Conformational and Stereoelectronic Control in Ring-Transformations of *cis*-4,5-Dialkoxytetrahydropurine-2,6,8-triones

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Divergent acid-catalysed ring-openings of 4,5-dimethoxytetrahydropurine-2,6,8-triones **2** at position 4, yielding 1-(5-methoxyhydantoin-5-carbonyl)ureas **4** (R^7 = Me) or 5-methoxy-5-ureido-2,4,6-pyrimidinetriones **5** (R^7 = H), can be rationalized by assuming a preference for one of two conformational isomers of the *cis*-fused system, associated with the *N*-substitution effects. Intramolecular transamidation **5**→**4** presumably occurs *via* a bicyclic acid aminal type intermediate **3**, heretofore misassigned as the reaction product. A curious base-catalysed rearrangement was encountered with the **5** (R^1 = R^3 = Me, R^7 = H) cases, which afforded 5-methoxy-1,5-bis(methylaminocarbonyl)hydantoins **7**. Remarkable stability of the conformationally rigid propellane type 4,5-ethylenedioxytetrahydropurine-2,6,8-triones **9** toward acids, shows that the mode of ring-opening at position 4 is controlled by powerful stereoelectronic factors. However, an alternative ring-opening at the 1,6-bond has occurred on heating aqueous solutions of **9a** (R^7 = H); the ensuing decarboxylative rearrangement leads to 1,3-dimethylallantoin (**12**) and its precursor, 1-(2-hydroxyethoxy)-2,4-dimethyl-3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]octane (**11**).

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Chemistry of the quinonoid form of uric acid is replete with rearrangements in which the ring is transformed to an exceptional variety of products. Covalent diadducts have been studied for more than 100 years [1,2], but in many instances their assigned structures were proven to be incorrect [3-5]. Inferential evidence for the transient formation of covalent hydrates was provided in electrochemical and peroxidase-mediated oxidation of uric acids **1** [6-8]. It has been suggested that the *cis*- and *trans*-fusion of rings in the intermediate diadducts could account for divergent uricolytic pathways [9]. Studies of molecular conformation in crystals [10,11] have shown that the covalent diadducts exist in two isomeric ring-twisted conformations of the *cis*-fused system (Figure 1), having inverse signs of the torsion angles of junction (ϕ)

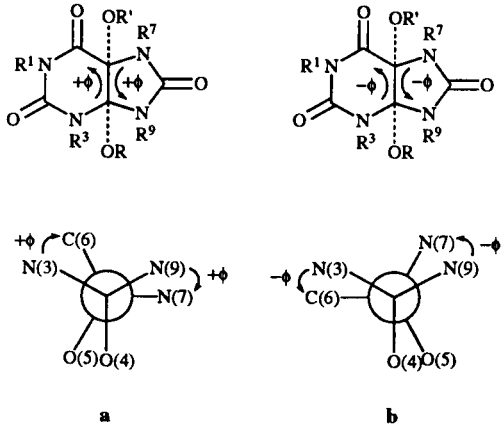


Figure 1. Designation of conformational isomers of the *cis*-fused tetrahydropurinetrione ring, using the torsion angle ($\pm\phi$) convention [12]; Newman projections along the C(4)-C(5) axis show the signs of torsion angles of junction: (a) (+ϕ)-conformer; (b) (-ϕ)-conformer.

[12]. Regioselective ring opening reactions thus become intelligible on the basis of stereoelectronic principle [13], implying that a simple conformational change from the (+ϕ)-conformer with one ester aminal C-N bond perpendicular to the C-N-C plane of the pyrimidine ring (Figure 2a) to the (-ϕ)-form with the C-N bond perpendicular to the C-N-C plane of the imidazolone ring (Figure 2b), can act as a switch controlling the mode of uricolytic transformation. Given the assigned role which covalent adducts play in the interpretation of regio- and stereochemical course of enzymic uricolysis [14], we describe in this communication the synthesis, characterization, and ring-opening reactions of model 4,5-dialkoxytetrahydropurine-2,6,8-triones.

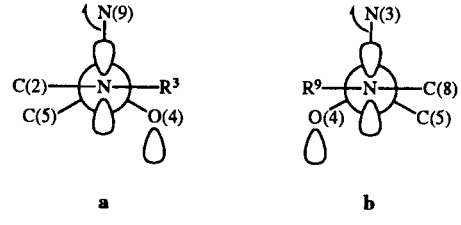


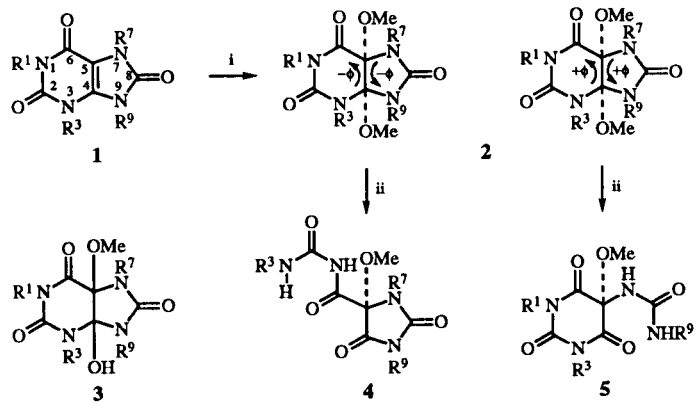
Figure 2. Newman projections showing the alignment of non-bonding orbitals with the cleaving C-N bond of the ester (acid) aminal grouping at C(4): (a) (+ϕ)-conformer (viewed down the N(3)-C(4) axis) and (b) (-ϕ)-conformer (viewed down the N(9)-C(4) axis).

