

Table 4. Intermolecular O...O distances and the corresponding hydrogen-bond geometry

	O...O (Å)	O-H (Å)	H...O (Å)	$\angle$ O-H...O (°)
O(2)...O(5)( $x, y, 1+z$ )	2.850	1.01	1.94	148
O(4)...O(3)( $-x+1, -\frac{1}{2}+y, \frac{1}{2}-z+1$ )	2.817	1.01	1.96	141
O(5)...O(4)( $-x+1, -\frac{1}{2}+y, \frac{1}{2}-z+1$ )	2.766	1.00	1.77	180

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## Structure and Absolute Configuration of (–)-*trans*-4-Methyl-10b-methoxy-carbonyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide Monohydrate

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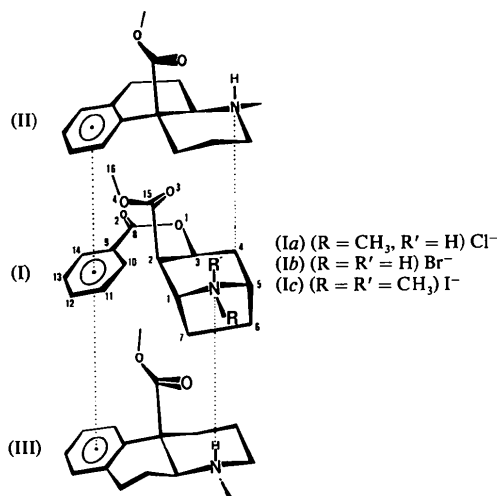
(Received 8 November 1977; accepted 8 March 1978)

**Abstract.** C<sub>16</sub>H<sub>24</sub>BrNO<sub>3</sub>, m.p. 178–180.5°C,  $[\alpha]_D^{23}$  (95% ethanol) =  $-69.1 \pm 0.5^\circ$  ( $c = 0.0365$ ), space group *P2<sub>1</sub>*,  $a = 12.720$  (3),  $b = 6.906$  (2),  $c = 9.204$  (2) Å,  $\beta = 93.84$  (1)°,  $Z = 2$ ,  $D_x = 1.475$ ,  $D_m = 1.46$  g cm<sup>-3</sup> (flotation: CCl<sub>4</sub>-C<sub>6</sub>H<sub>6</sub>). The structure was solved with *MULTAN*. Full-matrix least-squares refinement converged to  $R = 0.049$  for the 4a*R*:10b*S* configuration and to  $R = 0.042$  for the 4a*S*:10b*R* ( $P < 0.005$ ) configuration. The ring junction is *trans*. The Br<sup>-</sup> and H(N)<sup>+</sup> groups are linked through hydrogen bonds to water. Active transport of norepinephrine is

more strongly inhibited by the (–)-antipode in agreement with the more complete superimposability on 2*R*:3*S*-(–)-cocaine, the prototype inhibitor. This suggests that a *transoid*, noncontiguous, phenethylamine conformation for (–)-cocaine has biological significance.

**Introduction.** Active transport of norepinephrine (NE) into neurons is inhibited by central nervous system stimulants such as 2*R*:3*S*-(–)-cocaine.HCl (*Ia*) and

contiguous *trans*-phenethylamines suggesting that (Ia) adopts a similar *transoid*, non-contiguous, phenethylamine conformation\* at the receptor (Maxwell, Chaplin, Eckhardt, Soares & Hite, 1970). To test this hypothesis, both antipodes (II) and (III) were prepared (Aggarwal, Nieforth & Hite, 1977). The stereochemistry of the ring junction was inferred by NMR and by stereomechanistic considerations. The HBr salts† were tested as inhibitors of the uptake of NE (Neckers & Sze, 1975).



The more active (–)-salt, based upon superimposability on (I), should have the 4a*S*:10b*R* configuration (III). This report provides proof of the stereochemistry of the (–)-salt (III) and suggests structural superimposability of (Ia) on (III) in solution.

