

## O.r.d. Studies of $\beta$ -Amino Ketones. II. The Crystal Structure and Absolute Configuration of (+)-[(-)-1-Methyl-3-benzoylpiperidine *R*:*R*-(+)-Bitartrate] Monohydrate

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Crystals of (+)-[(-)-1-methyl-3-benzoylpiperidine *R*:*R*-(+)-bitartrate] monohydrate [ $C_{17}H_{25}NO_8$ ] are orthorhombic with space group  $P2_12_12_1$ ; lattice translations,  $a = 29.552$  (9),  $b = 7.780$  (5),  $c = 7.766$  (5) Å,  $D_x = 1.381$ ,  $D_m(\text{HCC}_3\text{-C}_6\text{H}_6) = 1.384$  g cm $^{-3}$ ;  $Z = 4$ ; and forms {100}, {201}, {210}. The structure was solved by direct methods. Atomic parameters were refined by the block-diagonal, least-squares procedure to  $R(\text{weighted}) = 0.040$ . The absolute configuration of the (-)-amine component is *S*. The benzoyl group is equatorial and the O(1)-C(7)-C(3)-C(2) torsion angle is 17°. The evidence suggests that electrostatic attraction across the short, non-bonded O(1)-C(2) distance (2.66 Å) is a factor in stabilizing this conformation. This, together with the rotatory dispersion data for the (-)-amine component in aqueous acid, is consistent with antiocant behavior.

### Introduction

A solution of 30 g of racemic 1-methyl-3-benzoylpiperidine (I) (Smisman & Hite, 1959) in 500 ml of acetone was added to a solution of 22.5 g of *R*:*R*-(+)-tartaric acid in 3 l of acetone. The 10 g of dextrorotatory salt which crystallized was repeatedly recrystallized from 1:4 ethanol:acetone in an open flask until there was no significant change in the specific rotation of the salt: m.p. 101–102°;  $[\alpha]_D^{27}$  (H $_2$ O)  $38.2 \pm 0.3^\circ$  ( $c$  5.00); analysis calculated for  $C_{17}H_{23}NO_7 \cdot H_2O$ : C, 54.98, H, 6.79, N, 3.77, O, 34.47; found: C, 54.9, H, 6.87, N, 3.59, O (by difference) 34.6.

An aqueous solution of the salt, alkalized with dilute sodium carbonate solution, was extracted with petroleum ether (b.p. 40–60°). The extract was dried over sodium sulfate, filtered and concentrated to give (-)-I: m.p. 59–60°;  $[\alpha]_D^{27}$  (octane)  $-59.1 \pm 0.5^\circ$  ( $c$  0.131); analysis calculated for  $C_{13}H_{17}NO$ : C, 76.81, H, 8.43, N, 6.89, O, 7.87; found: C, 77.0, H, 8.33, N, 6.89, O (by difference) 7.66; R.D. in 0.1*N* aqueous hydrochloric acid ( $c$  0.17), 19°, positive Cotton effect:  $[\alpha]_{540} + 67^\circ$ ,  $[\alpha]_{406} + 92^\circ$ ,  $[\alpha]_{400} + 154^\circ$ ,  $[\alpha]_{360} + 317^\circ$ ,  $[\alpha]_{340} + 618^\circ$ ,  $[\alpha]_{331} + 938^\circ$ ,  $[\alpha]_{320} + 584^\circ$ ,  $[\alpha]_{306} - 52^\circ$ ,  $[\alpha]_{302} - 135^\circ$ ; R.D. in octane ( $c$  0.131), 19°, negative Cotton effect:  $[\alpha]_{470} - 69^\circ$ ,  $[\alpha]_{420} - 104^\circ$ ,  $[\alpha]_{376} - 241^\circ$ ,  $[\alpha]_{361} - 374^\circ$ ,  $[\alpha]_{353} - 266^\circ$ ,  $[\alpha]_{349} - 298^\circ$ ,  $[\alpha]_{340} - 197^\circ$ ,  $[\alpha]_{320} + 286^\circ$ ,  $[\alpha]_{300} + 775^\circ$ ,  $[\alpha]_{290} + 915^\circ$ .

A crystal of (+)-[(-)-1-methyl-3-benzoylpiperidine *R*:*R*-(+)-bitartrate] monohydrate was mounted on a Nonius, CAD-IV, automated diffractometer. Graphite monochromated, Cu  $K\alpha$  radiation ( $\lambda = 1.5418$  Å) was used to measure 2142 independent reflections for which  $\sin \theta/\lambda \leq 0.063$  Å $^{-1}$  and for which  $h$ ,  $k$ , and  $l$  were positive with respect to a right handed crystal

axial system. Other than systematic absences, there were 594 unobservably weak reflections [ $I \leq 2\sigma(I)$ ]. These were assigned values of  $I = \sigma(I)/2$ . Three standard reflections remained constant [ $\pm 2\sigma(Iv)$ ] throughout data collection.

