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O.r.d. Studies of β -Amino Ketones. V. The Crystal Structure and Absolute Configuration of (–)-[1-Methyl-3-methoxy-3-benzoylpiperidine Methiodide] Chloroform

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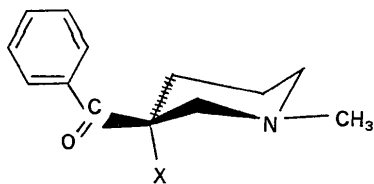
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(–)-[1-Methyl-3-methoxy-3-benzoylpiperidine methiodide] chloroform, $C_{15}H_{22}NO_2I.HCCl_3$, crystallizes in space group $P2_1$, with unit-cell dimensions $a = 11.716(4)$, $b = 8.102(3)$, $c = 11.166(4)$ Å, $\beta = 106.14(1)^\circ$. There are two formula weights per unit cell giving $D_x = 1.614$ and $D_m(CH_3I-CCl_3) = 1.617$ g cm $^{-3}$. The structure was solved by the heavy-atom method. The positional and thermal parameters were refined by full-matrix procedures, converging at $R = 0.055$. The S configuration was established on the basis of anomalous scattering. The benzoyl group is equatorial. The O(2)–C(8)–C(3)–C(2) torsion angle is 0° . The absolute configuration, observed conformation, and o.r.d. data are consistent with octant behavior.

Introduction

While the optical rotatory dispersion (o.r.d.) curves (Djerassi, 1960) for (–)-(I) in octane and in aqueous acid are of opposite sign, the curves for the configurationally identical (+)-(I) (Patel & Hite, 1965) have the same sign in both solvents (Smismman & Hite, 1960).



- (I) X = Cl
 (II) X = OH
 (III) X = OCH $_3$
 (IV) X = OCH $_3$.methiodide.HCCl $_3$
 (V) X = CH $_3$.methiodide

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Other ketones in this series also exhibit solvent dependent sign inversion which has been attributed to stabilization of rotameric populations about an equatorial (e) acyl-to-ring bond (Smismman & Hite, 1960; Hite & Soares, 1973; Djerassi, 1960; Djerassi, Fournaguera & Mancera, 1959). The loss of sign inversion in the o.r.d. curves of (II) was rationalized on the basis of $N \cdots H-O$ hydrogen bonding in the free amine (Smismman & Hite, 1960). Accordingly, (+)-(III) was prepared from (+)-(II) (Zalucky, Malspeis & Hite, 1964) in order to continue the study of a possible relationship between the loss of sign reversal and hydrogen bonding. While sign inversion was again observed (Soares, 1971) for (+)-(III), the signs were opposite to those observed for (–)-(I) in octane and aqueous acid. Since this could be due to some interesting and unanticipated conformational characteristics of (III), a crystallographic study of the quaternary and protonated tertiary ammonium salts of (III) was undertaken. A report on the latter salt will follow.

Experimental

A sample of (-)-(III) was prepared from (-)-(II) (Smitsman & Hite, 1960) as described earlier (Zalucky *et al.*, 1964). An ethereal solution of (-)-(III) was treated with methyl iodide. The solid was filtered off after 24 h and recrystallized from chloroform to give (-)-(IV). The crystals lose solvent on exposure to air and *in vacuo* (0.01 mm Hg) at 85° for 24 h: m.p. 243.5–245.5°; $[\alpha]_D^{25}(\text{water}) = -2.1 \pm 0.5^\circ$ ($c = 1.1$); R.D. (Fig. 1) in methanol ($c = 0.225$), 25°, negative CEC: $[\alpha]_{500} - 5^\circ$, $[\alpha]_{450} - 7^\circ$, $[\alpha]_{400} - 27^\circ$, $[\alpha]_{377} - 94^\circ$, $[\alpha]_{369} - 53^\circ$, $[\alpha]_{361} - 129^\circ$, $[\alpha]_{354} 0^\circ$, $[\alpha]_{352} + 9^\circ$, $[\alpha]_{350} 0^\circ$, $[\alpha]_{348} - 18^\circ$, $[\alpha]_{345} 0^\circ$, $[\alpha]_{340} + 115^\circ$, $[\alpha]_{320} + 240^\circ$, $[\alpha]_{314} + 254^\circ$, $[\alpha]_{302} + 226^\circ$.

