Acta Cryst. (1985). C**41**, 1491–1496

Structure of Gallamine Bromide Iodide Aqueous Ethanol Methanol Solvate: Simulation of an Acetylcholine Receptor Site by Computer Graphics

BY JASMINE HUSAIN, IAN J. TICKLE AND REX A. PALMER

Department of Crystallography, Birkbeck College, Malet Street, London WC1E 7HX, England

(*Received* 16 *November* 1984; *accepted* 20 *June* 1985)

Abstract. Neuromuscular blocker gallamine ('flaxedil' *ex* May and Baker Ltd) crystallized as $4(C_{30}H_{60}N_3O_3)^{3+}.11Br^-.I^-.CH_3OH.C_2H_5OH.11H_2O$, $M_r = 3327{\cdot}5$, $P1$, $a = 14{\cdot}216$ (7), $b = 14{\cdot}081$ (7), $c = 20{\cdot}895$ (9) Å, $\alpha = 104{\cdot}90$ (6), $\beta = 92{\cdot}60$ (5), $\gamma = 94{\cdot}50$ (5)°, $V = 4020{\cdot}2$ Å^3, $Z = 1$, $D_m = 1{\cdot}36$ (1) (flotation), $D_x = 1{\cdot}38$ Mg m^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54178$ Å; $\mu = 5{\cdot}056$ mm^{-1}, $F(000) = 1742$, room temperature, $R = 0{\cdot}083$ for 2352 reflections with $I(hkl) \geq 3\sigma[I(hkl)]$. There are four independent molecules of gallamine, pairs of which are related by non-crystallographic twofold axes or mirror planes and the crystal structure thus comprises both left- and right-handed pseudo-equivalent conformations, similar to the model structure proposed by Pauling & Petcher [*Chem. Biol. Interactions* (1973), **6**, 351–365]. Of the three side chains *A*, *B* and *C* in each gallamine molecule, *A* and *C* are roughly mirror related, while *B* is disposed asymmetrically between them. The *A* and *C* chain conformations are such as to rotate their N^+ atoms as far as possible from the benzene-ring plane, while for the *B* side chains the N^+ atoms are roughly coplanar with the benzene rings. All $N^+\cdots N^+$ distances between 8–11 Å observed in (+)-tubocurarine are present in the gallamine structure. The complex solvent structure is distributed along prominent channels running parallel to the crystallographic **c** direction.

Introduction. Gallamine triethiodide, also known as flaxedil (Fig. 1*a*), is a synthetic neuromuscular blocking agent, used clinically since 1949 (Barlow, 1968). Its pharmacological properties are listed in *A Practice of Anaesthesia* (Churchill-Davidson, 1978). Although it is a true non-depolarizing agent whose action can be opposed by the introduction of neostigmine and edrophonium, gallamine has been found also to block glutamate-activated synaptic channels (Cull-Candy & Miledi, 1983). The serendipitous occurrence of four independent molecules of gallamine, together with a large number of ions and solvent molecules, may provide some indication as to its *in vivo* behaviour.

Experimental. Gallamine triethiodide was dissolved in water and passed through a column of 'amberlite' IRA-400 resins which had been prepared previously by washing with water and then treated first with NaOH and then HBr. The solution was then partially fast evaporated and a mixture of ethanol/methanol/acetone was added. After a considerable length of time, on evaporation at room temperature, soft colourless crystals of indefinite shape and size appeared at the bottom of the glass container in a soft wet cake of the residue. Several crystals were mounted for precession photography to determine the cell parameters. A precession photograph of a reasonably good crystal ($0{\cdot}1 \times 0{\cdot}3 \times 0{\cdot}4$ mm) mounted about [301] indicated measurable diffraction data to $\theta \leq 40°$ (Cu $K\alpha$ radiation). The same crystal was mounted on a four-circle Y290 Hilger & Watts diffractometer fitted with a helium path, and its orientation adjusted so that φ was parallel to **a***. Final cell parameters determined by least-squares refinement of the θ, χ, φ values of 12 reflections ($\theta \geq 20°$) with a wide spread of *hkl* values. A search for higher-symmetry lattices failed to find

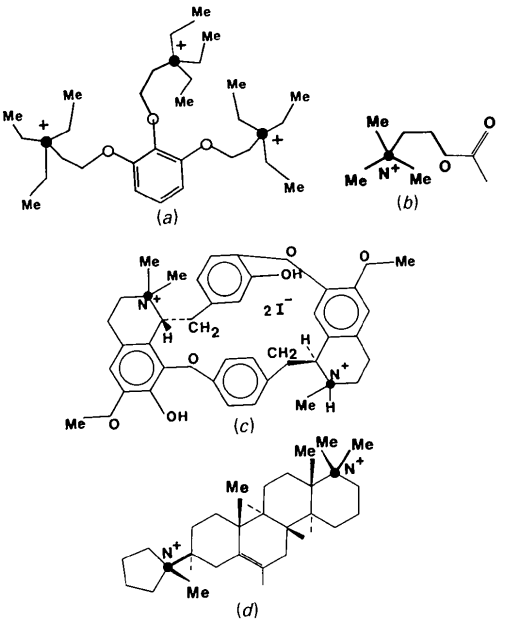

Fig. 1. Chemical formulae: (*a*) gallamine (open circles O, filled circles N), (*b*) acetylcholine, (*c*) (+)-tubocurarine, (*d*) chandonium (HS310).

