filling 0·64 (*vs.* 0·68 for b.c.c.), radius ratio U:Si 1·321, tetragonal c/a ratio 0·495, fractional positional parameters U, $x=0{\cdot}3117$; Si, $x=0{\cdot}1111$. In Zachariasen's (1949) setting the theoretical parameters are U, $x=0{\cdot}1883$; Si, $x=0{\cdot}3889$. The Si_2U_3 types for which the atomic positions are known, *i.e.*, Si_2U_3, Si_2Th_3, Al_2Th_3, Ga_2Ta_3, Ga_2Zr_3, Ge_2Th_3 (see Pearson, 1967), have x values that are quite close to the theoretical ones for spherical packing, but the defect types $CoGa_3$ and $CoIn_3$ are distorted noticeably. In them the effect of having $x>0{\cdot}3117$ is to rotate clockwise the cube of In(1) located in the center of the cell, Fig. 1. This shortens the In(1)–In(1) nearest-neighbor distance to 2·980 Å. It also decreases the cell constant a, and that is why the In(1) cube can appear compressed down the c axis while c/a still exceeds the theoretical 0·495. For cobalt, $x>0{\cdot}1111$, and consequently the cobalt nearest neighbors that touch in the rigid-sphere model, are separated to 2·896 Å (Table 2). Note that twice the C.N. 12 radius of cobalt is only 2·50 Å. Contrast this with the short Si–Si distance in Si_2U_3 which is observed to be 2·30 Å, a figure much smaller than the sum of the C.N. 12 radii (2·64 Å). The separation of the cobalt neighbors is accompanied by a contraction of the distance Co–In(1) to 2·593 or 2·601 Å. The sum of the C.N. 12 radii is 2·91 Å, the sum of the Slater (1972) radii is 2·90 Å. Better agreement is found with the sum of the Pauling (1960) radii assuming C.N. 6 for the cobalt atom to fix the bond number. The distance so derived is predicted to be 2·58 Å. The distortion against the rigid-sphere model is, then, attributable to a tendency of cobalt and indium to form a bond of that length.

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O.r.d. Studies of β-Amino Ketones. I. The Crystal Structure and Absolute Configuration of (+)-(1-Methyl-3-benzoyl-3-bromoacetoxypiperidine Hydrobromide)

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(+)-(1-Methyl-3-benzoyl-3-bromoacetoxypiperidine hydrobromide), $[(C_{15}H_{19}NO_3Br)^+Br^-]$ (IV) crystallizes in the orthorhombic space group $P2_12_12_1$. The lattice translations are $a=7{\cdot}200$ (3), $b=11{\cdot}312$ (4), $c=20{\cdot}776$ (7) Å. There are four molecules per unit cell; $D_x=1{\cdot}65$ and D_m ($HCCl_3$–$HCBr_3$) $=1{\cdot}64$ g cm^{-3}. The structure was determined by the heavy-atom method. Refinement of positional and thermal parameters by the block-diagonal, least-squares procedure converged at $R=0{\cdot}050$. The R-(+)-configuration was established from the anomalous scattering of the bromine atoms. The C(4)–C(3)–O(1)–C(7)–C(8) fragment is *trans–trans*. The benzoyl group is equatorial and the O(3)–C(9)–C(3)–C(2) torsion angle is 21·3°. Evidence is cited to support the predominance of the 21·3° rotamer in aqueous acid solutions of analogs configurationally related to IV by unequivocal chemical methods. Based on this conformation and configuration, optical rotatory dispersion data for analogs of IV in aqueous acid are consistent with antioctant behavior.

Introduction

Negative Cotton effects (Djerassi, 1960) have been reported for (+)-I and (−)-II in 0·1 N hydrochloric acid (Smissman & Hite, 1960), (Fig. 1). These compounds have the same configuration (Zalucky, Malspeis & Hite, 1964; Zalucky, Marathe, Malspeis & Hite, 1965; Patel & Hite, 1965*a*,*b*; Patel & Hite, 1967). Acetylation of (+)-I afforded (+)-III (Zalucky, Malspeis & Hite, 1964): m.p. 66–67°; $[\alpha]_D^{25}$ (ethanol) +34·7° (c 10·56); $[\alpha]_D^{25}$ (0·5 N HCl) +72·3° (c 11·14). R.D. (Fig. 1) in

