

A CONVERSION OF [1,2,5]OXADIAZOLO[3,4-d]PYRIMIDINE 1-OXIDES
INTO PURINES⁺

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Treatment of [1,2,5]oxadiazolo[3,4-d]pyrimidine 1-oxides with amines led to the formation of the corresponding 8-substituted purine derivatives, along with other heterocyclic compounds in some cases.

[1,2,5]Oxadiazolo[3,4-d]pyrimidine-5,7(4H,6H)-dione 1-oxides (furazano[3,4-d]pyrimidine-5,7(4H,6H)-dione 1-oxides) are of synthetic utility. For example, 4,6-dimethyl-[1,2,5]oxadiazolo[3,4-d]pyrimidine-5,7(4H,6H)-dione 1-oxide (Ia) has been shown to be a versatile intermediate for the syntheses of alloxazine 5-oxides,¹ furazano[3,4-d]pyrimidine² and pyrimidopteridine derivatives.² Such ring transformations seem to be scope for further development. Here, we report a reaction of I with amines which includes a novel conversion into purines.

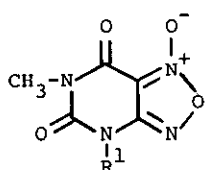
Heating of Ia with a slight excess of equimolar amount of benzylamine in hexamethylphosphoramide (HMPA) (170 °C, 4 hr) and in N,N-dimethylformamide (DMF) (reflux, 4 hr) gave 8-phenyltheophylline (IIa)³ in 55 and 38 % yields, respectively. Fusion (210 °C, 1 hr) or refluxing in acetic acid (4 hr) of these starting materials gave also IIa in lower yields (25 %). From the latter two procedures, 1,3-dimethyl-5,7-diphenylpyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (III) was obtained as a by-product in 15 % yield.

Similarly, the reaction of Ia with phenethylamine in DMF (reflux, 3 hr) gave 8-benzyltheophylline (IIb)⁴ (22 %) along with 1,3,7,9-tetramethylpyrimido[5,4-g]pteridine-2,4,6,8(1H,3H,7H,9H)-tetrone (IV)⁵ (20 %).

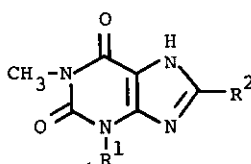
⁺Dedicated to Professor Tetsuji Kametani on the occasion of his retirement from Tohoku University.

Heating of 6-methyl-[1,2,5]oxadiazolo[3,4-d]pyrimidine-5,7(4H,6H)-dione 1-oxide (Ib) with benzylamine in HMPA (170 °C, 5 hr) and in DMF (reflux, 5 hr) afforded 1-methyl-8-phenylxanthine (IIc)⁶ in 50 and 39 % yields, respectively. On treatment of Ib with benzylamine under milder conditions (warming in dioxane) the key intermediate, 6-benzylamino-3-methyl-5-nitrosouracil (V)⁴ was obtained in 67% yield.

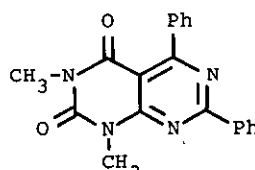
The starting material Ib was first synthesized in our laboratory by the action of potassium nitrate in acetic acid on 6-hydroxyamino-3-methyluracil (VI), prepared by the condensation of 6-chloro-3-methyluracil and hydroxylamine (see Experimental). Subsequently, Ib was alternatively prepared by the thermal decomposition of a triazolopyrimidine derivative.⁷ This furoxan (Ib) could also be readily prepared by the nitrosative cyclization of VI according to our procedure.²



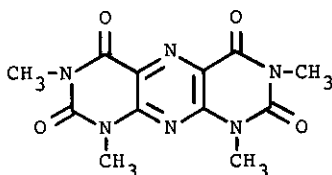
Ia; R¹ = CH₃
Ib; R¹ = H



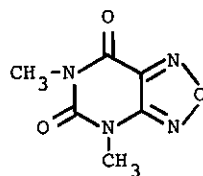
IIa; R¹ = CH₃, R² = Ph
IIb; R¹ = CH₃, R² = CH₂Ph
IIc; R¹ = H, R² = Ph



