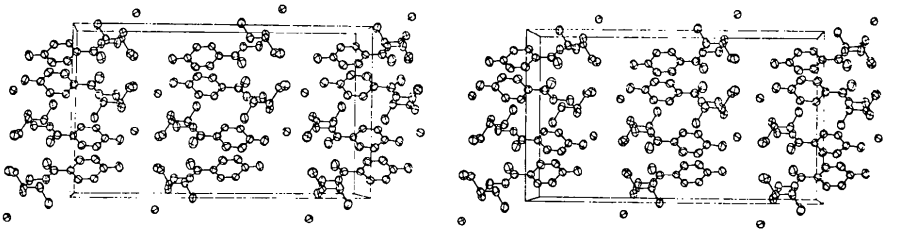

Fig. 3. Stereodiagrams showing packing of procaine HCl. $a\rightarrow$, $c\uparrow$, and b into the paper.

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The Crystal and Molecular Structure of Serotonin Picrate Monohydrate

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Red crystals of serotonin picrate monohydrate ($C_{10}H_{13}N_2O.C_6H_2N_3O_7.H_2O$) are monoclinic, space group $P2_1/c$, with $a=14{\cdot}172$, $b=6{\cdot}908$, $c=18{\cdot}749$ Å, and $\beta=101{\cdot}65°$. 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 $R=0{\cdot}073$. 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 (charge-transfer) 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-

sity for forming donor–acceptor (charge-transfer) complexes with biological electron acceptors (Szent-Györgyi, 1960, 1961; Green, 1966). Several studies have demonstrated that serotonin, as well as a variety of related indoles, form donor-acceptor complexes with aromatic acceptors (Wilson, 1966; Shifrin, 1968; Deranleau & Schwyzer, 1970; Foster & Hanson, 1964; Shifrin, 1969; Isenberg, Szent-Györgyi & Baird, 1960; Isenberg & Szent-Györgyi, 1958; Alivisatos, Ungar, Jibril & Mourkides, 1961; Cilento & Giusti, 1959; Cilento & Tedeschi, 1961).

Serotonin can be crystallized as a red picric acid salt (Rapport, 1949). Since serotonin is colorless and the picrate ion is pale yellow, the red color of the picrate salt is unexpected and suggests the formation of a donor–acceptor complex. We have determined the crystal structure of serotonin picrate monohydrate in order to examine the solid-state interactions between serotonin and the picrate ion. The structural formula is shown in Fig. 1.

A preliminary report of this work has been published (Bugg & Thewalt, 1970); we report here details of the crystallographic analysis.

Experimental

Serotonin picrate monohydrate was crystallized as large red prisms by slowly cooling a hot, saturated aqueous solution containing approximately equimolar quantities of serotonin creatinine sulphate and picric acid. Weissenberg and oscillation photographs showed the Laue symmetry to be $2/m$ (C_{2h}). The space group is $P2_1/c$ as indicated by the systematic absence of reflections $0k0$ with k odd and $h0l$ with l odd. A prism of approximate dimensions $0{\cdot}30 \times 0{\cdot}25 \times 0{\cdot}12$ mm was mounted on a Picker FACS-1 diffractometer with the b axis parallel to the φ axis of the diffractometer. The 2θ values for a number of high-angle (Cu $K\alpha_1$, $\lambda =$ 1·54051 Å) reflections were measured, and unit-cell parameters were obtained from a least-squares analysis of these measurements. Crystal data are listed in Table 1.

Intensity data were collected with the diffractometer, using a scintillation counter, nickel-filtered copper radiation, and a θ–2θ scanning technique. A scanning speed of 2°/min was employed, and a 10 sec background measurement was performed at each end of the scans. Measurements were made for the 2966 independent reflections in the range $4° \le 2\theta \le 128°$, representing about 72% of the unique reflections in the copper sphere.

Table 1. *Crystal data*

Stoichiometry	$C_{10}H_{13}N_2O.C_6H_2N_3O_7.H_2O$
Z	4
Space group	$P2_1/c$
a	14·172 (3) Å
b	6·908 (2)
c	18·749 (3)
β	101·65 (2)°
Cell volume	1797·7 Å
ϱ (calculated)	1·56 g.cm^{-3}
ϱ (observed)	1·55
μ	11·3 cm^{-1}

Unit-cell parameters were measured at 25 ± 2°C. Reported standard deviations are ten times those obtained from the least-squares analysis.

Intensity values were assigned variances, $\sigma^2(I)$, according to the statistics of the scan and background counts plus an additional term $(0{\cdot}03s)^2$, s being the scan counts. Intensities and their estimated standard deviations were corrected for Lorentz and polarization factors, but no correction for absorption effects was applied. Structure factors were placed on an approximately absolute scale by means of a K curve (Karle & Hauptman, 1953), and normalized structure-factor magnitudes ($|E|$) were derived. The statistical distribution of the $|E|$ values, along with theoretical values for centrosymmetric space groups given in parentheses, are: $\langle|E|\rangle = 0{\cdot}81$ (0·798), $\langle|E^2|\rangle = 1{\cdot}00$ (1·000), $\langle|E^2-1|\rangle =$ 0·96 (0·968).

After data collection, we discovered that the incident beam collimator on the diffractometer was slightly misaligned, causing the sample to be positioned on the edge of the incident beam, instead of in the center where the beam is uniform. This misalignment apparently had little or no effect on data obtained from small crystals (maximum dimensions less than 0·15 mm) which were completely immersed in the uniform central region of the beam. Since a small crystal was used to initially calibrate, align, and check the precision of the diffractometer, the misalignment went unnoticed until we had collected several sets of data from large samples. In fact, the misalignment was noticed only when it became apparent that data from small crystals refined extremely well, whereas data from large crystals did not refine appropriately. The exact nature of the misalignment was finally determined by taking a direct X-ray photograph of the central beam while a highly absorbing sample was aligned on the diffractometer; in the photograph the shadow of the sample was situated on the edge of the beam image.

It is likely that the misalignment of the diffractometer caused small errors in the intensity measurements. This problem was not discovered until after the structure analysis was completed; since the final results of the

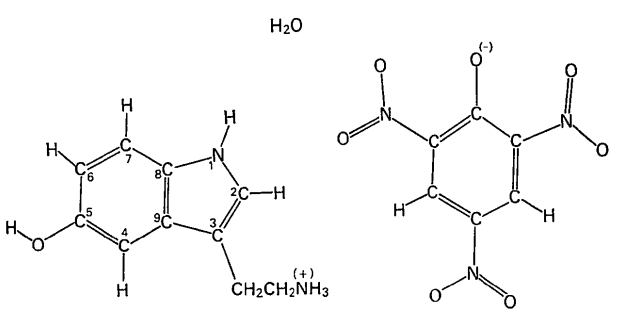


Fig. 1. Structural formula of serotonin picrate monohydrate.

refinement (reasonable bond lengths and angles, adequate R indices, and ability to locate and refine hydrogen atom positions) were satisfactory, we did not feel it necessary to recollect the data.