Seven of eleven acceptable solutions provided by *MULTAN* (Germain, Main & Woolfson, 1970) from 250 of the highest ( $> 1.5$ ) renormalized  $|E|$ 's were essentially the same. One of the group of seven solutions was chosen to provide an *E* map from which the positions of all non-hydrogen atoms were determined. Isotropic thermal parameters (3.5 Å $^2$ ) were initially assigned to all atoms. Atomic parameters were refined by a block-diagonal, least-squares procedure until convergence at  $R_{\text{all}} \{(\sum |d|/\sum |F_{\text{meas}}|)\} = 0.107$  and  $R_{\text{obs}} = 0.077$ . All but four hydrogen atoms were located in a difference Fourier map. A further refinement, in which unobservably weak reflections were assigned zero weight, converged at  $R_{\text{all}} = 0.084$  and  $R_{\text{obs}} = 0.052$ . Thermal parameters (3.5 Å $^2$ ) for hydrogen atoms were not refined. The remaining hydrogen atoms were located in a difference Fourier map. The final cycles of refinement converged at  $R_{\text{all}} = 0.074$  and  $R_{\text{obs}} = 0.044$  with a weighted†  $R = 0.040$ . The final atomic parameters are listed in Table 1. Since these define the correct (Bijvoet, Peerdeman & van Bommel, 1951; Bijvoet, 1955) absolute configuration (*R*:*R*) (Chan, 1964) for the (+)-tartaric acid moiety, the *S*-configuration provided by the atomic parameters for the (-)-amine component is also correct.‡ The bond

† Weighted  $R = \sqrt{\sum (\omega \Delta^2)} / \sqrt{\sum (\omega |F_{\text{meas}}|^2)}$  where  $\omega = [1/\sum (F)]^2$  and  $\Delta = (|F_{\text{meas}}| - |F_{\text{calc}}|)$ .

‡ The table of  $|F_{\text{meas}}|$  and  $|F_{\text{calc}}|$  has been deposited with the National Lending Library, England, as Supplementary Publication No. SUP 30198. Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH 1 1NZ, England.

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Table 1. Atomic positional and thermal parameters

The estimated standard deviations are shown in parentheses and refer to the last digit(s) of the respective values. The positional parameters ( $x, y, z$ ) are fractions of the lattice translations.

The anisotropic temperature factor expression used is  $\exp[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23})]$ .

