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Structure of *cis*-1-{2-[(2-Butoxy)phenylcarbamoyloxy]cycloheptylmethyl}piperidinium Chloride

BY VIKTOR KETTMANN, JÚLIUS SIVÝ AND EVA FREŠOVÁ

Department of Analytical Chemistry, Faculty of Pharmacy, Komensky University, Odbojarov 10,
CS-83232 *Bratislava, Czechoslovakia*

AND FRIDRICH GREGÁŇ

Department of Organic Chemistry, Faculty of Pharmacy, Komensky University, Odbojarov 10,
CS-83232 *Bratislava, Czechoslovakia*

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Abstract. $C_{24}H_{39}N_2O_3^+.Cl^-$, $M_r = 439.0$, monoclinic, $P2_1/n$, $a = 11.749\,(7)$, $b = 7.083\,(4)$, $c = 28.763\,(21)$ Å, $\beta = 97.15\,(6)°$, $V = 2375\,(3)$ Å^3, $Z = 4$, $D_m = 1.23\,(1)$, $D_x = 1.227$ Mg m^{-3}, $\lambda(\text{Mo } K\alpha) = 0.71069$ Å, $\mu = 0.184$ mm^{-1}, $F(000) = 952$, $T = 293$ K, final $R = 0.060$ for 1624 unique observed reflections. The title compound, which is a potent local anaesthetic of the phenylcarbamate type, was designed to explore the stereostructural requirements of the anaesthetic receptor by locking the phenylcarbamate–amine link into a semirigid system. The mean planes of the piperidine (chair conformation) and the cycloheptane (twist-chair form) rings make a dihedral angle of 110.3 (4)° with each other. The lone pairs of electrons on the ether O atom and, to a lesser extent, on the amide N atom are delocalized through the adjacent aromatic system and there is an intramolecular hydrogen-bond interaction between the amidic N—H moiety and the ether O atom [N···O = 2.531 (3) Å]. The principal interaction between the cations and the chloride anions is an $N^+—H\cdots Cl^-$ hydrogen bond [N···Cl = 3.067 (3) Å].

Introduction. The title compound belongs to the phenylcarbamate class of local anaesthetics which are esters of 2-alkoxyphenylcarbamic acid with primary or secondary aminoalcohols. In order to explore the spatial relationship between primary anaesthesiophoric moieties (the phenylcarbamate and the ammonium groups), we report herein the crystal structure of the *cis* isomer of a semirigid derivative containing a central seven-membered ring system.

Experimental. Single crystals were grown from an ethanol solution. A colourless crystal of dimensions 0.20 × 0.25 × 0.50 mm was selected. D_m was determined by flotation. Systematic absences $k = 2n + 1$ for $0k0$ and $h + l = 2n + 1$ for $h0l$ were determined from Weissenberg photographs. A Syntex $P2_1$ diffractometer with graphite-monochromated Mo $K\alpha$ radiation was used for the collection of the intensity data ($h = 0$ to 12, k = 0 to 7, $l = -30$ to 30). The unit-cell parameters and their e.s.d.'s were determined by a least-squares refinement of 15 reflections with $15 < 2\theta < 40°$. The θ–2θ scan mode was used with the scan rate ranging from 2.0 to 29.3° min^{-1}, depending on intensity. The background time to scan time used was 1.0, with a scan range from -1.0 to 1.0 (2θ) about the $K\alpha$ doublet. Two check reflections ($11\bar{3}$ and $3\bar{1}\bar{3}$) were measured after every 100 reflections and only random fluctuation was observed. The intensities were corrected for Lorentz–polarization effects but not for absorption. Of the 3022 unique ($R_{\text{int}} = 0.024$) reflections measured ($2\theta_{\max} = 45°$), 1624 with $I > 2\sigma(I)$ were considered observed. The structure was solved by direct methods using *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and refined by block-diagonal least-squares

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Table 1. *Final atomic coordinates* ($\times 10^4$) *and equivalent isotropic displacement parameters* (Å^2) *with e.s.d.'s in parentheses*

