hydrogen bonds between hydroxyls, as observed in the alditols, thereby permitting other alternatives which may involve conformational changes as in this pair of structures.

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Aza Analogs of Nucleic Acid Constituents. IV. The Crystal and Molecular Structure of 6-Azauracil

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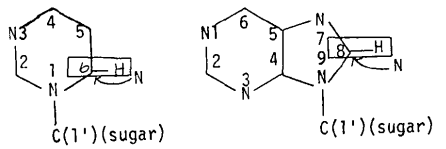
The crystal and molecular structure of 6-azauracil, $C_3N_3O_2H_3$, has been determined from three-dimensional X-ray data obtained on an automatic four-circle diffractometer equipped with a graphite monochromator and Mo $K\alpha$ radiation. The material crystallizes in space group $P2_12_12_1$ of the orthorhombic system with four molecules in a cell of dimensions $a=4{\cdot}875$ (4), $b=17{\cdot}611$ (15), and $c=5{\cdot}022$ (3) Å; the observed and calculated densities are 1·73 (2) and 1·74 g cm^{-3}, respectively. The structure has been refined by full-matrix least-squares techniques using 714 independent data to a conventional R index of 0·037. The azapyrimidine ring is roughly planar, with all possible donor and acceptor atoms except N(6) participating in intermolecular hydrogen bonding. This latter feature is in contrast to the structure of uracil, in which only one of the oxygen atoms participates in hydrogen bonding. Consequently, in 6-azauracil the C–O bond lengths are equal (1·224 Å) while in uracil they are markedly unequal. The effect on the ring geometry of the substitution of N(6) for C(6)–H is discussed.

Introduction

Many aza analogs of purines, pyrimidines and their nucleosides are anti-neoplastic and fungistatic agents (Skoda, 1963; Roblin, Lampen, English, Cole & Vaughan, 1945). Biological effects of 6-azauracil have been investigated extensively. It has been shown to inhibit animal tumors (Schindler & Welch, 1957) and

human acute leukemia (Schnider, Frei, Tuohy, Gorman, Freireich, Brindley & Clements, 1960). It was also shown to have powerful inhibitory effects on the growth of a large number of microorganisms (Sorm & Skoda, 1956; Handschumacher & Welch, 1956). 6-Azauracil, in a bacterial system, is converted to its riboside, 6-azauridine, and finally to its 5′-nucleotide, 6-azauridine 5′-phosphate, the latter acting as the inhibitor of the enzyme orotidylic acid decarboxylase (Skoda, 1963).

Structurally, the azapurines and azapyrimidines differ from the normal bases of the nucleic acids in having a nitrogen atom in place of a carbon atom at some position in the ring. Although this is a minor structural modification, when effected at a strategic location in the ring it has the potential of bringing about enormous changes in the enzymatic processes and coding properties of nucleic acids in various species. Two of these locations on the ring are the 6-position on the pyrimidine ring and the 8-position on the purine ring (I). The importance of these positions lies in the fact that they are next to the glycosidic bond, C(1′)–N, C(1′) being the first carbon atom of the sugar in the corresponding nucleoside. Therefore, the formal substitution of N for CH may alter the hydrogen-bonding pattern and cause electronic perturbations, especially in the vicinity of the substitution. It may also alter the relative orientation of the sugar and the base both by removing one of the principal barriers to rotation (Donohue & Trueblood, 1960; Haschemeyer & Rich, 1967) around the glycosidic bond, namely, the H atom shown boxed in (I), and by giving rise to intramolecular electrostatic interactions between the electronegative nitrogen atom (Schwalbe & Saenger, 1973) and the exocyclic oxygen atom, O(5′), of the nucleoside or nucleotide (Saenger & Suck, 1973; Prusiner & Sundaralingam, 1973; Wood, Hruska, Mynott & Sarma, 1973).



(I)

The length and, therefore, presumably the strength (Stroud, 1973) of the glycosidic bond, however, and the rotation around it (Abola & Sundaralingam, 1973) as expressed by the glycosidic torsion angle, φ_{CN}, (Donohue & Trueblood, 1960) may be affected significantly even if the substitution on the base does not take place immediately next to the glycosidic bond. We are, therefore, investigating the structures of the aza analogs of nucleic acid bases and their nucleosides. We report here in detail the crystal and molecular structure of 6-azauracil. A preliminary account of this structure together with the structure of 6-azathymine has previously appeared (Singh & Hodgson, 1973).

