washed with aq. sodium thiosulfate and water. Evaporation of the solvent *in vacuo* after drying left a residue, which was chromatographed on silica gel column to yield 50 mg of product **7**, mp 228° (from MeOH). *Anal.* Calcd. for $C_{20}H_{27}O_5I$: C, 50.64; H, 5.74; mol. wt., 474. Found: C, 50.47; H, 5.97, Mass Spectrum *m/e*: 474, (M^+). IR ν_{max} cm^{-1}: 1755, 1720, 1180. NMR δ: 8.20 (1H, s, –OCHO), 4.70 (2H, s, C-20 H_2), 4.34 br (1H, t, C-1-H), 3.92 (1H, s, C-5-H).

Hypoiodite Reaction with Dihydroenmein 3-Acetate (9)——A mixture of 1.2 g of lead tetraacetate and 400 mg of calcium carbonate in 80 ml of cyclohexane was warmed to 60°, to which 200 mg of dihydroenmein 3-acetate (**9**) and 214 mg of iodine were added. The mixture was subjected to hypoiodite reaction as described above to yield 60 mg of product **10** after chromatography on silica gel column of the crude product. Recrystallization from MeOH gave the pure compound, mp 195°. *Anal.* Calcd. for $C_{22}H_{29}O_7I$: C, 49.62; H, 5.45; I, 23.87; mol. wt., 532.095. Found: C, 49.48; H, 5.54; I, 23.95, Mass Spectrum *m/e*: 532.098 (M^+). IR ν_{max} cm^{-1}: 1765, 1725, 1230, 1180. NMR δ: 8.19 (1H, s, –OCHO), 5.13 (1H, t, J=3 Hz, C–3–H), 4.67 br (1H, t, C–1–H), 4.25 (1H, s, C–5–H), 2.13 (3H, s, –OAc).

Synthesis of Isodotricin 3-Acetate (11)——A solution of 200 mg of compound **13**[3] in a mixture of each 2 ml of acetic anhydride and pyridine was allowed to stand overnight. Usual treatment of the mixture and purification by chromatography of the crude product gave 162 mg of acetate of **13**, which was refluxed for 4 hr with 60 mg of oxalic acid, 15 ml of water, and 10 ml of MeOH. The mixture, after dilution with water, was extracted with chloroform, and the organic layer was washed with 10% aq. Na_2CO_3 then water. After drying over Na_2SO_4, the solvent was evaporated off *in vacuo* to leave a mixture which was shown to consist of unchanged material and three products by their thin-layer chromatography (TLC) spots. Separation of this mixture through chromatography on silica gel column gave 42 mg of isodotricin 3-acetate (**11**) as an oily substance. *Anal.* Calcd. for $C_{23}H_{32}O_8$: mol. wt., 436.209. Found: Mass Spectrum *m/e*: 436.213 (M^+). IR ν_{max} cm^{-1}: 1760, 1730, 1240. NMR δ: 5.40 (1H, s, C–6–H), 4.90 (1H, t, J=3 Hz, C–3–H), 4.67 (1H, q, J=11 and 7 Hz, C–1–H), 4.01 (2H, s, C–20 H_2), 3.65 (2H, m, C–17 H_2), 3.35 (3H, s, OMe).

Hypoiodite Reaction with Isodotricin 3-Acetate (10)——A mixture of 300 mg of lead tetraacetate and 100 mg of calcium carbonate in 20 ml of cyclohexane was warmed to 60°, to which 50 mg of isodotricin 3-acetate (**10**) and 54 mg of iodine were added. The mixture on hypoiodite reaction and usual treatment of the reaction mixture as described above yielded 34 mg of product **12** as an amorphous substance. *Anal.* Calcd. for $C_{22}H_{31}O_7I$: Mass Spectrum *m/e*: 534.111, (M–CO). Found: 534.112 (M^+–CO). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1730, 1230, 1180. NMR δ: 8.2 (1H, s, OCHO), 5.15 (1H, t, J=3 Hz, C–3–H), 4.67 (2H, s, C–20 H_2), 4.67 br (1H, t, J=8 Hz, C–1–H), 4.25 (1H, s, C–5–H), 3.67 (2H, m, C–17 H_2), 3.35 (3H, s, OMe), 2.13 (3H, s, OAc).