A crystal of (-)-(IV) (0.11 × 0.42 × 0.20 mm) in a capillary containing mother liquor was mounted on a Nonius CAD-IV automatic diffractometer equipped for data collection with graphite-monochromated Cu $K\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$). With $\theta/2\theta$ scans, independent reflections of the forms hkl (2234) and $h\bar{k}l$ (1652) were collected, for which $\theta \leq 75^\circ$ and for which h , k and l were positive with respect to a right-handed crystal axial system. Other than systematic absences, there were 142 unobservably weak reflections (hkl) [$I \leq \sigma(I)$] which were assigned values of $I = \sigma(I)$. Three standard reflections remained constant [$\pm 4\sigma(I)_{av}$] throughout data collection. Preliminary data reduction included an absorption correction ($\mu = 162.9 \text{ cm}^{-1}$, Cu $K\alpha$) (Busing & Levy, 1957). The iodine coordinates were determined by the heavy-atom method. The chlorine coordinates were determined by multiple superposition using the minimum function. Several cycles of structure-factor calculation and Fourier

syntheses were required to determine the positions of the remaining non-hydrogen atoms. Full-matrix refinement (hkl) of all atomic parameters, first with isotropic and then with anisotropic temperature factors, converged at $R_w = 0.074$ ($w = 1/\sigma^2$). Hydrogen atom positions were not determined. The final atomic positional and thermal parameters are listed in Table 1.* The S configuration was confirmed (Hite & Craven, 1973) from an examination of 27 Bijvoet pairs.* For each pair, the signs of $(\Delta I/I_{av})_{obs}$ and $(\Delta I/I_{av})_{calc}$ were in agreement.† For the total data set, values of R_{anom} ‡ are 0.36 for the S configuration and 1.89 for the R configuration. All atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1968); the anomalous dispersion factors for iodine and chlorine were those of Cromer (1965). Computer programs used in this study were written or modified for the IBM 1130 and DEC 1070 systems by Shiono (1963–73) and Abola (1973).

Discussion

The bond distances and angles (Fig. 2) are not significantly different from expected values (Hite & Soares, 1975). The benzoyl group is *e* (Fig. 3) and the O(2)–C(8)–C(3)–C(2) torsion angle is 0° . In view of this and the -67° C(2)–C(3)–O(1)–C(7) torsion angle, the aromatic ring might be expected to bisect the O(1)–C(3)–C(4) angle. However, the greater steric bulk of the C(4) methylene unit relative to O(1) forces the phenyl ring to rotate 17° out of the O(2)–C(8)–C(9) plane. Other than the non-bonded distances between the iodide ion and Cl(1), Cl(3) and $C_{ca}(1)$ [3.652 (5), 3.856 (5) and 4.11 (1) Å respectively], there are no intermolecular contacts closer than the sum of the van der Waals radii (I = 2.15, Cl = 1.80, $\text{CH}_2 \approx \text{CH}_3 = 2.0$ Å; Pauling, 1960). This suggests that the conformation is representative of the solution conformation and is not unique to the crystalline state.

The benzoyl group in the 3-methyl analog (V) (Ruble, Hite & Soares, 1976) is axial (*a*). This conformational difference can be rationalized in the following way. On steric grounds, a 1,3-(*aa*) dimethyl interaction in (V) would be thermodynamically less favorable than the 1,3-(*aa*) methyl/benzoyl interaction in (V) (Eliel, Allinger, Angyal & Morrison, 1965). However, electrostatic attraction between the carbonyl oxygen and both C(2) (Hite & Craven, 1973) and $C_{ax}(1)$ is possible in the benzoyl-*a* conformers, while in the benzoyl-*e* conformers the only significant intramolecular electrostatic attraction possible is that between the carbonyl oxygen