0108-2701/85/101491-06$01.50

anything other than a triclinic unit cell and the analysis was undertaken on this basis. 10 394 reflections including Friedel equivalents were measured using Cu $K\alpha$ radiation in the ω–2θ scan mode for $2\theta \leq 80°$ using a floating-window technique (Tickle, 1975). Four reflections measured after each 50 intensity counting cycles indicated tolerable crystal stability. The shell $30° \leq \theta \leq 40°$ was almost void of measurable intensities. Lorentz, polarization and absorption corrections (max. 2·10, min. 0·13) (North, Phillips & Matthews, 1968) were applied. 4867 unique reflections; R_{int} = 1·6% calculated for repeat measurements and equivalents; 2352 considered observed [$I > 3\sigma(I)$]; index range $h \pm 11$, $k \pm 11$, l 0/17. E-value distributions were distinctly non-centrosymmetric justifying the assignment of space group $P1$, which was also borne out by the subsequent structure analysis and refinement. Heavy-atom positions indeterminable by Patterson methods appeared as the largest peaks in an E map calculated from the second most probable phase set produced by *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978) and the remaining 161 non-H atoms in the asymmetric unit were located from successive electron density maps. Restrained least-squares methods using the program *SHELX*76 (Sheldrick, 1976; Quick, 1982) were used to refine the structure (on F) in order to make economically effective use of the data. Soft restraints were applied to bonds C–C 1·52 to 1·54, C–N^+ 1·50, C–O 1·44 Å, C···C 1·38 Å and cross-bond (angle) restraints were also applied (see Fig. 2). Of the 12 expected heavy counter ions, 8 refined as well behaved Br^- anions; the rest were subject to statistical disorder and refined with partial occupancies (Table 1*c*). One of the diffuse counter ions refined as I^- disordered into four sites; the rest refined as Br^- (Table 1*c*). A total of 12 well defined water molecules were located from difference maps, and, subsequently, one methanol molecule and one ethanol molecule (all atoms refined as C) were added to the refinement. H atoms were inserted in calculated positions and allowed to ride on their attached heavy atoms during refinement. Anisotropic thermal parameters were refined for the ordered water O atoms and Br^- anions. All other atoms were refined isotropically. The refinement, using unit weights, was carried out in five blocks – one per gallamine molecule and one block for the Br^- and I^- anions and other solvent molecules. In the final refinement cycle $(\Delta/\sigma)_{max}$ = 0·35, 0·40, 0·36, 0·37 and 0·57 for the five blocks. A final difference electron density map contained no region greater than 0·4 e $Å^{-3}$. No correction for secondary extinction. Atomic scattering factors as in *SHELX*76.

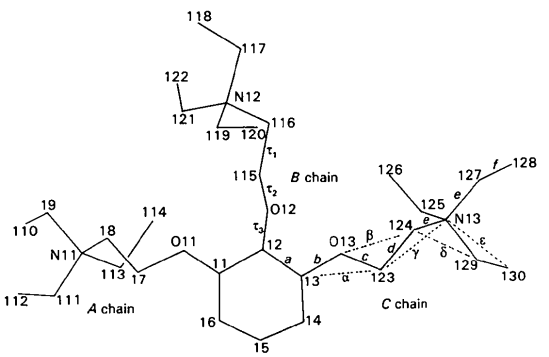

Fig. 2. Gallamine [molecule (1)] showing the atom-numbering scheme. Molecules (2), (3) and (4) are numbered in a similar way, C(11) becoming C(21), C(31) or C(41) *etc.* In the discussion of conformation (see text), the three side chains for each molecule are indicated by *A*, *B* or *C* respectively, each defined by torsion angles τ_1, τ_2, τ_3. Bonds subjected to constrained refinement are labelled *a*–*f*, cross-bonds subjected to constraints α–ε (see Table 2).

Discussion. Atomic parameters are listed in Table 1.* The atom-numbering scheme is indicated in Fig. 2. Bond lengths and cross-bond lengths subjected to constrained refinement in the program *SHELX*76 are indicated in Fig. 2 and results of the refinement are summarized in Table 2. The average bond angles in the phenyl rings are 119·6 (1·9), 119·7 (2·4), 119·6 (2·8) and 119·8 (2·8)° respectively. The required bond lengths have all been achieved within the specified tolerances and similar comments apply to the cross-bond lengths which effectively refine the conventional bond angles. These results justify the procedure adopted which has thus produced a satisfactory result, particularly in view of the immensity of the problem in terms of number of parameters and the relatively poor quality of the diffraction data. This procedure whilst not refining bond lengths and angles in the conventional manner permits torsion angles to refine fairly freely, the results of which are discussed below.

Side-chain conformations

In order to produce a consistent description for the four molecules the following scheme has been adopted. The side-chain conformations in gallamine can be described in terms of three unrestrained torsion angles τ_1, τ_2 and τ_3 (Fig. 2, Table 3), for each of the three side chains *A*, *B* or *C* in any of the four molecules. As will be seen, the absolute conformation of chains *A* and *C* is controlled largely by τ_1 while that of the central *B* chains depends on both τ_1 and τ_3. τ_1 has been calculated as N^+–C–C–O, τ_2 as C–C–O–C_R and τ_3 as

* Lists of structure amplitudes, anisotropic temperature factors for the ordered solvent atoms, coordinates of H atoms, and bond lengths and angles for the gallamine molecules have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42330 (39 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, CH1 2HU, England.

