

The X-ray Structure of the Molecular Complex 9-Ethyladenine-Parabanic Acid

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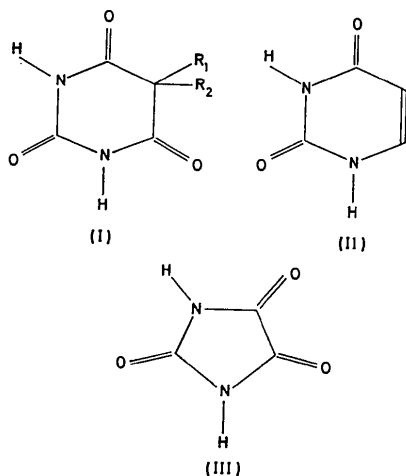
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The hydrogen-bonded complex 9-ethyladenine-parabanic acid, $C_{10}H_{11}N_7O_3$, crystallizes in the space group *Pbcn* with unit-cell parameters $a = 21.386$ (8), $b = 7.119$ (5) and $c = 16.288$ (6) Å, with eight complexes per unit cell. Intensity data were measured with monochromated Mo $K\alpha$ radiation. The structure was solved by direct methods and was refined by full-matrix least-squares procedures to a final $R = 0.059$ based on 1137 observed unique reflections. The adenine and parabanic acid molecules associate through a Hooft pairing that includes an extremely long N-H...O hydrogen bond. The parabanic acid accepts no other hydrogen bonds. In contrast, through two additional hydrogen bonds, each with unusual features, all three of the adenine hydrogen-bond acceptor sites are utilized. The structure exhibits no unusual carbonyl-carbonyl contacts.

Introduction

The barbiturates (I) form hydrogen-bonded complexes with adenine derivatives which in $CHCl_3$ solutions have association constants that are an order of magnitude greater than those of analogous complexes incorporating derivatives of uracil (II) (Kyogoku, Lord & Rich, 1968; Kyogoku & Yu, 1970). Yet crystallographic studies (Voet, 1972; Gartland & Craven, 1974; Hsu & Craven, 1974; Voet, 1975) indicate that barbiturate carbonyl oxygen atoms have little tendency to participate in hydrogen-bonding interactions.



In an effort to explain this apparent dilemma we have undertaken a program to investigate the crystal structures of barbiturate-like molecules complexed with adenine derivatives. Parabanic acid (III) can be considered to be a barbiturate in which the tetrahedral ring carbon atom has been eliminated. In a previous communication (Shieh & Voet, 1975) we reported

the elucidation of the structure of what was initially thought to be the complex 9-ethyladenine-(parabanic acid)₂ dihydrate. However it was soon discovered that one of the parabanic acid molecules in the complex had suffered a hydrolytic ring opening to form oxaluric acid. Hence the crystal structure actually consisted of the isomeric complex 9-ethyladenine-parabanic acid-oxaluric acid monohydrate. Therefore, although the analysis of this crystal structure quite clearly indicated that parabanic acid was a poor hydrogen-bond acceptor, the unexpected appearance of the oxaluric acid molecule presented serious difficulties in correlating the structural features of the complex with those of adenine-barbiturate complexes.

In the present study we report the crystal-structure determination of the complex 9-ethyladenine-parabanic acid. It will be seen below that the hydrogen-bonding interactions of this complex closely resemble those of various adenine-barbiturate complexes.

Experimental

Crystals of 9-ethyladenine-parabanic acid (A.P), with the form of colorless elongated rectangular plates, were grown by the slow evaporation of an ethanol solution of 9-ethyladenine (Cyclo Chemical) and parabanic acid (Aldrich Chemical) in equimolar ratio. The ultraviolet spectrum of an aqueous solution of a washed crystal was identical with that obtained from an aqueous solution of 9-ethyladenine and parabanic acid in equimolar amounts.

A crystal measuring $0.30 \times 0.05 \times 0.16$ mm that had been cut from a larger crystal was mounted for use in X-ray diffraction measurements. Preliminary Weissenberg and precession photographs showed that the crystal had orthorhombic symmetry. The systematic absences of the $0kl$ reflections for k odd, the $h0l$ reflections for l odd and the $hk0$ reflections for $h+k$ odd indicated that the space group of the crystal was *Pbcn*. All subsequent X-ray measurements were

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made on a Picker FACS-I diffractometer equipped with a pyrolytic graphite monochromator and employing Mo $K\alpha$ radiation ($\lambda=0.71069$ Å). The unit-cell dimensions, which were determined by the least-squares fit of the angular positions of twelve reflections with $2\theta \geq 23.5^\circ$, are presented in Table 1.

