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Acta Cryst. (1976). **B32**, 128

O.r.d. Studies of β -Amino Ketones. IV.* The Crystal Structure and Absolute Configuration of (+)-[1,3-Dimethyl-3-benzoylpiperidine Methiodide]

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(Received 5 September 1974; accepted 22 May 1975)

(+)-[1,3-Dimethyl-3-benzoylpiperidine methiodide], $C_{15}H_{22}NOI$, crystallizes in space group $P2_1$, with unit-cell dimensions $a = 10.977(5)$, $b = 7.734(4)$, $c = 9.502(4)$ Å and $\beta = 96.94(3)^\circ$. There are two molecules per unit cell giving $D_x = 1.489$ and $D_m(CCl_4-C_6H_6) = 1.495$ 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 $R = 0.071$. The S configuration was established on the basis of anomalous scattering. The benzoyl group is axial. The O–C(8)–C(3)–C(2) torsion angle is -24° . The absolute configuration and conformation observed, taken together with the o.r.d. data, are consistent with octant behavior. Precedented conformational considerations and o.r.d. data for the corresponding protonated tertiary amine salt are consistent with antiocant behavior.

Introduction

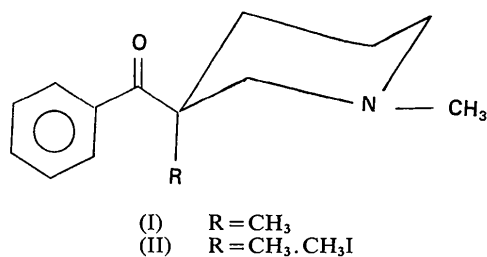
This study was undertaken as part of an investigation of the optical rotatory dispersion (o.r.d.) characteristics (Djerassi, 1960) of β -amino ketones (Hudec, 1970). β -Amino ketones in this series [cf. (I)] have shown solvent-dependent sign inversion of the Cotton effect curve (CEC) in going from octane to aqueous acid solutions (Smisssman & Hite, 1960; Hite & Soares, 1973). This was interpreted in terms of solvent-dependent rotation about the C(3)–C(8) acyl-to-ring bond

(Smisssman & Hite, 1960; Djerassi, 1960; Djerassi & Geller, 1958; Djerassi, Fournaguera & Mancera, 1959). However, (I) and its protonated salt exhibit positive CEC's (Soares, 1971) in octane and water, respectively. This unexpected behavior of (I) prompted an investigation of its absolute configuration and conformation. Inability to obtain a crystallographically suitable protonated salt of (I) with a structurally simple counterion as well as our interest in the o.r.d. behavior of quaternary salts of compounds in this series and the fact that all protonated salts in this series examined to date afford Cotton effect curves of the same sign as the configurationally identical quaternary salts, led to our choice of (I) methiodide (II), which is related in an

* Part III: Soares & Hite (1975).

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obvious manner to (I) HCl, as a rational initial subject of this investigation.



Experimental

A sample of levorotatory, (+)-dibenzoyltartaric acid salt of (+)-(I) [m.p. 138–9°, $[\alpha]_D^{25}$ (methanol) = $-58.2 \pm 0.5^\circ$ (*c* 0.50)] (Soares & Hite, 1975) was recrystallized from acetone until no change occurred in the specific rotation [m.p. 148–9°, $[\alpha]_D^{25}$ (methanol) = $-70.7 \pm 1.2^\circ$ (*c* 0.50)]. The amine was treated with CH₃I in ether.

