# Procaine: A Comparative Study of Two Independent Structure Determinations; Conformations in Different Solid-State Environments

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The results of a second, and independent, study of the procaine hydrochloride crystal structure are compared with a prior determination by means of a half-normal probability plot. The coordinate standard deviations obtained from the least-squares refinements appear to be underestimated by a factor of two. An examination of two solid-state conformations of procaine shows that the major conformational features are preserved in the different crystal environments.

#### Introduction

The solid-state conformation of the local anesthetic procaine (2-diethylaminoethyl *p*-aminobenzoate) has been determined in a *p*-nitrophenyl phosphate complex (Sax, Pletcher & Gustaffson, 1970) and in the hydrochloride salt (Beall, Herdklotz & Sass, 1970). The results of an independent determination of the procaine HCl structure are compared with those of Beall, Herdklotz & Sass (1970), (hereafter referred to as BHS) by means of a half-normal probability plot (Abrahams & Keve, 1971) and the conformations of procaine found in two different solid-state environments are examined.

### Structure determination and refinement

The crystal data of procaine HCl and a comparison of cell dimensions determined here with those of BHS and of Rose (1958) are summarized in Table 1. For the present study a crystal, approximately  $0.18 \times 0.22 \times 0.23$ 

### Table 1. Crystal data of procaine HCl and comparison of cell dimensions

Form M.W Syste Space	nula matic absences e group	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub> .HCl 272·77 0kl for l odd, h0l for h odd Pcab			
Cell	volume	2948∙6 Å			
ρ (X-	ray)	1.229 g.cm <sup>-3</sup>			
$\rho$ (flc	tation; Rose, 1958)	1.232 g.cm <sup>-3</sup>			
Z		8			
μ		22.7 cm <sup>-1</sup>			
	This work*	BHS (1970)	Rose (1958)		
а	25·017±0·001 Å	25·023 Å	25·04 Å		
b	$8.305 \pm 0.0005$	8.280	8.28		
с	$14.192 \pm 0.001$	14.157	14.35		

\* Lattice parameters and standard deviations were obtained from a least-squares calculation with  $2\theta$  values of general high-angle reflections.

mm, was cut from a large needle and mounted on a computer-controlled GE diffractometer with **b** along

Table 2. Final coordinates and thermal parameters\* of procaine hydrochloride

	x	У	z	$U_{11}$	$U_{22}$	$U_{33}$	$U_{12}$	$U_{13}$	$U_{23}$
C(1)	2986 (2)	1136 (5)	3510 (3)	6.6 (2)	8.1 (3)	5.8 (2)	0.5 (2)	0.0 (2)	1.5 (2)
Č(2)	3101 (1)	9360 (4)	3614 (2)	5.3 (2)	6.5 (2)	4.7 (2)	-0.9(2)	-0.5(1)	-0.1 (2)
C(3)	4270 (1)	9327 (5)	5382 (3)	4.3 (2)	7.8 (3)	7.7 (2)	0.2(2)	-0.5(2)	-2.2(2)
C(4)	3980 (1)	9575 (4)	4462 (2)	3.9 (1)	5.1 (2)	6.5 (2)	-0.7(1)	0.6 (1)	-1.0(2)
C(5)	3349 (1)	7260 (4)	4801 (2)	3.9 (1)	5.6 (2)	5.4 (2)	-0.2(1)	0.5 (1)	0.3 (1)
C(6)	3545 (1)	6018 (4)	4112 (3)	4.5 (2)	4.9 (2)	7.1 (2)	-0.5(1)	-0.6(2)	-0.4(2)
C(7)	4356 (1)	4887 (4)	3556 (2)	5.3 (2)	4.8 (2)	5.0 (2)	0.0 (1)	-0.1(1)	0.0 (1)
C(8)	4935 (l)	5049 (4)	3533 (2)	4.9 (2)	4.5 (2)	4.2(1)	0.3 (1)	0.4 (1)	0·4 (1)
C(9)	5238 (1)	4034 (4)	2942 (2)	6.1 (2)	5.2 (2)	5.2 (2)	-0.1(2)	0.5 (1)	-0.7 (2)
C(10)	5776 (1)	4179 (4)	2869 (2)	6.1 (2)	5.5 (2)	5.4 (2)	0.8 (2)	1.3 (1)	-1·2 (2)
C(11)	6058 (1)	5370 (4)	3369 (2)	4.5 (2)	5.5 (2)	4.8 (2)	0.7 (1)	0.6 (1)	0.8 (1)
C(12)	5762 (1)	6330 (4)	3995 (2)	4.9 (2)	4.8 (2)	4.7 (2)	0.4 (1)	-0.1 (1)	-0·4 (1)
C(13)	5218 (1)	6182 (4)	4062 (2)	4.8 (2)	4.7 (2)	4.3 (2)	0.4 (1)	0.5 (1)	0.0 (1)
N(1)	3410 (1)	8990 (3)	4504 (2)	3.7 (1)	4.6 (1)	4.3 (1)	-0·1 (1)	0.4 (1)	-0.3(1)
N(2)	6597 (1)	5529 (4)	3295 (2)	4.8 (2)	7.2 (2)	7.1 (2)	0.6 (1)	0.9 (1)	-0.9 (2)
O(1)	4115 (1)	6060 (3)	4067 (1)	4·0 (1)	4·9 (1)	6·0 (1)	0.1 (1)	0.1 (1)	<b>−0.8</b> (1)
O(2)	4095 (1)	3857 (3)	3175 (2)	6.1 (1)	6.1 (1)	9.4 (2)	-1.1 (1)	-1.1 (1)	-3·3 (1)
CÍ	29008 (3)	07854 (11)	61733 (5)	4.73 (4)	7.79 (6)	4.78 (4)	1.62 (4)	-0.11(3)	-1.10 (4)