The first structural proposal to the uric acid glycol diethers advanced by Fischer in 1882 [1], was supported through the nmr spectra of twelve 4,5-dimethoxytetrahydropurine-2,6,8-triones **2**, accessible by chlorination of uric acids **1** in methanol [15], which clearly excluded the *trans*-fused structure as a possible alternative (see Experimental). Compounds

2 ($R^3 = R^7 = H$) adopt a (+ϕ)-conformation [10a,11a]. The propensity for the (-ϕ)-conformation effected by *N*(7)-substitution can be ascribed to steric crowding and the resultant repulsive *gauche-gauche* *N*(7)Me ↔ OC(6) and *N*(7)Me ↔ MeO(5) interactions [10b-d]. Substitution at *N*(3) also favours the (-ϕ)-form [11b], as a result of the *gauche* *N*(3)Me ↔ O(4) interaction; since the (+ϕ)-form is observed in the corresponding propellane [11c] (*vide infra*), it seems that the barrier for the conformational change depends on the bridgehead substitution.

The regioselectivity of the acid-catalysed ring opening reactions of diadducts **2** indicated a strong dependence on *N*-substitution in complete agreement with the stereoelectronic principle. The products are determined by the conformation (Figure 2), where the cleaving bond is always oriented antiperiplanar to one oxygen lone pair and aligned with the *p*-orbital of the ureide nitrogen. This approach proved to be successful in uncovering the previously misassigned identity of products, which have long been considered to have unusual acid aminal type bicyclic structures **3**, dubbed the uric acid glycol half-ethers [2,3d]. Accordingly, (-ϕ)-conformers **2** (R^7 = Me) were found to undergo a facile cleavage of the 3,4-bond (Figure 2b) to give 1-(5-methoxyhydantoin-5-carbonyl)ureas **4**. The possible attainment of the side-chain (*Z*)-isomeride is confined to R^1 = H cases; the *X*-ray parameters (*viz.* N(3)...O(6) and N(1)...O(5) distances of 2.6 Å) in the related 1-(5-hydroxyhydantoin-5-carbonyl)urea [3a] suggest an important stabilization *via* two H-bondings. The mode of the acidic hydrolysis of (+ϕ)-conformational types of **2** (R^7 = H), however, switched round completely to cleavage of the 4,9-bond (Figure 2a), affording 5-methoxy-5-ureido-2,4,6-pyrimidinetriones **5**, usually called 5-methoxypseudouric acids [2] (Scheme 1).

Scheme 1



i, Cl_2/MeOH; ii, HCl/dioxane.

a, $R^1 = R^3 = R^7 = R^9 = H$; **b**: R^1 = Me, $R^3 = R^7 = R^9 = H$; **c**, R^3 = Me, $R^1 = R^7 = R^9 = H$; **d**, R^7 = Me, $R^1 = R^3 = R^9 = H$; **e**, R^9 = Me, $R^1 = R^3 = R^7 = H$; **f**, $R^1 = R^3$ = Me, $R^7 = R^9 = H$; **g**, $R^1 = R^7$ = Me, $R^3 = R^9 = H$; **h**, $R^1 = R^9$ = Me, $R^3 = R^7 = H$; **i**, $R^3 = R^7$ = Me, $R^1 = R^9 = H$; **j**, $R^3 = R^9$ = Me, $R^1 = R^7 = H$; **k**, $R^7 = R^9$ = Me, $R^1 = R^3 = H$; **l**, $R^1 = R^3 = R^7$ = Me, $R^9 = H$; **m**, $R^1 = R^3 = R^9$ = Me, $R^7 = H$; **n**, $R^1 = R^7 = R^9$ = Me, $R^3 = H$; **o**, $R^3 = R^7 = R^9$ = Me, $R^1 = H$; **p**, $R^1 = R^3 = R^7 = R^9$ = Me.

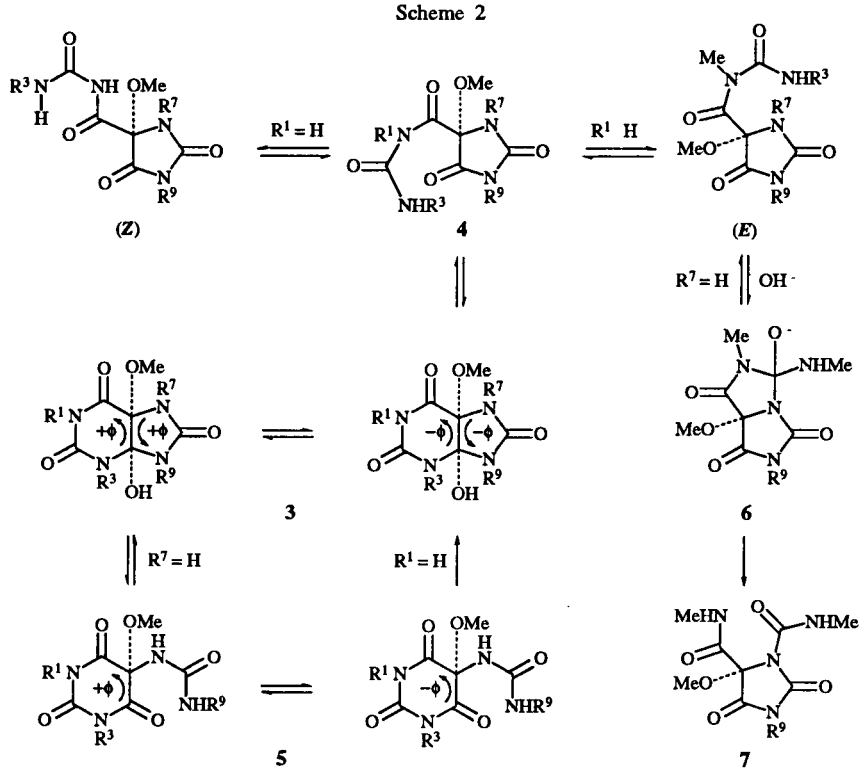
Consequently, the nmr spectra of an unstable product derived from the (-ϕ)-diadduct **2l** (R^7 = Me) under acidic conditions, originally thought to be a 5-methoxypseudouric acid **5l** [15i], revealed its actual structure **4l** (see Experimental).

