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# Stereochemistry of Anticholinergic Agents. XV.* Structure of 2-(Diethylamino)ethyl 1-Cyclohexylcyclohexanecarboxylate Hydrochloride (Dicyclomine Hydrochloride)

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## Abstract

$C_{19}H_{36}NO_2^+.Cl^-$, $M_r = 345{\cdot}95$, is orthorhombic, space group *Pbca*, with $a = 11{\cdot}57$ (1), $b = 31{\cdot}95$ (2), $c = 11{\cdot}08$ (1) Å, $U = 4096$ Å$^3$, $D_c = 1{\cdot}12$ Mg m$^{-3}$, $F(000) = 1520$, $Z = 8$, $\mu$(Mo $K\alpha$) = 0·159 mm$^{-1}$. The final $R$ is 6·8% for 1206 observed counter amplitudes. The cyclohexyl rings are in the chair conformation and the ester group is substituted axially. The acetylcholine-like moiety adopts the same conformation as acetylcholine in crystals of the chloride salt, with the C(=O)–O–C–C grouping antiplanar, and O–C–C–$N^+$ synclinal. The overall shape of the cation is similar to that observed for other anticholinergic agents.

## Introduction

Dicyclomine hydrochloride (Tilford, Van Campen & Shelton, 1947) belongs to a class of synthetic anticholinergic drugs which differ from acetylcholine itself in possessing ring substituents in the acyl group, and larger groups on the N atom. Its activity as measured by the inhibition of the spasmodic effect of acetylcholine stimulation of rabbit intestine is *ca* one eighth that of atropine (Tilford *et al.*, 1947; Barlow, 1964). Later studies (McGrath, Lewis & Kuhn, 1964), however, showed that dicyclomine has a dual antispasmodic effect, acting both competitively at the parasympathetic post-glanglionic receptor, and directly on the intestine, and that its peripheral (atropine-like) anticholinergic activity is only some 5% of that of atropine. It also has antihistamine properties (Tilford *et al.*, 1947) and local anaesthetic effects, and impairs release of transmitter from autonomic nerve-endings (Johns, Tasker, Johnson, Theman & Paton, 1976). The crystal structure of the closely related anticholinergic agent 2-(diethylamino)ethyl 1-phenylcyclopentanecarboxylate hydrochloride (parpanit) has been determined previously (Griffith & Robertson, 1972).

## Experimental

Thin plates were obtained by crystallization from 2-butanone. A crystal 0·4 × 0·2 × 0·05 mm was mounted along the direction of elongation which coincided with $x$. After preliminary examination by photographic methods, intensities and final lattice parameters were measured with a Stoe STADI-2 diffractometer and graphite-monochromated Mo $K\alpha$ radiation, $\lambda = 0{\cdot}71069$ Å, by the $\omega$-scan technique. Systematic absences $0kl$ $k$ odd, $h0l$ $l$ odd, $hk0$ $h$ odd defined space group *Pbca*. Reflexions were scanned in the range $0{\cdot}1 < \sin\theta/\lambda < 0{\cdot}6$ Å$^{-1}$ and 1206 with $I > 2{\cdot}5\sigma(I)$ were used in the analysis. The scan rate was 0·6° min$^{-1}$ and 30 s background counts were taken at each end of the scan. For layers $0kl$–$2kl$ the scan range was 1·2° and for $3kl$–$12kl$ a variable scan range was used, $\Delta\omega$ being calculated from $[1{\cdot}0 + (0{\cdot}5 \sin\mu/\tan\theta')]°$ where $\mu$ is the equi-inclination angle and $2\theta'$ the azimuth angle. Three standard $0kl$ reflexions, remeasured after each layer of data collection, showed no significant variation of intensity.