\* Positional parameters for Cl are  $\times 10^5$ , for H,  $\times 10^3$  and for all others,  $\times 10^4$ . The  $U_{ij}$ 's are  $\times 10^2$ . E.s.d.'s are those obtained from the least-squares refinement and refer to the last decimal place given. The form of the anisotropic temperature factor is: exp  $\left[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)\right]$ .

#### Table 2 (cont.)

	x	У	2
H(1)	272 (1)	134 (4)	299 (2)
H(2)	276 (1)	151 (4)	406 (2)
H(3)	332 (1)	160 (4)	334 (2)
H(4)	272 (1)	388 (4)	127 (2)
H(5)	333 (1)	397 (4)	192 (2)
H(6)	041 (1)	004 (4)	038 (2)
<b>H(</b> 7)	061 (1)	320 (4)	456 (2)
H(8)	094 (1)	-024 (4)	087 (2)
H(9)	416 (1)	409 (4)	107 (2)
H(10)	392 (1)	078 (4)	434 (2)
H(11)	298 (1)	212 (4)	008 (2)
H(12)	149 (1)	219 (4)	462 (2)
H(13)	346 (1)	514 (4)	437 (2)
H(14)	345 (1)	104 (4)	151 (2)
H(15)	005(1)	188 (4)	260 (2)
H(16)	098 (1)	143 (4)	249 (2)
H(17)	095 (1)	285 (4)	064 (2)
H(18)	000 (1)	303 (4)	050 (2)
H(19)	174 (1)	377 (4)	156 (2)
H(20)	173 (1)	-011 (4)	284 (2)
H(21)	173 (1)	458 (4)	506 (2)

the  $\varphi$  axis. Peak heights of 3033 unique reflections with  $2\theta < 150^{\circ}$  (Cu  $K\bar{\alpha}$ ;  $\lambda = 1.5418$  Å) were measured using the stationary-crystal stationary-counter technique and a take-off angle of 4°. The 2486 reflections for which  $I_p > 2\sigma(I_p)$  were treated as observed. Approximate integrated intensities were obtained from the peak heights, as described by Alexander & Smith (1962), and were corrected for Lorentz and polarization factors but not for absorption.

The structure was determined routinely after chloride ion coordinates were deduced from an  $E^2-1$ vector map. Refinement by least-squares methods with isotropic and then anisotropic temperature factors led to a final R of 0.072. Hydrogen atoms were included in the refinement, with isotropic temperature factors fixed at 4.0 Å<sup>2</sup>. Before the last three cycles 15 reflections which had been mismeasured were removed from the reflection list. In the last cycle the average shift for all 227 variables was  $0.2\sigma$  and the maximum shift was less than  $1.0\sigma$ . A final difference map showed no positive peak larger than about 0.3e.

Final coordinates and thermal parameters are presented in Table 2. Bond distances and angles are listed in Table 3. Observed and calculated structure factors are given in Table 4. Fig. 1(a) is an ORTEP (Johnson, 1965) drawing of the molecule.

Most calculations were carried out with the XRAY67 programs (Stewart, 1967) and their 1970 revisions. The quantity minimized in the least-squares refinement was  $\sum w(|F_{o}| - |F_{c}|)^{2}$  with all reflections receiving unit weight. Mean planes were computed using the routine of Ahmed, Hall, Pippy & Saunderson (1966). Scattering factors for carbon, nitrogen, and oxygen were taken from International Tables for X-ray Crystallography (1962), for hydrogen from Stewart, Davidson & Simpson (1965), and for chlorine from Cromer & Waber (1965).

