New Catalysts for the Nucleoside Synthesis by Fusion Method

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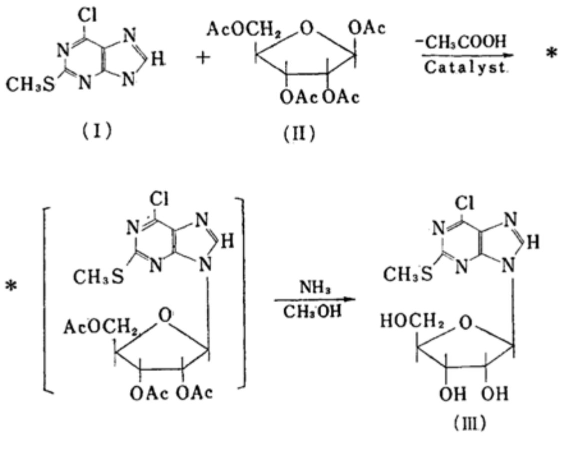
Recent studies[1] in this laboratory indicated that purine nucleosides could be synthesized merely by fusing a mixture of purine and 1-*O*-acyl sugar derivatives under reduced pressure in the presence of *p*-toluenesulfonic acid or zinc chloride. For example, the synthesis of 9-β-D-ribofuranosyl 2-methylthio-6-chloropurine (III) from 2-methylthio-6-chloropurine (I) and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (II) may be formulated as follows:



For the synthesis of *O*-glycosides by the similar fusion method, various acidic catalysts have been used[2].

Recently, Helferich et al.[3] scrutinized the catalytic effect of several acids, including newly hydrochloric acid, sulfuric acid, oxalic acid and phosphoric acid, for the *O*-glycoside formation and found anhydrous methanesulfonic acid to be the most effective catalyst as far as being examined.

The present authors wish to report that anhydrous methanesulfonic acid was less effective than concentrated sulfuric acid and that concentrated phosphoric acid was almost ineffective for nucleoside (*N*-glycoside) synthesis.

7-β-D-Ribofuranosyl theophylline (VI):—To a fused mixture of an equivalent amount of theophylline (V) and II, concentrated sulfuric acid was added, and the mixture was subjected to react at 130~140°C for about ten minutes, in vacuo. The cooled reaction mixture was then dissolved into chloroform, and a small amount of unchanged V was filtered off. After neutralization of the filtrate with methanolic ammonia, the solvent was removed in vacuo to dryness, and then deacetylated with methanolic ammonia in the usual manner. The deacetylated syrup was crystallized by trituration with a small amount of ethanol and recrystallized from ethanol. IV was obtained as fine needles in 48% yield of theoreticals, m. p. 189~190°C, $[\alpha]_D^{15}+25°$ (*c* 0.50, water). This showed no depression on admixture with an authentic specimen[4]. When anhydrous methanesulfonic acid was used as a catalyst, the yield was 41% theoreticals (m. p. 182~186°C).

In the similar manner, III (in both cases of concentrated sulfuric acid and of anhydrous methanesulfonic acid, the yields were 39 and 15%

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[1] T. Sato, T. Simadate and Y. Ishido, *J. Chem. Soc. Japan. Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **81**, 1440 (1960); ibid., **81**, 1442 (1960); T. Simadate, Y. Ishido and T. Sato, ibid., in print, T. Simadate, ibid., in print.

[2] B. Helferich and E. Schmitz-Hillebrecht, *Ber.*, **66**, 378 (1933); ibid., **67**, 1667 (1934); ibid., **68**, 790 (1935); K. Sisido, *J. Soc. Chem. Ind. Japan* (*Kōgyō Kwagaku Zasshi*), **39**, 456, 459 (1936); H. Bretschneider and K. Beran, *Monatsh.*, **80**, 262(1949); B. Helferich and D. V. Kasheliker, *Chem. Ber.*, **90**, 2094 (1957); B. Helferich and F. Eckenstein, ibid., **93**, 2467 (1960) etc.

[3] B. Helferich and L. Forstoff, ibid., **94**, 158 (1961).

[4] G. A. Howard, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, **1947**, 1052.

respectively), 9-β-D-ribofuranosyl 2-methythio-6-bromopurine (30.5% yield, in the former case) and 9-β(?)-D-ribofuranosyl 2-methylthio-6-iodopurine {44.8% yield, in the former, m. p. 188~189°C (decomp.), $[\alpha]_D^{24} -24.1°$ (c 0.38, 50% methanol), λ_{max}=237 mμ (ε=17490), 262 mμ (ε=14840) in water. Found: C, 31.39; H, 3.11; N, 13.35. Calcd. for $C_{11}H_{13}N_4O_4SI$: C, 31.37; H, 3.07; N, 13.21%} were obtained.

Detailed results will be published elsewhere.

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