## Determination of the structure

The structure was solved by Patterson and Fourier methods. Refinement was by least squares, first with isotropic, then anisotropic temperature factors. H atoms were included in the calculations in their theoretical positions but their coordinates were not refined. One overall isotropic temperature factor for all the H atoms refined to $U = 0{\cdot}11$ Å$^2$. Least-squares calculations were terminated when all shifts were $<0{\cdot}1\sigma$ and $R = 6{\cdot}8\%$ for the 1206 observed amplitudes. The weighting scheme was $w = 1/[\sigma^2(F)]$, where $\sigma(F)$ is the standard deviation in the observed amplitudes based on counting statistics. A final difference

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Table 1. *Fractional atomic coordinates* ($\times 10^4$) *and equivalent isotropic temperature factors* ($Å^2 \times 10^3$)

The $U_{eq}$ were calculated by the method of Willis & Pryor (1975).

| | $x$ | $y$ | $z$ | $U_{eq}$ |
|---|---|---|---|---|
| C(1) | 1011 (7) | 4065 (2) | 4265 (8) | 60 (6) |
| C(2) | −18 (9) | 4235 (3) | 5015 (10) | 86 (7) |
| C(3) | −21 (16) | 4063 (3) | 6287 (15) | 128 (11) |
| C(4) | 1078 (24) | 4143 (4) | 6951 (10) | 144 (13) |
| C(5) | 2132 (14) | 3969 (4) | 6222 (15) | 126 (11) |
| C(6) | 2133 (9) | 4139 (3) | 4955 (12) | 90 (8) |
| C(7) | 977 (11) | 4271 (2) | 2943 (10) | 100 (8) |
| C(8) | 1223 (13) | 4721 (4) | 2961 (11) | 124 (11) |
| C(9) | 994 (17) | 4914 (4) | 1635 (17) | 169 (15) |
| C(10) | 1616 (14) | 4713 (5) | 728 (12) | 126 (11) |
| C(11) | 1432 (13) | 4271 (5) | 739 (12) | 122 (11) |
| C(12) | 1656 (11) | 4074 (3) | 1988 (11) | 112 (10) |
| C(13) | 777 (8) | 3607 (2) | 4022 (7) | 52 (5) |
| C(14) | 1604 (7) | 2939 (2) | 3666 (6) | 46 (5) |
| C(15) | 2759 (6) | 2750 (2) | 3355 (6) | 48 (5) |
| C(16) | 2881 (7) | 2201 (3) | 5027 (7) | 59 (5) |
| C(17) | 2609 (8) | 1851 (3) | 4157 (8) | 73 (6) |
| C(18) | 3763 (7) | 2901 (3) | 5336 (7) | 66 (6) |
| C(19) | 4518 (8) | 3248 (3) | 4813 (9) | 86 (7) |
| N | 3433 (5) | 2576 (2) | 4404 (5) | 45 (4) |
| O(1) | 1759 (4) | 3371 (1) | 4016 (4) | 47 (3) |
| O(2) | −145 (5) | 3459 (2) | 3782 (5) | 66 (4) |
| Cl | 545 (2) | 2194 (1) | 1740 (2) | 55 (1) |
| H¹(2) | 74 | 4574 | 5054 | |
| H²(2) | −808 | 4157 | 4567 | |
| H¹(3) | −149 | 3725 | 6227 | |
| H²(3) | −724 | 4199 | 6779 | |
| H¹(4) | 1053 | 4007 | 7844 | |
| H²(4) | 1190 | 4480 | 7038 | |
| H¹(5) | 2934 | 4045 | 6655 | |
| H²(5) | 2013 | 3637 | 6178 | |
| H¹(6) | 2829 | 4001 | 4452 | |
| H²(6) | 2261 | 4475 | 5011 | |
| H(7) | 83 | 4239 | 2636 | |
| H¹(8) | 724 | 4875 | 3652 | |
| H²(8) | 2125 | 4752 | 3136 | |
| H¹(9) | 1076 | 5246 | 1605 | |
| H²(9) | 82 | 4879 | 1418 | |
| H¹(10) | 1495 | 4843 | −152 | |
| H²(10) | 2528 | 4759 | 993 | |
| H¹(11) | 537 | 4237 | 524 | |
| H²(11) | 1957 | 4118 | 60 | |
| H¹(12) | 2568 | 4107 | 2222 | |
| H²(12) | 1431 | 3749 | 1975 | |
| H¹(14) | 1247 | 2766 | 4417 | |
| H²(14) | 1015 | 2921 | 2908 | |
| H¹(15) | 2621 | 2504 | 2707 | |
| H²(15) | 3274 | 2996 | 2948 | |
| H¹(16) | 2085 | 2296 | 5453 | |
| H²(16) | 3468 | 2081 | 5704 | |
| H¹(17) | 2472 | 1608 | 4811 | |
| H²(17) | 3347 | 1776 | 3601 | |
| H³(17) | 1850 | 1879 | 3587 | |
| H¹(18) | 2966 | 3039 | 5657 | |
| H²(18) | 4206 | 2755 | 6087 | |
| H¹(19) | 4740 | 3432 | 5598 | |
| H²(19) | 4164 | 3451 | 4126 | |
| H³(19) | 5272 | 3092 | 4475 | |
| H(N) | 4215 | 2464 | 3982 | |