Table 3. Bond distances and angles of procaine hydrochloride

C(1) - C(2)	1·511 (6) Å	C(6) - H(14)	0.91(3)Å
C(1) - H(1)	1.01(3)	C(7) - O(1)	1.356 (4)
C(1) - H(2)	1.01(3)	C(7) - O(2)	1.210(4)
C(1) - H(3)	0·95 (3)	C(7) - C(8)	1.457 (4)
C(2) - N(1)	1.512(4)	C(8) - C(9)	1.409 (4)
C(2) - H(4)	1.07 (3)	C(8) - C(13)	1.396 (4)
C(2) - H(5)	1.02 (3)	C(9) - C(10)	1.356 (5)
C(3) - C(4)	1.508(5)	C(9) - H(15)	1.01 (3)
C(3)-H(6)	0.99 (3)	C(10) - C(11)	1.407 (5)
C(3)–H(7)	0.98 (3)	C(10) - H(16)	0.90 (3)
C(3)-H(8)	0.95 (3)	C(11) - C(12)	1.405 (4)
C(4) - N(1)	1.506 (4)	C(11) - N(2)	1.359 (4)
C(4)–H(9)	0.98 (3)	C(12) - C(13)	1.367 (4)
C(4) - H(10)	1.02 (3)	C(12) - H(17)	0.98 (3)
C(5) - N(1)	1.505 (4)	C(13) - H(18)	1.05 (3)
C(5)-C(6)	1.503 (5)	N(1) - H(21)	0.87 (3)
C(5) - H(11)	0.93 (3)	N(2) - H(19)	0.72 (4)
C(5) - H(12)	0.92(3)	N(2)—H(20)	0.81 (3)
C(6) - O(1)	1.427 (4)		
C(6) - H(13)	0.85 (3)		
C(1) = C(2) = N(1)	112·2 (3)°		
C(3) = C(4) = N(1)	112 2 (3) 112 2 (3)		
C(2) - N(1) - C(4)	$112 \cdot 7 (2)$		
C(2) - N(1) - C(5)	$112 \cdot 1 (2)$		
C(4) - N(1) - C(5)	114.5(2)		
C(5) - N(1) - C(6)	$116 \cdot 1 (3)$		
C(5) - C(6) - O(1)	104.7 (3)		
O(1) - C(7) - O(2)	121.0(3)		
O(1) - C(7) - C(8)	112.9 (3)		
O(2) - C(7) - C(8)	$126 \cdot 2(3)$		
C(7) - C(8) - C(9)	119.5 (3)		
C(7) - C(8) - C(13)	123.7 (3)		
C(4) - C(8) - C(13)	116.8 (3)		
C(8) - C(9) - C(10)	121.7 (3)		
C(9) - C(10) - C(11)	121.5 (3)		
C(10)-C(11)-C(12)	116.9 (3)		
C(10)-C(11)-N(2)	121.8 (3)		
C(12)-C(11)-N(2)	121.2 (3)		
C(11)-C(12)-C(13)	121.1 (3)		
C(8) - C(12) - C(13)	121.9 (3)		

## Comparison of the two procaine HCl structures

The same 227 variables were refined in both studies, but data sets differed in size and in collection technique. BHS based their analysis on 883 reflections measured by the fixed-counter moving-crystal method using silicon monochromatized Mo  $K\alpha$  radiation on an equiinclination diffractometer.

Abrahams & Keve (1971) have recently described how independent determinations of the same structure may be compared by means of a half-normal probability plot. The ordered statistic  $\delta p_i$  is plotted against the expected normal distribution

$$\delta p_i = \left| \left| p(\text{DDD})_i \right| - \left| p(\text{BHS})_i \right| \right| / [\sigma^2 p(\text{DDD})_i + \sigma^2 p(\text{BHS})_i]^{1/2}, \quad (1)$$

where  $p_i$  are the positional parameters obtained from the respective determinations (DDD are the initials of the present author) and  $\sigma p_i$  are the associated standard deviations. For correctly estimated  $\sigma p_i$  and random distribution of errors, this plot is linear with a slope of unity and an intercept of zero.

The individual  $\sigma p(BHS)_i$  are not given by BHS and have been estimated as follows: (a) since  $\sigma p_i \propto [no. of$ degrees of freedom]<sup>1/2</sup>, the larger number of reflections used in the present refinement would be expected to lead to standard deviations approximately one-half those of BHS; (b) BHS quote 0.01 Å as the estimated standard deviation for their bond distances and the corresponding standard deviations found here (Table 3) are roughly one-half as large. Fig. 2 shows the halfnormal probability plot that results, assuming

## $\sigma p(BHS)_i = 2\sigma p(DDD)_i$

for the 117 positional parameters of procaine HCl.



Fig. 1. (a) Perspective drawing of procaine hydrochloride. (b) Perspective drawing of procaine in the 1:1 procaine bisp-nitrophenyl phosphate complex. One ethyl group is disordered and has not been drawn. In (a) and (b) molecules are viewed normal to the benzene ring, and thermal ellipsoids are plotted at the 50% level.

The array of points in Fig. 2 is nearly linear and has an intercept of approximately zero. This indicates (Abrahams & Keve, 1971) that the two crystals studied are samples of the same material and that the errors in the data are mostly random. The slope of the array is approximately two, and Abrahams & Keve have shown that the most likely explanation for this is that the denominator of equation (1) has been underestimated by about one half. If the above estimate of the  $\sigma p(BHS)_l$  is appropriate, and both data sets are equally affected, then the standard deviations derived from the least-squares refinement are small by a factor of two.

After adjusting the scale of the  $\sigma$ 's, only five of the 117 parameters differ by more than  $2\sigma$ . The only discrepancies between the two structures are associated with the ends of the molecule: three with the hydrogen atoms in the ethyl groups, one with a hydrogen atom in the *p*-amino group, and one with a terminal carbon atom in an ethyl group.

### Comparison of procaine conformations

Fig. 1(b) shows the procaine molecule of the 1:1 procaine – bis-p-nitrophenyl phosphate complex (Sax et al., 1970). Major differences between procaine molecules in the salt and in the phosphate complex are: (a) a 145° relative rotation about the C(5)–N(1) bond, and (b) the quinonoid character of the p-aminobenzoate group. Some torsion angles along the side chain in the two molecules are compared in Table 5. Despite the rotation about the C(5)–N(1) bond, the molecules maintain largely similar conformations.