An intramolecular transamidation **5** → **4** (R^1 = H) occurred either by heating in aqueous solutions or by treatment with base and subsequent acidification. It is noteworthy that **5b**, which derives from **2b** (R^1 = Me), undergoes a regiospecific transformation into **4c** (R^1 = H). The first step in these conversions is almost certainly the formation of a bicyclic tetrahedral intermediate **3**. Hydrolysis of the ester aminal results in the removal of steric crowding and the barrier for conformational change (+ϕ)-**3** ⇄ (-ϕ)-**3** should therefore be lower that that for the corresponding diethers **2**. Alloxan-like systems can adopt two *sofa* conformations [3b], which are interconvertible through a ring-inversion process. Thus, **4** could arise from the ring closure of pseudoequatorial urea in 5-*sofa* (+ϕ)-conformer **5**, leading first to the tetrahedral intermediate (+ϕ)-**3**, which then must undergo a conformational change into (-ϕ)-**3**. The alternative closure of pseudoaxial urea in (-ϕ)-conformer **5**, however, gives directly (-ϕ)-**3**, which can only break down to **4**; the reverse process (-ϕ)-**3** → (-ϕ)-**5** is not allowed stereoelectronically (Scheme 2).

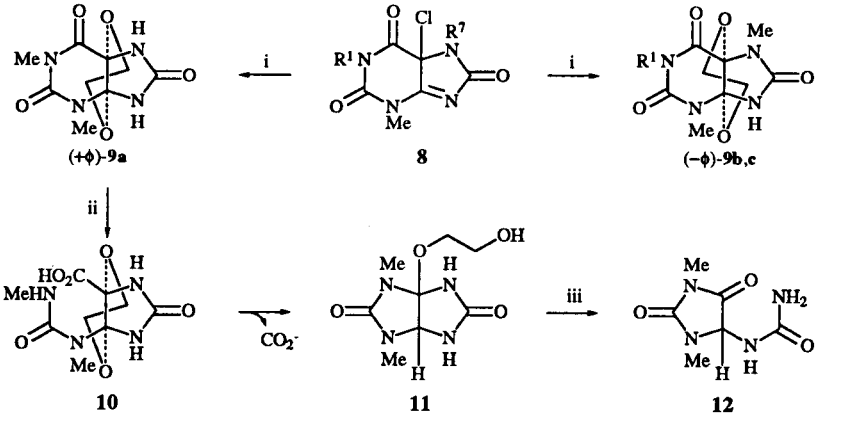
The structures **3** assigned to the products obtained from **5f** and **5m** under basic conditions represent yet another example of structural misinterpretation [2,15dj]. Their revised 5-methoxy-1,5-bis(methylaminocarbonyl)hydantoin (**7**) structures are based on spectral data (Experimental) and the curious rearrangement **5** → **7** can be interpreted on the same stereoelectronic grounds. Installation of two methyl groups in the pyrimidine ring introduces unfavorable steric interactions to the incipient ring-opened product **4**, and the peculiar reactivity of derivatives **5** ($R^1 = R^3$ = Me, R^7 = H) is readily explained by intervention of a cyclic orthocarbonate type transition state **6** [3d]; opening of the ring results in the removal of strain in the 2,3a,5-triazapentalene system (Scheme 2).

A clear demonstration of the importance of stereoelectronic effects was obtained by constructing conformationally rigid propellane type diadducts. 5-Chloro-5,7-dihydro-3*H*-purine-2,4,6-triones **8a-c** [5] smoothly reacted with ethylene glycol to give 4,5-ethylenedioxytetrahydropurine-2,6,8-triones **9a-c**, which stubbornly resisted the acid-catalysed C-N cleavage of the ester aminal group. Crystal structures [10c,11c] show that the propellane molecules have no properly oriented non-bonding orbitals; in (+ϕ)-conformer **9a**, the dioxane C-O(4) bond is antiperiplanar to the C(4)-N(9) bond (Figure 2a) while in (-ϕ)-conformer **9b** the C-O(4) bond is antiperiplanar to the C(4)-N(3) bond (Figure 2b) and the cleavage cannot occur with the help of stereoelectronic control. The conversion **9b** → **9c**

Scheme 2



Scheme 3



i, $HO(CH_2)_2OH$; ii, H_2O/Δ; iii, H^+. **a**, R^1 = Me, R^7 = H; **b**, R^1 = H, R^7 = Me; **c**, R^1 = Me, R^7 = Me

with ethereal diazomethane indicated their corresponding (-ϕ)-conformations. In contrast to *N*(7)-substituted analogues, propellane **9a** underwent a decarboxylative breakdown into 1,3-dimethylallantoin (**12**) by heating in aqueous solution. One factor which may have some importance is the (+ϕ)-geometry, where the C(6)-atom is nearly antiperiplanar to the C(4)-O(4) bond (Figure 1a). An important piece of evidence for the course of events, following the incipient ring-opening at the 1,6-bond, **9** → **10** [5,14], was obtained by isolation of the intermediate bicyclol ether **11** (Scheme 3).