The anhydrous (–)-salt forms a monohydrate on crystallization from water. Since the hydrate was considered potentially more relevant to solution conformation, it was chosen for this study. Photographs of the crystal (0.20 × 0.10 × 0.05 mm) revealed monoclinic symmetry. Systematic absences and molecular asymmetry led to assignment of space group *P*2<sub>1</sub>. Diffraction intensities were measured with Zr-filtered, Mo K<sub>α</sub> radiation (λ = 0.7093 Å) on an automated Picker FACS-I diffractometer. Integrated intensities were corrected for Lorentz and polarization effects. No absorption correction was applied (μ = 26.9 cm<sup>-1</sup>). Lattice parameters were refined by least-squares fitting of 18 automatically centered reflections (32° < 2θ < 46°). Three standard reflections remained constant [ $\pm 2\sigma(I)_{av}$ ] throughout data collection. Of 2030 independent reflections (2θ < 54°) of the form *hkl* and *hkl* with respect to a right-handed crystal axial system,

\* This conformation is untenable because of H(2)–H(10) steric hindrance. It is presented in this idealized form for comparison with (II) and (III) and is intended to serve only as a convenient approximation to the suggested bioactive conformation.

† The (+)-amine affords a (–)-salt.

203 were considered unobserved according to the criterion:  $|F_o| > 2.0\sigma$ . The structure was solved with *MULTAN* (Germain, Main & Woolfson, 1971). Normalized structure factors were calculated from the observed data and 200  $|E|$ 's (>1.46) were used to calculate a map. From the map and subsequent cycles of structure factor calculations and difference Fourier syntheses, all the non-hydrogen atoms were located. Full-matrix least-squares refinement (Busing, Martin & Levy, 1962) with a 1/σ<sup>2</sup> weighing scheme, zerovalent

Table 1. Positional parameters (× 10<sup>4</sup>; for H × 10<sup>3</sup>) in fractions of the lattice translations

Estimated standard deviations in the last figures are given in parentheses.

	x	y	z
Br	3325 (1)	8700	1726 (1)
O(1)	1540 (2)	4604 (6)	4603 (3)
O(2)	3246 (2)	4681 (6)	5219 (4)
O(3)	4796 (3)	7606 (7)	4625 (4)
N	3724 (3)	7960 (6)	7118 (4)
C(1)	1423 (3)	7848 (8)	6516 (5)
C(2)	2108 (4)	9322 (8)	5800 (6)
C(3)	3112 (4)	9766 (8)	6720 (6)
C(4a)	3025 (3)	6545 (7)	7893 (5)
C(5)	3642 (4)	4789 (9)	8500 (5)
C(6)	2935 (3)	3720 (11)	9522 (4)
C(6a)	1821 (3)	3443 (9)	8898 (4)
C(7)	1185 (4)	2122 (8)	9568 (5)
C(8)	136 (4)	1890 (9)	9129 (6)
C(9)	–301 (3)	2968 (9)	7982 (6)
C(10)	316 (3)	4261 (7)	7267 (5)
C(10a)	1387 (3)	4544 (7)	7728 (5)
C(10b)	2045 (3)	5988 (7)	6910 (5)
C(11)	4700 (4)	8464 (12)	8011 (6)
C(12)	2354 (3)	5031 (7)	5500 (5)
C(13)	1772 (4)	3717 (19)	3212 (5)
H(W1)	519 (4)	834 (9)	485 (6)
H(W2)	562 (4)	296 (10)	608 (7)
H(N)*	400 (5)	744 (11)	619 (7)
H(1ax)*	120 (3)	837 (8)	739 (5)
H(1eq)	78 (4)	755 (8)	584 (6)
H(2ax)	226 (3)	884 (10)	484 (4)
H(2eq)	174 (4)	52 (8)	585 (5)
H(3ax)*	303 (5)	14 (11)	771 (7)
H(3eq)	371 (5)	78 (9)	620 (6)
H(4a)	285 (3)	720 (6)	879 (4)
H(5a)	422 (3)	517 (7)	913 (5)
H(5β)	394 (3)	406 (9)	777 (5)
H(6a)	295 (4)	456 (8)	56 (6)
H(6β)	323 (3)	239 (7)	984 (5)
H(7)*	157 (3)	162 (8)	37 (5)
H(8)	–31 (3)	89 (7)	958 (5)
H(9)	–95 (4)	293 (8)	761 (6)
H(10)	–5 (3)	494 (7)	638 (5)
H(11-1)	452 (3)	849 (11)	893 (5)
H(11-2)	508 (4)	943 (7)	762 (5)
H(11-3)	523 (4)	729 (8)	806 (5)
H(13-1)	114 (4)	334 (10)	265 (6)
H(13-2)	217 (6)	209 (12)	338 (8)
H(13-3)	222 (4)	459 (8)	273 (5)

\* Located by geometric considerations.