Table 1. *Atomic parameters with e.s.d.'s in parentheses*

(*a*) Coordinates and isotropic thermal parameters (Å²) for non-H atoms of the gallamine molecules

	x	*y*	*z*	U_{iso}
C(11)	−0·0250 (16)	−0·0545 (18)	0·0885 (14)	0·042 (10)
C(12)	−0·1206 (17)	−0·0550 (17)	0·1039 (13)	0·054 (10)
C(13)	−0·1836 (14)	−0·1295 (19)	0·0635 (12)	0·034 (5)
C(14)	−0·1518 (18)	−0·2059 (20)	0·0153 (13)	0·034 (5)
C(15)	−0·0574 (18)	−0·2015 (22)	−0·0002 (15)	0·034 (5)
C(16)	−0·0001 (27)	−0·1200 (24)	0·0322 (16)	0·078 (13)
O(11)	0·0330 (15)	0·0227 (16)	0·1206 (11)	0·073 (6)
C(17)	0·1244 (16)	0·0404 (19)	0·0967 (13)	0·073 (6)
C(18)	0·1677 (19)	0·1413 (17)	0·1355 (11)	0·073 (6)
N(11)	0·2197 (14)	0·1488 (14)	0·2020 (9)	0·044 (8)
C(19)	0·3067 (20)	0·0943 (27)	0·1911 (18)	0·086 (14)
C(110)	0·3676 (28)	0·1333 (39)	0·1425 (24)	0·135 (20)
C(111)	0·2498 (23)	0·2561 (16)	0·2325 (13)	0·051 (10)
C(112)	0·2982 (31)	0·2733 (29)	0·3019 (15)	0·103 (16)
C(113)	0·1644 (25)	0·0945 (28)	0·2428 (19)	0·134 (20)
C(114)	0·0761 (24)	0·1444 (32)	0·2685 (21)	0·096 (15)
O(12)	−0·1419 (18)	0·0208 (15)	0·1513 (10)	0·078 (8)
C(115)	−0·1648 (25)	0·1064 (18)	0·1301 (12)	0·073 (13)
C(116)	−0·1905 (16)	0·1899 (16)	0·1859 (14)	0·075 (13)
N(12)	−0·2813 (13)	0·1783 (15)	0·2199 (9)	0·064 (9)
C(117)	−0·2774 (28)	0·0940 (26)	0·2514 (20)	0·138 (21)
C(118)	−0·2027 (34)	0·1198 (37)	0·3102 (21)	0·133 (20)
C(119)	−0·3634 (17)	0·1434 (19)	0·1695 (14)	0·049 (10)
C(120)	−0·3873 (22)	0·2167 (23)	0·1299 (15)	0·053 (11)
C(121)	−0·2863 (18)	0·2752 (16)	0·2708 (12)	0·030 (8)
C(122)	−0·3803 (30)	0·2768 (41)	0·3039 (29)	0·227 (36)
O(13)	−0·2660 (13)	−0·1267 (16)	0·0903 (10)	0·069 (8)
C(123)	−0·3456 (14)	−0·1912 (19)	0·0546 (11)	0·045 (10)
C(124)	−0·4329 (16)	−0·1761 (18)	0·0932 (15)	0·081 (13)
N(13)	−0·4689 (14)	−0·2561 (16)	0·1253 (10)	0·077 (10)
C(125)	−0·5601 (21)	−0·2233 (25)	0·1547 (19)	0·086 (14)
C(126)	−0·5967 (24)	−0·2952 (28)	0·1941 (19)	0·091 (14)
C(127)	−0·4878 (25)	−0·3531 (17)	0·0743 (15)	0·084 (13)
C(128)	−0·5604 (29)	−0·3490 (31)	0·0186 (17)	0·106 (16)
C(129)	−0·3910 (23)	−0·2732 (20)	0·1716 (14)	0·076 (13)
C(130)	−0·3631 (26)	−0·1803 (25)	0·2286 (15)	0·077 (13)
C(21)	−0·2713 (14)	−0·4324 (20)	0·2412 (13)	0·042 (10)
C(22)	−0·3208 (17)	−0·3864 (21)	0·2968 (11)	0·059 (11)
C(23)	−0·4160 (17)	−0·4238 (22)	0·3001 (12)	0·057 (11)
C(24)	−0·4554 (26)	−0·4892 (24)	0·2422 (14)	0·065 (12)
C(25)	−0·4085 (22)	−0·5291 (27)	0·1864 (18)	0·069 (12)
C(26)	−0·3117 (21)	−0·5078 (21)	0·1862 (14)	0·044 (10)
O(21)	−0·1796 (14)	−0·4046 (17)	0·2491 (11)	0·081 (8)
C(27)	−0·1178 (15)	−0·4557 (19)	0·2018 (14)	0·056 (11)
C(28)	−0·0185 (15)	−0·4050 (22)	0·2151 (14)	0·090 (14)
N(21)	0·0122 (14)	−0·3415 (14)	0·1694 (10)	0·027 (8)
C(29)	0·0164 (25)	−0·4058 (24)	0·1003 (11)	0·074 (13)
C(210)	0·0881 (33)	−0·4824 (30)	0·0980 (22)	0·127 (19)
C(211)	0·1074 (20)	−0·2899 (27)	0·1982 (18)	0·093 (15)
C(212)	0·1403 (32)	−0·2140 (33)	0·1607 (24)	0·130 (19)
C(213)	−0·0632 (21)	−0·2763 (19)	0·1611 (13)	0·054 (11)
C(214)	−0·0698 (27)	−0·1919 (23)	0·2235 (17)	0·077 (13)
O(22)	−0·2758 (17)	−0·3280 (15)	0·3512 (10)	0·072 (8)
C(215)	−0·2442 (22)	−0·3721 (17)	0·4025 (12)	0·066 (12)
C(216)	−0·2006 (16)	−0·2967 (23)	0·4639 (11)	0·102 (16)
N(22)	−0·1039 (13)	−0·2466 (14)	0·4580 (10)	0·040 (7)
C(217)	−0·1092 (25)	−0·1887 (24)	0·4069 (15)	0·087 (14)
C(218)	−0·1711 (32)	−0·1029 (27)	0·4286 (22)	0·111 (17)
C(219)	−0·0775 (21)	−0·1708 (32)	0·5227 (18)	0·143 (21)
C(220)	0·0299 (21)	−0·1506 (29)	0·5361 (19)	0·087 (14)
C(221)	−0·0409 (24)	−0·3250 (26)	0·4283 (18)	0·096 (15)
C(222)	−0·0176 (43)	−0·3861 (39)	0·4772 (30)	0·185 (29)
O(23)	−0·4565 (13)	−0·3775 (14)	0·3536 (9)	0·041 (6)
C(223)	−0·5544 (15)	−0·4038 (23)	0·3614 (15)	0·117 (18)
C(224)	−0·5840 (21)	−0·3453 (18)	0·4275 (13)	0·075 (12)
N(23)	−0·6153 (16)	−0·2440 (15)	0·4290 (11)	0·073 (10)
C(225)	−0·5446 (26)	−0·1906 (27)	0·3960 (17)	0·102 (16)
C(226)	−0·4598 (26)	−0·1398 (35)	0·4436 (24)	0·126 (19)
C(227)	−0·6344 (31)	−0·1935 (23)	0·4990 (13)	0·082 (14)
C(228)	−0·6699 (39)	−0·0917 (26)	0·5047 (23)	0·142 (22)