Experimental

Large plate-like crystals of 6-azauracil were grown from an aqueous solution containing a small amount of $HgCl_2$. Our previous attempts to crystallize 6-azauracil from aqueous ethanol and aqueous methanol yielded only medium-size crystals, all of which were apparently twinned. Rohrer & Sundaralingam (1970) have also observed that the presence of certain metal salts promotes the growth of single crystals of purines and pyrimidines. We have successfully crystallized other compounds by this technique, some of which did not yield good crystals by other methods. The pertinent crystallographic data for 6-azauracil are presented in Table 1. The space group was determined from Weissenberg and precession photographs of a crystal mounted along the a axis, which is the longest crystal dimension. The unit-cell constants were determined by accurately centering 12 general reflections on a Picker FACS-1 automatic diffractometer, equipped with a pulse-height analyzer and a graphite monochromator, using a molybdenum tube at a take-off angle of 0·5° (narrow source). The intensity data were collected on the same instrument at a take-off angle of 2·3° with the $\theta/2\theta$ scan technique at a scan rate of 0·5° min^{-1}. Each reflection was scanned from 1·25° below the calculated $K\alpha_1$ peak position to 1·25° above the calculated $K\alpha_2$ peak position. The backgrounds were counted for 40 s at the beginning and at the end of each scan. Intensities of three standard reflections, monitored after every 50 measurements, remained essentially constant. All independent reflections occurring within 60° in 2θ were measured. Some of the strongest E's (normalized structure factors) were obtained from the data beyond the copper sphere ($2\theta > 55·5°$).

Table 1. *Crystallographic data for 6-azauracil*

$a = 4·875\ (4)$	$\alpha=\beta=\gamma=90°$
$b = 17·611\ (15)$	$d_c = 1·74$ g cm^{-3}
$c = 5·022\ (3)$	$d_o = 1·73$ g ml^{-1}
$V = 431·2$ Å^3	$Z = 4(C_3N_3O_2H_3)$

Systematic absences: $h00$ for h odd
$0k0$ for k odd
$00l$ for l odd

Space group: $P2_12_12_1$

The data were processed by the method of Corfield, Doedens & Ibers (1967) using a local program written in PL1 for the IBM 370. The intensities were assigned standard deviations according to the formula:

$$\sigma(I) = [C + 0·25(\mathrm{ts/tb})^2(\mathrm{BH} + \mathrm{BL}) + (pI)^2]^{1/2}$$

where the symbols have their usual meanings (Corfield *et al.*, 1967). The value of p was chosen as 0·06. The values of $|F_o|^2$ and $\sigma(F_o)^2$ were obtained on an arbitrary scale by correcting the intensities, I, and e.s.d.'s $\sigma(I)$, for Lorentz and polarization factors. No absorption correction was applied to the data, since the small value of μ (1·6 cm^{-1}) indicates that absorption effects are

minimal. Of the 791 independent intensities measured, 714 were greater than three times their estimated standard deviations; only these 714 data were used in the refinement.

Solution and refinement of the structure

The structure was solved by direct methods using the $\sum_2$ relationship of Hauptman & Karle (1953) in a symbolic addition procedure for non-centrosymmetric crystals as suggested by Karle & Karle (1966). Starting from a set of structurally incoherent points, the tangent formula converged to the correct solution.

The positional parameters obtained as above and individual isotropic temperature parameters for all C, N and O atoms in the molecule were refined by full-matrix least-squares calculations to the usual discrepancy values $R=\sum||F_o|-|F_c||/\sum|F_o|$ and $R_w=[w(|F_o|-|F_c|)^2/\sum w(F_o)^2]^{1/2}$, of 0·077 and 0·136. A difference Fourier map calculated at this stage revealed the locations of all three hydrogen atoms in the molecule. The next round of refinement was carried out on the positional and anisotropic thermal parameters of C, N and O atoms and positional and isotropic thermal parameters of H atoms which resulted in the discrepancy values $R=0·041$ and $R_w=0·076$. Examination of the $|F_o|$ and $|F_c|$ values suggested that there was probably a small error due to secondary extinction since for strong low-order reflections $|F_o|$ was systematically smaller than $|F_c|$. Inclusion of the extinction correction (Zachariasen, 1968) as described elsewhere (Meyer, Singh, Hatfield & Hodgson, 1972) yielded the final discrepancy values $R=0·037$ and $R_w=0·059$. In the final cycle, no parameter experienced a shift of greater than 0·4 times its e.s.d.; examination of the values of $|F_o|$ suggested that our weighting scheme was appropriate. The least-squares refinements were carried out on F, the function minimized being $\sum w(|F_o|-|F_c|/g)^2$, where g is a function of the variable extinction parameter (Zachariasen, 1968; Hodgson & Ibers, 1969); weights, w, were taken as $w=4F_o^2/\sigma^2(F_o)^2$. The form factors for O, N and C were from the tabulation of Ibers (1962), while those for H were from Stewart, Davidson & Simpson (1965).

