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Dimethylamination and Nitrosation of Pyrimidines with N-Nitrosodimethylamine[1]

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Reaction of a chloropyrimidine and a 5-activated pyrimidine in N-nitrosodimethylamine (NDA) resulted in the simultaneous formation of a dimethylaminopyrimidine and a 5-nitrosopyrimidine which is further transformed. A special type of Vilsmeier–Haack reaction using a mixture of NDA and phosphorus oxychloride (NDA+$POCl_3$) for 5-activated pyrimidines has been accomplished. The reaction of 6-amino-1,3-dimethyluracil with NDA+$POCl_3$ under cooling gave bis(6-amino-1,3-dimethyluracil-5-yl)methane, which was converted into 1,3,7,9-tetramethyl(1H,3H,7H,9H)-pyrido[2,3-*d*,6,5-*d'*]dipyrimidine-2,4,6,8-tetrone.

Recent reports[3,4] have shown that dimethylformamide (DMF) is an useful dimethylamination reagent for active halogeno-compounds. In the course of our stiudes on the dimethylamination by DMF, it was found that reaction of a chloropyrimidine and a 5-activated pyrimidine in DMF resulted in the simultaneous formation of a dimethylaminopyrimidine and a 5-formylpyrimidine.[4,5] We report here analogous reactions using N-nitrosodimethylamino (NDA), the azalogue of DMF, which involve the intermolecular simultaneous dimethylamination and nitrosation; we also describe a special type of Vilsmeier–Haack reaction using a mixture of NDA and phosphorus oxychloride.

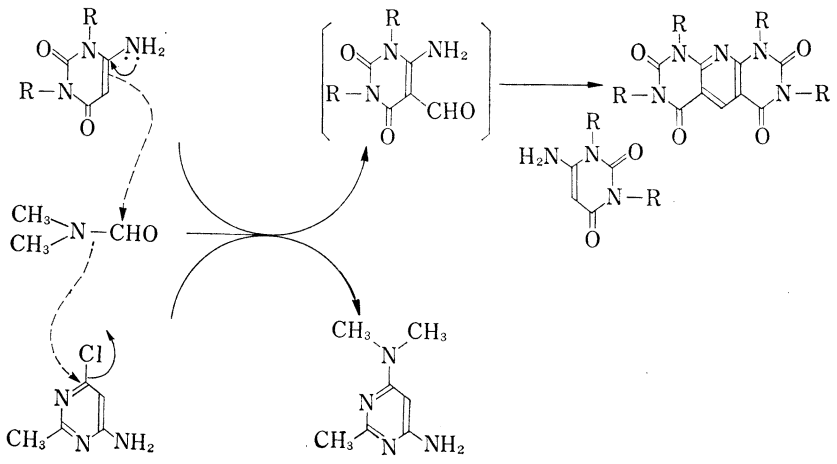

Chart 1

1) A part of this work has been summarized in a recent communication: F. Yoneda, K. Senga, and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **20**, 2063 (1972).
2) Location: *a*) *Oe-honmachi, Kumamoto*; *b*) *Shinanomachi, Shinjuku-ku, Tokyo.*
3) N.D. Heindel and P.D. Kennewell, *Chem. Commun.*, **1969**, 38.
4) S. Nishigaki, K. Senga, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **19**, 1526 (1971).
5) K. Senga, F. Yoneda, and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **19**, 215 (1971).

Heating 4-amino-6-chloro-2-methylpyrimidine (I)[6] with an equimolar amount of 6-amino-1,3-dimethyluracil (II)[7] in excess NDA at 175—180° for 3 hr gave a mixture of 4-amino-6-dimethylamino-2-methylpyrimidine (III)[8] (66%) and 1,3,7,9-tetramethyl-(1H,3H,7H,9H)-pyrimido[5,4-*g*]pteridine-2,4,6,8-tetrone (IV)[9] (59% theoretically). The use of 6-amino-1,3-diethyluracil (V)[7] instead of II in this reaction afforded the corresponding 1,3,7,9-tetraethylpyrimido[5,4-*g*]pteridinetetrone (VI)[10] (44% theoretically) and III (60%). The formation of IV (or VI) may be initiated by nitrosation of II (or V) followed by condensation of the resulting 6-amino-1,3-dialkyl-5-nitrosouracil with unchanged II (or V). When II (or V) alone was heated in NDA under the same conditions, only a trace of IV (or VI) was obtained with the starting material being recovered. On the other hand, treatment of I alone with NDA under the same conditions gave III (65%) as sole product. This fact shows that NDA can be used as a dimethylamination reagent.