C(229)	−0·6947 (23)	−0·2533 (32)	0·3772 (19)	0·127 (19)
C(230)	−0·7861 (23)	−0·3059 (37)	0·3928 (25)	0·126 (19)
C(31)	0·0279 (18)	0·0577 (21)	−0·0767 (17)	0·082 (13)
C(32)	0·1189 (21)	0·0519 (19)	−0·0995 (15)	0·083 (8)
C(33)	0·1882 (15)	0·1306 (27)	−0·0768 (18)	0·083 (8)
C(34)	0·1667 (28)	0·2034 (29)	−0·0220 (19)	0·083 (8)
C(35)	0·0753 (25)	0·2064 (31)	−0·0023 (22)	0·095 (16)
C(36)	−0·0011 (21)	0·1391 (20)	−0·0306 (14)	0·033 (9)
O(31)	−0·0270 (16)	−0·0192 (16)	−0·1126 (11)	0·075 (8)
C(37)	−0·1233 (17)	−0·0379 (23)	−0·0972 (16)	0·100 (16)
C(38)	−0·1644 (22)	−0·1386 (21)	−0·1380 (14)	0·109 (16)
N(31)	−0·2220 (17)	−0·1451 (21)	−0·2023 (12)	0·128 (15)
C(39)	−0·2968 (24)	−0·0736 (27)	−0·1884 (20)	0·106 (16)
C(310)	−0·3709 (27)	−0·1101 (35)	−0·1466 (24)	0·123 (18)
C(311)	−0·2554 (45)	−0·2527 (23)	−0·2307 (27)	0·200 (31)
C(312)	−0·3338 (29)	−0·2670 (31)	−0·2863 (20)	0·118 (18)
C(313)	−0·1644 (22)	−0·0982 (22)	−0·2468 (15)	0·055 (11)
C(314)	−0·0802 (27)	−0·1575 (37)	−0·2702 (24)	0·123 (18)
O(32)	0·1502 (16)	−0·0184 (15)	−0·1464 (10)	0·059 (7)
C(315)	0·1714 (23)	−0·1075 (17)	−0·1292 (12)	0·068 (12)
C(316)	0·1910 (18)	−0·1884 (17)	−0·1888 (14)	0·080 (13)
N(32)	0·2846 (16)	−0·1760 (19)	−0·2196 (12)	0·105 (13)
C(317)	0·2835 (23)	−0·0932 (23)	−0·2528 (16)	0·079 (13)
C(318)	0·2060 (29)	−0·1133 (32)	−0·3092 (19)	0·109 (16)
C(319)	0·3617 (22)	−0·1332 (26)	−0·1654 (18)	0·092 (15)
C(320)	0·3848 (38)	−0·2086 (38)	−0·1266 (24)	0·162 (24)
C(321)	0·3043 (32)	−0·2765 (23)	−0·2595 (29)	0·176 (27)
C(322)	0·3959 (24)	−0·2713 (28)	−0·2948 (19)	0·078 (13)
O(33)	0·2773 (15)	0·1278 (17)	−0·0920 (11)	0·069 (8)
C(323)	0·3535 (15)	0·1820 (26)	−0·0460 (11)	0·090 (15)
C(324)	0·4438 (15)	0·1750 (16)	−0·0816 (13)	0·046 (10)
N(33)	0·4715 (12)	0·2548 (13)	−0·1161 (9)	0·036 (7)
C(325)	0·5523 (20)	0·2176 (20)	−0·1569 (16)	0·057 (11)
C(326)	0·6017 (27)	0·2998 (27)	−0·1828 (21)	0·108 (16)
C(327)	0·4812 (27)	0·3531 (17)	−0·0652 (16)	0·103 (16)
C(328)	0·5592 (28)	0·3572 (29)	−0·0111 (16)	0·095 (15)
C(329)	0·3863 (20)	0·2733 (21)	−0·1549 (13)	0·062 (11)
C(330)	0·3642 (27)	0·1946 (28)	−0·2207 (15)	0·092 (15)
C(41)	0·2722 (16)	0·4343 (25)	−0·2427 (16)	0·077 (13)
C(42)	0·3239 (19)	0·3913 (22)	−0·2968 (11)	0·062 (11)
C(43)	0·4219 (20)	0·4126 (29)	−0·2935 (16)	0·098 (15)
C(44)	0·4711 (24)	0·4829 (24)	−0·2426 (15)	0·058 (11)
C(45)	0·4190 (25)	0·5276 (30)	−0·1909 (19)	0·082 (14)
C(46)	0·3254 (25)	0·4961 (28)	−0·1881 (18)	0·085 (14)
O(41)	0·1842 (15)	0·3940 (16)	−0·2469 (12)	0·075 (8)
C(47)	0·1169 (17)	0·4509 (19)	−0·2080 (17)	0·088 (14)
C(48)	0·0226 (16)	0·3901 (22)	−0·2186 (13)	0·077 (13)
N(41)	−0·0045 (15)	0·3340 (15)	−0·1679 (11)	0·046 (10)
C(49)	−0·0051 (23)	0·4044 (23)	−0·1006 (12)	0·077 (13)
C(410)	−0·0791 (25)	0·4792 (24)	−0·0962 (18)	0·077 (13)
C(411)	−0·0996 (19)	0·2805 (26)	−0·1948 (15)	0·076 (13)
C(412)	−0·1428 (24)	0·2310 (29)	−0·1439 (18)	0·086 (14)
C(413)	0·0681 (24)	0·2646 (23)	−0·1615 (14)	0·086 (14)
C(414)	0·0817 (27)	0·1867 (25)	−0·2260 (17)	0·082 (13)
O(42)	0·2841 (17)	0·3282 (16)	−0·3512 (11)	0·070 (8)
C(415)	0·2552 (29)	0·3698 (19)	−0·4044 (14)	0·131 (20)
C(416)	0·2107 (17)	0·2927 (22)	−0·4645 (11)	0·069 (12)
N(42)	0·1108 (16)	0·2478 (18)	−0·4617 (12)	0·140 (17)
C(417)	0·1059 (22)	0·1916 (22)	−0·4101 (15)	0·068 (12)
C(418)	0·1679 (29)	0·1059 (26)	−0·4218 (21)	0·100 (15)
C(419)	0·0728 (17)	0·1977 (20)	−0·5309 (11)	0·031 (8)
C(420)	−0·0194 (24)	0·1332 (32)	−0·5308 (21)	0·123 (19)
C(421)	0·0455 (25)	0·3224 (27)	−0·4315 (19)	0·115 (18)
C(422)	0·0378 (29)	0·4029 (25)	−0·4682 (21)	0·090 (14)
O(43)	0·4646 (18)	0·3711 (21)	−0·3471 (14)	0·119 (11)
C(423)	0·5611 (18)	0·4044 (20)	−0·3538 (14)	0·067 (12)
C(424)	0·5938 (24)	0·3454 (19)	−0·4186 (13)	0·107 (16)
N(43)	0·6257 (16)	0·2435 (16)	−0·4228 (12)	0·100 (12)
C(425)	0·5510 (23)	0·1768 (29)	−0·4038 (21)	0·130 (19)
C(426)	0·4599 (21)	0·1633 (31)	−0·4487 (21)	0·094 (15)
C(427)	0·6504 (33)	0·2062 (24)	−0·4939 (14)	0·098 (16)
C(428)	0·6913 (32)	0·1063 (23)	−0·5074 (20)	0·101 (16)
C(429)	0·7100 (20)	0·2527 (26)	−0·3751 (17)	0·083 (13)
C(430)	0·7906 (23)	0·3209 (33)	−0·3910 (23)	0·119 (18)

