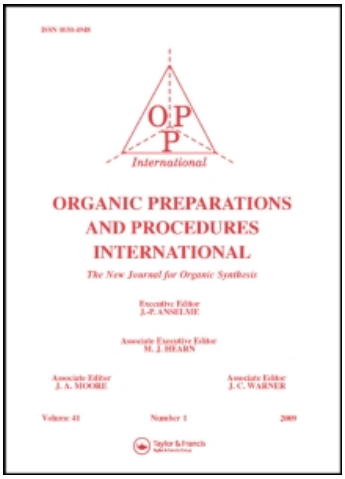

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OXIDATIVE REARRANGEMENT OF THE PURINE RING USING MAGNESIUM MONOPERPHTHALATE

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OXIDATIVE REARRANGEMENT OF THE PURINE RING USING MAGNESIUM MONOPERPHTHALATE†

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(04/08/93)

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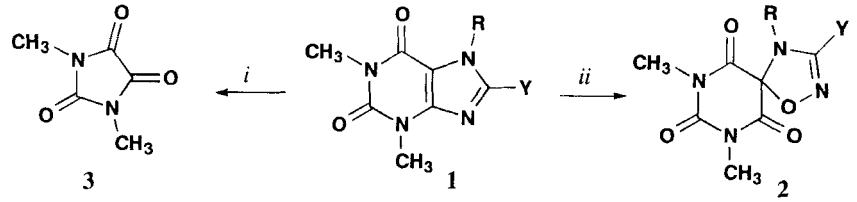
The novel oxidative rearrangement of the caffeine system[1] (**1**) to 4,7,9-trisubstituted-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-triones (**2**) has been shown to occur generally with xanthines.[2] A structural prerequisite for this rearrangement is the presence of an alkoxy or dialkylamino substituent at the 8 position of xanthine and caffeine rings. [1,2] In these cases, *m*-chloroperbenzoic acid was used as an oxidizing agent to bring about this novel rearrangement



i) 30% H_2O_2-CF_3CO_2H; *ii*) MMPP/$Me_3(C_{14}H_{30})N^+Br^-$, H_2O-$CHCl_3$

a) R = CH_3, Y = $N(CH_3)Ph$ b) R = CH_3, Y = $N(CH_2CH_2)_2O$ c) R = CH_3, Y = OCH_3
d) R = CH_3, Y = OC_2H_5 e) R = CH_3, Y = OC_6H_5 f) R = CH_3, Y = $OCH_2CH(CH_3)_2$
g) R = CH_2Ph, Y = OC_2H_5

Because *m*-chloroperbenzoic acid (MCPBA) is shock-sensitive and potentially explosive, it was thought that this transformation could be achieved with 30% H_2O_2-trifluoroacetic acid.[3] However, when this reagent was tested on **1b** and **1c**, N,N'-dimethylimidazolidinetrione (**3**) was isolated as the main product. The presence of **2** as well as of N,N'-dimethylalloxane was only detected by TLC. This observation was also reported earlier[2,4] when 30% H_2O_2 or SeO_2-30% H_2O_2 was used as an oxidizing agent. We then examined the use of magnesium monoperphthalate hexahydrate (MMPP), a recently developed peroxygen source[5] which is non-deflagrating and not shock-sensitive. Thus the results of the oxidation of **1** in a two-phase system in the presence of a phase-transfer catalyst showed MMPP to be an effective and valuable addition to the existing methodology.

EXPERIMENTAL SECTION

All melting points are uncorrected. Analytical TLC was performed using an ascending technique with EM silica gel $60F_{254}$ precoated on plastic sheets. IR spectra were measured as KBr pellets on a Perkin-Elmer model 599 spectrometer. ^1H NMR spectra were recorded on Bruker AC-250 spectrometer. A Hewlett-Packard 5995 Gas Chromatograph/Mass spectrometer was used to record MS data at 70 eV. Compounds **1a-g** were prepared as previously reported.[6-8]

General Procedure for (2).- To a stirred solution of **1** (10 mmol) in chloroform (5 mL) containing trimethyltetradecylammonium bromide (0.06 g), was added dropwise a solution of MMPP (25 mmol) in water (10 mL) over a period of 1 hr. The mixture was stirred until TLC showed the disappearance of the starting material (~40 hrs). The organic layer was separated,washed with water and dried over anhydrous Na_2SO_4. After evaporation of chloroform under reduced pressure, **2** was obtained and purified by flash column chromatography on silica gel using ethyl acetate as an eluent.