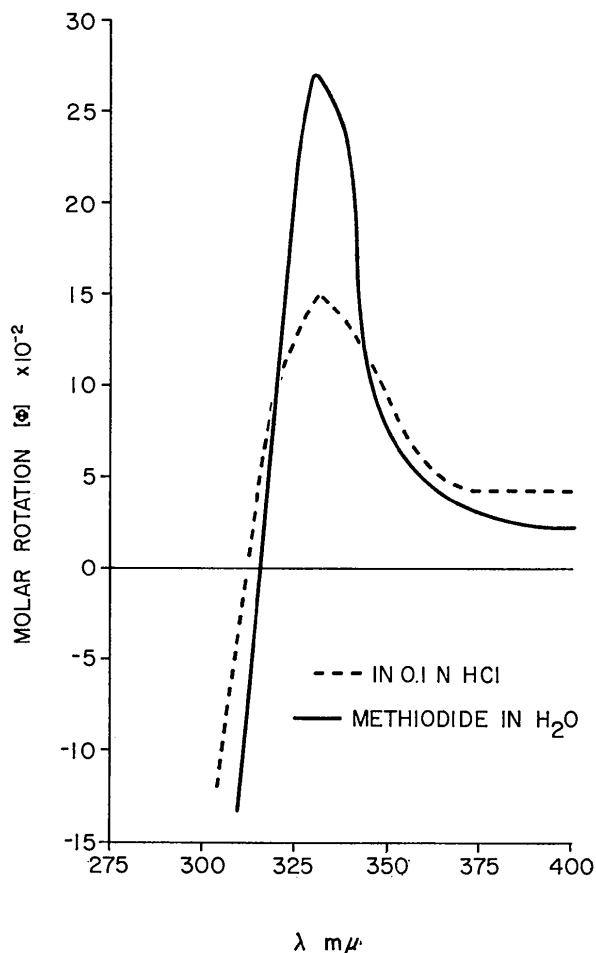


Fig. 1. Rotatory dispersion curves of (+)-[1,3-dimethyl-3-benzoylpiperidine].

The precipitate crystallized from acetone to give (+)-(II): m.p. 184–5°; $[\alpha]_D^{25}$ (water) = $+15.3 \pm 1.0^\circ$ (*c* 0.308); R.D. (Fig. 1) in water (*c* 0.308), 30°, positive CEC: $[\alpha]_{460} + 28^\circ$, $[\alpha]_{400} + 63^\circ$, $[\alpha]_{375} + 89^\circ$, $[\alpha]_{350} + 213^\circ$; (*c* 0.011), $[\alpha]_{340} + 623^\circ$, $[\alpha]_{330} + 697^\circ$, $[\alpha]_{325} + 441^\circ$, $[\alpha]_{320} + 369^\circ$, $[\alpha]_{310} - 327^\circ$, $[\alpha]_{307} - 996^\circ$; R.D. (Fig. 1) free amine [C₁₄H₁₉ON] in 0.1 N HCl (*c* 0.068), 25°, positive CEC: $[\alpha]_{400} + 166^\circ$, $[\alpha]_{370} + 168^\circ$, $[\alpha]_{360} + 200^\circ$, $[\alpha]_{350} + 366^\circ$, $[\alpha]_{340} + 532^\circ$, $[\alpha]_{332} + 600^\circ$, $[\alpha]_{325} + 500^\circ$, $[\alpha]_{320} + 300^\circ$, $[\alpha]_{315} + 159^\circ$, $[\alpha]_{312} 0^\circ$, $[\alpha]_{305} - 465^\circ$, $[\alpha]_{300} - 765^\circ$, $[\alpha]_{295} - 995^\circ$.

A crystal of (+)-(II) (0.08 × 0.07 × 0.04 mm) was mounted on a Nonius CAD-IV automatic diffractometer equipped for data collection with graphite-monochromated Cu K α radiation ($\lambda = 1.5418 \text{ \AA}$). Crystal defects required the use of 2° ω scans to measure intensities of independent reflections of the form hkl (1293) and $h\bar{k}l$ (1088) 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 66 unobservably weak (hkl) reflections [$I \leq 2\sigma(I)$] which were assigned values of $(I) = \sigma(I)/2$. Three standard reflections remained constant [$\pm 2\sigma(I)_{av}$] throughout data collection. Preliminary data reduction included an absorption correction ($\mu = 159.9 \text{ cm}^{-1}$, Cu K α) (Busing & Levy, 1957). The iodine coordinates were determined by the heavy-atom technique. Several cycles of structure-factor calculations 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, then anisotropic temperature factors, converged at $R_w = 0.085$ ($w = 1/\sigma^2$). Hydrogen atom positions were not determined. The final atomic positional and thermal parameters are listed in Table 1.* The *S* configuration was established from an examination of 38 Bijvoet pairs* differing by at least 0.10 $|F_{calc}|$. 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, the values of R_{anom} ‡ are 0.68 for the *S* configuration (Table 1) and 1.58 for the *R* configuration. All atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1968), and the anomalous dispersion factors for iodine 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).

