Covalently Linked Purine–Pyrimidine Analogs. Structure of 7-(4,6-Dioxo-5-pyrimidinyl)-theophylline Dihydrate,* $C_{11}H_{10}N_6O_4.2H_2O$

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Abstract. $M_r = 326 \cdot 27$, monoclinic, $P2_1/n$, $a = 9 \cdot 633$ (5), $b = 12 \cdot 794$ (9), $c = 11 \cdot 920$ (5) Å, $\beta = 101 \cdot 0$ (4)°, $V = 1442$ (2) Å^3, $Z = 4$, $D_x = 1 \cdot 50$, D_m(flotation) $= 1 \cdot 48_5$ Mg m^{-3}, λ(Mo $K\alpha$) $= 0 \cdot 71069$ Å, μ(Mo $K\alpha$) $= 0 \cdot 13$ mm^{-1}, $F(000) = 680$, room temperature, $R = 0 \cdot 045$ and $R_w = 0 \cdot 065$ for 2849 independent reflections with $I > 2 \cdot 5\sigma(I)$. Since the malonic site is deprotonated and the amidinic site is protonated, the dioxopyrimidine residue assumes a structure with a significant contribution of a mesomeric zwitterionic form in accordance with the charge distribution on the malonic and amidinic sites deducible from the net residual charges computed for the atoms of this ring. Also, an intermolecular interaction between a carbonylic O of the theophylline with the CH group of pyrimidine is in agreement with the positive net charges obtained for this group. Both couples of CO and NH groups of the dioxopyrimidine moiety are engaged in hydrogen bonding with the water molecules in the crystal.

Introduction. The interest in the synthesis (Cohen, 1972) and structure determinations of covalently linked purine–pyrimidine analogs is related to the possibility these compounds have to interfere with biological functions of cell components (Balis, 1968). In the present paper we have determined the structure of the title compound in which the bicyclic moiety, the theophylline, is linked to a dioxopyrimidine nucleus by an N—C single bond.

Experimental. The synthesis of the compound has been described (Carotti, De Laurentis, Ferappi & Ottolino, 1977). Single crystals suitable for X-ray analysis obtained from an aqueous solution by slow evaporation. Approximate unit-cell dimensions and space group determined from oscillation and Weissenberg photographs. Crystal $0 \cdot 5 \times 0 \cdot 3 \times 0 \cdot 2$ mm. Automatic Syntex $P2_1$ diffractometer, graphite monochromator, Mo $K\alpha$ radiation. Unit-cell parameters:

least-squares fit of the angular settings of 15 reflections in the range $5° < \theta < 20°$. $2\theta_{max} = 60 \cdot 0°$, ω-scan technique. Three reflections (339, 532, 061) measured after every 100 showed only small random deviations. 4212 independent reflections recorded; 2850 with $I > 2 \cdot 5\sigma(I)$ considered observed and used for the calculations. Lorentz and polarization corrections. No corrections for extinction or absorption. Structure solved by *MULTAN* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). 300 reflections and 2116 $\sum_2$ relationships used in the phase-determining procedure. An E map computed with the phases from the set with the highest figures of merit revealed all the non-H positions, which were refined isotropically then anisotropically by block-diagonal least squares. $\sum w(|F_o| - |F_c|)^2$ minimized; $w = (a + |F_o| + c|F_o|^2)^{-1}$ with a and c equal to $2F_{o(min)}$ and $2/F_{o(max)}$ respectively. A difference Fourier map computed at this stage showed all the H atoms in stereochemically feasible positions. H-atom positional parameters and isotropic thermal parameters derived from those of the carrier atoms included and held fixed in the refinement. Reflection 020 excluded from the last stages of refinement since it was judged to be influenced by extinction. In final refinement cycle $(\Delta/\sigma)_{max} = 0 \cdot 05$. Final R $0 \cdot 045$ and R_w $0 \cdot 065$ for all observed reflections; goodness of fit $0 \cdot 32$. Scattering factors from *International Tables for X-ray Crystallography* (1974). All calculations carried out on the HP 21MX minicomputer (Cerrini & Spagna, 1977) of the CNR Research Area and on the Univac 1110 of the University of Rome.