## (a) Non-hydrogen atoms

	$x$	$y$	$z$	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
O(1T)	0.2834 (1)	0.4730 (3)	0.8688 (4)	0.0009 (1)	0.0100 (4)	0.0232 (6)	0.0007 (1)	-0.0007 (1)	0.0039 (5)
O(2T)	0.2087 (1)	0.4492 (3)	0.8350 (3)	0.0009 (1)	0.0068 (4)	0.0188 (5)	-0.0005 (1)	-0.0004 (1)	0.0009 (4)
C(1T)	0.2475 (1)	0.5325 (4)	0.8289 (4)	0.0009 (1)	0.0087 (6)	0.0096 (6)	-0.0001 (1)	-0.0002 (1)	-0.0018 (6)
C(2T)	0.2414 (1)	0.7162 (4)	0.7658 (4)	0.0006 (1)	0.0071 (5)	0.0091 (6)	0.0000 (1)	-0.0003 (1)	-0.0002 (5)
O(3T)	0.2848 (1)	0.7956 (3)	0.7610 (3)	0.0006 (1)	0.0106 (4)	0.0116 (4)	-0.0002 (1)	0.0002 (1)	0.0026 (4)
C(3T)	0.2101 (1)	0.8178 (4)	0.8872 (4)	0.0007 (1)	0.0066 (5)	0.0094 (6)	-0.0002 (1)	0.0000 (1)	-0.0001 (5)
O(4T)	0.2251 (1)	0.8070 (3)	1.0585 (3)	0.0012 (1)	0.0113 (4)	0.0091 (4)	-0.0002 (1)	0.0003 (1)	0.0008 (4)
C(4T)	0.2047 (1)	1.0043 (4)	0.8198 (4)	0.0006 (1)	0.0075 (5)	0.0117 (6)	0.0001 (1)	0.0006 (1)	0.0000 (6)
O(5T)	0.1941 (1)	1.0217 (3)	0.6665 (3)	0.0013 (1)	0.0110 (4)	0.0104 (4)	0.0005 (1)	-0.0006 (1)	0.0002 (4)
O(6T)	0.2104 (1)	1.1231 (3)	0.9251 (3)	0.0017 (1)	0.0074 (4)	0.0128 (5)	-0.0001 (1)	-0.0002 (1)	-0.0010 (4)
C(1)	0.3653 (1)	0.6041 (6)	1.0576 (5)	0.0013 (1)	0.0226 (9)	0.0152 (9)	0.0002 (2)	0.0003 (2)	0.0033 (9)
N(1)	0.3693 (1)	0.6467 (3)	0.8721 (4)	0.0006 (1)	0.0116 (5)	0.0169 (6)	0.0002 (1)	0.0003 (1)	0.0024 (5)
C(2)	0.3972 (1)	0.8049 (4)	0.8492 (5)	0.0008 (1)	0.0117 (6)	0.0157 (7)	-0.0002 (1)	-0.0001 (2)	0.0000 (7)
C(3)	0.4038 (1)	0.8547 (4)	0.6612 (5)	0.0006 (1)	0.0111 (6)	0.0151 (7)	-0.0003 (1)	-0.0001 (2)	-0.0003 (7)
C(4)	0.4216 (1)	0.7019 (5)	0.5557 (5)	0.0011 (1)	0.0161 (8)	0.0157 (8)	0.0001 (2)	0.0005 (2)	-0.0002 (7)
C(5)	0.3906 (1)	0.5470 (5)	0.5828 (5)	0.0012 (1)	0.0121 (8)	0.0208 (9)	-0.0006 (2)	0.0006 (2)	-0.0035 (8)
C(6)	0.3881 (1)	0.5002 (5)	0.7699 (6)	0.0011 (1)	0.0099 (7)	0.0259 (9)	-0.0002 (2)	0.0008 (2)	-0.0012 (8)
C(7)	0.4367 (1)	1.0046 (5)	0.6552 (5)	0.0009 (1)	0.0132 (7)	0.0190 (8)	-0.0005 (2)	-0.0003 (2)	0.0035 (8)
O(1)	0.4605 (1)	1.0383 (4)	0.7779 (4)	0.0020 (1)	0.0300 (8)	0.0235 (7)	-0.0043 (2)	-0.0032 (2)	0.0077 (7)
C(8)	0.4424 (1)	1.1027 (4)	0.4896 (5)	0.0007 (1)	0.0117 (6)	0.0161 (8)	0.0000 (1)	-0.0002 (2)	0.0004 (7)
C(9)	0.4142 (1)	1.0822 (5)	0.3481 (5)	0.0008 (1)	0.0128 (7)	0.0198 (8)	0.0002 (1)	0.0000 (2)	0.0009 (7)
C(10)	0.4222 (1)	1.1749 (5)	0.1989 (5)	0.0012 (1)	0.0172 (8)	0.0175 (9)	0.0007 (2)	-0.0004 (2)	0.0017 (8)
C(11)	0.4578 (1)	1.2876 (5)	0.1894 (6)	0.0012 (1)	0.0202 (8)	0.0296 (9)	0.0003 (2)	0.0010 (2)	0.0057 (9)
C(12)	0.4860 (1)	1.3105 (5)	0.3298 (6)	0.0010 (1)	0.0201 (9)	0.0291 (9)	-0.0011 (2)	0.0005 (2)	0.0050 (9)
C(13)	0.4780 (1)	1.2192 (5)	0.4804 (6)	0.0008 (1)	0.0163 (7)	0.0212 (9)	-0.0010 (2)	-0.0008 (2)	0.0034 (8)
O(W)	0.3368 (1)	0.1383 (3)	0.8580 (4)	0.0010 (1)	0.0147 (5)	0.0282 (7)	0.0001 (1)	0.0000 (1)	0.0083 (6)

Table 1 (cont.)