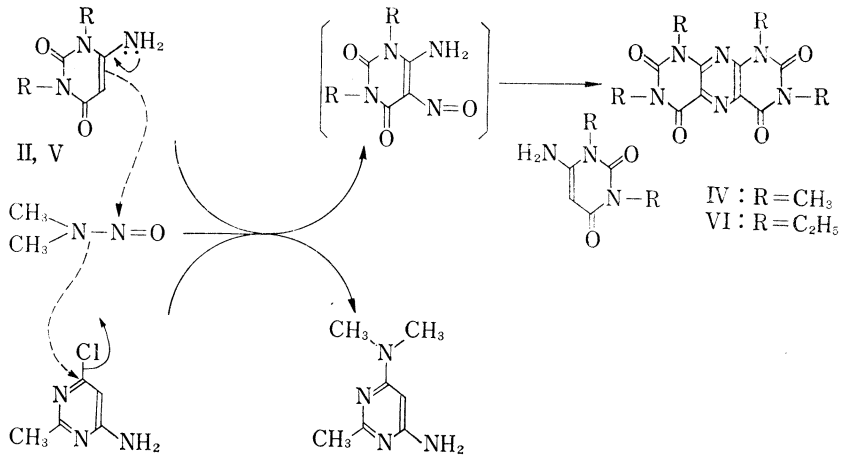

Chart 2

Similarly, the reaction of I and 4-amino-6-hydroxy-2-phenylpyrimidine (VII)[11] in NDA under the same conditions gave III (60%) and 2,8-diphenyl-(3H,7H)-pyrimido[5,4-*g*]pteridine-4,6-dion (VIII) (36% theoretically), whose structure was ascertained by comparison with the authentic sample prepared by an alternative route.[12]

The reaction of I and 6-benzylamino-1,3-dimethyluracil (IX)[13] in NDA gave a mixture of III (76%) and 8-phenyltheophylline (X)[14] (84%), whereas the reaction of I and 6-benzylamino-1-methyluracil (XI)[13] in NDA gave a noncyclized product, 5-(6-benzylamino-3-methyl-

6) Z. Fördi, G.V. Fodor, I. Demjen, H. Szeker, and I. Halmos, *Chem. Ber.*, **75**, 755 (1942).
7) J.H. Speer and A.L. Raymond, *J. Am. Chem. Soc.*, **75**, 114 (1953).
8) F. Craveri and G. Zoni, *Bull. Sci. Fac. Chim. Ind. Bologna*, **16**, 126 (1958) [*C.A.*, **53**, 13161 (1959)].
9) *a*) E.C. Tayler, G.K. Cain, and H.M. Loux, *J. Am. Chem. Soc.*, **76**, 1874 (1954); *b*) F. Yoneda and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **19**, 1060 (1971).
10) A.F. Daglish, R. Vonderwahl, and G.A. Tillotson, Ger. Pat. 1087609 [*C.A.*, **58**, 9094h (1958)].
11) F. Bergmann, A. Kalmus, H.V. Waron, and H.K. Bovrin, *J. Chem. Soc.*, **1963**, 3729.
12) This compound could be synthesized by the condensation of 4-amino-6-hydroxy-2-phenylpyrimidine with 4-amino-6-hydroxy-5-nitroso-2-phenylpyrimidine in acetic acid; F. Yoneda, K. Shinomura, M. Ichiba, and S. Nishigaki, unpublished results.
13) H. Goldner, G. Dietz, and E. Carstens, *Ann.*, **691**, 142 (1966).
14) *a*) E.C. Taylor and E.E. Garcia, *J. Am. Chem. Soc.*, **86**, 4722 (1964); *b*) F. Yoneda, K. Ogiwara, M. Kanahori, and S. Nishigaki, *Chem. Commun.*, **1970**, 1068.