A packing diagram of the hydrochloride salt (Fig. 3) shows layers of procaine molecules, their phenyl rings stacked in the familiar herringbone array, alternating with layers of chloride ions. The protonated tertiary amino nitrogen N(1) is hydrogen-bonded to a chloride ion 3.08 Å distant. Each chloride ion also interacts with two *p*-amino groups, 3.39 and 3.44 Å away. These nitrogen–chlorine interactions affect not only the conformation of the alkylamino end of the molecule, but





also the quinonoid character of the *p*-aminobenzoate group. The N(2)–C(11), C(9)–C(10), and C(12)–C(13) distances of 1.359 (4), 1.356 (5), and 1.367 (4) Å, respectively, tend to be shorter than the corresponding

distances in the phosphate complex [1.377(7), 1.381(8), 1.369(7) Å]. In the hydrochloride salt, the average of the interior angles at the *para* positions of the phenyl ring is 5.0° less than the average of the other interior

# Table 4. Observed and calculated structure factors for procaine HCl

Columns are h,  $10F_o$  and  $10F_c$ . Unobserved reflections are marked with an asterisk and the extinguished reflection by E.

Mode       Mode
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Table 4 (cont.)

H+++10 8 314 -32 9 129 131 10 191 -197	H.4.16 D 46 36 1 39 -53 2 34 36	18 73 -68 19 31 -30 20 32 -28 21 299 -17 22 71 -56	20 27* -24 21 90 -87 22 34 27 23 23* -10	H,5,14 0 82 91 1 31 -25 2 29 -25	4 154 -159 5 107 118 6 276 262 7 172 170 8 223 -237	12 27° -1 13 225 22 14 64 6 15 95 -9 16 27° -	7 14 44 65 4 3 H16+13 8 1 23 -19	12 123 126 13 270 7 14 66 67 15 131 122 16 183 -175	12 27 -26 13 41 41 14 25• -13 15 28 -36 16 22• 14	10 66 -63 11 256 8 12 35 28 13 266 9 14 286 -6	2 /3 44 3 61 -58 4 48 -40 5 230 -18 6 230 3	12 240 17 13 240 17 14 210 18 H,9,5
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3 93 75 4 20 -5 5 21 -18 6 38 -34 H.f.1	25 280 17 24 210 5 25 204 -1 26 80 74 H.5.5	H,5,9 1 199 243 2 26 31 3 148 158 4 96 95 5 177 - 176	3 69 67 4 94 86 5 87 -79 6 39 -43 7 37 -37 8 32 -39 9 55 44	138 -135 10 188 197 11 64 -69 12 289 10 13 46 -36 14 210 -196 15 34 33	17 121 -11 18 172 16 19 270 -1 20 159 -15 21 103 -10 22 35 3	- 2 77 -72 4 3 130 -122 7 4 108 -106 7 5 199 0 1 6 31 -22 8 7 66 -68 8 63	17 92 95 18 90 -92 19 67 64 20 27* 11 21 25* -14 22 59 -67	H,7,10 0 46 50 1 103 120 2 24 -32 3 101 -99	16 38 -37 17 38 -48 18 249 -9 19 27 -40 H18-3	8 290 27 9 58 -60 10 40 -45 11 29 -37 12 60 80	1 48 55 2 239 -10 3 239 -12 4 50 42 5 219 -6 6 65 -64
10 102 98 19 280 7 20 35 34 21 42 -39 22 240 5	1 18* 23 3 428 420 4 226 221 5 619 -615 6 25 -27 7 96 94	1 29 -16 2 42 58 3 210 -5 4 113 -127 5 282 271 6 146 139	6 99 -93 7 173 168 8 208 203 9 146 -144 10 114 -114	10 69 70 11 67 -93 12 56 -73 H.5,15	16 46 51 17 159 162 18 55 -45 19 79 80 20 177 173 21 289 1	H+6+8 0 24* 1 26 -4 2 218 28 3 20* -	9 31 32 10 249 12 5 11 219 13 2 H.6.14 6	H,7,5 1 159 207 2 220 12 3 88 -92 4 75 72	4 62 -63 5 23 -23 6 240 -30 7 240 23 8 32 -29 9 56 -54	1 122 -150 2 240 34. 3 82 -80 4 99 -107 5 175 177	14 22# -22 H1819 1 22# -16 2 37 40	7 240 0 8 68 63 9 33 30 10 54 -60 11 200 -18 12 230 -25
H.4.11 1 170 -195 2 163 172 3 180 193 4 139 -141	8 49 54 9 44 42 10 200 -275 11 69 60 12 150 155 13 250 -7	7 332 -325 8 194 -193 9 173 176 10 36 22 11 46 ~40 12 106 -108	12 300 -2 13 185 174 14 59 54 15 52 -58 16 43 -30 17 44 42	1 200 -29 2 210 6 3 210 -19 4 66 -54 5 190 -3 6 74 -55	22 45 -39 23 259 6 24 44 41 25 95 98 H, 624	4 117 -12 5 29 -2 6 32 - 7 51 8 74 7 9 60 -5	5     0     66     77       9     1     33     36       9     2     36     -28       4     3     21*     19       7     4     5     36       6     5     36     23	5 163 160 6 188 -176 7 166 -156 8 109 -126 9 35 31 10 105 -105	10 37 41 11 39 34 12 249 5 13 62 -66 14 27 -31 15 47 68	6 31 20 7 32 -32 8 59 -48 9 299 -5 10 310 28 11 55 -60	3 39 -27 4 35 37 5 24e 2 6 135 103 7 53 52 8 28e 11	H.9.6 0 146 -135 1 220 2 2 210 25
