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 (±)-α-Promedol Alcohol

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

Division of Biological Sciences, National Research Council of Canada, Ottawa K1A 0R6, Canada

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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 (±)-α-1,2*a*,5*e*-trimethyl-4*e*-phenylpiperidin-4*a*-ol, where *a* = axial and *e* = equatorial. The unit cell is monoclinic, $P2_1/c$, $a = 8{\cdot}311$, $b = 15{\cdot}970$, $c = 10{\cdot}434$ Å, and $\beta = 109{\cdot}62°$. 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 Prostakov, Yagodovskaya & Mikheeva (1964), and by Vlasova & Sheinker (1970), α-promedol was assigned the configuration *t*-2-CH_3, *t*-5-CH_3, *r*-4-C_6H_5.† However, a study of the p.m.r. spectrum by Casy & McErlane (1971, 1972) led to a different configuration assignment, namely *t*-2-CH_3, *c*-5-CH_3, *r*-4-C_6H_5. The present X-ray analysis, as described in a brief report by De Camp & Ahmed (1972*b*), has substantiated the former assign-

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

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

ment. The same conclusion has been confirmed from a carbon-13 magnetic resonance study by Jones, Casy & McErlane (1972).

Crystal data

(±)-α-1,2,5-Trimethyl-4-phenylpiperidin-4-ol
$C_{14}H_{21}ON$, F.W. 219·33.
Source: A.F. Casy; no recrystallization was needed.
Crystal habit: Needle-shaped, colourless,
m.p. 96·5–97·0 °C.
Crystal dimensions: 0·05 × 0·1 × 0·4 mm.
Unit cell: monoclinic, $P2_1/c$,
$a = 8{\cdot}311$ (2), $b = 15{\cdot}970$ (2), $c = 10{\cdot}434$ (2) Å,
$\beta = 109{\cdot}62$ (4)°, $V = 1304{\cdot}5$ Å^3, $Z = 4$,
$D_x = 1{\cdot}116$ g.cm^{-3}, $D_m = 1{\cdot}109$ g.cm^{-3}
(flotation in KI solution, 21 °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

Automatic 4-circle diffractometer, b^* along φ axis, θ–2θ scan, two background measurements per reflexion, $\sin\theta/\lambda \leq 0{\cdot}586$. Reflexions scanned = 2191, observed = 1227, unobserved = 964; number of observations per parameter = 5·4.

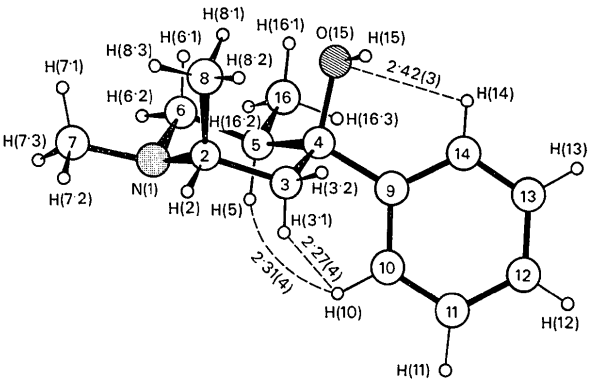

Fig. 1. Perspective view of α-promedol alcohol. Short intramolecular distances are in Å.

Corrections, f-curves, computer programs

As in part III (De Camp & Ahmed, 1972*d*).

Structure determination

By the direct method; C, N, O atoms were determined from E map with 256 reflexions having $|E| \geq 1{\cdot}50$, and H atoms from difference map.

