

Stereochemistry of Anticholinergic Agents. Part VIII.¹ Crystal and Molecular Structure of *O*-Benzoyltropine Hydrochloride

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The structure of *O*-benzoyltropine hydrochloride, a relatively weak anticholinergic agent, has been determined by a single-crystal *X*-ray analysis from three-dimensional counter data. Crystals are monoclinic, space group $P2_1/c$, with $Z = 4$ in a cell of dimensions $a = 6.87(1)$, $b = 12.02(1)$, $c = 17.33(1)$ Å, $\beta = 94.0(1)^\circ$. The structure was established by Patterson and Fourier methods and refined by least-squares calculations to R 6.1% for 1 521 observed structure amplitudes. Mean estimated standard deviations for bond lengths, bond angles, and torsion angles are 0.007 Å, and 0.4 and 0.6°. The cation does not have the overall shape and dimensions characteristic of potent anticholinergic agents.

O-BENZOYL TROPINE, although closely related to atropine, is a relatively weak anticholinergic agent. The anti-muscarinic potency of the hydrochloride salt, as measured by the inhibition of spasms in isolated guinea-pig and rabbit ileum, is 0.6—1% of that of atropine.² Its effect

¹ Part VII, J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1975, 1074.

² L. Gyermek, *Nature*, 1953, **171**, 788; L. Gyermek and K. Nador, *J. Pharm. Pharmacol.*, 1957, **9**, 209.

in blocking the action of carbamoylcholine on blood pressure in the cat is also similar.³ The conformations of benzoyltropine and of its epimer, benzoyl- ψ -tropine, have been studied⁴ in solution by use of dipole-moment and n.m.r. data. In this paper the crystal structure of

³ L. Gyermek and K. Nador, *Acta Physiol. Acad. Sci. Hung.*, 1952, **3**, 183.

⁴ K. Nador and P. Scheiber, *Arzneim.-Forsch. (Drug. Res.)*, 1972, **22**, 459.

benzoyltropine hydrochloride is reported. The results of the crystallographic analysis demonstrate that the solid-state conformation is consistent with the results obtained for solutions.

EXPERIMENTAL

Crystallographic Measurements.—Benzoyltropine hydrochloride was recrystallised from butan-2-one. After initial measurements from oscillation and Weissenberg photographs, the final cell dimensions and intensity data were measured with a Stoe two-circle computer-controlled diffractometer. The crystal of dimensions $0.5 \times 0.2 \times 0.2$ mm, was set about the direction of elongation (a), and reflections scanned within the range $0.1 \leq \sin \theta/\lambda \leq 0.69$ by use of Mo- K_{α} radiation and a scintillation counter. Of these, 1 521 having intensities $I > 2.5 \sigma(I)$ were considered observed and were used in the structure analysis. The ω -scan technique was used, the scan-range being calculated by the expression $(A + B \sin \mu/\tan \theta)^\circ$, with $A = 1.1$ and $B = 0.6$, μ being the equi-inclination angle and 2θ the azimuth angle. The stepping interval was 0.01° and the step time 1 s. Backgrounds were measured for 30 s at each end of the scan. Three standard reflections were re-measured after each layer of data collection. Based on these measurements, interlayer scale factors ranging from 1.0 to 1.04 were derived. Intensities were converted into structure amplitudes in the usual way, but absorption corrections were not applied.

Crystal Data.— $C_{15}H_{19}NO_2 \cdot HCl$, $M = 281.8$. Monoclinic, $a = 6.87 \pm 0.01$, $b = 12.02 \pm 0.01$, $c = 17.33 \pm 0.01$ Å, $\beta = 94.0 \pm 0.1^\circ$, $U = 1 427.6$ Å³, $Z = 4$, $D_c = 1.311$ g cm⁻³, $F(000) = 600$. Systematic absences: $h0l$ when l is odd, $0k0$ when k is odd, space group $P2_1/c$ (C_{2h}^5). Mo- K_{α} radiation, $\lambda = 0.710 69$ Å; $\mu(\text{Mo-}K_{\alpha}) = 2.7$ cm⁻¹.