Determination of the structure

A suitable trial structure was obtained by the symbolic-addition procedure (Zachariasen, 1952; Karle & Karle 1963), using a Fortran program (Thewalt, 1970). The starting set of reflections comprised three origin-defining reflections, three reflections that were assigned symbols, and two reflections whose signs could be deduced with high probability [$S(020)=-$, since there are many relations of type $(020)=(\bar{h}1\bar{l})+(h1l)$ where l is even and $E(h1l)$ is large; $S(620)=+$ from the $\sum_1$ formula]. The starting set of reflections is described in Table 2. Beginning with this set of eight reflections and considering only reflections with $|E|>2{\cdot}5$, we assigned phases or symbols to additional reflections by iterative application of the $\sum_2$ formula. As the iteration proceeded, reflections with lower $|E|$ values were automatically included. A new phase assignment was automatically accepted, if there were a number of supporting indications and no, or in later cycles relatively few, contraindications. The set of phases was continuously expanded by this procedure until an adequate number of reflections was available for the calculation of E maps. During the final iteration cycles one symbol was eliminated, leaving two symbols with four different possible phase combinations. E maps were calculated with each of these four phase conbinations, and the correct structure was readily recognized in one of the maps. Coordinates for all nonhydrogen atoms were obtained from this correct E map.

Table 2. *Starting set of reflections for the structure determination by symbolic addition*

Reflection indices			$\|E\|$	Assumed sign (or symbol) for E
8	1	10	5·9	+
1	2	1	3·4	+
3	6	2	3·6	+
6	2	0	2·7	+
0	2	0	3·7	−
12	1	−6	5·0	*a*
1	2	2	2·7	*b*
10	1	−14	3·2	*c*

Refinement of the structure

The trial structure was refined by block-diagonal least-squares methods. The quantity minimized was $\sum w(F_o - 1/k|F_c|)^2$, where k is a scale factor and the weight w is equal to $[(2F_o/\sigma(F_o^2)]^2$. Atomic scattering factors for the heavy atoms were obtained from *International Tables for X-ray Crystallography* (1962), and those for hydrogen were taken from Stewart, Davidson & Simpson (1965). Initially, both the heavy-atom positional and anisotropic temperature parameters were refined to an R index ($=\sum||F_o|-|F_c||/\sum|F_o|$) of 0·11. At this stage, a difference Fourier map clearly revealed the positions of the 17 hydrogen atoms.

Further refinement of the positional parameters, along with anisotropic temperature factors for the heavy atoms and isotropic temperature factors for the hydrogen atoms, reduced the R index to 0·077. The general agreement between observed and calculated structure factors was consistent with the estimated errors in the values of $|F_o|$, but we noticed that 16 reflections showed discrepancies greatly exceeding the estimated errors.

Table 3. *Final heavy-atom parameters and their e.s.d.'s*

Values have been multiplied by 10^5. Temperature factors are in the form:
$T=\exp(-\beta_{11}h^2-\beta_{22}k^2-\beta_{33}l^2-\beta_{12}hk-\beta_{13}hl-\beta_{23}kl)$.

	x	y	z	β_{11}	β_{12}	β_{13}	β_{22}	β_{23}	β_{33}
N(1)	72014(14)	24987(33)	59258(11)	387(10)	15(40)	213(12)	1838(53)	-102(30)	203(6)
C(2)	62765(18)	30325(40)	56428(13)	440(13)	9(49)	48(16)	1547(61)	39(36)	194(7)
C(3)	57645(16)	32509(36)	61835(13)	312(11)	-112(42)	38(14)	1163(52)	40(33)	202(7)
C(4)	63549(16)	28205(38)	75875(13)	255(10)	12(41)	112(14)	1541(58)	-133(34)	210(7)
C(5)	71499(17)	23295(39)	81025(13)	349(12)	-51(46)	112(14)	1611(59)	-123(35)	187(7)
O(5)	70616(12)	23556(29)	88266(9)	379(9)	64(36)	108(11)	2412(49)	-54(27)	191(5)
C(6)	80218(17)	18085(40)	79119(14)	278(11)	169(46)	-24(16)	1766(62)	-82(38)	239(7)
C(7)	81137(16)	18388(38)	71957(13)	260(10)	144(43)	154(14)	1628(59)	-177(37)	255(7)
C(8)	73134(16)	23429(36)	66664(13)	302(11)	-50(40)	143(14)	1152(52)	-133(32)	217(7)
C(9)	64283(15)	28191(36)	68523(12)	241(10)	-144(40)	83(14)	1202(52)	-162(32)	217(7)
C(10)	47408(18)	38835(41)	61095(14)	348(12)	163(48)	6(17)	1634(63)	40(39)	274(8)
C(11)	40737(16)	23635(42)	63136(13)	265(11)	103(47)	77(15)	2160(66)	-110(38)	208(7)
N(12)	39585(13)	7153(32)	57940(10)	280(9)	-133(37)	7(12)	1712(50)	173(29)	174(5)
C(13)	22687(16)	24506(37)	90842(12)	254(10)	-32(42)	21(14)	1557(56)	12(34)	168(6)
O(13)	25568(12)	27934(32)	97416(9)	342(8)	-624(38)	89(10)	3521(60)	-277(29)	160(5)
C(14)	28398(16)	25281(35)	85203(12)	223(10)	41(39)	34(13)	1229(51)	24(32)	196(6)
N(14)	38392(13)	30726(30)	86979(10)	240(8)	69(34)	105(11)	1386(46)	-61(28)	211(6)
O(14)	42922(11)	32260(31)	82085(9)	320(8)	-270(37)	273(10)	2976(56)	3(30)	255(5)
O(14)'	42365(11)	33979(30)	93382(9)	281(8)	-392(35)	21(11)	2656(50)	-341(28)	208(5)
C(15)	24784(16)	21481(37)	77967(12)	321(11)	197(42)	122(14)	1349(56)	20(33)	189(6)
C(16)	15271(16)	16187(37)	75717(12)	313(11)	157(44)	18(14)	1407(54)	-77(33)	162(6)
N(16)	11565(15)	11867(36)	68106(11)	403(11)	191(45)	-7(14)	2332(60)	-228(33)	176(6)
O(16)	16955(14)	13775(37)	63806(9)	593(11)	-151(48)	143(12)	3781(67)	-200(32)	167(5)
O(16)'	3193(14)	6243(38)	66304(11)	390(10)	-389(48)	-124(13)	4433(73)	-638(37)	263(6)
C(17)	9301(16)	14173(39)	80704(13)	234(11)	29(43)	-1(14)	1668(58)	0(36)	212(7)
C(18)	12863(15)	18594(38)	87842(12)	236(10)	-131(43)	115(13)	1723(60)	62(34)	182(6)
N(18)	6056(14)	16876(36)	92698(11)	274(9)	-119(41)	56(12)	2416(59)	165(33)	198(6)
O(18)	25(13)	3828(34)	91528(10)	443(10)	-1145(40)	157(13)	3352(60)	164(33)	300(6)
O(18)'	6390(13)	28541(33)	97654(10)	462(9)	-350(41)	317(11)	3195(60)	-398(32)	276(5)
O(19)	85634(13)	18207(33)	49534(10)	366(9)	212(40)	195(12)	3087(60)	-150(33)	311(6)

