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The Structure of Procaine

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Abstract. $C_{13}H_{20}N_2O_2$, m.p. 332.5–334.0 K, monoclinic, $P2_1/a$, $a = 11.56(2)$, $b = 14.38(1)$, $c = 8.202(7)$ Å, $\beta = 98.0(1)^\circ$, $V = 1350(3)$ Å³, $D_m = 1.17$, $D_x = 1.162$ Mg m⁻³, $Z = 4$, final $R = 0.098$ for 1690 non-zero reflexions. The carbonyl oxygen atom accepts two hydrogen bonds from the amino groups of the molecules related by a 2_1 axis and glide plane. A double-layered molecular sheet is formed by the hydrogen bonds on (001). The benzene ring shows the quinonoid structure. The conformation of the C–O–C–C–N side chain is *trans-gauche* [$\tau(C-O-C-C) = 147.1(4)^\circ$, $\tau(O-C-C-N) = -82.6(5)^\circ$], as found in salts of procaine and related compounds.

Introduction. Procaine is known as a local anesthetic. Structural studies on salts of procaine have been carried out (Beall, Herdtklotz & Sass, 1970; Sax, Pletcher & Gustaffson, 1970; Dexter, 1972; Freeman & Bugg, 1975). Work on the un-ionized molecule is desirable to establish the structure–activity relationship. The conformation of the side chain is interesting in view of the concept of pharmacophores (Kier, 1971).

Crystals were obtained from a ligroin solution as monoclinic prisms bounded by {110} and {001}. Intensity data were collected on Weissenberg photographs with specimens $0.65 \times 0.70 \times 0.63$ mm for the layers $0kl$ to $8kl$, and $0.22 \times 0.24 \times 0.25$ mm for the layers $hk0$ to $hk6$. Visually estimated intensities were corrected for Lorentz and polarization factors and for spot shape, but no absorption correction was made

[$\mu(Cu K\alpha) = 0.64$ mm⁻¹]. Intensities of 1690 non-zero reflexions (55% of the reflexions within the Cu $K\alpha$ sphere, $\lambda = 1.5418$ Å) were placed on an approximately absolute scale by a Wilson plot ($B = 5.9$ Å²).

The structure was solved by a symbolic addition procedure. The H atoms were located from a difference Fourier map. The refinements were made by block-diagonal least-squares calculations. The weighting scheme was: $w = 1.0$ for $0 < |F_o| \leq 8.0$, $w = (8.0/|F_o|)^2$ for $|F_o| > 8.0$. Atomic scattering factors

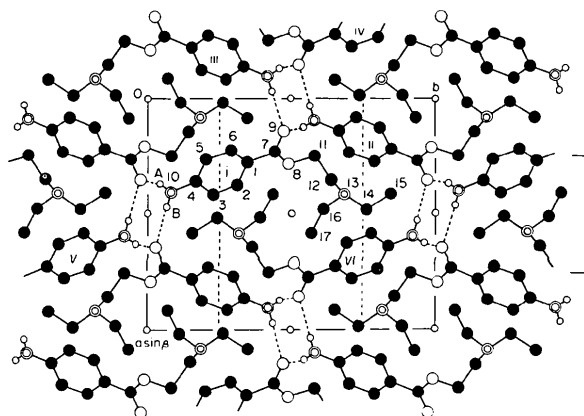


Fig. 1. Projection of the crystal structure along c , and numbering of the atoms (\circ : O, \odot : N, \bullet : C and \circ : H). The H atoms attached to the C atoms are omitted. Broken lines indicate hydrogen bonds. Symmetry code: (i) x, y, z ; (ii) $\frac{1}{2} - x, \frac{1}{2} + y, 1 - z$; (iii) $-\frac{1}{2} + x, \frac{1}{2} - y, z$; (iv) $-x, 1 - y, 1 - z$; (v) $1 - x, -y, 1 - z$; (vi) $1 - x, 1 - y, 1 - z$.