Refinement

By block-diagonal least-squares minimizing $\sum w(\Delta F)^2$, where $w = 1/\{1 + [(|F_o| - 15)/8]^4\}$, $2{\cdot}0 \leq |F_o| \leq 125{\cdot}5$, and

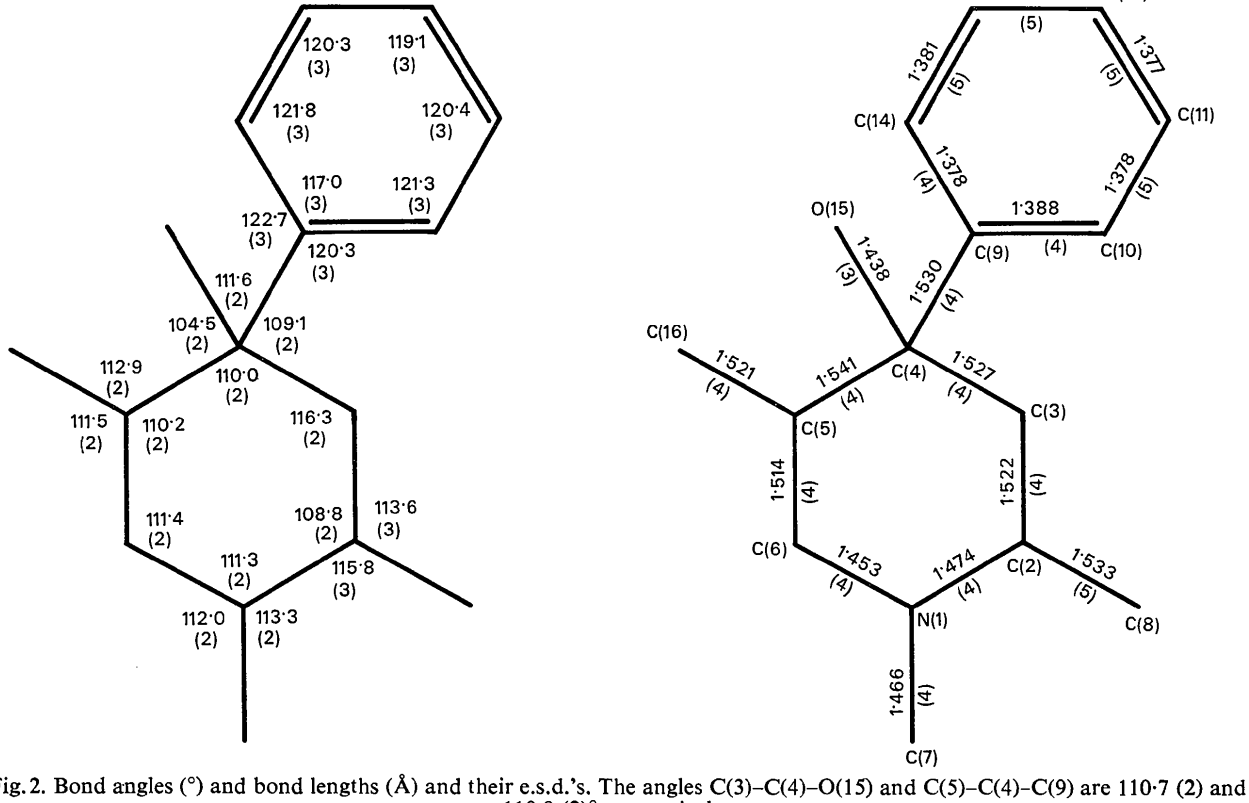

Fig. 2. Bond angles (°) and bond lengths (Å) and their e.s.d.'s. The angles C(3)–C(4)–O(15) and C(5)–C(4)–C(9) are 110·7 (2) and 110·9 (2)°, respectively.

excluding the unobserved reflexions. Mean and maximum $\Delta/\sigma=0{\cdot}3$ and 1·2 for C, N, O, and 0·4 and 1·7 for H, in the final cycle.

Final agreement

$R=0{\cdot}049$ and $R_w=0{\cdot}049$ for the observed reflexions. $|F_c|\leq|F_{th}|$ for 939 unobserved reflexions, and $|F_{th}|<|F_c|\leq 1{\cdot}3\ |F_{th}|$ for 25 unobserved.

Residual electron density

$-0{\cdot}23\leq\Delta\varrho\leq 0{\cdot}17$, $\sigma(\varrho)=0{\cdot}10$ e.Å^{-3}.