Consequently, intensities of these reflections were remeasured on the diffractometer; however these measurements did not differ significantly from those recorded initially. Apparently, the 16 reflections, as well as others in the data set, were affected by extinction or Renninger (1937) effects. Extinction effects are obvious since many strong, low-angle reflections display observed structure-factor amplitudes that are much smaller than the calculated amplitudes. Renninger effects apparently account for the discrepancies in the *h2l* reflections which have observed structure-factor amplitudes exceeding calculated amplitudes; in most cases, the discrepancies are attributed to double reflections composed of strong coupling with the strong 020 reflection. Zero weights were assigned to the 16 reflections, and all parameters were then refined further. During the final refinement cycle, the average shift in parameters was about 0·2 times the e.s.d.'s and the maximum shift [in the x coordinate of atom C(15)] was equal to 0·5 times the parameter's e.s.d.'s.

The final R index for all reflections is 0·073. The R index based on F^2 values, $(\sum|F_o^2-F_c^2|/\sum F_o^2)$, is 0·11. The weighted R index, $\{[\sum w(|F_o|-|F_c|)^2/\sum wF_o^2]\}^{1/2}$, is 0·068. The goodness-of-fit, $\{\sum[1/\sigma^2(F_o^2)](F_o^2-F_c^2/k^2)^2/$

Table 4. *Final hydrogen-atom parameters and their e.s.d.'s*

Positional parameters have been multiplied by 10^3.

	x	y	z	B(Å^2)
H(1)	766 (2)	223 (5)	563 (2)	5·9 (0·8)
H(2)	607 (2)	327 (4)	516 (1)	3·4 (0·6)
H(4)	577 (2)	316 (4)	772 (1)	2·8 (0·5)
H(5)	764 (2)	241 (4)	913 (2)	4·7 (0·7)
H(6)	858 (2)	149 (4)	829 (1)	3·6 (0·6)
H(7)	872 (2)	151 (4)	708 (1)	4·3 (0·6)
H(10)	448 (2)	426 (4)	562 (1)	3·6 (0·6)
H(10′)	471 (2)	502 (4)	645 (1)	2·9 (0·5)
H(11)	339 (2)	280 (3)	630 (1)	2·6 (0·5)
H(11′)	434 (2)	186 (4)	682 (1)	2·8 (0·5)
H(12)	358 (2)	105 (4)	535 (1)	4·7 (0·7)
H(12′)	460 (2)	019 (5)	579 (1)	5·2 (0·7)
H(12″)	365 (2)	−033 (4)	597 (1)	4·6 (0·7)
H(15)	28° (2)	226 (4)	743 (1)	4·5 (0·7)
H(17)	028 (2)	110 (4)	791 (1)	2·9 (0·5)
H(19)	860 (3)	059 (6)	496 (2)	10·0 (1·2)
H(19′)	916 (2)	229 (5)	505 (2)	7·2 (0·9)

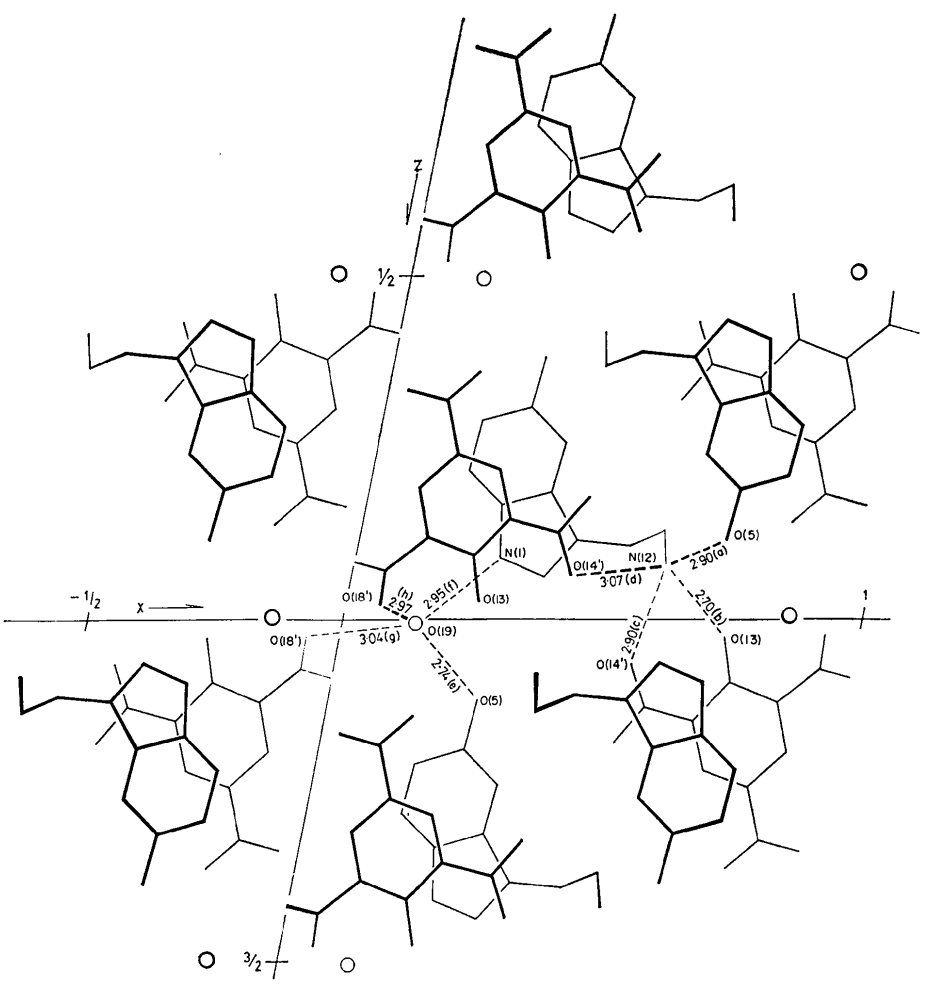


Fig. 2. The structure viewed down the b axis. Dashed lines represent hydrogen bonds. Hydrogen-bond labels correspond to those used in Table 6.

