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THE STRUCTURE OF THEOBROMURIC ACID

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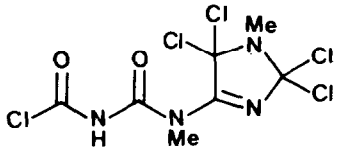
Summary — The structure of theobromuric acid was revised and the correct 8a-hydroxy-1,2,3,4,6,7,8,8a-octahydro-1,7-dimethyl-2,4,6,8-tetraoxo-imidazo[1,5-a]-1,3,5-triazine (5a) formula was assigned on the basis of chemical and spectroscopic evidence.

The electrochemical and enzymic oxidations of purines have been the subject of much recent interest.[1] A knowledge of degradation pathways and structure of intermediates[2] takes on added importance in view of the β-cytotoxic nature of some compounds and their possible role in aetiology of diabetes mellitus.[3] Theobromuric acid, an unusual oxidation product of theobromine (1), was first described by Fischer and Frank in 1897;[4] its formula 3 and that of the pentachloro precursor 2 were inferred mainly from the hydrolytic breakdown into the carbon dioxide, methylparabanic acid, and methylurea.[4-6] In view of the formal relationship between 3 and dehydro-allantoins, recently synthesized in our laboratory,[7] we have re-examined the classical structure and are reporting here on a new structural assignment of theobromuric acid.



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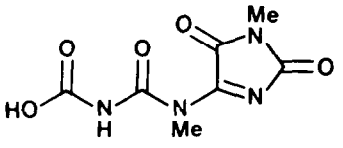

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The chlorination of 1 in boiling chloroform[4,5] afforded a reactive pentachloro derivative $C_7H_7Cl_5N_4O_2 \cdot CHCl_3$, m. p. 135-6° decomp, which, on treatment with water or alcohols, is smoothly converted into theobromuric acid or its esters, respectively. Elemental analyses and spectroscopic data[8] show the products to be 5 formed from 1 by pyrimidine ring opening and recyclization into an imidazo[1,5-*a*]-*sym*-triazine. Compound 5a is a stable crystalline solid, m. p. 180-1° decomp (H_2O); the mass spectrum has a very weak parent ion at m/e

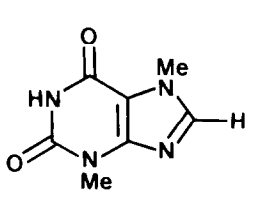
228, a characteristic ion at m/e 211(M-*OH*,10), and a breakdown pattern consistent with the formulation. The IR spectrum does not exhibit bands attributable to a carboxylic acid: 3300,3190,3095,1830,1755,1740,1705 cm^{-1}. NMR spectra revealed the unique acid aminal grouping at a ring junction of 5a; ^1H NMR, δ 11.20 (NH), 8.73(OH), 3.05, 2.96(NMe); ^{13}C NMR, δ 165.2(C_8), 151.1(C_2), 148.8(C_6), 143.9 (C_4), 87.7(C_{8a}), 27.9, 24.7(NMe). Careful neutralization of 5a with cold 2*N* NaOH affords a crystalline sodium theobromurate, m. p. 105-6° decomp, IR 1805,1740, 1730,1700 cm^{-1}, which reverts to 5a on reacidification.

The spectra of theobromuric esters 5b-d were also consistent with the basic imidazo[1,5-*a*]-*sym*-triazine skeleton containing an ester aminal functionality at the bridgehead; 5b, m. p. 200-1° (MeOH); MS, m/e 242(M^+,10), 211(M-*OMe*,60). IR 3180,3080,1830,1760,1735,1705,1685 cm^{-1}. ^1H NMR, δ 11.17(NH), 3.28(OMe), 3.05,2.99 (NMe). ^{13}C NMR, δ 163.5(C_8), 150.7(C_2), 149.1(C_6), 143.9(C_4), 91.2(C_{8a}), 51.0(OMe), 28.1, 25.0(NMe). 5c, m. p. 211-2° (EtOH); MS, m/e 256(M^+,28), 211(M-*OEt*,83); ^1H NMR, δ 11.15(NH), 3.43, 1.13(qt,OEt,*J*=7), 3.04, 2.98(NMe). Reaction of 5a or 5b with an excess of ethereal diazomethane gave 5d, m. p. 187-8° (MeOH); MS, m/e 256(M^+,6), 225(M-*OMe*,34); IR 1837,1750,1730,1693 cm^{-1}; ^1H NMR, δ 3.21(OMe), 3.09 3.08, 3.00(NMe); ^{13}C NMR, δ 163.4(C_8), 150.9(C_2), 149.0(C_6), 144.2(C_4), 90.0(C_{8a}), 51.1(OMe), 29.1, 28.4, 25.1(NMe).