III

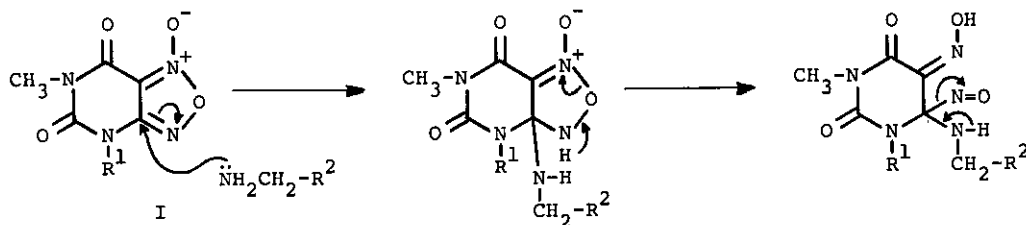


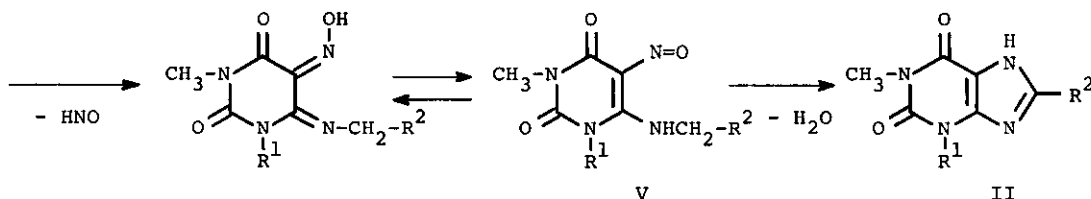
IV



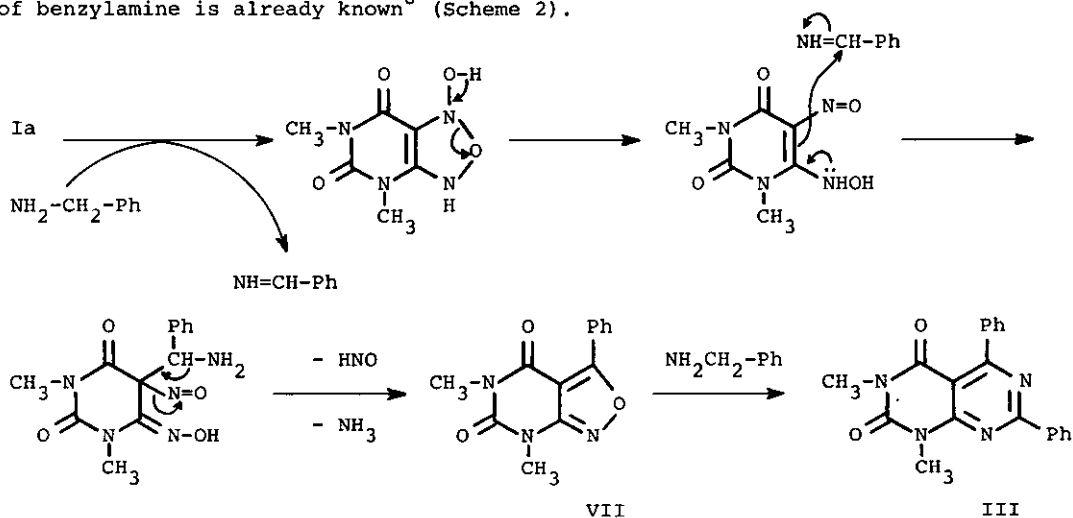
VIII

We suggest that this purine formation involves a nucleophilic attack of amines on the 3a position of I, followed by nitrogen-oxygen bond cleavage and the elimination of hyponitrous acid to give the corresponding 5-nitroso-6-(substituted-amino)-uracils (V), which undergo intramolecular cyclization to give the corresponding xanthine derivatives (II) (see Scheme 1).





The formation of 1,3-dimethyl-5,7-diphenylpyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (III) can be rationalized in terms of initial oxidation-reduction reaction between Ia and benzylamine giving 6-hydroxyamino-5-nitrosouracil and iminobenzaldehyde. These two would condense with concomitant elimination of hyponitrous acid, followed by intramolecular cyclization to give 5,7-dimethyl-3-phenylisoxazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (VII). Ring transformation of VII into III by means of benzylamine is already known⁸ (Scheme 2).



Aliphatic amines did not react in the same way as arylalkylamines to give purines. For example, heating of Ia with *n*-butylamine in HMPA gave a mixture of IV (24 %) and 4,6-dimethyl-[1,2,5]oxadiazolo[3,4-d]pyrimidine-5,7(4H,6H)-dione (VIII)⁹ (10 %). The scope and limitation of such conversion of I are currently under investigation.

EXPERIMENTAL

The melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Identity of the compounds was confirmed by comparison

of the IR spectra determined in Nujol on a JASCO IR-A1 spectrometer.

6-Hydroxyamino-3-methyluracil (VI). — Hydroxylamine hydrochloride (1.8 g, 0.026 mole) was neutralized with sodium (0.55 g, 0.024 atom) in dry ethanol (40 ml). To this solution, 6-chloro-3-methyluracil¹⁰ (3.2 g, 0.002 mole) was added and the mixture was refluxed for 3 hr. The precipitates were filtered and the filtrate was evaporated into dryness. Recrystallization of the residue from ethanol gave colorless crystals (0.25 g, 81 %), mp 190 °C. Anal. Calcd. for C₅H₇N₃O₃: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.10; H, 4.52; N, 26.39.

6-Methyl-[1,2,5]oxadiazolo[3,4-d]pyrimidine-5,7(4H,6H)-dione 1-Oxide (Ib). — To a solution of VI (2.0 g, 0.013 mole) in acetic acid (40 ml) was introduced gradually nitric oxide generated from sodium nitrite (69 g) and 50 % sulfuric acid (280 ml). The reaction mixture was evaporated into dryness and the residue was recrystallized from ethanol to give colorless platelets (1.57 g, 67 %), mp 210 °C¹¹ [lit., 211-212 °C].⁷ Anal. Calcd. for C₅H₄N₄O₄: C, 32.62; H, 2.19; N, 30.43. Found: C, 32.47; H, 2.17; N, 30.29.

Conversion of I into Purines. General Procedure. — A mixture of Ia (0.2 g, 0.001 mole) and benzylamine (0.13 g, 0.012 mole) in HMPA (2 ml) was heated at 170 °C for 4 hr. The reaction mixture was diluted with ethanol and allowed to stand overnight to precipitate crystals, which were filtered off and recrystallized from DMF to give colorless needles of 8-phenyltheophylline (0.14 g, 55%), mp >360 °C.

REFERENCES AND NOTES

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