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ACID-CATALYZED AND AUTOCATALYTIC REACTIONS OF ACETYLATED SUGARS WITH PURINE DERIVATIVES IN ORGANIC SOLVENTS (1, 2)*

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The fusion reaction of fully acetylated sugars with purines (3 – 5), and acylpurines (6) in the presence of various acidic catalysts (7) and the non-catalytic (autocatalytic) fusion reaction (8, 9) have been reported from our laboratory. Moreover, other catalysts, i. e., bis-(p-nitrophenyl) hydrogen phosphate (10) and halogen (11), have been reported. Generally, the reactions were carried out at high reaction temperature (130 – 190°), and were accompanied with considerable browning inconvenient for purification of the products except in a few cases. Therefore, a modification of the procedure to carry out the reactions under milder conditions than ever applied has been attempted in our laboratory on the basis of the procedures of Bretschneider and Beran (12), and Lemieux and Shyluk (13) for the synthesis of variously substituted phenyl glycosides.

In the present paper, the authors wish to describe acid-catalyzed and autocatalytic reactions of fully acetylated sugars with purine derivatives in organic solvents. At the outset of this investigation, the reactions were carried out in nitromethane, which was reported by Yamaoka et al. (14) as an excellent solvent for the condensation reaction of acetohalogenosugars with purine derivatives. The reactions were also carried out in anisole, a solvent used by Bretschneider and Beran (2).

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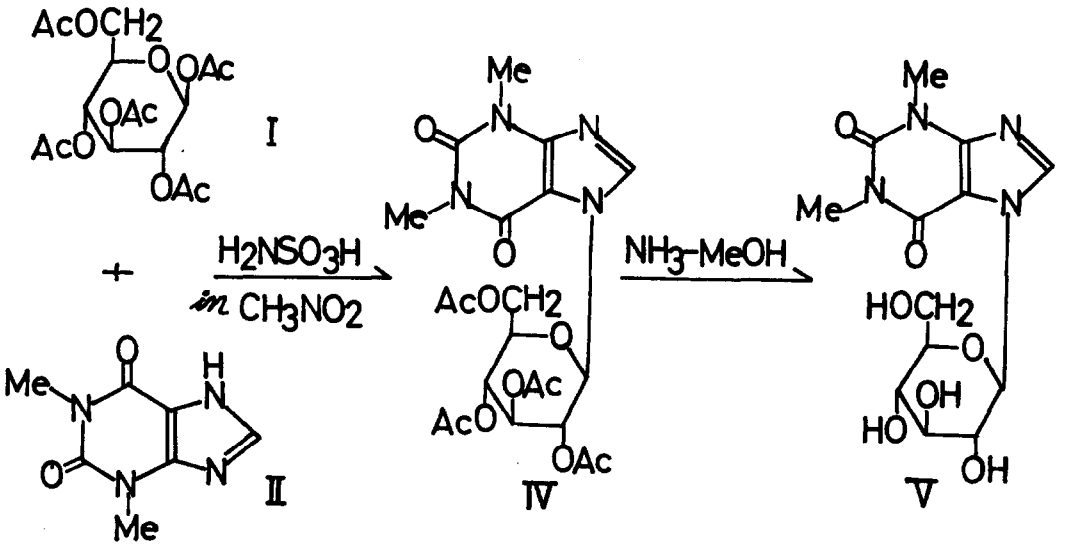
Recently, other similar procedures, in which the reactions of fully acetylated sugars with purines were carried out in 1, 2-dichloroethane or chlorobenzene in the presence of aluminium chloride or stannic chloride (15), and in nitromethane in the presence of halogens (16), were independently reported.

Acid-catalyzed reaction

As a model experiment, the reaction of 1, 2, 3, 4, 6-penta-O-acetyl-β-D-glucopyranose (I) and theophylline (II) in the presence of sulfamic acid (III) as catalyst was investigated. A suspension of I (0.01 mole), II (0.01 mole), and III (0.03 mole) in nitromethane (70 ml.) was refluxed with stirring for 6 hours. After the solvent was removed by evaporation in vacuo to dryness, the residue was extracted with chloroform (50 ml. x 2), and the combined extract was washed in turn with aqueous sodium bicarbonate solution to remove the co-produced acetic acid and III, and then with water. The chloroform layer was dried over anhydrous calcium chloride and the solution was concentrated in



vacuo to a hard sirup. NMR spectrum of the sirup showed the formation of 7-(2′, 3′, 4′, 6′-tetra-O-acetyl-β-D-glucopyranosyl)-theophylline (IV) in 67% yield. The yield was calculated according to the integration curve of the acetyl region of its spectrum [equatorial 2′-O-acetyl: $\tau_{TMS}(CDCl_3)$ 8.10 (17),

and other O-acetyls: $\tau_{TMS}(CDCl_3)$ 7.8 – 8.0]. Crystalline IV [m. p. 164 – 166.5°, $[\alpha]_{578}^{21}$ -19.0°, $[\alpha]_{546}^{21}$ -23.0° (c 1.0, $CHCl_3$)] was obtained in 30% yield by crystallizing the sirup from hot water. However, 7-β-D-glucopyranosyl theophylline (V) [m. p. 265 – 266.5°, $[\alpha]_{578}^{21}$ -3° (c 1.0, H_2O), $\lambda_{max}^{H_2O}$ 275 mμ (ε 7200)] was obtained in 51% yield by deacetylation of the sirup with methanolic ammonia. IV and V were identified with the corresponding authentic samples (18), respectively. The yield of IV was decreased as the amount of III was decreased, and the reaction period was shortened. In anisole, on the other hand, IV was obtained in 53% yield from 0.01 mole each of I and II applying 1 mmole of III and refluxing for 4 hours. It is thus clarified that the amount of III for the reaction must be considerably varied in compliance with the properties of the solvents.

Autocatalytic reaction

Purine derivatives with electron-withdrawing groups such as 2, 6-dichloropurine (VI) are known to be condensed by fusion with fully acetylated sugars even in the absence of the acidic catalysts in vacuo (8, 9). After refluxing a suspension of 1, 2, 3, 5-tetra-O-acetyl-β-D-ribofuranose (0.01 mole) and VI (0.01 mole) in nitromethane (50 ml.) for 1 hour, the solvent was evaporated in vacuo to dry ness, and the residue was recrystallized from ethanol with the use of active charcoal (3 times) to give 2, 6-dichloro-9-(2′, 3′, 5′-tri-O-acetyl-β-D-ribofuranosyl)-purine [m. p. 158 – 159°, $[\alpha]_D^{20}$ -5.0° (c 1.0, $CHCl_3$)] in 10% yield, and the product was identified with the authentic sample (9, 19).

A further investigation of the reaction in organic solvents is now in progress in our laboratory.

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