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The Crystal Structure of a 1:1 Procaine–Bis-*p*-nitrophenyl Phosphate Complex

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The crystal structure of a 1:1 complex consisting of procaine and bis-*p*-nitrophenyl phosphate has been determined from three-dimensional X-ray diffraction data. The intensities were measured with a four-circle automated diffractometer with Cu $K\alpha$ radiation. The space group is $P2_1/c$; $Z=4$. The unit-cell dimensions are $a=15{\cdot}737$, $b=8{\cdot}866$, $c=21{\cdot}309$ Å, and $\beta=69{\cdot}11°$. The structure was solved by the direct method and with the aid of Fourier difference syntheses. It was refined by least-squares methods to an R index of 0·071 for 4679 reflections. The molecules in this complex are in ionized forms. The acidic proton is attached to the tertiary amine nitrogen atom in procaine. Hydrogen bonds, 2·954 and 3·022 Å, connect the *p*-amino nitrogen atom with the phospho oxygen atoms to form infinite spirals about the screw axes. A stronger hydrogen bond, 2·804 Å, between the protonated nitrogen and a phospho oxygen atom, crosslinks spirals of opposite senses. One of the methyl groups in procaine is disordered and is contiguous to a nitro group having abnormally large thermal factors. The respective torsion angles at the ester bond and in the O–C–C–N$^+$ moiety of procaine are 178·8 and 65·2° giving the expected *trans* and *gauche* conformations. The C–N bonds in the trialkylammonium group average 1·50 Å, exceeding the C–N single bond length by about 0·03 Å, which probably is associated with the larger coordination number of nitrogen. The *p*-aminobenzoate group shows the same small contribution of the quinoid structure that is observed in *p*-aminobenzoic acid.

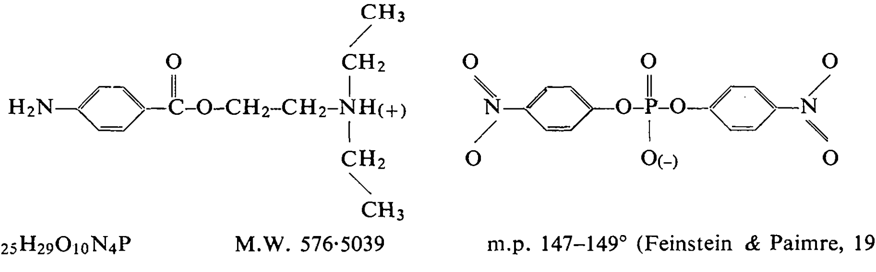
Introduction

Local anesthetics react specifically with the phosphodiester groups in acidic phospholipids, phosphoproteins, ribonucleic acid or synthetic phosphodiesters, but not with phosphomonoesters, pyrophosphates or triphosphates (Feinstein & Paimre, 1966). This affinity for acidic phospholipids, like the cephalins, is a basic factor in a proposed mechanism of local anesthetic action (Feinstein, 1964; Blaustein & Goldman, 1966). The nature of the bonds formed between the reactants in these complexes has been the subject of speculation. Both ionic and charge transfer interactions have been suggested. The crystal structure analysis of procaine–bis-*p*-nitrophenyl phosphate was determined in order to show in detail the nature of the intermolecular bonding in one of these complexes.

Experimental

Single crystals of the complex were prepared by the method of Feinstein & Paimre (1966). The space group was determined from Weissenberg photographs. Unit-cell dimensions were derived from measurements of axial reflections made on a Picker diffractometer equipped with a full circle crystal orienter. Cu $K\alpha$ radiation was used exclusively throughout the analysis. Table 1 contains the crystal data.

Table 1. *Crystal data for procaine–bis-p-nitrophenyl phosphate*



$C_{25}H_{29}O_{10}N_4P$ M.W. 576·5039 m.p. 147–149° (Feinstein & Paimre, 1966)

Monoclinic, space group $P2_1/c$, from systematic absences: $h0l$ absent for l odd, $0k0$ absent for k odd.

$Z=4$
$a=15.737\pm0{\cdot}004$ Å
$b=8{\cdot}866\pm0{\cdot}004$
$c=21{\cdot}309\pm0{\cdot}004$
$\beta=69{\cdot}11\pm0{\cdot}05°$

$V=2777.7$ Å^3
$\gamma(\mathrm{Cu}\ K\alpha)=1{\cdot}5418$ Å
$\gamma(K\alpha_1)=1{\cdot}5405$
$\gamma(K\alpha_2)=1{\cdot}5443$
$\mu(\mathrm{Cu}\ K\alpha=14{\cdot}22\ \mathrm{cm}^{-1}$

$D_m=1{\cdot}377$ g.cm^{-3} by flotation in a carbon tetrachloride–benzene mixture. $D_x=1{\cdot}378$ g.cm^{-3}

The intensity data were collected on a Picker four circle automated diffractometer which was operated in the θ:2θ scanning mode at a rate of 2°min^{-1} for one minute. Background counts were recorded for 15 seconds at both limits of the scan. Five reflections were chosen as standards, and at least a pair of these were monitored at intervals of approximately two hours. Intensity measurements that exceeded the linear counting range were remeasured with a direct beam of lower intensity. Scale factors for these data were determined by also measuring the five standards at the lower direct beam intensity. During the data collection, there was a gradual ten per cent decrease in the intensities of the standard reflections. This loss of intensity was later traced to a deterioration of the NaI crystal in the scintillation counter. Scale factors based on the five standards compensate to a large extent for the time dependent decrease. However, there may be some error in the data from this source, since the detector response was somewhat non-uniform across the counter window.

