# Non-catalytic Fusion Reaction of 1, 2, 3, 5-Tetra-*O*-acetyl-β-D-ribofuranose with Purine Derivatives*1,*2

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In a previous communication,[1] the present authors reported that some purines and phenols with electron-withdrawing substituents react with acetylated sugars even in the absence of any catalyst. In this paper, the non-catalytic fusion of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (I) with some purine derivatives will be described in comparison with the catalytic reaction.

Helferich and Gootz[2] reported that 1-*O*-trichloroacetyl-2, 3, 4, 6-tetra-*O*-acetyl-β-D-glucopyranose

*1 This paper was presented at the 18th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1965.

*2 Studies on Nucleosides and Nucleotides. XIX. The previous paper (XVIII) was contributed to *Carbohydrate Res.*

1) Y. Ishido, T. Matsuba, A. Hosono, K. Fujii, H. Tanaka, K. Iwabuchi, S. Isome, A. Maruyama, Y. Kikuchi and T. Sato, This Bulletin, **38**, 2019 (1965).

2) B. Helferich und R. Gootz, *Ber.*, **62**, 2788 (1929).

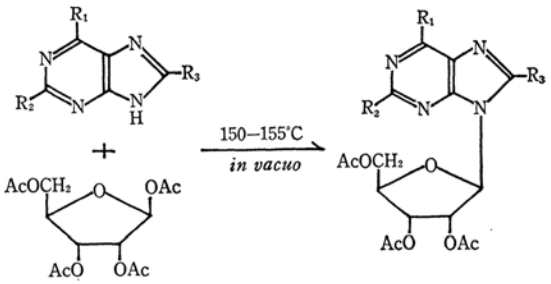
TABLE 1. THE NON-CATALYTIC FUSION REACTION OF 1,2,3,5-TETRA-*O*-ACETYL-β-D-RIBOFURANOSE WITH SOME PURINE DERIVATIVES

| Purine | Acylated sugar | The corresponding nucleoside | | |
|---|---|---|---|---|
| | | mp, °C | non-catalytic yield, % | catalytic yield, % |
| 6-Chloropurine[6] | | 171[12] | 10 (30)[a] | 14 (30) |
| 6-Cyanopurine[6] | | 210—213[5] | 21 (80) | 23 (15) |
| 2,6-Dichloropurine[8] | 1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose[7] | 158—159[5] | 50—55 (4) | 75 (4) |
| 2(6)-Chloro-6(2)-iodopurine[6] | | 151—152[10] | 67 (30) | 67 (30) |
| 2,6,8-Trichloropurine[9] | | 161—162[13] | 64 (10) | 24 (8) |
| 2,6-Dichloropurine[8] | 1-*O*-Trichloroacetyl-2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranose[2] | 132.5—133[11] | 57 (30) | — |

a) Direct amination of the reaction product with methanolic ammonia gave adenosine in 21% yield. Numbers in parentheses in the last two columns represent each reaction period in minute. All the reactions were carried out in the scale of 0.01 molar at 150—155°C except in the case of the last example (160—170°C) *in vacuo*. The amount of sulfamic acid used were 0.1—1 mmol.

(II) can be condensed with phenol to give phenyl 2′, 3′, 4′, 6′-tetra-*O*-acetyl-β-D-glucopyranoside in 71% yield. A similar result was also reported with the α-anomer of II.[3] Onodera *et al.* applied the α-anomer to catalytic[4a] and non-catalytic[4b] fusion reactions with some purines to obtain the corresponding purine nucleosides. In view of these results, it can be considered that the activation of the 1-*O*-acyl group by introducing an electron withdrawing group such as the halogenoacyl group increases the reactivity of the acylated sugars in the reaction.

In a number of previous experiments on the catalytic fusion reaction, it was found that 2,6-dichloropurine (III) was always condensed with I in the presence of any catalyst, thus giving 2,6-dichloro-9-(2′, 3′, 5′-tri-*O*-acetyl-β-D-ribofuranosyl)-purine in good yield.[5] The result suggests that purines with electron-withdrawing substituents such as III might be condensed with ordinary acetylated sugars, even in the absence of the catalyst, to give the corresponding nucleosides. The non-catalytic fusion reaction of II with III and that with theophylline was carried out, and it




| $R_1$ | $R_2$ | $R_3$ |
|---|---|---|
| Cl | H | H |
| CN | H | H |
| Cl | Cl | H |
| Cl | I | H |
| Cl | Cl | Cl |

was clarified that the corresponding β-D-nucleosides tetra-*O*-acetate was obtained, only in the former case, at 160—170°C *in vacuo* for 30 min in 57% yield, as in the last line of Table 1. Accordingly, it may be deduced that the acidity of purines is another important factor in the non-catalytic fusion reaction.

