BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 1836—1839 (1973)

A New Synthesis of Substituted 8-Aminopurine Derivatives[1]

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(Received November 4, 1972)

The treatment of 6-amino-5-nitrosopyrimidines with Vilsmeier-type reagents (substituted formamides and phosphorus oxychloride) afforded substituted 8-aminopurines; the treatment of 6-amino-4-hydroxy-2-methyl-5-nitrosopyrimidine gave 2-chloromethyl-8-dimethylamino-6-hydroxypurine.

Most substituted 8-aminopurine derivatives have been synthesized by the following two routes: the introduction of substituted amino groups into the preformed 8-chloro- or 8-methylmercapto-purine derivatives,[2] and the dehydrative or dethiohydrative cyclization of the 5-ureido- or 5-thioureido-6-aminopyrimidines obtained by the reaction of 5,6-diaminopyrimidines with substituted isocyanates or isothiocyanates.[3] We wish now to report a convenient new method of synthesizing substituted 8-aminopurine derivatives; the method consists of the treatment of 6-amino-5-nitrosopyrimidines with a mixture of substituted formamides and phosphorus oxychloride (Vilsmeier-type reagent).

The heating of 6-amino-1,3-dimethyl-5-nitrosouracil (**1**) with phosphorus oxychloride in dimethylformamide at 180 °C for 1 hr, the concentration of the reaction mixture by partial evaporation, and then dilution with water caused the separation of 8-dimethylaminotheophylline (**2a**) in a good yield. The structure of **2a** was established by a comparison of it with an authentic sample prepared by the treatment of 8-chlorotheophylline with dimethylformamide. This procedure is an application of the known dimethylamination of active chloro compounds using dimethylformamide.[4] Analogous reactions were observed in the condensation of **1** with methylformamide, diethylformamide, and *N*-methylformanilide in the presence of phosphorus oxychloride; in all cases, the substituted amino groups of the formamides were introduced into the 8-position of the final theophyllines. However, formamide did not react in the same way as substituted formamides to give the desired 8-aminotheophylline; rather, the formation of a small amount of 1,3-dimethylpyrimido-

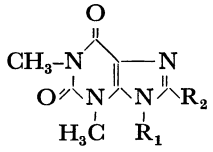
1) A part of this paper has been reported in a preliminary form; see F. Yoneda, T. Matsumura, and K. Senga, *Chem. Commun.*, **1972**, 606.

2) For example, R. K. Robins, *J. Amer. Chem. Soc.*, **80**, 6671 (1958).

3) For example, A. H. Cook, and G. H. Thomas, *J. Chem. Soc.*, **1950**, 1888.

4) S. Nishigaki, K. Senga, and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **19**, 1526 (1971).

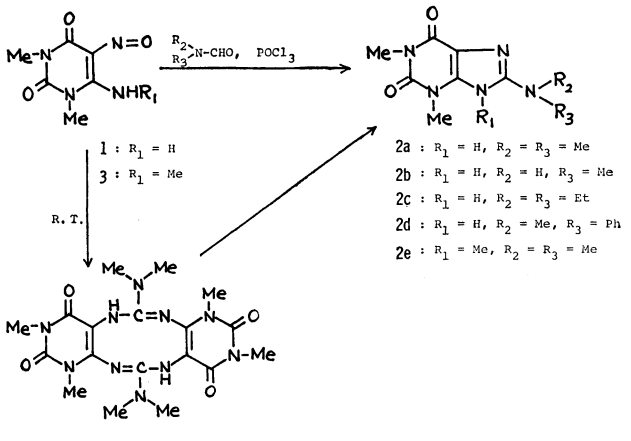
TABLE 1. SUBSTITUTED 8-AMINOTHEOPHYLLINES