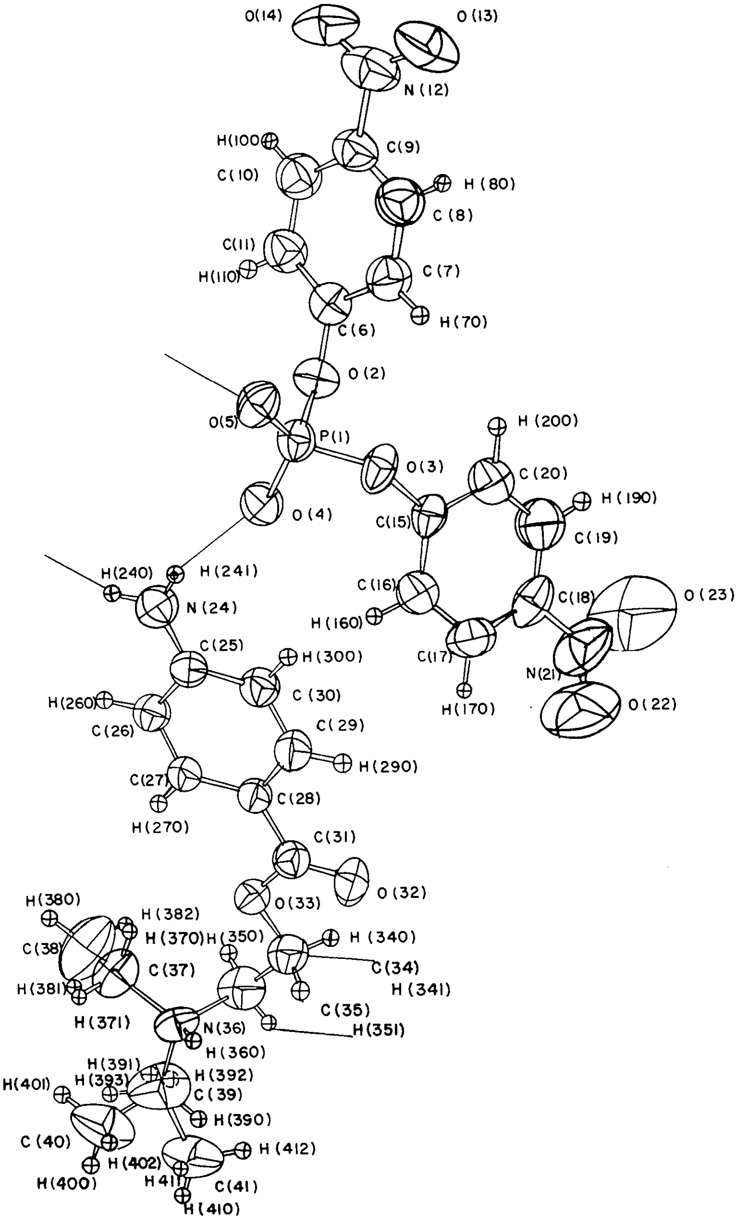


Fig. 1. The atomic numbering scheme. The shapes and relative magnitudes of the thermal ellipsoids at the 50 per cent probability level are shown for atoms other than hydrogen (Johnson, 1965). Atoms C(40) and C(41) represent a disordered methyl group. The two hydrogen positions H(390) and H(391) are associated with the C(40) methyl position while H(392) and H(393) are associated with the alternate methyl position, C(41).

A total of 4679 intensities were measured and 1123 of these were less than 3 σ over the background, where σ is given by

$$[I_o+4(I_{B1}+I_{B2})]^{1/2};$$

I_o is the integrated intensity and both I_{B1} and I_{B2} are background counts. Lorentz, polarization and absorption corrections were made. In calculating the latter correction, the crystal shape was approximated by eight bounding planes. The coefficients of the equations defining these planes are given in Table 2. The coordinates of the crystal corners and its volume are listed there also. The crystal was mounted with $-\mathbf{b}$ parallel to the φ axis.

Table 2. *The crystal faces and corners*

The x,y,z orthogonal axes are in the direction of $\mathbf{a}^*$, $-\mathbf{c}$, $\mathbf{b}^*$ respectively, and the unit is cm. Crystal volume $=1{\cdot}01\times10^{-5}$ cm^3. Crystal dimensions measured against an optical scale calibrated at 0·00095 cm per division.

Coefficients in $Ax+By+Cz-D=0$.

Table 2 (*cont.*)

Faces

A	*B*	*C*	*D*
−0·1845	−0·9828	−0·0000	−0·0180
−0·0776	−0·3800	0·9217	0·0245
0·9551	−0·0608	−0·2898	−0·0065
0·9829	−0·1839	0·0000	0·0035
0·0000	−0·0000	0·9999	−0·0342
0·9544	−0·2974	−0·0235	−0·0019
0·9775	0·2103	−0·0058	−0·0062
0·8593	−0·5112	−0·0071	0·0069

Corners

x	*y*	*z*
0·0046	0·0174	0·0341
0·0067	0·0170	0·0341
0·0042	0·0175	0·0326
0·0067	0·0170	−0·0342
0·0026	0·0178	−0·0342
−0·0020	−0·0172	0·0192
0·0014	−0·0114	0·0219
−0·0044	−0·0086	0·0094
−0·0024	−0·0179	0·0181
0·0016	−0·0103	−0·0342
−0·0050	−0·0070	−0·0342
−0·0027	−0·0177	−0·0342

Table 3. *Observed and calculated structure factors*

The columns within each group in order from left to right are: the running index l, $10F_o$ and $10F_c$. Starred reflections were assigned zero weight in the least-squares refinement, and their measured intensities were $\le 3\sigma$ over the background.

Table 3 (*cont.*)