[Chem. Pharm. Bull. 22(7)1658—1660(1974)]

UDC 547.857.7.057

Syntheses of Substituted 8-Aminopurine Derivatives

FUMIO YONEDA and MASATSUGU HIGUCHI

Faculty of Pharmaceutical Sciences, Kumamoto University[1]

(Received September 21, 1973)

In our previous paper[2] it was reported that the condensation of 6-amino-5-nitrosopyrimidines with the Vilsmeier reagents (substituted formamides and phosphorus oxychloride) offers a new route to substituted 8-aminopurine derivatives, and a possible reaction mechanism has been proposed for this condensation. Although the 8-aminopurine-7-oxide is a reasonable intermediate, we could not demonstrate the presence of this intermediate in spite of several efforts. The present paper reports a reaction which suggests the intermediacy of the 8-aminopurine-7-oxide; additionally we wish to describe a conversion of 8-nitropurine derivative to 8-aminopurine derivative using dimethylformamide in the presence of tosyl chloride or phosphorus oxychloride.

1) Location: *Oe-honmachi, Kumamoto.*

2) F. Yoneda, N. Higuchi, T. Matsumura and K. Senga, *Bull. Chem. Soc. Japan*, **46**, 1836 (1973).

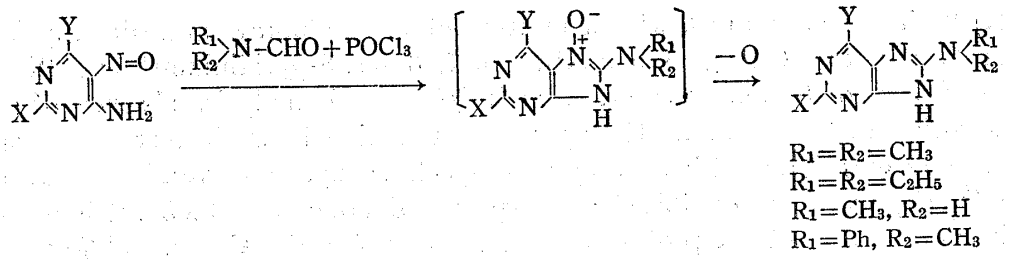

Chart 1

The heating of 6-amino-1,3-dimethyl-5-nitrosouracil (**1**) with tosyl chloride in dimethylformamide at 230° (oil bath) for 3 hr, followed by dilution with ethanol caused separation of 8-methylaminotheophylline (**2**)[2] as the major product. The latter was also prepared by the condensation of **1** with tosyl chloride in methylformamide. 8-Dimethylaminotheophylline (**3**)[2] did not react with tosyl chloride in dimethylformamide under those conditions, the starting material being completely recovered. Therefore, the reaction would be explicable by the tosylation of the proposed intermediate, 8-dimethylaminotheophylline-7-oxide (**4**), with tosyl chloride, followed by the intermolecular migration into **5** which is readily hydrolyzed with adventitous water into **2**.