(*b*) Solvent atoms: fractional coordinates and equivalent isotropic temperature factors (Å²) for the ordered sites refined anisotropically; $U_{eq} = (U_{11}U_{22}U_{33})^{1/3}$

	x	*y*	*z*	U_{eq}
O(*W*1)	0·0058 (24)	0·3191 (27)	0·1707 (26)	0·136
O(*W*2)	0·3052 (27)	0·8844 (34)	0·0445 (22)	0·151
O(*W*3)	−0·2846 (25)	0·1220 (24)	−0·0429 (15)	0·089
O(*W*4)	0·5565 (32)	0·4422 (33)	0·4403 (18)	0·155
O(*W*5)	0·2524 (26)	0·5210 (32)	0·2449 (20)	0·141
O(*W*6)	0·2488 (29)	0·4446 (27)	−0·0439 (16)	0·101
O(*W*7)	−0·2396 (35)	0·4648 (40)	−0·2345 (27)	0·191
O(*W*8)	−0·2956 (25)	0·1027 (31)	−0·2685 (20)	0·113
O(*W*9)	0·0038 (29)	−0·3095 (40)	−0·1679 (21)	0·152
O(*W*10)	−0·2888 (36)	−0·1088 (32)	−0·4065 (21)	0·152
O(*W*11)	−0·2395 (21)	−0·4410 (19)	0·0394 (15)	0·077
Br(1)	0·5035 (1)	0·0026 (1)	0·0001 (1)	0·126
Br(2)	0·5125 (6)	0·9598 (8)	0·6701 (5)	0·162
Br(3)	−0·3390 (5)	−0·4056 (5)	−0·1014 (3)	0·097
Br(4)	0·3414 (5)	0·4061 (6)	0·0989 (4)	0·109
Br(5)	−0·1177 (5)	0·0675 (6)	−0·3661 (4)	0·108
Br(6)	0·1210 (5)	0·9341 (6)	0·3648 (4)	0·114
Br(7)	0·8373 (9)	0·3344 (9)	0·0498 (6)	0·220
Br(8)	0·1697 (4)	−0·3317 (4)	−0·0490 (2)	0·017

Table 1 (*cont.*)