EXPERIMENTAL

Melting points were determined on a Tottoli apparatus and are corrected. Infrared spectra (in cm^{-1}) were taken on a Perkin-Elmer FT-IR 1725X spectrometer as potassium bromide disks. The ^1H- and ^{13}C-nmr spectra were recorded in (D_6)dimethyl sulphoxide with a Varian Gemini-300 (^1H, 300 MHz; ^{13}C, 75 MHz) instrument. Chemical shifts are given in δ units (ppm) from internal tetramethylsilane and coupling constants are expressed in Hz (br broad, s singlet, d doublet, t triplet, q quartet,

m multiplet); multiplicities in ^{13}C spectra were determined by off-resonance decoupling. Mass spectra were measured on a Varian MAT CH-7 instrument at 70eV, 100 μA; m/z values are given with relative intensities (%) in parentheses.

General Procedure for Chlorination of Uric Acids (1) in Methanol.

Chlorination of uric acids **1** in methanol (0-5°), according to Biltz's procedure [15] afforded *cis*-4,5-dimethoxytetrahydropurine-2,6,8-triones **2** in 70-85% yields; attempts to prepare derivatives **2c,e,h** and **o** were unsuccessful.

cis-4,5-Dimethoxytetrahydropurine-2,6,8-trione (**2a**).

This compound was obtained as colorless needles (methanol-ether), mp 202° dec (lit [15a] 202-203°); ir: ν NH 3320, 3200, ν CO 1750 sh, 1725, 1712; ms: m/z 230 (11), 215 (1), 202 (8), 199 (5), 187 (5), 183 (9), 174 (24), 155 (20), 144 (23), 140 (17), 129 (15), 128 (9), 101 (80), 74 (66), 70 (29), 69 (37), 58 (100), 54 (14), 44 (29), 43 (18); ^1H-nmr: δ 10.80 (s, 1H, NH), 8.64 (s, 1H, NH), 8.37 (s, 1H, NH), 8.00 (s, 1H, NH), 3.40 (s, 3H, OMe), 3.30 (s, 3H, OMe); ^{13}C-nmr: δ 166.0 (s, C-6), 156.9 (s, C-8), 149.7 (s, C-2), 94.5 (s, C-4), 83.5 (s, C-5), 51.8 (q, OMe), 51.3 (q, OMe).

cis-4,5-Dimethoxy-1-methyltetrahydropurine-2,6,8-trione (**2b**).

This compound was obtained as colorless plates (water), mp 225-226° dec (lit [15b] 225°); ir: ν NH 3300, 3200, ν CO 1753, 1718, 1681; ^1H-nmr: δ 8.81 (s, 1H), 8.36 (s, 1H), 8.05 (s, 1H), 3.40 (s, 3H), 3.31 (s, 3H), 3.07 (s, 3H); ^{13}C-nmr: δ 165.2 (s), 156.5 (s), 149.8 (s), 94.4 (s), 83.4 (s), 51.9 (q), 51.3 (q), 28.5 (q).

cis-4,5-Dimethoxy-7-methyltetrahydropurine-2,6,8-trione (**2d**).

This compound was obtained as colorless prisms (water), mp 211-212° dec (lit [15c] 211°); ir: ν NH 3300, 3200, ν CO 1748 sh, 1720, 1700; ^1H-nmr: δ 10.89 (s, 1H), 8.82 (s, 1H), 8.35 (s, 1H), 3.32 (s, 3H), 3.16 (s, 3H), 2.65 (s, 3H); ^{13}C-nmr: δ 163.1 (s), 156.2 (s), 149.6 (s), 96.0 (s), 85.7 (s), 52.0 (q), 51.7 (q), 25.7 (q).

cis-4,5-Dimethoxy-1,3-dimethyltetrahydropurine-2,6,8-trione (**2f**).

This compound was obtained as colorless prisms (water), mp 199-201° dec (lit [15d] 200°); ir: ν NH 3240, 3120, ν CO 1738, 1718, 1659; ^1H-nmr: δ 8.87 (s, 1H), 8.61 (s, 1H), 3.45 (s, 3H), 3.18 (s, 3H), 3.10 (s, 3H), 2.86 (s, 3H); ^{13}C-nmr: δ 164.4 (s), 156.3 (s), 149.9 (s), 97.1 (s), 83.4 (s), 52.0 (q), 51.3 (q), 28.5 (q), 28.0 (q).

cis-4,5-Dimethoxy-1,7-dimethyltetrahydropurine-2,6,8-trione (**2g**).

This compound was obtained as colorless prisms (water), mp 171° dec (lit [15e] 171°); ir: ν NH 3310, 3200, ν CO 1740 sh, 1720, 1690; ^1H-nmr: δ 8.91 (s, 1H), 8.36 (s, 1H), 3.34 (s, 3H), 3.20 (s, 3H), 3.11 (s, 3H), 2.65 (s, 3H); ^{13}C-nmr: δ 162.9 (s), 156.3 (s), 149.7 (s), 96.3 (s), 85.9 (s), 52.1 (q), 51.6 (q), 28.6 (q), 25.4 (q).

cis-4,5-Dimethoxy-3,7-dimethyltetrahydropurine-2,6,8-trione (**2i**).

This compound was obtained as colorless prisms (water), mp 217° dec (lit [15f] 216-217°); ir: ν NH 3200, 3150 sh, ν CO 1750 sh, 1737, 1688, 1683; ^1H-nmr: δ 11.09 (s, 1H), 9.07 (s, 1H), 3.29 (s, 3H), 3.19 (s, 3H), 2.82 (s, 3H), 2.63 (s, 3H); ^{13}C-nmr: δ 163.0 (s), 156.4 (s), 149.6 (s), 97.1 (s), 85.5 (s), 52.2 (q), 51.7 (q), 27.5 (q), 25.6 (q).

cis-4,5-Dimethoxy-3,9-dimethyltetrahydropurine-2,6,8-trione (**2j**).