scattering factors, isotropic temperature factors and corrections for secondary extinction and anomalous dispersion (*International Tables for X-ray Crystallography*, 1974) was followed by anisotropic refinement and calculation of a difference Fourier map to locate the H atoms. Of the 31 strongest peaks, 20 proved to be H atoms. The remaining four H atoms were located among weaker peaks in the map by geometric considerations (Table 1). The final stage of refinement, starting with arbitrarily chosen isotropic temperature factors of 3.5 Å<sup>2</sup> for H, was accomplished in sections, first refining the H and then the heavier atoms until convergence was achieved. Final parameter shifts were less than 0.5σ. The final residuals were  $R = 0.042$  and  $R_w = 0.043$ , minimizing  $\sum w(|F_o| - |F_c|)^2$ . \* Changing the sign of the atomic positional parameters resulted in convergence at  $R = 0.049$  and  $R_w = 0.050$  indicating that the 4aS:10bR (III) configuration described by the positional parameters in Table 1 is correct ( $P < 0.005$ ) (Hamilton, 1965) for the (–)-salt. The ring junction is *trans* (Fig. 1).

**Discussion.** Bond lengths and angles and pertinent torsion angles and interatomic distances (Busing, Martin & Levy, 1964) are shown in Fig. 2. While bond lengths and angles are consistent with those found in (Ia) (Gabe & Barnes, 1963) in norcocaine.HBr (Ib) (Kelly, Knox, Lazer, Nieforth & Hite, 1977) and cocaine methiodide (Ic) (Shen, Ruble & Hite, 1975), all torsion angles† [C(1)–C(2)–C(15)–O(3) and C(4a)–C(10b)–C(12)–O(2)] about bonds joining the planar, *transoid* methoxycarbonyl (COOMe) groups to the ring systems in (I) and (III) vary widely. However, the

\* Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33462 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

† Note the difference in numbering systems in (II) and (III) compared with (I).

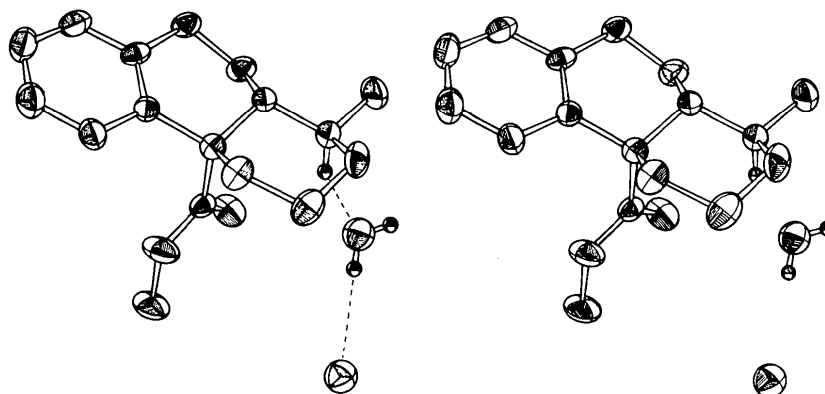


Fig. 1. Stereoprojection of the molecules down *b*. Dashed lines indicate hydrogen bonds.

relations between these solid-state torsion angles and the steric and electrostatic forces which govern them suggest that the torsion angle in (Ia), (Ib) and (III) in solution is the same as that in solid state (III). In (Ib), the axial hydrogen (*a*-H) on N forms a planar trigonal, bifurcated hydrogen bond (H-bond), intermolecularly with O(2)<sub>545</sub> (2.33 Å) and intramolecularly with O(3)<sub>555</sub> (2.14 Å). The O(2)<sub>545</sub> to O(3)<sub>555</sub> distance (3.49 Å) is larger than the sum of the van der Waals radii (2.80 Å). The O(3)···H–N<sup>+</sup> H-bond governs the C(1)–C(2)–C(15)–O(3) torsion angle (+54°). While there is also a planar, bifurcated H-bond to O(2) (2.28 Å) and O(3) (1.83 Å) in (III), the C(4a)–C(10b)–C(12)–O(2) torsion angle is –3°. The O(2) to O(3) distance (2.90 Å) is close to the sum of the van der Waals radii but the bifurcated H-bond is not trigonal (Fig. 2). The H-bond lengths and angles in (Ib) and (III)