Table 1. *Crystal data for 9-ethyladenine-parabanic acid*

Molecular formula $C_{10}H_{11}N_7O_3$	
$a=21.386$ (8) Å	F.W. 277.2
$b=7.119$ (5)	$V=2479.80$ Å ³
$c=16.288$ (6)	$d_{\text{obs}}=1.484$ g cm ⁻³
Space group <i>Pbcn</i>	$d_{\text{calc}}=1.481$
$Z=8$	$\mu(\text{Mo } K\alpha)=1.2$ cm ⁻¹
	$F(000)=1152$

The density of the crystals (Table 1), as determined by flotation in a mixture of n-hexane and CCl_4 is in excellent agreement with the calculated density for a unit cell containing eight molecules each of 9-ethyladenine and parabanic acid.

The X-ray diffraction data were measured to the limit $2\theta=50^\circ$ with the $\theta-2\theta$ scan mode, a scan rate of 1° min^{-1} and a scan width of 1.75° . Stationary background counts of 20 s each were taken at both limits of each scan. The intensities of the $\bar{1}0\bar{6}$, the 911 and the 043 reflections were monitored after every fiftieth measurement. They showed no significant variation during the data-collection process.

The measured intensities, I , were corrected for Lorentz and polarization effects. No absorption corrections were made due to the small size of the crystal and its low linear absorption coefficient for Mo $K\alpha$ radiation. Standard deviations, $\sigma(I)$, were calculated (Stout & Jensen, 1968) assuming an instrumental

instability factor of 0.02. Of the 2203 measured unique reflections, the 1137 with $I > 2.33\sigma(I)$ were considered to be observed.

The structure was solved in a straightforward manner with *MULTAN* (Main, Woolfson & Germain, 1971; Declercq, Germain, Main & Woolfson, 1973). All twenty expected non-hydrogen atoms in the asymmetric unit were located by the peak-search routine of this structure-solving system.

The structure was refined by the full-matrix least-squares method in which the quantity minimized was $\sum w(|F_o| - |F_c|)^2$. Here the summation is over the 1137 observed reflections and $w=1/\sigma^2(I)=1/\sigma^2(F_o)$. The atomic scattering factors for non-hydrogen atoms were taken from Cromer & Waber (1965) and those for hydrogen atoms were taken from Stewart, Davidson & Simpson (1965). Refinements of the overall scale factor and all atomic positional and isotropic thermal parameters followed by similar refinements in which the anisotropic thermal parameters were varied reduced R to 0.098. Several successive difference Fourier maps at this stage sufficed to reveal the positions of the eleven expected hydrogen atoms. Further refinement in which the anisotropic thermal parameters of the non-hydrogen atoms and the isotropic thermal parameters of the hydrogen atoms were varied caused R to converge to its final value of 0.059, based on the 1137 observed unique reflections.* The highest peak in the final difference Fourier map had a peak height of $0.33 \text{ e } \text{Å}^{-3}$.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31703 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Positional and thermal parameters for the complex 9-ethyladenine-parabanic acid*