3-(N-Methyl-N-phenylamino)-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-trione (2a), 40% yield, yellow crystals, mp. 167°, IR: 1690 cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.43 (s, 3H), 3.20 (s, 9H), 6.99-7.49 (m, 5H); Mass spectrum: (m/z, %):331 (M^+, 17), 301 (100), 175 (22), 132 (12), 106 (14), 77 (35).

Anal. Calcd. for $C_{15}H_{17}N_5O_4$: C, 54.37; H, 5.17; N, 21.14. Found: C, 54.59; H, 4.93; N, 20.95.

3-Morpholino-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-trione (2b), 57% yield, yellow crystals, mp.223°, lit.[1] 224°, 61%.

3-Methoxy-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-trione (2c), 65% yield, colorless crystals, mp. 183-184°, lit.[1] 188°, 58%.

3-Ethoxy-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-trione (2d), 63% yield, colorless crystals, mp. 173°, lit.[1] 176°, 41%.

3-Phenoxy-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-trione (2e), 52% yield, colorless crystals, mp.148°, IR (KBr): 1690 cm^{-1}. ^1H NMR($CDCl_3$): δ 2.93 (s, 3H), 3.35 (s, 6H), 7.38 (m, 5H); Mass spectrum: (m/z, %): 318 (M^+, 61), 288 (100), 205 (23), 134 (25), 83 (71), 77 (65).

Anal. calcd. for $C_{14}H_{14}N_4O_5$: C,52.83; H, 4.43; N, 17.60. Found: C, 52.81; H, 4.64; N, 17.60.

3-Isobutoxy-4,7,9-trimethyl-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-trione (2f), 30% yield, colorless crystals, mp. 153°, IR (KBr): 1690 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.95 (d, 6H), 2.30(m, 1H), 2.80 (s, 3H); 3.32 (s, 6H), 3.91 (d, 2H).

Anal. calcd. for $C_{12}H_{18}N_4O_5$: C,48.12; H, 5.99; N, 18.67. Found: C, 48.30; H, 6.12; N, 18.80.

3-Ethoxy-7,9-dimethyl-4-(phenylmethyl)-1-oxo-2,4,7,9-tetraazaspiro[4,5]dec-2-ene-6,8,10-trione (2g), 43% yield, colorless crystals, mp. 128-130°, IR (KBr): 1680 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.41 (t, 3H), 3.08 (s, 6H), 4.30(q, 2H), 4.34(s, 2H), 7.23 (m, 5H).

Anal. calcd. for $C_{16}H_{18}N_4O_5$: C, 55.48; H,5.24; N, 16.18. Found: C, 55.53; H, 5.21; N, 16.20.

N,N'-Dimethylimidazolidinetrione (3).- A solution of **1b** or **1c** (2.5 mmol) in trifluoroacetic acid (3 mL) and 30% H_2O_2 (1 mL) was stirred at room temperature untill TLC showed the disappearance of the starting material (~30 hrs). The excess H_2O_2 was decomposed with 10% Pd-C. The catalyst was removed by filtration, and the flitrate was evaporated. The residue was subjected to flash column chromatography on Silica gel with the use of ethyl acetate as the eluent to give 3 (10-15% yield) as a colorless crystals, mp. 148-151°, lit[9] 155.5°; ^1H NMR ($CDCl_3$): δ 3.16 (s); ^{13}C NMR ($CDCl_3$): δ 24.61 (q), 153.89 (s), 156.77 (s). MS (m/z, %): 142 (M^+, 100), 83 (29), 70 (17), 58 (41), 57 (25),26 (28),42 (13).

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AN ECONOMICAL PREPARATION OF 2-(2-BROMOETHYL)-1,3-DIOXANE

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2(2-Bromoethyl)-1,3-dioxane (**1**) is a useful three-carbon synthon, that has been used in an elegant cyclopentane annelation sequence[1]. Other uses includes preparation of γ-keto aldehydes,[2] the synthesis of optically active butyrolactones,[3,5] three-carbon homologation of aldehydes,[5] cyclohexene annelations[6] and prostaglandin synthesis.[7] The conventional preparation of **1** involve the use of gaseous HBr,[8,9] which is expensive and highly corrosive. We describe a modification of the existing