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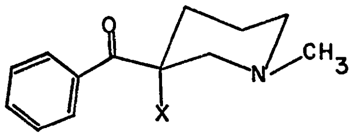
0·1 N HCl (c 0·005), 25°, negative Cotton effect curve: $[\alpha]_{600}+72°$, $[\alpha]_{550}+95°$, $[\alpha]_{500}+110°$, $[\alpha]_{450}+125°$, $[\alpha]_{400}+137°$, $[\alpha]_{375}+90°$, $[\alpha]_{360}-30°$, $[\alpha]_{350}-220°$, $[\alpha]_{330}-290°$, $[\alpha]_{320}+275°$, $[\alpha]_{310}+660°$. (+)-(1-Methyl-3-benzoyl-3-bromoacetoxypiperidine hydrobromide) (IV) was prepared (Hite & Craven, 1973) from (+)-I.



R-(+)-I	(X=OH)
R-(−)-II	(X=Cl)
R-(+)-III	($X=CH_3CO_2$)
R-(+)-IV	($X=BrCH_2CO_2$).HBr
S-(−)-V	(X=H)
R-(+)-VI	($X=OCH_3$)

A computer-controlled, four-circle diffractometer with graphite-monochromated Cu $K\alpha$ radiation ($\lambda=1·5418$ Å) was used to measure 2822 independent ($hkl,h\bar{k}l$) reflexions for which $\sin\theta\le0·90$ and for which h, k and l were positive with respect to a right-handed axial system. The $\theta/2\theta$ scans of 2° in 2θ were made at a rate of 2° min^{-1}, with background counts of 20 s at the limits of each scan. Other than systematic absences, there are 59 reflexions for which the integrated intensity (I) was less than $2\sigma(I)$. These were assigned values of $(I)=\sigma(I)/2$. Three standard reflexions remained constant [$\pm2\sigma(I_{\text{av}})$] throughout data collection. Preliminary data reduction included absorption ($\mu=87·20$ cm^{-1}, Cu $K\alpha$) corrections (Busing & Levy, 1957).

The phase problem was solved by the heavy-atom method. Non-hydrogen atoms were located after two cycles of structure factor calculation and Fourier synthesis. Isotropic thermal parameters of 3·5 Å^2 were initially assigned to all atoms. Atomic parameters were refined by the block-diagonal, least-squares (BDLS) procedure until convergence at $R=0·060$ $\{R=(\sum||F_{\text{meas}}|-|F_{\text{calc}}||/\sum|F_{\text{meas}}|)\}$. Positions of hydrogen atoms, other than H(15), were acceptably determined by a difference Fourier. The final cycles of refinement (BDLS) converged at $R=0·050$. The program included the anomalous dispersion corrections for the bromine atoms ($\Delta f'=-0·95$, $\Delta f''=1·4$, Cu $K\alpha$). The atomic parameters are listed in Table 1.[*] Change in sign of $\Delta f''$ resulted in convergence (BDLS) at $R=0·052$ indicating that the R configuration (Cahn, Ingold & Prelog, 1956) provided by the positional parameters of Table 1 is correct for IV (*cf.* Fig. 2). This was confirmed by agreement in sign of the observed and calculated values of $(\Delta I/\bar{I})$[†] for 52 of 54 Bijvoet pairs differing by at least $0·05|F_{\text{calc}}|$.

The bond lengths and angles and standard deviations (Fig. 2) are not significantly different from those found in related compounds (Kartha, Ahmed & Barnes, 1960; Ahmed, Barnes & Masironi, 1963; Ahmed & Barnes, 1963). A more complete listing is available, together with other pertinent conformational and

Table 1. *Atomic positional and thermal parameters*

Positional parameters are given as fractions of the lattice translations. Anisotropic temperature factors correspond to the expression: $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2hk\beta_{12}+2hl\beta_{13}+2kl\beta_{23})]$, and isotropic temperature factors to the expression: $\exp(-B\sin^2\theta/\lambda^2)$. Estimated standard deviations given in parentheses refer to the last digit(s) of the respective values.

