Crystal structure of benzocaine–a local anaesthetic [+]

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Abstract. The structure of the local anaesthetic benzocaine was solved by direct methods and refined to an R of 0·12 for 531 observed reflections. The packing of the molecule is stabilised by N–H . . . O hydrogen-bonds (2·97 Å). The alkyl chain attached to the benzene ring is in *trans-trans* conformation. The benzoic moiety shows a quinonoid character as found in some other local anaesthetics.

Keywords. Local anaesthetic; benzocaine; *trans-trans* conformation.

1. Introduction

Benzocaine is a local anaesthetic and is like procaine, a para-substituted amino benzoate ester. Its low solubility renders it unsuitable for injections but its slow absorption from mucous-lined surfaces makes it safer than other local anaesthetics for ulcers and wounds. Though the anaesthesia produced is not so complete as with other local anaesthetics, it has been used topically with considerable success. Besides, the structure and conformational analysis of benzocaine would be of interest as that of a local anaesthetic of the ester type without a tertiary amino nitrogen.

2. Experimental

Colourless needles elongated along the a axis were readily obtained from a saturated solution of the compound in ethanol. The cell parameters are $a = 5·302$ (2), $b = 8·217$ (1), $c = 20·87(2)$ Å and space group $P2_12_12_1$ with $Z = 4$, $C_9H_{11}NO_2$, $M_r = 165·2$, $F(000) = 342$, $D_m = 1·21$ (1), $D_c = 1·218$ Mgm^{-3}, $\lambda(MoK_\alpha) = 0·7093$ Å, $\mu = 0·9214$ cm^{-1}. The accurate values of the cell parameters were obtained by least squares refinement of measured angle values for 24 reflections in the range $45° \leqslant 2\theta \leqslant 55°$. A crystal of size $0·2 \times 0·3 \times 0·4$ mm was used for data collection on an automatic four circle CAD4 diffractometer with monochromatised MoK$_\alpha$ radiation ($\lambda = 0·7093$ Å) and $\theta/2\theta$ scan mode. The intensities recorded were very weak due to the poor quality of the crystal.

Repeated attempts at crystallisation under various conditions failed and the structure determination was carried out with the available data though the accuracy of the structure is limited. Out of a total of 803 reflections recorded, 753 were unique and 531 reflections with I net $\geqslant \sigma$ (I net) were considered observed. These reflections were corrected for Lorentz and polarisation factors but not for absorption.

The structure was solved using the program MULTAN 80 (Main *et al* 1980). An intitial model obtained from an E Map based on the best phase set failed to refine beyond $R = 0.20$. Hence, this model was assumed to be correctly oriented and used in the phase refinement procedure (Karle 1968) of program MULTAN 80. The phase set having the highest figure of merit and lowest residual revealed all the non-hydrogen atoms. A few cycles of block diagonal refinement (Shiono 1968) with isotropic thermal parameters reduced the R-factor to 0.18. Hydrogens located from the difference fourier map were included in the last cycles of refinement, in the full matrix least squares procedure using the program LALS (Gantzel *et al* 1961). The final $R = 0.12$ Hughes weighting scheme with $F_{0_{\min}} = 7.3$ was used in the refinement (Hughes 1941).

$$W = (1/\sigma^2), \quad \sigma = |F_0| \text{ if } |F_0| \geqslant |F_0|_{\min}$$
$$= |F_0|_{\min} \text{ if } |F_0| < |F_0|_{\min}.$$

During the final cycle of refinement, $(\triangle/\sigma)_{\max} = 1.0$ and $(\triangle/\sigma)_{\text{mean}} = 0.3$. The atomic scattering factors were taken from the International Tables for X-ray crystallography (1962). The final positional and thermal parameters of the non-hydrogen atoms are listed in table 1.