This compound was obtained as colorless prisms (methanol), mp 222-223° dec (lit [15g] 223°); ir: ν NH 3180, ν CO 1735, 1728, 1675; ^1H-nmr: δ 10.98 (s, 1H), 8.57 (s, 1H), 3.35 (s, 3H), 3.25 (s, 3H), 2.91 (s, 3H), 2.78 (s, 3H); ^{13}C-nmr: δ 165.2 (s), 156.6 (s), 150.0 (s), 98.5 (s), 83.5 (s), 52.2 (q), 51.8 (q), 28.4 (q), 26.3 (q).

cis-4,5-Dimethoxy-7,9-dimethyltetrahydropurine-2,6,8-trione (**2k**).

This compound was obtained as colorless plates (methanol), mp 187-188° dec (lit [15h] 187°); ir: ν NH 3300, 3180, ν CO 1740, 1720; ^1H-nmr: δ 11.00 (s, 1H), 8.38 (s, 1H), 3.30 (s, 3H), 3.20 (s, 3H), 2.80 (s, 3H), 2.67 (s, 3H); ^{13}C-nmr: δ 163.0 (s), 156.5 (s), 149.6 (s), 96.3 (s), 85.3 (s), 52.3 (q), 51.7 (q), 26.4 (q), 25.5 (q).

cis-4,5-Dimethoxy-1,3,7-trimethyltetrahydropurine-2,6,8-trione (**2l**).

This compound was obtained as colorless needles (water), mp 178-179° dec (lit [15i] 178°); ir: ν NH 3190, ν CO 1738, 1715, 1678; ^1H-nmr: δ 8.80 (s, 1H), 3.36 (s, 3H), 3.23 (s, 3H), 3.14 (s, 3H), 2.89 (s, 3H), 2.66 (s, 3H); ^{13}C-nmr: δ 162.1 (s), 155.8 (s), 149.5 (s), 95.7 (s), 85.2 (s), 52.0 (q), 51.6 (q), 28.5 (q), 28.3 (q), 25.3 (q).

cis-4,5-Dimethoxy-1,3,9-trimethyltetrahydropurine-2,6,8-trione (**2m**).

This compound was obtained as colorless plates (water), mp 127-128° dec (lit [15j] 128°); ir: ν NH 3200, ν CO 1737, 1710, 1680; ^1H-nmr: δ 8.62 (s, 1H), 3.34 (s, 3H), 3.20 (s, 3H), 3.13 (s, 3H), 2.91 (s, 3H), 2.83 (s, 3H); ^{13}C-nmr: δ 165.0 (s), 156.4 (s), 149.7 (s), 97.7 (s), 83.6 (s), 52.1 (q), 51.7 (q), 28.7 (q), 28.4 (q), 26.3 (q).

cis-4,5-Dimethoxy-1,7,9-trimethyltetrahydropurine-2,6,8-trione (**2n**).

This compound was obtained as colorless plates (methanol), mp 151-152° dec (lit [15k] 152°); ir: ν NH 3310, ν CO 1740, 1710, 1695; ^1H-nmr: δ 8.41 (s, 1H), 3.31 (s, 3H), 3.20 (s, 3H), 3.12 (s, 3H), 2.83 (s, 3H), 2.67 (s, 3H); ^{13}C-nmr: δ 162.8 (s), 155.9 (s), 149.8 (s), 96.6 (s), 85.4 (s), 52.2 (q), 51.6 (q), 28.7 (q), 26.4 (q), 25.6 (q).

cis-4,5-Dimethoxy-1,3,7,9-tetramethyltetrahydropurine-2,6,8-trione (**2p**).

This compound was obtained as colorless prisms (water), mp 133° dec (lit [15l] 133°); ir: ν CO 1741, 1720, 1700; ^1H-nmr: δ 3.28 (s, 3H), 3.16 (s, 3H), 3.11 (s, 3H), 2.97 (s, 3H), 2.84 (s, 3H), 2.68 (s, 3H); ^{13}C-nmr: δ 162.6 (s), 155.8 (s), 150.0 (s), 96.1 (s), 85.7 (s), 52.0 (q), 51.7 (q), 28.9 (q), 28.2 (q), 26.2 (q), 25.4 (q).

General Procedure for Acidic Hydrolysis of *cis*-4,5-Dimethoxytetrahydropurine-2,6,8-triones (**2**) at the Ester Aminal Function.

Hydrochloric acid (3 ml) saturated with hydrogen chloride at 0° and dioxane (10 ml) were added to powdered *cis*-4,5-dimethoxytetrahydropurine-2,6,8-triones **2** (0.01 mole). After being stirred for 30-45 minutes, the solution was filtered and the initial crystallization induced by scratching with a glass rod. The ring-opening products **4** or **5**, which separated on standing at 4°, were collected and recrystallized from an appropriate solvent.

1-(5-Methoxy-1-methylhydantoin-5-carbonyl)urea (**4d**).

This compound was obtained as fine colorless needles (ethanol-ether) in a 43% yield, mp 210-212° dec; ir: ν NH 3430, 3320, 3220, 3170, ν CO 1800, 1730, 1710, 1690; ^1H-nmr: δ

11.41 (s, 1H, NH), 9.60 (s, 1H, NH), 7.41 (s, 2H, NH_2), 3.24 (s, 3H, OMe), 2.77 (s, 3H, NMe).

Anal. Calcd. for $C_7H_{10}N_4O_5$: C 36.53; H 4.38; N, 24.34. Found: C, 36.25; H, 4.66; N, 24.07.

1-(5-Methoxy-1-methylhydantoin-5-carbonyl)-3-methylurea (**4i**).