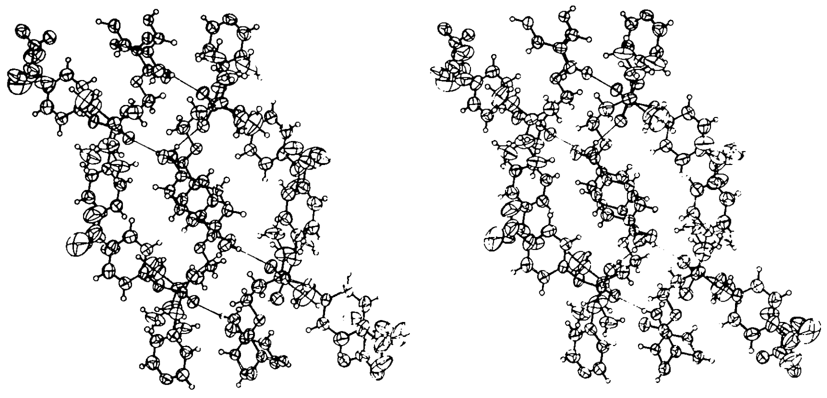
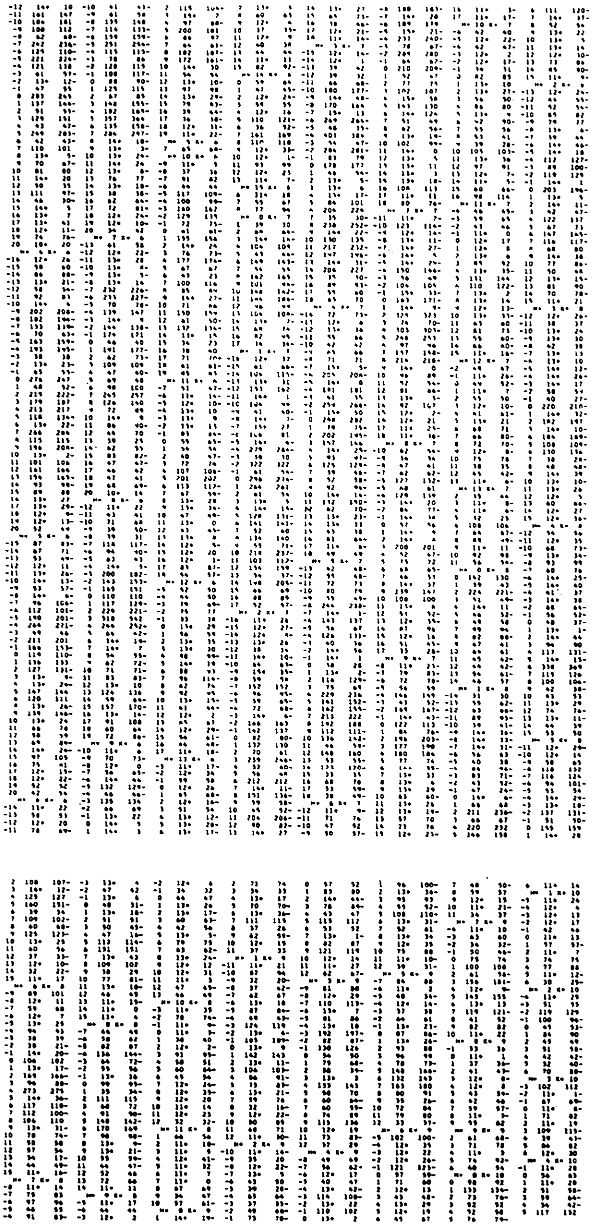


Fig. 2. A stereoscopic view of the unit cell down the *b* axis. The single lines connecting the anilino hydrogen to the phospho oxygen atoms denote the hydrogen bonds that form a spiral about a screw axis. The spirals are cross-linked by a hydrogen bond from the trialkyl ammonium group in the procaine chain to one of the oxygen atoms, O(5), of the phospho group.

Structure determination and refinement

After the observed structure factors were scaled and normalized to *E* values by means of a Wilson plot, the signs of 963 reflections were determined by Beurskens' (1963) method. The initial atomic coordinates were obtained from a Fourier synthesis calculated with these *E* factors. The structure was refined by full-matrix least-squares although no more than 175 parameters were varied in any given cycle. The Hughes (1941)

Table 3 (*cont.*)



weighting scheme was applied with $\sigma = F/8$ if $F > 8$ and with $\sigma = 1$ if $F \leq 8$. Unobserved reflections were assigned zero weight. The function minimized was $\Sigma w(F_o - KF_c)^2$ where K is a single scale factor. The atomic form factors were taken from *International Tables for X-ray Crystallography* (1962), except for the hydrogen scattering factors which are those of Stewart, Davidson & Simpson (1965). The final R index is 0·071 for the 4679 structure factors listed in Table 3. The atomic parameters are given in Tables 4 and 5 and Fig. 1 shows the molecular shape and the atomic numbering.

The computer programs used in this analysis are the Shiono (1965) and the Stewart (1964) versions of *ORFLS* (Busing, Martin & Levy, 1962), the Beurskens (1963) method for determining signs, a modification of the Zalkin Fourier Synthesis (Shiono, 1967), a program for the application of the Busing & Levy (1957) absorption correction procedure (Craven, 1963), a variety of programs included in *X-ray* 63 (Stewart *et al.*, 1964), and a number of those listed in the University of Pittsburgh, Crystallography Laboratory Technical Reports (Shiono, 1963–8).

The refinement was complicated by positional disorder in one of the methyl groups, C(40) and C(41), and by unreasonably large thermal parameters for the two oxygen atoms, O(22) andO (23), in the nitro group contiguous to the disordered methyl. Interestingly, the effect of the disorder could be recognized easily in the E map (Karle, Hauptman, Karle & Wing, 1958) from a comparison of the relative peak heights of chemically equivalent atoms. The peak heights at the alternate positions for the disordered methyl carbon atom, C(40) and C(41), were 6 and 7, compared with 16 for the ordered methyl carbon atom C(38). The disorder was confirmed by difference maps at various stages of the refinement. With the occupancy factors fixed at one half for C(40) and C(41), the least-squares refinement gave similar thermal factors for both half-atoms, and whenever the occupancy factors were allowed to vary during the refinement, the deviations from one half were not significant. Toward the end of the refinement we reconsidered an ordered structure with the methyl carbon restricted to the position of C(41), because of the chemically unreasonable C(39)–C(40) distance (Table 7). However, this model could not be refined to an R under 0·091 in comparison with 0·071 for the disordered model. Furthermore, the peak at C(40) reappeared in the difference Fourier synthesis. The ordered model was contraindicated clearly. Accordingly, it was eliminated from further consideration. Although two positions of nearly equal occupancy appeared in the Fourier syntheses for the disordered methyl carbon atom, only single maxima could be found for O(22) and O(23). These oxygen peaks were very diffuse, however, and extended over a large volume. Evidence for the high thermal factors was present also in the E map where the peak heights at O(13) and O(14) in the nitro group with normal thermal parameters were 28 and 25 respectively, while O(22) and O(23) had maxima of 10.

The coordinates of the hydrogen atoms that are bonded to carbon were calculated assuming trigonal hybridization in the aromatic ring and tetrahedral orbitals in the aliphatic chain. The C–H bond was assigned a length of 0·95 Å in both cases. Since the remaining three hydrogen atoms are on the amino groups and participate in intermolecular hydrogen bonds, which are of primary interest in this analysis, their coordinates were derived from the difference Fourier synthesis and were included in the refinement. The isotropic thermal parameters of the hydrogen atoms listed in Table 5 were assigned arbitrarily. For the most part they approximate the B factors computed in the last cycle of isotropic refinement ($R=0\cdot152$) for the atoms to which the hydrogen atoms are bonded. The hydrogen atoms attached to C(39) were disordered on two sites with occupancy factors of one half corresponding to the two orientations of the disordered methyl group. H(390) and H(391) are occupied simultaneously with C(40) while H(392) and H(393) coincide in occupancy with C(41). The hydrogen atoms on C(40) and C(41) were also given half weight.

