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]pyrimidine[2] 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.

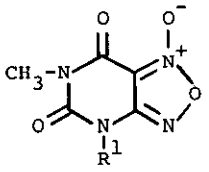
Heating of Ia with a slight excess of equimolar amount of benzylamine in hexamethylphosphoramide (HMPA) (170 °C, 4 hr) and in N,N-dimethylformamide (DMF) (reflux, 4 hr) gave 8-phenyltheophylline (IIa)[3] in 55 and 38 % yields, respectively. Fusion (210 °C, 1 hr) or refluxing in acetic acid (4 hr) of 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 %).

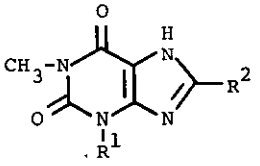
[+]Dedicated to Professor Tetsuji Kametani on the occation of his retirement from Tohoku University.

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.

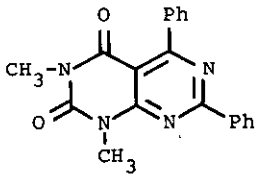
The starting material Ib was first synthesized in our laboratory by the action of potassium nitrate in acetic acid on 6-hydroxyamino-3-methyluracil (VI), prepared by the condensation of 6-chloro-3-methyluracil and hydroxylamine (see Experimental). Subsequently, Ib was alternatively prepared by the thermal 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]



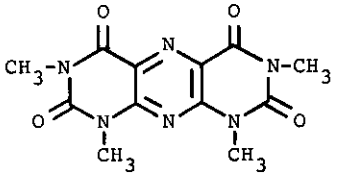
Ia; $R^1 = CH_3$
Ib; $R^1 = H$



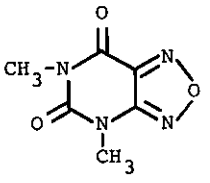
IIa; $R^1 = CH_3$, $R^2 = Ph$
IIb; $R^1 = CH_3$, $R^2 = CH_2Ph$
IIc; $R^1 = H$, $R^2 = Ph$



III

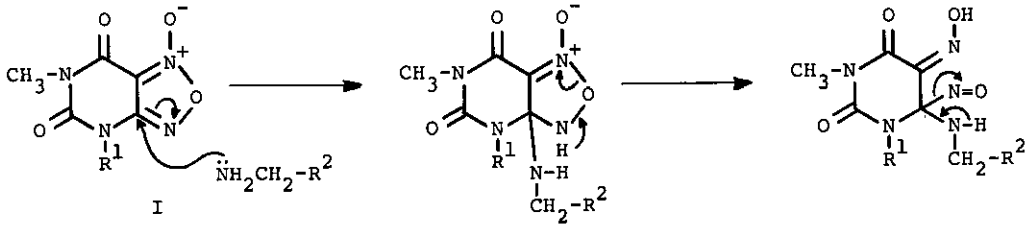


IV

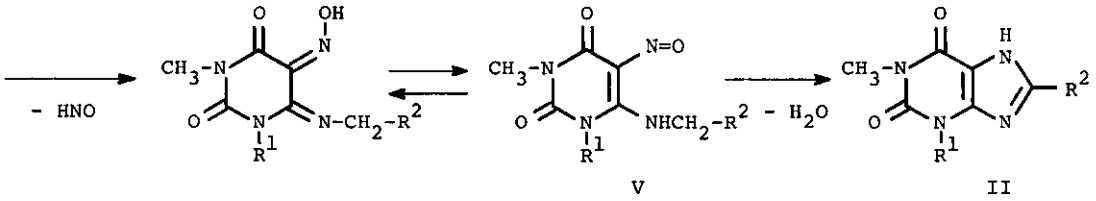


VIII

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).

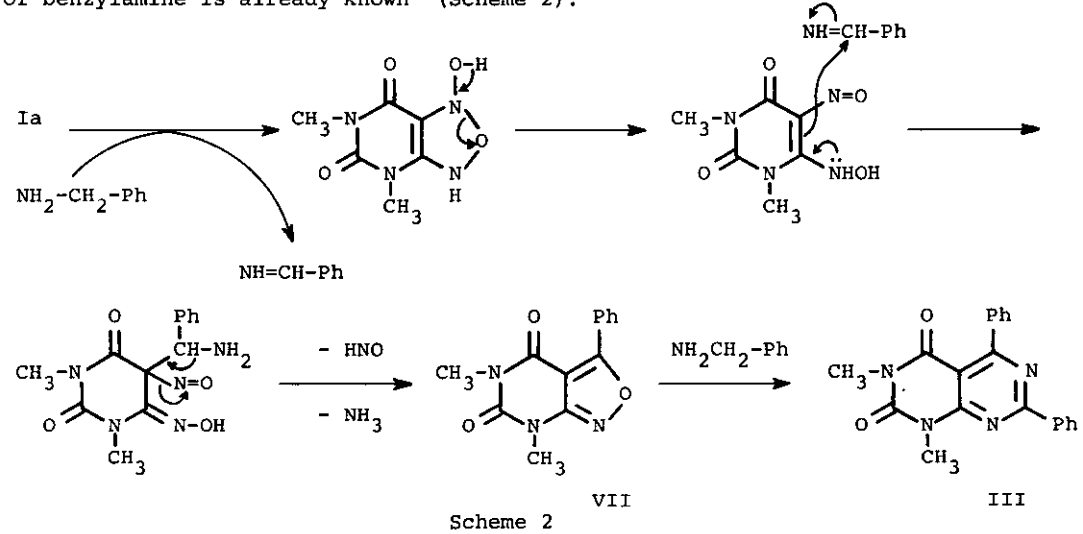


I



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 known[8] (Scheme 2).



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-Al 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-methyluracil[10] (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 $C_5H_7N_3O_3$: 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 °C[11] [lit., 211-212 °C].[7] Anal. Calcd. for $C_5H_4N_4O_4$: 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

1) F. Yoneda, Y. Sakuma, and S. Matsumoto, Heterocycles, 1975, 3, 113.
2) F. Yoneda and Y. Sakuma, J. Heterocyclic Chem., 1973, 10, 993.
3) G. P. Hager and C. Kaiser, J. Amer. Pharm. Assoc., 1954, 43, 148.
4) H. Goldner, G. Dietz, and E. Carstens, Ann., 1966, 691, 142.
5) F. Yoneda and S. Nishigaki, Chem. Pharm. Bull., 1971, 19, 1060.
6) F. Yoneda and T. Nagamatsu, J. Chem. Soc. Perkin I, 1976, 1547.
7) R. Nutiu and A. J. Boulton, J. Chem. Soc. Perkin I, 1976, 1327.
8) F. Yoneda, T. Yano, M. Higuchi, and A. Koshiro, Chemistry Letters, 1979, 155.
9) E. C. Taylor, Y. Maki, and A. McKillop, J. Org. Chem., 1972, 37, 1601.
10) G. Nübel and W. Pfleiderer, Chem. Ber., 1962, 95, 1605.
11) In the earlier communication,[12] this furoxan (Ib) was reported as melting above 300 °C, which was in error.
12) F. Yoneda, Y. Sakuma, and M. Ueno, J. Heterocyclic Chem., 1973, 10, 415.

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