3. Discussion

Figure 1 shows a stereo-view of the molecule. Benzocaine is structurally similar to procaine and has many features in common. But there are several significant

Table 1a. Fractional atomic parameters for the non-hydrogen atoms ($\times 10^4$) and the equivalent temperature factors with c.s.d. in parentheses.
$$B_{\text{eq}} = \tfrac{4}{3}(b_{11}a^2 + b_{22}b^2 + b_{33}c^2)$$

Atom	x	y	z	$B_{\text{eq}}(\text{Å}^2)$
C(1)	2131(30)	848(21)	669(6)	5.74
C(2)	1229(25)	$-648(21)$	488(5)	4.40
C(3)	1934(30)	$-2130(18)$	700(6)	4.10
C(4)	3985(33)	$-2249(16)$	1092(6)	4.05
C(5)	5119(30)	$-799(19)$	1267(7)	4.40
C(6)	4381(33)	636(20)	1057(7)	4.60
C(7)	4874(20)	$-3788(16)$	1292(5)	2.69
C(8)	7882(43)	$-5187(24)$	1971(8)	6.43
C(9)	9831(35)	$-4838(21)$	2455(8)	5.80
N	1357(28)	2297(14)	431(6)	5.28
O(1)	6717(21)	$-3706(12)$	1731(4)	4.78
O(2)	4008(26)	$-5047(11)$	1125(5)	5.50

**Table 1b.** Anisotropic thermal parameters ($\times 10^3$) for the non-hydrogen atoms with e.s.d. in parentheses.

Atom	b_{11}	b_{22}	*b_{33}	b_{12}	b_{13}	b_{23}
C(1)	50(7)	30(3)	2(0)	5(9)	7(3)	1(2)
C(2)	27(5)	41(3)	2(0)	18(8)	$-3(2)$	6(2)
C(3)	49(7)	21(3)	3(0)	26(8)	$-3(3)$	2(2)
C(4)	52(8)	19(2)	3(0)	$-6(8)$	5(3)	2(2)
C(5)	50(7)	25(3)	3(0)	6(9)	8(3)	4(2)
C(6)	57(8)	25(3)	3(0)	$-41(8)$	$-2(3)$	$-2(2)$
C(7)	19(4)	19(2)	2(0)	$-9(6)$	$-3(2)$	$-2(1)$
C(8)	85(10)	34(4)	4(0)	$-2(12)$	$-10(4)$	8(2)
C(9)	47(7)	34(4)	5(0)	1(9)	$-6(3)$	11(2)
N	48(6)	26(2)	5(0)	19(7)	$-5(3)$	3(2)
O(1)	48(4)	25(2)	4(0)	$-3(5)$	$-10(2)$	1(2)
O(2)	70(6)	20(2)	5(0)	0(6)	$-18(3)$	$-2(1)$

*e.s.d's for b_{33} are less than 0·0005

$T = \exp -(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)$

Table 1c. Fractional coordinates ($\times 10^3$) of the hydrogen atoms and isotropic thermal factors with e.s.d. in parentheses.

Atom	x	y	z	B_{iso}(Å^2)
HC(2)	48(31)	$-59(17)$	14(6)	1·68
HC(3)	79(31)	$-30(17)$	59(7)	3·27
HC(5)	607(32)	$-106(17)$	156(7)	4·51
HC(6)	482(34)	158(16)	115(6)	3·10
HC(8)1	661(37)	$-605(20)$	221(8)	0·08
HC(8)2	817(38)	$-588(20)$	156(7)	13·05
HC(9)1	857(32)	$-428(18)$	283(7)	11·11
HC(9)2	1087(32)	$-561(17)$	266(7)	5·92
HC(9)3	1120(32)	$-398(17)$	228(7)	8·22
HN(1)1	$-18(34)$	224(18)	24(7)	8·87
HN(1)2	189(34)	298(17)	62(7)	6·49
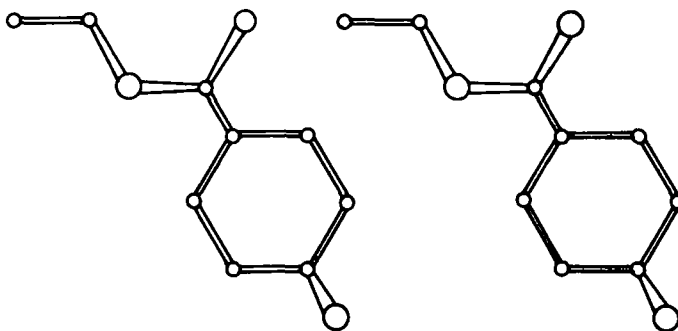
Figure 1. Stereo view of the molecule.