The positional parameters, derived from the last cycle of least-squares refinement, and their associated standard deviations as estimated from the inverse matrix, are presented in Table 2. Thermal parameters and their e.s.d.'s are presented in Table 3.* The final value of the extinction parameter, c, is $1·1\times10^{-8}$ ($\sigma=0·3\times10^{-8}$), which, although, not very large, is probably significant. The estimated standard error in an observation of unit weight is 1·2.

Table 2. *Positional parameters for 6-azauracil, with e.s.d.'s in parentheses*

	x	y	z
N(1)	0·5141 (3)	0·0596 (1)	0·5611 (3)
C(2)	0·4360 (4)	0·0996 (1)	0·7814 (3)
N(3)	0·5873 (3)	0·1643 (1)	0·8276 (3)
C(4)	0·8051 (3)	0·1872 (1)	0·6789 (3)
C(5)	0·8657 (4)	0·1378 (1)	0·4541 (3)
N(6)	0·7269 (3)	0·0773 (1)	0·4002 (3)
O(2)	0·2442 (3)	0·0808 (1)	0·9240 (3)
O(4)	0·9365 (3)	0·2446 (1)	0·7294 (2)
H(1)	0·384 (6)	0·017 (2)	0·503 (6)
H(3)	0·555 (6)	0·193 (2)	0·977 (6)
H(5)	0·000 (6)	0·152 (2)	0·325 (6)

Description and discussion

A view of the molecule is seen in Fig. 1. The bond lengths and angles for 6-azauracil and the most precise values for uracil (Stewart & Jensen, 1967) are compared in Fig. 2. Both of these determinations are of comparable precision (mean e.s.d., σ, of 0·002 Å in bond lengths and of 0·2° in bond angles not involving the hydrogen atoms). The ring bond lengths which differ significantly in the two structures are N(3)–C(4) (6·0σ), C(4)–C(5) (13·0σ) and C(5)–N(6), [C(5)–C(6) in uracil] (24·5σ). The last of these three bonds has different lengths in the two compounds because in 6-azauracil it is a C=N bond while in uracil it is a C=C bond.

* The table of $|F_o|$, corrected for extinction, and $|F_c|$ has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30364 (6pp.). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 3. *Thermal parameters for 6-azauracil, with e.s.d.'s in parentheses*

The form of the anisotropic thermal ellipsoid is $\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

	β_{11} or B(Å^2)	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
N(1)	0·0360 (7)	0·0017 (0)	0·0268 (6)	0·0012 (1)	−0·0010 (6)	−0·0015 (1)
C(2)	0·0258 (6)	0·0014 (0)	0·0202 (5)	−0·0002 (1)	−0·0021 (6)	0·0005 (1)
N(3)	0·0279 (6)	0·0017 (0)	0·0180 (4)	−0·0008 (1)	0·0016 (4)	−0·0009 (1)
C(4)	0·0231 (6)	0·0017 (0)	0·0160 (5)	−0·0003 (2)	−0·0015 (5)	−0·0002 (1)
C(5)	0·0250 (6)	0·0022 (1)	0·0177 (5)	0·0007 (1)	0·0019 (5)	−0·0009 (1)
N(6)	0·0333 (6)	0·0020 (0)	0·0235 (5)	0·0006 (1)	−0·0005 (5)	−0·0016 (1)
O(2)	0·0340 (6)	0·0023 (0)	0·0312 (5)	−0·0018 (1)	0·0061 (5)	0·0006 (1)
O(4)	0·0358 (6)	0·0023 (0)	0·0235 (5)	−0·0034 (1)	0·0025 (5)	−0·0014 (1)
H(1)	4·6 (7)					
H(3)	3·6 (5)					
H(5)	3·7 (6)					