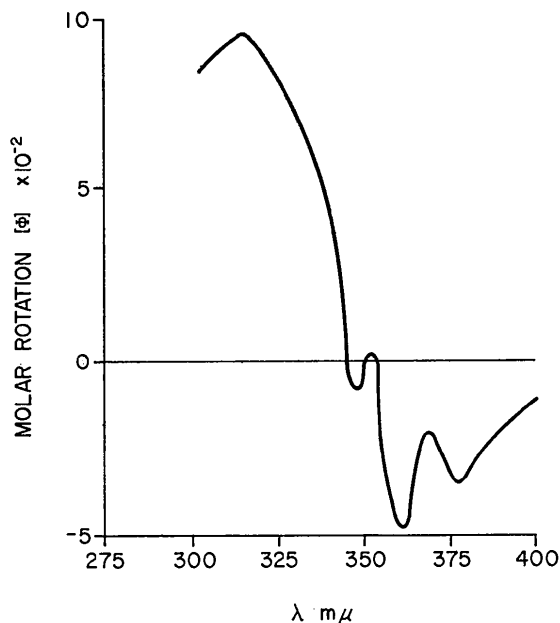


Fig. 1. Rotatory dispersion curve of (-)-[1-methyl-3-methoxy-3-benzoylpiperidine methiodide].

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31160 (33 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

† $\Delta I/I_{av} = 2(|F|_{hkl}^2 - |F|_{\bar{h}\bar{k}l}^2) / (|F|_{hkl}^2 + |F|_{\bar{h}\bar{k}l}^2)$.

‡ $R_{anom} = (\sum |\Delta I_{obs} - \Delta I_{calc}|) / (\sum |\Delta I_{obs}|)$, where $\Delta I_{obs} = |F_{obs}|_{hkl}^2 - |F_{obs}|_{\bar{h}\bar{k}l}^2$.

and C(2). Accordingly, the O-C_{ax}(1) electrostatic attraction represents the principal stabilizing force governing the conformation of (V).

On steric grounds, the 1,3-(*aa*) methyl-methoxy interaction in (IV) is only slightly more thermodynamically favorable than a 1,3-(*aa*) methyl/benzoyl interaction as in (V) (Eliel, Allinger, Angyal & Morrison, 1965). This is reflected in the differences in deviation from ideal (60°) ring torsion angles in (IV) (19°) and (V) (22°). While this may not be significant in itself, the fact that C(2) is further from the N-C(6)-C(4)-C(3) plane in (IV) than in (V) also indicates less steric compression in (IV) than in (V). This would favor a higher population of the benzoyl-*e* conformer in (IV) than in (V). A more compelling feature for stabilization of the benzoyl-*e* conformation of (IV) is based upon electrostatic considerations. In the benzoyl-*a* conformer of (IV), electrostatic attractions would exist between O(2) and both C_{ax}(1) and C(2). By analogy with (V) (Ruble, Hite & Soares, 1976) these interaction distances in the benzoyl-*a* conformer of (IV) would be about 3.0 and 2.8 Å, respectively. In the benzoyl-*e* conformer of (IV), O(2) interacts with C(2) (2.6 Å), while O(1) interacts with C_{ax}(1) (3.0 Å). The O(1)-C(2) interaction is common to both conformers of (IV), and need not be considered. Since the pertinent electrostatic interaction distances cited for both conformers of (IV) are nearly identical, the paramount feature is the effective magnitudes of the electrostatic charges acting across these distances. The magnitude of the interaction energy is primarily a function of the partial negative charges on O(2) and O(1). The partial negative