Discussion of the structure

Some details of the structure appearing in Tables 5 to 8 inclusive deviate from normally expected values. For instance, extraordinarily large thermal factors are listed in Table 5 for O(22) and O(23). Also in the same Table the sequence of the β_{11} coefficients reported for N(36), C(39), C(40) or C(41) is abnormal in that an intermediate value is expected for C(39) rather than the largest magnitude. The realistic situation is observed in the ordered but chemically equivalent series, N(36), C(37) and C(38). The C(39)–C(40) and N(21)–O(22) bond lengths given in Table 7 are shorter than expected, while the intermolecular contacts recorded in Table 8 for C(40)–O(23), C(41)–O(22) and C(7)–O(23) are less than the van der Waals distances. All of these anomalies involve either the disordered methyl carbon atom or the contiguous nitro group.

The apparently unrealistic β_{11} for C(39) results from a slight disordering of this atom. The two slightly displaced positions for C(39) would correspond to the two alternative locations for the terminal methyl group; namely C(40) and C(41). In order to demonstrate this

Table 4. *Fractional atomic coordinates and their estimated standard deviations*

	Fractional coordinates $\times 10^4$		
	x	y	z
P(1)	−1932 (1)	1154 (1)	2765 (0·4)
O(2)	−2466 (2)	−0038 (3)	3335 (2)
O(3)	−2729 (2)	1879 (3)	2547 (2)
O(4)	−1306 (2)	0266 (3)	2216 (1)
O(5)	−1641 (2)	2455 (2)	3077 (1)
C(6)	−2931 (3)	0314 (5)	4000 (2)
C(7)	−3648 (4)	1337 (6)	4194 (3)
C(8)	−4105 (3)	1606 (5)	4867 (2)
C(9)	−3847 (2)	0864 (4)	5328 (2)
C(10)	−3149 (4)	−0173 (6)	5144 (3)
C(11)	−2686 (3)	−0455 (6)	4476 (2)
N(12)	−4334 (3)	1157 (5)	6049 (2)
O(13)	−5000 (3)	1966 (5)	6208 (2)
O(14)	−4040 (3)	0593 (6)	6455 (2)
C(15)	−3101 (2)	1146 (4)	2134 (2)
C(16)	−2653 (3)	1118 (4)	1452 (2)
C(17)	−3075 (4)	0449 (6)	1054 (2)
C(18)	−3938 (3)	−0186 (5)	1369 (2)
C(19)	−4366 (3)	−0154 (6)	2040 (3)
C(20)	−3956 (3)	0527 (6)	2422 (2)
N(21)	−4373 (4)	−0949 (7)	0949 (3)
O(22)	−4060 (5)	−0933 (9)	0375 (3)
O(23)	−5098 (5)	−1529 (11)	1233 (3)
N(24)	−0310 (3)	3653 (5)	3685 (2)
C(25)	−0218 (3)	3115 (5)	4264 (2)
C(26)	−0851 (3)	2115 (6)	4696 (2)
C(27)	−0756 (3)	1617 (5)	5276 (2)
C(28)	−0018 (3)	2101 (5)	5452 (2)
C(29)	0619 (3)	3067 (6)	5015 (2)
C(30)	0523 (3)	3564 (6)	4429 (3)
C(31)	0110 (2)	1635 (4)	6070 (2)
O(32)	0726 (2)	2060 (4)	6242 (1)
O(33)	−0521 (2)	0634 (3)	6451 (1)
C(34)	−0354 (3)	0105 (5)	7038 (2)
C(35)	−1072 (3)	−1017 (5)	7416 (2)
N(36)	−2002 (2)	−0351 (3)	7705 (1)
C(37)	−2504 (3)	−0332 (5)	7229 (2)
C(38)	−2766 (6)	−1897 (6)	7066 (4)
C(39)	−2539 (5)	−1102 (5)	8367 (2)
C(40)	−3391 (9)	−0542 (14)	8690 (6)
C(41)	−2432 (8)	−0475 (11)	8984 (4)

	Fractional coordinates $\times 10^3$		
	x	y	z
H(70)	−382	185	387
H(80)	−460	230	501
H(100)	−299	−069	548
H(110)	−220	−117	434
H(160)	−206	155	126
H(170)	−279	042	058
H(190)	−495	−060	224
H(200)	−426	058	290
H(240)	−074 (3)	343 (4)	357 (2)
H(241)	004 (3)	425 (4)	339 (2)
H(260)	−135	178	458
H(270)	−119	094	556
H(290)	113	339	512
H(300)	097	422	414
H(340)	023	−036	690
H(341)	−037	094	732
H(350)	−108	−180	712
H(351)	−092	−142	777
H(360)	−186 (2)	070 (4)	780 (2)
H(370)	−213	013	682
H(371)	−304	024	742
H(380)	−308	−189	676
H(381)	−314	−236	747
H(382)	−223	−247	687
H(390)	−221	−099	866
H(391)	−260	−214	828
H(392)	−236	−213	833
H(393)	−317	−104	843
H(400)	−373	−101	910
H(401)	−373	−065	840
H(402)	−334	050	878
H(410)	−277	−095	940
H(411)	−261	056	902
H(412)	−181	−054	893

point, C(39) was replaced by two half-weight carbon atoms, C(39*A*) and C(39*B*). The 'half' atoms were initially assigned the same coordinates and thermal parameters as C(39) except that β_{11} was set equal to 88×10^{-4}. This value seemed plausible since it was selected by comparing corresponding thermal parameters in the ordered and disordered ethyl groups. The coordinates of the half atoms were refined in three cycles of least-squares with fixed temperature factors. As expected, C(39*A*) shifted 0·215 Å away from the original position and C(39*B*) moved 0·194 Å in the opposite direction. The respective *xyz* coordinates of C(39*A*) are −0·2666, −0·1102, and 0·8367, while for C(39*B*) the corresponding values are −0·2421, −0·1144, and 0·8371. With C(39) disordered in this way the bond lengths in the ethyl group in one orientation are 1·510 Å for N(36)–C(39*B*) and 1·529 Å for C(39*B*)–C(40), while the N(36)–C(39*B*)–C(40) valency angle is 106·6°. In the second orientation of the ethyl group N(36)–C(39*A*) and C(39*A*)–C(41) equal 1·538 and 1·572 Å respectively, while N(36)–C(39*A*)–C(41) is 111·1°. These bond lengths and angles agree much better with normally observed values than do the corresponding ones listed in Tables 6 and 7. Although the *R* index of 0·075 is somewhat higher for this model, the more reasonable parameters give credence to our interpretation of the anomalous β_{11} magnitude for C(39) and the short C(39)–C(40) bond. The same explanation can be offered for the excessive thermal factors on O(22) and O(23), namely that the large β's compensate for the synchronous shift of these atoms to accommodate the two alternative disordered positions of the terminal methyl group, C(40) and C(41). Since the alternate positions for O(22) and O(23) are undetermined, our model gives only the average of these positions which could account for the short contacts involving them.