synthesis showed no significant features. Final atomic coordinates are in Table 1.*

Computations were carried out on the Birmingham University ICL 1906A computer mainly with *SHELX* (Sheldrick, 1978).

## Results and discussion

The structure and atom labelling of the dicyclomine cation are shown in Fig. 1. Bond lengths, bond angles and selected torsion angles are listed in Table 2 and the results of mean-plane calculations in Table 3.

The two cyclohexyl rings are in the normal (Bucourt, 1974), slightly flattened chair conformation, ring torsion angles in the range ±53–57°. Each ring is substituted equatorially by the other ring, torsion angles C(5)–C(6)–C(1)–C(7) and C(1)–C(7)–C(12)–C(11) being 176 and 173°. C(13) is oriented axially, C(3)–C(2)–C(1)–C(13) = 70°. The conformation about the inter-ring bond, C(1)–C(7), is close to the perfectly staggered arrangement (Table 2). The ester group C(1), C(13), C(14), O(1), O(2) is planar to within ±0·04 Å (Table 3) with a torsion angle C(1)–C(13)–O(1)–C(14) of −174°, typical of esters.

Comparison with parpanit (Griffith & Robertson, 1972) shows a close similarity in conformation. Torsion angles for C(1)–C(13), C(13)–O(1), O(1)–C(14), C(14)–C(15), C(15)–N agree to within 8° and the orientations of the *N*-ethyl groups are also closely similar. The non-bonded distances between N and O(1), O(2), C(13), C(1) and C(2) listed in Table 2 are all within 0·06 Å of the corresponding distances in parpanit. The acetylcholine-like fragment adopts essentially the same conformation as acetylcholine itself in crystals of the chloride (Herdklotz & Sass, 1970),

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36038 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

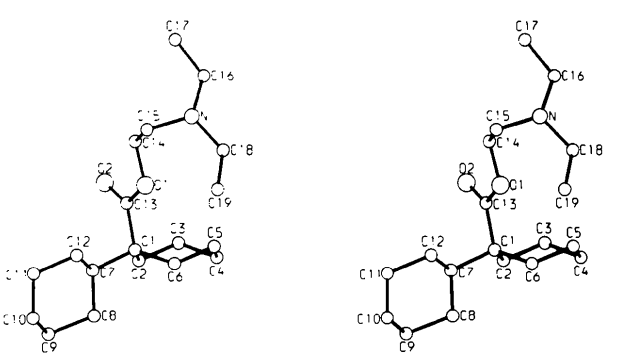


Fig. 1. Stereoscopic view of the dicyclomine cation. H atoms have been omitted.

