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The 2:1 Crystal Complex of 2-Aminopyridine and 5,5-Diethylbarbituric Acid (Barbital)

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The 2:1 complex of 2-aminopyridine ($C_5H_6N_2$) and 5,5-diethylbarbituric acid (barbital, $C_8H_{12}N_2O_3$), m.p. 82°C, is triclinic, space group $P\bar{1}$ with $a=9{\cdot}914$ (2), $b=10{\cdot}004$ (2), $c=10{\cdot}861$ (2) Å, $\alpha=108{\cdot}76$ (2), $\beta=92{\cdot}28$ (2), $\gamma=104{\cdot}24$ (2)°, (reduced cell) and with observed density (1·265 g cm^{-3}) in agreement with a calculated value (1·262 g cm^{-3}) for $4(C_5H_6N_2).2(C_8H_{12}N_2O_3)$ in the unit cell. The structure determination by direct methods was based on 4032 integrated intensities measured on a computer-controlled four-circle diffractometer with graphite monochromated Cu $K\alpha$ radiation. Least-squares refinement of two large blocks of atomic parameters gave a final R value of 0·065 for all data. The structure contains two strong NH···N hydrogen bonds with N···N distances 2·81, 2·85 Å, in which the two barbital NH groups are donors and pyridine nitrogen atoms are acceptors. These distances are similar to those reported for hydrogen bonds in which barbiturate or uracil is donor and adenine atom (N1) is acceptor. There are four weak NH···O=C hydrogen bonds with N···O distances 3·02, 3·03, 3·13 and 3·14 Å.

Introduction

The strong association of barbiturates with adenine derivatives in solution may be significant for an understanding of barbiturate drug action (Kyogoku, Lord & Rich, 1968). Structure determinations of crystal complexes of barbiturates with adenine derivatives (Kim & Rich, 1968; Voet & Rich, 1972; Voet, 1972) have shown examples of hydrogen bonding both in the Watson–Crick and Hoogsteen modes. The Watson–Crick mode of hydrogen bonding which involves one NH···N hydrogen bond with barbital as donor and adenine N(1) as acceptor, and a second NH···O=C hydrogen bond with the adenine amino group as donor and a barbital oxygen atom as acceptor, is very similar to the mode of hydrogen bonding which is observed in the complex of barbital with 2-aminopyridine.

Experimental

Prismatic crystals of the 2:1 complex 2-aminopyridine–barbital previously reported in the patent literature* were grown from a supersaturated solution of both components in a solvent mixture of 3 ml ethanol and 3 ml hexane. The crystals were observed to become opaque after about a week's exposure to air. A transparent crystal of dimensions 0·4 × 0·3 × 0·2 mm was coated with epoxy resin to prevent deterioration. The unit-cell dimensions and X-ray intensities were measured on a four-circle automatic diffractometer using graphite monochromated Cu $K\alpha$ radiation ($\lambda=1{\cdot}5418$ Å), and with the coated crystal oriented with [011] approximately along the goniostat φ axis. Reflections were scanned in the θ–2θ mode, with a θ scan width of $(0{\cdot}8+0{\cdot}5\tan\theta)°$. Among a total of 4032 independent reflections in the range $\theta \leq 75°$, there were 726 reflections for which the integrated intensity (I) was less than $2\sigma(I)$ as calculated from the counting statistics. These reflections were assigned intensities of $\sigma(I)/2$. X-ray absorption and extinction corrections were not applied.

The crystal structure was determined by direct methods (Germain, Main & Woolfson, 1971). Because of computing limitations, atomic parameters (Table 1) were refined alternately in two blocks by a least-squares procedure. The first block consisted of parameters for all heavier atoms and the second block consisted of parameters for all hydrogen atoms together with those of the atoms to which the hydrogens are bonded. The function minimized was $\sum_H w_H \Delta_H^2$, where $\Delta_H=|F_H^o|-|F_H^c|$. The weights were $w_H^{-1}=0{\cdot}13+0{\cdot}0034|F_H|^2$. The atomic scattering factors were those of Cromer & Waber (1965) for carbon, nitrogen and oxygen, and of Stewart, Davidson & Simpson (1965) for hydrogen. All hydrogen atom positions were obtained from a difference Fourier synthesis which was calculated after some refinement of heavier atom anisotropic thermal parameters. Hydrogen-atom thermal parameters were refined isotropically. In the final cycles of refinement, reflections with $I<2\sigma(I)$ and 14 strong reflections for which $|F_H^c|>|F_H^o|$ were given zero weight. The final R index* was 0·065 for all reflections and 0·044 for reflections with non-zero weights.†

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* Chemische Fabrik von Heyden A-G. Fr. 769586 (1934).