Table 1. Final atomic parameters (positional $\times 10^4$, for H $\times 10^3$) with e.s.d.'s in parentheses
$$B_{eq} = \frac{4}{3} \sum_i \beta_{ii} / a_i^{*2}$$

	x	y	z	B_{eq} or B_{iso} (\AA^2)
C(1)	2776 (3)	3465 (2)	2796 (4)	4.3 (2)
C(2)	3709 (3)	3111 (2)	2101 (4)	4.5 (2)
C(3)	4130 (3)	2232 (2)	2438 (4)	4.8 (2)
C(4)	3615 (3)	1660 (2)	3527 (4)	4.7 (2)
C(5)	2662 (3)	2011 (3)	4213 (4)	5.2 (2)
C(6)	2257 (3)	2887 (2)	3870 (4)	4.8 (2)
C(7)	2305 (3)	4398 (2)	2450 (4)	4.7 (2)
O(8)	2901 (2)	4875 (2)	1451 (3)	5.5 (1)
O(9)	1467 (3)	4726 (2)	3002 (4)	6.6 (2)
N(10)	4022 (3)	777 (2)	3854 (5)	6.7 (2)
C(11)	2508 (4)	5812 (3)	968 (5)	6.1 (2)
C(12)	3551 (4)	6401 (3)	753 (5)	6.0 (2)
N(13)	4152 (3)	6785 (2)	2315 (4)	6.3 (2)
C(14)	4821 (5)	7609 (3)	2092 (6)	7.4 (3)
C(15)	4127 (5)	8464 (3)	1646 (7)	8.2 (3)
C(16)	4820 (4)	6105 (4)	3401 (6)	7.3 (3)
C(17)	5825 (5)	5642 (4)	2731 (7)	9.5 (4)
H(2)	404 (3)	349 (3)	142 (5)	4.3 (9)
H(3)	487 (3)	200 (3)	193 (4)	3.8 (8)
H(5)	228 (4)	162 (3)	487 (5)	4.8 (10)
H(6)	161 (4)	315 (3)	435 (5)	4.8 (10)
H(10A)	372 (4)	42 (3)	475 (5)	4.6 (10)
H(10B)	468 (4)	64 (3)	350 (5)	4.9 (10)
H(11A)	192 (4)	575 (3)	-6 (5)	5.5 (11)
H(11B)	223 (5)	611 (4)	180 (7)	8.9 (15)
H(12A)	415 (3)	603 (3)	9 (5)	4.4 (9)
H(12B)	335 (4)	693 (3)	3 (6)	6.8 (12)
H(14A)	550 (5)	739 (4)	111 (7)	10.0 (17)
H(14B)	560 (4)	772 (4)	326 (6)	8.2 (14)
H(15A)	360 (5)	841 (4)	45 (7)	11.0 (18)
H(15B)	443 (5)	913 (4)	153 (7)	8.7 (15)
H(15C)	355 (6)	850 (5)	235 (7)	11.9 (20)
H(16A)	500 (4)	651 (3)	465 (6)	6.5 (12)
H(16B)	421 (5)	554 (4)	389 (6)	8.1 (14)
H(17A)	547 (5)	536 (4)	142 (7)	8.2 (14)
H(17B)	641 (6)	527 (5)	305 (8)	11.4 (19)
H(17C)	624 (5)	619 (4)	236 (6)	8.6 (15)