$B_{eq} = (4/3)\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	B_{eq}
C(1)	2930 (2)	1854 (5)	1240 (1)	4.41 (9)
C(2)	1959 (3)	2533 (5)	901 (1)	5.14 (10)
C(3)	820 (3)	1927 (6)	1027 (1)	5.31 (10)
C(4)	699 (2)	2438 (5)	1523 (1)	4.82 (9)
C(5)	1686 (2)	1748 (5)	1861 (1)	4.06 (8)
C(6)	3755 (2)	1706 (5)	2070 (1)	3.76 (8)
C(7)	4895 (2)	2705 (5)	2031 (1)	4.31 (9)
C(8)	5828 (2)	1556 (5)	1861 (1)	4.09 (9)
C(9)	5933 (3)	−490 (5)	2022 (1)	5.27 (12)
C(10)	5872 (3)	−782 (5)	2541 (1)	5.18 (12)
C(11)	6407 (3)	720 (6)	2861 (1)	5.77 (11)
C(12)	5593 (3)	2347 (6)	2918 (1)	5.50 (11)
C(13)	5339 (3)	3664 (5)	2500 (1)	4.75 (10)
C(14)	6496 (2)	1675 (5)	1113 (1)	3.76 (8)
C(15)	6736 (3)	1994 (4)	277 (1)	3.77 (18)
C(16)	6104 (2)	2384 (4)	−145 (1)	3.41 (8)
C(17)	6624 (3)	2624 (5)	−542 (1)	4.74 (10)
C(18)	7808 (3)	2424 (5)	−506 (1)	4.60 (9)
C(19)	8425 (3)	2060 (5)	−90 (1)	5.20 (11)
C(20)	7897 (3)	1813 (5)	311 (1)	4.49 (9)
C(21)	4231 (3)	3032 (5)	−543 (1)	4.48 (8)
C(22)	3039 (3)	3060 (5)	−411 (1)	4.44 (10)
C(23)	2165 (3)	3359 (6)	−840 (1)	5.37 (10)
C(24)	949 (3)	3300 (6)	−717 (1)	7.00 (13)
N(1)	2796 (2)	2395 (4)	1723 (1)	3.50 (6)
N(2)	6089 (2)	1762 (4)	654 (1)	4.14 (7)
O(1)	5595 (2)	1522 (4)	1354 (1)	4.99 (7)
O(2)	7465 (2)	1705 (4)	1281 (1)	5.61 (7)
O(3)	4954 (2)	2519 (3)	−131 (1)	4.56 (6)
Cl(1)	2158 (1)	1712 (1)	3194	5.27 (2)

methods with anisotropic atomic displacement parameters for the non-H atoms. Although most of the H atoms appeared on a $\Delta\rho$ map, all H atoms were included in their calculated positions with B_{iso} set 0.5 Å^2 higher than the B_{eq} values of the associated C or N atoms. The function minimized was $\sum w(\Delta F)^2$, where $w = |F_o|/18$ if $|F_o| < 18$ and $w = 18/|F_o|$ if $|F_o| > 18$, in order to make $w(\Delta F)^2$ approximately independent of $|F_o|$ and $\sin\theta/\lambda$. 271 parameters were refined. The final error indices were $R = 0.060$, $wR = 0.075$ and $S = 1.47$. The largest shift/e.s.d. ratio in the final cycle of refinement was 0.09. The maximum and minimum heights in the final $\Delta\rho$ synthesis were 0.22 and -0.21 e Å^{-3}, respectively. Scattering factors for neutral atoms were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). All calculations except those using *MULTAN* were performed with a local version of the *NRC* program package (Ahmed & Singh, 1973).

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

N(1)—C(1)	1.469 (4)	O(1)—C(14)	1.340 (3)
C(1)—C(2)	1.484 (4)	C(14)—N(2)	1.349 (4)
C(2)—C(3)	1.493 (5)	C(14)—O(2)	1.179 (3)
C(3)—C(4)	1.496 (5)	N(2)—C(15)	1.408 (4)
C(4)—C(5)	1.497 (4)	C(15)—C(16)	1.371 (5)
C(5)—N(1)	1.483 (2)	C(16)—C(17)	1.370 (4)
N(1)—C(6)	1.492 (4)	C(17)—C(18)	1.390 (5)
C(6)—C(7)	1.530 (4)	C(18)—C(19)	1.346 (4)
C(7)—C(8)	1.495 (4)	C(19)—C(20)	1.386 (4)
C(8)—C(9)	1.521 (5)	C(20)—C(15)	1.362 (4)
C(9)—C(10)	1.518 (5)	C(16)—O(3)	1.360 (4)
C(10)—C(11)	1.494 (6)	O(3)—C(21)	1.417 (4)
C(11)—C(12)	1.519 (6)	C(21)—C(22)	1.495 (5)
C(12)—C(13)	1.523 (5)	C(22)—C(23)	1.519 (5)
C(13)—C(17)	1.543 (4)	C(23)—C(24)	1.514 (5)
C(8)—O(1)	1.451 (4)		