* $R=\sum_H|\Delta_H|/\sum_H|F_H^o|$.

† The list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30319 (25 pp., 1 microfiche). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Discussion

(i) *Barbital*

The barbital bond lengths and angles (Fig. 1) are similar to those in barbital II (Craven, Vizzini & Rodrigues, 1969), the most significant differences being in the internal ring angles at the nitrogen atoms (125·5° *vs.* 126·8°) and at C(2) (116·8° *vs.* 115·1°). The e.s.d.'s in these differences are 0·3°. Corresponding bond lengths and angles are very similar on each side of the C(2)···C(5) ring diagonal, in contrast to the slight differences which have consistently been reported in other barbiturate crystal structures, in which atom O(4) is hydrogen bonded, but O(6) is not (Craven, Cusatis, Gartland & Vizzini, 1973). In the complex with 2-aminopyridine, both atoms O(4) and O(6) are hydrogen bonded and no such differences in bond lengths and angles are expected. The pyrimidine ring atoms are nearly coplanar except for C(5), which is displaced 0·06 Å from the best least-squares plane of the other five. The hydrocarbon chain C(10)–C(9)–C(5)–C(7)–C(8) is fully extended except for a twist of 3·1° ($\sigma=0\cdot1°$) about the C(5)–C(7) bond.

(ii) 2-*Aminopyridine*

There is excellent agreement between corresponding

Table 1. *Atomic parameters with e.s.d.'s*

Positional parameters are given as fractions of the lattice translations. Anisotropic thermal parameters are given according to the expression: $T=\exp\,[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$ and isotropic thermal parameters according to the expression: $T=\exp\,[-B\sin^2\theta/\lambda^2]$. Estimated standard deviations given in parentheses refer to the least significant figures in the parameter values.

(*a*) Non-hydrogen atom parameters (× 10⁴)

(i) Barbital molecule

	x	*y*	*z*	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	3588 (1)	3452 (1)	1232 (1)	95 (1)	76 (1)	118 (1)	8 (1)	25 (1)	7 (1)
O(2)	5857 (1)	4420 (1)	1049 (1)	108 (1)	109 (1)	176 (1)	15 (1)	60 (1)	10 (1)
N(3)	4829 (1)	5862 (1)	2543 (1)	84 (1)	80 (1)	110 (1)	2 (1)	19 (1)	9 (1)
C(4)	3717 (1)	6143 (1)	3165 (1)	95 (1)	83 (1)	95 (1)	10 (1)	18 (1)	14 (1)
O(4)	3844 (1)	7328 (1)	4030 (1)	126 (1)	102 (1)	135 (1)	7 (1)	36 (1)	−17 (1)
C(6)	2374 (1)	3548 (1)	1738 (1)	87 (1)	87 (1)	109 (1)	4 (1)	16 (1)	16 (1)
O(6)	1331 (1)	2497 (1)	1369 (1)	103 (1)	107 (1)	174 (1)	−16 (1)	31 (1)	−6 (1)
C(7)	1245 (1)	5586 (1)	2193 (1)	97 (1)	121 (2)	118 (1)	31 (1)	22 (1)	24 (1)
C(8)	1657 (2)	6027 (2)	1022 (2)	143 (2)	194 (2)	147 (2)	48 (2)	23 (2)	76 (2)
C(9)	1818 (2)	4654 (2)	3997 (1)	130 (2)	140 (2)	112 (1)	6 (1)	32 (1)	41 (1)
C(10)	2783 (2)	4065 (2)	4661 (2)	198 (3)	224 (3)	163 (2)	5 (2)	−4 (2)	109 (2)