Table 2. Bond lengths (\AA) and angles ($^\circ$) with e.s.d.'s in parentheses

C(1)–C(2)	1.385 (5)	O(8)–C(11)	1.459 (6)
C(2)–C(3)	1.369 (6)	C(11)–C(12)	1.504 (7)
C(3)–C(4)	1.406 (6)	C(12)–N(13)	1.477 (6)
C(4)–C(5)	1.399 (6)	N(13)–C(14)	1.440 (6)
C(5)–C(6)	1.360 (6)	N(13)–C(16)	1.468 (6)
C(6)–C(1)	1.405 (5)	C(14)–C(15)	1.486 (8)
C(1)–C(7)	1.461 (5)	C(16)–C(17)	1.508 (8)
C(4)–N(10)	1.368 (6)	N(10)–H(10A)	1.00 (4)
C(7)–O(8)	1.332 (5)	N(10)–H(10B)	0.87 (4)
C(7)–O(9)	1.220 (5)		
C(2)–C(1)–C(6)	117.7 (3)	O(8)–C(7)–O(9)	122.3 (4)
C(2)–C(1)–C(7)	123.2 (3)	C(7)–O(8)–C(11)	118.3 (3)
C(6)–C(1)–C(7)	119.0 (3)	O(8)–C(11)–C(12)	109.1 (4)
C(1)–C(2)–C(3)	122.1 (4)	C(11)–C(12)–N(13)	113.4 (4)
C(2)–C(3)–C(4)	119.9 (4)	C(12)–N(13)–C(14)	113.2 (4)
C(3)–C(4)–C(5)	118.1 (4)	C(12)–N(13)–C(16)	114.9 (4)
C(3)–C(4)–N(10)	120.2 (4)	C(14)–N(13)–C(16)	112.3 (4)
C(5)–C(4)–N(10)	121.7 (4)	N(13)–C(14)–C(15)	115.5 (4)
C(4)–C(5)–C(6)	121.3 (4)	N(13)–C(16)–C(17)	116.1 (4)
C(1)–C(6)–C(5)	120.9 (4)	C(4)–N(10)–H(10A)	118 (2)
C(1)–C(7)–O(8)	112.4 (3)	C(4)–N(10)–H(10B)	116 (3)
C(1)–C(7)–O(9)	125.2 (4)	H(10A)–N(10)–H(10B)	123 (4)

were taken from *International Tables for X-ray Crystallography* (1974). Computations were carried out at the Okayama University Computer Center. The programs used were *SIGM*, *TANG*, *HBL5-5* and *DAPH* (Ashida, 1973), and *MOLCON* (Fujii, 1979).

The final atomic parameters are listed in Table 1.* A projection of the crystal structure viewed along **c** is shown in Fig. 1. Bond lengths and angles are given in Table 2.

Discussion. The carbonyl group of procaine participates in hydrogen bonding, unlike those in procaine hydrochloride (Beall *et al.*, 1970) and procaine-bis-(*p*-nitrophenyl) phosphate complex (Sax *et al.*, 1970). Molecules on (001) are linked together by C=O...HN hydrogen bonds [O(9ⁱ)...N(10ⁱⁱ) 3.108 (5), O(9ⁱ)...H(10Aⁱⁱ) 2.13 (4) \AA , O(9ⁱ)...H(10Aⁱⁱ)–N(10ⁱⁱ) 165 (3) $^\circ$; O(9ⁱ)...N(10ⁱⁱⁱ) 3.090 (5), O(9ⁱ)...H(10Bⁱⁱⁱ) 2.22 (4) \AA , O(9ⁱ)...H(10Bⁱⁱⁱ)–N(10ⁱⁱⁱ) 171 (4) $^\circ$] around 1 at (0, $\frac{1}{2}$, $\frac{1}{2}$) and ($\frac{1}{2}$, 0, $\frac{1}{2}$) to form a double-layered sheet. The molecules extend along **b**, and the benzene rings related by a glide plane overlap with a dihedral angle of 41.6 (1) $^\circ$. The sheets are stacked along **c** by van der Waals interactions.

The formation of the hydrogen-bonded double-layered sheet alters the crystal structure from that of procaine hydrochloride, in which the arrangement of the aromatic portions is similar to that observed in pyrrolidinium *para*-substituted benzoates (Kashino, Kataoka & Haisa, 1978) and acetanilides (Haisa, Kashino, Ueno, Shinozaki & Matsuzaki, 1980) in *Pbca*, the dihedral angle between the nearest benzene rings related by a glide plane being 84.2 $^\circ$.

The *p*-aminophenyl group is planar within 0.010 (6) \AA , and the ester group composed of C(1), C(7), O(8), O(9) and C(11) is planar within 0.014 (4) \AA . The dihedral angle between them is 1.6 (2) $^\circ$. C(12) deviates from the plane of the ester group by 0.777 (7) \AA . The benzene ring takes a quinonoid structure as found in *p*-aminobenzoic acid (Lai & Marsh, 1967) and *p*-aminoacetophenone (Haisa, Kashino, Yuasa & Akigawa, 1976). The inner angles at C(1) and C(4) are significantly smaller than 120 $^\circ$. The sum of the angles about N(10) is 357 (9) $^\circ$, indicating that the amino N adopts an sp^2 hybridization. The C(4)–N(10) bond length is smaller than 1.404 (3) \AA in 2-amino-5-nitrophenol (Haisa, Kashino & Kawashima, 1980) and 1.391 (3) \AA in 1,2-diaminobenzene (Stålhandske, 1976), in which no quinonoid structure is observed. The C(1)–C(7) bond length is smaller than

* Lists of structure factors, anisotropic thermal parameters and least-squares planes of the benzene ring and ester group have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36702 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. The torsion angles ($^{\circ}$) of the side chain and the intramolecular O \cdots N distances (\AA) of procaine and related compounds

See text for the definition of τ_1 , τ_2 and τ_3 .