Table 5. *Observed and calculated structure factors*

From left to right, columns contain values of h, $10F_o$, and $10F_c$. An asterisk signifies a reflection assigned zero weight during the latter stages of refinement (see text).

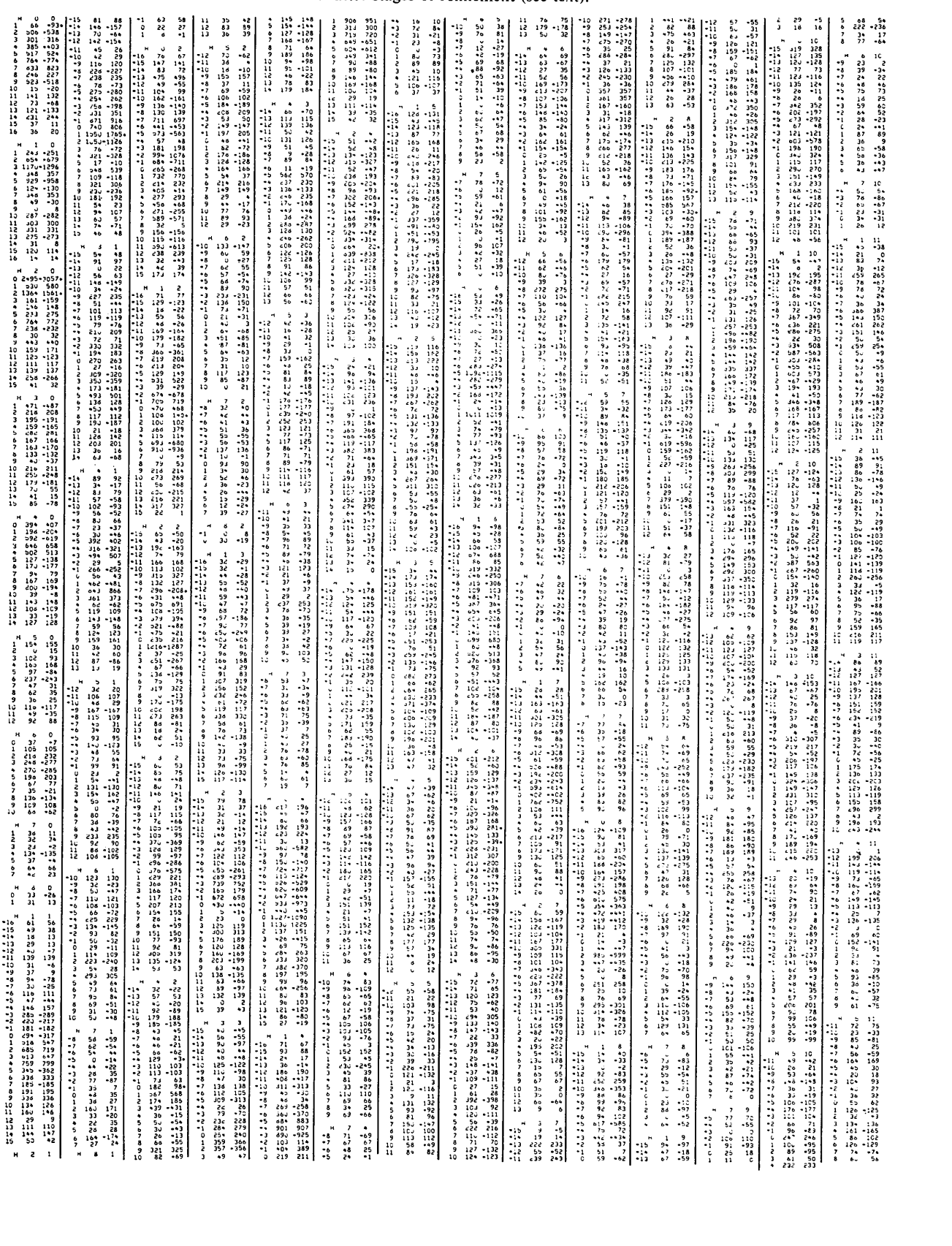
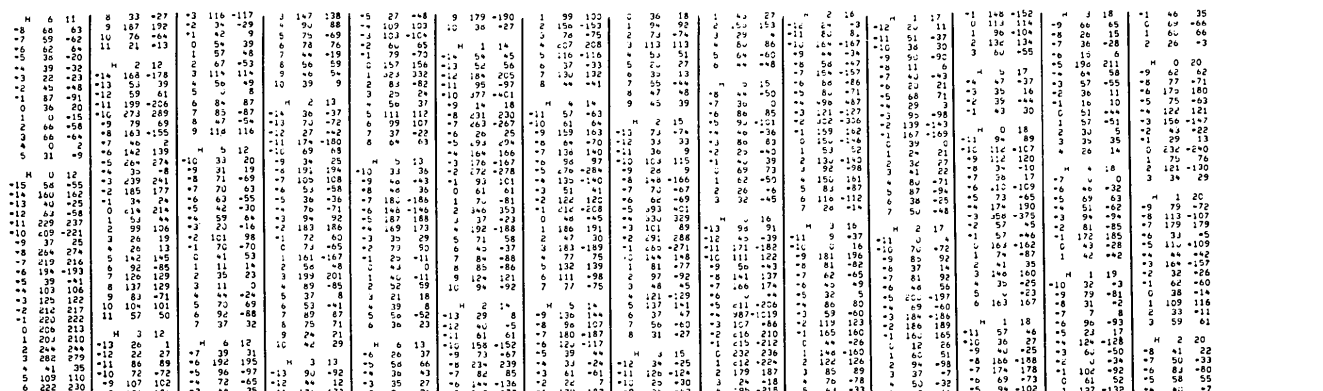


Table 5 (*cont.*)



$(m-s)\}^{1/2}$, where m is the number of reflections used and s is the number of parameters refined, is 1·96; deviation from an ideal value of 1·0 is probably due to misalignment of the diffractometer (see *Experimental*), plus the extinction and Renninger effects. Average e.s.d.'s in the positional coordinates of the heavy atoms are 0·002–0·003 Å, and those for the hydrogen atoms are 0·03–0·04 Å; this corresponds to e.s.d.'s of about 0·004 Å for bond lengths involving only heavy atoms and 0·04 Å for bond lengths involving hydrogen atoms. The e.s.d.'s in bond angles are approximately 0·3° for angles involving only heavy atoms and 2° for angles involving hydrogen atoms. Since the block-diagonal approximation was used for the least-squares refinement, these e.s.d.'s are probably underestimates of the true values.