Table 2. *Molecular dimensions*

(*a*) Bond lengths (Å); e.s.d.'s are 0·01–0·02 Å

| | | | |
|---|---|---|---|
| C(1)–C(2) | 1·55 | C(12)–C(7) | 1·46 |
| C(2)–C(3) | 1·51 | C(13)–C(1) | 1·51 |
| C(3)–C(4) | 1·49 | C(13)–O(2) | 1·20 |
| C(4)–C(5) | 1·56 | C(13)–O(1) | 1·36 |
| C(5)–C(6) | 1·50 | C(14)–O(1) | 1·44 |
| C(6)–C(1) | 1·52 | C(14)–C(15) | 1·51 |
| C(7)–C(1) | 1·61 | C(15)–N | 1·50 |
| C(7)–C(8) | 1·46 | C(16)–N | 1·52 |
| C(8)–C(9) | 1·62 | C(16)–C(17) | 1·51 |
| C(9)–C(10) | 1·39 | C(18)–N | 1·51 |
| C(10)–C(11) | 1·43 | C(18)–C(19) | 1·52 |
| C(11)–C(12) | 1·54 | | |

(*b*) Bond angles (°); e.s.d.'s are 1°

| | | | |
|---|---|---|---|
| C(13)–C(1)–C(2) | 107 | C(8)–C(9)–C(10) | 113 |
| C(13)–C(1)–C(6) | 113 | C(9)–C(10)–C(11) | 112 |
| C(13)–C(1)–C(7) | 103 | C(10)–C(11)–C(12) | 113 |
| C(2)–C(1)–C(7) | 109 | C(11)–C(12)–C(7) | 112 |
| C(2)–C(1)–C(6) | 109 | C(1)–C(13)–O(2) | 126 |
| C(6)–C(1)–C(7) | 114 | C(1)–C(13)–O(1) | 113 |
| C(1)–C(2)–C(3) | 112 | O(2)–C(13)–O(1) | 121 |
| C(2)–C(3)–C(4) | 113 | C(13)–O(1)–C(14) | 115 |
| C(3)–C(4)–C(5) | 110 | O(1)–C(14)–C(15) | 110 |
| C(4)–C(5)–C(6) | 111 | C(14)–C(15)–N | 115 |
| C(5)–C(6)–C(1) | 114 | C(15)–N–C(16) | 115 |
| C(1)–C(7)–C(8) | 113 | C(15)–N–C(18) | 114 |
| C(1)–C(7)–C(12) | 118 | C(16)–N–C(18) | 110 |
| C(8)–C(7)–C(12) | 109 | N–C(16)–C(17) | 112 |
| C(7)–C(8)–C(9) | 109 | N–C(18)–C(19) | 113 |

(*c*) Selected torsion angles (°). E.s.d.'s are *ca* 1·5°. Also present in the crystal are the centrosymmetrically related rotamers with torsion angles of opposite sign.

| | | | |
|---|---|---|---|
| C(1)–C(2)–C(3)–C(4) | 56 | C(5)–C(6)–C(1)–C(7) | 176 |
| C(2)–C(3)–C(4)–C(5) | −55 | C(3)–C(2)–C(1)–C(13) | 70 |
| C(3)–C(4)–C(5)–C(6) | 54 | C(8)–C(7)–C(1)–C(13) | −178 |
| C(4)–C(5)–C(6)–C(1) | −55 | C(12)–C(7)–C(1)–C(13) | −49 |
| C(5)–C(6)–C(1)–C(2) | 54 | C(2)–C(1)–C(13)–O(1) | −145 |
| C(6)–C(1)–C(2)–C(3) | −53 | C(6)–C(1)–C(13)–O(1) | −24 |
| C(7)–C(8)–C(9)–C(10) | −55 | C(7)–C(1)–C(13)–O(1) | 100 |
| C(8)–C(9)–C(10)–C(11) | 53 | C(1)–C(13)–O(1)–C(14) | −174 |
| C(9)–C(10)–C(11)–C(12) | −53 | C(13)–O(1)–C(14)–C(15) | 164 |
| C(10)–C(11)–C(12)–C(7) | 55 | O(1)–C(14)–C(15)–N | 86 |
| C(11)–C(12)–C(7)–C(8) | −57 | C(14)–C(15)–N–C(16) | 65 |
| C(12)–C(7)–C(8)–C(9) | 55 | C(14)–C(15)–N–C(18) | −62 |
| C(1)–C(7)–C(12)–C(11) | 173 | C(15)–N–C(16)–C(17) | 54 |
| C(6)–C(1)–C(7)–C(12) | 74 | C(15)–N–C(18)–C(19) | −60 |
| C(6)–C(1)–C(7)–C(8) | −55 | C(14)–C(15)–N–H(N) | −179 |
| C(2)–C(1)–C(7)–C(8) | 68 | | |