No.	R_1	R_2	Yield (%)	Recrystl. Solvent	Mp (°C)	MS (M^+)	Formula	Analyses Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
2a	H	NMe_2	72	DMF	>330	223	$C_9H_{13}N_5O_2$	48.42	5.87	31.38	48.31	6.03	31.37
2b	H	NHMe	30	DMF	>330	209	$C_8H_{11}N_5O_2$	45.93	5.30	33.48	46.07	5.21	33.23
2c	H	NEt_2	43	dioxane	254	251	$C_{11}H_{17}N_5O_2$	52.57	6.82	27.87	52.30	6.79	27.65
2d	H	N(Me)Ph	40	ethanol	261	285	$C_{14}H_{15}N_5O_2$	58.93	5.30	24.55	58.84	5.38	24.44
2e	Me	NMe_2	30	methanol	295	237	$C_{10}H_{15}N_5O_2$	50.62	6.37	29.52	50.51	6.18	29.38

[4,5-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione[5] was observed. The treatment of 1,3-dimethyl-6-methylamino-5-nitrosouracil (**3**) with a mixture of dimethylformamide and phosphorus oxychloride led to the formation of 8-dimethylaminoisocaffeine (**2e**). The results are summarized in Table 1.

When **1** was treated with a mixture of dimethylformamide and phosphorus oxychloride at room temperature, a dimeric product (**4**) was obtained. The latter was converted into **2a** by further heating in the same reagent or by sublimating *in vacuo*. The structure of **4** was deduced from the following evidences; the molecular ion peak at *m/e* 446 in the mass spectrum and the elemental analysis correspond to the assigned formula. The NMR spectrum (CF_3COOH) displays a pair of six-proton singlets at 3.27 and 3.74 δ corresponding to the *N*-methyl groups of uracil and a twelve-proton singlet at 3.61 δ corresponding to the dimethylamino groups. Two two-proton broad singlets, at 5.77 and 5.94 δ, were assigned to the NH and NH^+ protons respectively.



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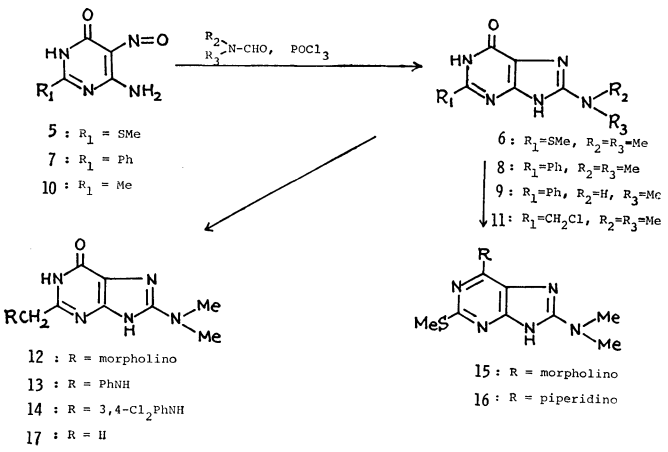
Scheme I.

The heating of 6-amino-4-hydroxy-2-methylthio-5-nitrosopyrimidine (**5**) with a mixture of dimethylformamide and phosphorus oxychloride at 130 °C for 1 hr, the subsequent concentration of the reaction mixture by partial evaporation, and the treatment of the residue with ethanol gave 8-dimethylamino-6-hydroxy-2-methylthiopurine (**6**). Similarly, 6-amino-4-hydroxy-5-nitroso-2-phenylpyrimidine (**7**) and a mixture of dimethylformamide or methylformamide and phosphorus oxychloride led to 8-dimethylamino-6-hydroxy-2-phenylpurine (**8**) or 6-hydroxy-8-methylamino-2-phenylpurine (**9**). It is interesting to note that the reaction of 6-amino-4-hydroxy-2-methyl-5-nitrosopyrimidine (**10**) with a mixture of dimethylformamide and phosphorus oxychloride under the same conditions gave 2-chloromethyl-8-dimethylamino-4-hydroxypurine (**11**) (Table 2). The nuclear magnetic resonance spectrum (CF_3COOH) of **11** shows singlets at 3.57 (NMe_2) and 4.86 δ (CH_2Cl). The mass spectrometry reveals a parent ion (*m/e* 227) and the M+2 ion, suggesting that one chlorine atom is contained in the molecule.