The positional parameters are expressed as fractions of a unit-cell edge. The anisotropic parameters have the functional form $T = \exp[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + 2hk\beta_{12} + 2hl\beta_{13} + 2kl\beta_{23}) \times 10^{-4}]$. Isotropic temperature factors have the functional form $T = \exp[-B \sin^2 \theta/\lambda^2]$. Standard deviations as determined from the variance-covariance matrix of the final cycle of least-squares refinement are given in parentheses and refer to the least significant digits of their corresponding parameters. The prefixes A and P refer to the 9-ethyladenine and the parabanic acid molecules respectively.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
AN(1)	0.9349 (1)	0.1275 (6)	0.3255 (2)	13 (1)	224 (13)	26 (2)	5 (3)	3 (1)	0 (4)
AC(2)	0.8748 (2)	0.1416 (8)	0.3482 (3)	17 (1)	229 (17)	28 (2)	0 (4)	-3 (1)	-6 (5)
AN(3)	0.8506 (1)	0.1936 (6)	0.4208 (2)	13 (1)	205 (12)	25 (2)	-1 (3)	1 (1)	-4 (4)
AC(4)	0.8962 (2)	0.2300 (7)	0.4750 (3)	13 (1)	134 (14)	23 (2)	0 (3)	0 (1)	4 (4)
AC(5)	0.9596 (2)	0.2187 (7)	0.4611 (3)	10 (1)	167 (14)	25 (2)	-4 (3)	2 (1)	8 (4)
AC(6)	0.9789 (2)	0.1674 (7)	0.3818 (3)	13 (1)	178 (14)	32 (2)	5 (3)	5 (1)	7 (5)
AN(7)	0.9918 (1)	0.2720 (5)	0.5309 (2)	14 (1)	230 (13)	25 (1)	-1 (3)	1 (1)	0 (4)
AC(8)	0.9478 (2)	0.3135 (8)	0.5841 (3)	16 (1)	251 (18)	23 (2)	-5 (3)	0 (1)	7 (5)
AN(9)	0.8890 (1)	0.2939 (6)	0.5537 (2)	13 (1)	179 (12)	22 (1)	5 (2)	2 (1)	0 (3)
AN(6)	1.0390 (2)	0.1569 (8)	0.3593 (3)	13 (1)	353 (16)	27 (2)	0 (4)	4 (1)	0 (5)
AC(1')	0.8299 (2)	0.3243 (8)	0.5983 (3)	15 (1)	200 (17)	26 (2)	5 (4)	2 (1)	1 (5)
AC(2')	0.8087 (3)	0.1534 (11)	0.6425 (5)	28 (2)	242 (21)	51 (3)	-16 (5)	16 (2)	0 (7)
PN(1)	1.1125 (2)	0.3173 (6)	0.5865 (2)	12 (1)	260 (15)	31 (2)	-4 (3)	-1 (1)	-9 (4)
PC(2)	1.1652 (2)	0.2884 (7)	0.5396 (3)	18 (1)	174 (15)	33 (2)	-9 (4)	0 (1)	1 (5)
PN(3)	1.2153 (2)	0.3408 (6)	0.5876 (2)	11 (1)	239 (14)	32 (2)	2 (3)	-1 (1)	-8 (4)
PC(4)	1.1973 (2)	0.4096 (8)	0.6629 (3)	17 (1)	200 (16)	28 (2)	2 (3)	0 (1)	11 (5)
PC(5)	1.1254 (2)	0.3860 (8)	0.6621 (3)	17 (1)	218 (17)	26 (2)	-1 (4)	1 (1)	-3 (5)
PO(2)	1.1664 (1)	0.2300 (5)	0.4706 (2)	23 (1)	290 (12)	31 (1)	-7 (3)	0 (1)	-24 (4)
PO(4)	1.2289 (1)	0.4693 (6)	0.7167 (2)	23 (1)	363 (13)	35 (1)	-11 (3)	-8 (1)	-22 (4)
PO(5)	1.0905 (1)	0.4254 (6)	0.7168 (2)	21 (1)	392 (14)	38 (2)	8 (3)	7 (1)	-16 (4)

Table 2 (cont.)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
AH(1)	0.846 (2)	0.113 (5)	0.305 (2)	2.0 (0.9)
AH(2)	1.045 (2)	0.149 (6)	0.308 (2)	2.8 (1.1)
AH(3)	1.067 (2)	0.191 (7)	0.389 (3)	3.9 (1.4)
AH(4)	0.956 (1)	0.352 (6)	0.643 (2)	2.4 (0.9)
AH(5)	0.799 (1)	0.383 (6)	0.556 (2)	2.4 (0.9)
AH(6)	0.838 (2)	0.426 (6)	0.637 (2)	2.4 (1.0)
AH(7)	0.769 (2)	0.175 (7)	0.668 (3)	5.7 (1.4)
AH(8)	0.841 (2)	0.113 (8)	0.683 (3)	6.3 (1.6)
AH(9)	0.802 (2)	0.063 (8)	0.604 (3)	6.0 (1.8)
PH(1)	1.072 (2)	0.289 (6)	0.565 (2)	4.3 (1.2)
PH(2)	1.254 (2)	0.322 (6)	0.575 (2)	2.0 (1.0)

The molecular structures

The molecular configuration of the crystal structure of A.P is illustrated in Fig. 1 together with the atomic numbering scheme used in this report. Table 2 contains the final atomic positional and thermal parameters of the structure. The covalent bond distances and angles in the structure are presented in Fig. 2.

The covalent-bond parameters of the 9-ethyladenine molecule are in excellent agreement with the average values of the corresponding parameters in previously reported adenine-containing structures (Voet & Rich, 1970). The relatively large thermal parameters of the

methyl group probably indicate that this group, as is often the case with methyl groups, has a large degree of rotational freedom.

