliminary report by De Camp & Ahmed (1971).

Crystal data

(±)-γ-1,2,5-Trimethyl-4-phenylpiperidin-4-ol
$C_{14}H_{21}ON$; F.W. 219·33
Source: A. F. Casy; recrystallized from 30–60° petroleum spirit.
Crystal habit: Needle shaped, acicular *c*, colourless, m.p. 104–105°C.
Crystal dimensions: Approximately 0·2 × 0·2 × 0·5 mm.
Unit cell: monoclinic, $P2_1/c$,
$a = 10{\cdot}806\ (2)$, $b = 11{\cdot}569\ (2)$, $c = 10{\cdot}460\ (2)$ Å,
$\beta = 98{\cdot}75\ (5)°$, $V = 1292{\cdot}4$ Å^3, $Z = 4$, $D_x = 1{\cdot}127$ g.cm^{-3},
$D_m = 1{\cdot}116$ g.cm^{-3} (flotation in KI solution, 20°C).
Radiation: Cu $K\alpha$, Ni-filter, $\lambda(K\alpha_1) = 1{\cdot}54050$,
$\lambda(K\alpha_2) = 1{\cdot}54434$ Å, μ(Cu) = 5·51 cm^{-1}.

Experimental

Intensities

Eulerian cradle automatic diffractometer, crystal mounted along *c*, θ–2θ scan at 2°.min^{-1}, two background measurements per reflexion, $\sin\theta/\lambda \le 0{\cdot}586$; number scanned = 2176, observed = 1565, unobserved = 611; number of observations per parameter = 6·8.

Corrections

(1) For crystal decomposition, empirically with the aid of two standard reflexions; (2) 1/Lp; (3) Absorption using Gaussian integration (Ahmed, 1970), $1{\cdot}065 \le \exp(\mu R) \le 1{\cdot}248$.

Structure determination

Direct method of symbolic addition; all C, N, O atoms located from *E* map with 246 reflexions; all H atoms from difference map.

Refinement

Block-diagonal least-squares minimizing $\sum w(\Delta F)^2$ where $w = 1/\{1 + [(|F_o| - 30)/20]^4\}$ and $2 \le |F_o| \le 112$; anisotropic for C, N, O and isotropic for H; three reflexions affected by extinction and all the unobserved are excluded; mean $(\Delta/\sigma) = 0{\cdot}4$ and maximum $(\Delta/\sigma) = 1{\cdot}8$ in final cycle.

Final agreement

$R = 0{\cdot}048$ for observed reflexions; $|F_c| \le |F_{th}|$ for 607 unobserved reflexions, and $|F_{th}| < |F_c| \le 1{\cdot}5|F_{th}|$ for 4 unobserved.

Residual electron density

$|\Delta\varrho| < 0{\cdot}2$, $\sigma(\varrho) = 0{\cdot}05$ e.Å^{-3}.

f-Curves

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

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

The isotropic temperature factors of the H atoms are in Å^2.

	x	y	z	U11	U22	U33	2U23	2U13	2U12
N(1)	8941(1)	2382(1)	308(1)	476(9)	646(11)	401(9)	136(17)	23(15)	-18(18)
C(2)	8876(2)	3047(2)	1498(2)	506(12)	637(14)	405(11)	131(21)	-82(18)	-212(22)
C(3)	7560(2)	2995(2)	1825(2)	559(12)	428(12)	399(10)	-8(19)	-11(18)	-100(19)
C(4)	7093(2)	1776(1)	2021(2)	524(11)	401(11)	354(10)	73(18)	-49(17)	-38(20)
C(5)	7213(2)	1086(2)	786(2)	587(12)	442(12)	412(10)	-12(19)	-9(18)	26(21)
C(6)	9532(2)	1187(2)	468(2)	609(13)	619(14)	421(11)	80(21)	46(19)	214(24)
C(7)	10235(2)	2336(2)	30(2)	509(13)	1170(21)	618(14)	333(28)	150(22)	165(29)
C(8)	9264(2)	4303(2)	1351(2)	818(17)	776(17)	674(15)	-36(27)	149(25)	-750(28)
C(9)	5757(2)	1774(2)	2300(2)	511(11)	410(11)	368(10)	-85(19)	61(17)	-136(20)
C(10)	4344(2)	2471(2)	1628(2)	527(13)	618(14)	721(14)	201(25)	107(22)	-120(24)
C(11)	3626(2)	2467(2)	1273(2)	550(13)	738(16)	935(17)	10(29)	123(25)	-23(26)
C(12)	3285(2)	1752(2)	2797(2)	603(14)	925(18)	811(16)	-448(30)	425(24)	-367(28)
C(13)	4164(2)	1033(2)	3463(2)	806(17)	915(19)	593(14)	36(28)	387(24)	-536(30)
C(14)	5386(2)	1047(2)	3222(2)	652(14)	681(15)	525(12)	144(24)	119(21)	-269(24)
O(15)	7907(1)	1221(1)	3050(1)	626(8)	513(8)	402(7)	104(13)	-111(12)	69(15)
O(16)	6844(2)	-183(2)	853(2)	1027(18)	487(14)	734(16)	-281(25)	374(27)	-210(28)