C(1)—N(1)—C(5)	112.0 (2)	C(8)—O(1)—C(14)	117.1 (2)
C(1)—N(1)—C(6)	112.7 (2)	O(1)—C(14)—N(2)	107.6 (3)
C(5)—N(1)—C(6)	109.7 (2)	O(1)—C(14)—O(2)	125.0 (3)
N(1)—C(1)—C(2)	111.9 (3)	O(2)—C(14)—N(2)	127.3 (3)
C(1)—C(2)—C(3)	112.7 (3)	C(14)—N(2)—C(15)	126.8 (3)
C(2)—C(3)—C(4)	110.9 (3)	N(2)—C(15)—C(16)	114.9 (3)
C(3)—C(4)—C(5)	112.5 (3)	N(2)—C(15)—C(20)	124.5 (3)
C(4)—C(5)—N(1)	111.2 (3)	C(16)—C(15)—C(20)	120.6 (3)
N(1)—C(6)—C(7)	113.3 (2)	C(15)—C(16)—C(17)	121.0 (3)
C(6)—C(7)—C(8)	117.1 (3)	C(15)—C(16)—O(3)	114.6 (3)
C(6)—C(7)—C(13)	110.1 (3)	C(17)—C(16)—O(3)	124.4 (3)
C(8)—C(7)—C(13)	110.1 (3)	C(16)—C(17)—C(18)	118.2 (3)
C(7)—C(8)—C(9)	117.0 (3)	C(17)—C(18)—C(19)	120.5 (3)
C(7)—C(8)—O(1)	106.4 (2)	C(18)—C(19)—C(20)	121.2 (3)
C(9)—C(8)—O(1)	106.7 (3)	C(19)—C(20)—C(15)	118.5 (3)
C(8)—C(9)—C(10)	114.7 (3)	C(16)—O(3)—C(21)	119.1 (2)
C(9)—C(10)—C(11)	116.2 (3)	O(3)—C(21)—C(22)	105.9 (3)
C(10)—C(11)—C(12)	112.6 (3)	C(21)—C(22)—C(23)	110.9 (3)
C(11)—C(12)—C(13)	116.3 (3)	C(22)—C(23)—C(24)	111.6 (3)
C(12)—C(13)—C(7)	115.7 (3)		

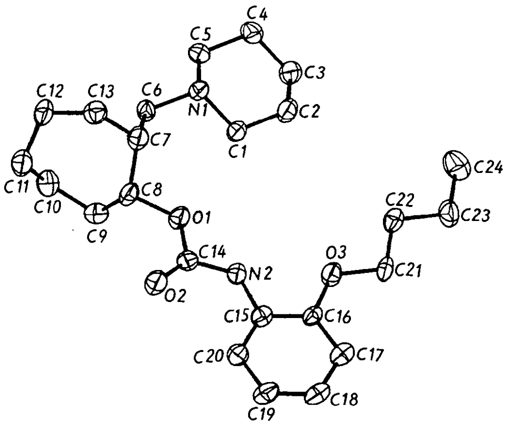

Fig. 1. A perspective view of the title compound showing the numbering of the atoms. The thermal ellipsoids are drawn at the 50% probability level.

Discussion. The final atomic coordinates of the non-H atoms and their equivalent isotropic B values are listed in Table 1,* while bond distances and angles are given in Table 2. A view of the molecule with atom numbering is shown in Fig. 1, which also displays the overall conformation of the molecule.