(a) Atoms other than hydrogen ($\times10^4$)

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br(1)	3241 (1)	2160 (1)	2796 (1)	242 (1)	66 (1)	30 (1)	3 (1)	−14 (1)	−5 (1)
Br(2)	3681 (1)	3372 (1)	5306 (1)	528 (4)	160 (1)	26 (1)	103 (2)	−27(1)	2 (1)
C(1)	1439 (15)	4777 (7)	1862 (3)	477 (29)	93 (7)	22 (2)	14 (12)	28 (6)	1 (3)
C(2)	909 (9)	5436 (5)	2972 (3)	217 (13)	56 (5)	18 (1)	−1 (6)	−5 (3)	1 (2)
C(3)	101 (8)	5153 (5)	3635 (3)	176 (12)	47 (4)	18 (1)	−4 (6)	0 (3)	0 (2)
C(4)	−1919 (8)	4764 (5)	3561 (3)	140 (11)	68 (5)	27 (2)	0 (7)	3 (4)	−6 (2)
C(5)	−2066 (10)	3726 (6)	3098 (3)	239 (17)	77 (6)	27 (2)	−11 (8)	−11 (4)	−10 (2)
C(6)	−1260 (11)	4065 (6)	2447 (3)	283 (19)	92 (6)	24 (2)	24 (9)	−32 (5)	−17 (3)
C(7)	2810 (8)	4238 (5)	4077 (3)	176 (13)	67 (5)	19 (1)	12 (6)	−3 (3)	4 (2)
C(8)	3538 (10)	3118 (5)	4392 (3)	223 (15)	66 (5)	26 (2)	21 (7)	−10 (4)	7 (2)
C(9)	226 (8)	6251 (5)	4052 (3)	150 (11)	52 (4)	21 (1)	−15 (6)	2 (3)	−2 (2)
C(10)	49 (8)	6216 (5)	4766 (3)	163 (12)	61 (5)	19 (1)	4 (6)	−4 (3)	0 (2)
C(11)	510 (9)	7255 (6)	5098 (3)	208 (14)	63 (5)	27 (2)	0 (8)	−4 (4)	−7 (3)
C(12)	334 (10)	7293 (6)	5751 (3)	252 (16)	74 (6)	30 (2)	13 (8)	−3 (5)	−16 (3)
C(13)	−322 (10)	6339 (7)	6093 (3)	213 (15)	116 (7)	23 (2)	25 (9)	2 (4)	−10 (3)
C(14)	−771 (11)	5309 (7)	5772 (3)	294 (19)	93 (7)	23 (2)	2 (9)	9 (5)	0 (3)
C(15)	−583 (10)	5245 (6)	5106 (3)	269 (17)	63 (5)	23 (2)	−2 (8)	9 (4)	−3 (2)
N(1)	682 (8)	4431 (5)	2502 (2)	265 (14)	72 (5)	18 (1)	21 (6)	5 (3)	0 (2)
O(1)	1027 (5)	4143 (3)	3928 (2)	164 (8)	46 (3)	19 (1)	−7 (4)	−1 (2)	3 (1)
O(2)	3747 (6)	5095 (4)	3986 (2)	183 (10)	81 (4)	42 (2)	−21 (5)	−12 (3)	13 (2)
O(3)	367 (8)	7198 (4)	3773 (2)	408 (15)	51 (3)	24 (1)	−14 (6)	−5 (3)	5 (2)

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[*] The table of $|F_{\text{meas}}|$ and $|F_{\text{calc}}|$ has been deposited with the National Lending Library, England, as Supplementary Publication No. SUP 30197. Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester. CH1 1NZ, England.

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

Table 1 (*cont.*)

(*b*) Hydrogen atoms (× 10^3)

	x	y	z	B (Å^2)
H(N)	147 (14)	382 (9)	258 (5)	10·3 (2·9)
H(1,1)	136 (12)	412 (7)	161 (4)	8·2 (2·2)
H(1,2)	260 (12)	515 (8)	196 (4)	8·4 (2·3)
H(1,3)	24 (15)	539 (9)	165 (5)	10·4 (2·9)
H(2*a*)	14 (7)	610 (5)	284 (3)	2·7 (1·1)
H(2e)	224 (7)	564 (4)	307 (2)	1·8 (1·0)
H(4a)	−255 (9)	536 (6)	334 (3)	4·7 (1·6)
H(4e)	−258 (10)	461 (6)	400 (3)	5·4 (1·8)
H(5a)	−150 (9)	301 (6)	328 (3)	4·6 (1·5)
H(5e)	−345 (11)	353 (7)	302 (3)	6·3 (1·9)
H(6a)	−130 (11)	336 (7)	221 (4)	5·7 (1·9)
H(6e)	−194 (13)	464 (8)	226 (4)	9·1 (2·5)
H(8,1)	256 (14)	256 (8)	426 (4)	8·8 (2·7)
H(8,2)	467 (13)	283 (8)	417 (4)	7·3 (2·5)
H(11)	97 (7)	794 (5)	487 (2)	2·5 (1·1)
H(12)	60 (9)	788 (6)	593 (3)	3·7 (1·5)
H(13)	−36 (9)	647 (6)	659 (3)	3·6 (1·4)
H(14)	−132 (12)	451 (7)	603 (4)	7·8 (2·2)
H(15)	−58 (10)	442 (6)	495 (3)	5·5 (1·8)