5 187 -180 6 134 125 7 205 189 8 31# -23 9 166 -169 10 30# 3	14 107 108 15 182 -187 16 44 30 17 96 -97 18 166 159 19 313 -327	13 127 -133 14 270 10 15 148 147 16 42 40 17 7470 18 95 -88	18 114 104 19 124 -119 20 266 -3 21 266 10 22 25 25	7 22* 0 H.6+0 0 861 -838 1 139 159	0 99 105 1 134 -164 3 22* -13 4 80 81 5 258 257	10 153 -15 11 46 -4 12 246 -5 13 200 - 14 48 -4 15 49 -5	5 6 200 21 8 2 H.7.1 7 1 143 -206 5 2 59 -140	11 23° 12 12 93 -105 13 81 73 14 34 36 15 28° 29 16 37 -31	H,7,11 J 25 36 Z 210 -16 J 73 -65	12 88 -94 13 42 -39 14 264 -13 15 63 67 16 274 -1 17 28 19	9 270 28 10 33 40 11 170 -7 12 230 -21 H,8,10	3 + 9 + 41 4 - 37 - 23 5 - 208 6 - 66 - 54 7 - 68 - 56 8 - 52 - 63
11 270 15 12 55 48 13 280 -19 14 280 17 15 260 -12 16 78 82	20 128 -116 21 165 160 22 41 42 23 29* 26 24 82 -72 25 136 -127	19 97 95 20 72 66 21 115 -106 22 124 -121 23 34 31 24 95 81	H, 5, 10 0 240 -25 1 27 -4 2 181 205 3 232 -247	2 230 384 3 172 166 4 173 169 5 110 -92 6 35 -50 7 147 -140	6 25 24 7 59 -63 8 66 -79 9 76 74 10 221 227 11 63 70	16 270 1 17 92 8 16 260 -1 19 66 -6 20 39 -3 21 230 -1	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	17 109 -100 18 41 -42 19 32 42 20 132 -133 21 134 -141	5 87 74 6 72 67 7 230 4 8 49 51 9 260 0	10 61 76 19 61 84 H,8,4 0 139 -116	0 56 58 1 58 73 2 39 33 3 220 -6 6 66 -58	10 66 -82 11 24 -43 H, 9, 7
17 167 162 18 87 -87 19 120 -125 20 67 66 21 112 119	26 208 -2 27 41 45 H.5.2 1 176 219	25 36 38 26 21 25 Hi5.6 0 180 172	4 185 -192 5 45 31 6 121 -120 7 65 76 8 48 46 9 299 -17	$\begin{array}{c} -8 & 267 & 274 \\ 8 & 123 & -148 \\ 10 & 152 & -170 \\ 11 & 106 & 124 \\ 12 & 59 & 51 \\ 13 & 289 & 51 \\ 13 & 289 & 51 \\ \end{array}$	12 325 -349 13 42 -28 14 64 65 15 89 86 16 153 -138 17 52 47 18 71 -75	H#6#9 1 53 7 2 54 7 3 44 4 107 10	10 113 113 11 45 -41 5 12 154 163 7 13 60 -53 3 14 169 -162	0 170 -175 1 107 -138 2 95 -149 3 86 82 4 229 -5	11 220 8 12 230 -34 H.7.12 0 121 121	2 162 -270 3 230 -20 4 230 14 5 240 -8 6 91 88 7 58 53	6 46 -49 7 81 64 8 240 -23 9 240 1 H18-11	2 210 24 3 210 12 4 24 -7 5 90 -79 6 65 51 7 210 3
0 54 55 1 102 125 2 64 -73 3 126 -119 4 230 17	4 44 33 5 135 -129 6 150 -158 7 528 -475 8 264 7 9 319 -336	2 166 -242 3 176 172 4 220 210 5 137 130 6 22° 15 7 186 -181	10 07 -05 11 165 160 12 175 174 13 162 -152 14 53 -64 15 266 10 16 279 23	15 160 -163 16 385 374 17 299 -2 18 148 157 19 164 -168 20 299 -11	19 125 122 20 109 102 21 98 -89 22 279 -17 23 259 3 24 69 66	5 103 -8 6 230 - 7 125 11 8 132 -13 9 50 -5 10 300 -1	8         16         90         67           4         17         65         67           9         18         46         45           8         19         32         -22           6         20         27*         4           4         21         70         67	5 78 ~68 6 155 165 7 240 20 8 310 15 9 57 52 10 123 -130	1 99 113 2 26 -19 3 49 44 4 22° 17 5 71 53 6 22° 0	8 300 -0 9 122 119 10 31 -3 11 57 -48 12 145 -150 13 118 105	1 57 65 2 190 1 3 190 13 4 63 -51	8 29 29 9 35 29 Hy948 0 42 29
5 77 82 6 76 63 7 43 42 8 34 -28 9 30# -21	10 313 -325 11 193 210 12 202 216 13 177 -169 14 43 30 15 153 158	8 122 -124 9 316 -42 10 172 176 11 67 -69 12 187 -216 13 81 84	17 258 -7 16 31 -29 19 260 2 20 250 -2 21 42 39	21 142 135 22 162 159 23 93 99 24 142 -129 25 81 -96	H, 6, 5 1 72 -81 2 112 -176 3 79 -96	11 25° 2 12 85 -7 13 111 10 14 27° -2 15 79 -6 1 104 8	7 22 274 28 3 23 24 -7 3 0 H,7,2 4 5 0 101 115	11 139 -138 12 269 18 13 102 99 14 279 -1 15 175 -164 16 41 27	7 65 48 8 259 -14 9 45 -48 H,7,13	14 62 -53 15 64 -65 16 67 -67 17 240 17 18 72 78	H,9,1 1 153 -190 2 49 -79 3 41 -33 4 110 -107	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$
11 182 167 12 299 -30 13 92 -87 14 278 7 15 96 92 16 258 -9	16         189         195           17         222         -210           18         203         -197           19         317         -216           20         189         -187           21         30*         -23	14 198 198 15 205 -202 16 33 2 17 167 162 18 26 -19 19 57 58	H+5+11 1 238 308 2 42 -44 3 45 -54 4 240 22	Hyőy1 1 210 6 2 210 34 3 210 -17 4 44 35	4 119 110 5 306 293 6 80 -65 7 109 -102 8 50 -60 9 157 -167	25 1 .6 24 -2 19 25• -2 20 22• 2 H,6,10	0 1 95 124 5 2 26° 2 7 3 186 -192 1 4 25° -3 5 86 80 6 53 53	17 74 67 18 104 111 19 264 41 20 234 2 H,7,7	1 190 12 2 40 -41 3 91 -84 H.8.0	×.8,5 1 55 -63 2 50 -70 3 53 47 4 250 -27	5 25 25 6 50 32 7 54 50 8 64 -62 9 35 -41 10 81 87	H, 10,0 0 172 154 1 54 59 2 51 71
17 7859 17 52 51 62 56 H.4.13	22 41 28 23 288 -17 24 48 -41 25 142 137 26 84 76 27 84 -84	20 28 -10 21 73 -60 22 33 -38 23 198 185 24 76 69 25 89 -83	5 26 27 6 72 71 7 249 -5 8 309 -8 9 33 -29 10 57 62	5 130 -133 6 363 355 7 210 191 8 32 -32 9 310 -32 10 132 141 11 41 44	11 96 -98 12 106 87 13 41 35 14 83 -78 15 175 154	0 220 -23 1 58 -5 2 99 -12 3 76 -8 4 98 -9 5 70 -7	5 8 88 -97 8 9 63 -73 7 10 110 -127 5 11 140 145 7 12 42 44	1 125 -161 2 23* 24 3 36 -46 4 72 -75 5 82 -77	1 236 272 2 155 248 3 178 157 4 29 11 5 74 55 6 36 37	6 60 -50 7 26* 9 8 74 83 9 120 -116 10 79 -82 11 65 -69	12 260 42 13 62 -70 14 50 -63 15 220 -1	4 58 37 5 135 104 6 93 75 7 64 -44 8 234 4
2 52 -53 3 96 -97 4 149 -160 5 248 1 6 76 76 7 68 -66	H+5+3 1 86 -123 2 145 305 3 26 33 4 137 -131	H,5,7 1 406 -515 2 92 -124 3 69 -73 6 158 -157	12 64 -61 13 146 143 14 26* 10 15 38 28 16 45 36	12 04 -67 13 28° 1 14 27° -28 15 154 -152 16 189 174 17 40 44	17 270 13 18 116 110 19 34 -27 20 179 -161 21 96 -94 22 28 4	6 39 4 7 269 2 8 45 -3 9 75 8 10 114 -11 11 62 -6	0 14 167 150 8 15 152 143 7 16 37 -23 2 17 67 -61 0 18 120 -104 5 19 269 -14	7 123 120 8 44 60 9 81 -90 10 31* -28 11 35 -46 12 27 -23	7 45 -30 8 49 36 9 145 -148 10 314 -48 11 84 94 12 149 165	12 260 -26 13 63 53 14 270 -17 15 48 40 16 250 -16 17 230 16	0 39 35 1 62 -66 2 105 -154 3 136 -128 4 42 33	H, 10, 1 1 73 67 2 63 73 3 52 -21 4 210 14
8 107 107 9 30* 30 10 29* 12 11 62 62 12 27* =16 13 26* 6	5 385 390 6 76 -64 7 244 -229 8 28 -15 9 276 272 10 65 56	5 113 -99 6 240 -16 7 198 194 8 142 162 9 138 -139 10 117 -119	18 25+ 5 19 22+ 3 H15+12 0 51 67	18 37 50 19 84 82 20 224 209 21 284 14 22 98 -82 23 274 -23	23 259 19 24 29 -34 H,6,6 0 231 221	12 32 13 43 -3 14 95 -10 15 33 3 16 43 3 17 230 -2	6 20 27° -25 7 21 26° -19 3 22 34 -36 5 7 H.7.3	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	13 28° -36 14 28° 21 15 115 103 16 36 26 17 27° -5 18 69 -70	H+8+6 0 240 -31 1 210 -11 2 210 9	5 62 56 6 50 47 7 69 41 8 75 -11 9 87 75 10 299 2	5 64 52 6 52 -50 7 48 -38 8 244 -18 10,2
14 270 4 15 260 -16 16 240 -16 17 57 -77 H.4.14	11 82 -99 12 101 -111 13 205 -216 14 92 106 15 341 339 16 145 -127	11 124 -143 12 42 44 13 69 -60 14 55 -68 15 131 -140 16 280 -23	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	24 29 -23 25 46 45 H.6.2 0 129 -121	1 27 27 2 78 114 3 209 -7 4 51 31 5 67 63 6 70 -60	18 220 1 H,0,11 1 33 -1 2 59 6	3 1 107 130 2 240 47 3 38 -37 4 176 179 3 5 199 202 8 6 82 -77	19 230 -5 H,7,8 0 213 -213 1 64 -94	19 46 -63 20 23* -11 H.8.1 1 81 104	3 240 -11 4 50 54 5 36 -22 6 32 -21 7 65 65 8 280 14	11 40 51 12 62 -88 13 48 -52 14 76 76 15 224 19 4.6.3	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
