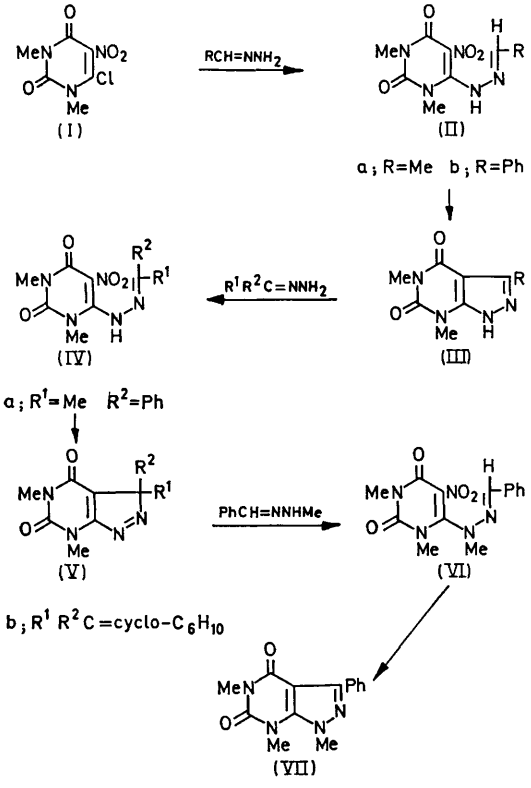
A New Synthesis of Pyrazolo[3,4-*d*]pyrimidines

By Y. MAKI,* K. IZUTA, and M. SUZUKI
(*Gifu College of Pharmacy, Mitahora, Gifu, Japan*)

Summary Treatment of 6-chloro-3,4-dimethyl-5-nitrouracil with a wide variety of ketone and aldehyde hydrazones provides a novel one-step synthesis of pyrazolo[3,4-*d*]pyrimidines.

ALTHOUGH much effort has been directed toward the synthesis of the pyrazolo[3,4-*d*]pyrimidine system, which is of biological and medicinal interest,[1] a convenient synthetic method is still lacking. We have found that 6-chloro-1,3-dimethyl-5-nitrouracil (I)[2] reacts readily with various ketone and aldehyde hydrazones to afford 3-(or 3,3-) substituted pyrazolo[3,4-*d*]pyrimidines, (III), (V), and (VII) (see Scheme 1).

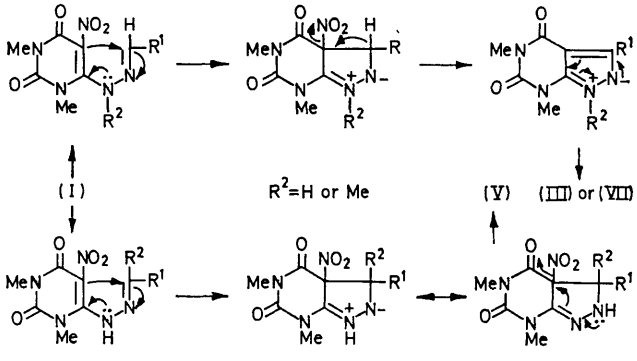


SCHEME 1

A solution of a ketone or aldehyde hydrazone (1·2 mole) in an appropriate solvent is added portionwise with stirring to a solution of (I) (1 mole) in chloroform. The resulting solution is heated at reflux for about 1 h, during which time the solution changes its colour from yellow to red. After removal of the solvent, the oily residue is solidified by addition of a small amount of ether and purified by recrystallization to give (III) and (V)† in 55—80% yields. 3,5,7-Trimethyl-4,6(5*H*,7*H*)-pyrazolo[3,4-*d*]pyrimidinedione (IIIa) prepared in this way was identical in every respect with an authentic sample prepared by the reaction of 6-hydrazino-1,3-dimethyluracil with boiling acetic anhydride.[3] During this reaction, the liberation of nitrous acid was detected and intermediates, (II) and (IV), were isolated from the reaction mixture prior to reflux. The stability of the intermediates appears to depend upon the nature of the substituents in the hydrazones employed. For example, 6-acetylidenehydrazino-1,3-dimethyl-5-nitrouracil (IIa) is so unstable that its purification by recrystallization from methanol results in contamination with (IIIa). On the other hand, benzylidenehydrazinouracil (IIb) is more stable, and therefore the conversion into (IIIb) requires more drastic conditions (reflux in dimethylformamide).

