SHORT COMMUNICATIONS

An Improved Fusion Method for the Synthesis of Purine Nucleosides. The Acid-catalyzed Reactions of $N_{(7)}$- or $N_{(9)}$-Acylpurines with Acylated Sugars

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(Received May 25, 1964)

In previous papers⁽¹⁾ from our laboratory, the acid-catalyzed fusion reaction of purines with acylated sugars has been reported. Recently, the method has been applied to the synthesis of nucleosides of D-xylose,⁽²ᵃ⁾ 2-deoxy-D-ribose,⁽²ᵇ,³⁾ and deoxyaminosugars.⁽³⁾

The extensive experiments on the acidic catalysts for this reaction made it clear that the compounds formulated as R-SO_3H, picric acid, and many inorganic acidic compounds were effective. It is of great interest that amphoteric acids, such as sulfanilic and sulfamic acids, showed fairly good catalytic effects.⁽⁴⁾

On the other hand, perspective observation of the reactivity of purine derivatives in the fusion reaction made us aware of the fact that there is no rational correlation between the reactivity of purines and the polar effect of their substituent groups on the reaction centers, though such correlation was confirmed in the fusion reaction of phenols with acylated sugars.⁽³⁾ Accordingly, it was deduced that this fact was probably due to the fusibility of purine derivatives.⁽⁴ᵇ,ᶜ⁾

In fact, the reactions of purines with a high fusibility, such as 2, 6-dichloropurine (I) [m. p. 181°C (decomp.)⁽⁵⁾], halogenopurines, and theophylline, proceeded in a homogeneous state to yield the corresponding purine nucleosides, 2, 6-dichloro-9-(2′, 3′, 5′-tri-*O*-acetyl-β-D-ribofuranosyl) purine (II)⁽⁴ᵇ,ᶜ⁾ {m. p. 158∼159°C, $[\alpha]_D^{21.5}$ $-5.7°$ (*c* 1.05, chloroform), λ_{max}^{EtOH} 253 mμ (ε, 6100) and 274.5 mμ (ε, 9800), λ_{min}^{EtOH} 258 mμ (ε, 5800)}, and others, generally in a good yield (40∼80% yield of the theoretical yileds)⁽⁴⁾. On the other hand, amino- or hydroxypurines with extremely high melting points were usually hard to fuse on the reaction and were not practically reactive.⁽⁴⁾ These results have led to the suggestion that easily-fusible purine derivatives might be favorable for the fusion reaction.

Thereupon, purines which are acylated at a nitrogen atom of the imidazole nucleus and have much lower melting points than those of the parent purines have been applied to the reaction.

Birkofer⁽⁶⁾ prepared diacyladenines by refluxing adenine with excess acid anhydrides. Montgomery⁽⁷⁾ also obtained monoacethlyalogenopurines by refluxing diaminohalogenopyrimidines with ethyl orthoformate in acetic anhydride. He deduced from the infrared spectra that the acetyl group should be linked to a nitrogen atom of the imidazole moiety of the purine nucleus. The melting points of these acyl purines are much lower (30∼200°C) than those of the parent purine.

We have newly obtained acyl derivatives of theophylline ($N_{(7)}$-acetyl, m. p. 156∼157°C;

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2) a) W. W. Lee, A. P. Martinez, G. L. Tong and L. Goodman, *Chem. Ind.* (*London*), **1963**, 2007; b) M. J. Robins, W. A. Bowles and R. K. Robins, *J. Am. Chem. Soc.*, **86**, 1251 (1964).

3) Y. Ishido, T. Matsuba, A. Hosono and T. Sato, International Symposium on the Chemistry of Natural Products, Kyoto, Japan, April, 1964.

4) a) Y. Ishido and T. Sato, 15th Annual Meeting of Chemical Society of Japan, Kyoto, April, 1962; b) Y. Ishido, Doctoral Thesis, Tokyo Institute of Technology, Japan, March, 1963; c) Y. Ishido, A. Hosono, Y. Kikuchi and T. Sato; Y. Ishido, A. Hosono, Y. Kikuchi and T. Sato; Y. Ishido, A. Hosono, Y. Kikuchi, S. Isome, A. Maruyama, and T. Sato, 17th Annual Meeting of the Chmical Society of Japan, Tokyo, Japan, March, April, 1964.

5) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3508 (1956).

6) L. Birkofer, *Ber.*, **76**, 769 (1943).

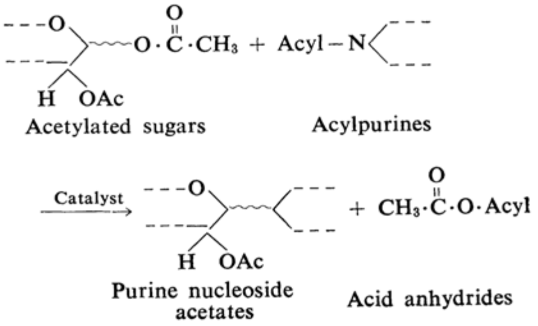
7) J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956).

$N_{(7)}$-propionyl, m. p. 129~130°C; $N_{(7)}$-*n*-butyryl, m. p. 88~90°C), I ($N_{(9)}$-propionyl, m. p. 169~171°C; $N_{(9)}$-*n*-butyryl, m. p. 104~106°C), guanine (2-*NH*-, $N_{(9)}$-diacetyl, m. p. 261~263°C), and 5, 6-dimethyl-benzimidazole (*N*-acetyl, m. p. 136~139°C), etc. The yields of these derivatives range from 70 to 90% of the theoretical yields.

Among these derivatives, the acetyl derivatives gave the best results on the reaction with 1, 2, 3, 5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of sulfamic acid as the catalyst at a suitable temperature. Thus, 7-β-D-ribofuranosyltheophylline, II, 2-methylthioadenosine, adenosine, and guanosine were obtained in 82, 82, 57, 14, and 28% yield of the theoretical yields respectively. It was found that the yields of these nucleosides were raised by 10 to 30% compared with those reported previously.[1−4a,b)]

The concomitant production of acid anhydrides in this modified fusion reaction was confirmed by infrared spectra, while acetic acid was formed in the reaction of free purines with acetylated sugars. This fact provides a further chemical proof of the interpretation[7)] based on the infrared spectra of monoacetylhalogenopurines.

In view of the above facts, the most reasonable scheme of the modified reaction may be written as follows:



A detailed investigation of the improved method and related matters will be reported in the near future.

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