The covalent-bond parameters of the parabanic acid molecules indicate that the crystal structure has imposed small but significant distortions on the twofold molecular symmetry of the parabanic acid molecule. The parabanic acid bond parameters are in reasonable agreement with the corresponding quantities of parabanic acid molecules reported in other structural studies (Davies & Blum, 1955; Colman & Medlin, 1970*a,b*; Shieh & Voet, 1975). Both the 9-ethyladenine and the parabanic acid molecules appear to suffer small but significant distortions from planarity as can be seen from Table 3.

The intermolecular associations

A major feature of the crystal structure of A.P is the hydrogen-bonded associations among its component molecules. The parameters describing these interactions are given in Table 4.

The adenine ring forms a Hoogsteen-like base pair with a neighboring parabanic acid molecule. The least-squares planes of these molecules form a dihedral angle of 6.1°. The PN(1)–PH(1)···AN(7) hydrogen

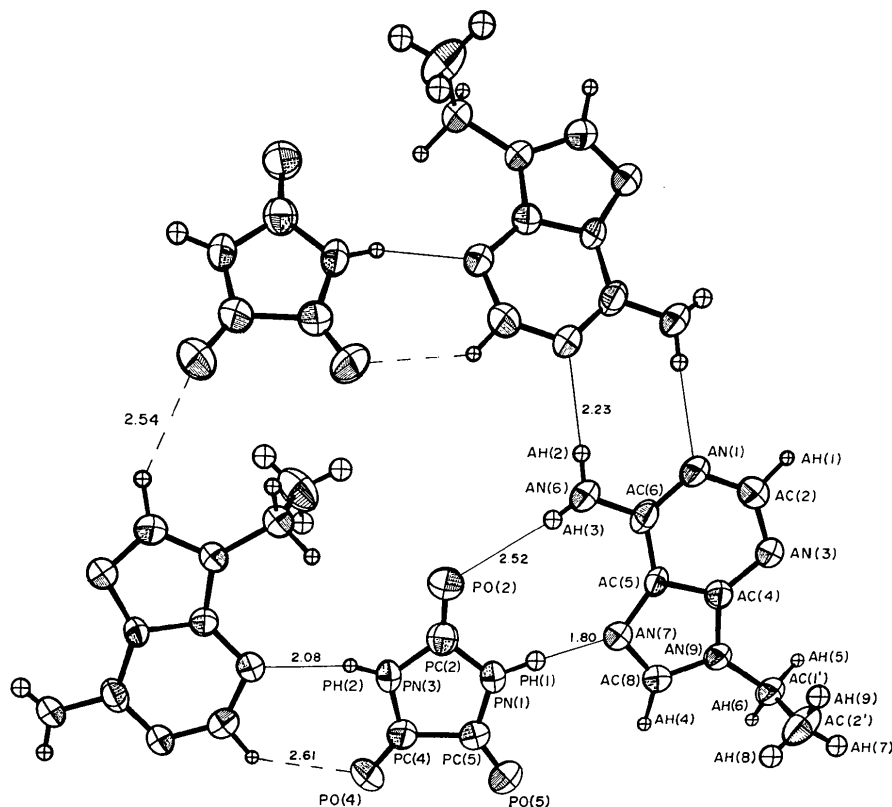


Fig. 1. A perspective drawing of a section of the crystalline complex 9-ethyladenine-parabanic acid illustrating the hydrogen-bonding interactions in the structure. Non-hydrogen atoms are illustrated as thermal ellipsoids at the 50% level. Hydrogen atoms are shown as spheres at the 25% level. Hydrogen bonds and C–H···O hydrogen-bond-like interactions are represented by thin lines and dashed lines, respectively, accompanied by their distances in Å.

Table 3. Deviations of atoms from the least-squares plane through the indicated atoms

Adenine atom	Deviation†	Parabanic acid atom	Deviation‡
N(1)	-0.017 Å	N(1)	-0.005 Å
C(2)	0.002	C(2)	-0.007
N(3)	0.006	N(3)	0.017
C(4)	0.023	C(4)	-0.018
C(5)	0.028	C(5)	0.014
C(6)	-0.013	O(2)	-0.031*
N(7)	0.007	O(4)	-0.038*
C(8)	-0.011	O(5)	0.022*
N(9)	-0.025	H(1)	-0.015*
N(6)	-0.055*	H(2)	0.132*
C(1')	-0.009*	R.m.s.	
H(2)	-0.25*	deviation	0.013
H(3)	-0.15*		
R.m.s. deviation	0.017		

* Atoms not included in calculating the least-squares plane.