Then, the non-catalytic reaction of some purines with electron-withdrawing substituents, such as 6-chloro-, 6-cyano-, III, 2(6)-chloro-6(2)-iodo- and 2,6,8-trichloropurine, with I was examined under the conditions described in the footnote to Table 1. As the table shows, all the purines expectedly gave the corresponding β-D-ribonucleoside

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4) a) K. Onodera and H. Fukumi, *Agr. Biol. Chem.*, **27**, 864 (1963); b) K. Onodera, S. Hirano, H. Fukumi and F. Masuda, *Carbohydrate Res.*, **1**, 254 (1965).
5) Y. Ishido, A. Hosono, K. Fujii, Y. Kikuchi and T. Sato, *Nippon Kagaku Zasshi, (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **87**, 752 (1966).
6) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3508 (1956).
7) H. Zinner, *Ber.*, **83**, 517 (1950).
8) J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956).
9) J. Davoll and B. A. Lowy, *ibid.*, **73**, 2936 (1951).
10) Y. Ishido, T. Matsuba, A. Hosono, Y. Ohgo, K. Fujii, T. Tada and T. Sato, contributed to *Carbohydrate Res.*
11) N. Yamaoka, K. Aso and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965): mp 162°C and $[\alpha]_D$ −84° (chloroform).
12) G. B. Brown and U. S. Welikey, *J. Biol. Chem.*, **204**, 1019 (1953).
13) J. Davoll and B. A. Lowy, *J. Am. Chem. Soc.*, **74**, 1563 (1952).

tri-*O*-acetates in almost the same as, or a superior yield to, those obtained by the catalytic fusion reaction.

In the case of the former two purines only, the yields were calculated from the amount of the deacetylated derivatives because the acetates could not be crystallized. It is of interest that polyhalogenopurines gave the corresponding nucleosides, which are useful for the preparation of various other derivatives, in fairly good yields without the utilization of 1-*O*-trichloroacetyl derivatives.[4] 6-Iodopurine[6] gave a crystalline product (mp 166°C) after deacetylation with methanolic ammonia, however, the analytical value of its carbon was inconsistent with that calculated for the corresponding nucleoside in spite of several recrystallizations from water. Contrary to the results mentioned above, 6-methoxypurine[14] with an electron-releasing substituent gave no product under the same conditions. Thus, it can be generalized that the acidity of purines is one of the factors causing the non-catalytic fusion reaction. In addition, the acetyl derivative of III reported in a previous paper,[10] together with other acyl purines, gave no product in 3 hr under the same conditions.

## Experimental†

**General Procedure for the Experiment.** To illustrate the procedure for the preparation of purine nucleosides by the non-catalytic fusion reaction, the preparation of 2, 6-dichloro-9-(2′, 3′, 4′, 6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-purine will be described. An equimolar mixture of 1-*O*-trichlroacetyl-2, 3, 4, 6-tetra-*O*-acetyl-β-D-glucopyranose[2] (4.7 g, 0.01 mol) and 2, 6-dichloropurine[8] (1.9 g, 0.01 mol) was fused in an oil bath heated previously at 160—170°C *in vacuo* for 30 min. The resultant mixture was dissolved in hot ethanol (20 m*l*) and chilled in an ice-water bath. The precipitated raw crystals were recrystallized from ethanol, by the use of active charcoal, to give white needles. Yield: 3.4 g (57%); mp 132.5—133°C; $[\alpha]_D^{19.5}$ −13.5° (*c* 1.11, chloroform); $\lambda_{max}^{EtOH}$ 250.5 mμ (ε 5850) and 273 mμ (ε 8900); $\lambda_{min}^{EtOH}$ 257 mμ (ε 4960).

Found: C, 43.60; H, 3.91; N, 10.97%. Calcd for $C_{19}H_{20}O_9N_4Cl_2$: C, 43.93; H, 3.85; N, 10.79%. The melting point and specific rotation of the product are inconsistent with those reported by Yamaoka *et al.*[11]

**The Equimolar Adduct of Ammonia and 6-Cyano-D-ribofuranosylpurine.** The deacetylation of the resulting residue with methanolic ammonia as usual, followed by recrystallization from water, gave the adduct.

Found: C, 44.28; H, 4.50; N, 28.30%. Calcd for $C_{11}H_{14}O_4N_6$: C, 44.98; H, 4.80; N, 28.56%. $\lambda_{max}^{H_2O}$ 290 mμ (ε 14900) and 303 mμ (ε 13200).

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14) S. F. Mason, *J. Chem. Soc.*, **1951**, 2071.

† All the melting points are uncorrected.