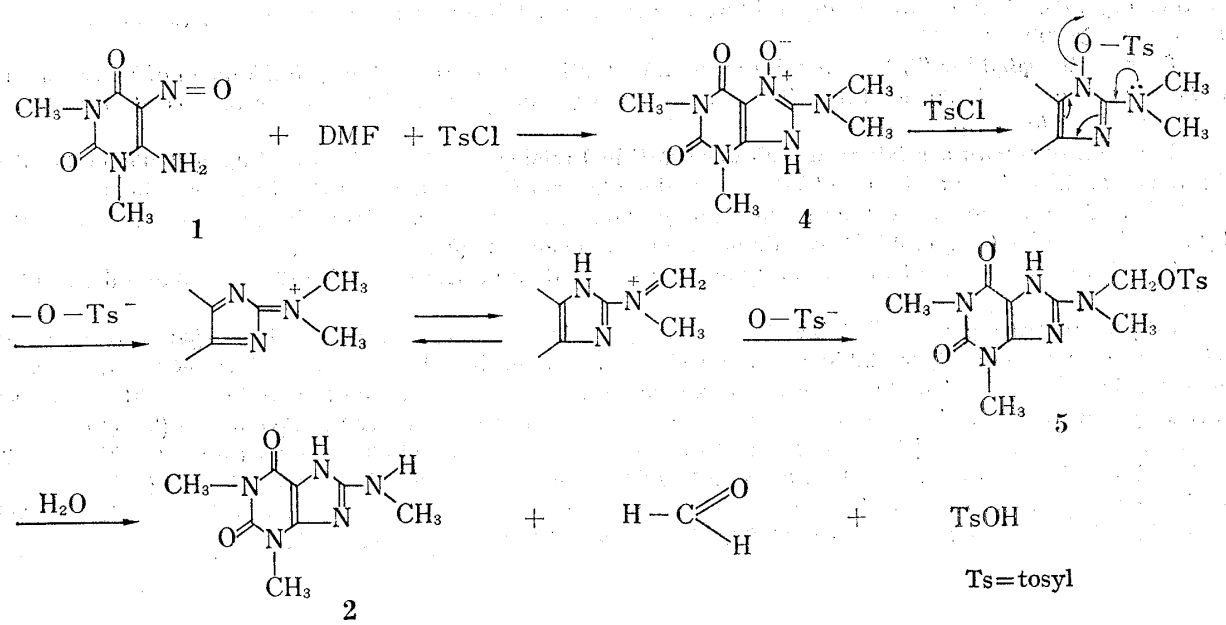

Chart 2

Next, the heating of 8-nitrotheophylline (**6**)[3] with a mixture of tosyl chloride and dimethylformamide at 230° (oil bath) for 6 hr gave **3** in a good yield. The reaction of **6** with a mixture of phosphorus oxychloride and dimethylformamide also gave **3** in almost the same yield. The dimethylamination proceeds without doubt *via* chlorination, because the initial reaction mixture includes only the intermediate 8-chlorotheo-

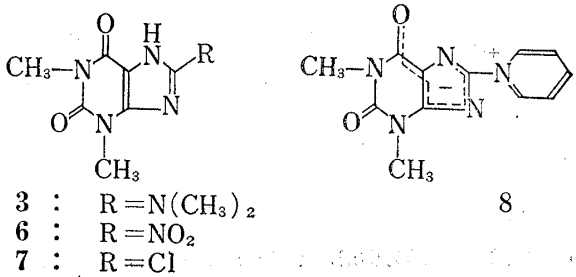

Chart 3

3) B.F. Duessel, H. Berman and R.J. Schachter, *J. Am. Pharm. Assoc.*, **43**, 619 (1954).

phylline (**7**).[4] The reaction of **6** with a mixture of tosyl chloride and dimethylformamide in pyridine at 150° for 10 hr gave a mixture of **7**, **3** and 8-pyridiniumtheophylline betaine (**8**). The structure of **8** was apparent from its elemental analysis, absence of secondary amino absorption in the infrared (IR) spectrum, negative Beilstein test for halogen, and by the molecular weight determination by mass spectroscopy. Moreover, its nuclear magnetic resonance (NMR) spectrum exhibited a two-proton doublet at δ 9.65 attributable to the α-pyridinium protons and three protons centered around δ 8.65. Compound (**8**) was alternatively prepared by treatment of **7** with pyridine.