† The equation of the least-squares plane is:

$$-0.0478x - 6.7884y + 4.9059z = 0.7034 \text{ \AA.}$$

‡ The equation of the least-squares plane is:

$$1.6605x - 6.6008y + 5.9683z = 3.2587 \text{ \AA.}$$

bond in this pairing is shorter (2.754 and 1.80 Å, respectively for the N...N and H...N distances) than any of the N-H...N hydrogen bonds between the adenine derivatives and uracil-like molecules that were tabulated by Hsu & Craven (1974). In contrast, the nearly linear AN(6)-AH(3)...PO(2) interaction in this pairing is so long (3.313 and 2.52 Å, respectively for the N...O and H...O distances) that it violates the criterion of Hamilton & Ibers (1968) that the H...O distance in a hydrogen bond should be at least 0.2 Å shorter than its van der Waals distance [2.6 Å (Pauling, 1960)].

Gartland & Craven (1974) have tabulated many N-H...O hydrogen bonds with N...O distances greater than 3.10 Å. Among these are two N-H...O interactions that are almost as long as the above interaction. These occur in the Hoogsteen pairings of the crystalline complexes 9-ethyladenine-5,5-diethylbarbituric acid (Voet, 1972) and 9-ethyladenine-5-isopropyl-5-bromallylbarbituric acid (Voet & Rich,

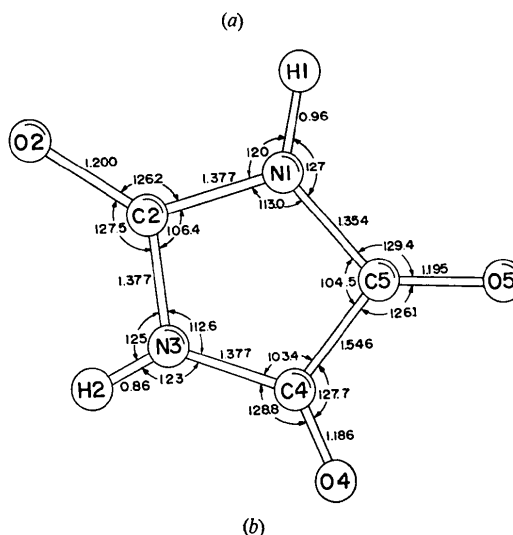
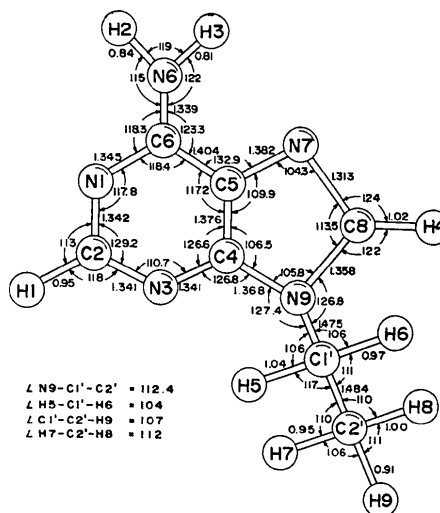


Fig. 2. The covalent distances (Å) and angles (°) for (a) 9-ethyladenine and (b) parabanic acid. The average standard deviations of these quantities are 0.005 Å and 0.4°, respectively, for bonds involving only non-hydrogen atoms and 0.4 Å and 3°, respectively, for bonds involving hydrogen atoms.

Table 4. Hydrogen-bonding interactions

The prefixes A and P refer to the 9-ethyladenine and the parabanic acid molecules respectively.

Hydrogen bond <i>D-H...A</i>	Distance <i>D...A</i> (Å)	Distance <i>H...A</i> (Å)	Angle <i>D-H...A</i> (°)
(1) Normal hydrogen bonds			
AN(6)-AH(3)...PO(2)	3.313	2.52	167
PN(1)-PH(1)...AN(7)	2.754	1.80	171
AN(6)-AH(2)...AN(1 ⁱ)	3.069	2.23	178
PN(3)-PH(2)...AN(3 ⁱⁱ)	2.908	2.08	163
(2) C-H...O hydrogen-bond-like interactions			
AC(8)...AH(4)...PO(5 ⁱⁱⁱ)	3.438	2.54	147
AC(2 ⁱⁱ)-AH(1 ⁱⁱ)...PO(4)	3.388	2.61	140

Superscripts refer to atoms related to those in Table 2 by the following symmetry operations: (i) $2-x \ y \ \frac{1}{2}-z$; (ii) $\frac{1}{2}+x \ \frac{1}{2}-y \ 1-z$; (iii) $2-x \ y \ \frac{1}{2}-z$.

1972). The N...O distances in these pairings are 3.387 and 3.339 Å, respectively, and the H...O distance in the former complex is 2.47 Å. This information together with the observation that crystal structures rarely fail to form all of their potential hydrogen bonds, suggests that the AN(6)-AH(3)...PO(2) interaction should be classified as a hydrogen bond.

Neighboring adenine rings that are related by a crystallographic twofold axis of symmetry parallel to the *b* axis associate through the formation of two N(6)-H(2)...N(1) hydrogen bonds. Similar adenine self-pairings have been observed in several other crystal structures: 9-methyladenine-1-methyl-5-bromouracil (Baklagina, Vol'kenshtein & Kondrashev, 1966); 8-bromo-9-ethyladenine-8-bromo-9-ethylhypoxanthine (Sakore & Sobell, 1969); and 2,6-diamino-9-ethylpurine-(1-methyl-5-fluorouracil)₂ (Chandross & Rich, 1971). However in all of these latter complexes the paired adenine rings are related by a center of symmetry and hence are parallel. In the present structure the least-squares planes of the two paired adenine rings form a dihedral angle of 35.1°. This can be seen in Fig. 3. Nevertheless the N(6)-H(2)...N(1) hydrogen bond is of normal length (its N...N distance is 3.069 Å) for adenine-adenine interactions (Hsu & Craven, 1974) and is essentially linear (178°).

This is apparently due to the fact that the atoms of the adenine amine group depart considerably from coplanarity with the adenine ring as is indicated in Table 3.

The parabanic acid N(3)-H(3) group forms a hydrogen bond with atom N(3) of a second neighboring adenine residue. This interaction is flanked by a marginal C-H...O hydrogen-bond-like interaction involving the adenine C(2)-H(1) group and the parabanic acid O(4) atom in an H...O contact of 2.61 Å. Each parabanic acid molecule also participates in a weak C-H...O hydrogen-bond-like interaction involving parabanic acid atom O(5) and the C(8)-H(4) group of a third neighboring adenine residue. The H...O distance of this association is 2.54 Å. The non-linearity of this C-H...O system is typical of such interactions.

The stacking interactions in the crystal structure of A.P are illustrated in Fig. 4. It can be seen that these interactions are characterized by a few atom-atom contacts. There are no distances closer than van der Waals distances among these contacts.

The methyl group of the adenine ring appears to be crowded against neighboring parabanic acid molecules. The PO(2)...AH(9) ($2-x, -y, 1-z$) and PO(4)...AH(7) ($\frac{1}{2}+x, \frac{1}{2}+y, \frac{3}{2}-z$) distances of 2.51 and 2.53 Å are less than the minimal O...H van der

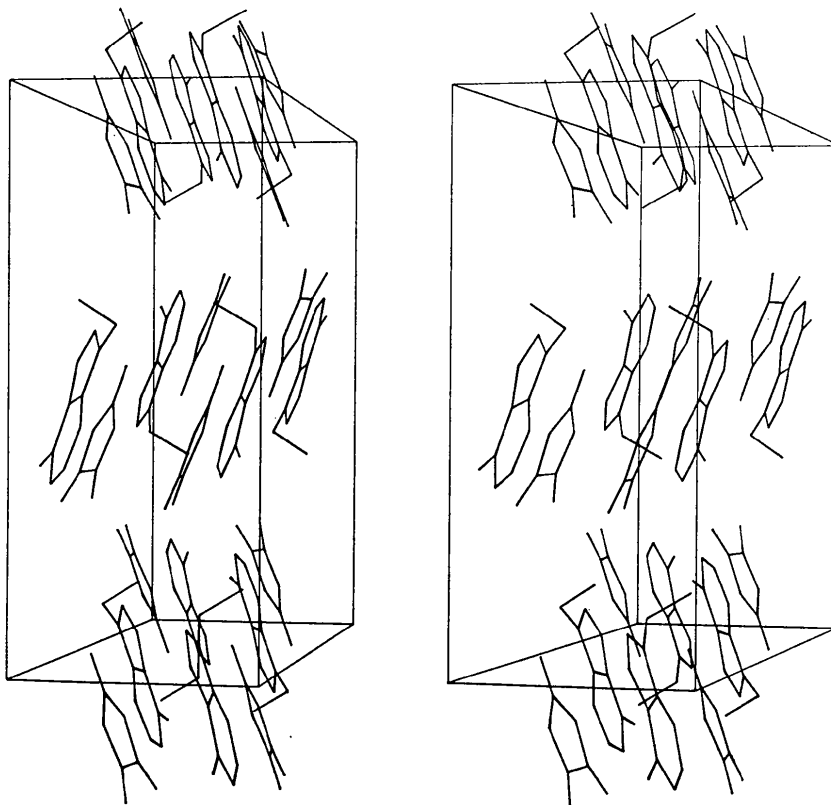


Fig. 3. A stereographic drawing illustrating the packing of the crystalline complex 9-ethyladenine-parabanic acid into its unit cell. Hydrogen atoms have been omitted for the sake of clarity.

Waals contact distance of 2.6 Å (Pauling, 1960). A similar crowding of a 9-ethyladenine methyl group against a parabanic acid oxygen atom is observed in the complex 9-ethyladenine-parabanic acid-oxaluric acid monohydrate (Shieh & Voet, 1975).

Discussion

The intermolecular associations in the present structure constitute further evidence indicating that carbonyl groups in small ring compounds bearing several such groups are poor hydrogen-bond acceptors (Voet, 1972; Hsu & Craven, 1974; Gartland & Craven, 1974; Shieh & Voet, 1975). Thus, although parabanic acid appears to have six hydrogen-bond acceptor sites, in the complex A.P the parabanic acid molecule accepts only one rather questionable hydrogen bond. In contrast, all three adenine hydrogen-bond acceptor sites are utilized in A.P. The parabanic acid molecules in the complexes 9-ethyladenine-parabanic acid-oxaluric acid monohydrate (Shieh & Voet, 1975) and urea-parabanic acid (Colman & Medlin, 1970a) display a similar reluctance to act as hydrogen-bond acceptors.

Shieh & Voet (1976) have suggested that there is insufficient mobile electron density available in planar ring compounds bearing several carbonyl groups, such as barbiturates or parabanic acid, to allow each carbonyl oxygen atom to build up its normal electronic charge. Therefore, due to the Coulombic nature of hydrogen-bonding interactions (Pauling, 1960), these carbonyl groups are poor hydrogen-bond acceptors.

The adenine N(3) atom has not been observed to participate in hydrogen-bonding interactions in adenine-uracil complexes (Voet & Rich, 1970; Sobell, 1972). However it acts as the acceptor in N-H...N hydrogen bonds in the adenine-barbiturate derivative complexes 8-bromo-9-ethyladenine-5-allyl-5-isobutyl-barbituric acid (Epstein, Zeiger, Crocker & Voet, 1976); 9-ethyladenine-parabanic acid-oxaluric acid monohydrate (Shieh & Voet, 1975); 8-bromo-9-ethyladenine-cyanuric acid monohydrate (Shieh & Voet, 1976); and A.P. The N...N distances in these interactions range from 2.91 to 3.04 Å and average 2.97 ± 0.05 Å. In contrast, the N...N distances, as tabulated by Gartland & Craven (1974) for hydrogen bonds in adenine-uracil or adenine-barbiturate complexes in which adenine atoms N(1) or N(7) are the acceptor groups, are considerably shorter. They range from 2.78 to 2.94 Å and average 2.83 ± 0.04 Å. This suggests that the N(3) atom of adenine is a weak hydrogen-bond acceptor. The foregoing accounts for the difference in lengths between the PN(1)...AN(7) and the PN(3)...AN(3) hydrogen bonds. Although parabanic acid, due to its chemical resemblance to barbiturates, is expected to be a strong hydrogen-bonding donor (Gartland & Craven, 1974), both a strong donor and acceptor group are required for the formation of a short hydrogen bond.

Several barbiturate-derivative-containing crystal structures, including that of 9-ethyladenine-parabanic acid-oxaluric acid monohydrate (Shieh & Voet, 1975), exhibit contacts involving carbonyl groups which are closer than van der Waals contacts. However no such interactions are found in the present structure. This further corroborates the suggestion that such carbonyl-carbonyl interactions are inherently weak (Epstein, Zeiger, Crocker & Voet, 1976; Shieh & Voet, 1976).

