

Fig. 2. The Newman projection along the N(3)—C(4) axis showing the alignment of non-bonded electron pairs and the cleaving C(4)—N(9) bond in the ester aminal function; N and O electron escorts are pictured as sp^2 - and sp^3 -hybridized, respectively.

We thank the Croatian Republic Research Fund for financial support and M. Bruvo, MSc, for data collection.

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Acta Cryst. (1987). **C43**, 542–545

Stereoelectronic Effects in Oxidative Transformations of Purines. II. Structure of 4,5-Dihydro-4,5-dimethoxy-3,7-dimethyluric Acid*

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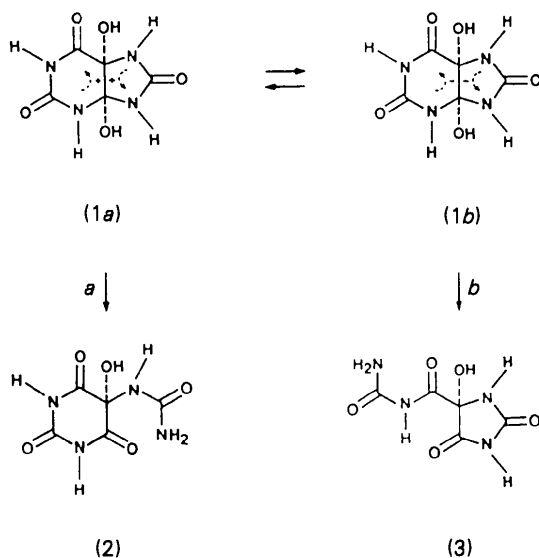
(Received 7 February 1986; accepted 17 September 1986)

Abstract. $C_9H_{14}N_4O_5$, $M_r = 258.24$, triclinic, $P\bar{1}$, $a = 12.443(6)$, $b = 7.508(4)$, $c = 6.883(4)$ Å, $\alpha = 107.60(4)$, $\beta = 91.56(5)$, $\gamma = 100.05(3)^\circ$, $V = 601.3(5)$ Å³, $Z = 2$, $D_x = 1.426$ g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0.7107$ Å, $\mu = 1.26$ cm⁻¹, $F(000) = 272$, room temperature, $R = 0.038$ for 2478 observed reflections. Substitution at N(7) causes steric overcrowding which favours the ring-twisted conformation of the *cis*-fused bicyclic system defined by the bridgehead torsion angle N(3)—C(4)—C(5)—N(7) of $92.0(1)^\circ$. The nearly orthogonal N(3)—C(4)—N(9)—C(8) array [$-95.3(1)^\circ$]

with N(9) antiperiplanar to the 4-methoxy group allows the cleavage of the N(3)—C(4) bond to take place with stereoelectronic control.

Introduction. The crystal-structure determination of the title compound was undertaken in continuation of our studies of conformational properties of tetrahedral intermediates in oxidative transformations of purines. We felt that the knowledge of bond-breaking processes and the required conformational changes of specific enzyme transformations could be gained through the application of stereoelectronic principles (Deslongchamps, 1984).

* Uric acid is 7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione.



The structure of 4,5-dihydro-4,5-dimethoxy-1-methyluric acid has already been determined, revealing that its ring-twisted conformation, which corresponds to the conformer (1a), and proper orientation of one non-bonded electron pair of the 4-methoxy group allow five-membered-ring opening (path *a*) to occur with the help of the stereoelectronic effect (Poje & Vicković, 1987). It was therefore of particular interest to establish the structure of a model of the conformer (1b), 4,5-dihydro-4,5-dimethoxy-3,7-dimethyluric acid, undergoing an alternative regiospecific ring opening at the N(3)–C(4) bond (path *b*), which mimics the key step of the caffolide pathway for degradation of purines (Poje, Paulus & Ročić, 1980; Poje, Palković, Perina, Vicković & Bruvo, 1985).