The cycloheptane ring has a twist-chair conformation (Flapper & Romers, 1975) with a pseudo-twofold axis passing through C(9) and the midpoint of the C(12)—C(13) bond; the asymmetry parameter (Duax, Weeks & Rohrer, 1976), ΔC_2[C(9)], is 6.7°. Such a conformation has been found in most other cycloheptane derivatives (Ponnuswamy & Trotter, 1985), thus supporting the prediction of Hendrickson

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* Lists of structure factors, anisotropic displacement parameters, H-atom parameters and least-squares planes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55844 (16 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: KA1006]

(1967), rather than that made by Bocian, Pickett, Rounds & Strauss (1975) that the boat is the most stable conformation.

The butoxy group lies approximately in the plane of the phenyl ring [torsion angle C(15)—C(16)—O(3)—C(21) = 176.2 (3)°; torsion angles along the butyl chain are close to 180°]. The mean plane of the carbamate moiety [atoms N(2), C(14), O(1) and O(2)] makes a dihedral angle of 10.4 (4)° with the mean plane of the phenyl ring and there is intramolecular hydrogen-bond formation between the amide N(2)—H group and O(3) [N(2)···O(3) = 2.531 (3), H···O(3) = 2.12 Å, N(2)—H···O(3) = 98° (H calculated)]. The N(2)—C(14) bond distance of 1.349 (4) Å is somewhat longer than the range of values 1.32–1.33 Å typically found for the N—C distances in the amide group, and the C(15)—N(2) bond length [1.408 (4) Å] is slightly shorter than the value of 1.425 (3) Å found for a pure $C(sp^2)$—N single bond (Adler, Goode, King, Mellor & Miller, 1976). These results suggest some degree of delocalization of the lone pair of electrons on the amide N atom through the phenyl ring, obviously owing to the coplanarity of the carbamate and phenyl groups and to the polarizing effect of the N(2)—H···O(3) hydrogen bond.

From the pharmacological point of view, the most important structural feature of the phenylcarbamate type local anaesthetics is the three-dimensional disposition of the common functional groups, *i.e.* the protonated amino N atom, the N^+—H vector and the phenylcarbamate function (namely, the carbonyl O atom and the π-excessive phenyl ring), which are assumed to define the interaction with the anaesthetic receptor (Remko & Scheiner, 1988). The spatial relationship between these primary anaesthesiophoric groups is defined by torsion angles along the N(1)—C(6)—C(7) chain as follows: τ_1[C(1)—N(1)—C(6)—C(7)] = 69.3 (3), τ_2[N(1)—C(6)—C(7)—C(8)] = −111.8 (3) and τ_3[C(6)—C(7)—C(8)—O(1)] is fixed at 81.9 (3)° by the *cis* position of C(6) and O(1) and by the twist-chair conformation of the cycloheptane ring. As a result, the mean planes of the piperidine and cycloheptane rings make a dihedral angle of 110.3 (4)° with one another.

The principal interaction between the cations and the chloride anions is an $N(1)^+—H\cdots Cl^-(\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z)$ hydrogen bond [N(1)···Cl = 3.067 (3), H···Cl = 2.04 Å, N(1)—H···Cl = 176° (H calculated)]. Other packing forces are of coulombic and van der Waals types acting at distances > 3.2 Å.

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Structures of Three Electron Donor–Acceptor Complexes of Dibenz[*a*,*h*]anthracene (DBA)

By David E. Zacharias

The Institute for Cancer Research, The Fox Chase Cancer Center, Philadelphia, PA 19111, *USA*

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Abstract. (I) Dibenz[*a*,*h*]anthracene–1,3,5-trinitrobenzene (1/2) (DBA–TNB), $C_{22}H_{14}.2C_6H_3N_3O_6$, M_r = 704.57, monoclinic, $P2_1/a$, a = 25.744 (3), b = 7.889 (1), c = 7.442 (1) Å, β = 91.61 (1)°, V = 1510.8 (4) Å^3, Z = 2, D_x = 1.549 Mg m^{-3}, λ(Cu $K\alpha$) = 1.5418 Å, μ = 0.978 mm^{-1}, F(000) = 724, T = 293 K, R = 0.043 for 2619 data; (II) dibenz[*a*,*h*]anthracene–pyromellitic dianhydride (1/1) (DBA–