At the conclusion of the refinement, a three-dimensional electron-density difference map was calculated with only the heavy-atom contributions included in the values for the calculated structure factors. This map showed regions of electron density in excess of 0·4 e.Å^{-3} at all calculated hydrogen positions, and no additional peaks or throughs exceeding 0·44 e.Å^{-3} in magnitude. A final difference Fourier map, calculated with both heavy-atom and hydrogen-atom contributions included in the values for the calculated structure factors, showed no peaks or troughs exceeding 0·3 e.Å^{3} in magnitude.

Final heavy-atom parameters and their e.s.d.'s are listed in Table 3; hydrogen-atom parameters and their e.s.d.'s are listed in Table 4. Observed and calculated structure factors are given in Table 5.

Crystal packing and hydrogen bonding

Fig. 2 shows the crystal structure projected down the **b** direction. Picrate and hydroxyindole moieties are arranged in alternating stacked arrays to form continuous columns running parallel to the *b* axis. These columns form an approximate hexagonal array. Picrate and hydroxyindole planes are approximately parallel (dihedral angle between the planes is 6°, with an average interplanar spacing of 3·3–3·4 Å) and are nearly perpendicular to the *b* axis. The ethylamino groups and water molecules occupy channels that run between the columns of hydroxyindole and picrate moieties.

The hydrogen-bonding scheme is depicted in Fig. 2, and hydrogen-bond distances and angles are listed in Table 6. All hydrogen atoms that are covalently bonded to nitrogen or oxygen atoms participate in hydrogen bonding. A relatively long hydrogen bond occurs between atom N(12) of serotonin and atom O(14′) of an adjacent picrate ion within the stacked columns; no other hydrogen bonds are found between ions within the stacked arrays. Hydrogen atom H(12) appears to form a bifurcated hydrogen bond to atoms O(13) and O(14′) in which the bond to atom O(13) is shorter and more nearly linear than that to atom O(14′).

Molecular structure

Bond distances and angles are given in Fig. 3 and Table 7; Table 8 lists deviations from the least-squares plane through the indole ring. The only previous determination of a serotonin structure is that reported for the

Table 6. *Hydrogen-bond distances and angles*

Hydrogen-bond labels correspond to those shown in Fig. 2.

Hydrogen-bond label	Donor atom	Hydrogen atom	Acceptor atom	Distances Donor–acceptor	Hydrogen–acceptor	Donor–hydrogen–acceptor angle
a	N(12)	H(12″)	O(5)	2·898Å	1·97Å	171°
b	N(12)	H(12)	O(13)	2·705	1·84	155
c	N(12)	H(12)	O(14′)	2·901	2·30	122
d	N(12)	H(12′)	O(14′)	3·070	2·11	164
e	O(5)	H(5)	O(19)	2·739	1·88	157
f	N(1)	H(1)	O(19)	2·948	1·99	176
g	O(19)	H(19′)	O(18′)	3·041	2·26	146
h	O(19)	H(19)	O(18′)	2·970	2·19	154

Table 7. *Bond lengths and angles involving hydrogen atoms of the ethylamino group of serotonin*

C(10)–H(10)	0·95 Å	C(3)—C(10)–N(10)	111°	C(11)—C(10)–H(10)	107°
C(10)–H(10′)	1·01	C(3)—C(10)–H(10′)	109	C(11)–C(10)–H(10′)	106
		H(10)–C(10)–H(10′)	110		
C(11)–H(11)	1·02	C(10)–C(11)–H(11)	116	N(12)–C(11)–H(11)	104
C(11)–H(11′)	1·01	C(10)–C(11)–H(11′)	110	N(12)–C(11)–H(11′)	109
		H(11)–C(11)–H(11′)	107		
N(12)–H(12)	0·93	C(11)–N(12)–H(12)	112	H(12)–N(12)–H(12′)	116
N(12)–H(12′)	0·99	C(11)–N(12)–H(12′)	108	H(12)–N(12)–H(12′)′	107
N(12)–H(12″)	0·93	C(11)–N(12)–H(12″)	111	H(12′)–N(12)–H(12″)	103

serotonin cation in the crystal structure of serotonin creatinine sulphate (Karle, Dragonette & Brenner, 1965). Bond lengths and angles found for the serotonin cation are not significantly different from those found in the serotonin creatinine sulphate structure. However, the conformation of the ethylamino group is different in the two crystal structures. The ethylamino group in this crystal structure folds over the hydroxyindole plane, but in the serotonin creatinine sulphate structure the side chain assumes a more extended configuration with the terminal nitrogen atom, N(12), lying closer to the hydroxyindole plane. The displacement of atom N(12) from the hydroxyindole plane is 2·4 Å in this structure and 0·5 Å in the serotonin creatinine sulphate structure. A comparison of the C(3)–C(10)–C(11)–N(12) torsion angles also reveals the difference in sero-

Table 8. *Deviations* (Å) *of atoms from the least-squares plane through the indole ring of serotonin*

Atom	Deviation	Atom	Deviation
N(1)	−0·015*	O(5)	−0·042
C(2)	−0·003*	C(10)	−0·016
C(3)	0·013*	H(1)	0·01
C(4)	−0·009*	H(2)	−0·05
C(5)	−0·014*	H(4)	−0·02
C(6)	0·014*	H(5)	−0·31
C(7)	0·003*	H(6)	−0·01
C(8)	0·002*	H(7)	−0·00
C(9)	0·009*		

* Atoms included in the calculation of the plane.

The equation of the least-squares plane, where the coefficients of X, Y and Z are equal to direction cosines with respect to the axes a, b and c^*, and X, Y, Z are orthogonal ångstrom coordinates, is: $0{\cdot}2661\,X + 0{\cdot}9600\,Y + 0{\cdot}0876\,Z = 4{\cdot}174$ Å.