Results

The molecular structure and the short intramolecular contacts are shown in the perspective view given in Fig. 1. The refined atomic parameters and the corresponding structure factor data are listed in Tables 1 and 2, respectively. The bond lengths and angles, uncorrected for thermal vibrations, are presented in the schematic drawing in Fig. 2. The C–H bond lengths are 0·88–1·07 (e.s.d. = 0·03–0·04) Å, their mean is 0·99 Å, and O–H = 0·81 (4) Å.

Discussion

This analysis shows that α-promedol alcohol has the configuration *t*-2-CH_3, *t*-5-CH_3, *r*-4-C_6H_5, and that its conformation in the solid state is 1,2*a*,5*e*-trimethyl-4*e*-phenylpiperidin-4*a*-ol, where *a* = axial and *e* = equatorial. Thus, the main difference between this molecule and the γ-isomer (De Camp & Ahmed, 1972*a*) is an interchange of the 2-H and 2-CH_3 substituents. The piperidine ring in both molecules has the chair form, except that it is somewhat distorted in the α-isomer as a result of the *syn*-axial interactions between the 2-CH_3, 4-OH and the axial 6-H substituents. Opposite sides of the ring are significantly skew in α-promedol. As an example, atoms C(2), C(3), C(5) and C(6) are at ±0·026 Å from their mean plane, and atoms N(1) and C(4) are at 0·68 and −0·60 Å from this plane.

The distortion of the piperidine ring can also be seen from the non-uniformity of the six torsion angles (τ) summarized in Table 3 for each of the four promedol alcohol crystal structures. The standard deviation, $\sigma(\tau)=[(\sum_i|\tau_i|-\bar{\tau})/(n-1)]^{1/2}$, of each ring is smallest, 2·2°, for the γ-isomer where OH is the only large axial substituent, and considerably higher, 6·6–7·1°, for the β and α-structures. The increased distortion probably results in a lower energy barrier to ring inversion and an increased chance of a conformational change.

The phenyl ring in α-promedol alcohol assumes a more symmetrical orientation, relative to the piperidine ring, than in the γ-isomer. Its plane makes a dihedral angle of 86·6° with the mean plane of the piperidine ring, and 1·8° with the bisecting plane through atoms C(7), N(1), C(4), C(9), O(15), as compared with 73·7 and 16·2°, respectively, in the γ-isomer. This rotation of about 15° round the C(4)–C(9) bond which joins the two rings places H(10) at equal distances of 2·27 (4) and 2·31 (4) Å from atoms H(3,1) and H(5,1), as shown in Fig. 1. The intramolecular distance O(15)...H(14) is virtually unchanged in the two structures.

All the corresponding bonds in the α and γ molecules

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

B for H atoms is in Å^2.

	x	y	z	U11	U22	U33	2U23	2U13	2U12
N(1)	6492(3)	3434(1)	5996(2)	520(15)	456(14)	413(13)	-49(21)	320(23)	-219(24)
C(2)	7519(4)	2790(2)	5614(3)	390(16)	592(21)	448(16)	89(29)	195(27)	-25(31)
C(3)	6393(4)	2033(2)	5050(3)	515(18)	457(17)	396(15)	177(27)	398(28)	155(30)
C(4)	4687(3)	2208(2)	3935(2)	458(17)	404(17)	281(13)	33(24)	322(25)	-39(27)
C(5)	3786(3)	2952(2)	4346(2)	423(16)	389(16)	321(13)	17(24)	330(25)	23(27)
C(6)	5019(4)	3675(2)	4839(3)	544(17)	350(16)	477(16)	15(26)	486(28)	-27(29)
C(7)	7496(5)	4161(2)	6674(3)	776(25)	656(22)	669(23)	-292(37)	488(38)	-615(41)
C(8)	8524(4)	3088(2)	4708(4)	563(21)	833(26)	712(22)	6(41)	654(36)	-233(40)
C(9)	3579(4)	1420(2)	3700(3)	506(18)	406(16)	342(14)	53(25)	299(26)	61(29)
C(10)	3151(5)	1070(2)	4761(3)	858(26)	592(21)	433(17)	-39(31)	418(35)	-474(39)
C(11)	2194(5)	348(2)	4582(3)	926(28)	601(22)	606(21)	160(35)	422(40)	-426(42)
C(12)	1655(5)	-52(2)	3341(4)	657(22)	437(18)	837(24)	131(37)	179(37)	-130(35)
C(13)	2045(5)	287(2)	2283(3)	731(24)	504(19)	625(20)	-293(33)	256(36)	-143(38)
C(14)	2997(4)	1014(2)	2464(3)	650(22)	534(19)	440(17)	-130(30)	396(32)	-79(35)
O(15)	4952(3)	2478(1)	2706(2)	612(12)	469(10)	340(9)	75(17)	491(18)	96(22)
C(16)	2172(4)	3223(2)	3216(3)	510(20)	645(22)	529(18)	155(33)	373(31)	270(35)