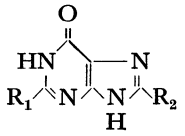
The new synthesis of substituted 8-aminopurines can best be explained by assuming an initial nucleophilic attack of the oxime of the imino oxime tautomeric form (**18**) of the 6-amino-5-nitrosopyrimidines on the Vilsmeier-type reagent to form the adduct (**19**). Prototropic rearrangement would then give the protonated nitrone (**20**), which is suited for intramolecular cyclization to **21**. The subsequent elimination of a dichlorophosphoric acid and deoxygenation of the purine 7-oxide (**22**) would lead to the substituted 8-aminopurine. The formation of a dimeric product (**4**) in



Scheme II.

5) H. Bredereck, F. Effenberger, and R. Sauter, *Chem. Ber.*, **95**, 2049 (1962).

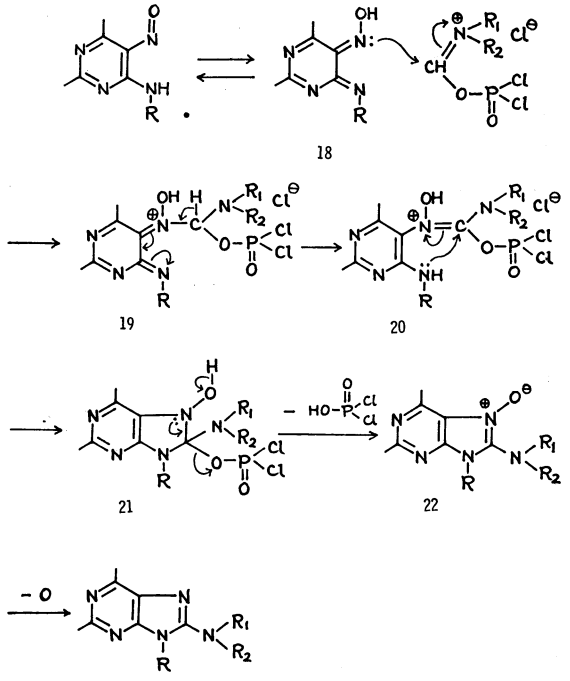
Table 2. Substituted 8-aminopurines



No.	R_1	R_2	Yield (%)	Recrystl. Solvent	Mp (°C)	MS (M^+)	Formula	Analyses					
								Calcd			Found		
								C	H	N	C	H	N
6	SMe	NMe_2	75	DMF	>330	225	$C_8H_{11}N_5OS$	42.66	4.92	31.10	42.50	4.87	30.85
8	Ph	NMe_2	68	DMF	>330	255	$C_{13}H_{13}N_5O$	61.16	5.13	27.44	61.08	5.06	27.21
9	Ph	NHMe	38	DMF	>330	241	$C_{12}H_{11}N_5O$	59.74	4.60	29.03	59.85	4.52	29.24
11	CH_2Cl	NMe_2	83	AcOH	>330	227	$C_8H_{10}N_5OCl$	42.20	4.43	30.77	42.10	4.42	30.52

the reaction at a low temperature can be explained in terms of an alternative course *via* the dimerization of the initially formed nitrone (**20**), followed by the elimination of dichlorophosphoric acid and oxygen.

Compounds **6** and **11** served as starting materials for several nucleophilic reactions. For example, the displacement of the chlorine in **11** by morpholino and anilino groups yielded the respective 2-morpholinomethyl- (**12**) and 2-anilinomethyl-purine derivatives (**13** and **14**). It will be noted that the methylthio group of **6** was stable against nucleophilic substitutions. That is, in the reaction of **6** with morpholine the methylthio group survived completely and the product was 8-dimethylamino-2-methylthio-6-morpholinopurine (**15**), whose structure was established by the analytical and spectral data. Similarly, the heating of **6** with piperidine gave the corresponding 6-piperidinopurine (**16**). The reduction of **11** with triphenylphosphine in dimethylformamide gave 8-dimethylamino-6-hydroxy-2-methylpurine (**17**).