(*d*) Selected non-bonded distances (Å); mean e.s.d. 0·015 Å

| | | | |
|---|---|---|---|
| N···O(1) | 3·22 | N···centre of ring C(1)–(6) | 5·91 |
| N···C(13) | 4·52 | N···centre of ring C(7)–(12) | 7·19 |
| N···O(2) | 5·06 | | |
| N···C(1) | 5·52 | | |
| N···C(2) | 6·67 | | |

perchlorate (Mahajan & Sass, 1974) and β-resorcylate (Jensen, 1975). The O(1)–C(14)–C(15)–$N^+$ torsion angle of 86° is characteristic of this grouping.

The dicyclomine cation has a shape which appears to be typical of anticholinergic agents, the cationic head and cyclohexyl ring C(1)–C(6) forming the extremities of a claw-like arrangement with the ester group acting as connector between them (Guy & Hamor, 1975). The distance between the extremities of the claw, expressed as the $N^+$···centre-of-ring separation, is 5·91 Å, which compares with 5·85 Å for the corresponding separation in parpanit, and falls well within the range of distances found in other anticholinergics.

Table 3. *Mean-plane calculations*

(*a*) Deviations (Å) of atoms from least-squares planes; e.s.d.'s are *ca* 0·015 Å

(I) Cyclohexyl ring C(1)–(6)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C(1) | −0·22, | C(2) | 0·22, | C(3) | −0·23, | C(4) | 0·22, |
| C(5) | −0·22, | C(6) | 0·23, | C(13) | −1·72 | | |

(II) Cyclohexyl ring C(7)–(12)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C(7) | −0·25, | C(8) | 0·23, | C(9) | −0·21, | C(10) | 0·21, |
| C(11) | −0·20, | C(12) | 0·23, | C(1) | −0·03, | C(13) | −0·55 |

(III) Ester group C(1), C(13), C(14), O(1), O(2)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| C(1) | −0·03, | C(13) | 0·03, | C(14) | −0·04, | O(1) | 0·04, |
| O(2) | 0·00, | N | 0·73, | C(2) | 0·81, | C(3) | 2·29, |
| C(4) | 2·80, | C(5) | 1·98, | C(6) | 0·50, | C(7) | −1·59, |
| C(8) | −1·89, | C(12) | −2·58, | C(15) | −0·41 | | |

(*b*) Interplanar angles (°); e.s.d.'s are *ca* 1°

| | | | | | |
|---|---|---|---|---|---|
| (I)–(II) | 74, | (I)–(III) | 81, | (II)–(III) | 88 |

Table 4. *Intermolecular contacts* (Å)

Distances involving only C, N and O atoms are listed up to 3·5 Å and those involving the chloride ion up to 3·8 Å. E.s.d.'s are *ca* 0·01 Å. H atom contacts are not included.

| | | | |
|---|---|---|---|
| N···$Cl^{I}$ | 3·01 | C(16)···$Cl^{I}$ | 3·65 |
| C(16)···$O(2^{II})$ | 3·38 | C(15)···$Cl^{I}$ | 3·68 |
| C(14)···Cl | 3·42 | C(17)···$Cl^{I}$ | 3·71 |
| C(15)···Cl | 3·60 | C(17)···Cl | 3·75 |
| C(14)···$Cl^{III}$ | 3·64 | O(1)···$Cl^{III}$ | 3·79 |

Superscripts refer to the following equivalent positions: (i) $\frac{1}{2}+x$, $y$, $\frac{1}{2}-z$; (ii) $\frac{1}{2}+x$, $\frac{1}{2}-y$, $1-z$; (iii) $x$, $\frac{1}{2}-y$, $\frac{1}{2}+z$.