Experimental[5]

8-Methylaminotheophylline (2)[2]——A: To a suspension of 1 g (0.005 mole) of 6-amino-1,3-dimethyl-5-nitrosouracil (**1**) in 4 ml of dimethylformamide (DMF) was added 1.9 g (0.01 mole) of TsCl and the mixture was refluxed at 230° (oil bath) for 3 hr. After cooling, the mixture was diluted with 50 ml of EtOH and allowed to stand overnight to separate crystals, which were collected by filtration, washed with EtOH and recrystallized from DMF to give 0.6 g (55%) of colorless prisms, mp>300°.

B: To a suspension of 1 g (0.005 mole) of **1** in 4 ml of methylformamide was added 1.9 g (0.01 mole) of TsCl and treated as described above to give 0.5 g (46%) of colorless prisms, mp>300°.

8-Dimethylaminotheophylline (3)[2]——A mixture of 0.5 g (0.002 mole) of 8-nitrotheophylline (**6**) and 1.9 g (0.01 mole) of TsCl in 10 ml of DMF was heated under reflux at 230° (oil bath) for 6 hr. After cooling, the crystals which separated were collected by filtration. The filtrate was evaporated *in vacuo* to precipitate further crystals. The combined crystals were recrystallized from DMF to give 0.32 g (64%) of colorless needles, mp>300°.

8-Chlorotheophylline (7)[4]——A mixture of 2.5 g (0.01 mole) of **6** and 7.65 g (0.05 mole) of $POCl_3$ in 8 ml of DMF was heated at 120° for 1 hr. The reaction mixture was diluted with ice water to separate 1.3 g (54%) of **7**, mp>290° (decomp.).

Reaction of 6 with a Mixture of TsCl and DMF in Pyridine——To a mixture of 0.5 g (0.002 mole) of **6**, 1 g (0.005 mole) of TsCl and 5 ml of DMF was added 20 ml of pyridine and the mixture was heated at 150° for 10 hr. After standing the reaction mixture overnight, the yellow needles which separated were collected by filtration to give 0.1 g (18%) 8-pyridiniumtheophylline betaine (**8**).

The filtrate was concentrated to half volume to separate a mixture of 0.12 g (24%) of **3** and 0.2 g (43%) of **7**.

8-Pyridiniumtheophylline Betaine (8)——One gram (0.005 mole) of **7** was added to 30 ml of pyridine. The mixture was refluxed for 20 hr and allowed to stand overnight to separate yellow needles which were collected by filtration. The filtrate was refluxed again for 10 hr and allowed to stand overnight to separate further yellow needles. The combined crystals were recrystallized from H_2O to give 0.63 g (53%) of yellow needles, mp>300°. UV $\lambda_{max}^{H_2O}$ nm (log ε): 245 (4.09), 267 (3.88), 380 (4.03). NMR (in CF_3COOH) δ: 3.70 (3H, s, N-CH_3), 3.88 (3H, s, N-CH_3), 8.30—9.10 (3H, m, β- and γ-pyridinium protons), 9.65 (2H, d, $J_{\alpha,\beta}$= 7.2 Hz, α-pyridinium protons). The mass spectrometry revealed a strong parent ion at *m/e* 257. *Anal.* Calcd. for $C_{12}H_{11}O_2N_5$: C, 56.02; H, 4.31; N, 27.23. Found: C, 55.93; H, 4.30; N, 27.05.

4) K. Karcz, D. Dabrowska and W. Wojtkiewicz, Polish Pat., 44172 (1961) [*C.A.*, **58**, 10217*e* (1963)].

5) Identity of compouds was confirmed by comparison of infrared spectra determined on a Japan Spectroscopic Co., Ltd., Model IR-A spectrophotometer. The homogeneity of the products was confirmed by thin-layer chromatography. NMR spectra were taken on a Japan Electron Optics Lab. Model JNM-C-60-H instrument in trifluoroacetic acid using TMS as an internal reference. The chemical shifts were expressed in δ values.