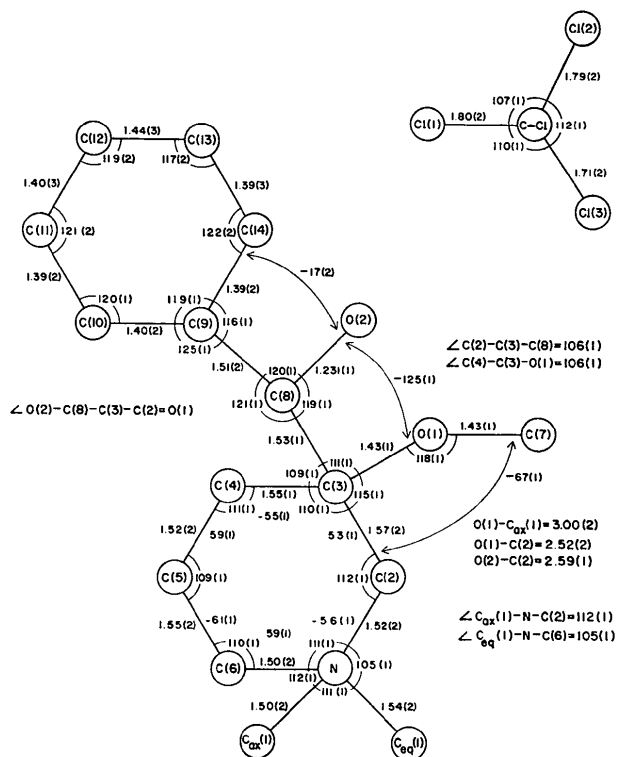


Fig. 2. Bond distances (Å) and angles (°), piperidine ring torsion angles (°), and other pertinent torsion angles (°) for (-)-[1-methyl-3-methoxy-3-benzoylpiperidine methiodide] chloroform. Estimated standard deviations are given in parentheses.

Table 1. Atomic parameters

Positional parameters are given as fractions of the lattice translations. Anisotropic temperature factors correspond to the expression $T = \exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$. Estimated standard deviations are given in parentheses. Positional parameters $\times 10^3$ (except $I \times 10^5$ and $Cl \times 10^4$), thermal parameters $\times 10^3$ (except $I \times 10^4$).

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I	69265 (5)	25000 (0)	85391 (7)	528 (3)	482 (4)	1042 (6)	-35 (5)	300 (3)	-38 (7)
Cl(1)	1244 (4)	589 (6)	9420 (5)	55 (2)	81 (3)	88 (3)	2 (2)	18 (2)	21 (2)
Cl(2)	243 (3)	2311 (7)	7094 (3)	75 (1)	85 (4)	72 (2)	-16 (2)	6 (1)	9 (2)
Cl(3)	1165 (4)	4132 (7)	9397 (5)	65 (2)	87 (3)	89 (3)	12 (2)	18 (2)	-6 (2)
C-Cl	42 (1)	239 (3)	874 (1)	38 (4)	90 (11)	82 (7)	0 (8)	15 (4)	-4 (10)
N	508 (1)	259 (2)	170 (1)	40 (3)	37 (3)	40 (3)	1 (6)	10 (2)	-2 (6)
C _{ax} (1)	585 (1)	410 (2)	189 (2)	56 (8)	37 (8)	87 (10)	-9 (6)	15 (7)	3 (7)
C _{eq} (1)	430 (1)	249 (3)	34 (1)	52 (4)	73 (7)	44 (4)	28 (8)	0 (3)	11 (8)
C(2)	580 (1)	100 (2)	192 (1)	43 (6)	45 (7)	29 (5)	5 (5)	12 (4)	2 (5)
C(3)	647 (1)	74 (1)	333 (1)	31 (3)	35 (5)	41 (4)	-2 (3)	8 (3)	-6 (4)
C(4)	557 (1)	88 (1)	412 (1)	47 (4)	54 (6)	44 (5)	3 (4)	22 (4)	0 (4)
C(5)	490 (1)	250 (3)	388 (1)	63 (5)	57 (6)	55 (5)	17 (8)	32 (4)	-2 (8)
C(6)	422 (1)	263 (3)	248 (1)	46 (3)	60 (6)	54 (4)	7 (8)	22 (3)	6 (8)
O(1)	738 (1)	191 (1)	384 (1)	46 (3)	41 (3)	45 (3)	-13 (3)	13 (3)	-9 (3)
C(7)	842 (1)	188 (2)	339 (1)	43 (5)	62 (7)	86 (8)	-13 (5)	28 (5)	-10 (6)
C(8)	697 (1)	-102 (1)	344 (1)	38 (4)	40 (5)	44 (5)	2 (4)	10 (3)	-1 (4)
O(2)	679 (1)	-186 (1)	249 (1)	65 (4)	54 (5)	51 (4)	14 (3)	5 (3)	-14 (3)
C(9)	761 (1)	-174 (2)	469 (1)	41 (5)	52 (7)	42 (6)	-1 (5)	12 (4)	4 (5)
C(10)	804 (1)	-82 (2)	578 (1)	38 (5)	52 (7)	50 (7)	-8 (5)	6 (4)	12 (5)
C(11)	856 (1)	-162 (2)	689 (1)	48 (7)	81 (11)	36 (6)	5 (7)	-2 (5)	5 (7)
C(12)	855 (2)	-334 (3)	697 (2)	61 (9)	82 (14)	102 (13)	10 (9)	37 (9)	23 (11)
C(13)	819 (2)	-430 (2)	584 (2)	80 (10)	86 (13)	55 (8)	17 (9)	20 (7)	15 (8)
C(14)	767 (1)	-345 (2)	474 (1)	60 (7)	43 (8)	62 (8)	1 (5)	12 (6)	2 (6)

charge on O(1) must be higher than on O(2) since the former is bonded to two tetrahedral carbon atoms of lower electronegativity than O, while the latter is bonded to an sp^2 carbon atom which is more electro-