configurational detail.* The C(4)–C(3)–O(1)–C(7)–C(8) fragment (Fig. 2) is *trans–trans*. The planar benzoyl group is equatorial and the O(3)–C(9)–C(3)–C(2) torsion angle is 21·3° (Fig. 3). There are no intermolecular contacts significantly shorter than the sums of the van der Waals radii.

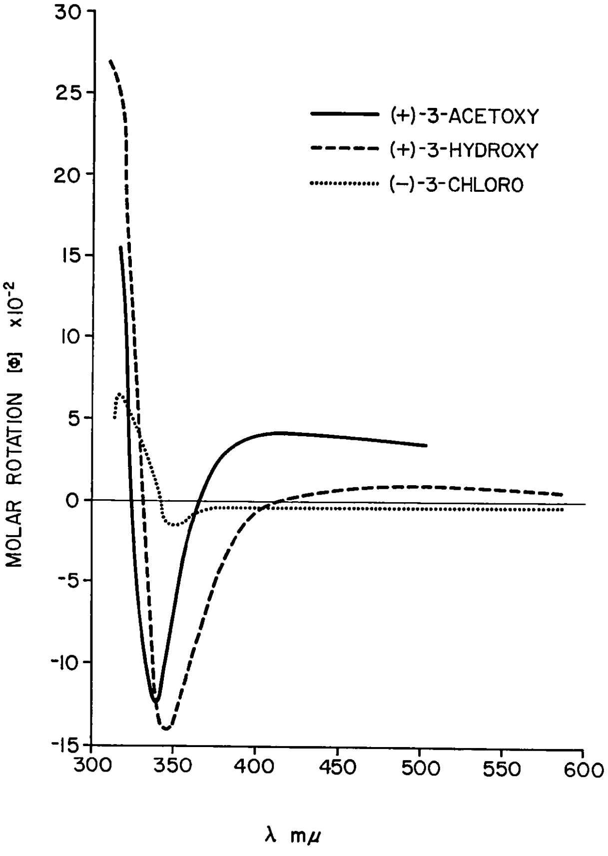

Fig. 1. Rotatory dispersion curves of some 1-methyl-3-benzoyl-piperidines in 0·1 N HCl.

The anomalous dispersion parameters for bromine and all the atomic scattering factors were taken from the *International Tables for X-ray Crystallography* (1968). Computer programs used in this study were written for the IBM 1130 and 7090 systems (Shiono, 1963–71).

Discussion

The empirical octant rules (Djerassi, 1960; Moffitt, Woodward, Moskowitz, Klyne & Djerassi, 1961) permit assignment of absolute configuration based upon the character of the o.r.d. curve or the assignment of conformation based upon a known configuration and the character of the o.r.d. curve. Some β-amino ketones (Hudec, 1970) and other compounds (Bartlett, Kirk, Klyne, Wallis, Erdtman & Thorén, 1970) reportedly violate octant rules (antioctant behavior). To determine whether I–III and analogous compounds in the form of the free amine, protic and quaternary salts follow octant or antioctant rules, it is necessary to determine the o.r.d. curves, absolute configurations and predominant solution conformations of some prototypes.