	x	y	z	B		x	y	z	B
H(2)	9416(15)	2585(15)	2200(15)	5.2(0.4)	H(8,3)	9194(19)	4757(19)	2128(20)	9.2(0.6)
H(3,1)	6997(14)	3334(13)	1096(14)	3.8(0.4)	H(10)	5122(16)	2954(15)	972(16)	5.5(0.5)
H(3,2)	7509(14)	3460(13)	2662(14)	3.7(0.4)	H(11)	3041(19)	2982(17)	1368(18)	7.6(0.6)
H(5)	6656(14)	1432(14)	126(14)	3.9(0.4)	H(12)	2454(17)	1757(16)	2963(17)	6.2(0.5)
H(6,1)	9136(14)	762(13)	1190(14)	3.9(0.4)	H(13)	3907(17)	544(16)	4145(17)	5.8(0.5)
H(6,2)	8591(15)	738(14)	-413(15)	4.8(0.4)	H(14)	6007(15)	562(14)	3707(15)	4.4(0.4)
H(7,1)	10869(15)	2364(15)	817(17)	6.0(0.5)	H(15)	8071(18)	1663(18)	3693(18)	7.4(0.6)
H(7,2)	10443(21)	3115(20)	-171(22)	9.1(0.7)	H(16,1)	7393(18)	-581(18)	1551(18)	8.5(0.6)
H(7,3)	10287(21)	1724(19)	-719(20)	8.2(0.6)	H(16,2)	6911(18)	-555(17)	52(18)	7.7(0.6)
H(8,1)	8343(15)	4635(16)	504(18)	8.0(0.6)	H(16,3)	5989(18)	-271(16)	1100(18)	6.7(0.6)
H(8,2)	10124(19)	4370(18)	1339(19)	7.4(0.6)					

Computer programs

The NRC Crystallographic Programs for the IBM/360 System by Ahmed, Hall, Pippy & Huber (1966).

Results

A perspective view of the molecular structure showing the conformation, the numbering system, and the short intramolecular contacts is presented in Fig. 2. The refined atomic parameters and their estimated standard deviations, as obtained from the block-diagonal least-squares refinement, are listed in Table 2. The corresponding structure factor data are given in Table 3.

The bond lengths and angles, not corrected for thermal vibration, are shown in Fig. 3. The C–H bond lengths are in the range 0·94 to 1·07 Å, their mean is

Table 3. *Observed and calculated structure factor data* ($\times 10$)

* Indicates unobserved reflexion and $|F_{\text{th}}|$ in place of $|F_o|$. Reflexions 110, 102, and 210 appear to be affected by extinction and were excluded from the refinement.

0·98 Å, and the O–H distance is 0·84 Å. The e.s.d. for these bonds is 0·02 Å.

Discussion

In the solid state, the molecular structure of (±)-γ-promedol alcohol may be described as 1,2*e*,5*e*-trimethyl-4*e*-phenylpiperidin-4*a*-ol, where *e* stands for equatorial and *a* for axial. The corresponding configuration, therefore, is *cis* 2-Me/4-Ph and *trans* 5-Me/4-Ph which is the same as that predicted from the earlier p.m.r. and infrared studies, and analogous to that found for alphaprodine.