Scheme III.

Experimental

All the melting points are uncorrected. The NMR spectra were determined at 60 MHz, using tetramethylsilane as the internal standard. The chemical shifts were expressed in δ values (s: singlet, bs: broad singlet).

8-Dimethylaminopurines. General Procedure: A solution of 0.01 mol of 6-amino-5-nitrosopyrimidine and 0.015 mol of phosphorus oxychloride in 15 ml of dimethylformamide was heated at 150—180 °C for 1 hr and evaporated *in vacuo*, and water was added to the resulting residue. The solid separated was collected by filtration, washed with water, dried, and recrystallized from solvents as specified in Table 1 to give colorless needles.

8-Methylaminotheophylline (2b). A mixture of 1.84 g (0.01 mol) of 6-amino-1,3-dimethyl-5-nitrosouracil (**1**) and 2.3 g (0.015 mol) of phosphorus oxychloride in 5 ml of methylformamide was heated at 130 °C for 1 hr. The reaction mixture was diluted with methanol, and then the crystals separated were collected by filtration, washed with water, dried, and recrystallized to give colorless prisms.

8-Diethylaminotheophylline (2c). To a mixture of 0.92 g (0.005 mol) of **1** and 1 g (0.005 mol) of diethylformamide was added, 2.3 g (0.015 mol) of phosphorus oxychloride drop by drop at room temperature; the mixture was then heated at 120 °C for 30 min. After cooling, the reaction mixture was neutralized with 5% aqueous ammonia. The crystals precipitated were collected by filtration, washed with water, dried, and recrystallized to give colorless needles.

8-N-Methylanilinotheophylline (2d). To a mixture of 0.92 g (0.005 mol) of **1** and 1.35 g (0.01 mol) of *N*-methylformanilide, a 2.3 g portion (0.015 mol) of phosphorus oxychloride was added, drop by drop, at room temperature, and then the mixture was heated at 140 °C for 30 min with stirring. The reaction mixture was poured into 200 ml of ice water, and the crystals thus precipitated were collected by filtration, washed with water, dried, and recrystallized to give colorless needles.

8-Dimethylaminoisocaffeine (2e). To a mixture of 0.59 g (0.003 mol) of 1,3-dimethyl-6-methylamino-5-nitrosouracil (**3**) in 5 ml of dimethylformamide, 0.92 g (0.009 mol) of phosphorus oxychloride was added, drop by drop, at room temperature, and then the mixture was heated at 160 °C for 30 min. After the reaction mixture had been evaporated under reduced pressure, the resulting syrup was diluted with 20 ml of water, neutralized with 5% aqueous ammonia, and extracted with chloroform. The chloroform extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The residue was recrystallized from aqueous methanol to give colorless needles.

Formation of the Dimeric Product (4). Into a suspension of 1.84 g (0.01 mol) of **1** in 20 ml of dimethylformamide, 3.1 g (0.02 mol) of phosphorus oxychloride was added portionwise with stirring. The resulting clear solution was stirred at room temperature for 3 hr, during which time colorless needles were gradually separated. The crystals were collected by filtration, washed with water, dried, and recrystallized from dimethylformamide to give 1.18 g (53%) of colorless needles; mp>330 °C. MS 446 (M^+). Found: C, 48.72; H, 5.79; N, 31.09%. Calcd for $C_{18}H_{26}N_{10}O_4$: C, 48.42; H, 5.87; N, 31.38%.

Conversion of 4 into 2a. (A) A suspension of 0.8 g (0.0018 mol) of **4** and 0.77 g (0.005 mol) of phosphorus oxychloride in 10 ml of dimethylformamide was heated with stirring at 180 °C for 2 hr and then allowed to stand overnight. The crystals separated were collected by filtration and washed with ethanol to give 0.4 g (50%) of **2a**.