The molecules in this complex are in ionized forms. Procaine possesses a positively charged trialkyl ammonium group, and bis-*p*-nitrophenylphosphate has a negatively charged phospho group. Besides the ionic

Table 5. *Anisotropic thermal parameters*

Estimated standard deviations ($\times 10^4$) in the form:
$\exp\left[-(h^2\beta_{11}+\ldots+2kl\beta_{23})\right]$.

	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
P(1)	38 (< 1)	102 (1)	24 (< 1)	4 (1)	−13 (4)	−4 (< 1)
(O2)	64 (2)	85 (3)	25 (1)	−1 (2)	−9 (1)	−2 (1)
O(3)	52 (2)	108 (4)	34 (1)	14 (2)	−25 (1)	−11 (2)
O(4)	51 (1)	189 (4)	30 (1)	31 (2)	−12 (1)	−19 (1)
O(5)	58 (1)	120 (3)	32 (1)	−15 (2)	−23 (1)	−3 (1)
C(6)	46 (2)	98 (5)	27 (1)	−5 (3)	−9 (1)	−1 (2)
C(7)	64 (3)	166 (7)	31 (1)	34 (4)	−18 (2)	−4 (3)
C(8)	61 (2)	179 (6)	36 (1)	30 (3)	−11 (1)	−7 (2)
C(9)	52 (2)	173 (6)	25 (1)	15 (3)	−5 (1)	1 (2)
C(10)	54 (3)	178 (8)	32 (1)	5 (4)	−13 (2)	13 (3)
C(11)	50 (2)	143 (6)	31 (1)	9 (3)	−11 (1)	6 (2)
N(12)	72 (2)	228 (7)	33 (1)	−20 (3)	−1 (1)	0 (2)
O(13)	92 (3)	329 (8)	41 (1)	34 (4)	6 (1)	−14 (3)
O(14)	114 (3)	395 (10)	29 (1)	2 (5)	−15 (1)	12 (3)
C(15)	42 (1)	107 (4)	28 (1)	5 (2)	−16 (1)	0 (2)
C(16)	49 (2)	157 (5)	29 (1)	−5 (3)	−12 (1)	2 (2)
C(17)	77 (3)	216 (7)	27 (1)	14 (4)	−18 (1)	−2 (2)
C(18)	70 (2)	177 (6)	43 (1)	−16 (3)	−34 (2)	−5 (2)
C(19)	60 (2)	284 (9)	42 (1)	−45 (4)	−22 (2)	−5 (3)
C(20)	49 (2)	237 (7)	32 (1)	−25 (3)	−11 (1)	7 (2)
N(21)	126 (4)	340 (11)	58 (2)	−48 (6)	−54 (2)	−4 (4)
O(22)	183 (5)	670 (18)	48 (2)	−82 (8)	−49 (3)	−46 (4)
O(23)	218 (6)	993 (30)	98 (3)	−338 (13)	−75 (4)	3 (7)
N(24)	60 (2)	185 (7)	27 (1)	−17 (3)	−17 (1)	5 (2)
C(25)	42 (2)	131 (5)	22 (1)	5 (3)	−10 (1)	10 (2)
C(26)	41 (2)	156 (6)	25 (1)	−16 (3)	−12 (1)	−7 (2)
C(27)	37 (2)	155 (6)	23 (1)	−4 (3)	−11 (1)	−8 (2)
C(28)	37 (2)	147 (6)	23 (1)	9 (3)	−10 (1)	−15 (2)
C(29)	41 (2)	169 (7)	32 (1)	−4 (3)	−16 (1)	−7 (2)
C(30)	47 (2)	155 (7)	30 (1)	−15 (3)	−12 (1)	−6 (3)
C(31)	39 (1)	173 (5)	27 (1)	20 (2)	−15 (1)	−17 (2)
O(32)	48 (1)	270 (5)	36 (1)	4 (2)	−23 (1)	−9 (2)
O(33)	48 (1)	184 (4)	23 (1)	10 (2)	−16 (1)	−5 (1)
C(34)	58 (2)	224 (7)	28 (1)	40 (3)	−19 (1)	−6 (2)
C(35)	80 (3)	163 (6)	34 (1)	45 (3)	−22 (2)	5 (2)
N(36)	66 (2)	112 (4)	25 (1)	3 (2)	−17 (1)	5 (1)
C(37)	80 (3)	127 (5)	41 (1)	4 (3)	−32 (2)	3 (2)
C(38)	154 (5)	164 (8)	79 (3)	−19 (5)	−75 (3)	−11 (4)
C(39)	136 (5)	159 (6)	37 (1)	−38 (4)	−24 (2)	30 (2)
C(40)	106 (8)	258 (14)	41 (3)	−25 (11)	7 (4)	−3 (7)
C(41)	109 (7)	217 (15)	25 (2)	18 (9)	−2 (3)	10 (5)

	B
H(70)	4·8
H(80)	5·4
H(100)	5·3
H(110)	4·5
H(160)	5·1
H(170)	5·0
H(190)	6·8
H(200)	5·7
H(240)	4·7
H(241)	4·7
H(260)	3·6
H(270)	3·9
H(290)	4·3
H(300)	4·6
H(340)	4·7
H(341)	4·7
H(350)	5·3
H(351)	5·3
H(360)	4·3
H(370)	5·1
H(371)	5·1
H(380)	8·0
H(381)	8·0
H(382)	8·0
H(390)	5·5
H(391)	5·5
H(392)	5·5
H(393)	5·5
H(400)	5·0
H(401)	5·0
H(402)	5·0
H(410)	5·0
H(411)	5·0
H(412)	5·0