(*c*) Solvent atoms and anions: refined fractional coordinates and isotropic thermal parameters (Å^2), and refined occupancy factors for the disordered I and Br atoms

	x	*y*	*z*	Occupancy	U_{iso}
C1(*M*1)	0·7412 (34)	0·4646 (31)	0·5023 (20)	1·0	0·102 (2)
O1(*M*1)	0·7739 (18)	0·3858 (19)	0·4434 (12)	1·0	0·059 (8)
C1(*E*1)	0·5485 (81)	0·5564 (59)	0·5345 (64)	1·0	0·334 (64)
C2(*E*1)	0·6216 (50)	0·6488 (66)	0·5473 (44)	1·0	0·206 (40)
C3(*E*1)	0·5657 (76)	0·7395 (58)	0·5748 (55)	1·0	0·315 (64)
I(1*A*)	−0·1762 (23)	−0·4246 (23)	−0·3846 (16)	0·261 (17)	0·244 (19)
I(1*B*)	0·0714 (16)	0·6120 (16)	0·6658 (11)	0·339 (19)	0·206 (13)
I(1*C*)	−0·0516 (14)	0·5713 (14)	0·6878 (9)	0·304 (17)	0·160 (10)
I(1*D*)	0·3142 (48)	−0·0980 (50)	0·2675 (34)	0·136 (16)	0·255 (38)
Br(2*A*)	0·4940 (10)	0·0490 (16)	0·3348 (13)	0·710 (50)	0·128 (6)
Br(2*B*)	0·4829 (17)	0·0135 (28)	0·3042 (22)	0·244 (49)	0·068 (16)
Br(3*A*)	−0·0607 (14)	0·4059 (15)	0·3261 (10)	0·413 (26)	0·144 (11)
Br(3*B*)	0·0885 (15)	0·4403 (16)	0·3135 (10)	0·443 (27)	0·166 (12)
Br(3*C*)	0·4046 (50)	0·3205 (51)	0·4451 (36)	0·183 (28)	0·228 (40)
Br(5*A*)	0·2242 (14)	0·6087 (15)	0·5599 (10)	0·637 (25)	0·230 (11)
Br(5*B*)	0·2579 (23)	0·4628 (23)	0·4474 (16)	0·477 (31)	0·287 (21)

Table 2. *Constrained bond lengths and cross-bond lengths: target values, tolerances requested, average values and e.s.d.'s obtained in the refinement* (*see also Fig.* 2)

Bond or cross-bond label in Fig. 2	Type	Target value and tolerance (Å)	Average value and e.s.d. achieved (Å)
a	$Csp^2\cdots Csp^2$ (phenyl)	1·380 (25)	1·392 (16)
b	Csp^2–O	1·320 (5)	1·322 (1)
c	O–Csp^3	1·440 (5)	1·441 (1)
d	Csp^3–Csp^3 (chain)	1·510 (5)	1·515 (5)
e	Csp^3–N^+	1·500 (15)	1·502 (5)
f	Csp^3–Csp^3 (cationic head)	1·540 (15)	1·534 (4)
α	Csp^2OCsp^3 |·····|	2·380 (30)	2·380 (20)
β	$OCsp^3Csp^3$ |·····|	2·450 (30)	2·428 (25)
γ	$Csp^3Csp^3N^+$ |·····|	2·570 (30)	2·593 (14)
δ	$Csp^3N^+Csp^3$ |·····|	2·460 (30)	2·457 (33)
ε	$N^+Csp^3Csp^3$ |·····|	2·480 (30)	2·510 (17)

C–O–C_R–$C_{R'}$, where C_R is the apical ring atom for a given chain *A*, *B* or *C*; for chains *A* or *C*, $C_{R'}$ is the apical ring atom for the central chain *B* (*i.e.* $C_{R'} = C_B$) while for the *B* chains $C_{R'}$ is the apical ring atom for chain *C* (*i.e.* $C_{R'} = C_C$). Side chains *A* and *C* are distinguished by having different characteristic $N^+\cdots N_B^+$ separations, side chain *C* being chosen such that side chain *B* is rotated towards it and $N_C^+\cdots N_B^+$ is thus less than $N_A^+\cdots N_B^+$ by about 1 Å. The average values for the four molecules are $N_C^+\cdots N_B^+ = 6{\cdot}22$ (7), $N_A^+\cdots N_B^+ = 7{\cdot}26$ (5) Å, while $N_A^+\cdots N_C^+$ has an average value of 10·71 (9) Å. Within each molecule, side chains *A* and *C* are asymmetrically disposed with respect to the central chain *B*. As can be seen from Table 3 and Fig. 3, there is an approximately enantiomorphic relationship between *A*-chain conformations and *C*-chain conformations and also between molecular pairs (1)–(3) and (2)–(4), molecules (1) and (2), and (3) and (4) having similar conformations. The organic part of the structure thus forms a pseudo $P\bar{1}$ arrangement, but this is substantially reduced by the asymmetric distribution of solvent molecules which forces it into a true *P*1 structure. Average values are as follows: for chains *A*, *C* $|\tau_1| = 92{\cdot}8 \pm 10{\cdot}9$, $|\tau_3| = 166{\cdot}9 \pm 11{\cdot}4°$; for chains *B* $|\tau_1| = 71{\cdot}5 \pm 4{\cdot}7$, $|\tau_3| = 94{\cdot}5 \pm 4{\cdot}0°$; for all chains $|\tau_2| = 179{\cdot}5 \pm 5{\cdot}7°$. In each case the spread of values indicates the deviation from true symmetry or equivalence. Chain lengths including the five atoms in the sequence N^+–C–C–O–C are sensibly constant with average values over the four molecules of 4·54 (8) Å for *A*/*C*-type side chains and 4·41 (1) Å for type *B*. This chain length is controlled by torsion angle τ_2 which as stated above is remarkably close to 180° (*trans*) for all twelve side chains. Side chains *A* and *C* are approximately coplanar with the benzene ring except for the N^+ atoms which are rotated by τ_1 to be almost as far as possible away from the plane. Side chains *B* are coiled such that the nitrogen N_B^+ is closer to the benzene-ring plane.