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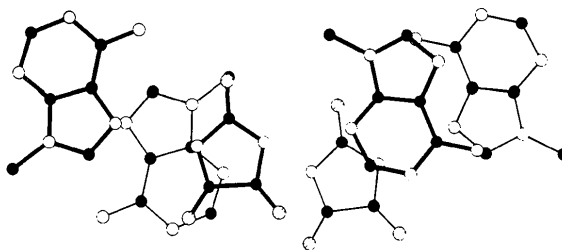


Fig. 4. A projection of a portion of two consecutive layers of the crystalline complex 9-ethyladenine-parabanic acid illustrating the stacking relationships within the structure. Atoms are represented by circles of arbitrary radii with carbon atoms as filled circles, nitrogen atoms as unfilled circles and oxygen atoms as shaded circles. Hydrogen atoms have been omitted for the sake of clarity.

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The Crystal and Molecular Structure of *N*-t-Butyloxycarbonyl-L-thiazolidine-4-carboxylic Acid (C₉H₁₅NO₄S)

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The title compound (C₉H₁₅NO₄S) is orthorhombic with $a = 11.937$ (12), $b = 12.552$ (12), $c = 7.836$ (8) Å, $Z = 4$, space group $P2_12_12_1$. 1186 independent reflexions were collected on an automatic diffractometer with Cu $K\alpha$ radiation. The structure was solved by direct methods and refined by full-matrix least squares to a final R of 0.039. Except for two of the methyl groups, the t-butyloxycarbonyl group is planar. The peptide unit and the thiazolidine ring conformation are similar to those found in thiazolidine-4-carboxylic acid. The packing of the molecules is governed by hydrogen bonding and van der Waals contacts.

Introduction

In a previous study of cyclo-glycyl-3-thiaprolyl (Haar, Femandjian, Robert, Lefebvre-Soubeyran & Savrda, 1976) we have shown that the molecule adopts the same conformation as its analogue cyclo-L-prolyl-glycyl (Pettit, Von Dreele, Bollinger, Traxler & Brown, 1973; Von Dreele, 1975). It is interesting to know whether the diketopiperazine ring has any influence on the thiazolidine ring and to show that the substitution of an S atom does not disturb the proline ring conformation. The structure of the title compound was solved to compare it with cyclo-glycyl-3-thiaprolyl and with thiazolidine-4-carboxylic acid (Goodman, Niu & Su, 1970; Goodman, Chen, Benedetti, Pedone & Corradini, 1972; Loscalzo, Kallen & Voet, 1973) where the carboxyl group was found to have a zwitterionic structure.

Experimental

The crystals are colourless needles. The unit-cell dimensions were preliminarily determined from oscillation and Weissenberg photographs. The orthorhombic space group corresponding to the systematic absences is $P2_12_12_1$. For data collection a $0.20 \times 0.25 \times 0.60$ mm crystal was mounted parallel to a on a CAD 3 Enraf-Nonius diffractometer. The measurement and least-squares refinement of ten high-Bragg-angle reflexions led to: $a = 11.937$ (12), $b = 12.552$ (12), $c = 7.836$ (8) Å, $V = 1174$ Å³.

With $Z = 4$, $d_c = 1.32$ which agrees with $d_o = 1.31$ g cm⁻³. 1186 independent reflexions were collected with Cu $K\alpha$ ($\lambda = 1.5418$ Å) Ni-filtered radiation in the θ - 2θ scan mode up to $\theta = 66^\circ$. The scan range varied according to $\Delta\theta = 1.5 + 0.4 \text{ tg } \theta$. Two standard reflexions were measured every 40 reflexions and showed no systematic variation. 88 reflexions with $I < 3\sigma(I)$ where $\sigma(I)$ is the standard deviation based on counting statistics were considered as unobserved and omitted from the refinement. The intensities were corrected for the Lorentz-polarization factor but not for absorption ($\mu = 25$ cm⁻¹). A Wilson plot gave the scale and overall temperature factor ($B = 3.63$ Å²).

Structure determination and refinement

The structure was solved by direct methods. Normalized structure factors E_{hkl} were calculated and introduced in a *MULTAN* procedure (Germain, Main & Woolfson, 1971). 272 reflexions with $E > 1.20$ were used to determine the starting sets. The E map computed from the most probable starting set gave the positions of all non-hydrogen atoms. A full-matrix least-squares refinement led to an R of 0.130 ($R = \sum w||F_o| - |F_c|| / \sum w|F_o|$) which fell to 0.067 with anisotropic thermal parameters. At this stage a difference synthesis showed all the H atoms in their expected positions. In the last least-squares cycles all parameters were varied except the thermal parameters of the H atoms which were those of their attached atom. The function min-