The sign of the Cotton effect curve for the $n \rightarrow \pi^*$ electronic transition of the carbonyl chromophore in (−)-II is negative in acid and positive in octane (Smissman & Hite, 1960). Solvent-dependent sign inversion observed in cyclohexanones has been attributed to the difference in the conformational equilibrium in polar and non-polar solvents (Djerassi & Geller, 1958). Sign inversion is also observed for (−)-V and (+)-VI (Soares, 1971; Hite & Soares, 1973). This suggested that the O(3)–C(9)–C(3)–C(2) torsion angle differs so that the carbonyl chromophore experiences different asymmetric environments in the two solvents. It was proposed that the 30° rotamer (*cf.* Figs. 2, 3) is stabilized in acid by electrostatic attraction between the electrons on O(3) and the cationic center and that the 210° rotamer, for example, is stabilized in octane by weak dipolar repulsion between the electrons on O(3) and the non-bonding electrons on N (Smissman & Hite, 1960). This study deals with protic salts of I–III in which electrostatic attraction was expected to play a major role in determining molecular conformation in both the solid state and in solution. Additional reports of protic (Hite & Soares, 1973) and quaternary salts and free amines in this series will appear shortly.

The absolute configuration of (+)-I, (−)-II and (+)-III is R. All exhibit negative Cotton effect curves in 0·1 N acid (Fig. 1). The solution n.m.r. spectra of the salts are too complex to provide conformational information. However, the following strongly suggests that the solid-state conformation of the protic salts is the predominant species in acidic solution.

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Quantum mechanical calculations indicate that charge is delocalized over the four carbon atoms (C_α^+) attached to the quaternary nitrogen atom of acetylcholine (Kier, 1967; Ajo, Bossa, Damiani, Fidenzi, Gigli, Lanza & Lapiccirrella, 1972; Pullman, Courriere & Coubelis, 1971; Beveridge & Radna, 1971; Pullman & Courriere, 1972; Liquori, Damiani & DeCoen, 1968; Liquori, Damiani & Elefante, 1968). This is in accord with C_α deuteration of quaternary amines in deuterated solvents containing base (von Doering & Hoffmann, 1955; Shiner & Smith, 1958). The crystal structures of both quaternary and tertiary amine salts exhibit O-to-C_α^+ distances shorter than van der Waals contacts (Abrahamsson & Pascher, 1966; Sundaralingam & Jensen, 1965; Herdklotz & Sass, 1970; Canepa, Pauling & Sørum, 1966; Shefter, Sackman, Stephan & Smissman, 1970; Hjortås & Sørum, 1971; Craven & Hite, 1973; Gabe & Barnes, 1963; Dexter, 1972; Beall, Herdklotz & Sass, 1970; Sax, Pletcher & Gustaffson, 1970). This has been ascribed to electrostatic attraction. In the 21·3° rotamer of IV, the O(3)-to-C(2) distance is 2·63 Å. This is shorter than any comparable O-to-C_α^+ distance observed to date. On steric grounds, the 98·7° rotamer in which the O(3)-to-C(2) separation would be larger, should be as stable as the 21·3° rotamer. The fact that the 21·3° rotamer is the one found in the solid state supports electrostatic attraction. The O(3)–C(9)–C(3), C(2)–C(3)–C(9) and C(4)–C(3)–C(9) bond angles of 116·9 (5), 108·6 (5) and 110·5 (5)° respectively, also represent a trend in support of electrostatic attraction. It may also be pertinent that the O(2)-to-C(2) internuclear distance in IV is 2·96 Å. Solution studies of acetylcholine by n.m.r. confirm that the O–C–C–N *gauche* crystallographic conformation predominates in aqueous solution (Culvenor & Ham, 1966; Culvenor & Ham, 1970; Partington, Feeney & Brugen, 1972). This information strongly suggests that the 21·3° rotamer is the predominant form of these amines (I–IV) in aqueous acid and that it is not unique to the crystalline state.

In the octant diagram (Fig. 4) the phenyl, C(1), C(2), N and C(3) atoms are nodal or close to the *xz* nodal plane and thus do not contribute singificantly to