differences observed between them. The benzoic moiety is planar in procaine (Sinha *et al* 1984; Kashino *et al* 1982) and its nitrophenyl phosphate complex (Sax *et al* 1970). But in the present structure the phenyl ring is non-planar ($\chi^2 = 45\cdot3$). The atom O(1) of the ether group deviates from the least squares plane through the phenyl ring by ($-0\cdot12\text{Å}$). Similar deviations have been observed in the *bis-p*-nitrophenyl complex of benzocaine (Pletcher *et al* 1972). Such a non-planarity has been ascribed to small conformational changes in the alkyl chain (Sax *et al* 1971). The torsion angle about the ester bond is $-178(1)°$ which is close to the value found in nitrophenyl phosphate complex of procaine [$178\cdot1(4)°$], but differs significantly from that in the benzocaine complex [$-168\cdot6(2)°$] and procaine [$147\cdot1(4)°$]. These conformational variations may be the result of packing and other steric requirements (Pletcher *et al* 1972) of these molecules. The rotation of the carbonyl group about the C(4)−C(7) bond is $3(2)°$ as compared to $9\cdot4°(7)$ in the benzocaine complex and $2\cdot5°(6)$ in the procaine complex and $-2\cdot0(6)°$ in procaine.

The para-substituted amino group is unprotonated and the benzoic moiety exhibits a quinonoid character as in procaine. The bond lengths and bond angles in the benzene ring indicate significant contribution of this character as is evident from the fact that C(1)–C(2) and C(1)–C(6) bonds are longer than the C(2)–C(3) and C(6)–C(5) bonds, and also the angles C(2)–C(1)–C(6) and C(3)–C(4)–C(5) are smaller than the other angles in the ring. The angle C(2)–C(1)–C(6) [$109(1)°$] is significantly smaller than the corresponding angles observed in procaine [$118\cdot1(3)°$] and 2-amino-3-methyl benzoic acid [$118\cdot8(2)°$]. Such deformations may be due to the electron-releasing nature of the para-substituent (Domenicano *et al* 1975). The quinonoidal character of the benzoic moiety has not been observed in the *p*-nitrophenyl phosphate complex of benzocaine and it has been explained as being the consequence of the protonation of the para-substituted amino nitrogen in the complex. In benzocaine and procaine, the quinonoidal character can be ascribed to the conjugation of the amino nitrogen with the benzoic moiety down to the carbonyl group.

The C(1)–N(1) bond length [$1\cdot35(2)\text{Å}$] is significantly different from those observed in benzocaine complex [$1\cdot464(9)\text{Å}$], procaine [$1\cdot458(8)\text{A}$] and amino phenyl hydrochloride (Cesur and Richards 1965) [$1\cdot474(9)\text{Å}$], but it is close to that observed in 2-amino 3-methyl benzoic acid [$1\cdot37(1)\text{Å}$] and this shortness has been ascribed to the hybridization effects (Brown and Marsh 1963). All other bond lengths and angles are comparable within experimental error to those in similar structures (figure 2).