Discussion. The final atomic parameters of the non-H atoms are given in Table 1,† while Fig. 1 shows the

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* Theophylline is 3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione.

Table 1. *Final fractional coordinates and B_{eq} values of the non-H atoms with e.s.d.'s in parentheses*

$$B_{eq} = \tfrac{4}{3}\sum_i\sum_j b_{ij}\mathbf{a}_i\cdot\mathbf{a}_j.$$

	x	y	z	$B_{eq}(\text{Å}^2)$
N(1)	0.8079 (2)	0.3394 (1)	0.5421 (1)	3.2 (1)
C(1)	0.8537 (3)	0.4433 (2)	0.5854 (2)	5.3 (1)
C(2)	0.7594 (2)	0.2725 (2)	0.6184 (1)	3.3 (1)
O(2)	0.7632 (2)	0.2985 (2)	0.7175 (1)	5.2 (1)
N(3)	0.7076 (2)	0.1774 (1)	0.5777 (1)	3.3 (1)
C(3)	0.6536 (3)	0.1046 (2)	0.6541 (2)	4.8 (1)
C(4)	0.7064 (2)	0.1518 (1)	0.4656 (1)	2.7 (1)
C(5)	0.7533 (2)	0.2199 (1)	0.3924 (1)	2.5 (1)
C(6)	0.8119 (2)	0.3192 (1)	0.4271 (1)	2.8 (1)
O(6)	0.8617 (2)	0.3824 (1)	0.3689 (1)	4.2 (1)
N(7)	0.7317 (2)	0.1681 (1)	0.2882 (1)	2.6 (1)
C(8)	0.6772 (2)	0.0735 (1)	0.3075 (1)	3.2 (1)
N(9)	0.6601 (2)	0.0601 (1)	0.4142 (1)	3.5 (1)
N(11)	0.8515 (2)	0.2033 (1)	0.0156 (1)	3.3 (1)
C(12)	0.7692 (2)	0.2796 (2)	−0.0303 (1)	3.4 (1)
N(13)	0.6771 (2)	0.3226 (1)	0.0229 (1)	3.2 (1)
C(14)	0.6556 (2)	0.2887 (1)	0.1306 (1)	2.6 (1)
O(14)	0.5599 (2)	0.3311 (1)	0.1704 (1)	3.6 (1)
C(15)	0.7471 (2)	0.2085 (1)	0.1800 (1)	2.5 (1)
C(16)	0.8486 (2)	0.1634 (1)	0.1252 (1)	2.8 (1)
O(16)	0.9324 (2)	0.0921 (1)	0.1613 (1)	4.2 (1)
O(3)	0.5364 (2)	0.4629 (1)	0.8834 (1)	5.1 (1)
O(1)	0.9954 (2)	0.1100 (1)	0.8780 (1)	4.5 (1)

numbering scheme adopted together with the bond lengths and angles involving non-H atoms.

The geometry of the theophylline residue is in agreement with that of some recent structure determinations (Kojić-Prodić, 1979; Kojić-Prodić, Coffou & Ružić-Toroš, 1979; Ružić-Toroš, Kojić-Prodić & Coffou, 1981). The largest atomic deviation from the least-squares plane computed for the nine atoms of the theophylline ring is 0·027 (19) Å for the C(6) atom.