This compound was obtained as plates (methanol), mp 247-248° (lit [15f] 248°); ir: ν NH 3315, 3130, ν CO 1787, 1735, 1720, 1690, 1675; ^{1}H-nmr: δ 11.42 (s, 1H), 9.61 (s, 1H), 7.90 (q, 1H, J = 4.5), 3.25 (s, 3H), 2.78 (s, 3H), 2.72 (d, 3H, J = 4.5).

1-(5-Methoxy-3-methylhydantoin-5-carbonyl)-3-methylurea (**4j**).

This compound was obtained as colorless prisms (methanol), mp 204-205° dec (lit [15g] 204°); ir: ν NH 3320, 3260, 3220, 3150, ν CO 1796, 1722, 1710, 1684; ^{1}H-nmr: δ 9.40 (s, 1H), 8.85 (s, 1H), 7.93 (q, 1H, J = 4.5), 3.26 (s, 3H), 2.93 (s, 3H), 2.73 (d, 3H, J = 4.5).

1-(5-Methoxy-1,3-dimethylhydantoin-5-carbonyl)urea (**4k**).

This compound was obtained as colorless plates (methanol), mp 184-185° dec (lit [15h] 184°); ir: ν NH 3420, 3325, 3220, 3160, ν CO 1786, 1735 sh, 1715, 1690; ^{1}H-nmr: δ 9.64 (s, 1H), 7.43 (s, 2H), 3.23 (s, 3H), 2.96 (s, 3H), 2.77 (s, 3H).

1-(5-Methoxy-1-methylhydantoin-5-carbonyl)-1,3-dimethylurea (**4l**).

This compound was obtained as colorless prisms (water), mp 190-191° dec (lit [15i] 189-191°); ir: ν NH 3329, 3162, ν CO 1780, 1755, 1747, 1742, 1738, 1733, 1699, 1695; ^{1}H-nmr: δ 11.53 (s, 1H), 8.20 (q, 1H, J = 4.5), 3.17 (s, 3H), 3.13 (s, 3H), 2.72 (s, 3H), 2.67 (d, 3H, J = 4.5); ^{13}C-nmr: δ 168.8 (s), 164.5 (s), 156.0 (s), 155.5 (s), 93.0 (s), 51.7 (q), 34.0 (q), 27.3 (q), 25.1 (q).

1-(5-Methoxy-1,3-dimethylhydantoin-5-carbonyl)-3-methylurea (**4o**).

This compound was obtained as colorless plates (water) by reaction of 1-(5-methoxy-1-methylhydantoin-5-carbonyl)-3-methylurea (**4i**, 0.01 mole) with an excess of ethereal diazomethane, mp 186-187° (lit [15j] 186-187°); ir: ν NH 3180, ν CO 1790, 1737, 1711; ^{1}H-nmr: δ 9.90 (s, 1H), 7.92 (q, 1H, J = 4.5), 3.25 (s, 3H), 2.98 (s, 3H), 2.78 (s, 3H), 2.72 (d, 3H, J = 4.5).

5-Methoxy-5-ureido-2,4,6-pyrimidinetrione (**5a**).

This compound was obtained as colorless prisms (water), mp 202-203° dec (lit [15a] 202-204°); ir: ν NH 3495, 3390, 3350, 3180, ν CO 1765, 1735, 1720, 1700, 1663, 1657; ^{1}H-nmr: δ 11.45 (s, 2H, ring NH), 7.45 (s, 1H, NH), 5.50 (s, 2H, NH_2), 3.32 (s, 3H, OMe); ^{13}C-nmr: δ 166.9 (s, C-4 and C-6), 157.8 (s, CO), 149.4 (s, C-2), 79.9 (s, C-5), 53.0 (q, OMe).

5-Methoxy-1-methyl-5-ureido-2,4,6-pyrimidinetrione (**5b**).

This compound was obtained as plates (water), mp 192-193° dec (lit [15b] 192°); ir: ν NH 3485, 3375, 3350, 3185, ν CO 1760, 1735 sh, 1722, 1700, 1652; ^{1}H-nmr: δ 11.76 (s, 1H), 7.57 (s, 1H), 5.80 (s, 2H), 3.32 (s, 3H), 3.14 (s, 3H).

5-Methoxy-5-(3-methylureido)-2,4,6-pyrimidinetrione (**5e**).

This compound was obtained as colorless plates (methanol) by chlorination of a suspension of powdered 9-methyluric acid (**1e**, 0.01 mole) in methanol (10 ml, 5°) and subsequent precipitation with ether, mp 196° dec (lit [16a] 195-196°); ir: ν NH 3350, 3180, ν CO 1760, 1733, 1715, 1700, 1670; ^{1}H-nmr: δ 11.40 (s, 2H), 7.55 (s, 1H), 7.40 (q, 1H, J = 4.6), 3.29 (s, 3H), 2.69 (d, 3H, J = 4.6).

5-Methoxy-1,3-dimethyl-5-ureido-2,4,6-pyrimidinetrione (**5f**).

This compound was obtained as colorless prisms (water), mp 186-187° dec (lit [15d] 186°); ir: ν NH 3417, 3355, 3315, 3230 sh, 3195, ν CO 1765 sh, 1735, 1710, 1690, 1676; ms: m/z 244 (14), 229 (24), 216 (15), 214 (38), 201 (40), 197 (46), 186 (9), 170 (9), 157 (35), 156 (26), 143 (34), 142 (38), 141 (41), 130 (24), 129 (16), 116 (28), 115 (21), 114 (15), 102 (24), 98 (18), 97 (24), 72 (31), 70 (18), 58 (100), 44 (84); ^{1}H-nmr: δ 7.63 (s, 1H), 5.90 (br s, 2H), 3.31 (s, 3H), 3.19 (s, 6H); ^{13}C-nmr: δ 166.2 (s), 157.8 (s), 150.1 (s), 80.4 (s), 53.1 (q), 28.6 (q).