Figure 3 shows the packing of the molecule down the *a* axis. The amino nitrogen is hydrogen-bonded to the carbonyl oxygen as in the structure of the benzocaine complex. The N–H . . . O hydrogen bond distance is $2\cdot97(2)\text{Å}$ with the N–H . . . O angle $172(1)°$ and the H . . . A distance 2.25 Å.
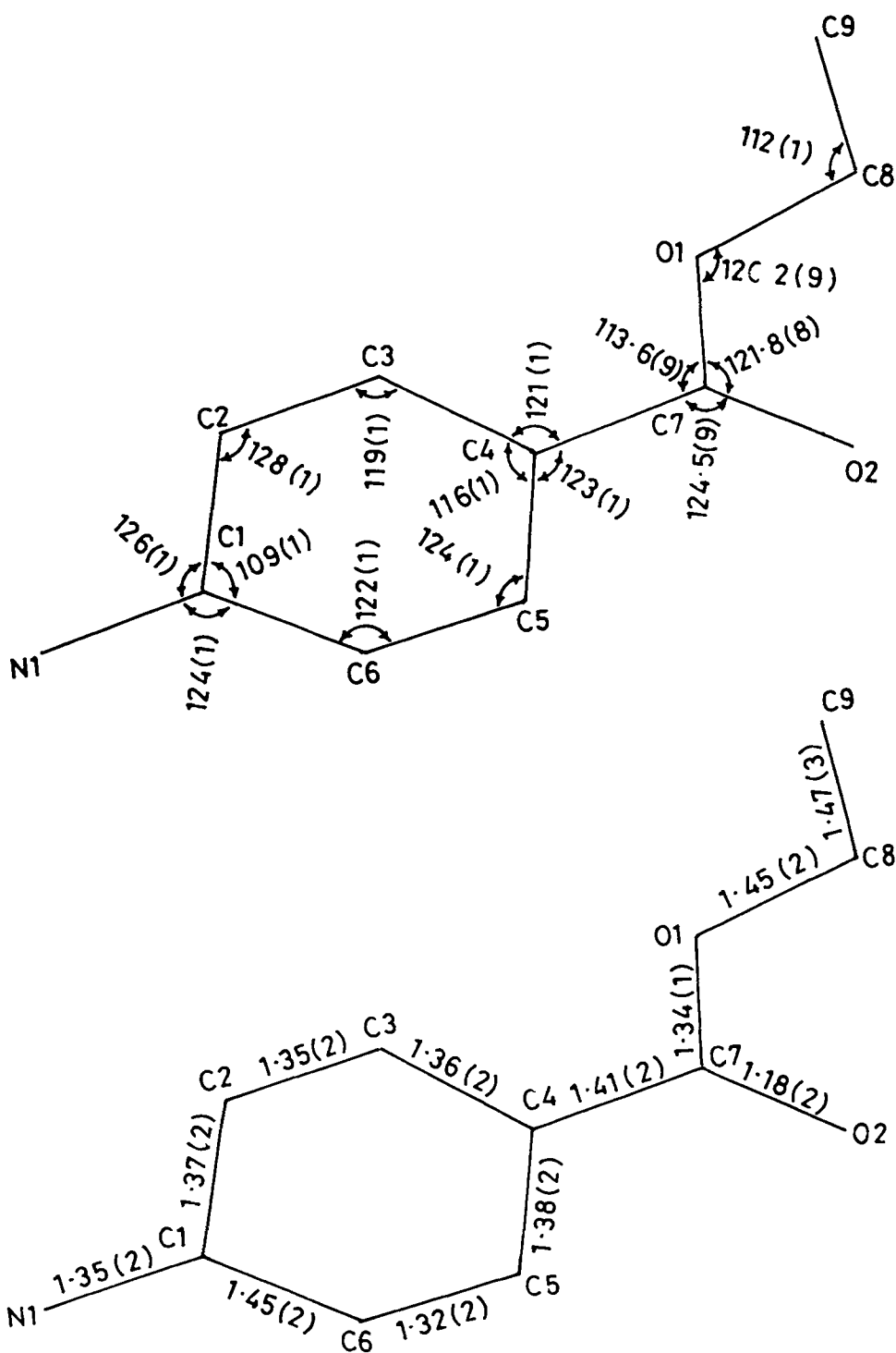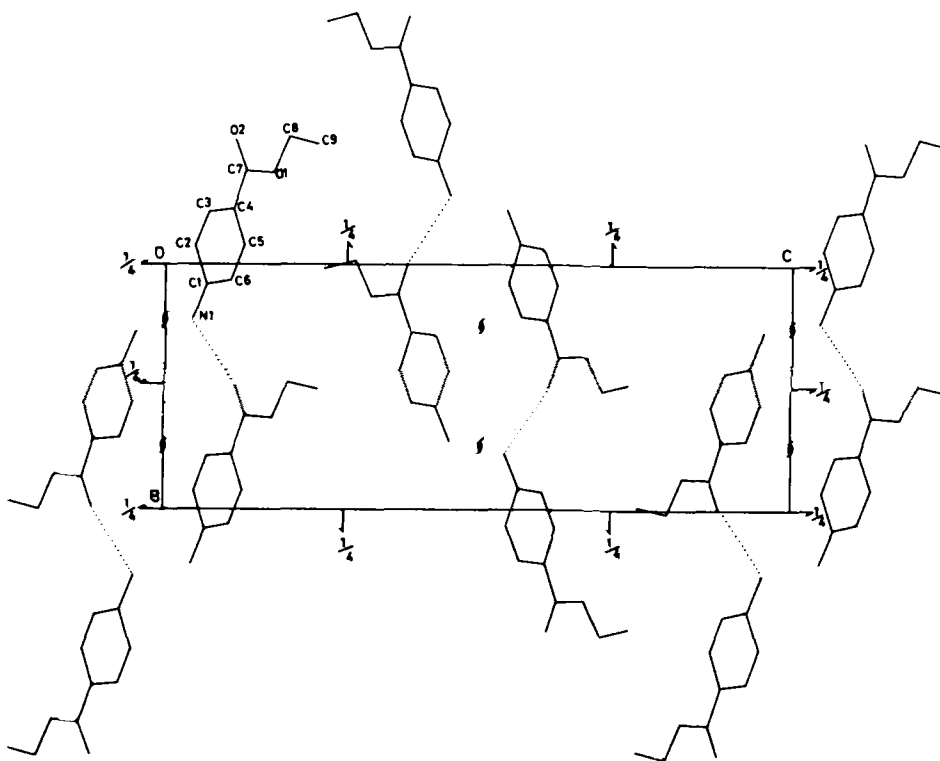
Figure 2. (a) Bond lengths (Å) with e.s.d. in parentheses. b. Bond angles (°) with e.s.d. in parentheses.