Discussion

The bond distances and angles (Fig. 2) are not significantly different from expected values (Hite & Craven,

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31159 (20 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

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

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

1973; Hite & Soares, 1973). The benzoyl group is axial (*a*) (Fig. 3) and the O–C(8)–C(3)–C(2) torsion angle is -24° . The O–C(2) and O–C_{ax}(1) interatomic distances of 2.81 and 3.01 Å, respectively, suggest electrostatic attraction between O and the cationic center (Hite & Craven, 1973; Hite & Soares, 1973). The effects of steric crowding in the 1,3-(*aa*) system are observable in the opening of the C(2)–N–C_{ax}(1), C(2)–C(3)–C(8) and C(4)–C(3)–C(8) bond angles of 115, 114 and 115° , respectively, in the closing of the C(7)–C(3)–C(8) and C(2)–C(3)–C(7) bond angles of 105 and 103° , respectively, in the C(2)–C(3)–C(8)–O torsion angle of -24° , and in the ring conformation angles (Fig. 2). The ring torsion angles are symmetric with respect to the 1,3-(*aa*) units [approximate mirror plane through C(2) and C(5)]. The steric crowding results in a larger decrease in the ring torsion angles (ideally 60°) more proximal to the 1,3-(*aa*) interaction and C(2) is closer to the N–(6)–C(4)–C(3) plane than C(5) (0.62 Å *vs* 0.68 Å). The rotation of the benzene ring with respect to the carbonyl group [O–C(8)–C(9)–C(14) torsion angle = $50(3)^\circ$] appears to be the result of relief of steric compression between C(10) and C(4) caused by rotation of the O–C(8)–C(3)–C(2) torsion angle from 0 to -24° . Other than the non-bonded distances between the iodide ion and C_{eq}(1), C_{ax}(1), C(2) and C(6) [4.06 (3), 4.08 (3), 3.92 (3) and 3.87 (3) Å, respectively], there are no significant intermolecular contacts closer than the sum of the van der Waals radii ($I = 2.15$ Å, $CH_2 \approx CH_3 = 2.0$ Å; Pauling, 1960). This suggests that this conformation is representative of the solution conformation and is not unique to the crystalline state.

In this structure C(7) is normal to the nodal plane of the carbonyl group and occupies the lower, rear, positive octant (Fig. 4). It, rather than more distal and more nearly nodal substituents, should control the sign of the CEC.

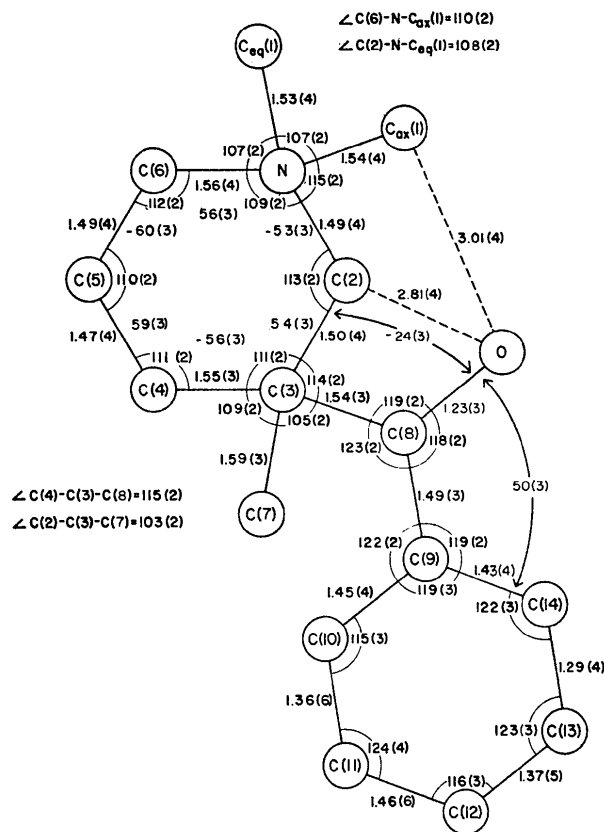


Fig. 2. Bond distances (Å) and angles ($^\circ$), piperidine internal ring torsion angles ($^\circ$), and pertinent benzoyl torsion angles ($^\circ$) for (+)-[1,3-dimethyl-3-benzoylpiperidine methiodide]. Dashed lines indicate potential electrostatic intramolecular interactions. Estimated standard deviations 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 $I \times 10^4$), thermal parameters $\times 10^2$ (except $I \times 10^3$).