	x	y	z	B
H(2)	8376(39)	2622(19)	6413(31)	5.0(0.7)
H(3,1)	6161(36)	1797(17)	5730(28)	3.5(0.6)
H(3,2)	7086(39)	1628(19)	4713(31)	5.2(0.8)
H(5)	3440(32)	2756(15)	5128(24)	2.8(0.5)
H(6,1)	5435(34)	3916(17)	4111(26)	3.4(0.6)
H(6,2)	4405(31)	4138(15)	5144(24)	2.8(0.6)
H(7,1)	7917(43)	4520(21)	6066(34)	6.6(0.9)
H(7,2)	8557(50)	3875(27)	7404(43)	8.4(1.1)
H(7,3)	6713(43)	4531(21)	7093(34)	6.7(0.9)
H(8,1)	7812(44)	3263(21)	3863(34)	6.8(0.9)
H(8,2)	9355(47)	2626(22)	4561(36)	7.2(0.9)
H(8,3)	9336(45)	3501(21)	5160(36)	6.6(0.9)
H(10)	3529(35)	1349(17)	5640(28)	4.1(0.7)
H(11)	1807(43)	132(21)	5392(33)	6.2(0.8)
H(12)	970(47)	-539(22)	3224(37)	6.9(0.9)
H(13)	1684(42)	34(23)	1399(33)	5.7(0.8)
H(14)	3295(43)	1238(21)	1766(34)	6.2(0.9)
H(15)	5509(42)	2143(20)	2448(35)	6.3(0.9)
H(16,1)	2413(46)	3441(21)	2475(36)	6.6(0.9)
H(16,2)	1548(39)	3612(19)	3576(31)	4.7(0.7)
H(16,3)	1317(50)	2720(23)	2868(40)	8.1(1.0)

are of equal lengths, within the normal distribution range for the accuracies quoted. However, several of the corresponding angles are significantly different in the two molecules, especially N(1)–C(2)–C(8), C(3)–C(2)–C(8) and C(6)–N(1)–C(7) where the differences are 4·6 (4), 3·6 (4) and 4·5 (3)°, respectively.

The only short intermolecular distance in the α-promedol structure is the H(15)...N(1′) contact of 2·16 Å between the molecules at (x, y, z) and $(x, \frac{1}{2}-y, \frac{1}{2}+z)$, whereas the expected H···N van der Waals contact is 2·7 Å. This is ample evidence of hydrogen bonds linking alternating (+) and (−) molecules into infinite

Table 2. *Structure factor data* (×10)

