A New Synthesis of Disubstituted 8-Aminopurine Derivatives

By FUMIO YONEDA* and TAKAFUMI MATSUMURA

(*Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto, Japan*)

and KEITARO SENGA

(*Pharmaceutical Institute, School of Medicine, Keio University, Shinjuku-ku, Tokyo, Japan*)

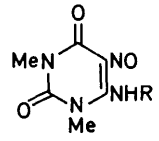
Summary Treatment of 6-amino-5-nitrosopyrimidines with the Vilsmeier reagent (dimethylformamide and phosphorus oxychloride) afforded in general the respective 8-dimethylaminopurines; treatment of 6-amino-4-hydroxy-2-methyl-5-nitrosopyrimidine gave 2-chloromethyl-8-dimethylamino-6-hydroxypurine.

MOST disubstituted 8-aminopurine derivatives[1] have been prepared by the introduction of the disubstituted amino groups into the preformed 8-chloro- or 8-methylmercaptopurine derivatives. We report a new convenient synthesis of disubstituted 8-aminopurine derivatives consisting of treatment of 6-amino-5-nitrosopyrimidines with the Vilsmeier reagent.

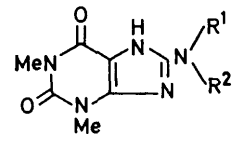
Heating 6-amino-1,3-dimethyl-5-nitrosouracil (I) with phosphorus oxychloride in dimethylformamide (the Vilsmeier reagent) at 150 °C for 1 h, concentration of the reaction mixture by partial evaporation, and then dilution with water caused 8-dimethylaminotheophylline[2]† (II) (m.p. >300°) to separate (72%). However, formamide did not react in the same way as dimethylformamide to give the desired 8-aminotheophylline. Treatment of (I) with diethylformamide and *N*-methylformanilide in the presence of phosphorus oxychloride led to the formation of 8-diethylamino- (III) (m.p. 254°) (43%) and 8-*N*-methylanilino-theophylline (IV)[2] (m.p. 261°) (40%). 1,3-Dimethyl-6-methylamino-5-nitrosouracil (V) and the Vilsmeier reagent led to 8-dimethylaminoisocaffeine (VI) (m.p. 295°) (30%).

Heating 6-amino-4-hydroxy-2-methylmercapto-5-nitrosopyrimidine (VII) with the Vilsmeier reagent at 130° for 1 h, concentration of the reaction mixture by partial evaporation, and treatment of the residue with ethanol gave 8-dimethylamino-6-hydroxy-2-methylmercaptopurine (VIII) (m.p. >300°) (75%), which was converted into 8-dimethylamino-6-hydroxy-2-morpholinopurine (IX) (m.p. >300°) by treatment with morpholine at reflux.

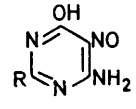
It is interesting to note that the reaction of 6-amino-4-hydroxy-2-methyl-5-nitrosopyrimidine (X) with the Vilsmeier reagent under the same conditions gave 2-chloromethyl-8-dimethylamino-4-hydroxypurine (XI) (m.p. >300°) (83%). Treatment of (XI) with anilines led to the 2-anilinomethyl derivatives (XII) (m.p. >300°) and (XIII) (m.p. >300°).



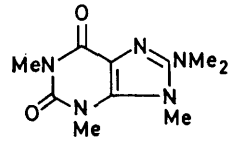
(I) R = H
(V) R = Me



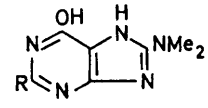
(II) $R^1 = R^2 = Me$
(III) $R^1 = R^2 = Et$
(IV) $R^1 = Me = R^2 = Ph$



(VII) R = SMe
(X) R = Me



(VI)

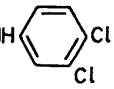


(VIII) R = Me

(IX) R = N O

(XI) R = CH_2Cl

(XII) R = CH_2NH 

(XIII) R = CH_2NH 

(*Received, 28th February* 1972; *Com.* 328.)

† Satisfactory elemental analyses, and i.r., n.m.r., and mass spectra were obtained for all the products.

[1] R. K. Robins in 'Heterocyclic Compounds,' ed. R. C. Elderfield, vol. 8, Wiley, New York, 1967, pp. 162—406.
[2] E. C. Taylor and F. Sowinski, *J. Amer. Chem. Soc.*, 1968, **90**, 1374.