The reaction of (I) with benzaldehyde methylhydrazone gives the stable intermediate (VI), whose cyclization to (VII) is more difficult than in the cases of (II) and (IV).

The Table summarizes some synthetic and physical data for the pyrazolo[3,4-*d*]pyrimidines.



SCHEME 2

We tentatively suggest the mechanism outlined in Scheme 2. The first step is simple substitution of the 6-chlorine in (I) by hydrazone, affording intermediates (II), (IV), and (VI). The second step seems to be an intramolecular nucleophilic addition. The cyclic intermediates thus formed undergo elimination of nitrous acid followed by an electron shift leading to the final products.

TABLE

Some synthetic and physical data of pyrazolo (3,4-d)*pyrimidines.*

Hydrazone	Intermediate	M.p.	Solvent[a]	Pyrazolo[3,4-*d*]pyrimidine	M.p.	Yield %[b]
$MeCH{=}NNH_2$	(IIa)	135—136°	MeOH	(IIIa)	282—284°	75
$PhCH{=}NNH_2$	(IIb)	201—202°	$HCONMe_2$	(IIIb)	258—259°	77
$Me(Ph)C{=}NNH_2$	(IVa)	146—147°	$HCONMe_2$	(Va)	172—173°	55
Cyclohexylidene$=NNH_2$	(IVb)	128—130°	MeOH	(Vb)	145—146°	80
$PhCH{=}NNHMe$	(VI)	192—194	Me_2SO	(VII)	183—184°	20

[a] Solvent employed for cyclization.
[b] Yield in direct cyclization without isolation of intermediate.

† All new compounds described gave satisfactory elemental analyses and i.r. and n.m.r. spectra consistent with the structures assigned.

There have been many examples demonstrating the enamine character of 6-amino-[4] or -hydrazino-uracil.[3] The unusual lability of a 5-nitro-group on a uracil ring[5] towards elimination has been also reported. The intermediates (II), (IV), and (VI) all contain an enamine moiety, a labile nitro-group, and an electron-deficient azomethine carbon. Thus the molecules are perfectly arranged for intramolecular cyclization to the pyrazolo[3,4-*d*]pyrimidine system.

The cyclization, however, may be considered as an electrocyclic reaction, which has been predicted in the known photochemical cyclization of the vinyl amine system.‡[6]

(*Received, September 9th*, 1971; *Com.* 1577.)

‡ We have observed a novel photochemical cyclization of (VI) to (VII) together with 3,4,6-trimethyl-5,7(4*H*,6*H*)-triazolo[4,5-*d*] pyrimidine *N*-oxide. The details will be reported in a separate paper.

[1] For an excellent review of pyrazolo[3,4-*d*]pyrimidines, see R. K. Robins in "Heterocyclic Compounds", ed .R. C. Elderfield, Vol. 8, Wiley, New York, 1967, pp. 406—421.
[2] T. K. Liao and C. C. Cheng, *J. Heterocyclic Chem.*, 1964, **1**, 212.
[3] W. Pfleiderer and K. H. Shunderhutte, *Annalen*, 1958, **615**, 42.
[4] C. W. Noell and R. K. Robins, *J. Heterocyclic Chem.*, 1964, **1**, 34; W. Pfleiderer, F. Sagi, and L. Grozinger, *Chem. Ber.*, 1966, **99**, 3330; H. Bredereck, F. Effenberger, and G. Simchen, *ibid.*, 1964, **97**, 1403.
[5] E. C. Taylor, F. Sowinski, T. Lee, and F. Yoneda, *J. Amer. Chem. Soc.*, 1967, **89**, 3369; H. U. Blank and J. J. Fox, *ibid.*, 1968, **90**, 7175.
[6] O. L. Chapman and G. L. Eian, *J. Amer. Chem. Soc.*, 1968, **90**, 5329; O. L. Chapman, G. L. Eian, A. Bloom, and J. Clardy, *ibid.* 1971, **93**, 2918.