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

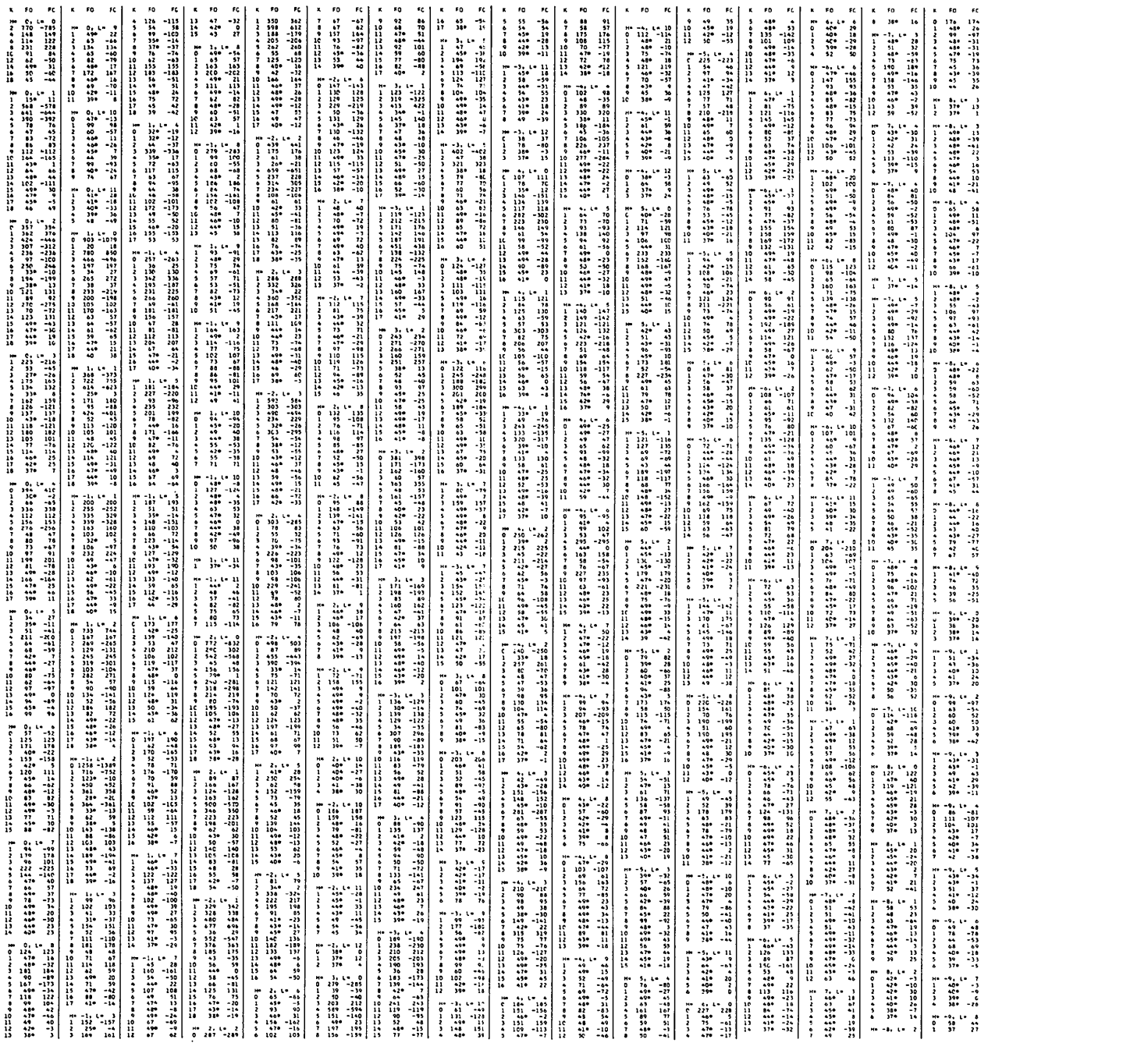

Table 3. *Torsion angles* (°) *of the piperidine ring in the promedol alcohols*

A = monoclinic, B = rhombohedral.