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
I	242 (1)	2500 (0)	2011 (1)	46 (1)	42 (1)	48 (1)	5 (1)	18 (0)	0 (1)
O	393 (1)	202 (2)	506 (2)	6 (1)	6 (1)	4 (1)	-1 (1)	2 (1)	0 (1)
N	138 (1)	242 (4)	674 (2)	4 (1)	3 (1)	4 (1)	-1 (1)	1 (1)	1 (1)
C _{eq} (1)	0 (2)	240 (7)	624 (2)	3 (1)	7 (2)	6 (1)	1 (2)	0 (1)	-2 (2)
C _{ax} (1)	189 (3)	407 (4)	613 (4)	4 (1)	1 (1)	8 (2)	0 (1)	3 (1)	0 (1)
C(2)	191 (3)	76 (5)	631 (3)	5 (2)	4 (2)	3 (1)	0 (1)	1 (1)	-1 (1)
C(3)	320 (2)	48 (2)	697 (2)	5 (1)	3 (1)	5 (1)	-1 (1)	2 (1)	0 (1)
C(4)	328 (2)	64 (3)	860 (2)	5 (1)	5 (1)	4 (1)	1 (1)	2 (1)	1 (1)
C(5)	281 (2)	232 (5)	901 (2)	6 (1)	6 (2)	3 (1)	-1 (1)	1 (1)	0 (1)
C(6)	152 (2)	253 (7)	839 (2)	5 (1)	6 (1)	3 (1)	-3 (2)	2 (1)	-2 (2)
C(7)	344 (2)	-149 (3)	658 (3)	8 (2)	2 (1)	11 (2)	0 (1)	6 (2)	0 (1)
C(8)	417 (2)	152 (3)	630 (3)	4 (1)	3 (1)	8 (2)	0 (1)	3 (1)	-1 (1)
C(9)	537 (2)	203 (3)	709 (3)	3 (1)	3 (2)	5 (1)	0 (1)	1 (1)	1 (1)
C(10)	617 (3)	76 (5)	786 (4)	5 (2)	11 (3)	9 (2)	1 (2)	0 (2)	5 (2)
C(11)	727 (3)	139 (6)	846 (5)	3 (2)	10 (3)	11 (3)	3 (2)	1 (2)	3 (3)
C(12)	762 (3)	321 (5)	843 (4)	4 (1)	11 (3)	6 (1)	0 (2)	1 (1)	0 (2)
C(13)	681 (3)	430 (4)	767 (3)	5 (2)	8 (2)	4 (1)	1 (2)	-1 (1)	0 (1)
C(14)	574 (3)	380 (4)	709 (3)	4 (2)	4 (2)	6 (2)	0 (1)	1 (1)	-1 (1)

This, and the positive CEC observed for (+)-II (Fig. 1), is consistent with octant behavior. In either the benzoyl-*a* or equatorial (*e*) orientations of (I) HCl, both steric and electrostatic forces should stabilize an O-C(8)-C(3)-C(2) torsion angle of 0°. Precedents for this are the -1° torsion angle in the crystal structure of the bitartrate salt of the 3-ethyl-*e* analog of (I) (Ruble, Hite & Soares, 1976), the 0° torsion angle in the crystal structure of the 3-methoxy-*a* analog of (II) (Ruble, Blackmond & Hite, 1976) and in the 17° torsion angle

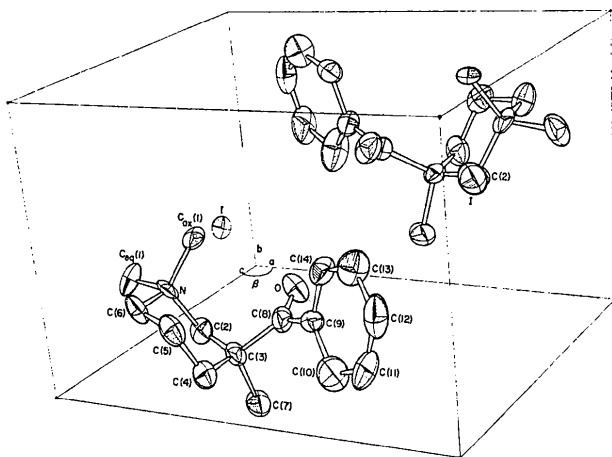


Fig. 3. Unit-cell diagram showing the conformation of (+)-[1,3-dimethyl-3-benzoylpiperidine methiodide].

in the crystal structure of the bitartrate salt of the 3-*H-a* analog of (I) (Hite & Soares, 1973). In the last case, the torsion angle would tend from 17° toward 0° as the size of the substituent increased from H to CH_3 . Both conformations of (I) HCl predicate identical signs for the CEC.