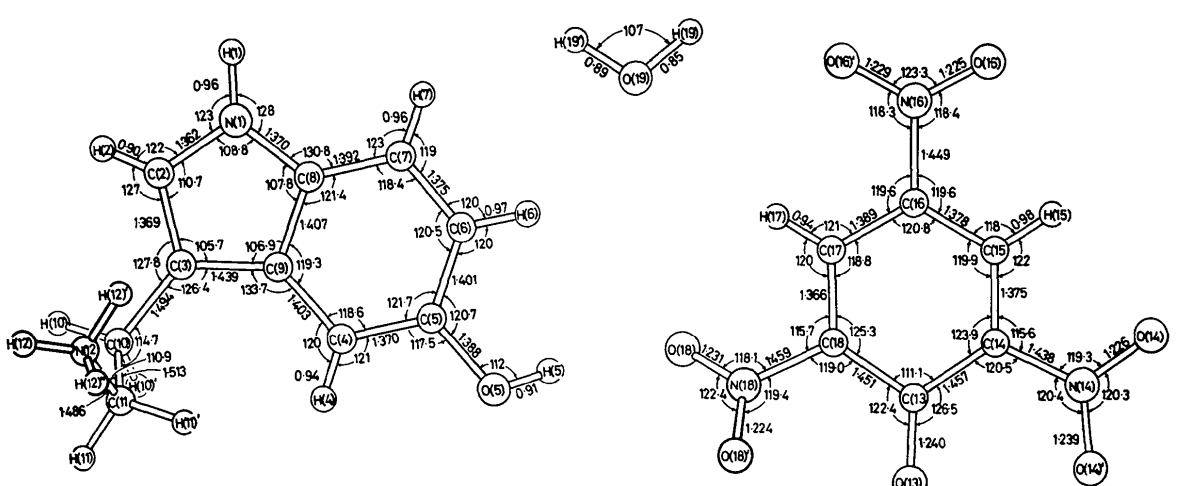


Fig. 3. Bond distances (Å) and angles (°). Additional bond lengths and angles are listed in Table 7.

tonin conformation. This angle is −67° for serotonin picrate monohydrate and 173° for serotonin creatinine sulphate. In both structures, torsion angles around the C(10)–C(11) bonds are such that the bonds assume approximately staggered arrangements. The difference in conformation of the ethylamino groups probably can be attributed to differences in the hydrogen-bonding schemes.

Table 9 shows a comparison between bond lengths within the picrate ion and those found for the picrate ions in the crystal structures of ammonium and potassium picrate (Maartmann-Moe, 1969); the three structures agree closely. Table 10 lists deviations of atoms from least-squares planes through the picrate ion. The benzene ring is approximately planar, with the immediate ring substituents lying nearly in the plane. Two of the nitro groups [N(14), O(14), O(14′) and N(16), O(16), O(16′)] are twisted slightly out of the plane of the benzene ring, making dihedral angles of about 3° with the benzene ring. The other nitro group [N(18), O(18), O(18′)] is twisted considerably and intersects the benzene plane with a dihedral angle of 53°. This is in contrast to the crystal structures of ammonium and potassium picrate, where the *ortho* nitro groups are twisted 26° out of the benzene plane and the *para* nitro groups are only slightly twisted.

Stereoscopic views of the serotonin and picrate ions, including ellipsoids of thermal vibration, are shown in Fig. 4.

Table 9. *Comparison of bond lengths within the picrate ion with those found in ammonium picrate and potassium picrate*

Picrate ions in the ammonium and potassium salts have a two-fold axis passing through atoms C(13), C(16), O(13), and N(16). E.s.d.'s in bond lengths are about 0·004 Å for this structure and 0·006 Å for ammonium and potassium picrate.

	This structure	Ammonium picrate	Potassium picrate
C(13)–C(14)	1·457 Å	1·450 Å	1·453 Å
C(13)–C(18)	1·451		
C(14)–C(15)	1·375	1·372	1·372
C(17)–C(18)	1·366		
C(15)–C(16)	1·378	1·368	1·382
C(16)–C(17)	1·389		
C(13)–O(13)	1·240	1·239	1·243
C(14)–N(14)	1·438	1·461	1·457
C(18)–N(18)	1·459		
N(14)–O(14)	1·226	1·206	1·229
N(18)–O(18)	1·231		
N(14)–O(14′)	1·239	1·237	1·232
N(18)–O(18′)	1·224		
C(16)–N(16)	1·449	1·457	1·436
N(16)–O(16)	1·225	1·212	1·243
N(16)–O(16′)	1·229		
C(18)–N(18)	1·459	1·461	1·457

Table 10. *Deviations* (Å) *of atoms from least-squares planes through the picrate anion*

	Planes				
	A	*B*	*C*	*D*	*E*
C(13)	0·009*	0·009*			
C(14)	−0·015*	−0·008*		0·001*	
C(15)	0·002*	0·008*			
C(16)	0·016*	0·013*	−0·001*		
C(17)	−0·020*	−0·030*			
C(18)	0·008*	−0·001*			0·002*
O(13)	0·006	0·006*			
N(14)	−0·025	−0·009*		−0·003*	
O(14)	0·026	0·047		0·001*	
O(14′)	−0·073	−0·056		0·001*	
N(16)	0·009	0·006*	0·004*		
O(16)	−0·047	−0·057	−0·002*		
O(16′)	0·043	0·046	−0·002*		
N(18)	0·022	0·006*			−0·007*
O(18)	−0·616	−0·639			0·003*
O(18′)	0·682	0·665			0·003*
H(15)	0·02	0·03			
H(17)	0·02	0·00			

* Atoms included in calculations of planes.

The equations of the least-squares planes, where the coefficients of X, Y and Z are equal to direction cosines with respect to axes a, b and c^*, and X, Y, Z are orthogonal ångstrom coordinates, are:

Plane *A*: $0{\cdot}2358\,X - 0{\cdot}9585\,Y + 0{\cdot}1600\,Z = 1{\cdot}002$ Å
B: $0{\cdot}2296\,X - 0{\cdot}9599\,Y + 0{\cdot}1606\,Z = 1{\cdot}012$
C: $0{\cdot}2768\,X - 0{\cdot}9476\,Y + 0{\cdot}1593\,Z = 0{\cdot}96$
D: $0{\cdot}2434\,X - 0{\cdot}9631\,Y + 0{\cdot}1146\,Z = 0{\cdot}31$
E: $0{\cdot}5225\,X - 0{\cdot}6026\,Y + 0{\cdot}6033\,Z = 8{\cdot}17$

Discussion

An outstanding feature of the crystal structure is the stacking association of approximately parallel picrate and hydroxyindole planes. The two types of stacking interactions found in the crystal structure, along with the closest interatomic contacts between adjacent picrate and hydroxyindole planes, are shown in Fig. 5(*a*) and (*b*). Although interatomic distances are not significantly shorter than the sums of the van der Waals radii of the atoms involved, a number of intimate contacts are formed.