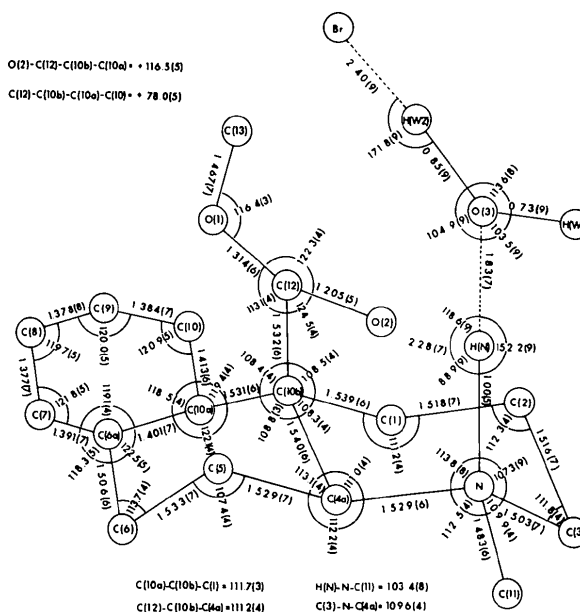


Fig. 2. Bond distances (Å), bond angles (°), and selected torsion angles (°) with standard deviations in the last place shown (in parentheses).

are consistent with the expectation that a more polar water molecule should form a stronger (shorter and more linear) H-bond than a carbonyl group. The dictates the nearly axial (152°) disposition of O(3) in (III). To sterically accommodate O(3), O(2) had to be displaced, relative to O(3) in (Ib), by rotation about the C(10b)–C(12) bond. Because mesomeric and electro-meric polarization of an ester imparts higher electron density to a carbonyl O than to an ether O, the rotation is negative (–57°) rather than positive to preserve the stronger O(2)···H–N<sup>+</sup> interaction in (III).

The COOMe group in (Ia) is rotated 115 or 172° about the C(2)–C(15) bond relative to rotations about the corresponding bonds [C(2)–C(15) and C(10b)–C(12)] in (Ib) and (III) respectively. The +169° C(1)–C(2)–C(15)–O(3) torsion angle places the ether O [O(4)] in a position near that occupied by the carbonyl O [O(2)] in (III). The C(1)–C(2)–C(15)–O(4) torsion angle in (Ia) is –17°. This rotamer of (Ia) is preferred to that 180° opposed to it (*cf.* III) because electrostatic repulsion between O(3) and Cl<sup>–</sup> is stronger than that between O(4) and Cl<sup>–</sup>. The Cl<sup>–</sup>, like O(3) in (III), forms an H-bond with the *a*-H on N. The Cl<sup>–</sup> is closer to O(4) than to O(3) (3.39 *vs* 3.68 Å). Steric crowding and/or electrostatic repulsion is also suggested by the skewed orientation of Cl<sup>–</sup> relative to C(1) and C(5) (4.20 *vs* 3.60 Å). However, electrostatic repulsion is the more plausible driving force since the Cl<sup>–</sup> to O distances are larger than the sum of the van der Waals radii (3.20 Å). Furthermore, although the Cl<sup>–</sup> to C(15) distance (3.48 Å) is slightly shorter than the sum of the van der Waals radii (3.60 Å), no significant distortion in bond distances or bond angles can be detected on comparing (Ia) and (Ib).

These considerations are in accord with structural features observed in (Ic) in which the C(1)–C(2)–C(15)–O(3) torsion angle is 133°. The *α*-methyl, unlike the Cl<sup>–</sup> in (Ia), is thus nearly symmetrically disposed with respect to the COOMe O atoms [O(3) = 3.35, O(4) = 3.31 Å] and the bridgehead C atoms [C(5) = 2.57, C(1) = 2.63 Å]. While the former distances are close to the sum of the van der Waals radii (3.4 Å), interplay between steric repulsive and electrostatic attractive forces (Craven & Hite, 1973; Hite & Craven, 1973; Hite & Soares, 1973; Ruble, Hite & Soares, 1976) is perceptible. The only significant distortion in bond distances or angles observable in comparing (Ic) with (Ia) and (Ib) is an increase in the C(1)–C(2)–C(15) bond angle caused by the C(15) to *α*-methyl contact of 2.98 Å. This is much shorter than the sum of the van der Waals radii (3.80 Å) and in view of the small angular distortion suggests attraction between the *α*-methyl and COOMe O atoms. It is not clear from either inter- or intramolecular interactions why the +133° rotamer rather than the –47° rotamer is preferred.

While steric effects of the *a* ligands on N dictate rotation about the C(2)–C(15) or C(10b)–C(12)

bond, electrostatic effects dictate the sign and magnitude of the rotation in a rational manner. Accordingly, these torsion angles for (Ia), (Ib) and (III) in solution and for (III) in the solid state should be approximately the same since, at physiological pH, the amines, like solid-state (III), should be nearly totally protonated, solvated (H-bonded to water), and solvent separated from their counterions.

Superimposability of (Ia) on (III) is less complete with respect to the benzoate group. The C(2)–C(3)–O(1)–C(8) conformation is *gauche* in (Ia) (–76°) and (Ic) (–73°) as required and although it is *trans* in (Ib), this is governed by the intermolecular O(2)···H<sub>a</sub>–N<sup>+</sup> H-bond. While the C(3)–O(1)–C(8)–C(9) conformation is consistently *trans* (Ia –179°, Ib 176°, Ic 167°) rotation about the C(8)–O(1) bond is the *only* conformational change required to develop the rotamer shown in (I). Physical evidence clearly shows that the *transoid* conformation of esters is the most thermodynamically stable conformation (Owen & Sheppard, 1963; LeFèvre & Sundaram, 1962) but the energetics of the drug receptor association could provide the driving force.

These considerations, the configuration of the (–)-salt (III) and its potency relative to the (+)-salt (II) are consistent with the view that a *transoid*, non-contiguous, phenethylamine conformation close to that shown in (Ia) (*cf.* III) has biological significance in inhibition of NE uptake.

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## 9-*tert*-Butylthioxanthene

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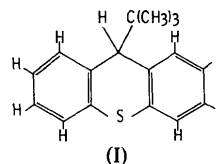
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**Abstract.** C<sub>17</sub>H<sub>18</sub>S, orthorhombic, *Pmn*2<sub>1</sub>, *Z* = 2, *M<sub>r</sub>* = 254.39, *a* = 16.096 (2), *b* = 6.002 (1), *c* = 7.133 (1) Å, *V* = 689.17 (20) Å<sup>3</sup>, *D<sub>x</sub>* = 1.226 g cm<sup>-3</sup>, λ(Cu *Kα*) = 1.5418 Å, μ(Cu *Kα*) = 18.33 cm<sup>-1</sup>. Final residual *R* = 0.045. The *tert*-butyl group is in a boat-axial conformation with respect to the central thioxanthene ring.

**Introduction.** 9-*tert*-Butylthioxanthene is one of a series of thioxanthene derivatives whose crystal structures have been studied in this laboratory. The crystal structure of 9-isobutylthioxanthene (Chu, 1973) has already been determined. This work will determine the effect of a more bulky *meso* substituent, a *tert*-butyl group, on the stereochemistry of the thioxanthene ring system.

Single crystals of 9-*tert*-butylthioxanthene (I) were obtained through the courtesy of Dr Andrew L. Ternay Jr, of the Chemistry Department of the University of Texas at Arlington. The unit-cell parameters were obtained by measuring the 2θ values of 15 reflections. The space group, *Pmn*2<sub>1</sub>, was deduced from systematic absences (*h*0*l* absent with *h* + *l* odd). The intensity data were collected on a Syntex P2<sub>1</sub> automatic diffractometer with a crystal of approximately 0.16 × 0.61 × 0.32 mm. A θ/2θ scanning mode with graphite-monochromatized Cu *Kα* radiation was used to measure 646 independent reflections with 2θ values below 130°, of which 636 reflections were considered observed by the criterion *I* > 3.0σ(*I*), where σ(*I*) was determined from counting statistics. The intensity data were reduced to structure amplitudes by the application of Lorentz and polarization factors, and no absorption corrections were applied.



The structure was determined by the heavy-atom method. Since there are only two molecules in a unit cell with space group *Pmn*2<sub>1</sub>, the molecule is situated at the special position with the two halves of the molecule related by a mirror plane. The refinement was carried out by the full-matrix least-squares method (Busing, Martin & Levy, 1962) with isotropic temperature factors and the block-diagonal least-squares method (Shiono, 1971) with anisotropic temperature factors. Some H positions were located on a difference Fourier synthesis, and the rest were calculated with reasonable bond lengths and bond angles with respect to the atoms to which they are bonded. The isotropic temperature factors were used for the H atoms in the refinement. The weight of a reflection was assigned as 1/[σ(*F*)]<sup>2</sup>, where σ(*F*) was calculated from counting statistics. The quantity  $\sum w(|F_o| - |F_c|)^2$  was minimized. The final *R* index ( $\sum ||F_o| - |F_c|| / \sum |F_o|$ ) was 0.045.\* The magnitude,  $[\sum w(F_o - F_c)^2 / (m - n)]^{1/2}$ , where *m* is the number of reflections and *n* is the number of parameters refined, was 0.80. The atomic scattering factors used for S and C atoms were those from *Inter-*

\* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33463 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.