(b) Hydrogen atoms ( $B=3.5 \text{ \AA}^2$ )

	$x$	$y$	$z$
H(O2T)	0.209 (1)	0.338 (4)	0.854 (4)
H(O3T)	0.298 (1)	0.859 (4)	0.659 (4)
H(C2T)	0.226 (1)	0.711 (4)	0.661 (4)
H(C3T)	0.179 (1)	0.751 (4)	0.890 (4)
H(O4T)	0.251 (1)	0.870 (4)	1.064 (4)
H(C1)1	0.350 (1)	0.692 (4)	1.134 (4)
H(C1)2	0.398 (1)	0.578 (4)	1.106 (4)
H(C1)3	0.351 (1)	0.671 (4)	1.050 (4)
H(N1)	0.338 (1)	0.659 (4)	0.838 (4)
H(C2A)	0.429 (1)	0.778 (4)	0.902 (4)
H(C2E)	0.381 (1)	0.905 (4)	0.921 (4)
H(C3)	0.374 (1)	0.892 (4)	0.614 (4)
H(C4A)	0.453 (1)	0.663 (4)	0.595 (4)
H(C4E)	0.424 (1)	0.730 (4)	0.428 (4)
H(C5A)	0.357 (1)	0.569 (4)	0.546 (4)
H(C5E)	0.404 (1)	0.450 (4)	0.513 (4)
H(C6A)	0.422 (1)	0.481 (4)	0.826 (4)
H(C6E)	0.368 (1)	0.406 (4)	0.798 (4)
H(C9)	0.390 (1)	1.001 (4)	0.354 (4)
H(C10)	0.404 (1)	1.163 (4)	0.102 (4)
H(C11)	0.467 (1)	1.342 (4)	0.080 (4)
H(C12)	0.513 (1)	1.401 (4)	0.324 (4)
H(C13)	0.497 (1)	1.234 (4)	0.574 (4)
H(O'W)1	0.321 (1)	0.164 (4)	0.797 (4)
H(O'W)2	0.319 (1)	0.105 (4)	0.947 (4)

exceptional (Fig. 1).<sup>\*</sup> The benzoyl group is equatorial and the O(1)-C(7)-C(3)-C(2) torsion angle is  $17.1^\circ$ . The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1968). Computer programs used in this study were written for the IBM 1130 and the DEC-1070 and 1055 systems (Shiono 1968-1971).

## Discussion

This study was undertaken as part of an investigation of the optical rotatory dispersion (o.r.d.) characteristics (Djerassi, 1957) of  $\beta$ -aminoketones.

The Cotton effects ( $n \rightarrow \pi^*$ ) for I and for the 3-chloro analog (II) change sign when the solvent is changed from octane to aqueous acid (Smismann & Hite, 1960; Soares, 1971). This suggested that the most representative O(1)-C(7)-C(3)-C(2) torsion angles are about  $30^\circ$  in acid and  $210^\circ$  in octane since the stability of these rotamers was thought to arise from electrostatic attraction (Craven & Hite, 1973; Hite & Craven, 1973) and repulsion (Smismann & Hite, 1960; Soares, 1971) between the electron clouds on O(1) and either the cationic center or the free electron pair on N(1), respectively. Precedent exists for solvent-dependent shift in conformational equilibrium and an associated

distances, bond angles and torsion angles for the bitartrate ion (van Bommel & Bijvoet, 1958) and for the protonated amine (Hite & Craven, 1973) are un-

\* A more complete list of interatomic distances, bond angles and torsion angles is contained in SUP 30198. (See footnote on p. 2935.)

inversion in the sign of the Cotton effects (Djerassi & Geller, 1958). Sign inversion arises from the different chiral environments experienced by the carbonyl chromophore at 30° and 210°. Evidence cited earlier (Hite & Craven, 1973) suggests that the solid state, 21.3° rotamer of III, the 3-bromoacetoxy analog hydrobromide, represents the predominant form of I-III and the 3-hydroxy (IV) and 3-acetoxy (V) analogs in aqueous acid solution. On the basis of this conformation and the *R*-configuration of (-)-II, (+)-IV and (+)-V, the negative Cotton effects of these in acid (Hite & Craven, 1973) are consistent with antiocant behavior (Moffitt, Woodward, Moskowitz, Klyne & Djerassi, 1961; Bartlett, Kirk, Klyne, Wallis, Erdtman & Thorén, 1970; Hudec, 1970).

The O(1)-C(7)-C(3)-C(2) torsion angle of 17.1° and the O(1)-C(2) internuclear distance of 2.66 Å in (-)-I are close to those found in *R*(+)-III, 21.3° and 2.63 Å. The O(2)-C(3)-C(7) and C(4)-C(3)-C(7) bond

angles of 107.9° and 111.0°, respectively, support the view of intramolecular electrostatic stabilization of the 17.1° rotamer about the C(7)-C(3) bond. The short, intermolecular interactions shown in Fig. 2\* are further support for the existence and nature (B:δ<sup>-</sup>...δ<sup>+</sup>Cα-N≡) of the intramolecular electrostatic attraction O(1)-C(2) (Hite & Craven, 1973; Craven & Hite, 1973). Other than the network of hydrogen bonds shown in Fig. 2, there are no other solid state, intra- or intermolecular contacts significantly different from the sum of van der Waals radii. This suggests that there are no severe non-bonded repulsions in this conformation in the crystalline state and that this C(7)-C(3) rotamer is, therefore, representative of the solution conformation and is not unique to the crystalline state.