The reduction of 5a-c with hydriodic acid gave Biltz's hydro-theobromuric "anhydride" 6,[4,5] m. p. 263-4° decomp (H_2O); MS, m/e 212(M^+,15); IR 3200,3075, 1822,1750,1690 cm^{-1}; ^1H NMR, δ 10.63(NH), 5.61(CH), 3.00, 2.93(NMe); ^{13}C NMR, δ 165.4(C_8), 152.4(C_2), 150.1(C_6), 144.7(C_4), 85.2(d,C_{8a}), 28.8, 24.8(NMe). Sequential hydrolysis of 6 (Scheme), according to Biltz's procedure,[5] yielded hydrotheobromuric acid (7a), as a monohydrate, m. p. 230° decomp (H_2O), and theuric acid (8a), m. p. 253-5° decomp (H_2O); the corresponding esters were prepared by heating the parent acid with a large excess of methanol and thionyl chloride: 7b, m. p. 223-4° decomp (MeOH); IR 3350,3190,3080,1740,1705 cm^{-1}; ^1H NMR, δ 10.54 (NH), 8.35, 2.78(qd,NHMe,*J*=4.8), 6.20(CH), 3.76(CO_2Me), 3.03(NMe). 8b, m. p. 202-4° decomp (MeOH); IR 3200,3070,1755,1710,1697 cm^{-1}. ^1H NMR, δ 9.61(NH), 8.49(d,NH,*J*= 4.5), 5.14(d,CH,*J*=4.5), 3.78(CO_2Me), 2.90(NMe).

On warming with concd hydrochloric acid theobromuric acid (5a) affords oxalic acid and 1,7-dimethyltriuret (10, 50%), m. p. 200-1° (H_2O); ^1H NMR, δ 9.77(NH), 7.43, 2.71(qd,NHMe,*J*=4.6), along with variable quantities of methylparabanic acid (9) and methylurea. This controversial reaction,[9] which was previously postulated to involve a complex mechanism, is unexceptional and readily accomodated by the bicyclic structure 5a.

The rearrangement 1 → 5a has no precedent in the purine chemistry. This type of ring transformation has been little explored in related heterocyclic systems and an example of rearrangement of 2-amino-5,8-dihydro-4-hydroxy-5-methyl-6,7-diphenylpteridine to a pyrazino[1,2-*a*]-*sym*-triazine on auto-oxidation was unexpected.[10] The structure of theobromuric acid (5a) represents an interesting



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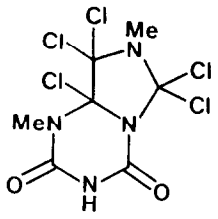

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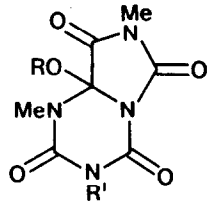

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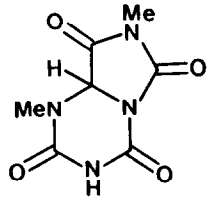

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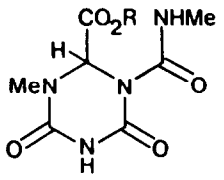

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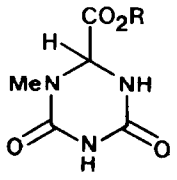

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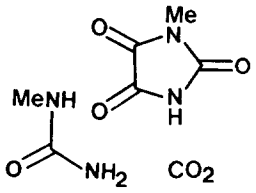

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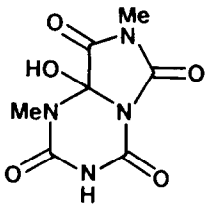

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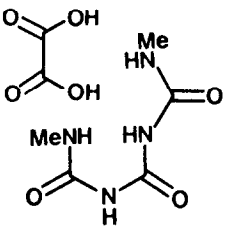

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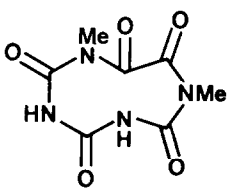
SCHEME. a: R = R' = H; b: R = Me, R' = H; c: R = Et, R' = H; d: R = R' = Me. i, $Cl_2/CHCl_3$,Δ; ii, H_2O (ROH)/∇; iii, HI(d=1.94)/P,Δ; iv, 20% NaOH, then HCl (R=H); $SOCl_2$/MeOH,Δ (R=Me); v, 2*N* Na_2CO_3,Δ, then HCl (R=H); $SOCl_2$/MeOH,Δ (R=Me); vi, H_2O/Δ; vii, concd HCl/Δ.



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but virtually unknown array, the acid aminal function, formally derivable from the tetrazonine 11 by a transannular amide-ureide interaction. The appearance of the array in theobromuric acid is reminiscent of the structure of tetrodotoxin[11] and cyclol-peptide alkaloids[12] and is yet another example of co-operation of normally non-interacting groups, appositely attached to a medium ring, in the formation of structural groupings which are not observed in simpler systems.

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[8] M. ps. were determined on a Tottoli apparatus and are corrected. Analyses of the elements were within ±0.3% of the calculated values. IR spectra were recorded for KBr disks on a Perkin-Elmer 257 spectrophotometer. NMR spectra were measured on a JEOL FX-100 spectrometer for DMSO-d_6 solutions. Chemical shifts are given in ppm relative to internal TMS, and coupling constants are expressed in Hz. Mass spectra were determined on a Varian MAT CH-7 instrument; m/e values are given with relative intensities (%) in parentheses.

[9] The symmetrical structure of dimethyltriuret has been proposed to account for the formation of an identical product from phosgene and methylurea.[4] An alternative interpretation is that implied by structure 3, involving a ring opening and rearrangement to formic acid and *asym*-dimethyltriuret.[5]

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