Experimental. The chlorination of theobromine in glacial acetic acid afforded 5-chloro-3,7-dimethylisouric acid, which was converted into the title compound by reaction with cold methanol. Recrystallization from water gave prism-shaped crystals. Crystal dimensions 0.38 × 0.33 × 0.23 mm, Philips PW 1100 diffractometer, graphite-monochromatized Mo *K*α radiation, cell parameters from 16 reflections ($6.8 \leq \theta \leq 9.4^\circ$); ω mode, scan width 1.2° , scan speed $0.03^\circ \text{ s}^{-1}$. From 2636 independent reflections ($-17 \leq h \leq 17$, $-10 \leq k \leq 10$, $0 \leq l \leq 9$, $5.8 \leq 2\theta \leq 60.0^\circ$), 89 intensities below $3\sigma(I)$, 60 background having $F_o \geq 0.025(F_o)_{\max}$, and nine strong reflections ($1\bar{1}0$, 200 , 110 , $3\bar{2}1$, $3\bar{1}1$, $2\bar{1}1$, $0\bar{1}1$, $\bar{1}01$, 101) apparently affected by secondary extinction were ignored. Three standard reflections showed no significant variation in intensity. Lorentz–polarization (locally written program) and absorption correction (Harkema, 1978) with transmission factor 0.960–0.976 were applied. Direct methods (*MULTAN80*, Main *et al.*, 1980) were used; with ambiguous $|E|$ statistics a noncentrosymmetric

solution was obtained. Although the structure was solved up to $R = 0.037$, the discrepancies between equivalent bonds in the two independent molecules and a comparison with related structures led to the centrosymmetric solution by shifting the origin 0.2 along *x*, *y*, *z* axes. All H atoms found in a ΔF map entered as input data to calculate the best positions of all H atoms (Vicković, 1985). At the end of the refinement ureide H atoms were relocated by a ΔF synthesis in order to confirm their specific geometry. In the last cycle, all atomic coordinates [except those for H(1) and H(9) atoms] were refined, non-H atoms anisotropically and H atoms isotropically, by full-matrix least-squares procedure using *F* magnitudes; $R = 0.038$, $wR = 0.053$, $w = \sigma^{-2}(F_o)$ (derived from counting statistics), $S = 0.18$, $(\Delta/\sigma)_{\max} = 0.19$ (for non-H atoms), $(\Delta/\sigma)_{\text{av}} = 0.1$. The highest electron density in final ΔF map $\Delta\rho_{\max} = 0.31 \text{ e } \text{Å}^{-3}$. 2478 observed intensity data, 213 parameters, atomic scattering factors and anomalous-dispersion-correction coefficients as defined by *XRAY76* (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976). All calculations were carried out using a Univac 1110/42 computer.

Discussion. Final atomic coordinates and equivalent isotropic thermal parameters are given in Table 1,* main bond lengths and angles and hydrogen-bond geometry in Table 2. An *ORTEP* drawing (Johnson, 1971) of the molecule is shown in Fig. 1 with the numbering scheme and the hydrogen-bonding pattern.

The ring-twisted conformation of the *cis*-fused bicyclic system which is defined by the bridgehead torsion angle N(3)–C(4)–C(5)–N(7) of $92.0(1)^\circ$ and a nearly orthogonal N(3)–C(4)–N(9)–C(8) array [$-95.3(1)^\circ$] represents a perfect model for conformer (1b). It is interesting to observe that C(10) and C(11) of the glycol ether grouping [O(4)–C(4)–C(5)–O(5)– $18.2(2)^\circ$] are here antiperiplanar to N(9) and C(6), respectively; the rotation of the 4-methoxy group with respect to the bicyclic system is such that there is a *gauche* N(3)⋯C(10) interaction of $2.796(3) \text{ Å}$, below the sum of the van der Waals radii (3.35 Å). The N(7) and N(9) atoms deviate significantly from planarity; the distances from the planes through their three adjacent atoms are $0.116(1)$ and $-0.154(2) \text{ Å}$, respectively.