0 165 182 1 45 55 2 66 57 3 121 -130 4 25 24 5 258 11	17 108 105 18 159 -164 19 171 168 20 281 267 21 55 52 22 47 -44 23 288 -19	17 131 130 18 69 64 19 28 17 20 112 -105 21 200 10 22 42 41	8 31* -2 9 138 -135 10 64 89 11 40 46 12 27* 15 13 97 -96	2 44 104 3 121 128 4 106 103 5 139 133 6 106 -107 7 292 -271	8 47 39 9 72 68 10 38 53 11 36 31 12 279 -16	4 133 -12 5 56 6 6 159 15 7 230 8 119 -11 9 65 -6	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	3 26 -24 4 57 50 5 47 -45 6 57 52 7 240 -35 8 30 -35	3 230 -24 4 240 -4 5 59 63 6 29 34 7 46 -39 8 104 -105	10 36 40 11 228 -24 12 268 -10 13 45 39 14 39 32 15 41 -50	1 76 83 2 61 77 3 112 91 4 127 110 5 50 50	6 55 50 7 206 -2 He10e3 1 44 43
6 3231 7 28* 18 8 29*26 9 6469 10 58 63 11 89 101	24 25* -6 25 45 -31 26 41 -38 H+5+4	24 220 -7 H+5+8 0 361 -373 1 214 -303	14 39 -42 15 71 68 16 49 44 17 26 8 H,5,13	8 290 0 9 171 -190 10 72 63 11 36 50 12 77 -80 13 27 -19	14 173 159 15 294 -26 16 294 -21 17 56 64 18 264 -17 19 124 115	10 99 10 11 30 12 250 13 44 -3 14 49 -4 15 250 3	3 14 32 39 7 15 107 111 5 16 79 -72 8 17 26m 2 1 18 50 41 5 19 78 78	9 32 21 10 176 -171 11 48 -61 12 33 31 13 26* -13	9 61 52 10 38 -20 11 35 43 12 70 -82 13 270 -7 14 57 58	16 26 38 H,8,7 1 47 59 2 39 58	6 41 -34 7 230 -17 8 278 -4 9 57 39 10 42 -47 11 200 10	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
12 38 45 13 72 -92 14 86 101 15 220 -31 H14415	0 271 274 1 83 105 2 38 50 3 39 26 4 78 -84 5 231 217	2 78 -84 3 108 102 4 163 168 5 176 170 6 269 -15 7 66 -70	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	14 69 -65 15 28* -9 16 30 31 17 54 45 18 103 -93 19 102 -99	20 46 40 21 53 54 22 259 7 23 54 -57 H <sub>2</sub> 6,7	16 93 10 H+6+12 0 179 18 1 67 8	9 20 27° 25 21 26° -16 22 26 19 7 H.7.4	15 46 -43 16 70 66 17 220 -6 18 45 64 H.7.9	15 274 -17 16 53 49 17 52 -46 18 61 -66 19 244 31	3 28 25 4 69 72 5 116 -111 6 25 -14 7 136 125 8 87 91	12 250 34 13 200 42 14 31 38 H,94	F, 10,4 0 55 -57 1 50 -62 2 32 -35 3 184 -7
1 28 37 2 220 17 3 120 -110 4 71 79 5 89 76	6 36 31 7 43 11 8 54 -64 9 106 -110 1C 33 -12 11 1C0 109	8 33° 28 9 133 132 10 123 -127 14 49 47 12 149 -155 13 131 117	6 120 114 7 67 -65 8 29 -33 9 276 6 10 69 71 11 74 -73	20 60 -54 21 69 -65 22 299 22 23 87 87 24 27 -27 25 22 25	1 276 373 2 42 -56 3 89 -87 4 286 279 5 77 -77	2 40 -4 3 45 -3 4 63 -3 5 98 -9 6 33 -2 7 39 -3	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	1 49 47 2 23* 37 3 95 92 4 105 -94 5 13* -121	H, d, 2 0 274 22 1 24 31 2 248 -32 3 238 -7	9 30° -35 10 85 -92 11 22° 13 12 25° 13 13 49 54 14 43 51	0 82 62 1 21° 13 2 24° -20 3 29 28 4 23° -10 5 22° 5	• 20 -1•
6 23° -15 7 82 -84 8 126 133 9 131 136 10 32 -35 11 43 -41	12 105 118 13 155 -164 14 49 43 15 94 94 16 28* -10 17 194 188	14 121 116 15 74 -67 16 95 83 17 97 98 18 40 39 19 89 81	17 32 -19 13 240 1 14 246 -18 15 220 13	H,6,3 1 260 -336 2 70 -150 3 38 -30	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	0 270 10 84 11 259 -3 12 260 -4 13 35 -3	1 6 57 51 3 7 79 72 4 8 47 -41 5 9 67 -68 1 10 32° 24 2 11 62 -61	6 37 33 7 89 89 8 59 64 9 73 -72 10 274 -4 11 91 61	4     27     -30       5     58     -53       6     79     82       7     75     -74       8     304     -8       9     66     -63	13 67 -89 H,8,8 0 29 -37 1 66 80	7 33 33 6 34 31 9 27• 12 10 27• 7 31 29 -45	

