A New Purine Synthesis

By FUMIO YONEDA,* KAZUKO OGIWARA, MICHIKO KANAHORI, and SADAO NISHIGAKI
(*School of Medicine, Keio University, Shinanomachi, Shinjuku-ku, Tokyo, Japan*)

Summary Reaction of 6-amino-5-nitrosouracil derivatives with various substituted hydrazones of aldehydes led to the formation of the corresponding xanthine derivatives.

THE reaction of 6-amino-1,3-dimethyl-5-nitrosouracil with various aldehyde hydrazones was recently developed as a new route to 7-azapteridines.[1]

We now describe the ready formation of the corresponding purines when a 6-amino-5-nitrosopyrimidine is allowed to react with a substituted hydrazone of an aldehyde. For example, heating 6-amino-1,3-dimethyl-5-nitrosouracil (**1**) under reflux with a slight excess of the benzaldehyde 1,1-dimethylhydrazone for 5 hr in dimethylformamide or dimethyl sulphoxide gave 8-phenyltheophylline[2] without the formation of a 7-azapteridine derivative. This reaction is equally applicable to other aldehyde 1,1-dimethylhydrazones (see Table).† Reaction of (**1**) with benzaldehyde acetylhydrazone in dimethylformamide also yielded 8-phenyltheophylline in moderate yield.

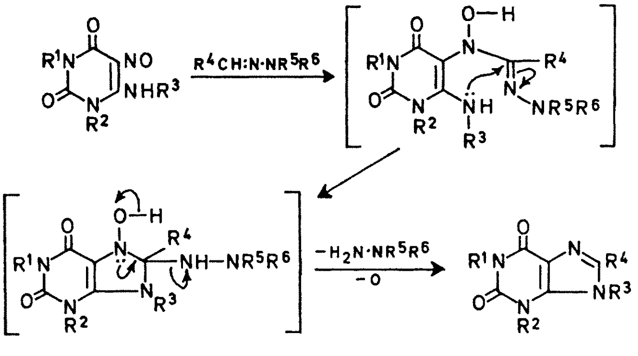
Treatment of 3-methyl-6-methylamino-5-nitrosouracil (**2**) with aldehyde methyl- or 1,1-dimethyl-hydrazones gave the respective 1,9-dimethyl-8-substituted-xanthines along with the self-condensation product of (**2**), 1-methylxanthine. The condensation of (**2**) with unsubstituted hydrazones of aldehydes does not lead to the expected 7-azapteridines, but rather to the same 1,9-dimethyl-8-substituted-xanthines described above (see Table).

Xanthine formation by reaction of 6-*amino*-5-*nitrosouracil with aldehyde hydrazone in dimethylformamide or dimethyl sulphoxide*

6-Amino-5-nitroso-uracil	Aldehyde hydrazone	Product[a]	Yield %
6-Amino-1,3-dimethyl-5-nitrosouracil (**1**)	Benzaldehyde 1,1-dimethylhydrazone	8-Phenyltheophylline	61
(**1**)	*p*-Chlorobenzaldehyde 1,1-dimethylhydrazone	8-*p*-Chlorophenyltheophylline	56
(**1**)	Isonicotinaldehyde 1,1-dimethylhydrazone	8-Isonicotinyltheophylline	27
(**1**)	Benzaldehyde acetylhydrazone	8-Phenyltheophylline	43
1-Methyl-6-methylamino-5-nitrosouracil (**2**)	Benzaldehyde methylhydrazone	1,9-Dimethyl-8-phenylxanthine	52
(**2**)	Nicotinaldehyde 1,1-dimethylhydrazone	1,9-Dimethyl-8-nicotinylxanthine	50
(**2**)	Benzaldehyde hydrazone	1,9-Dimethyl-8-phenylxanthine	68
(**2**)	*p*-Chlorobenzaldehyde hydrazone	1,9-Dimethyl-8-*p*-chlorophenylxanthine	76
(**2**)	*p*-Bromobenzaldehyde hydrazone	1,9-Dimethyl-8-*p*-bromophenylxanthine	30
(**2**)	Thiophen-2-aldehyde hydrazone	1,9-Dimethyl-8-(2-thienyl)xanthine	59

[a] None of the products melted below 320°.

The formation of 8-phenyltheophylline by treatment of (**1**) with benzaldehyde in dimethylformamide has been reported.[3] However, reaction of (**2**) with benzaldehyde in dimethylformamide did not give 1,9-dimethyl-8-phenylxanthine, but only the self-condensed 1-methylxanthine. Furthermore, (**2**) did not react with hydrazines (which might be liberated from their hydrazones during reaction) starting material being recovered under the same conditions. From these facts, the new purine synthesis is best rationalized by assuming initial nucleophilic attack of the electron-rich-α-carbon of the hydrazones on the nitroso-group of the pyrimidines to form hydroxylamine intermediates, followed by intramolecular cyclization by the addition of the *o* amino-substituent to the anil carbon of the intermediate. Elimination of a hydrazine and deoxygenation of the purine 7-oxide by the hydrazine could yield the purine.



SCHEME

(*Received, June 9th,* 1970; *Com.* 896.)

---

† Satisfactory analysis, u.v., and i.r. spectral data were obtained for all the products.

[1] F. Yoneda, M. Kanahori and S. Nishigaki, unpublished results.

[2] G. P. Hager and C. Kaiser, *J. Amer. Pharm. Assoc.*, 1954, **43**, 148.

[3] E. C. Taylor and E. E. Garcia, *J. Amer. Chem. Soc.*, 1964, **86**, 4721.