A comparison with the inverted ring-twisted conformation (1a) of the 1-methyl analogue (Poje & Vicković, 1987) shows that the conformational properties of the

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, bond distances and angles involving H atoms and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43419 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

cis-fused system are dependent on substitution at the N atoms; with N(7) bearing a methyl group the repulsive interaction which dominates is the $C(7)H_3 \leftrightarrow O(5)$ repulsion, which leads to a preference for conformer (1*b*).

As a result of this arrangement primary stereoelectronic effects (Fig. 2) strongly favour the regio-specific N(3)–C(4) bond cleavage (path *b*). Consequently, the cleaving bond is longer than the C(4)–

Table 1. Fractional atomic coordinates ($\times 10^4$) and U_{eq} ($\text{\AA}^2 \times 10^3$) values

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}^\dagger
N(1)	9057 (1)	9457 (2)	1962 (2)	37 (<1)
C(2)	8876 (1)	7745 (2)	384 (2)	33 (<1)
O(2)	9426 (1)	7580 (2)	-1078 (2)	48 (<1)
N(3)	8088 (1)	6320 (2)	544 (2)	34 (<1)
C(3)	7958 (2)	4469 (2)	-1078 (3)	49 (<1)
C(4)	7443 (1)	6364 (2)	2296 (2)	29 (<1)
O(4)	7683 (1)	5058 (1)	3223 (2)	36 (<1)
C(5)	7538 (1)	8443 (2)	3810 (2)	29 (<1)
O(5)	7520 (1)	8512 (2)	5856 (2)	42 (<1)
C(6)	8582 (1)	9852 (2)	3751 (2)	32 (<1)
O(6)	8914 (1)	11277 (2)	5171 (2)	46 (<1)
N(7)	6611 (1)	9012 (2)	3005 (2)	35 (<1)
C(7)	6364 (1)	10909 (2)	3723 (4)	56 (<1)
C(8)	5852 (1)	7459 (2)	1884 (2)	34 (<1)
O(8)	4937 (1)	7509 (2)	1220 (2)	50 (<1)
N(9)	6288 (1)	5870 (2)	1660 (2)	37 (<1)
C(10)	8831 (1)	5296 (3)	3850 (3)	44 (<1)
C(11)	6531 (2)	7696 (4)	6514 (4)	63 (1)

$$\dagger U_{eq} = \frac{1}{3}[U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aba^*b^*\cos\gamma + 2U_{13}aca^*c^*\cos\beta + 2U_{23}bcb^*c^*\cos\alpha].$$

Table 2. Bond lengths (\AA) and angles ($^\circ$) and geometry of the hydrogen bonds (*e.s.d.*'s in parentheses)