Structure Analysis.—The co-ordinates of the chloride ion were obtained from a three-dimensional Patterson synthesis and structure factors calculated (R 58%). The calculated phase angles were then used with the observed amplitudes to evaluate a three-dimensional electron-density distribution. From this, 24 electron-density maxima were selected as possible sites for lighter atoms and these were now included as carbon atoms in three rounds of least-squares calculations. The R value was thereby reduced to 25% but the temperature factors of seven of the atoms had become anomalously high, while an electron-density difference map based on phases calculated from the refined atomic parameters showed one high (4.7 eÅ⁻³) maximum. By rejecting the seven 'atoms' with high temperature factors and including the one atom located from the difference map, a reasonable model for the benzoyltropine cation was obtained. The oxygen and nitrogen atoms were now assigned appropriate scattering factors and further least-squares refinement of positional and isotropic thermal parameters reduced R to 13%. The atoms were now allowed to vibrate anisotropically and refinement continued till R was reduced to 10.2%. Hydrogen atoms were located from a difference synthesis and were included in the calculations in their theoretical positions, but their parameters were not refined. Refinement was terminated when all calculated shifts in the atomic parameters were $< 0.1 \sigma$ and R 6.1% for the 1 521 observed structure amplitudes.*

* Observed and calculated structure factors are listed in Supplementary Publication No. SUP 21689 (16 pp., 1 microfiche). See Notice to Authors No. 7 in *J.C.S. Perkin II*, 1975, Index issue.

TABLE 1

Fractional atomic co-ordinates ($\times 10^4$), with estimated standard deviations in parentheses

	x	y	z
C(1)	1 935(5)	4 481(4)	950(2)
C(2)	1 152(6)	3 414(4)	943(3)
C(3)	2 323(6)	2 497(4)	831(2)
C(4)	4 290(6)	2 647(4)	734(2)
C(5)	5 076(5)	3 705(4)	742(3)
C(6)	3 908(5)	4 627(4)	847(2)
C(7)	606(6)	5 437(4)	1 059(2)
C(8)	310(5)	7 426(4)	1 097(2)
C(9)	1 176(6)	8 360(4)	637(2)
C(10)	2 901(5)	8 947(3)	1 054(2)
C(11)	2 108(5)	8 313(3)	2 276(2)
C(12)	303(5)	7 685(4)	1 957(2)
C(13)	4 584(5)	8 164(4)	1 332(3)
C(14)	4 051(5)	7 748(4)	2 134(2)
C(15)	3 547(5)	10 228(4)	2 198(2)
N	2 220(4)	9 381(3)	1 814(2)
O(1)	1 488(4)	6 430(2)	977(2)
O(2)	-1 076(4)	5 342(2)	1 207(2)
Cl	-1 648(1)	610(1)	1 464(1)
H[C(2)]	-380	3 299	1 027
H[C(3)]	1 707	1 670	821
H[C(4)]	5 214	1 935	650
H[C(5)]	6 612	3 816	664
H[C(6)]	4 534	5 453	851
H[C(8)]	-1 203	7 283	866
H [†] [C(9)]	26	8 981	499
H [‡] [C(9)]	1 659	8 006	96
H[C(10)]	3 382	9 642	701
H[C(11)]	1 988	8 506	2 892
H [†] [C(12)]	-993	8 195	2 052
H [‡] [C(12)]	212	6 896	2 275
H [†] [C(13)]	4 688	7 460	930
H [‡] [C(13)]	5 979	8 616	1 380
H [†] [C(14)]	5 185	7 991	2 582
H [‡] [C(14)]	3 888	6 838	2 132
H [†] [C(15)]	4 994	9 849	2 312
H [‡] [C(15)]	3 653	10 936	1 801
H [†] [C(15)]	3 052	10 542	2 747
H[N]	862	9 764	1 736