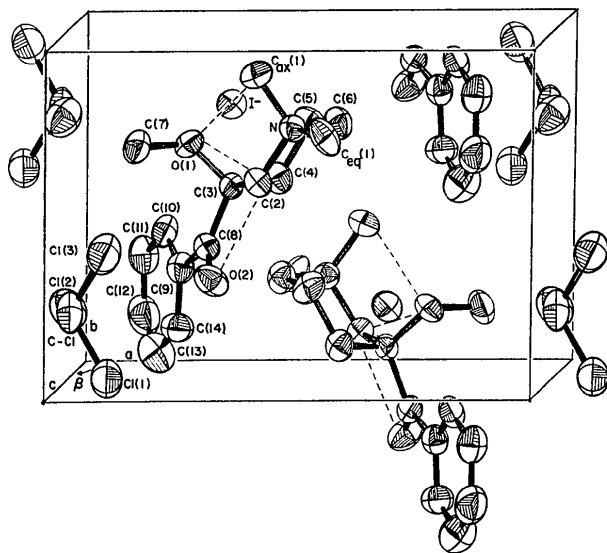


Fig. 3. Unit-cell diagram showing the conformation of (-)-[1-methyl-3-methoxy-3-benzoylpiperidine methiodide] chloroform. Dashed lines indicate potential electrostatic intramolecular interactions.

negative than an sp^3 carbon atom and is also in conjugation with the aromatic ring which is also electronegative relative to an sp^3 carbon atom. Finally, in the benzoyl-*a* conformer of (IV), the π electrons of the carbonyl group, not the non-bonded p electrons, would be directed toward $C_{ax}(1)$, while in the $C(7)-O(1)-C(3)-C(4)-ap$ fragment of the benzoyl-*e* conformer, the more polarizable non-bonded p electrons of O(1) are directed toward $C_{ax}(1)$. Accordingly, the $O(1)-C_{ax}(1)$ interaction should be stronger than the $C_{ax}(1)-O(2)$ interaction. This difference represents the principal stabilizing force for the benzoyl-*e* conformation of (IV). Precedent for this rationale exists in the structures of cocaine salts in which the ether oxygen rather than the carbonyl oxygen of the methoxycarbonyl group is closer to the bridgehead carbon atom. These distances are 2.66 *vs.* 3.74 Å in the hydrochloride salt of cocaine (Gabe & Barnes, 1963), and 2.84 *vs.* 3.60 Å in the methiodide salt of cocaine (Shen, Ruble & Hite, 1975).

In the present structure (Fig. 4) the effects of $C_{ax}(1)$ and C(6) on the rotatory dispersion cancel by reflection through the carbonyl nodal plane; $C_{eq}(1)$, C(2) and N are in the nodal plane and do not contribute to the CEC. The only contributors are C(4) and C(5) in the lower, rear, right positive octant and O(1) and C(7) in the upper, rear, right negative octant. Since the effects of C(7) and C(5) virtually cancel, the sign of the CEC is controlled by the more electronegative substituent, O(1), rather than by C(4). Thus, the observed negative