Solvent distribution and crystal packing

The distribution of solvent molecules in the gallamine crystal structure is quite complex (Fig. 4) and the analysis based on the X-ray data requires a more detailed study than has been possible to date. Such results will be published later together with any implications for the biological activity of gallamine which may transpire. Fig. 5 shows a view of the packing of the gallamine molecules which clearly indicates the presence of dominant solvent channels in

Table 3. *Unrestrained side-chain torsion angles* (°) (*see text for notation used*); *e.s.d's range from* 1·2–1·6°

	Side chains in molecule (1)			Side chains in molecule (2)			Side chains in molecule (3)			Side chains in molecule (4)		
Chain	*A*	*C*	*B*	*A*	*C*	*B*	*A*	*C*	*B*	*A*	*C*	*B*
τ_1	94	−115	−75	86	−99	−71	−84	82	64	−82	100	76
τ_2	167	179	−179	−175	175	−179	173	−177	175	−172	177	176
τ_3	−176	−175	−95	−173	166	−88	160	−142	96	−180	−163	99

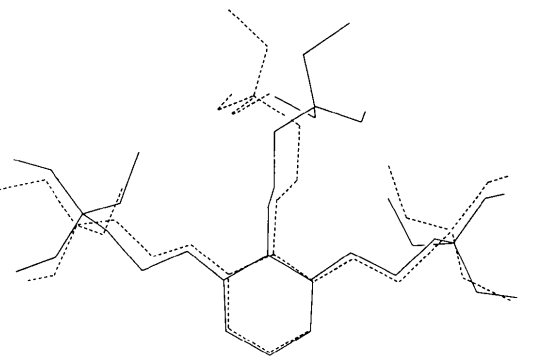

Fig. 3. Superposition of the phenyl rings in molecules (2) (full lines) and (3) (dashed) indicating the approximate mirror relationship. A similar relationship exists for molecules (1) and (4).

the structure (shown dotted). Over 100 contacts in the range 3·0–4·0 Å occur between the various solvent components and drug molecules. Of these, 82 involve gallamine–bromine contacts. Solvent–solvent contacts, of which nearly 50 have been recognized to date, include 20 between water and bromine, see Table 4. These distributions are quite sensible and lend confidence to the validity of the analysis. Fig. 4 clearly indicates the hydrophobic core formed in the crystal structure.

Acetylcholine receptor site: computer-graphics simulation

Non-depolarizing neuromuscular blockers compete with the neurotransmitter acetylcholine (Fig. 1*b*) for binding to its receptor sites. The acetylcholine molecule comprises a quaternary ammonium cationic head for Coulombic attachment to a negatively charged pocket (*P*) on the receptor, and a strongly polarized ester moiety which is capable of accepting hydrogen bonds from the so-called esterophilic centre (*S*) of the receptor

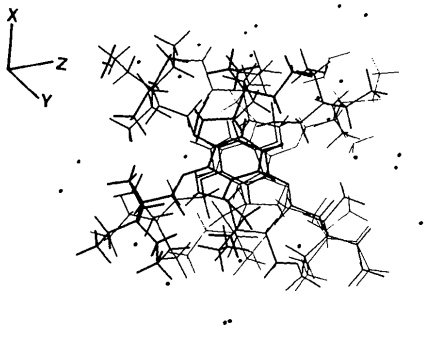

Fig. 4. A view of the molecules and solvent distribution seen roughly perpendicular to the four-molecule ring stack. Note the hole through the hydrophobic core formed by the phenyl rings in this stack.

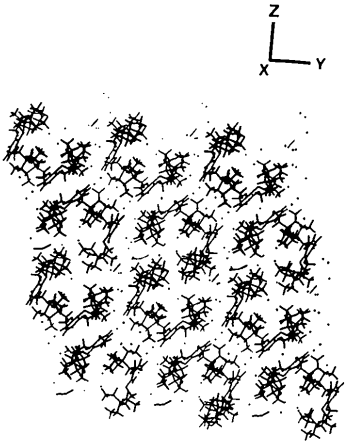

Fig. 5. Packing of the molecules in the crystal structure showing predominant solvent channels running parallel to **c**.

Table 4. *Intermolecular contact distances in the gallamine structure*

Contact type	Number of contacts	Average contact distance (Å)	Distribution minimum (Å)	Distribution maximum (Å)
Gallamine–bromide	82	3·75	3·16	3·95
Gallamine–iodide	17	3·83	3·65	4·01
Gallamine–water	9	3·33	3·27	3·39
Gallamine–ethanol	7	3·42	3·25	3·59
Gallamine–methanol	2	3·40	3·32	3·48
Water–bromide	20	3·31	2·50	3·58
Water–iodide	4	3·54	3·20	3·88
Water–ethanol	4	2·87	2·43	3·31
Water–methanol	2	3·00	2·81	3·19
Water–water	5	3·50	3·38	3·62
Bromide–bromide	6	3·38	2·90	3·86
Bromide–ethanol	2	3·51	3·22	3·80
Iodide–methanol	2	3·24	2·62	3·86
Methanol–ethanol	2	3·19	3·08	3·30

(Michelson & Zeimal, 1973). The potent muscle-relaxant neuromuscular blockers invariably contain at least two cationic heads, both usually quaternary but sometimes one may be tertiary, as in (+)-tubocurarine itself (Fig. 1*c*), perhaps the best known drug having this type of activity. High potency of neuromuscular blocking is associated with an interonium distance of 10·8 (3) Å spanning hydrophilic or other groups in the molecule which can compete for the secondary binding site (*S*) at the esterophilic centre of the receptor. This is basically the model proposed by Pauling & Petcher (1973) which still seems to fit the molecular requirements for potent inhibition of the acetylcholine receptor. However, it is still not known exactly how neuromuscular blockers work – whether both cationic heads bind simultaneously in separate pockets for instance, or whether their dual presence merely affords the drug with better binding affinity.