The structure of the dioxopyrimidine ring is unexpected (Carotti, De Laurentis, Ferappi & Ottolino, 1977). Bond lengths and angles show, within the limits of the errors, mirror symmetry perpendicular to this ring through atoms C(12) and C(15). Furthermore, bonds C(12)–N(11) and C(12)–N(13) [respectively 1·310 (3) and 1·306 (4) Å] are considerably shorter than bonds C(14)–N(13) and C(16)–N(11) [respectively 1·407 (2) and 1·408 (2) Å]; bonds C(14)–C(15) and C(15)–C(16) [respectively 1·407 (3) and 1·399 (4) Å] are of aromatic type; carbonyl bonds C(14)–O(14) and C(16)–O(16) [respectively 1·239 (4) and 1·239 (3) Å] are a little longer than the usual carbonyl bond lengths [see bonds C(2)–O(2) and C(6)–O(6); respectively 1·220 (2) and 1·221 (3) Å]. The pyrimidine ring is planar; the largest deviation from the least-squares plane computed for its six atoms is 0·018 (13) Å for the N(13) atom. Moreover, the malonic site is deprotonated and both the N atoms of this ring are protonated, as found in the final difference Fourier synthesis. This situation, although not strictly corresponding to a mesoionic state (Ollis & Ramsden, 1976) could be ascribed to a significant contribution of the mesomeric zwitterionic form (I) which was formerly

hypothesized for a quaternary derivative of 4,6-dioxopyrimidine (Prystas, 1967).

(I)
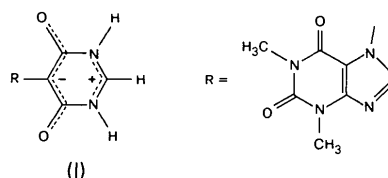
Both acidic and basic strengths, respectively, of the malonic and amidinic portions of this heterocycle appear to be sufficiently high to promote deprotonation of the malonic site and protonation of the amidinic site. Residual net atomic charges have been computed for the atoms of the dioxopyrimidine ring by an *ab initio* HF-MO-LCAO-SCF STO-3G calculation (Binkley, Whiteside, Krishnan, Seeger, DeFrees, Schlegel, Topiol, Kahn & Pople, 1980) and are shown in Fig. 2. The geometry of the non-H atoms used for this calculation is that found in the present crystal structure analysis. The three H atoms of the amidinic site were generated at distances of 1·00 and 1·08 Å respectively for the NH and CH groups, in the plane of the ring, and bisecting the valence angles of the atoms to which they are bound. The two H atoms attached to the imidazolic N atom were generated as saturators in the same directions of the simulating atoms C(5) and C(8) at a distance of 1·00 Å. As can be seen from Fig. 2, partial positive and negative charges can be obtained, respectively, for the amidinic and malonic sites.
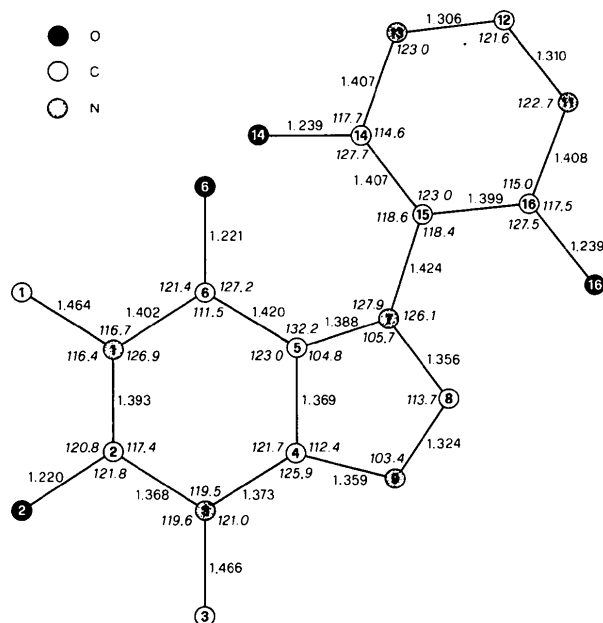

Fig. 1. The numbering scheme adopted together with bond lengths (Å) and angles (°). E.s.d.'s are in the ranges 0·002–0·004 Å and 0·2–0·4° respectively.

The dihedral angle between the imidazole and the pyrimidine rings is 67·3 (6)°.