TABLE 2

Anisotropic thermal parameters ($\times 10^4$) for the heavier atoms

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	382	403	367	-34	17	-3
C(2)	398	459	520	-64	49	12
C(3)	490	377	555	-45	-34	-5
C(4)	522	484	450	93	-5	25
C(5)	412	550	544	-12	78	50
C(6)	386	479	518	-74	55	32
C(7)	397	431	495	-87	44	-72
C(8)	333	437	491	39	4	-42
C(9)	444	469	397	21	-41	3
C(10)	396	448	353	-12	62	15
C(11)	412	429	375	9	34	67
C(12)	370	433	515	8	118	13
C(13)	360	459	516	16	87	-47
C(14)	380	478	498	52	-67	40
C(15)	445	451	508	-90	-1	-50
N	296	401	431	4	10	-3
O(1)	399	363	601	-33	83	-47
O(2)	385	536	967	-93	189	-98
Cl	379	521	814	64	64	5

Temperature factors are in the form: $T = \exp[-2\pi^2(U_{11}h^2a^{*2} + \dots + 2U_{12}hka^*b^* + \dots)]$.

Atomic scattering factors for non-hydrogen atoms were taken from ref. 5 and for hydrogen from ref. 6. Weights

⁵ H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Cryst.*, 1964, **17**, 1040.

⁶ R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, 1965, **42**, 3175.

for the least-squares refinement were based on counting statistics. Atom positional and thermal parameters are listed in Tables 1 and 2.

TABLE 3

Molecular dimensions

(a) Bonded distances (Å), with estimated standard deviations ($\times 10^3$) in parentheses			
C(1)—C(2)	1.390(6)	C(8)—C(9)	1.522(7)
C(1)—C(6)	1.390(6)	C(8)—C(12)	1.524(6)
C(1)—C(7)	1.487(6)	C(9)—C(10)	1.519(8)
C(2)—C(3)	1.386(6)	C(10)—C(13)	1.541(7)
C(3)—C(4)	1.385(6)	C(10)—N	1.521(7)
C(4)—C(5)	1.380(7)	C(11)—C(12)	1.522(7)
C(5)—C(6)	1.388(6)	C(11)—C(14)	1.532(6)
C(7)—O(1)	1.351(5)	C(11)—N	1.517(5)
C(7)—O(2)	1.206(6)	C(13)—C(14)	1.546(7)
C(8)—O(1)	1.467(5)	C(15)—N	1.492(7)
(b) Selected non-bonded distances (Å)			
N...O(1)	3.85	N...Ph*	7.30
N...O(2)	5.43	O(1)...C(13)	3.01
N...C(1)	6.08	O(1)...C(14)	3.02
(c) Bond angles (°); mean standard deviation 0.4°			
C(2)—C(1)—C(6)	119.7	C(8)—C(9)—C(10)	114.4
C(2)—C(1)—C(7)	118.2	C(9)—C(10)—C(13)	114.1
C(6)—C(1)—C(7)	122.1	C(9)—C(10)—N	107.2
C(1)—C(2)—C(3)	120.4	C(13)—C(10)—N	102.0
C(2)—C(3)—C(4)	119.6	C(12)—C(11)—C(14)	114.8
C(3)—C(4)—C(5)	120.2	C(12)—C(11)—N	107.3
C(4)—C(5)—C(6)	120.5	C(14)—C(11)—N	102.3
C(1)—C(6)—C(5)	119.6	C(8)—C(12)—C(11)	113.5
C(1)—C(7)—O(1)	112.7	C(10)—C(13)—C(14)	105.0
C(1)—C(7)—O(2)	124.1	C(11)—C(14)—C(13)	105.4
O(1)—C(7)—O(2)	123.3	C(10)—N—C(11)	101.4
C(9)—C(8)—C(12)	113.0	C(10)—N—C(15)	113.9
C(9)—C(8)—O(1)	106.7	C(11)—N—C(15)	113.2
C(12)—C(8)—O(1)	110.2	C(7)—O(1)—C(8)	116.8
(d) Selected torsion angles † (°); mean standard deviation 0.6°			
C(2)—C(1)—C(7)—O(1)	-173.7		
C(2)—C(1)—C(7)—O(2)	6.4		
C(6)—C(1)—C(7)—O(1)	5.7		
C(6)—C(1)—C(7)—O(2)	-174.2		
C(1)—C(7)—O(1)—C(8)	-178.3		
O(2)—C(7)—O(1)—C(8)	1.6		
C(7)—O(1)—C(8)—C(9)	-154.5		
C(7)—O(1)—C(8)—C(12)	82.5		
O(1)—C(8)—C(9)—C(10)	-83.9		
O(1)—C(8)—C(12)—C(11)	81.6		
C(8)—C(9)—C(10)—N	-56.7		
C(9)—C(10)—N—C(11)	73.5		
C(10)—N—C(11)—C(12)	-74.4		
N—C(11)—C(12)—C(8)	57.9		
C(11)—C(12)—C(8)—C(9)	-37.6		
C(12)—C(8)—C(9)—C(10)	37.3		
C(10)—N—C(11)—C(14)	46.7		
N—C(11)—C(14)—C(13)	-28.4		
C(11)—C(14)—C(13)—C(10)	-0.2		
C(14)—C(13)—C(10)—N	28.6		
C(13)—C(10)—N—C(11)	-46.7		
C(8)—C(9)—C(10)—C(13)	55.5		
C(9)—C(10)—C(13)—C(14)	-86.6		
C(13)—C(14)—C(11)—C(12)	87.4		
C(14)—C(11)—C(12)—C(8)	-55.0		
C(15)—N—C(10)—C(9)	-164.6		
C(15)—N—C(10)—C(13)	75.2		
C(15)—N—C(11)—C(12)	163.2		
C(15)—N—C(11)—C(14)	-75.7		

* Centre of phenyl ring. † Sign convention as defined by W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521. (Also present in the crystal are the centrosymmetrically related rotamers with torsion angles of opposite sign.)

The major part of the computations were carried out on a CDC 7600 at the University of Manchester Regional Computer Centre by use of the 'X-Ray '72' system of crystallographic programs.†

RESULTS AND DISCUSSION

The structure of the benzoyltropine cation is illustrated in Figure 1 which also shows the atom numbering scheme. Molecular parameters are listed in Tables 3 and 4, and intermolecular distances in Table 5. A view of

TABLE 4

Mean plane calculations

(a) Deviations (Å) of atoms from least-squares planes. In the equations of the planes, x , y , and z are fractional coordinates relative to the cell axes

Plane (a): C(1)—(6)

$$0.926x - 0.810y + 16.931z = 1.424$$

Plane (b): C(1), C(7), C(8), O(1), O(2)

$$1.455x - 0.021y + 16.643z = 1.843$$

[C(1) -0.009, C(7) 0.004, C(8) -0.011, O(1) 0.014, O(2) 0.002, C(2) 0.113, C(3) 0.127, C(4) 0.003, C(5) -0.122, C(6) -0.126, C(9) 0.631, C(10) -0.315, C(11) -2.234, C(12) -1.442, C(13) -1.023, C(14) -2.281, C(15) -2.310, N -1.480]

Plane (c): C(9)—(12)

$$-3.898x + 9.815y + 2.498z = 7.910$$

[C(9) 0.004, C(10) -0.004, C(11) 0.004, C(12) -0.004, C(8) 0.468, N -0.885]

Plane (d): C(8)—(12), N

$$-5.332x + 7.565y + 0.386z = 5.573$$

[C(8) 0.079, C(9) -0.148, C(10) 0.311, C(11) 0.321, C(12) -0.154, N -0.409]