It should be noted, however, that in each case the observed bond length is very similar to that predicted for a double bond (Pauling, 1960; Sutton, 1965). The other two bonds cited above simply show the effects of altered electron distribution in the azapyrimidine system as compared with that in the normal pyrimidine. This altered electron density in 6-azauracil is also reflected in the N(1)–N(6) bond length (1·351 Å) which has approximately the same length as N(1)–C(6) (1·358 Å) in uracil, thus indicating less double-bond character in the former. A similar result was observed for this bond in 6-azauridine (Schwalbe & Saenger, 1973). The bonds C(2)–N(3) and C(4)–N(3) have the same length in uracil (1·376 and 1·371 Å respectively) but differ by 0·019 Å in 6-azauracil. The largest differences in the bond angles between 6-azauracil and uracil are at N(6), where the ring angle (117·8°) is smaller than that at C(6) by 4·5°, and at C(5), where the ring angle is larger by the same amount (Fig. 2). All other angles in the two compounds, except N(1)–C(2)–N(3), also differ significantly. The angles observed here for 6-azauracil, however, are similar to those found in 6-azauridine (Schwalbe & Saenger, 1973); as can be seen in Table 4, however, the bond lengths in the pyrimidine moiety of 6-azauridine are generally shorter than those in 6-azauracil. It should be noted that the internal ring angles at the three nitrogen atoms N(1), N(3) and N(6) are in general agreement with Singh's (1965) rule for pyrimidine ring angles at protonated (~125°) and at non-protonated (~115°) N atoms.

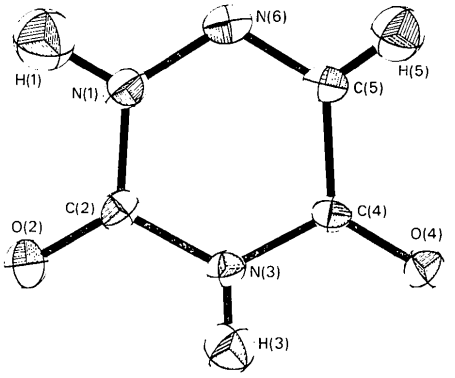


Fig. 1. View of the 6-azauracil molecule, showing the conventional numbering scheme. Thermal ellipsoids are drawn at the 40% probability level.

Table 4. *Bond lengths in 6-azauracil (AUC) and in the pyrimidine moiety of 6-azauridine, (AUD) (not including hydrogen atoms), and their differences, Δ(AUC–AUD)*

	AUC*	AUD†	Δ(AUC–AUD)
N(1)–C(2)	1·366	1·382	−0·016
C(2)–N(3)	1·378	1·386	−0·008
N(3)–C(4)	1·359	1·377	−0·018
C(4)–C(5)	1·456	1·468	−0·012
C(5)–N(6)	1·291	1·289	+0·002
N(6)–N(1)	1·351	1·371	−0·020
C(2)–O(2)	1·224	1·213	−0·011
C(4)–O(4)	1·224	1·200	−0·004

* This investigation
† Schwalbe & Saenger (1973).

It is clear, therefore, that the substitution of N for CH has a significant effect on the geometry of the ring not only near the site of the substitution but also at positions far removed from it.

The two carbonyl bond lengths in 6-azauracil are of the same length (1·224 Å) whereas in uracil they differ by 0·030 Å. While it is possible that these differences between the two compounds may in part be due to the N substitution a more probable explanation lies in the different extent of hydrogen-bond formation by the two compounds (Craven, Cusatis, Gartland & Vizzini,