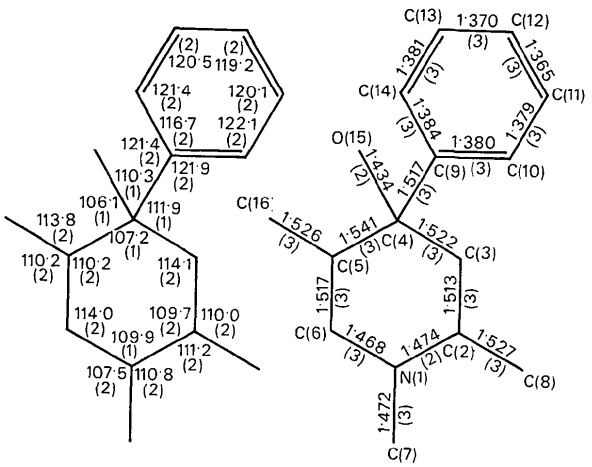


Fig. 3. Schematic drawing showing the bond angles (°), and lengths (Å), not corrected for the thermal vibration, and their e.s.d.'s in parentheses referring to the least significant digits. The angles C(3)–C(4)–O(15) and C(5)–C(4)–C(9) are 109·8 (1) and 111·4 (1)° respectively.

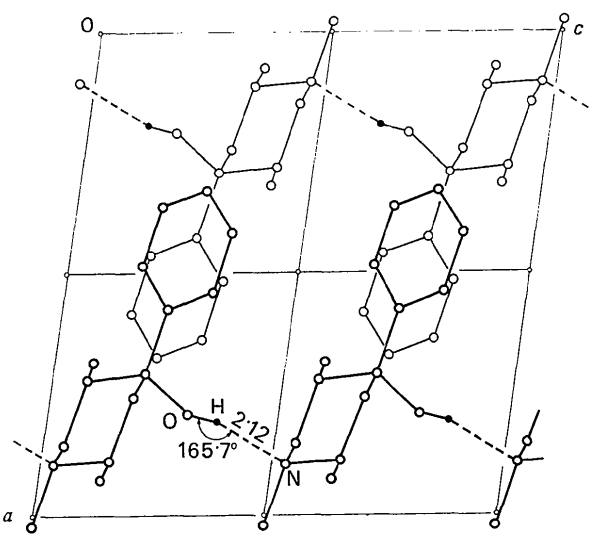


Fig. 4. Projection of the unit-cell contents down the *b* axis. The intermolecular hydrogen bonds are identified by broken lines.

The piperidine ring has the chair form, and its six atoms are nearly equally distributed at ±0·23 Å from their mean plane. Its atoms N(1) and C(4) lie on opposite sides of the mean plane through C(2), C(3), C(5), and C(6) at distances 0·66 and −0·68 Å, respectively. The mean plane of the phenyl ring makes a dihedral angle of 73·7° with the mean plane of the six atoms of the piperidine ring, and 16·0° with the plane through atoms O(15), C(4), and C(9). In this orientation, the phenyl ring makes two rather short intramolecular contacts between its *ortho* hydrogen atoms and the axial substituents on C(3) and C(4). Thus, H(10)···H(3,1) = 2·07 (2) and H(14)···O(15) = 2·39 (2) Å, whereas based on the atomic radii given by Pauling (1960), the corresponding normal van der Waals contacts should be 2·4 and 2·6 Å, respectively. It is, however, unlikely that C(14) is hydrogen bonded to O(15) since the angle C(14)–H(14)···O(15) is only 103° showing that the C–H bond is not directed towards the O atom.

It is of interest to note that the mean C–N bond length in the γ-promedol alcohol is 1·471 ($\sigma_{\text{w.m.}}$ = 0·002) Å, which is in excellent agreement with the value of 1·472 ± 0·005 Å given by Sutton (1965) for C(sp^3)–N(sp^3). The corresponding mean C–N bond lengths in alphaprodine HCl, betaprodine HCl, and betaprodine HBr are 1·508, 1·495, and 1·495 Å, respectively, and their mean is 1·499 Å. This difference of 0·028 Å is presumably a consequence of the N atom being neutral in the γ-promedol alcohol, and positively charged in the prodine salts.