In the benzoyl-*e* conformer of (I) HCl (torsion angle $\approx 0^\circ$) the effects of C(4) and C(7) cancel by reflection through the nodal plane of the carbonyl group; C(1), C(2) and N are nodal and only C(5) and C(6), lying in the upper, rear, right, negative octant, contribute to the sign of the CEC. In the benzoyl-*a* conformer of (I) HCl (torsion angle $\approx 0^\circ$) (*cf.* Fig. 4) the effects of C(4) and C(7) cancel by reflection through the nodal plane of the carbonyl group; C(2), C(6) and N are nodal and only C(1) and C(5), lying in the upper, front, right, positive and the upper, rear, right, negative octants, respectively, contribute to the sign of the CEC. Since C(5) is closer to the optically active chromophore, it should dominate the sign of the CEC. Thus, the observed positive CEC for this protonated, exocyclic, β -amino ketone [(I) HCl] like others in this series reported to date (Hite & Craven, 1973; Hite & Soares, 1973) is consistent with anti-octant behavior.

This study was supported by the U.S. Public Health Service, National Institutes of Health Grant Nos. GM-01728 (J.R.R.), GM-49037 (G.H.) and NB-03593 (G.H. and J.R.S.). The authors are indebted to Barbara Blackmond for technical assistance.

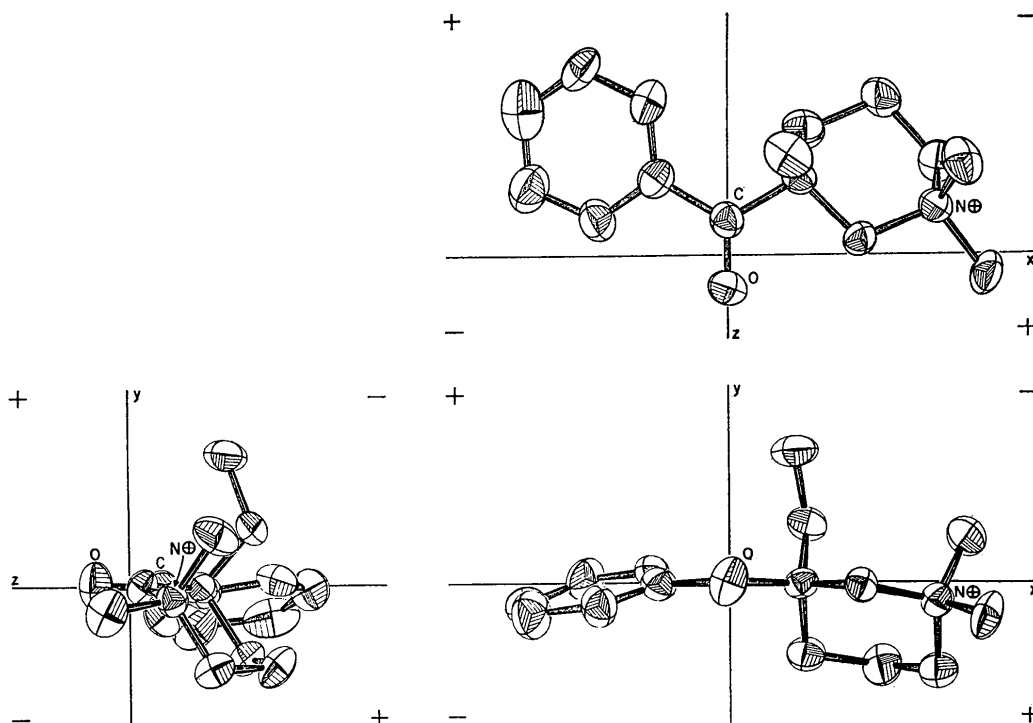


Fig. 4. Octant diagram for (+)-[1,3-dimethyl-3-benzoylpiperidine methiodide]. Views are down *x*, *y* and *z* axes, with the four forward octants signed for the *x* and *y* projections, and the four rear octants signed for the *z* projection.

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Acta Cryst. (1976). **B32**, 132

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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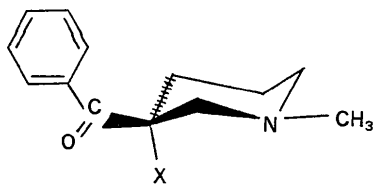
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(Received 5 September 1974; accepted 22 May 1975)

(–)-[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 $D_m(CH_3I-CCl_4) = 1.617$ 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.