Table 6. *Bond angles and estimated standard deviations*

i	*j*	*k*	Angle (*ijk*)
O(2)	P(1)	O(3)	103·3 (2)°
O(2)	P(1)	O(4)	105·9 (2)
O(2)	P(1)	O(5)	109·5 (2)
O(3)	P(1)	O(4)	110·8 (2)
O(3)	P(1)	O(5)	102·4 (2)
O(4)	P(1)	O(5)	123·3 (2)
P(1)	O(2)	C(6)	125·0 (3)
P(1)	O(3)	C(15)	122·9 (2)
O(2)	C(6)	C(7)	122·0 (5)
O(2)	C(6)	C(11)	117·2 (4)
C(7)	C(6)	C(11)	120·7 (4)
C(6)	C(7)	C(8)	119·3 (5)
C(7)	C(8)	C(9)	119·3 (4)
C(8)	C(9)	C(10)	122·1 (4)
C(8)	C(9)	N(12)	119·4 (4)
C(10)	C(9)	N(12)	118·5 (4)
C(9)	C(10)	C(11)	119·3 (5)
C(6)	C(11)	C(10)	119·2 (5)
C(9)	N(12)	O(13)	118·1 (5)
C(9)	N(12)	O(14)	118·5 (4)
O(13)	N(12)	O(14)	123·4 (4)
O(3)	C(15)	C(16)	120·5 (3)
O(3)	C(15)	C(20)	118·2 (3)
C(16)	C(15)	C(20)	121·2 (4)
C(15)	C(16)	C(17)	118·6 (4)
C(16)	C(17)	C(18)	118·3 (4)
C(17)	C(18)	C(19)	122·2 (5)
C(17)	C(18)	N(21)	118·4 (4)
C(19)	C(18)	N(21)	119·3 (4)
C(18)	C(19)	C(20)	119·0 (4)
C(15)	C(20)	C(19)	120·7 (4)
C(18)	N(21)	O(22)	121·9 (6)°
C(18)	N(21)	O(23)	117·1 (6)
O(22)	N(21)	O(23)	120·9 (8)
C(25)	N(24)	H(240)	123 (3)
C(25)	N(24)	H(241)	128 (3)
H(240)	N(24)	H(241)	109 (4)
N(24)	C(25)	C(26)	122·0 (5)
N(24)	C(25)	C(30)	119·5 (4)
C(26)	C(25)	C(30)	118·5 (5)
C(25)	C(26)	C(27)	121·1 (5)
C(26)	C(27)	C(28)	120·5 (4)
C(27)	C(28)	C(29)	118·3 (4)
C(27)	C(28)	C(31)	123·1 (3)
C(29)	C(28)	C(31)	118·7 (4)
C(28)	C(29)	C(30)	121·1 (5)
C(25)	C(30)	C(29)	120·6 (4)
C(28)	C(31)	O(32)	124·6 (3
C(28)	C(31)	O(33)	114·5 (3)
O(32)	C(31)	O(33)	120·9 (4)
C(31)	O(33)	C(34)	114·0 (3)
O(33)	C(34)	C(35)	110·0 (4)
C(34)	C(35)	N(36)	113·5 (4)
C(35)	N(36)	C(37)	113·7 (3)
C(35)	N(36)	C(39)	110·5 (4)
C(35)	N(36)	H(360)	101 (2)
C(37)	N(36)	C(39)	112·6 (4)
C(37)	N(36)	H(360)	110 (2)
C(39)	N(36)	H(360)	108 (2)
N(36)	C(37)	C(38)	113·4 (5)
N(36)	C(39)	C(40)	115·6 (7)
N(36)	C(39)	C(41)	117·1 (5)
C(40)	C(39)	C(41)	79·6 (8)

Table 7. *Bond lengths and standard deviations*

P(1)	O(2)	1·603 (3) Å
P(1)	O(3)	1·616 (4)
P(1)	O(4)	1·462 (3)
P(1)	O(5)	1·484 (3)
O(2)	C(6)	1·378 (5)
O(3)	C(15)	1·381 (5)
C(6)	C(7)	1·390 (7)
C(6)	C(11)	1·387 (8)
C(7)	C(8)	1·377 (6)
C(8)	C(9)	1·358 (7)
C(9)	C(10)	1·379 (7)
C(9)	N(12)	1·475 (5)
C(10)	C(11)	1·371 (7)
N(12)	O(13)	1·214 (7)
N(12)	O(14)	1·224 (7)
C(15)	C(16)	1·370 (5)
C(15)	C(20)	1·377 (5)
C(16)	C(17)	1·384 (7)
C(17)	C(18)	1·400 (7)
C(18)	C(19)	1·345 (7)
C(18)	N(21)	1·471 (9)
C(19)	C(20)	1·350 (8)
N(21)	O(22)	1·145 (8)
N(21)	O(23)	1·199 (10)
N(24)	C(25)	1·377 (7)
C(25)	C(26)	1·404 (6)
C(25)	C(30)	1·390 (8)
C(26)	C(27)	1·369 (7)
C(27)	C(28)	1·410 (7)
C(28)	C(29)	1·393 (6)
C(28)	C(31)	1·461 (6)
C(29)	C(30)	1·381 (8)
C(31)	O(32)	1·212 (5)

Table 7 (*cont.*)

C(31)	O(33)	1·364 (4)
O(33)	C(34)	1·447 (5)
C(34)	C(35)	1·505 (6)
C(35)	N(36)	1·492 (6)
N(36)	C(37)	1·492 (7)
N(36)	C(39)	1·515 (5)
C(37)	C(38)	1·522 (8)
C(39)	C(40)	1·364 (14)
C(39)	C(41)	1·492 (12)
All C–H distances have been calculated to 0·95 Å.		
N(24)	H(240)	0·83 (5)
N(24)	H(241)	0·85 (3)
N(36)	H(360)	1·00 (4)

Table 8. *Some intermolecular and non-bonded intramolecular distances and angles*

Atoms	Distance (*ij*)	Angle (*ijk*)
In the hydrogen bonds		
H(241)···O(4)P(1)	2·15 Å	158°
O(4)·····H(241)N(24)		157
H(240)···O(5)P(1)	2·21	150
O(5)·····H(240)N(24)		165
H(360)···O(5)P(1)	1·81	115
O(5)·····H(360)N(36)		173
N(24)····O(4)P(1)	2·954	164
N(24)····O(5)P(1)	3·022	146·9
N(36)····O(5)P(1)	2·804	117·3
N(24)···O(5)···N(36)		92·3
H(240)···O(5)···H(360)		92

Table 8 (*cont.*)

In the trialkylammonium ester chain		
O(33)····N(36)	2·983	
O(33)····C(37)	3·086	
O(33)····H(370)	2·41*	
H(360)···H(341)	2·21*	
H(350)···H(382)	2·13*	
H(371)···H(401)	2·13*	
H(381)···H(391)	2·19*	
H(351)···H(390)	2·26*	
H(351)···H(392)	2·25*	
In non-hydrogen-bonded intermolecular contacts		Symmetry operations applied to the second atom
O(23)····C(40)	2·962	$(\bar{1}, \bar{1}01)$
O(23)····C(7)	3·095	$(2_1, \bar{1}\bar{1}0)$
O(23)····H(70)	2·30*	$(2_1, \bar{1}\bar{1}0)$
O(22)····C(41)	3·177	$(1, 00\bar{1})$
O(5)·····C(34)	3·238	$(c, 00\bar{1})$
O(5)·····C(41)	3·277	$(c\ \ 00\bar{1})$
O(3)·····C(37)	3·128	$(c, 00\bar{1})$
C(11)····O(32)	3·242	$(\bar{1}, 00\bar{1})$
H(110)···O(32)	2·35*	$(\bar{1}, 00\bar{1})$
O(4)·····C(35)	3·359	$(c, 0\bar{1}\bar{1})$
O(2)·····C(39)	3·429	$(c, 0\bar{1}\bar{1})$

* Interatomic distances based on at least one hydrogen position for which the coordinates were calculated (not experimentally determined).

interaction, there is hydrogen bonding between these groups. Indeed, both nitrogen atoms in procaine function as donors in hydrogen bonds to the phosphate oxygen atoms. The molecular packing arrangement and the hydrogen bonding system can be seen in the stereographic plot (Fig. 2) and the disposition relative to the crystallographic axes is shown in Fig. 3. The procaine molecules lie in a column parallel to the *b* axis with adjacent molecules in the array related centrosymmetrically and thereby oriented in opposite directions. Those procaine benzene rings related by the symmetry center at $(0,0,\frac{1}{2})$ lie in planes which are 3·39 Å apart, whereas the interplanar distance between those related by the center at $(0,\frac{1}{2},\frac{1}{2})$ is 3·54 Å. Atoms H(240) and H(241) on the anilino nitrogen, N(24), are hydrogen bonded to O(5) and O(4) respectively, while H(360) on the trialkylammonium nitrogen atom, N(36), is hydrogen bonded to O(5). The N(24)···O(4) and O(5)···N(24) hydrogen bonds form an infinite spiral around one of the screw axes, which is crosslinked to another spiral of the opposite sense by N(36)···O(5). The *p*-nitrophenyl groups extend away from the spiral axis and are oriented such that nitro groups on C(18) and C(9) in glide related molecules almost overlap when viewed along the *b* axis as in Figs. 2 and 3. The evidence for

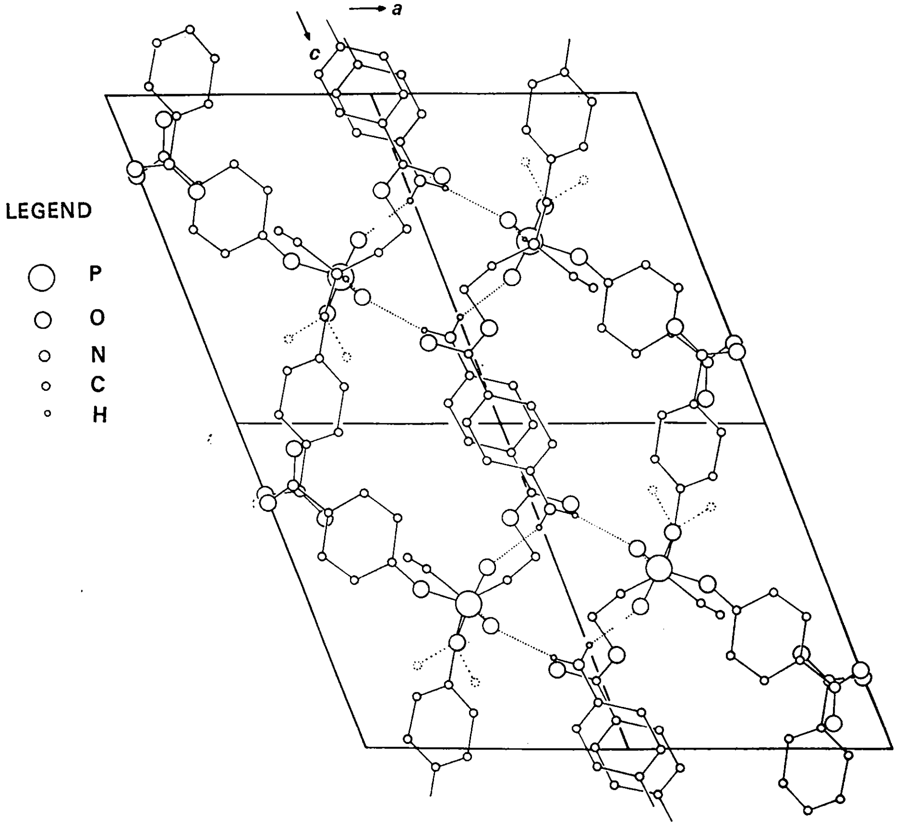


Fig. 3. The molecular packing. The two sites for the disordered methyl group, C(40) and C(41), are indicated by dotted circles, as are the bonds to C(39). Also the hydrogen bonds are dotted in. The conformation at N(36) accommodates the strong N(36) H(360)···O(5) hydrogen bond.

ionic and hydrogen bonding in the complex is easily discernible in the molecular packing arrangement and in the intermolecular contacts (Table 8). Furthermore, the disposition of the molecules is clearly inconsistent with the idea that there is bonding by charge transfer between procaine and the phosphodiester.