Bond lengths and angles generally agree with expected values. However, in cyclohexyl ring C(7)–(12), two of the bonds, C(9)–C(10), 1·39 (2), and C(10)–C(11), 1·43 (2) Å, are abnormally short and C(8)–C(9), 1·62 (2) Å, is long. Thermal-vibration parameters of the atoms involved in these bonds are relatively large, but inspection of difference maps gave no indication of disorder in the crystal structure.

Intermolecular contact distances are listed in Table 4. The $N^+$···$Cl^-$ distance (3·01 Å) indicates a strong hydrogen bond. The ammonium H atom, H(N), in its calculated position lies close to the $N^+$···$Cl^-$ line (angle H–$N^+$···$Cl^-$ 5°) at a distance of 1·94 Å from the $Cl^-$ ion. Other distances correspond to normal van der Waals interactions.

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# New Methods and Reagents in Organic Synthesis. XIII. Structure of 3β-(1-Pyrrolidinyl)-5α-cholestane-3α-carbonitrile

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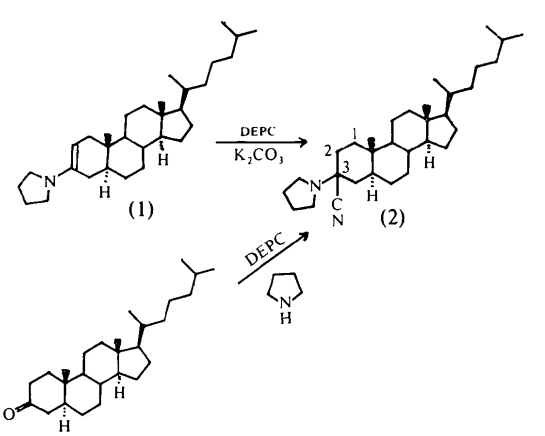
## Abstract

The reaction of 3-(1-pyrrolidinyl)-5α-cholest-2-ene with diethyl phosphorocyanidate or of 5α-cholestan-3-one with diethyl phosphorocyanidate and pyrrolidine was found to afford the title compound by X-ray diffraction methods. $C_{32}H_{54}N_2$, $M_r = 466{\cdot}8$, is monoclinic, space group $P2_1$ with $a = 10{\cdot}589\ (2)$, $b = 10{\cdot}335\ (2)$, $c = 13{\cdot}516\ (2)$ Å, $\beta = 98{\cdot}47\ (1)°$, $V = 1462{\cdot}9\ (5)$ Å$^3$, $Z = 2$, $D_m = 1{\cdot}032\ (1)$, $D_c = 1{\cdot}059$ Mg m$^{-3}$. Anisotropic least-squares refinement led to the residual value $R = 0{\cdot}084$ for a total number of 2672 independent reflections. The cyclopentane ring is best represented by a half-chair conformation and the side chain attached to C(17) by a *trans* zigzag one. In the crystal structure, the molecules are held together by normal van der Waals contacts, and neither hydrogen bonding nor a short contact is observed.

## Introduction

It was reported in our previous communication (Harusawa, Hamada & Shioiri, 1979*a*), that the reaction of 3-(1-pyrrolidinyl)-5α-cholest-2-ene (1) with diethyl phosphorocyanidate [DEPC, $(C_2H_5O)_2$-P(O)CN] gave 3-(1-pyrrolidinyl)-5α-cholestane-3-carbonitrile (2). (2) was also obtained by the reaction of 5α-cholestan-3-one (3) with DEPC and pyrrolidine (Harusawa, Hamada & Shioiri, 1979*b*). The configuration at C(3) of (2) was tentatively assigned as 3α-cyano and 3β-(1-pyrrolidinyl), from the comparison of thermodynamic stabilities of (2) and its epimer, the former being much more stable.

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