(ii) 2-Aminopyridine (molecule *A*, above; molecule *B*, below)

	x	*y*	*z*	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	3694 (1)	788 (1)	−623 (1)	105 (1)	94 (1)	96 (1)	16 (1)	13 (1)	25 (1)
	7432 (1)	8079 (1)	3181 (1)	100 (1)	91 (1)	101 (1)	14 (1)	18 (1)	24 (1)
C(2)	2752 (1)	−520 (1)	−960 (1)	110 (1)	97 (1)	96 (1)	16 (1)	−10 (1)	24 (1)
	7684 (1)	9440 (1)	4024 (1)	103 (1)	94 (1)	88 (1)	19 (1)	4 (1)	27 (1)
C(3)	2958 (2)	−1749 (2)	−1927 (2)	164 (2)	111 (2)	125 (2)	27 (2)	−20 (2)	0 (1)
	8893 (2)	10544 (1)	4051 (1)	128 (2)	99 (2)	130 (2)	0 (1)	1 (1)	30 (1)
C(4)	4146 (2)	−1593 (2)	−2522 (2)	208 (3)	183 (3)	103 (2)	93 (2)	4 (2)	−1 (2)
	9831 (2)	10199 (2)	3204 (2)	120 (2)	144 (2)	163 (2)	2 (1)	21 (1)	74 (2)
C(5)	5123 (2)	−241 (2)	−2171 (2)	162 (2)	216 (3)	109 (2)	76 (2)	42 (1)	54 (2)
	9584 (2)	8787 (2)	2336 (2)	128 (2)	166 (2)	153 (2)	43 (2)	58 (1)	70 (2)
C(6)	4854 (2)	903 (2)	−1222 (1)	129 (2)	145 (2)	113 (1)	33 (1)	34 (1)	50 (1)
	8378 (2)	7776 (2)	2358 (1)	129 (2)	116 (2)	123 (2)	33 (1)	36 (1)	30 (1)
N(7)	1625 (1)	−605 (1)	−286 (1)	108 (1)	121 (1)	157 (2)	−4 (1)	15 (1)	33 (1)
	6748 (1)	9710 (1)	4893 (1)	134 (2)	120 (1)	121 (1)	25 (1)	34 (1)	6 (1)

(*b*) Hydrogen atom parameters (× 10³)

(i) Barbital molecule

	x	*y*	*z*	*B* (Å²)
H(1)	359 (2)	258 (2)	64 (2)	5·6 (4)
H(3)	564 (2)	654 (2)	279 (2)	4·6 (3)
H(71)	30 (2)	482 (2)	193 (2)	5·7 (4)
H(72)	109 (2)	645 (2)	290 (2)	6·2 (4)
H(81)	93 (2)	637 (2)	64 (2)	6·6 (4)
H(82)	195 (3)	523 (3)	34 (2)	9·4 (6)
H(83)	246 (3)	681 (3)	129 (2)	9·3 (6)
H(91)	88 (2)	400 (2)	375 (2)	5·4 (4)
H(92)	169 (2)	555 (2)	464 (2)	5·3 (4)
H(101)	243 (3)	389 (3)	536 (3)	9·6 (7)
H(102)	300 (2)	312 (3)	403 (2)	7·5 (6)
H(103)	379 (3)	477 (3)	494 (2)	7·8 (6)

(ii) 2-Aminopyridine (molecule *A*, above; molecule *B*, below)

	x	*y*	*z*	*B* (Å²)
H(3)	229 (2)	−270 (2)	−210 (2)	7·5 (5)
	898 (2)	1156 (2)	466 (2)	6·8 (5)
H(4)	425 (2)	−250 (2)	−321 (2)	7·2 (5)
	1074 (2)	1096 (2)	323 (2)	7·3 (5)
H(5)	599 (2)	−7 (2)	−256 (2)	7·7 (5)
	1021 (2)	854 (2)	173 (2)	7·0 (5)
H(6)	552 (2)	191 (2)	−90 (2)	6·2 (4)
	814 (2)	673 (2)	179 (2)	6·1 (4)
H(71)	97 (2)	−128 (2)	−64 (2)	6·6 (5)
	595 (2)	908 (2)	471 (2)	6·0 (4)
H(72)	143 (2)	27 (2)	19 (2)	5·6 (4)
	672 (2)	1060 (2)	522 (2)	5·8 (4)