The conformational details of the molecules are described below, but the overall molecular shapes are indicated in the Figures. Equations of some planes of atoms and pertinent dihedral angles between them are given in Table 9. In bis-*p*-nitrophenyl phosphate the N(12)O(13)O(14) nitrogroup is rotated 6·9° about the N(12)–C(9) bond from coplanarity with the phenyl ring C(6)–C(11), whereas the nitro group N(21)O(22) O(23) is turned 4·0°out of the plane of the other phenyl ring. Atoms P(1)O(2)C(6) and the phenyl ring C(6)–C(11) lie in planes that intersect at 57·3° while P(1)O(2)C(6) and C(15)–C(20) make an angle of 77·3°. Bonds O(2)–C(6) and O(4)–P(1) intersect in an angle of 161·3° when viewed along P(1)O(2), while the corresponding angle between O(5)P(1) and O(3)C(15) as viewed along P(1)O(3) is 168·8°. The intersection angle between the planes of the phenyl rings in this molecule is 71·6°. In procaine the segment of aliphatic chain from O(33) to N(36) resembles in its conformation a number of other biological compounds containing this moiety (Pauling, 1968; Sundaralingam, 1968). The torsion angle at O(33)C(34) is 178·8° which corresponds to the *trans* conformation and the one commonly observed in esters (Mathieson, 1965). At C(34)C(35) the conformation is *gauche* as the torsional angle equals 65·2°. Evidently the orientation of the N(36)–H(360) bond in the direction of O(5) to form the hydrogen bond (Fig. 2 and Table 8) is an important factor in determining the conformation in this part of the molecule. From a CPK* model of the procaine molecule, it is obvious that the steric requirements of the hydrogen atoms in the trialkyl ammonium group also impose conformational restrictions on this moiety. In the observed structure when the methyl group occupies C(40) the intramolecular distances H(371)···H(401) and H(381)···H(391) are somewhat close. Occupancy of C(41) by the methyl group leads to a close contact between H(351) and H(392). These close approaches are listed in Table 8 along with others that occur in the chain. Although these have been calculated with assumed hydrogen atom parameters, the close distances can be seen also in the CPK models. In the *p*-aminobenzoate part of the molecule the *p*-amino and carboxyl groups are rotated by 1·8° and 2·5° from the planar arrangement, putting O(32) and H(241) on a common side of the benzene ring. However, these rotations are small enough for 12 atoms [C(34), C(35) and the non-hydrogen atoms in the *p*-aminobenzoate moiety] to attain an almost planar conformation (Fig. 1). The least-squares plane through these atoms passes between H(340) and H(341) (Table 9).

The mean P–O bond length and average OPO valence angle are 1·541 Å and 109·2°. The C–O phenolic ester bonds and the POC angles average 1·380 Å and 124·0°. In the trialkylammonium group, the mean C–N bond length, 1·50 Å, exceeds the commonly observed C–N single bond distance, 1·47 Å, which may be associated with the increased coordination number of nitrogen on protonation. The CNC angles in this group average 112·3°. The C–N bonds between the rings and the nitro groups give no indication of conjugation and they

Table 9. *Some least-squares planes through groups of atoms in the procaine–bis-p-nitrophenyl phosphate (1:1) complex*

Coefficients × 10^4 in $AX+BY+CZ-D=0$ referred to the crystallographic axes (X,Y,Z in Å).

Plane*	No.	A	B	C	D
Benzene ring in procaine	1	−3805	7824	3249	52325
Benzene ring C(6) to C(11)	2	−6808	7321	2202	−10686
Benzene ring C(15) to C(20)	3	−4793	8738	−2475	21051
p-Aminobenzoate group + C(24), C(25)	4	−4053	7623	3270	52226
Carboxyl group + C(28), C(34), C(35)	5	−4259	7457	3269	52237
O(33), C(34), N(36), C(37)	6	−789	9539	2425	38575
N(24), C(25), H(240), H(241)	7	−3567	7849	3463	54359

Plane No.	Displacements from the plane (Å × 10^3)
1	C(25) 11, C(26) −5, C(27) −6, C(28) 10, C(29) −4, C(30) −7, N(24) 39, C(31) 38.
2	C(6) 8, C(7) −5, C(8) −3, C(9) 7, C(10) −3, C(11) −4, O(2) −33, N(12) 14, O(13) −100, O(14) 154.
3	C(15) −4, C(16) −4, C(17) 7, C(18) −1, C(19) −7, C(20) 9, O(3) 66, N(21) −43, O(21) 36, O(23) −95.
4	N(24) 12, C(25) −7, C(26) 22, C(27) 29, C(28) 8, C(29) −50, C(30) −62, C(31) 42, O(32) 56, O(33) 33, C(34) −22, C(35) −29, H(341) 277, H(340) −804.
5	C(28) −25, C(31) 12, O(32) 0, O(33) 39, C(34) −14, C(35) −11, H(341) 249, H(340) −809.
6	C(34) −87, N(36) 101, O(33) 77, C(37) −91.

* Hydrogen atoms were excluded from the least-squares calculations of all planes excepting No. 7.

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* CPK atomic models by Ealing Corporation. CPK is an Ealing trademark.

average 1·473 Å. The dimensions in the *p*-aminobenzoate group agree well with those reported for *p*-aminobenzoic acid by Lai & Marsh (1967), showing the same small but significant contribution of the quinoid structure. The average value of the central bond distance in the benzene ring, 1·375 Å, and the mean of the remaining ring C–C distances, 1·399 Å, are the same in both crystal structures, while the exocyclic bonds, C(28)–C(31) and N(24)–C(25) in procaine for example, are shorter than single bonds in both molecules. The small quinoidal character shows up in the valency angles within the ring, where the two angles at the carbon atoms defining the *para* positions average 118·4° compared with a mean value of 120·8° for the other four endocyclic angles. In the free acid the corresponding values are 118·8 and 120·6°. Significant differences in the dimensions of the ester and the free acid occur in the carboxylate group where the carbonyl bond is 0·03 Å shorter and the C–O bond is 0·06 Å longer in the ester. As the carboxyl group in the crystal structure of *p*-aminobenzoic acid is involved in hydrogen bonds but the one in procaine is not, the different carboxyl group dimensions in the two structures may be due largely to the combined effects of resonance and hydrogen bonding (Craven, Cusatis, Gartland & Vizzini, 1968). There are two molecules in the asymmetric unit of the *p*-aminobenzoic acid crystal structure, and in both of these the configuration of the *p*-amino group is between tetrahedral and planar in contrast to the ester where it is planar. The hydrogen bonding environment is different at each of these *p*-amino groups. A single strong N–H···O bond spanning an N···O distance of 2·985 Å occurs at the *p*-amino group in one of the acid molecules, while only a very weak N–H···O bond (3·35 Å) is formed at the same group in the other acid molecule. In contrast both hydrogen atoms in the *p*-amino group of procaine are engaged in strong hydrogen bonds (Table 8).

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