Compound	τ_1	τ_2	τ_3	O(8) \cdots N(13)	O(9) \cdots N(13)
(1)	176.1 (4)	-178.7 (4)	-65.1 (5)	2.982 (4)	4.814 (5)
(2)	177.1 (4)	175.3 (4)	70.1 (5)	3.069 (6)	5.008 (6)
(3)	178.7 (3)	172.7 (3)	70.2 (4)	3.069 (4)	4.967 (4)
(4)	178.6 (2)	-165.6 (2)	-71.2 (2)	3.074 (3)	5.022 (3)
(5)	-178.1 (7)	179.9 (7)	-73.7 (10)	3.128 (8)	4.944 (8)
(6)	178.5 (3)	147.1 (4)	-82.6 (5)	3.139 (5)	4.382 (5)
(7)	-175.1 (3)	166.5 (4)	83.3 (4)	3.209 (4)	5.029 (5)
(8)	-174.7 (7)	-166.9 (7)	84.6 (10)	3.255 (9)	4.798 (9)
(9)	177.9 (5)	-170.6 (5)	-94.4 (6)	3.285 (7)	5.037 (7)

Compounds and references: (1) Procaine bis(*p*-nitrophenyl) phosphate; Sax, Pletcher & Gustaffson (1970). (2) Carbamoylcholine iodide; Jensen (1975). (3) Procaine hydrochloride; Dexter (1972). (4) Procaine dihydrogen orthophosphate; Freeman & Bugg (1975). (5) Acetylcholine perchlorate; Mahajan & Sass (1974). (6) Procaine; this work. (7) Adiphenine hydrochloride; Guy & Hamor (1973). (8) Acetylcholine chloride; Herdklotz & Sass (1970). (9) Caramiphen hydrochloride; Griffith & Robertson (1972).

1.484 (5) \AA in benzoic acid (Bruno & Randaccio, 1980), and 1.489 (5) and 1.494 (5) \AA in bis(2-hydroxyethyl) terephthalate (Kashino & Haisa, 1975). However, no significant differences are observed in the C(7)–O(8), C(7)–O(9) and O(8)–C(11) bond lengths from the corresponding lengths in aromatic esters having no quinonoid character (Kashino & Haisa, 1975; Haisa & Kashino, 1977).

The torsion angles τ_1 [C(1)–C(7)–O(8)–C(11)], τ_2 [C(7)–O(8)–C(11)–C(12)] and τ_3 [O(8)–C(11)–C(12)–N(13)] are compared with those of related compounds in Table 3. The conformations of $\tau_1 = \textit{trans}$, $\tau_2 = \textit{trans}$ and $\tau_3 = \textit{gauche}$ are favorably chosen in these compounds to yield similar pharmacophoric patterns. The O(8) \cdots N(13) distance determined by τ_3 takes the values in the range of 2.9 to 3.3 \AA in these compounds. The O(9) \cdots N(13) distance is determined by τ_1 , τ_2 and τ_3 , of which τ_2 in procaine is significantly smaller than for the other compounds, resulting in the smaller distance 4.382 (5) \AA compared with 4.8–5.0 \AA in the others.

The τ_4 [C(11)–C(12)–N(13)–C(16)], 72.4 (5) $^{\circ}$, is *gauche* as in the salts of procaine, while τ_5 [C(11)–C(12)–N(13)–C(14)], -156.8 (4) $^{\circ}$, is *trans*, differing from the salts. The N atom of the salts is protonated and hydrogen bonded to a bulky group, so that the C–C–N–H rather than the C–C–N–C is in the *trans* conformation.

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