Figure 3. Packing of the molecule projected down the *a* axis. Hydrogen-bonds are indicated by dashed lines.

References

Beall R, Herdklotz J and Sass R L 1970 *Biochem. Biophys. Res. Commun.* **39** 324
Brown G M and Marsh R E 1963 *Acta Cryst.* **B16** 191
Cesur A F and Richards J P G 1965 *Z. Kristallogr.* **122** 283
Domenicano A, Vaciago A and Coulson C A 1975 *Acta Cryst.* **B31** 221
Gantzel P K, Sparks R A and Trueblood K N 1961 Program LALS, University of California, USA
Hughes E W 1941 *J. Am. Chem. Soc.* **65** 1737
International Tables for X-ray Crystallography 1962 (Birmingham: Kynoch Press) Vol. 3
Karle J 1968 *Acta Cryst.* **B24** 182
Kashino S, Ishida M and Haisa M 1982 *Acta Cryst.* **B38** 1868
Main P, Fiske S J, Hull S E, Lessinger L, Germain G, Declercq J P and Woolfson M M 1980 A system of computer programs for the automatic solution of crystal structures from X-ray diffraction data, University of York, UK
Pletcher J, Sax M and Yoo C S 1972 *Acta Cryst.* **B28** 378
Sax M, Pletcher J and Gustaffson B 1970 *Acta Cryst.* **B26** 114
Sax M, Pletcher J, Yoo C and Stewart J M 1971 *Acta Cryst.* **B27** 1635
Shiono R 1968 Block diagonal least squares program for the IBM 1130, Department of Crystallography, University of Pittsburgh, USA
Sinha B K, Subramanian E, Vasantha Pattabhi and Trotter J 1984 *Indian J. Pure Appl. Phys.* **22** 249