The only short intermolecular contact in the crystals of γ-promedol alcohol is the N(1′)···H(15) distance of 2·12 (σ = 0·02) Å, for which the normal van der Waals contact should be 2·7 Å. The presence of this short distance with a large associated angle O(15)–H(15)···N(1′) of 165·7°, strongly indicates the existence of hydrogen bonds of the type O–H···N linking the molecules which are related by the glide planes, as shown in Fig. 4. The O···N distance for these hydrogen bonds is 2·939 (2) Å and the H···N–C angles are 100·4, 109·2, and 118·5°. The crystal structure, therefore, consists of infinite chains along **c**. Each chain contains molecules of opposite chirality linked by hydrogen bonds, and there are no cross linkages between the chains.

The authors are grateful to Drs A. F. Casy and K. McErlane of the University of Alberta for supplying the crystals and some unpublished data, to Dr R. D. Lapper for the p.m.r. spectra, and to Mrs M. E. Pippy for assistance with the computations.

References

AHMED, F. R. (1970). *Crystallographic Computing*, pp. 279–282. Copenhagen: Munksgaard.

AHMED, F. R. & BARNES, W. H. (1963). *Acta Cryst.* **16**, 1249.

AHMED, F. R., BARNES, W. H. & MASIRONI, L. D. (1963). *Acta Cryst.* **16**, 237.
AHMED, F. R., HALL, S. R., PIPPY, M. E. & HUBER, C. P. (1966). *IUCr World List of Crystallographic Computer Programs*, 2nd ed., Appendix, p. 52.
CASY, A. F. (1971). Private communication.
CASY, A. F. & MCERLANE, K. (1971). *J. Pharm. Pharmacol.* **23**, 68.
DE CAMP, W. H. & AHMED, F. R. (1971). *Chem. Commun.* p. 1102.
HANSON, H. P., HERMAN, F., LEA, J. D. & SKILLMAN, S. (1964). *Acta Cryst.* **17**, 1040.
KARTHA, G., AHMED, F. R. & BARNES, W. H. (1960). *Acta Cryst.* **13**, 525.
MACKAY, M. & HODGKIN, D. C. (1955), *J. Chem. Soc.* p. 3261.
PAULING, L. (1960). *The Nature of the Chemical Bond*, p. 260. Ithaca: Cornell Univ. Press.
PROSTAKOV, N. S. & MIKHEEVA, N. N. (1962). *Usp. Khim.* **31**, 1191. (*Russ. Chem. Rev. English transl.* p. 556).
PROSTAKOV, N. S., YAGODOVSKAYA, T. V. & MIKHEEVA, N. N. (1964). *Zh. Obshch. Khim.* **34**, 234. (*J. Gen. Chem. USSR, Engl. transl.* p. 233).
STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175.
SUTTON, L. E. (1965). *Tables of Interatomic Distances and Configurations in Molecules and Ions, Supplement*. Special Publication No. 18. London: The Chemical Society.
VLASOVA, T. F. & SHEINKER, Y. N. (1970). *Zh. Strukt. Khim.* **11**, 640. (*J. Struct. Chem. USSR, Engl. Transl.* p. 595).

Acta Cryst. (1972). B**28**, 1796

Structural Studies of Synthetic Analgetics. II. The Crystal and Molecular Structure of the Monoclinic Form of (±)-β-Promedol Alcohol

BY WILSON H. DE CAMP* AND F. R. AHMED

Biochemistry Laboratory, National Research Council of Canada, Ottawa, Canada K1A 0R6

(*Received* 4 *January* 1972)

The crystal structure of the monoclinic form of (±)-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 $R=0{\cdot}054$ 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···H = 1·97 and H···O = 2·44 Å. Intermolecular hydrogen bonds of the type O–H···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 $a=13{\cdot}298$, $b=7{\cdot}721$, $c=12{\cdot}776$ Å, $\beta=90{\cdot}09°$.

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

(±)-β-1,2,5-Trimethyl-4-phenylpiperidin-4-ol
$C_{14}H_{21}ON$; F.W. 219·33
Source: A. F. Casy; recrystallized from 30–60° petroleum spirit.
Crystal habit: tabular $(10\bar{1})$.
Crystal dimensions: 0·4 × 0·3 × 0·2 mm.

* N.R.C. Postdoctorate Fellow, 1970–1972.