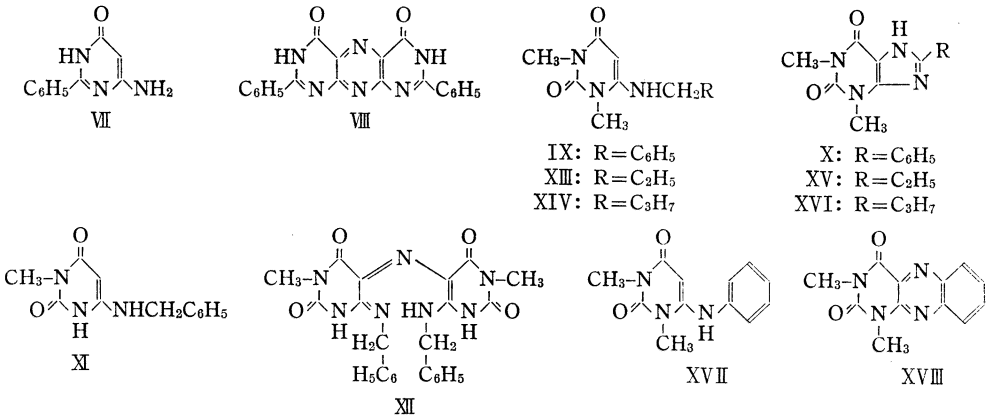

Chart 3

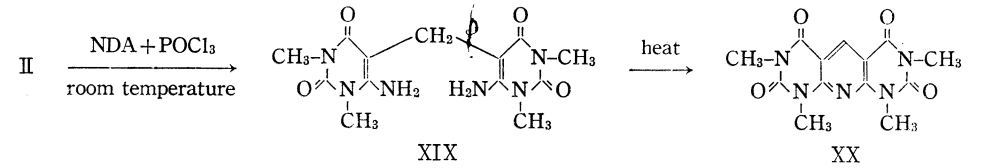

Chart 4

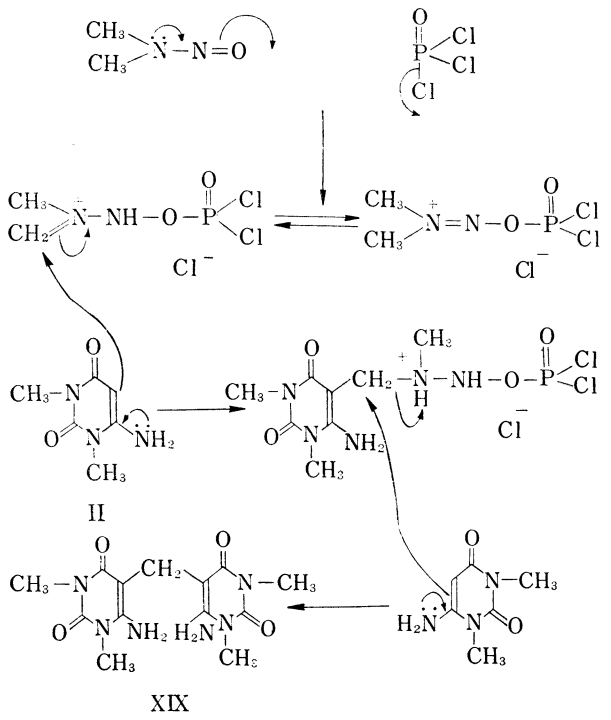

Chart 5

uracil-5-yl)imino-6-benzylimino-3-methyl-dihydrouracil (XII) (51% theoretically) and III (60%). The structure of XII was assigned on the basis of elemental analysis, molecular weight determination (a strong parent peak at *m/e* 473) and another spectroscopic evidences, and by consideration of its probable mode of formation.

Next, the reaction of 5-activated pyrimidine with NDA in the presence of phosphorus oxychloride (referred to hereafter as NDA+$POCl_3$) has been tried in order to study the nitrosation reaction which can be regarded as a special type of Vilsmeier–Haack reaction. Thus, heating IX with NDA+$POCl_3$ for a few minutes gave X (71%). Similarly, 1,3-dimethyl-6-*n*-propylaminouracil (XIII)[13] and 6-*n*-butylamino-1,3-dimethyluracil (XIV)[13] under similar conditions yielded 8-ethyltheophylline (XV)[13] (43%) and 8-*n*-propyltheophylline (XVI)[13] (30%), respectively. In latter two cases, compound IV was detected as a byproduct in 7 and 8% yield respectively.

The reaction of 6-anilino-1,3-dimethyluracil (XVII)[15] with NDA+$POCl_3$ under the same conditions gave 1,3-dimethylalloxazine (XVIII)[15–18] (42%). The use of II in this reaction afforded IV (30% theoretically) as expected.

When II was treated with NDA+$POCl_3$ at low temperature, to our surprise, bis(6-amino-1,3-dimethyluracil-5-yl)methane (XIX)[19] (66% theoretically) was obtained. The latter was thermally converted into 1,3,7,9-tetramethyl-(1H,3H,7H,9H)-pyride [2,3-*d*, 6,5-*d'*]dipyrimidine-2,4,6,8-tetrone (XX)[4,5,19,20] (66%).

The formation of XX described above is rationalized in the mechanism as seen in Chart 5.