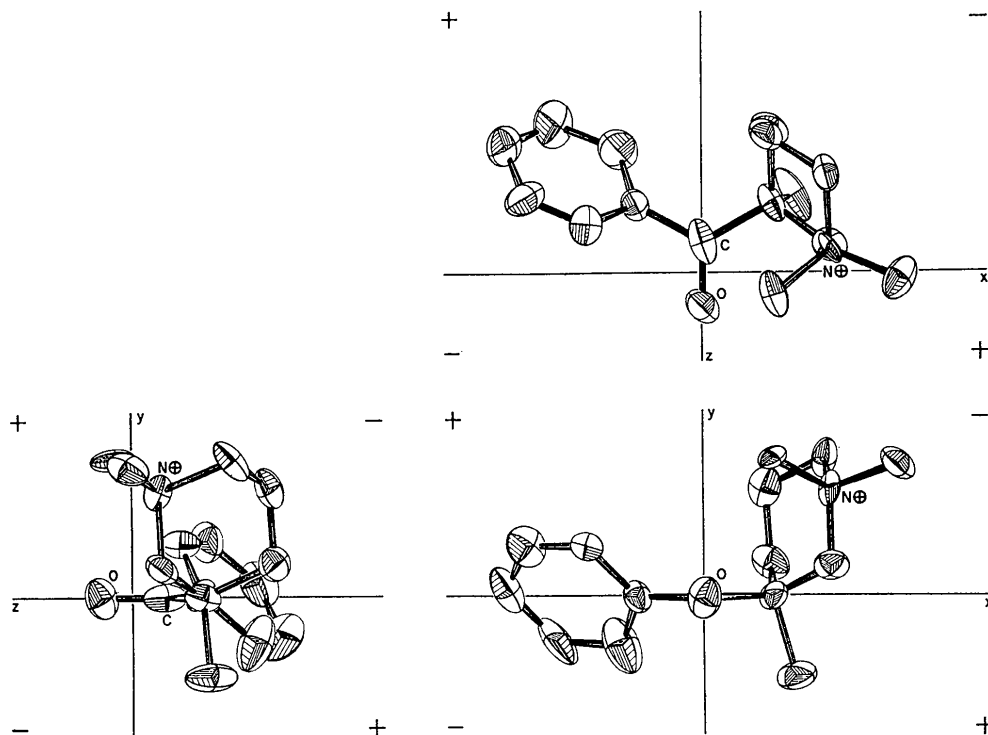


Fig. 4. Octant diagram for (-)-[1-methyl-3-methoxy-3-benzoylpiperidine methiodide]. Views are down the x , y , and z axes, with the four forward octants signed for the x and y projections and the four rear octants signed for the z projection.

CEC for (IV) (Fig. 3) is consistent with octant behavior which has also been observed for (V) (Ruble *et al.*, 1976).

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O.r.d. Studies of β -Amino Ketones. VI. The Crystal Structure and Absolute Configuration of (–)-[(–)-1-Methyl-3-ethyl-3-benzoylpiperidine *R*:*R*-(+)-Bitartrate]

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(–)-[(–)-1-Methyl-3-ethyl-3-benzoylpiperidine *R*:*R*-(+)-bitartrate], $C_{19}H_{27}NO_7$, crystallizes in space group $P2_1$, with unit-cell dimensions $a = 8.612(2)$, $b = 7.074(2)$, $c = 15.510(4)$ Å, $\beta = 98.111(8)^\circ$. There are two formula weights per unit cell giving $D_x = 1.355$ and $D_m(CCl_4-C_6H_6) = 1.353$ g cm $^{-3}$. The structure was solved by direct methods. The positional and thermal parameters were refined by full-matrix procedures, converging at $R = 0.041$. The configuration for the (–)-amine component is *R*. The benzoyl group is axial. The O–C(9)–C(3)–C(2) torsion angle is -1.1° . While other protonated amines in this series exhibit antioctant behavior, the absolute configuration and crystal conformation of the title compound, taken together with the optical rotatory dispersion data, are consistent with octant behavior.

Introduction

While the optical rotatory dispersion (o.r.d.) curves (Djerassi, 1960) for (–)-(I) in octane and in aqueous acid are of opposite sign, the curves for (–)-(II), which is isoelectronic with (–)-(I), have the same sign in both solvents (Soares, 1971). Other ketones in this series also

exhibit solvent-dependent sign inversion which has been attributed to stabilization of rotameric populations about an equatorial (*e*) acyl-to-ring bond (Smisssman & Hite, 1960; Hite & Soares, 1973; Djerassi, 1960; Djerassi, Fournaguera & Mancera, 1959; Djerassi & Geller, 1958). However, in (+)-(III) methiodide, the conformer with the benzoyl group axial (*a*) appears to be the more stable species (Ruble, Hite & Soares, 1976). In view of the role suggested for the ether oxygen

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