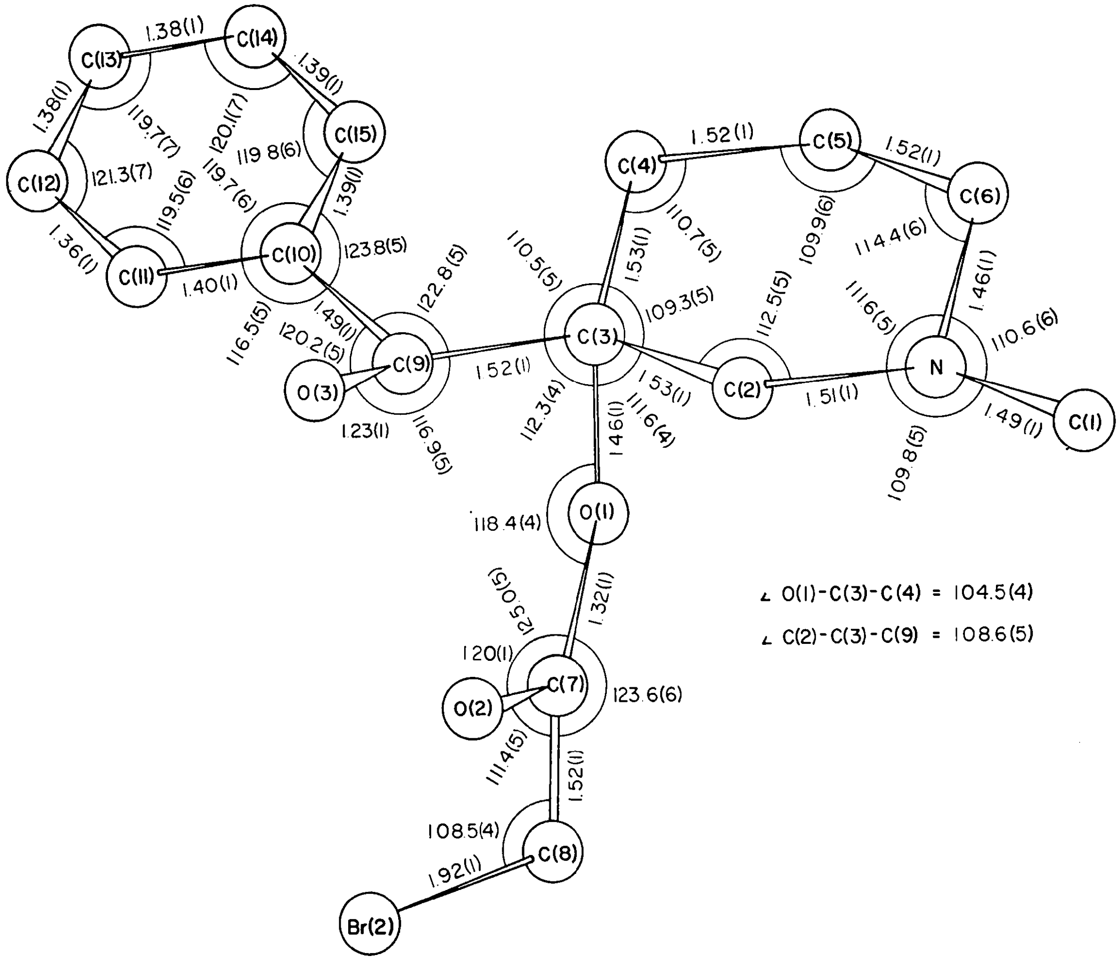

Fig. 2. Bond distances and angles with standard deviations for IV.

the sign of the Cotton effect. The C(4), C(5) and C(6) atoms are in a negative octant. The C(3)–C(4) bond is nearly orthogonal (*ca.* 99°) to the plane (*xz*) of the carbonyl group. The principal determinants of the signs of the Cotton effects in I–III are the more electronegative 3-axial atoms (Cl or O) which lie in a positive octant. The C(3)–O or C(3)–Cl bonds make an angle of about 125° with the *xz* plane. Thus, the octant rules require positive Cotton effect curves for *R*-(I–III) in acid. The negative Cotton effects observed (Fig. 1) are consistent with antioctant behavior. This is the first report of an antioctant α-chloroketone. Whatever electronic forces are responsible for overriding the normally powerful octant effects of α-chloro substituents on carbonyl chromophores, they are adequately strong to provide coherent application of antioctant rules to all protic salt analogs of I–III investigated to date (Soares, 1971; Hite & Soares, 1973).