N(1)–C(2)	1.387 (2)	C(5)–O(5)	1.394 (2)
N(1)–C(6)	1.354 (2)	C(5)–C(6)	1.535 (2)
C(2)–O(2)	1.220 (2)	C(5)–N(7)	1.449 (2)
C(2)–N(3)	1.353 (2)	O(5)–C(11)	1.425 (3)
N(3)–C(3)	1.476 (2)	C(6)–O(6)	1.209 (2)
N(3)–C(4)	1.462 (2)	N(7)–C(7)	1.450 (2)
C(4)–O(4)	1.388 (2)	N(7)–C(8)	1.371 (2)
C(4)–C(5)	1.575 (2)	C(8)–O(8)	1.226 (2)
C(4)–N(9)	1.441 (2)	C(8)–N(9)	1.364 (2)
O(4)–C(10)	1.446 (2)		
C(2)–N(1)–C(6)	127.4 (1)	C(4)–C(5)–N(7)	100.6 (1)
N(1)–C(2)–O(2)	119.3 (1)	O(5)–C(5)–C(6)	104.6 (1)
N(1)–C(2)–N(3)	117.9 (1)	O(5)–C(5)–N(7)	114.9 (1)
O(2)–C(2)–N(3)	122.8 (1)	C(6)–C(5)–N(7)	108.5 (1)
C(2)–N(3)–C(3)	117.1 (1)	C(5)–O(5)–C(11)	118.4 (2)
C(2)–N(3)–C(4)	126.1 (1)	N(1)–C(6)–C(5)	115.5 (1)
C(3)–N(3)–C(4)	116.3 (1)	N(1)–C(6)–O(6)	122.6 (1)
N(3)–C(4)–O(4)	110.6 (1)	C(5)–C(6)–O(6)	121.7 (1)
N(3)–C(4)–C(5)	112.2 (1)	C(5)–N(7)–C(7)	124.3 (1)
N(3)–C(4)–N(9)	110.8 (1)	C(5)–N(7)–C(8)	111.3 (1)
O(4)–C(4)–C(5)	114.1 (1)	C(7)–N(7)–C(8)	122.5 (1)
O(4)–C(4)–N(9)	107.5 (1)	N(7)–C(8)–O(8)	125.3 (1)
C(5)–C(4)–N(9)	101.2 (1)	N(7)–C(8)–N(9)	108.3 (1)
C(4)–O(4)–C(10)	114.3 (1)	O(8)–C(8)–N(9)	126.5 (1)
C(4)–C(5)–O(5)	113.2 (1)	C(4)–N(9)–C(8)	111.1 (1)
C(4)–C(5)–C(6)	115.4 (1)		

N–H...O	N–H	H...O	N...O	N–H...O
N(1)–H(1)...O(2 ^b)	0.86 (1) Å	2.04 (2) Å	2.881 (2) Å	163 (1)°
N(9)–H(9)...O(8 ^b)	0.87 (1)	1.98 (1)	2.852 (2)	171 (1)

Symmetry code: (i) 2–*x*, 2–*y*, –*z*; (ii) 1–*x*, 1–*y*, –*z*.

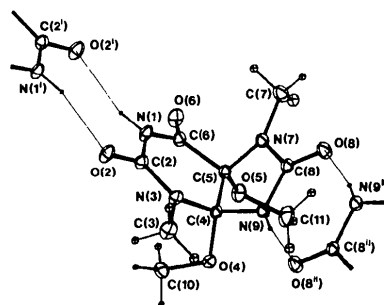


Fig. 1. Molecular conformation of the title compound (*R,R*-configuration).

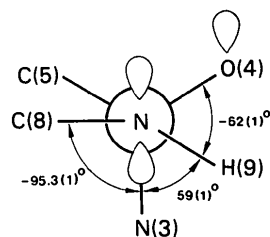


Fig. 2. The Newman projection along the N(9)–C(4) axis showing the alignment of non-bonded electron pairs and the cleaving N(3)–C(4) bond in the ester aminal function; the ureide-N and ether-O electron escorts are pictured as sp^2 - and sp^3 -hybridized, respectively.

N(9) bond, and the O(4) atom with an electron pair antiperiplanar to the N(3)–C(4) bond has a larger N(3)–C(4)–O(4) angle than the O(4)–C(4)–N(9) angle of the ester aminal function. Thus a conformational change (1*a*) \rightleftharpoons (1*b*) determines the different ring-opening pathways and the fundamental reason is due to stereoelectronic effects.

We thank the Croatian Republic Research Fund for financial support and also M. Bruvo, MSc, for data collection.

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Acta Cryst. (1987). **C43**, 545–547

Stereoelectronic Effects in Oxidative Transformations of Purines. III. Structure of 4,5-Ethylenedioxy-4,5-dihydro-3,7-dimethyluric Acid*

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(Received 7 February 1986; accepted 17 September 1986)