The packing is governed by hydrogen bonding. There are six hydrogen bonds that all the acceptor and donor sites of the dioxopyrimidine residue form with the two water molecules; on the other hand, each water is donor in two hydrogen bonds and acceptor in another. The atoms participating in hydrogen-bond formation together with some relevant geometrical values are summarized in Table 2, while the scheme of their interactions is depicted in Fig. 3.

An intermolecular C—H⋯O contact of 2·156 Å [C⋯O = 3·006 (2) Å], shorter than the van der Waals contact between H and O (2·40 Å; Donohue, 1968), which involves the C(12)—H group of the pyrimidine ring of one molecule and the theophylline carbonylic O(2) of another molecule translated along **c**, allows the molecules to interact head-to-tail along the **c** direction. This contact is even shorter than other analogous contacts that the imidazole CH realizes with carbonyl groups in the crystal structures of theophylline monohydrate (Sutor, 1958a), caffeine monohydrate (Sutor, 1958b), 1,3,7,9-tetramethyluric acid (Sutor, 1963), caffeine–5-chlorosalicylic acid (Shefter, 1968), theophylline–5-chlorosalicylic acid (Shefter, 1969), or with the O of the nitro group in the crystal of theophylline–p-nitrophenol (Aoki, Ichikawa, Koinuma & Iitaka, 1978). This interaction, in view of the
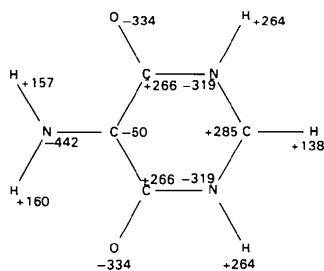
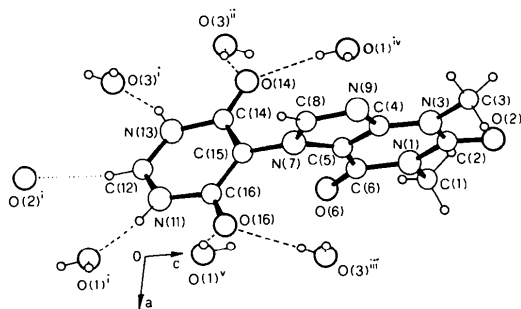Fig. 2. Residual net atomic charges (10^{-3} e) of the dioxopyrimidine residue.

Fig. 3. A view of the molecular conformation of the compound showing the hydrogen-bonding network with the water molecules (dashed lines). The dotted line represents the C—H⋯O interaction. The symmetry code is the same as in Table 2.

Table 2. *Hydrogen bonds between the dioxopyrimidine residue and the water molecules*

E.s.d.'s are in the ranges 0·002–0·007 Å and 0·2–0·4° respectively, for distances and angles involving non-H atoms.

D	A	D—H (Å)	D⋯A (Å)	H⋯A (Å)	D—H⋯A (°)
N(11)	O(1^i)	0·81	2·628	1·82	172
N(13)	O(3^i)	0·86	2·639	1·81	160
O(3^{ii})	O(14)	0·77	2·827	2·08	163
O(3^{iii})	O(16)	0·70	2·738	2·05	167
O(1^{iv})	O(14)	0·77	2·768	2·00	174
O(1^v)	O(16)	0·80	2·740	1·96	164

Symmetry code: (i) $x, y, z - 1$; (ii) $1 - x, 1 - y, 1 - z$; (iii) $\frac{1}{2} + x, \frac{1}{2} - y, -\frac{1}{2} + z$; (iv) $-\frac{1}{2} + x, \frac{1}{2} - y, -\frac{1}{2} + z$; (v) $2 - x, -y, 1 - z$.

angles C(12)—H(12)⋯O(2) and C(12)⋯O(2)—C(2) [respectively 149·7 (3) and 159·6 (2)°], and the angles N(11)—C(12)⋯O(2), N(13)—C(12)⋯O(2), H(12)⋯C(2)—N(1), H(12)⋯C(2)—N(3) [respectively 111·9 (3), 124·5 (2), 127·0 (3), 115·5 (3)°], may be a hydrogen bond, favored by the positive charges of the CH group as shown in Fig. 2.

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