5-Methoxy-1,3-dimethyl-5-(3-methylureido)-2,4,6-pyrimidinetrione (**5m**).

This compound was obtained as colorless prisms (water), mp 183-184° dec (lit [16b] 184°); ir: ν NH 3320, 3170, ν CO 1760, 1742, 1733 sh, 1700; ^{1}H-nmr: δ 7.57 (s, 1H), 7.42 (q, 1H, J = 4.6), 3.31 (s, 3H), 3.21 (s, 6H), 2.70 (d, 3H, J = 4.6).

Intramolecular Transamidation of 5-Methoxy-5-ureido-2,4,6-pyrimidinetriones **5** into 1-(5-Methoxyhydantoin-5-carbonyl)ureas **4**.

Compounds **5a**, **5b**, and **5e** (0.01 mole) were all dissolved in a minimal volume of 0.1*M* sodium hydroxide. Crystalline products, which separated on cautious neutralization with 0.2*M* hydrochloric acid and standing at 4°, were filtered off and recrystallized to give the transamidation products **4a**, **4c**, or **4e** in 65-75% yields. The same conversion was achieved by heating an aqueous solution of **5**, or, at room temperature, in the presence of bromine (0.2 ml).

1-(5-Methoxyhydantoin-5-carbonyl)urea (**4a**).

This compound was obtained as prisms (methanol), mp 203° dec (lit [15a] 202-203°); ms: m/z 216 (0.1), 199 (0.3), 198 (0.3), 188 (0.4), 184 (3), 172 (1), 156 (1), 143 (4), 130 (21), 129 (100), 115 (14), 114 (2), 113 (6), 102 (3), 70 (16), 58 (51), 44 (71); ir: ν NH 3385, 3325, 3220, 3185, ν CO 1805, 1750, 1730, 1705; ^{1}H-nmr: δ 11.45 (s, 1H, NH), 9.50 (s, 1H, NH), 8.92 (s, 1H, NH), 7.43 (s, 2H, NH_2), 3.28 (s, 3H, OMe); ^{13}C-nmr: δ 170.2 (s, C-4), 166.9 (s, CO), 157.3 (s, $CONH_2$), 152.8 (s, C-2), 90.1 (s, C-5), 52.0 (q, OMe).

1-(5-Methoxyhydantoin-5-carbonyl)-3-methylurea (**4c**).

This compound was obtained as colorless prisms (water) by reaction of **5b**, mp 207-208° dec (lit [15b] 207°); ir: ν NH 3315, 3200, 3130, ν CO 1800, 1735, 1720, 1680; ^{1}H-nmr: δ 11.40 (s, 1H), 9.55 (s, 1H), 8.87 (s, 1H), 7.87 (q, 1H, J = 4.5), 3.27 (s, 3H), 2.73 (d, 3H, J = 4.5).

1-(5-Methoxy-3-methylhydantoin-5-carbonyl)urea (**4e**).

This compound was obtained as colorless plates (water), mp 171° dec (lit [16a] 170-172°). The same product was prepared by reaction of **4a** with ethereal diazomethane; ir: ν NH 3489, 3323, 3293, ν CO 1793, 1735, 1715, 1660; ^{1}H-nmr: δ 9.59 (s, 1H), 8.88 (s, 1H), 7.42 (s, 2H), 3.26 (s, 3H), 2.97 (s, 3H).

General Procedure for the Base-promoted Rearrangement of 1,3-Dimethyl-5-methoxy-5-ureido-2,4,6-pyrimidinetriones **5**.

A solution of **5f** or **5m** (0.01 mole) in a minimal volume of 2*M* sodium hydroxide was neutralized with 10% hydrochloric acid. Colorless crystals of **7f** or **7m**, which separated at 4°, were collected, washed with cold water and ethanol, and recrystallized from water.

5-Methoxy-1,5-bis(methylaminocarbonyl)hydantoin (**7f**).

This compound was obtained as prisms, containing water of crystallization, mp 241-242° dec (lit [15d] 241°); ir: ν NH 3440, 3343, 3240, 3171, ν CO 1790, 1727, 1689; ms: m/z 245 (M+1, 4), 214 (2), 187 (90), 172 (41), 130 (100), 129 (37), 115 (81), 101 (9), 70 (9), 58 (73), 44 (17); ^{1}H-nmr: δ 12.30 (s, 1H, NH), 8.19 (q, 1H, NH, J = 4.6), 7.81 (q, 1H, NH, J = 4.6), 3.27 (s, 3H, OMe), 2.73 (d, 3H, NMe, J = 4.6), 2.64 (d, 3H, NMe, J = 4.6); ^{13}C-nmr: δ 167.7 (s, C-4), 163.6 (s, CO), 155.3 (s, CO), 149.8 (s, C-2), 90.6 (s, C-5), 52.0 (q, OMe), 26.3 (q, NMe), 26.0 (q, NMe).

5-Methoxy-3-methyl-1,5-bis(methylaminocarbonyl)hydantoin (**7m**).

This compound was obtained as prisms, mp 194-195° (lit [15j] 194°). The same product was obtained from **7f** with ethereal diazomethane; ms: m/z 259 (M+1, 1), 228 (3), 201 (62), 186 (34), 144 (68), 143 (50), 130 (100), 101 (8), 85 (3), 72 (11), 70 (9), 58 (65), 44 (9); ir: ν NH 3363, 3229, 3143, ν CO 1787, 1748, 1710; ^{1}H-nmr: δ 8.25 (q, 1H, J = 4.5), 7.82 (q, 1H, J = 4.5), 3.25 (s, 3H), 3.02 (s, 3H), 2.74 (d, 3H, J = 4.5), 2.66 (d, 3H, J = 4.5); ^{13}C-nmr: δ 166.6 (s), 163.3 (s), 154.7 (s), 149.3 (s), 89.9 (s), 52.2 (q), 26.4 (q), 26.0 (q), 24.8 (q).