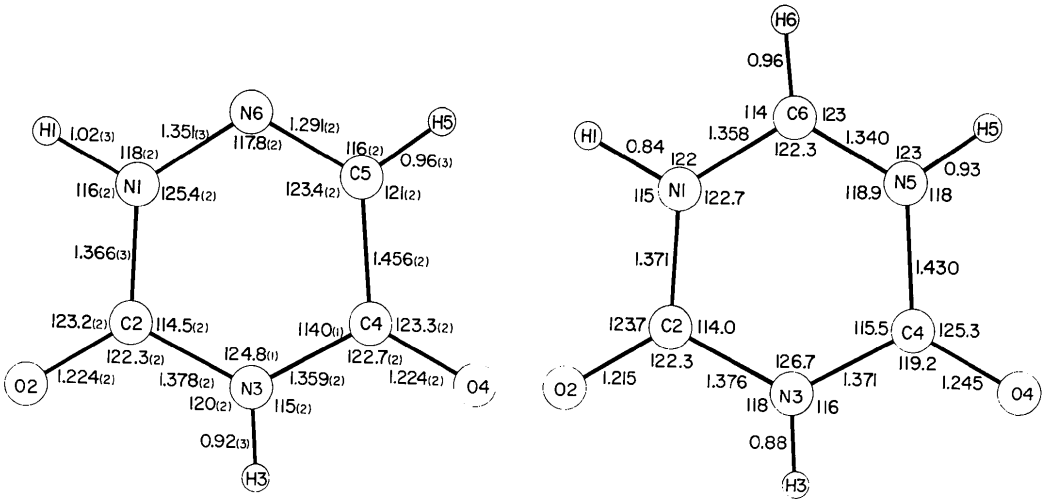


Fig. 2. Comparison of the bond lengths and angles in 6-azauracil (left) and uracil (Stewart & Jensen, 1967).

1973). In 6-azauracil there is one hydrogen bond to each carbonyl oxygen (see below), whereas in uracil there are two hydrogen bonds to O(4) and none to O(2).

The hydrogen-bonding scheme and the packing of molecules in the crystal are presented in Fig. 3. There are two unique hydrogen bonds in the structure: N(1)–H(1)···O(2) of length 2·858 Å with N–H–O angle of 160 (3)° and N(3)–H(3)···O(4) of length 2·839 Å and N–H–O angle of 172 (3)°; N(6) does not participate in any hydrogen-bond formation. There are two potential hydrogen-bond donors, N(1) and N(3), and three potential acceptors, O(2), O(4) and N(6), in 6-azauracil. There is, therefore, an excess of acceptors and this might be cited as the reason for the lack of participation in any hydrogen bonding by N(6). However, electronic rather than packing forces, such as a lack of electron-donating ability at N(6), might also be responsible for its non-participation, since in 6-azauridine N(6) has a charge of only −0·47 e whereas O(2) and O(4) have charges of −1·38 e (Schwalbe & Saenger, 1973).* It might be recalled that in uracil there are two donors O(2) and O(4), and two acceptors N(1) and N(3), and yet O(4) accepts two hydrogen bonds while O(2) accepts none. In the nucleoside 6-azauridine N(6) does not participate in any hydrogen-bond formation either and is, instead, in close contact with C(2′) of the sugar and its attached hydrogen. In the recently determined structure of 6-azacytidine in our laboratory (Singh & Hodgson, 1974) we have observed a similar non-participation of N(6) in any hydrogen-bond formation, and close contacts with C(2′) and its attached hydrogen. It appears, therefore, that the primary function of N(6) in 6-azapyrimidines and their nucleosides is not the provision of an extra hydrogen-bond acceptor; this is in contrast to the role attributed to N(8) in the azapurines 8-azaguanine (Sletten, Sletten & Jensen, 1968) and allopurinol (Prusiner & Sundaralingam, 1972). The function of N(6) is, however, to alter the geometry of the base and [by virtue of the absence of a proton associated with N(6)] to increase the freedom of rotation around the glycosidic bond; the latter results in an interaction between N(6) and the sugar atoms (see above).

The lengths of the two hydrogen bonds, 2·858 and 2·839 Å, are normal and the small difference between them is of little significance. The packing is rather simple with columns of screw-related molecules running parallel to the two short axes *a* and *c*.

Stacking interactions as depicted in Fig. 4 are minimal as is usually the case with pyrimidines (Bugg, Thomas, Rao & Sundaralingam, 1971). The main interaction is between the polar carbonyl group and the polarizable pyrimidine ring system. The intermolecular separations between the interacting molecules are normal except for C(2)···C(5) (3·30 Å) which is 0·10 Å shorter than the sum of the van der Waals radii of the two atoms (3·40 Å). The azapyrimidine ring is roughly planar, with no atom deviating from the best least-squares plane by more than 0·014 Å; oxygen atom O(4) is almost exactly in this plane, but O(2) is 0·024 Å out of the plane.