The hydroxyindole–picrate stacking interactions appear to be of the donor–acceptor type, as described for other aromatic complexes (Mulliken & Person, 1969; Andrews & Keefer, 1964; Briegleb, 1961; Wallwork, 1961; Bent, 1968; Boeyens & Herbstein, 1965). This interpretation is consistent with the fact that serotonin picrate displays a pronounced color change when crystallized. Also, the observed arrangement of the aromatic picrate and hydroxyindole moieties in alternating stacked arrays is similar to that found in the crystal structures of other aromatic donor–acceptor complexes (Wallwork, 1961; Boeyens & Herbstein, 1965). Finally, the formation of a hydroxyindole–picrate donor–acceptor complex would be expected from evidence that serotonin is a good donor (Isenberg *et al.*, 1960; Isenberg & Szent-Györgyi, 1958; Alivisatos *et al.*, 1961; Cilento & Giusti, 1959; Cilento & Tedeschi, 1961) and picric acid is a good acceptor (Briegleb & Delle, 1960*a*;

Kross & Fassel, 1957; Briegleb & Delle, 1960*b*; Mariella, Gruber & Elder, 1961). It has been found that serotonin and related indoles form colored donor–acceptor complexes with aromatic electron acceptors in solution and in the solid state; similarly, picric acid forms orange and red crystalline complexes with a variety of aromatic electron donors.

The stacking pattern in the crystal structure [Fig. 5(*a*) & (*b*)] appears to be dominated by interactions of the picrate nitro groups with the hydroxyindole moiety. This finding is consistent with the hypothesis that donor–acceptor complexes of nitro-substituted aromatic compounds are stabilized by interactions of the polar nitro groups with the polarizable π-electron systems of adjacent molecules (Briegleb, 1961; Briegleb & Delle, 1960*a*; Kross & Fassel, 1957; Briegleb & Delle, 1960*b*; Mariella *et al.*, 1961). Some studies suggest that such van der Waals interactions may contribute greatly to the ground-state stabilities of aromatic donor–acceptor complexes (Le Fèvre, Radford, Ritchie & Stiles, 1967; Le Fèvre, Radford & Stiles, 1968; Hertel & Kleu, 1931; Mulliken & Person, 1969, pp. 301–312; Briegleb, 1961; Lippert, Hanna & Trotter, 1969; Dewar & Thompson, 1966). In the crystal structures of strong donor–acceptor complexes, particularly those stabilized by interactions involving atoms with lone-pair electrons, it is often found that charge-transfer bonding produces alterations in the bond lengths within donor and acceptor moieties (Mulliken & Person, 1969, ch. 5; Bent, 1968; Hassel, 1970). However, Table 9 shows that the picrate ion of the serotonin complex has about the same bond lengths as found in the ammonium and potassium salts of picric acid. Although the spacing between picrate and hydroxyindole rings is shorter than the interplanar separations in crystals of polycyclic aromatic hydrocarbons, it is within the range found in crystals of other polar aromatic compounds where charge-transfer forces are not important (Bugg, Thomas, Sundaralingam & Rao, 1971). Possibly the charge-transfer resonance form is of only minor importance in the ground-state structure of the serotonin picrate complex.

No other crystal structures of picrate donor–acceptor complexes have been reported. The only previous studies of the crystal structures of indole donor–acceptor complexes are those reported for the trinitrobenzene

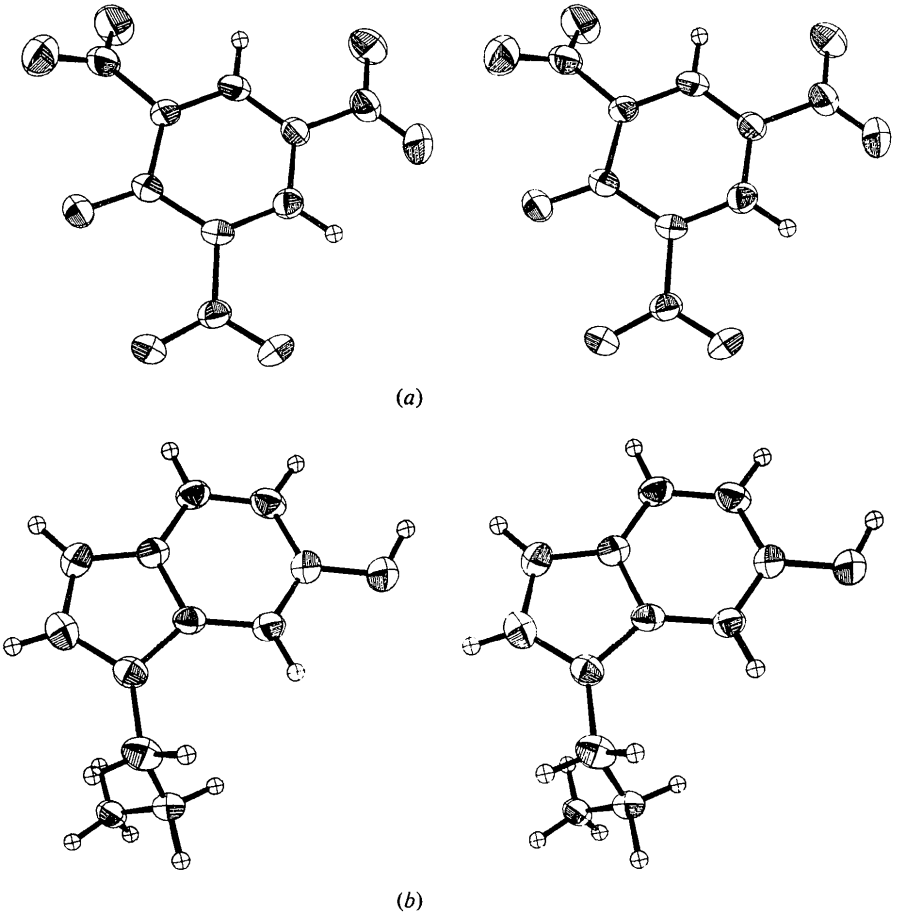


Fig. 4. Stereoscopic view of (*a*) serotonin cation and (*b*) picrate anion. Heavy atoms are represented by ellipsoids defined by the principal axes of thermal vibration and scaled to include 50% probability. Hydrogen atoms are represented by spheres of 0·1 Å radius. [This drawing was prepared using the computer program *ORTEP* (Johnson, 1965)].

complexes of indole and skatole whose crystals are isostructural (Hanson, 1964). The skatole–trinitrobenzene stacking interactions along with the closest interplanar contacts, are shown in Fig. 5(*c*) & (*d*). In contrast to serotonin picrate, indole and benzene rings are essentially superimposed with a great deal of ring overlap. As with serotonin picrate, two nitro groups form close contacts with the indole ring.