(B) **4** was sublimed at 260 °C under reduced pressure (10 mmHg) to yield **2a** in a good yield.

8-Dimethylamino-2-methylthio-6-morpholinopurine (15). A mixture of 0.3 g (0.0013 mol) of **6** in 10 g (0.12 mol) of morpholine was heated under gentle reflux for 1.5 hr. After the excess morpholine had been evaporated under reduced pressure, the residue was recrystallized from aqueous methanol to give 0.2 g (53%) of colorless prisms; mp>320 °C. NMR ($CDCl_3$) 2.62 (s, 3H, SMe), 3.28 (s, 6H, NMe_2), 4.01 (bs, 8H, morpholino CH_2). MS 294 (M^+). Found: C, 49.02; H, 6.15; N, 28.37%. Calcd for $C_{12}H_{18}N_6OS$: C, 48.97; H, 6.17; N, 28.56%.

8-Dimethylamino-2-methylthio-6-piperidinopurine (16). A mixture of 0.8 g (0.0036 mol) of **6** in 10 g (0.12 mol) of piperidine was treated under the same conditions to yield 1 g (95%) of colorless needles after recrystallization from aqueous methanol. MS 292 (M^+). Found: C, 53.22; H, 6.84; N, 28.49%. Calcd for $C_{13}H_{20}N_6S$: C, 53.41; H, 6.90; N, 28.75%.

2-Anilinomethyl-8-dimethylamino-6-hydroxypurine (13). A mixture of 1.5 g (0.0067 mol) of **11** and 4 g (0.043 mol) of aniline in 10 ml of dimethylformamide was heated at 130 °C for 1 hr. The reaction mixture was then evaporated under reduced pressure, and the resulting residue was recrystallized from ethanol to give 1.1 g (58%) of colorless needles; mp> 330 °C. MS 284 (M^+). Found: C, 58.97; H, 5.70; N, 29.32%. Calcd for $C_{14}H_{16}N_6O$: C, 59.14; H, 5.67; N, 29.56%.

2-(3,4-Dichloroanilino)methyl-8-dimethylamino-6-hydroxypurine (14). A mixture of 1.5 g (0.0067 mol) of 11 and 5 g (0.031 mol) of 3,4-dichloroaniline in 10 ml of dimethylformamide was heated at 160 °C for 2 hr and then treated in the manner described above to give 1.2 g (51%) of colorless needles; mp>330 °C. Found: C, 47.68; H, 4.04; N, 23.63%. Calcd for $C_{14}H_{14}H_6OCl_2$: C, 47.60; H, 3.99; N, 23.80%.

8-Dimethylamino-6-hydroxy-2-morpholinomethylpurine (12). A mixture of 0.8 g (0.0035 mol) of **11** and 10 g (0.12 mol) of morpholine was heated under reflux for 1 hr; then it was treated in the manner described for the preparation of **13** to yield 0.4 g (41%) of colorless needles (mp 260 °C) after recrystallization from methanol. MS 278 (M^+). Found: C, 51.62; H, 6.49; N, 30.31%. Calcd for $C_{12}H_{18}N_6O_2$: C, 51.78; H, 6.52; N, 30.20%.

8-Dimethylamino-6-hydroxy-2-methylpurine (17). A mixture of 0.3 g (0.0013 mol) of **11** and 0.45 g (0.0017 mol) of triphenylphosphine in 15 ml of dimethylformamide was heated under a mild reflux for 2 hr. The reaction mixture was then evaporated under reduced pressure, and the residue was diluted with 30 ml of methanol. The crystals precipitated were collected by filtration, washed with water, dried, and recrystallized from dimethylformamide to give 0.1 g (40%) of colorless prisms; mp>330 °C. MS 193 (M^+). Found: C, 50.02; H, 5.73; N, 36.03%. Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25%.