Tab	le	5.	Torsion	angles	in	procaine
~ ~ ~						P

Atoms involved	τ (°)	τ (°)*
(procaine HCl	Procaine	Phosphate
numbering)	HCl (DDD)	complex
O(2)-C(7)-O(1)-C(6)	1.0	2.8
C(7) = O(1) = C(6) = C(5)	173.3	178.8
O(1) - C(6) - C(5) - N(1)	70.1	61.6
C(6) - C(5) - N(1) - C(4)	69·0	92.2
C(6) - C(5) - N(1) - C(2)	-61.4	†
C(5) - N(1) - C(4) - C(3)	54.6	70·2
C(5) - N(1) - C(2) - C(1)	158-2	†
C(6)-C(5)-N(1)-H(21)	175.8	31.0

\* Calculated from the coordinates of Sax et al. (1970).

 $\dagger$  These angles involve the disordered part of the structure [See Fig. 1(b)] and were not calculated.

angles, while this difference is only  $2.5^{\circ}$  in the complex. In both structures, the benzene ring adopts a slight boat form; however, the deviations of C(8) and C(11) from the mean plane of the ring in the salt are twice those of their counterparts in the complex. The mean plane of the phenyl ring (0.1183X+0.6228Y-0.7394Z+2.4035=0) makes an angle of  $28^{\circ}$  with the plane of the *p*amino group (0.5672X+0.5904Y-0.5742Z+0.3296=0) and an angle of  $7.4^{\circ}$  with the plane of the carboxyl group (0.0655X+0.5746Y-0.8158Z+2.4946=0). For the phosphate complex, these angles are 1.6 and 2.8° respectively. (The coefficients in the mean plane equations are in Å and refer to an orthogonal set of axes where X lies along a, Y is in the (a, b), plane and Z lies along  $c^*$ .)

The author thanks Professor B. W. Low for her advice and encouragement in this work. Thanks also are due to Professor H. J. Mautner who supplied the crys-



Fig. 3. Stereodiagrams showing packing of proceine HCl.  $a \rightarrow , c^{\uparrow}$ , and b into the paper.

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# The Crystal and Molecular Structure of Serotonin Picrate Monohydrate

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## (Received 11 December 1970)

Red crystals of serotonin picrate monohydrate ( $C_{10}H_{13}N_2O$ .  $C_6H_2N_3O_7$ .  $H_2O$ ) are monoclinic, space group  $P_{2_1/c}$ , with a=14.172, b=6.908, c=18.749 Å, and  $\beta=101.65^{\circ}$ . Data were collected on an automated diffractometer; the structure was solved by the symbolic-addition procedure and was refined by block-diagonal least-squares methods to R = 0.073. The crystal structure features continuous columns of approximately parallel hydroxyindole and picrate moieties, intimately stacked with interplanar spacings of 3·3-3·4 Å. The stacking interaction appears to be of the donor-acceptor (chargetransfer) type. Bond lengths within the picrate ion are not significantly different from those found for other picrate salts. The serotonin cation assumes a conformation which is different from that found in the crystal structure of serotonin creatinine sulphate.

### Introduction

Serotonin (5-hydroxytryptamine) is an indolealkylamine found in all vertebrate and some invertebrate systems (Erspamer, 1961). Although the exact physiological functions of serotonin are unknown, there is evidence that the compound mediates a number of processes, including smooth muscle contraction (Erspamer, 1961) and synaptic transmission (Chase, Breese, Carpenter,

Schanberg & Kopin, 1968; Fuxe, Hökfelt & Ungerstedt, 1968; Bradley, 1968). In humans, serotonin affects the central nervous system, and abnormal metabolism of brain serotonin has been implicated in mental disorders (Woolley, 1962).

Little is known about the specific mechanisms by which serotonin affects biological systems; but it has been suggested that many of the physiological properties of the compound might be related to its propen-