Several experimental studies suggest that donor–acceptor complexes of indoles involve interactions of the acceptor molecules with specific regions of the indole ring (Szent-Györgyi, Isenberg & McLaughlin, 1961; Foster & Fyfe, 1966). Also, theoretical considerations implicate C(2) and C(3) as the atoms most likely to be involved in forming donor-acceptor complexes (Green & Malrieu, 1965). In addition to other contacts, serotonin picrate and skatole–trinitrobenzene complexes show interactions of nitro groups with atoms C(2) and C(3) of the indole rings. In serotonin picrate, a nitro group is sandwiched between two indole rings, with the nitro oxygen forming close contacts with atoms C(2) and C(4) of one ring [Fig. 5(*a*)] and the nitrogen atom forming a close contact with atom C(3) of the other ring [Fig. 5(*b*)]. A similar stacking association occurs in the skatole and indole trinitrobenzene complexes, in which a nitro group is sandwiched between two indole rings with close contacts between the nitrogen atom of the nitro group and the C(3) carbon atoms of the two rings [Figs. 5(*c*) and (*d*)].

In contrast to serotonin picrate, the serotonin creatinine sulphate complex (Karle *et al.*, 1965) is colorless and does not appear to be of the donor–acceptor type. Although the approximately parallel hydroxyindole and creatinine moities are stacked, the interplanar spacing is relatively large (3·4–3·5 Å) and the structure does not contain continuous columns of stacked rings as usually found in crystal structures of aromatic donor–acceptor complexes. The hydroxyindole–creatinine stacking pattern, along with the closest interatomic distances between the planes, is shown in Fig. 6. Note that contacts found in this structure are longer than those in the serotonin picrate and skatole–trinitrobenzene structures;

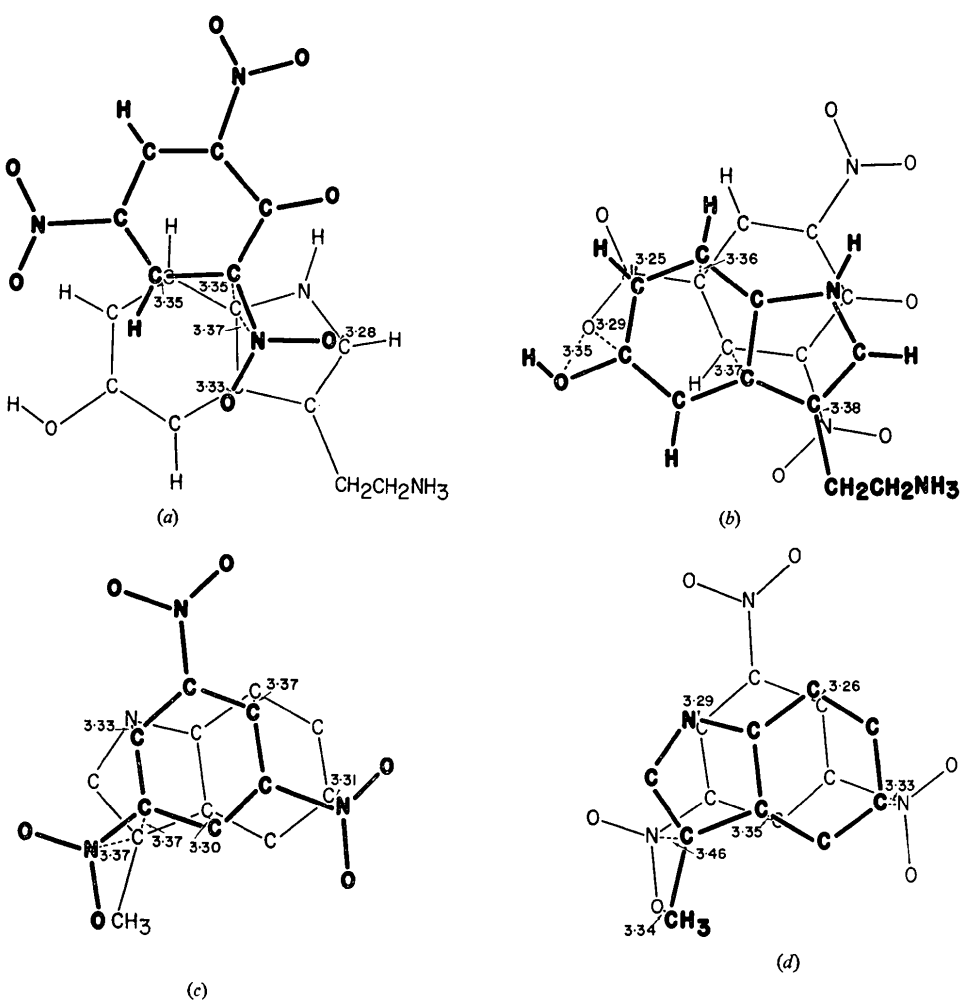


Fig. 5. Stacking patterns in crystals of serotonin picrate monohydrate [(*a*) and (*b*)] and skatole–trinitrobenzene [(*c*) and (*d*)]. All interplanar contacts shorter than 3·4 Å are shown; also, (*d*) shows the contact between the nitro group and atom C(3).

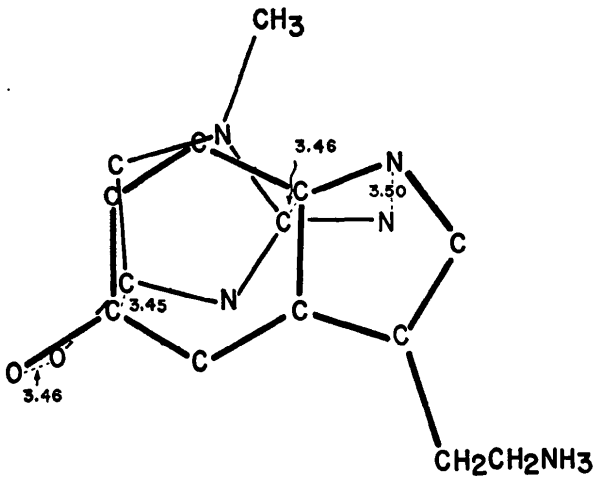


Fig. 6. Hydroxyindole–creatinine stacking pattern in the serotonin creatinine sulphate complex. All interplanar contacts shorter than 3·5 Å are shown.

apparently, this is not due entirely to charge repulsions between the serotonin and creatinine cations, since the formal positive charge on serotonin is confined to the ethylamino group which is not involved in the stacking.

Computer programs used in this study included *ORTEP* (Johnson, 1965), and a block-diagonal least-squares program obtained from Dr James Trotter, University of British Columbia. Other programs were written in our laboratories.

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