	α	$\beta(A)$	$\beta(B)$	γ
C(6)–N(1)–C(2)–C(3)	−58·2	−54·6	−50·1	−56·6
N(1)–C(2)–C(3)–C(4)	50·7	50·0	47·1	58·5
C(2)–C(3)–C(4)–C(5)	−46·6	−47·3	−46·5	−55·7
C(3)–C(4)–C(5)–C(6)	48·2	50·9	50·4	52·6
C(4)–C(5)–C(6)–N(1)	−58·8	−62·3	−61·6	−57·0
C(5)–C(6)–N(1)–C(2)	64·8	63·1	60·4	58·3
Mean $\|\tau\| = \bar{\tau}$	54·6	54·7	52·7	56·5
$\sigma(\tau) = [\frac{1}{5}\sum(\|\tau_i\| - \bar{\tau})^2]^{1/2}$	7·1	6·6	6·6	2·2

chains along **c**. The corresponding intermolecular O(15)···N(1′) distance is 2·912 Å, and the O(15)–H(15)···N(1′) angle is 156 (3)°. The H(15)···N(1′) vector makes angles of 106·4, 106·6 and 106·8° with N(1′)–C(2′), N(1′)–C(6′) and N(1′)–C(7′), respectively.

Conclusions

Some of the relevant structural features of the isomeric promedol alcohols (De Camp & Ahmed, 1972*a*, *c*, *d*), and the isomers of prodine HCl (Kartha, Ahmed & Barnes, 1960; Ahmed & Barnes, 1963) are summarized in Table 4. The analgetic potency of the promedol alcohols and their esters is in the order $\gamma < \alpha < \beta$, and that of the prodines is $\alpha < \beta$ (Casy & McErlane, 1971). Based on these results, the following conclusions can be drawn.

(1) The highest potency is achieved with a *cis* 5-Me/4-Ph configuration (≡*cis* 3-Me/4-Ph for the prodines).

(2) Where the configuration is *trans* 5-Me/4-Ph, the potency is highest for the *trans* 2-Me/4-Ph (α-promedol), intermediate where there is no 2-Me substituent (α-prodine), and lowest for the *cis* 2-Me/4-Ph (γ-promedol).

(3) The potency does not seem to be affected by the orientation of the equatorial phenyl ring relative to the piperidine ring, since the dihedral angle between the two rings is more for α-promedol alcohol than for the less active γ-isomer, but the reverse is observed for the prodine isomers.

The β-promedol alcohol is the only compound in the promedol and prodine series that has been found to crystallize in the axial 4-C_6H_5 conformation, and this occurs in both the monoclinic and rhombohedral crystal forms. In this conformation, the hydrogen donor (OH) and the hydrogen acceptor (N atom) are *cis* relative to the piperidine ring, and the phenyl ring is situated on the opposite side of the ring. This would enable the molecule to form two hydrogen linkages to the same receptor surface, which may be the reason why this promedol isomer has higher potency than the other promedols. The same argument would be applicable to β-prodine if it could invert easily from its solid state conformation. Since β-promedol alcohol occurs in the axial phenyl conformation in both the monoclinic and rhombohedral crystal forms, it is unlikely that this is far from a conformational energy minimum. The similarity between this molecule and morphine appears to suggest that interaction with the analgetic receptor may well involve an axial-phenyl conformation in 4-phenylpiperidines (Beckett & Casy, 1957).

Grateful acknowledgement is made to Drs A. F. Casy and K. McErlane for supplying the crystals, and to Mrs M. E. Pippy for assistance with the computations.

Table 4. *Structure–function relations for the promedol alcohols and prodines*

Me = CH_3, Ph = C_6H_5, *e* = equatorial, *a* = axial.