In addition to various local programs, the programs used in this analysis were modifications of Ibers's *NUCLS* least-squares program, Dellaca & Robinson's *FOURIER* program, Johnson's *ORTEP* plotting program, Busing, Martin & Levy's *ORFFE* function and error program, Huber & Brisse's *NRC*-5 phasing program, and Doedens's *RSCAN* program. We are grateful

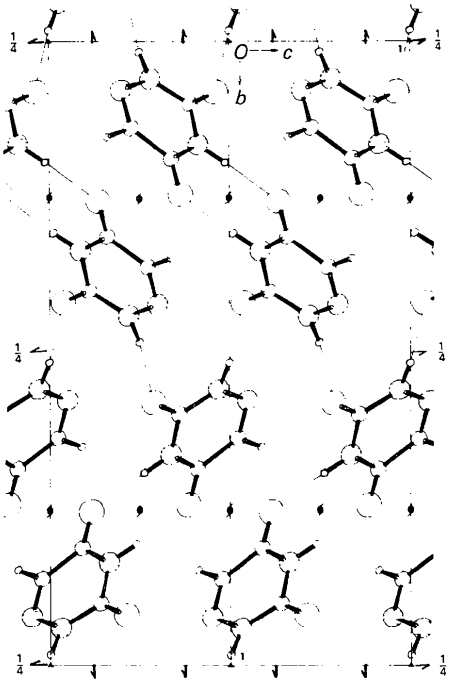


Fig. 3. View of the packing in crystals of 6-azauracil projected on the *bc* plane. Nitrogen atoms are shaded. Two unit cells are outlined, and the hydrogen bonds are shown as thin lines.

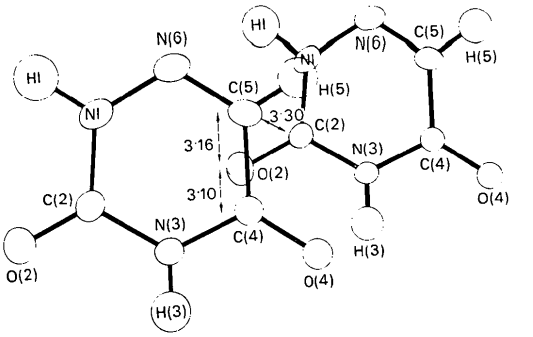


Fig. 4. Stacking interactions in the crystals of 6-azauracil. The shortest intermolecular contacts are indicated.

* The charges given here are derived from EHT and are gross overestimates. Our CNDO calculations give values of −0·01, −0·37, and −0·32e for N(6), O(2), and O(4) respectively. The conclusion that N(6) is less electron-rich than O(2) or O(4) is, of couse, unaffected.

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The Crystal Structure of the Triterpene Gymnemagenin, $C_{30}H_{50}O_6$

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Gymnemagenin, $C_{30}H_{50}O_6$, is the deacylated aglycone of 'gymnemic acid', the antisweet principle of *Gymnema sylvestre*. The compound crystallizes in the orthorhombic space group $P2_12_12_1$ with 4 molecules in a unit cell of dimensions $a = 12{\cdot}714$ (3), $b = 30{\cdot}99$ (1) and $c = 6{\cdot}954$ (1) Å. The crystal structure has been determined by direct methods, and refined to $R = 0{\cdot}036$ for 2630 observed reflections. The results confirm that the structure of gymnemagenin is 3β,16β,21β,22α,23,28-hexahydroxyolean-12-ene. Four intermolecular and two intramolecular hydrogen bonds per molecule employ all six hydrogens available for hydrogen bonding. Attempts to solve the structure by rigid-body Patterson search techniques led to ambiguous results; these were ultimately found to have arisen from a large, unanticipated distortion of the molecular skeleton from the assumed model.

Introduction

Gymnemagenin (Stöcklin, Weiss & Reichstein, 1967), is the hydrolysis product of gymnemic acid A, a glycoside present in the leaves of *Gymnema sylvestre* R. Br. (*Asclepiadaceae*). Acid A has been shown (Stöcklin *et al.*, 1967; Sinsheimer, Rao, McIlhenny, Smith, Maassab & Cochran, 1968) to be the chief contributor to the long-known strange property of this tropical plant, that of temporarily depressing the ability to taste sweet substances. Chemical and spectral evidence

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