It follows, that the positive Cotton effect obtained

\* See footnote p. 2935.

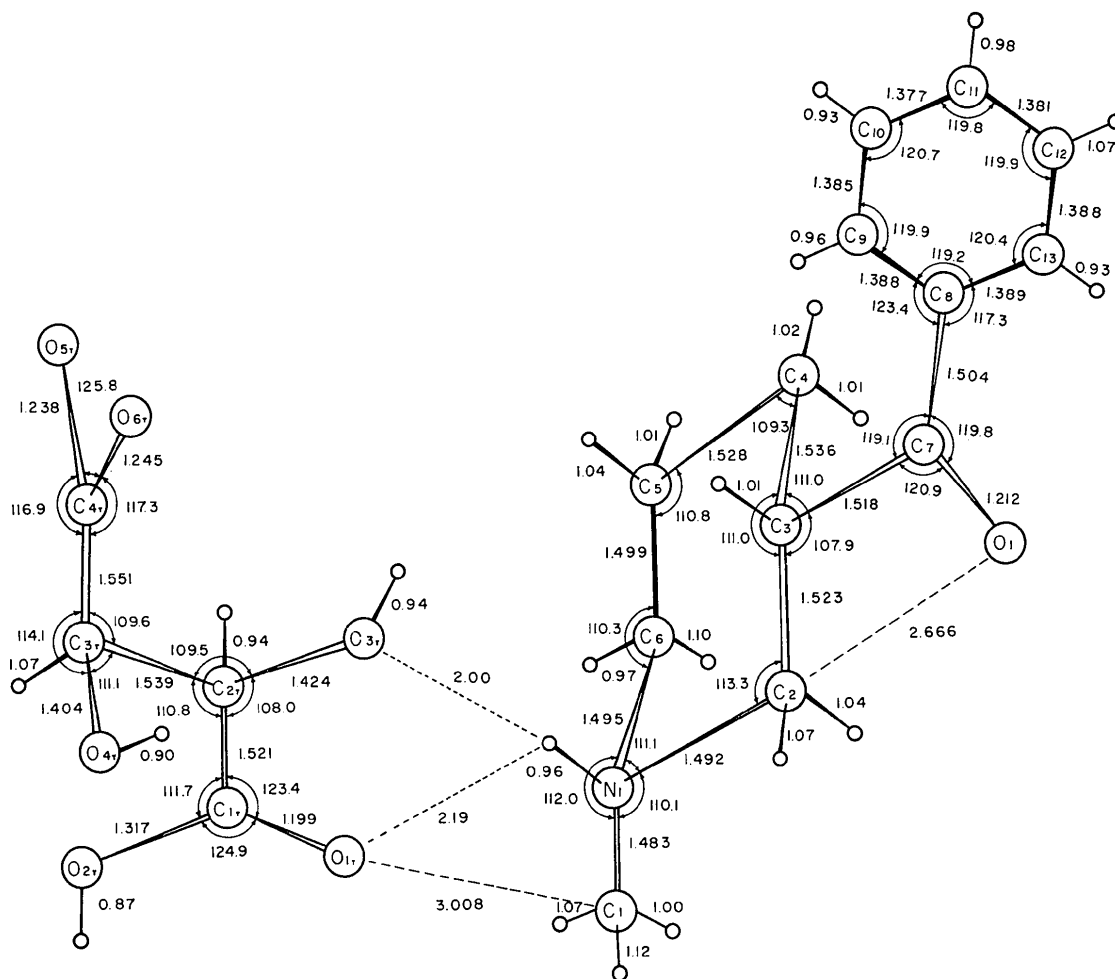


Fig. 1. Diagrams of the bitartrate and 1-methyl-3-benzoylpiperidinium ions of (+)-[*S*(-)-1-methyl-3-benzoylpiperidine *R*:*R*(+)-bitartrate] monohydrate showing all bond distances and only those bond angles involving carbon, nitrogen, and oxygen atoms. The average standard deviations in bond lengths are: carbon-carbon, carbon-oxygen, carbon-nitrogen, 0.005 Å; carbon-hydrogen, oxygen-hydrogen, nitrogen-hydrogen, 0.03 Å. The average standard deviation in bond angles is 0.3°.

