

## Structure of *trans*-5 $\alpha$ ,10b $\beta$ -Dimethoxycarbonyl-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrobromide

BY BRIAN M. CRAVEN

Department of Crystallography, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA

AND NARANJAN D. AGGARWAL, KARL A. NIEFORTH,  
JAMES B. ANDERSON AND GILBERT J. HITE\*

Section of Medicinal Chemistry, Pharmacognosy and Immunology, School of Pharmacy, and Institute of Materials Science, University of Connecticut, Storrs, Connecticut 06268, USA

(Received 7 August 1978; accepted 20 November 1978)

**Abstract.** C<sub>18</sub>H<sub>24</sub>NO<sub>4</sub><sup>+</sup>.Br<sup>-</sup>, m.p. 398 K; PMR (CDCl<sub>3</sub>):  $\delta$  2.32 p.p.m. (*s*,3H,NCH<sub>3</sub>); space group *P*2<sub>1</sub>/*c*, *a* = 11.430 (2), *b* = 13.619 (3), *c* = 12.299 (5) Å,  $\beta$  = 107.82 (3)°, *Z* = 4, *D*<sub>x</sub> = 1.457, *D*<sub>m</sub> (flotation: CCl<sub>4</sub>-C<sub>6</sub>H<sub>6</sub>) = 1.453 Mg m<sup>-3</sup>. The structure was solved by the heavy-atom method. Block-diagonal refinement converged with *R*(*F*) = 0.06. The ring junction is *trans* and the ester groups are *trans*. Ring *B* is in the boat conformation with C(6) and C(10b) at the bow and stern. These structural features are consistent with, although not predictable on the basis of, PMR and equilibrium studies which together with this X-ray study unequivocally establish the structure of a second isomer [m.p. 408 K; PMR (CDCl<sub>3</sub>):  $\delta$  2.63 p.p.m. (*s*,3H,NCH<sub>3</sub>)] as the thermodynamically less stable, *B/C trans*, C(5) epimer with ring *B* in the boat conformation. The piperidine ring is in the chair conformation and H(N) is hydrogen bonded to Br<sup>-</sup> (2.16 Å). It is in close contact (2.30 Å) with O(1), the ether oxygen of the C(10b) ester unit. This conformation of the C(10b) ester group is consistent with and predictable on the basis of electrostatic interactions first recognized in similar model compounds.

**Introduction.** Four isomers including the title compound were isolated chromatographically during attempts to prepare the 10b-monomethoxycarbonyl isomer (Aggarwal, Nieforth & Hite, 1977, 1978). Since these diesters, like the monoesters, are conformationally rigid *trans*-phenethylamines, stereochemically superimposable upon cocaine, it was of interest to determine the structures for correlation with biological activity (Anderson, Aggarwal, Nieforth & Hite, 1978). The principal differences in the PMR spectra of the four isomers (I–IV) are the NCH<sub>3</sub> absorptions at 2.32, 2.63, 2.20 and 2.63 p.p.m. respectively. It appeared that this could be used to assign *B/C* stereochemistry

since the *B/C trans* and *B/C cis* 10b-monoesters absorb at 2.31 and 2.68 p.p.m. respectively. However, it was subsequently shown (Aggarwal, Nieforth & Hite, 1978) that C(5) epimerization of (II) afforded (I) almost quantitatively under conditions that do not affect the *B/C* stereochemistry. Accordingly, the C(5) ester group and not the *B/C* stereochemistry dictates the NCH<sub>3</sub> chemical shifts in (I) and (II). Use of the relative *B/C* stereochemistries of the (I), (II) and (III), (IV) isomer pairs and the relative thermodynamic stabilities of (I) and (II) in model-building studies failed to provide a unique rationale for the chemical shifts or structures of (I)–(IV). The conformations of the *B* ring (boat, twist) in both the *B/C cis* and *B/C trans* molecular models profoundly affect the relative orientation of the NCH<sub>3</sub> and C(5) ester moieties. While this affects chemical shifts in a predictable way (Silverstein, Bassler & Morrill, 1974) the relative stabilities of the conformers were not obvious. Thus, a complete definition of the conformations of the ring junction, ester units and *B* ring of at least one isomer is essential for an unequivocal solution to this structural problem.