Abstract. $C_9H_{12}N_4O_5$, $M_r = 256.22$, triclinic, $P\bar{1}$, $a = 10.172$ (4), $b = 8.017$ (3), $c = 7.524$ (5) Å, $\alpha = 114.96$ (3), $\beta = 103.09$ (5), $\gamma = 89.94$ (4)°, $V = 538.7$ (5) Å³, $Z = 2$, $D_x = 1.579$ g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0.7107$ Å, $\mu = 1.41$ cm⁻¹, $F(000) = 268$, room temperature, $R = 0.036$ for 2590 observed reflections. N-containing rings of the hetero[4.4.3]propellane system adopt the ring-twisted conformation defined by the bridgehead torsion angle N(3)–C(4)–C(5)–N(7) of 83.9 (1)°; with the orthogonal N(3)–C(4)–N(9)–C(8) array [–89.7(1)°] and the O(4)–C(10) bond of the 1,4-dioxane chair antiperiplanar to the N(3)–C(4) bond, the ring opening in the conformationally rigid propellane is no longer stereoelectronically allowed.

Introduction. In the course of a study of the relationship between the molecular conformation and reactivity of appropriate chemical models it was shown that uric acid glycol, the key intermediate in oxidative breakdown of purines, can exist in two different ring-twisted conformations of the *cis*-fused bicyclic system. Regioselective ring opening requires that the π -type electron pair on one ureide N atom lies parallel and one non-bonded electron pair on the O atom antiperiplanar to the leaving N atom of the tetrahedral ester aminal array at C(4) (Poje & Vicković, 1987*a*, *b*).

In order to ascertain the stereoelectronic control in the cleavage of uric acid glycol, we have constructed a conformationally rigid propellane-type ether, 4,5-ethylenedioxy-4,5-dihydro-3,7-dimethyluric acid, in which non-bonded electrons on O(4) are oriented in such a way that the C–N bond cleavage of the ester aminal function cannot occur with the help of electronic

control. This derivative must, therefore, be unreactive and, indeed, it was completely stable under mild acidic conditions that are normally used for the hydrolysis of other uric acid glycol ethers.

Experimental. The title compound was synthesized by reaction of 5-chloro-3,7-dimethylisouric acid with cold anhydrous ethylene glycol. Recrystallization from water gave colourless prisms. Crystal size 0.21 × 0.25 × 0.38 mm, Philips PW 1100 diffractometer, graphite-monochromatized Mo $K\alpha$ radiation, unit-cell parameters from 25 reflections ($6 \leq \theta \leq 9^\circ$). Three standard reflections monitored every 2h showed no significant variation in intensity. A total of 2896 reflections were collected in the θ - 2θ mode, scan width 1.6°, scan speed 0.04° s⁻¹, $5 \leq 2\theta \leq 60.0^\circ$, $0 \leq h \leq 14$, $-11 \leq k \leq 11$, $-10 \leq l \leq 10$. From 2706 unique reflections 101 reflections with $I \leq 3\sigma(I)$ and 15 reflections (20 $\bar{2}$, 31 $\bar{2}$, 2 $\bar{1}\bar{1}$, 01 $\bar{1}$, 11 $\bar{1}$, 1 $\bar{1}$ 0, 200, 300, 110, 001, 101, 201, 011, 111, 211) due to secondary extinction were ignored. Data corrected for Lorentz and polarization effects but not for absorption. Structure solved by MULTAN80 (Main *et al.*, 1980). Six H atoms were located in a ΔF map and used to calculate 12 H atoms at idealized positions (Vicković, 1985); ureide H atoms were relocated by a ΔF synthesis to confirm their geometry; 2590 observed intensity data and 211 parameters in full-matrix least-squares refinement using F magnitudes; $R = 0.036$, $wR = 0.053$, $\sum w(|F_o| - |F_c|)^2$, $w = \sigma^{-2}(F_o)$ (derived from counting statistics), $S = 1.96$, $(\Delta/\sigma)_{\max} = 0.35$, $(\Delta/\sigma)_{\text{av}} = 0.01$ for all refined parameters; maximum peak height in final ΔF map $\Delta\rho_{\max} = 0.36$ eÅ⁻³. Atomic scattering factors and anomalous-dispersion-correction coefficients as defined by XRAY76

* Uric acid is 7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione.