Structures of N-Methyl-4-piperidinyl Diphenyl Acetate Methyl Iodide (I) and Hyoscine Methyl Iodide (II)

BY R. B. BARLOW,* J. A. K. HOWARD,† O. JOHNSON† AND T. M. SANDERS†

Departments of Inorganic Chemistry and Pharmacology, University of Bristol, Bristol BS8 1TS, England

(Received 22 September 1986; accepted 20 October 1986)

Abstract. (I): N,N-dimethyl-4-(diphenylacetoxy)piperidinium iodide, C_{21}H_{26}NO_{12}·I^{-}, Mr = 451.4, monoclinic, P2_{1}/c, a = 10·106 (4), b = 22·107 (6), c = 10·090 (3) Å, β = 114·11 (2)°, U = 2058 (1) Å³, Z = 4, D_{m} = 1·4, D_{x} = 1·46 g cm^{-3}, Mo Kα, λ = 0·71069 Å, μ = 15·5 cm^{-1}, F(000) = 912, T = 294 K, R(wR) = 0.059 (0.063) for 3386 reflections. (II): 7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2.4}]nonane bromide, C_{18}H_{24}NO_{12}·Br^{-}, Mr = 445.3, monoclinic, P2_{1}, a = 12·404 (1), b = 11·033 (1), c = 6·956 (1) Å, β = 95·04 (1)°, U = 948·3 (2) Å³, Z = 2, D_{m} = 1·6, D_{x} = 1·56 g cm^{-3}, Mo Kα, λ = 0·71069 Å, μ = 16·9 cm^{-1}, F(000) = 450, T = 294 K, R(wR) = 0·022 (0·023) for 1713 reflections. These two structures, both 4-substituted N,N-dimethylpiperidines, are conformationally quite different and yet both block muscarinic acetylcholine receptors. A comparison of these two structures with other hyoscine and hyoscyamine derivatives is discussed with relevance to their biological activity.

Introduction. Dale (1914) observed that the fall in blood pressure produced by low doses of acetylcholine was imitated by muscarine and the rise in blood pressure produced by much larger doses of acetylcholine was imitated by nicotine. These effects involve different receptors, muscarine-sensitive receptors in blood vessels and in the heart and nicotine-sensitive receptors in sympathetic ganglia and in the adrenal medulla. The muscarine-like effects are blocked by atropine (+)-hyoscyamine and the X-ray crystal structures of many atropine-like compounds have been studied (for a summary see Tollaneare, Moereels & Raymaekers, 1979). There is now reason to believe, however, that there is more than one class of 'muscarinic' receptor and the description M_{1} has been given to those receptors (in sympathetic ganglia in the peripheral nervous system and in the cortex and other areas in the central nervous system) which have high affinity for the compound pirenzepine (review: Birdsall & Hulme, 1983). Other muscarinic receptors are classified as M_{2} but there is evidence that these, too, may have to be subclassified, with muscarinic receptors in atria being different from those in gut and bronchial muscle.

This paper describes the crystal structure of 4-(diphenylacetoxy)-N-methylpiperidine methiodide (4DAMP methiodide), whose affinity for muscarinic receptors in guinea-pig ileum is about ten times that for muscarinic receptors in guinea-pig atria (Barlow, Berry, Glenton, Nikolau & Soh, 1976; Barlow & Shepherd, 1985).

A study of (-)-hyoscine methiodide (scopolamine methiodide) has also been made. This compound shows some (but less) selectivity for receptors in ileum (Barlow & Kitchen, 1982) and we wished to compare its structure with (-)-hyoscyamine hydrobromide, which shows little selectivity, and whose structure has been examined by Küssather & Haase (1972). We also wished to compare it with (-)-hyoscine hydrobromide, studied by Pauling & Petcher (1969).

Experimental. Suitable crystals for diffraction studies grown from aqueous ethanol giving transparent needles, m.p. 480·5-482·2 K (I) and white opaque needles, m.p. 480·6-481·1 K (II). D_{m} by flotation. Crystals mounted on glass fibres, intensity data recorded (Nicolet P3m) using experimental parameters in Table 1. Structures solved by Patterson and Fourier methods using unique absorption-corrected intensities. All non-H atoms refined with anisotropic thermal parameters; H atoms constrained geometrically to ride on ligated atom;
hydroxyl atom (II) located from difference Fourier synthesis and refined.*

Discussion. Atomic coordinates are given in Table 2, bond lengths and interbond angles for (I) and (II) in Tables 3 and 4, respectively. Figs. 1 and 2 show the molecular geometries and crystallographic numbering scheme for (I) and (II), respectively.

The conformation of hyoscine methiodide is similar to those of hyoscine hydrobromide (Pauling & Petcher, 1969) and hyoscyamine hydrobromide (Kissather & Haase, 1972). This can be seen in Fig. 3(a) in which the atoms of the piperidine rings of (−)-(s)-hyoscyamine (II) and (−)-(s)-hyoscine are fitted by least squares. The intramolecular N⋯O interatomic distances of a number of hyoscine derivatives are compared in Table 5. The epoxide O atom is closer in hyoscine than in its methiodide but otherwise the distances are similar. Values for buscopan [N-butylhyoscine methiodide (I)] and (-)-(s)-hyoscyamine are fitted by least squares. The intramolecular N⋯O interatomic distances are those of hyoscine hydrobromide (Pauling & Petcher, 1969) and hyoscyamine hydrobromide (Kissather & Haase, 1972). This can be seen in Fig. 3(a) in which the atoms of the piperidine rings of (−)-(s)-hyoscyamine (II) and (−)-(s)-hyoscine are fitted by least squares. The intramolecular N⋯O interatomic distances of a number of hyoscine derivatives are compared in Table 5. The epoxide O atom is closer in hyoscine than in its methiodide but otherwise the distances are similar. Values for buscopan [N-butylhyoscine methiodide (I)] and (-)-(s)-hyoscyamine are fitted by least squares. The intramolecular N⋯O interatomic distances are those of hyoscine hydrobromide (Pauling & Petcher, 1969) and hyoscyamine hydrobromide (Kissather & Haase, 1972). This can be seen in Fig. 3(a) in which the atoms of the piperidine rings of (−)-(s)-hyoscyamine (II) and (−)-(s)-hyoscine are fitted by least squares. The intramolecular N⋯O interatomic distances of a number of hyoscine derivatives are compared in Table 5. The epoxide O atom is closer in hyoscine than in its methiodide but otherwise the distances are similar. Values for buscopan [N-butylhyoscine methiodide (I)] and (-)-(s)-hyoscyamine are fitted by least squares. The intramolecular N⋯O interatomic distances are those of hyoscine hydrobromide (Pauling & Petcher, 1969) and hyoscyamine hydrobromide (Kissather & Haase, 1972). This can be seen in Fig. 3(a) in which the atoms of the piperidine rings of (−)-(s)-hyoscyamine (II) and (−)-(s)-hyoscine are fitted by least squares. The intramolecular N⋯O interatomic distances of a number of hyoscine derivatives are compared in Table 5. The epoxide O atom is closer in hyoscine than in its methiodide but otherwise the distances are similar. Values for buscopan [N-butylhyoscine methiodide (I)] and (-)-(s)-hyoscyamine are fitted by least squares. The intramolecular N⋯O interatomic distances are those of hyoscine hydrobromide (Pauling & Petcher, 1969) and hyoscyamine hydrobromide (Kissather & Haase, 1972). This can be seen in Fig. 3(a) in which the atoms of the piperidine rings of (−)-(s)-hyoscyamine (II) and (−)-(s)-hyoscine are fitted by least squares. The intramolecular N⋯O interatomic distances of a number of hyoscine derivatives are compared in Table 5. The epoxide O atom is closer in hyoscine than in its methiodide but otherwise the distances are similar. Values for buscopan [N-butylhyoscine methiodide (I)] and (-)-(s)-hyoscyamine are fitted by least squares. The intramolecular N⋯O interatomic distances are those of hyoscine hydrobromide (Pauling & Petcher, 1969) and hyoscyamine hydrobromide (Kissather & Haase, 1972). This can be seen in Fig. 3(a) in which the atoms of the piperidine rings of (−)-(s)-hyoscyamine (II) and (−)-(s)-hyoscine are fitted by least squares. The intramolecular N⋯O interatomic distances of a number of hyoscine derivatives are compared in Table 5. The epoxide O atom is closer in hyoscine than in its methiodide but otherwise the distances are similar. Values for buscopan [N-butylhyoscine methiodide (I)] and (-)-(s)-hyoscyamine are fitted by least squares. The intramolecular N⋯O interatomic distances are those of hyoscine hydrobromide (Pauling & Petcher, 1969) and hyoscyamine hydrobromide (Kissather & Haase, 1972). This can be seen in Fig. 3(a) in which the atoms of the piperidine rings of (−)-(s)-hyoscyamine (II) and (−)-(s)-hyoscine are fitted by least squares. The intramolecular N⋯O interatomic distances of a number of hyoscine derivatives are compared in Table 5. The epoxide O atom is closer in hyoscine than in its methiodide but otherwise the distances are similar. Values for buscopan [N-butylhyoscine methiodide (I)] and (-)-(s)-hyoscyamine are fitted by least squares. The intramolecular N⋯O interatomic distances are those of hyoscine hydrobromide (Pauling & Petcher, 1969) and hyoscyamine hydrobromide (Kiss...
little selectivity. The superposition of (−)-hyoscine methiodide (II) on 4DAMP methiodide (I) in Fig. 4(a), however, suggests that if the piperidine ring and charged N atoms fit the muscarinic receptor in the same way the benzene rings must fit quite differently.

Table 4. Bond lengths (Å) and angles (°) for hyoscine methiodide (II)

| C(1)–C(2) | 1.541 (8) | C(1)–C(7) | 1.537 (6) |
| C(1)–O(2) | 1.518 (5) | C(2)–C(3) | 1.538 (6) |
| C(3)–C(4) | 1.494 (8) | C(3)–N(1) | 1.353 (6) |
| C(4)–C(5) | 1.528 (8) | C(4)–O(1) | 1.449 (5) |
| C(5)–C(6) | 1.526 (7) | C(5)–O(1) | 1.399 (8) |
| C(6)–C(7) | 1.531 (7) | C(6)–N(1) | 1.529 (6) |
| N(1)–C(21) | 1.517 (7) | N(1)–C(22) | 1.504 (6) |
| O(2)–C(8) | 1.506 (6) | C(10)–O(4) | 1.384 (9) |
| C(8)–C(9) | 1.532 (6) |

Table 5. N⋯O interatomic distances (Å)

<table>
<thead>
<tr>
<th>Ether</th>
<th>Carbonyl</th>
<th>Epoxide</th>
<th>Hydroxyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>(−)-Hyoscine methiodide (II)</td>
<td>3.901</td>
<td>5.568</td>
<td>2.790</td>
</tr>
<tr>
<td>(−)-Hyoscine hydrobromide (Pauling &amp; Petcher, 1969)</td>
<td>3.88</td>
<td>5.41</td>
<td>2.47</td>
</tr>
<tr>
<td>(−)-Hyoscyamine hydrobromide (Kussather &amp; Haase, 1972)</td>
<td>3.745</td>
<td>5.296</td>
<td>—</td>
</tr>
<tr>
<td>Hyoscine butylbromide (Leger, Gadret &amp; Carpy, 1978)</td>
<td>3.239</td>
<td>4.688</td>
<td>2.706</td>
</tr>
</tbody>
</table>

Fig. 1. Molecular structure of 4DAMP methiodide (I) and the atomic numbering scheme.

Fig. 2. Molecular structure of hyoscine methiodide (II) and the atomic numbering scheme.

Fig. 3. Crystallographic fitting of the piperidine rings of (a) hyoscine methiodide (I, dashed) and hyoscyamine (solid), (b) buscopan (dashed) and hyoscine methiodide (II, solid).

Fig. 4. Crystallographic fitting of: (a) the planar four-C-atom parts of the piperidine rings of 4DAMP methiodide (I, dashed) and hyoscine methiodide (II, solid); (b) the piperidine rings of 4DAMP methiodide (I, dashed) and pirenzepine (solid).
We thank the SERC for support.

References


Synthesis and Structure of 3-(4-Carbamoylphenyl)-1,3-dimethyltriazene 1-Oxide

BY S. NEIDLE,* G. D. WEBSTER,* R. KURODA* AND D. E. V. WILMAN†
The Institute of Cancer Research, Clifton Avenue, Sutton, Surrey, SM2 5PX, England

(Received 30 April 1986; accepted 22 October 1986)

Abstract. C9H12N4O2, M r = 208.22, monoclinic, P21/c, a = 9.345(1), b = 5.059(1), c = 21.531(2) Å, β = 95.24(1)°, V = 1013.6 Å3, Z = 4, Dc = 1.364 g cm−3, λ(Cu Kα) = 1.5418 Å, μ(Cu Kα) = 7.95 mm−1, F(000) = 440, T = 298 K, R = 0.063 for 1112 significant reflections. The analysis confirms the N-oxide character of this compound. The triazene system is non-coplanar with the phenyl group, as a result of the relief of steric hindrance caused by the methyl group at N(1).

Introduction. Aryldialkyltriazenes have been examined extensively for possible antitumour activity in a continuing search for second-generation analogues of 5-(3,3-dimethyl-1-triazenyl)-1H-imidazole-4-carboxamide (DTIC; Wilman & Farmer, 1986). As a part of this study we have investigated different types of triazene N-oxide, including the title compound (I), in relation to both their structure and their antitumour activity (Wilman, 1985). The recent X-ray crystallographic analysis of 3-(4-carbamoylphenyl)-1-methyltriazene 1-oxide (II) (Kuroda & Wilman, 1985) has shown that, at least in the solid state, the N-oxide form is preferred to the N-hydroxyl.

The present study examines the geometry of the triazene analogue where N-methylation of (II) has forced the N-oxygenated substituent into the N-oxide form, since there is no longer a proton directly attached to an N atom (which instead now carries the methyl group).

Experimental. Compound (II) (Connors, Goddard, Merai, Ross & Wilman, 1976) was reacted successively in dimethylformamide with sodium hydride and iodo- methane by the method of Miesel (1976) to give the title compound (CB 10-439) following chromatography on silica gel (Merck 7734) with ethyl acetate as eluant and crystallization from benzene; m.p. 478–480 K, 40% yield. Analysis calculated for C9H12N4O2: C, 51.9; H, 5.8; N, 26.9%. Found: C, 52.0; H, 5.9; N, 27.4%.

Colourless elongated crystals were readily obtained from ethanolic solution, although their tendency to twin caused difficulties in the selection of suitable single crystals. A crystal used for data collection had dimensions 0.04 × 0.05 × 0.04 mm. Cell dimensions from least-squares refinement of 25 θ values measured on an Enraf–Nonius CAD-4 diffractometer. Intensity measurements with 0–2θ scans, 1.5 < θ < 65.0°, 0 ≤ h ≤ 10, 0 ≤ k ≤ 5, −25 ≤ l ≤ 25, max. scan time 90 s. No significant change in three control reflections measured every 3600 s. 1881 unique reflections were measured, of which 1112 had I > 2σ(I) and were used for refinement. Structure solved by MULTAN82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982). Refined by a full-matrix