Plane (e): C(10), C(11), C(13), C(14)

$$3.194x + 9.287y + 6.906z = 9.964$$

[C(10) 0.001, C(11) -0.001, C(13) -0.001, C(14) 0.001, N -0.709]

Plane (f): C(10), C(11), C(13), C(14), N

$$4.371x + 7.628y + 6.809z = 9.051$$

[C(10) 0.241, C(11) 0.239, C(13) -0.087, C(14) -0.083, N -0.310]

Plane (g): C(8), N, O(1)

$$1.821x + 4.069y - 15.931z = 1.331$$

[C(9) -1.271, C(10) -1.158, C(11) 1.191, C(12) 1.267, C(13) -0.705, C(14) 0.840, C(15) 0.025]

(b) Dihedral angles (°)

(a)—(b) 5.8, (a)—(d) 79.7, (a)—(f) 61.6, (a)—(g) 28.4, (b)—(d) 78.6, (b)—(f) 55.8, (b)—(g) 34.2, (d)—(f) 83.8, (d)—(g) 87.9, (f)—(g) 89.3

the crystal structure along a is shown in Figure 2. The intermolecular distances correspond to normal van der Waals interactions apart from the short $N^+ \cdots Cl^-$ contact of 3.06 Å. Hydrogen atom H[N] lies close to the $N \cdots Cl$ line at a distance of 2.03 Å from the chloride ion, indicating a strong hydrogen bond.⁷

The phenyl ring, C(1)—(6), is planar to well within the limits of experimental error. The ester grouping, C(1), C(7), C(8), O(1), and O(2), is also essentially planar. The angle between the mean planes through these groups is only 5.8°, so that atoms C(1)—(8), O(1), and O(2) are co-planar to within ± 0.09 Å. Bond lengths and angles

† J. M. Stewart, G. J. Kruger, H. L. Ammon, C. Dickinson, and S. R. Hall, 'The X-Ray System: version of June 1972,' Technical Report TR 192, Computer Science Center, University of Maryland.

⁷ W. C. Hamilton and J. A. Ibers, 'Hydrogen Bonding in Solids,' Benjamin, New York, 1968.

in the phenyl ring and the ester group are close to expected values.

The tropine system has an approximate mirror plane of symmetry passing through the nitrogen atom, C(8) and O(1) [Plane (g) in Table 4]. The piperidinium ring, C(8)—(12), N, is in a chair-like conformation which is, however, significantly flattened at C(8). Atoms C(9)—(12) are accurately co-planar, with N and C(8) displaced

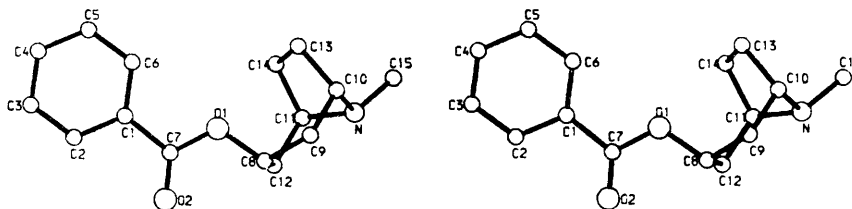


FIGURE 1 Stereoscopic view of the benzoyltropine cation along the *c* axis

by 0.885 and 0.47 Å on opposite sides of this plane. The small values of torsion angles C(11)—C(12)—C(8)—C(9) (-37.6°) and C(12)—C(8)—C(9)—C(10) (37.3°) are also

TABLE 5

Intermolecular contacts < 3.8 Å excluding hydrogen atoms

N \cdots Cl ^I	3.06	C(8) \cdots C(3 ^V)	3.69
C(15) \cdots O(2 ^{II})	3.35	C(11) \cdots O(2 ^{II})	3.69
C(5) \cdots O(2 ^{III})	3.35	C(15) \cdots Cl ^I	3.73
C(6) \cdots C(6 ^{IV})	3.51	C(9) \cdots C(2 ^V)	3.74
C(6) \cdots C(5 ^{IV})	3.52	C(8) \cdots C(2 ^V)	3.75
C(3) \cdots C(9 ^V)	3.53	C(1) \cdots O(2 ^V)	3.75
C(6) \cdots O(2 ^{III})	3.56	N \cdots O(2 ^{II})	3.75
C(15) \cdots C(14 ^{VI})	3.60	C(3) \cdots Cl	3.77
C(15) \cdots Cl ^{II}	3.65	C(12) \cdots Cl ^{III}	3.77
C(15) \cdots C(3 ^I)	3.67	C(15) \cdots C(6 ^{VI})	3.77
C(9) \cdots Cl ^I	3.68	C(7) \cdots C(1 ^V)	3.79
O(1) \cdots C(2 ^V)	3.68	C(14) \cdots C(4 ^{VI})	3.79

The superscripts refer to the following equivalent positions:

I $x, 1 + y, z$	V $-x, 1 - y, -z$
II $-x, \frac{1}{2} + y, \frac{1}{2} - z$	VI $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$
III $1 + x, y, z$	VII $1 + x, 1 + y, z$
IV $1 - x, 1 - y, -z$	

indicative of the ring flattening. The ester oxygen atom, O(1), is substituted axially and the *N*-methyl group equatorially. The bridging atoms C(13) and C(14), together with C(10), N, and C(11), form a five-membered ring which is in the envelope conformation, the nitrogen atom being displaced by 0.71 Å from the mean plane through the other four atoms. Angle C(10)—N—C(11) (101.4°) is typical for the angle at nitrogen in pyrrolidinium rings, but is unusually small for a nitrogen atom in a piperidinium ring.

In a model of the tropine molecule constructed on the basis of standard bond lengths and angles, the oxygen atom [O(1) in the present numbering scheme] is situated only *ca.* 2.4 Å from the bridging carbon atoms, C(13) and C(14), much closer than the sum of the van der Waals radii of carbon and oxygen. The repulsive interaction energies for such separations would be *ca.* 10 kJ mol⁻¹ calculated by the method given in ref. 8 but using a van

der Waals radius⁹ of 1.54 Å for oxygen. The effect of the ring flattening at C(8) is to swing the oxygen atom outwards and away from C(13) and C(14), so that the pertinent distances are increased to 3.01 and 3.02 Å, respectively, and the interaction energies decreased to *ca.* -0.3 kJ mol⁻¹. A similar deformation occurs also in solution.⁴

The orientation of the planar ester group relative to the

semi-rigid tropane system is determined by the conformation about the O(1)—C(8) bond. Torsion angles

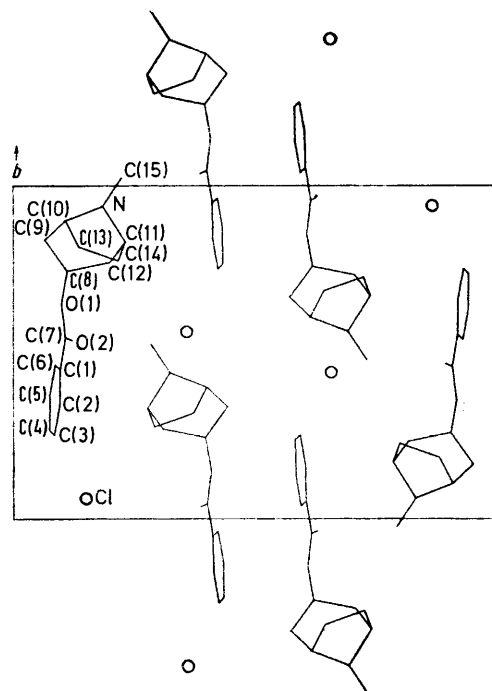


FIGURE 2 The crystal structure projected along the *a* axis

C(7)—O(1)—C(8)—C(9) and C(7)—O(1)—C(8)—C(12) are -154.5 and 82.5° , and the angle between the ester plane and the pseudo-mirror plane of the tropane group 34° . This orientation presumably tends to minimise repulsive interactions between the carbonyl oxygen atom and the equatorial hydrogen atoms at C(8) and C(12), the distances O(2) \cdots H[C(8)] and O(2) \cdots H²[C(12)] being 2.41 and 2.73 Å.

The benzoyltropine cation can thus be described in terms of the tropane group and an approximately planar

⁸ E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965.

⁹ N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tymiński, *J. Amer. Chem. Soc.*, 1969, **91**, 337.

benzoate group, C(8) of the tropane lying in the benzoate plane.

In the crystal structure of hyoscyamine (atropine) hydrobromide¹⁰ the tropane moiety has a similar conformation, but the accuracy of this structure determination is not high and a detailed comparison of conformations is not possible. The angle between the mean plane of the ester group and the pseudo-mirror plane of the tropane group is 34°, identical to the situation in benzoyltropine. In the crystal structure of scopolamine *N*-oxide hydrobromide monohydrate,¹¹ the *N*-methyl group is axial and the *N*-oxide group equatorial with respect to the piperidinium ring. The conformation of the tropane system is, however, very similar to that observed in benzoyltropine, with corresponding torsion angles differing by less than 4°, apart from two torsion angles in the pyrrolidinium ring, which are some 6° smaller in the scopolamine structure. This is probably due to the effect of repulsion between the epoxide and *N*-oxide groups. The angle between the mean plane of the ester group and the pseudo-mirror plane of the tropane group is 32°, again very similar to the corresponding angle in benzoyltropine hydrochloride.

The orientation of the phenyl ring relative to the plane of the ester group is, however, quite different in benzoyltropine. In the hyoscyamine¹⁰ and scopolamine *N*-oxide¹¹ structures, the phenyl ring is steeply inclined to the ester group (interplanar angles 90 and 78°) compared to the almost co-planar arrangement in benzoyltropine.

¹⁰ E. Kussäther and J. Haase, *Acta Cryst.*, 1972, **B28**, 2896.

¹¹ C. S. Huber, G. Fodor, and N. Mandava, *Canad. J. Chem.*, 1971, **49**, 3258.

The hyoscyamine cation (but not scopolamine *N*-oxide) has a 'claw-like' shape¹² (see Figure 3 of ref. 13), with the distance between the extremities of the claw, the cationic head and the phenyl ring, expressed as the nitrogen to centre-of-ring distance, 6.1 Å. This overall shape, with nitrogen-to-ring distances in the range 5.1—6.1 Å, is characteristic also of the crystal structures of potent anticholinergics derived from acetylcholine (see diagrams in refs. 12 and 13), and of certain other anticholinergics.^{1,14} The pertinent ring, which may be aromatic or saturated, is invariably steeply inclined to the plane of the ester group, and the nitrogen to centre-of-ring vector generally steeply inclined to the mean plane of the ring.

Benzoyltropine, however, cannot adopt such a shape, the actual nitrogen to centre-of-ring distance is 7.3 Å and the angle between this line and the plane of the phenyl ring 9°. The relatively low anticholinergic activity of benzoyltropine may thus be rationalised on steric grounds.

I thank Professor K. Nador and Dr. P. Scheiber for suggesting this problem and providing materials, Professors J. C. Tatlow and J. C. Robb for their interest in this work, and the staffs of the University of Manchester Regional Computer Centre and of the University of Birmingham Computer Centre for their assistance.

[5/2014 Received, 15th October, 1975]

¹² J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1975, 467.

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¹⁴ A. Del Pra, M. Mammi, G. Valle, P. Pratesi, and L. Villa, *Il Farmaco, Ed. Sci.*, 1973, **28**, 675.