bond lengths and angles in molecules *A* and *B* (Fig. 1). In each molecule, the pyridine ring atoms are coplanar, with root-mean-square atomic displacements from the best least-squares planes of 0·003 and 0·004 Å respectively. However, in molecules *A* and *B* the amino nitrogen atoms are distant (0·06 and 0·07 Å) from the pyridine ring planes on one side, and the amino hydrogen atoms are distant (0·18, 0·15 Å and 0·12, 0·22 Å) from these planes on the opposite side. The sums of the bond angles at the amino nitrogen atoms are 349·3° and 347·6°. The differences from 360° (10·7° and 12·4°) are possibly significant in terms of their e.s.d.'s (2·9° and 3·0°). Thus, the bonds at the amino nitrogen atom in both molecules appear to be pyramidal rather than coplanar. The hydrogen atoms all form more nearly collinear N–H···O hydrogen bonds (NHO angles 157, 171, 175 and 168°) than would be the case if the covalent bonds at the nitrogen atoms were coplanar.

(iii) *The molecular association*

Barbital molecules hydrogen bond exclusively with 2-aminopyridine and *vice versa*, forming ribbons as shown in Fig. 2. All hydrogen atoms capable of hydrogen bonding are, in fact, hydrogen bonded. Hydrogen atoms at C(6) of each 2-aminopyridine molecule are at H···O van der Waals distances (2·65, 2·68 Å) from the same barbital O(2) atom. These interactions are not hydrogen bonds. In addition to the crystallographic centers of symmetry in Fig. 2, there are pseudomirror planes which pass through atoms C(2), C(5) and the ethyl groups of each barbital molecule. The pyridine ring planes of molecules *A* and *B* are nearly parallel (dihedral angle, 2·5°). Both rings are tilted (13·2°, 14·2°) with respect to the plane of the barbital pyrimidine ring. The hydrogen bonded ribbons are stacked so that 2-aminopyridine molecules overlap each other (Fig. 3). Stacking also results in an association of antiparallel barbital C(2)=O(2) carbonyl groups, with C(2)···O(2) distances of 3·40 Å.

The barbital NH groups are both donors in hydrogen bonds with pyridine nitrogen acceptor atoms. The N···N distances are 2·81 and 2·85 Å, the H···N distances are 1·91 and 1·97 Å and the NH···N angles are 176° and 174°. These are strong hydrogen bonds with short N···N distances like those in Watson–Crick hydrogen bonded adenine/uracil or adenine/barbiturate pairing. Hsu & Craven (1974) list N···N distances for eight such hydrogen bonds, ranging from 2·78 Å to 2·85 Å with a mean value of 2·81 Å.

The four NH···O=C hydrogen bonds in which 2-aminopyridine is donor and a barbital oxygen atom is acceptor are weak, with N···O distances, 3·14, 3·02, 3·13 and 3·03 Å. These distances are longer than the longest (2·98 Å) of the 48 distances listed by Gartland & Craven (1974) for NH···O=C hydrogen bonds in which barbiturate is both donor and acceptor. The N···O distances in the 2-aminopyridine–barbital complex are more like those found in barbiturate–