Propellane-type 4,5-Ethylenedioxytetrahydropurine-2,6,8-triones (**9**).

Powdered 5-chloro-5,7-dihydro-3*H*-purine-2,6,8-triones (**8**, 0.1 mole) [5] were dissolved in dry ethylene glycol (60 ml). After being stirred for 30-40 minutes the crystalline product was filtered off, washed with dry ether and recrystallized from water, to give the corresponding propellanes **9a-c** in 80-85% yields.

4,5-Ethylenedioxy-1,3-dimethyltetrahydropurine-2,6,8-trione (**9a**).

This compound was obtained as colorless prisms, mp 214-215° dec; ms: m/z 256 (M^+, 1); ir: ν NH 3280, 3180, ν CO 1722, 1690; ^{1}H-nmr: δ 8.64 (s, 1H, NH), 8.35 (s, 1H, NH), 3.77, 3.68 (m, 4H, C_2H_4), 3.11 (s, 3H, NMe), 2.93 (s, 3H, NMe); ^{13}C-nmr: δ 164.6 (s, C-6), 157.8 (s, C-8), 150.2 (s, C-2), 90.7 (s, C-4), 80.0 (s, C-5), 60.2 (t, CH_2O), 59.4 (t, CH_2O), 28.4 (q, NMe), 28.0 (q, NMe).

Anal. Calcd. for $C_9H_{12}N_4O_5$: C, 42.19; H, 4.72; N, 21.87. Found: C, 42.00; H, 4.91; N, 21.71.

4,5-Ethylenedioxy-3,7-dimethyltetrahydropurine-2,6,8-trione (**9b**).

This compound was obtained as colorless prisms, mp 229-230° dec; ms: m/z 256 (M^+, 2); ir: ν NH 3206, ν CO 1739, 1688; ^{1}H-nmr: δ 11.2 (s, 1H), 8.72 (s, 1H), 3.75, 3.69 (m, 4H), 2.88 (s, 3H), 2.75 (s, 3H); ^{13}C-nmr: δ 163.9 (s), 157.3 (s), 149.8 (s), 91.2 (s), 80.8 (s), 60.4 (t), 59.8 (t), 27.3 (q), 25.2 (q).

Anal. Calcd. for $C_9H_{12}N_4O_5$: C, 42.19; H, 4.72; N, 21.87. Found: C, 41.91; H, 4.88; N, 21.65.

4,5-Ethylenedioxy-1,3,7-trimethyltetrahydropurine-2,6,8-trione (**9c**).

This compound was obtained as colorless prisms, mp 221-222° dec. The identical product was obtained from **9b** with an excess of ethereal diazomethane; ms: m/z 270 (M^+, 4); ir: ν NH 3229, 3115, ν CO 1742, 1721, 1688, 1683, 1674; ^{1}H-nmr: δ 8.81 (s, 1H), 3.79, 3.67 (m, 4H), 3.11 (s, 3H), 2.94 (s, 3H), 2.76 (s, 3H); ^{13}C-nmr: δ 163.8 (s), 157.6 (s), 150.4 (s), 90.4 (s), 81.1 (s), 60.6 (t), 60.0 (t), 28.6 (q), 28.1 (q), 25.3 (q).

Anal. Calcd. for $C_{10}H_{14}N_4O_5$: C, 44.45; H, 5.22; N, 20.73. Found: C, 44.20; H, 5.49; N, 20.46.

1-(2-Hydroxyethoxy)-2,4-dimethyl-3,7-dioxo-2,4,6,8-tetraazabicyclo[3.3.0]octane (**11**).

An aqueous solution (50 ml) of **9a** (2.6 g, 0.01 mole) was heated under reflux for 4 hours. The solution was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in a minimal amount of dry ethanol; 1,3-dimethylallantoin (**12**, 0.49 g, 26%), which slowly crystallized from the solution, was filtered off. The mother liquor was evaporated *in vacuo* and water removed by successive evaporation with dry ethanol. Dry ether was added to the residue; the crystals were collected, washed with ether and dried. The analytical sample of **11** (1.45 g, 63%) was obtained after two recrystallizations from ethanol-ether as colorless needles, mp 185-187°; ir: ν OH 3400, ν NH 3166, 3105, ν CO 1710; ^{1}H-nmr: δ 8.37 (s, 1H, NH), 7.72 (br s, 1H, NH), 5.06 (s, 1H, OH), 4.80 (d, 1H, CH, J = 1.7), 3.52 (m, 4H, C_2H_4), 2.70 (s, 3H, NMe), 2.65 (s, 3H, NMe); ^{13}C-nmr: δ 159.3 (s, C-3), 157.1 (s, C-7), 99.7 (s, C-1), 70.0 (s, C-5), 64.6 (t, OCH_2), 59.9 (t, CH_2OH), 27.5 (q, NMe), 24.8 (q, NMe).

Anal. Calcd. for $C_8H_{14}N_4O_4$: C, 41.74; H, 6.13; N, 24.34. Found: C, 42.05; H, 6.40; N, 24.41.

1,3-Dimethylallantoin (**12**).

A solution of **11** (1.15 g, 0.05 mole) in minimum water was acidified with hydrochloric acid (5 ml, 10%) and evaporated *in vacuo*. Addition of ethanol causes slow crystallization of **12** (0.9 g, 97%), mp 213-214° (lit [5] 214°).

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