Weissenberg photographs of monoclinic plates (0.6 × 0.3 × 0.1 mm) of isomer (I) elongated on *c* showed the space group to be *P*2<sub>1</sub>/*c*. Lattice parameters and intensity data were measured at 293 K using a computer-controlled four-circle diffractometer and graphite-monochromated Mo *K* $\alpha$  radiation ( $\lambda$  = 0.7093 Å). The crystal was mounted with *c* along the diffractometer  $\phi$  axis. Unit-cell dimensions were obtained by a least-squares fit of angular data for twelve reflections. Intensities were measured using  $\theta/2\theta$  scans for 2427 non-symmetry-related reflections with  $\sin \theta/\lambda \leq 0.55 \text{ \AA}^{-1}$ . The variance in an integrated intensity was assumed to be  $\sigma^2(I) = \sigma^2 + (0.02I)^2$  where  $\sigma^2$  is the variance due to counting statistics. No corrections were applied for X-ray absorption or extinction. Calculations for the structure determination and refinement were expedited by using only the 1671 reflections

\* To whom correspondence should be addressed.

Table 1. Atomic positional parameters (for  $Br^- \times 10^5$ ; for C, N, O  $\times 10^4$ ; for H  $\times 10^2$ ) and their e.s.d.'s

Least-squares e.s.d.'s are shown in parentheses and refer to the least significant digit in the parameter.

|        | x         | y         | z         |        | x   | y  | z  |
|--------|-----------|-----------|-----------|--------|-----|----|----|
| $Br^-$ | 24709 (9) | 10829 (8) | 34290 (8) | H(1)1  | 51  | 39 | 37 |
| C(1)   | 4357 (6)  | 3671 (6)  | 3208 (7)  | H(1)2  | 41  | 31 | 37 |
| C(2)   | 4794 (7)  | 3254 (6)  | 2243 (7)  | H(2)1  | 50  | 38 | 17 |
| C(3)   | 3797 (7)  | 2642 (6)  | 1457 (7)  | H(2)2  | 56  | 28 | 26 |
| C(4a)  | 2185 (6)  | 3695 (5)  | 1908 (6)  | H(3)1  | 40  | 24 | 7  |
| C(5)   | 996 (6)   | 4280 (5)  | 1334 (6)  | H(3)2  | 35  | 20 | 18 |
| C(6)   | 941 (7)   | 5258 (6)  | 1981 (6)  | H(4a)  | 20  | 31 | 25 |
| C(6a)  | 1525 (7)  | 5151 (6)  | 3247 (7)  | H(5)   | 9   | 45 | 4  |
| C(7)   | 969 (8)   | 5510 (6)  | 4037 (7)  | H(6)1  | 15  | 58 | 17 |
| C(8)   | 1562 (8)  | 5437 (7)  | 5193 (7)  | H(6)2  | 0   | 55 | 18 |
| C(9)   | 2725 (8)  | 5009 (7)  | 5579 (7)  | H(7)   | 0   | 58 | 37 |
| C(10)  | 3287 (7)  | 4640 (6)  | 4816 (6)  | H(8)   | 13  | 56 | 60 |
| C(10a) | 2707 (7)  | 4716 (5)  | 3663 (6)  | H(9)   | 32  | 49 | 64 |
| C(10b) | 3217 (7)  | 4332 (5)  | 2725 (6)  | H(10)  | 43  | 44 | 51 |
| C(11)  | 1650 (7)  | 2447 (6)  | 372 (7)   | H(11)1 | 14  | 20 | 9  |
| C(12)  | 3654 (7)  | 5227 (6)  | 2192 (6)  | H(11)2 | 20  | 21 | -2 |
| C(13)  | 3870 (7)  | 5923 (7)  | 493 (7)   | H(11)3 | 9   | 27 | 0  |
| C(14)  | -169 (7)  | 3711 (6)  | 1249 (7)  | H(13)1 | 34  | 65 | 4  |
| C(15)  | -1317 (8) | 2949 (7)  | 2316 (7)  | H(13)2 | 48  | 61 | 8  |
| N      | 2588 (5)  | 3191 (5)  | 987 (5)   | H(13)3 | 38  | 58 | -3 |
| O(1)   | 3402 (5)  | 5147 (4)  | 1069 (4)  | H(15)1 | -21 | 34 | 20 |
| O(2)   | 4202 (5)  | 5903 (4)  | 2746 (4)  | H(15)2 | -16 | 26 | 16 |
| O(3)   | -196 (5)  | 3399 (4)  | 2279 (4)  | H(15)3 | -13 | 26 | 31 |
| O(4)   | -979 (5)  | 3573 (5)  | 379 (5)   | H(N)   | 26  | 37 | 2  |

with  $|F_{obs}| > 3\sigma(F_{obs})$ . The structure was determined by the heavy-atom method and refined by a block-diagonal least-squares procedure so that the function minimized was:  $\sum_H w_H \Delta_H^2$  where  $\Delta_H = |F_{obs}| - |F_H^{calc}|$  and  $w_H = 1/\sigma^2(F_H^{obs})$ . Atomic form factors were taken from Cromer & Waber (1965), except for H (Stewart, Davidson & Simpson, 1965). All H atoms were found in an electron density difference map which was calculated after some refinement of anisotropic temperature factors for the heavier atoms. The refinement was completed with the H-atom positional parameters fixed as those obtained from the map and with a uniform fixed isotropic temperature factor,  $B = 5.0 \text{ \AA}^2$ . Convergence was obtained with  $R(F) = R_w(F) = 0.06$ , a quadratic mean error of 2.31 and final shifts less than  $0.4\sigma$  and  $0.13\sigma$  for thermal and positional parameters respectively. Final atomic positional parameters with e.s.d.'s are in Table 1.\*

**Discussion.** The bond lengths and angles (Fig. 1) are consistent with those reported for the 10b-monoester (Anderson, Aggarwal, Nieforth & Hite, 1978). The B/C ring juncture and the ester groups are *trans* (Fig. 2). Internal torsion angles for ring B (Fig. 1) indicate an imperfect boat conformation with C(6) and C(10b)

at the bow and stern positions. The torsion angles defining the relative orientation of the  $NCH_3$  and C(5) ester units (Fig. 1) show that the  $NCH_3$  protons should be nearly unaffected by the conical shielding and deshielding segments of the carbonyl group (Silverstein, Bassler & Morrill, 1974). In the C(5) epimer (II), deshielding (2.63 p.p.m.) of the  $NCH_3$  protons relative

- C(4a)-C(10b)-C(12) 116.5  
 C(1)-C(10b)-C(10a) 112.3  
 O(1)-C(12)-C(10b)-C(4a) -21.5  
 O(3)-C(14)-C(5)-C(6) -67.7

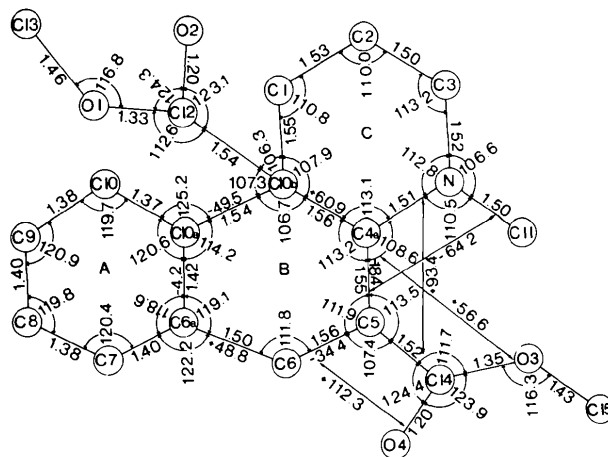


Fig. 1. Bond distances ( $\text{\AA}$ ) and angles ( $^\circ$ ) and selected torsion angles ( $^\circ$ ) [ $\sigma(d) = 0.01 \text{ \AA}$ ;  $\sigma(\theta) = 0.5^\circ$ ].

\* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34085 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

to (I) (2.32 p.p.m.) is consistent *only* with a boat conformation for ring *B* in (II). Thus, the driving force for epimerization of (II) to (I) is largely provided by relief of steric strain arising from the eclipsing of the N–C(4a) and C(5)–C(14) bonds in (II). Assignment of ester stereochemistry to (III) and (IV) is not warranted solely on the basis of PMR data, particularly in view of the larger number of possible conformers in this more mobile *B/C cis* system. Definitive experiments are in progress.

The axial H(N) is hydrogen bonded to Br<sup>-</sup> (Fig. 2). It is also involved in a weak interaction with O(1), the ether oxygen of the C(10b) ester group. This conformation about the C(10b)–C(12) bond is consistent with earlier observations (Anderson, Aggarwal, Nieforth & Hite, 1978) on similar compounds. Thus, the C(4a)–C(10b)–C(12)–O(1) torsion angle of –21.5° in (I), like the corresponding C(1)–C(2)–C(15)–O(4) torsion angle (+17°)\* in (+)-cocaine hydrochloride (Anderson, Aggarwal, Nieforth & Hite, 1978), places O(1) closer than O(2) to the Br<sup>-</sup>, as expected on electrostatic grounds. Further evidence in support of the role of electrostatic attractive and repulsive driving forces in governing the conformation about the C(10b)–C(12) bond is obtained from a comparison of the C(4a)–C(10b)–C(12)–O(2) torsion angles in (I) (+160°) and the hydrated hydrobromide salt of the (+)-*trans*-10b-monomethoxycarbonyl analog (+3°)\*. In the absence of the molecule of water of hydration bridging the H(N) and Br<sup>-</sup> atoms, the latter is closer to the C(10b) ester group and repels the more electropositive ester oxygen [O(2)], while in the presence of the molecule of water, the Br<sup>-</sup> is further from the ester group and the repulsive electrostatic effect of Br<sup>-</sup> on O(2) is diminished allowing the interaction of H(N) with O(2) rather than O(1).

\* The comparable torsion angle in (–)-cocaine is –17°. The value cited here is that for the mirror image stereochemically superimposable upon (I). For the purposes of this discussion and for the same reason the transformation in sign has also been applied to the observed (–3°) torsion angle [C(4a)–C(10b)–C(12)–O(2)] of the (–)-*trans*-10b-monomethoxycarbonyl hydrobromide hydrate.

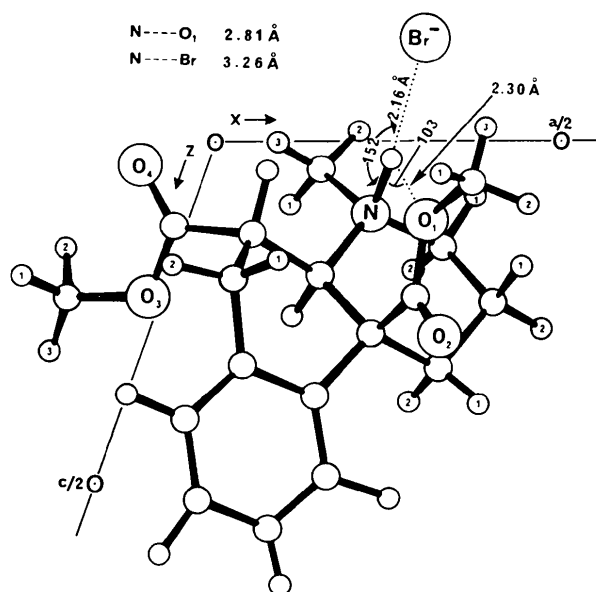


Fig. 2. ORTEP (Johnson, 1965) projection down the *b* axis.

This study was supported by the State of Connecticut Drug Dependency Trust and by US Public Health Service Grant RR 05743.

#### References

- AGGARWAL, N. D., NIEFORTH, K. A. & HITE, G. J. (1977). Abstr. 3rd Annu. NERMCIAP Meet., Boston, Mass., April 15–16, No. 6.
- AGGARWAL, N. D., NIEFORTH, K. A. & HITE, G. J. (1978). Abstr. Acad. Pharm. Sci. Meet., Hollywood, Florida, November 12–16, No. 11.
- ANDERSON, J. B., AGGARWAL, N. D., NIEFORTH, K. A. & HITE, G. J. (1978). *Acta Cryst.* B34, 2344–2348.
- CROMER, D. T. & WABER, J. T. (1965). *Acta Cryst.* 18, 104–109.
- JOHNSON, C. K. (1965). ORTEP. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee.
- SILVERSTEIN, R. M., BASSLER, G. C. & MORRILL, T. C. (1974). *Spectrophotometric Identification of Organic Compounds*, 3rd ed., p. 169. New York: John Wiley.
- STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* 42, 3175–3187.