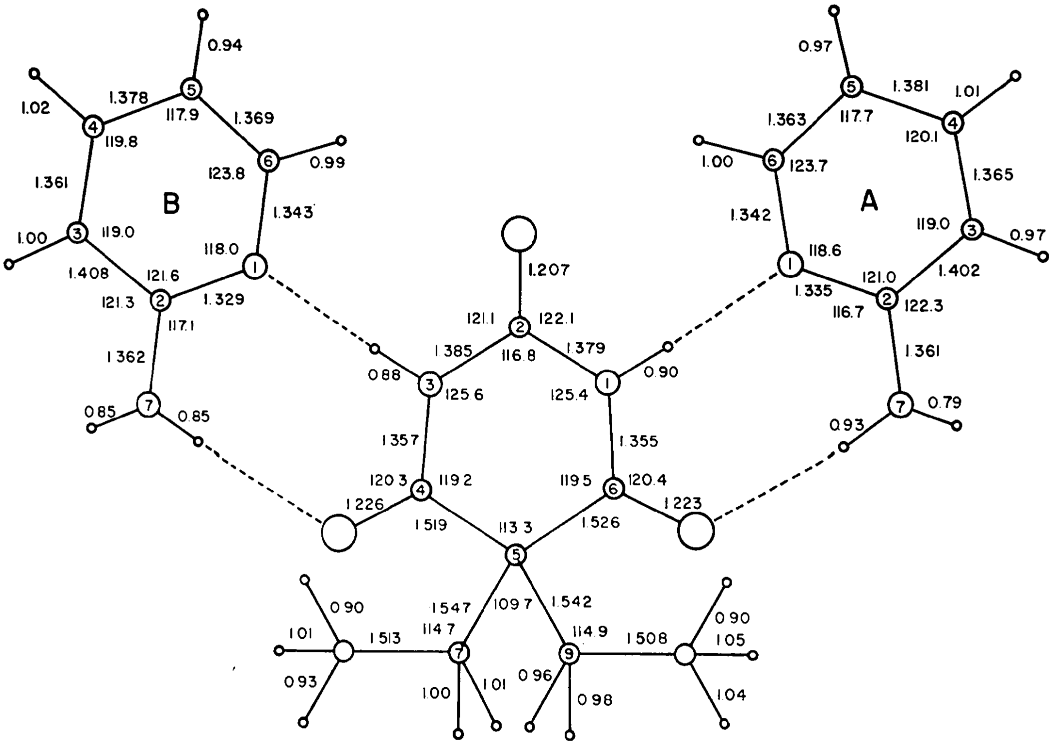

Fig. 1. Bond lengths and angles. The e.s.d.'s are 0·002 Å and 0·1° in bond lengths and angles which do not involve hydrogen atoms. The C–H and N–H bond lengths have e.s.d.'s of 0·02 Å.

adenine complexes. In these complexes, there are six NH···O=C hydrogen bonds in which adenine is donor and a barbiturate is acceptor. The N···O distances range from 2·97 to 3·39 Å, with a mean value of 3·21 Å. In the 1:1 complex of barbital with 9-ethyladenine, Voet (1972) attributes the long N···O distances (3·22 and 3·39 Å) to the constraint of crystal-packing forces which require molecules related by lattice translations to have the same orientation. However, this constraint does not apply to the 2-aminopyridine molecules *A* and *B* in the 2:1 complex with barbital. In this crystal structure, the vectors $C(2) \rightarrow NH_2$ in non-symmetry-related 2-aminopyridine molecules (Fig. 2) make an angle of 14·8°. Thus, the long NH···O=C hydrogen bonds between 2-aminopyridine or adenine and barbital appear to be due, at least in part, to the rather low affinity for hydrogen bonding of the donor and acceptor groups which are involved.

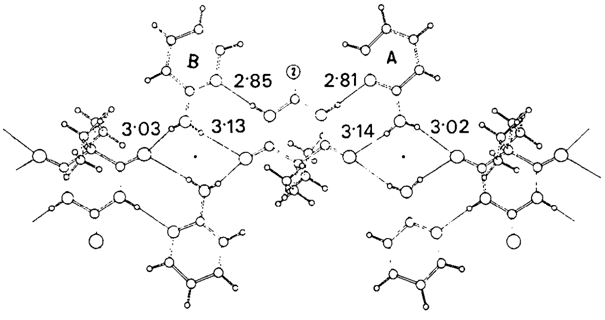

Fig. 2. The hydrogen bonding. Distances N···O and N···N are shown in Å.

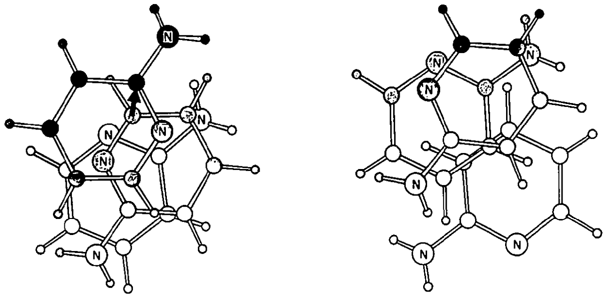

Fig. 3. The overlap of 2-aminopyridine molecules viewed normal to the plane of the central molecules *A* on the left and *B* on the right. The shortest interatomic distance between overlapping molecules (indicated by the arrow) is 3·46 Å.

In the crystal structures of the complexes of barbital with adenine, with 2-aminopyridine and with imidazole (Hsu & Craven, 1974), there is a recurrent pattern of short NH···N and long NH···O=C hydrogen bonds, both in the Watson–Crick and Hoogsteen configurations. A single NH···N hydrogen bond does not confer specificity upon the overall molecular interaction. However, this hydrogen bond appears to be important for the strong association of adenine or its analogs with barbiturate derivatives.

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