	Promedol alcohols				Prodines		
	γ	α	β		α	β	
Hot plate ED_{50} for the ester	1·6	0·58	0·18		0·92	0·18	mg.kg^{-1}
Configuration							
2-Me/4-Ph	*cis*	*trans*	*trans*		–	–	
5-Me*/4-Ph	*trans*	*trans*	*cis*		*trans*	*cis*	
Conformation in solid state							
2-Me	*e*	*a*	*e*		–	–	
4-Ph	*e*	*e*	*a*		*e*	*e*	
4-O	*a*	*a*	*e*		*a*	*a*	
5-Me*	*e*	*e*	*e*		*e*	*a*	
Dihedral angle			$P2_1/c$	$R\bar{3}$			
Ph-piperidine	73·7	86·6	77·0	80·4	66·1	45·1	°
Ph-[C(7), N(1), C(4), C(9), O(15)]	16·2	1·8	40·9	37·6	27·4	45·2	°
Displacement from mean plane of atoms C(2), C(3), C(5), C(6)							
C(2), C(3), C(5), C(6)	±0·004	±0·026	±0·040	±0·047	±0·017	±0·005	Å
N(1)	0·66	0·68	0·67	0·63	0·69	0·67	Å
C(4)	−0·68	−0·60	−0·63	−0·62	−0·68	−0·67	Å
Intramolecular N···O	3·50	3·58	4·20	4·16	3·49	3·43	Å

* For the prodines, substitute 3-Me for 5-Me.

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The Crystal and Molecular Structure of a 2*H*-Thiopyran *p*-Bromobenzylester, $C_{20}H_{22}O_4NS_2Br$

BY A. E. SMITH,* R. KALISH,† AND E. J. SMUTNY

Shell Development Company, Emeryville, California, U.S.A.

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The structure and configuration of the isostructural 1:1 adducts of maleic anhydride with a series of *N*-substituted methyl 3-aminodithioacrylates have been determined from three-dimensional data collected on an automatic diffractometer using graphite monochromated Mo $K\alpha$ radiation. All attempts to determine their structure by both chemical and spectroscopic methods had been unsuccessful. Crystals of a bromine derivative $C_{20}H_{22}O_4NS_2Br$ were used for the structure determination by X-rays. The unit cell is monoclinic, space group $P2_1$ (C_2^2), $a = 11{\cdot}36$ (1), $b = 8{\cdot}052$ (5), $c = 11{\cdot}77$ (1) Å, $\beta = 99{\cdot}86$ (5)°, with two molecules of $C_{20}H_{22}O_4NS_2Br$ per unit cell. The observed and calculated densities are 1·52 (4) and 1·516 g.cm^{-3} respectively. The structure was determined by Patterson–Fourier methods and refined by the full-matrix least-squares technique to an *R* index on *F* of 0·057 for 1429 reflections. The X-ray results show that the adduct possesses the 2*H*-thiopyran structure. The structure determination led to the postulation of a previously undetermined mechanism for the reaction between maleic anhydride and *N*-substituted methyl 3-aminodithioacrylates.

Introduction

In the course of a study (Smutny, 1967) of the chemistry of the 3-dialkylaminodithioacrylates, a reactive group of compounds readily derived from the trithiones, the dithioacrylates shown in Fig. 1, were observed to undergo rapid (*ca.* 1 hr) reaction with maleic anhydride in benzene at ambient temperature to afford in high yield a series of isostructural 1:1 adducts. Although the infrared and n.m.r. spectra (Kalish, Smith & Smutny, 1971) of these adducts clearly show them to be unsaturated carboxylic acids, neither the spectral parameters nor the results of chemical degradation allowed assignment of a unique structure. Without knowledge of the structure of the adduct it had not been possible to write a reasonable mechanism for the reaction between maleic anhydride and *N*-substituted methyl 3-aminodithioacrylates (Kalish *et al.*, 1971). An X-ray structure determination of the adduct was therefore carried out. The adduct from the dithioacrylate Fig. 1(*b*) and maleic anhydride was converted to the corresponding *p*-bromobenzylester $C_{20}H_{22}O_4NS_2Br$ (Fig. 2), which was used for the structure determination.

Collection and reduction of the data

Difficulties were encountered in growing crystals of the 1:1 adduct ($C_{20}H_{22}O_4NS_2Br$) large enough for X-ray examination. By repeated recrystallization by slow cooling (8–9 days) of a sealed vial of warm (70°C) saturated solution of the Br compound in a cyclo-

* Present address: 72 San Mateo Road, Berkeley, California 94707, U.S.A.

† Present address: Hoffman-La Roche Inc., Nutley, New Jersey 07110, U.S.A.