Experimental[21]

General Procedure for the Intermolecular Dimethylamination and Nitrosation——A mixture of I (0.003 mole) and a 5-activated pyrimidine (II, V, VII, IX or XI) (0.003 mole) in 5 ml of NDA was heated at 175—190° for 3 hr. After cooling at room temperature, separated crystals were collected by filtration, washed with EtOH and dried to give the crude crystals. Recrystallization from DMF gave the respective pure product (IV, VI, VIII, X or XII). None of the products melted below 320° except VI (mp 232°).

The filtrate was evaporated under reduced pressure. The resulting residue was extracted with $CHCl_3$, the extracts were dried (Na_2SO_4) and evaporated to dryness to give pale yellow crystals of III, mp 191°.

General Procedure for Synthesis of 8-Substituted Theophyllines (X, XV and XVI)——To a suspension of a 6-substituted-amino-1,3-dimethyluracil (IX, XIII or XIV) (0.003 mole) in 1 ml of DNA, $POCl_3$ (0.006 mole) was added dropwise and then heated at 90° (water bath) for 5 min. After cooling, the resulting brown syrup was diluted with 50 ml of H_2O to precipitate yellow crystals, which were collected by filtration and recrystallized from DMF to give IV.

The filtrate was evaporated to dryness and the residue was treated with a small amount of MeOH to separate crystals, which were filtered off and recrystallized from DMF+H_2O to give the respective 8-substituted theophylline (X, XV or XVI).

1,3-Dimethylalloxazine (XVIII)——To a suspension of 0.46 g (0.002 mole) of XVII in 2 ml of NDA, 0.6 g (0.004 mole) of $POCl_3$ was added dropwise and warmed at 90° (water-bath) for 5 min. The resulting brown syrup was treated with 30 ml of EtOH+H_2O (1:1) to separate crystals, which were collected by filtration and recrystallized from acetone to give 0.2 g (42%) of pale yellow prisms, mp 243.5°, identified with an authentic sample.

1,3,7,9-Tetramethyl-(1H,3H,7H,9H)-pyrimido[5,4-*g*]pteridine-2,4,6,8-tetrone (IV)——To a suspension of 0.62 g (0.004 mole) of II in 1 ml of NDA, 0.61 g (0.004 mole) of $POCl_3$ was added dropwise and then heated at 90° for 10 min. After cooling, the reaction mixture was diluted with 30 ml of H_2O. The precipitated crystals were collected by filtration and recrystallized from DMF to give 0.18 g (30% theoretically) of pale yellow prisms.

Bis(6-amino-1,3-dimethyluracil-5-yl)methane (XIX)——To a suspension of 0.62 g (0.004 mole) of II in 5 ml of NDA, 1.81 g (0.012 mole) of $POCl_3$ was added dropwise under cooling with ice-H_2O. After being stirred under cooling for 1 hr, the violet reaction mixture was diluted with 50 ml of H_2O, made alkaline with aq. NH_3 and concentrated to dryness. The residue was washed with hot H_2O and recrystallized from AcOH to give 0.42 g (66% theoretically) of colorless needles, mp >300°. The mass spectrometry revealed a strong parent ion at *m/e* 322. *Anal.* Calcd. for $C_{13}H_{18}O_4N_6$: C, 48.44; H, 5.63; N, 26.08. Found: C, 48.30; H, 5.48; N, 25.84.

1,3,7,9-Tetramethyl-(1H,3H,7H,9H)-pyrido[2,3-*d*, 6,5-*d'*]dipyrimidine-2,4,6,8-tetrone (XX)——After fusion of 0.32 g (0.01 mole) of XIX at 280° for 15 min, the resulting product was recrystallized from AcOH to give 0.2 g (66%) of colorless needles, mp 320°, which were in all respects identical with an authentic sample.

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16) E.C. Taylor, F. Sowinski, T. Yee, and F. Yoneda, *J. Am. Chem. Soc.*, **89**, 3369 (1967).
17) S. Nishigaki, S. Fukazawa, K. Ogiwara, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **19**, 206 (1971).
18) F. Yoneda and S. Fukazawa, *Chem. Commun.*, **1972**, 503.
19) R.C. Elderfield and M. Wharmby, *J. Org. Chem.*, **32**, 1638 (1967).
20) H. Bredereck, F. Effenberger, and R. Sauter, *Chem. Ber.*, **95**, 2049 (1962).
21) Melting points were uncorrected. Identity of compounds was confirmed by comparison of infrared spectra determined in KBr discs on a Japan Spectroscopic Co., Ltd. spectrophotometer, Model IR-E.