The comparative molecular geometry of selected potent neuromuscular blockers has been investigated using an Evans and Sutherland Picture System 2 for molecular graphics (Palmer, Tickle & Tickle, 1983). In all cases tried it was found possible to align simultaneously a pair of cationic centres and a pair of secondary (esterophilic binding) groups with a maximum error of about 0·3 Å using the program *FRODO* (Jones, 1978). The program *BILBO* (Pearl & Honegger, 1983) was used to simulate a single acetylcholine receptor binding site, incorporating this principle of superposition. The consistent model produced in this way is one of a receptor surface with a deep primary inner binding site (*P*) and a secondary lobe (*S*) closer to the entrance of the active-site pocket, corresponding to the esterophilic binding site. In the *BILBO* program one of the drug molecules (the object molecule) is used to generate a van der Waals surface, forming the topography of the proposed active site. A second (target) molecule may then be docked into the pocket formed by the object molecule, the corresponding active groups of the two molecules being aligned optimally for comparison. Fig. 6 shows how the

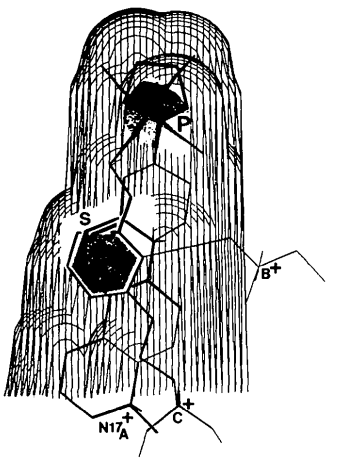

Fig. 6. *BILBO* graphics showing the docking of the gallamine *A*-chain quarternary nitrogen (N) into a proposed topographical receptor site formed by the van der Waals surface of the steroidal neuromuscular blocker chandonium iodide (HS310). The primary (inner) binding site (*P*) of the active centre is formed by the quaternary *A*-ring end of HS310 and the secondary (outer) esterophilic binding site (*S*) by the *B*-ring double bond of HS310 associated with enhanced neuromuscular blocking activity (Marshall, Paul & Singh, 1973).

molecular geometry of gallamine, determined in the present analysis, keys into the topography of the previously proposed active-site model (Palmer *et al.*, 1983). In this example the object molecule forming the active-site pocket is chandonium (Fig. 1*d*). The cationic head N_A^+ of gallamine is buried deeply within the pocket (*P*) and the phenyl group (φ) aligns with the C=C bond of chandonium, associated with enhanced potency, in the secondary outer binding site (*S*). This diagram also shows the close correspondence between the other cationic sites, $N(17)_A^+$ in chandonium and N_C^+ of gallamine, when the two molecules are superposed in this way. As mentioned previously the $N_A^+\cdots N_C^+$ separation in gallamine conforms to the requirements of Pauling & Petcher's (1973) model [as does the $N(31)^+\cdots N(17)_A^+$ separation of chandonium]. The proposed acetylcholine receptor model does not preclude the existence of two or more similar binding sites in the actual receptor assembly and therefore leaves open the question why a biscationic design for neuromuscular blocking agents has traditionally been so successful. The third cationic centre of gallamine, N_B^+, is suitably oriented so as not to interfere with the proposed receptor surface, and presumably merely acts to stabilize the molecular conformation and to potentiate the initial attraction of the molecule into the active-site pocket.

References

BARLOW, R. B. (1968). *Introduction to Chemical Pharmacology*, 2nd ed., p. 125. London: Methuen.

CHURCHILL-DAVIDSON, H. C. (1978). *A Practice of Anaesthesia*, 4th ed., p. 894. London: Lloyd-Luke.

CULL-CANDY, S. G. & MILEDI, R. (1983). *Proc. R. Soc. London*, **218**, 111–118.

JONES, T. A. (1978). *J. Appl. Cryst.* **11**, 268–272.

MAIN, P., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1978). *MULTAN*78. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.

MARSHALL, I. G., PAUL, D. & SINGH, H. (1973). *J. Pharm. Pharmacol.* **25**, 1441–1446.

MICHELSON, M. J. & ZEIMAL, E. V. (1973). *Acetylcholine, An Approach to the Molecular Mechanism of Action*. Oxford: Pergamon Press.

NORTH, A. C. T., PHILLIPS, D. C. & MATTHEWS, F. S. (1968). *Acta Cryst.* A**24**, 351–359.

PALMER, R. A., TICKLE, J. H. & TICKLE, I. J. (1983). *J. Mol. Graphics* **1**, 94–106.

PAULING, P. & PETCHER, T. J. (1973). *Chem. Biol. Interactions*, **6**, 351–365.

PEARL, L. H. & HONEGGER, A. (1983). *J. Mol. Graphics* **1**, 9–12.

QUICK, A. (1982). Document ACRYST. Univ. of London Computer Centre Bulletin.

SHELDRICK, G. M. (1976). *SHELX*76. Program for crystal structure determination. Univ. of Cambridge, England.

TICKLE, I. J. (1975). *Acta Cryst.* B**31**, 329–331.

Acta Cryst. (1985). C**41**, 1496–1499

The Structure of Methylenetriphenylphosphorane(*C–B*)triborane(7) at 185 K

BY STEVEN J. ANDREWS AND ALAN J. WELCH*

Department of Chemistry, University of Edinburgh, Edinburgh EH9 3JJ, Scotland

(*Received* 31 *January* 1985; *accepted* 27 *June* 1985)

Abstract. $C_{19}H_{24}B_3P$, $M_r = 315{\cdot}8$, monoclinic, $P2_1/n$, $a = 13{\cdot}854$ (3), $b = 8{\cdot}860$ (2), $c = 15{\cdot}667$ (2) Å, $\beta = 104{\cdot}66$ (1)°, $U = 1860{\cdot}5$ Å^3, $Z = 4$, $D_x = 1{\cdot}127$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}138$ mm^{-1}, $F(000) = 672$, $T = 185$ K, $R = 0{\cdot}0695$ for 2159 observed reflections. The title compound is zwitterionic, with the P atom positively charged and the negative charge delocalized over the borane ring. The

* To whom all correspondence should be addressed.

0108-2701/85/101496-04$01.50