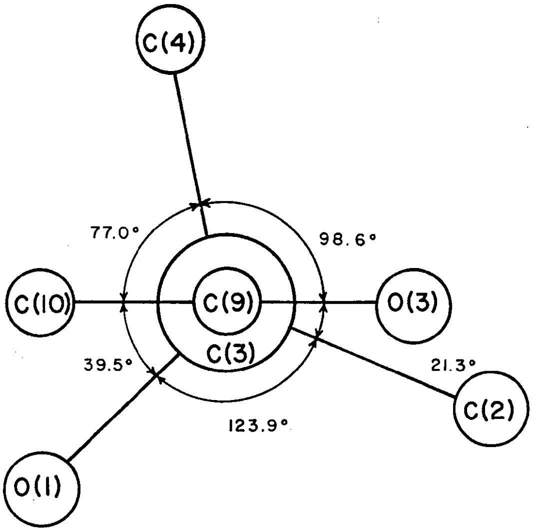

Fig. 3. The torsion angles about the C(3)–C(9) bond in IV.

The antioctant behavior of these β-amino exocyclic ketones is consistent with that of some β-amino endocyclic ketones. In all such cases, the non-bonding electron pair on the nitrogen atom of the free amine is *gauche* to the C_α–C_β bond of the ketonic fragment (Hudec, 1970) and protonation intensifies the antioctant effect.

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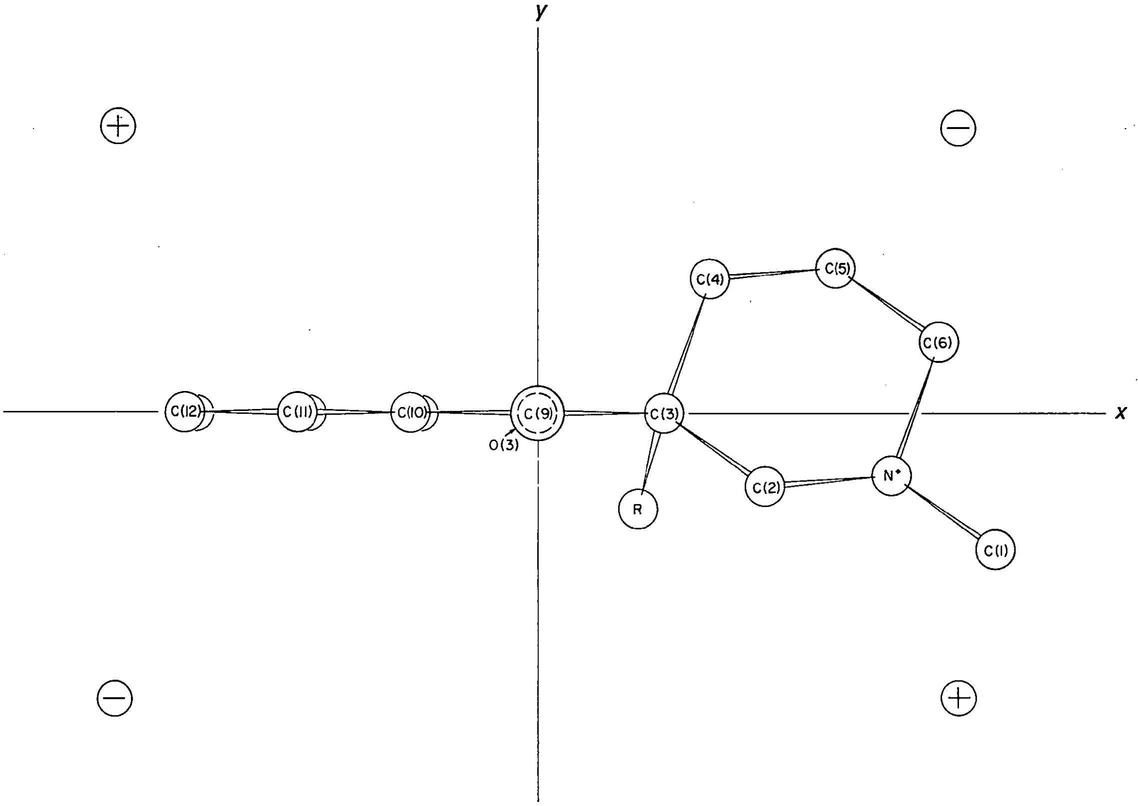

Fig. 4. Octant diagram with *z* axis orthogonal to the *xy* plane for R-(I-III) hydrochlorides employing the 21·3° C(3)–C(9) bond rotamer. R=OH, Cl and CH_3CO_2, respectively. Circled signs refer to the Cotton effect contributions of groups in the rear octants shown.

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