Carbohydrate Research, 97 (1981) 45–50
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

1,4-REARRANGEMENT OF 7-(2-ACETAMIDO-2,3-DIDEOXYHEX-2-ENOPYRANOSYL)THEOPHYLLINE DERIVATIVES*

NEVENKA PRAVDIĆ**

Department of Organic Chemistry and Biochemistry, "Rudjer Bošković" Institute, 41001 Zagreb, Croatia (Yugoslavia)

(Received March 16th, 1981; accepted for publication, June 1st, 1981)

ABSTRACT

Treatment of 7-(2-acetamido-2,3-dideoxyhex-2-enopyranosyl)theophylline derivatives with boron trifluoride etherate in boiling methanol led to the isolation of 7-(methyl 2-acetamido-2,3,4-trideoxyhex-2-enopyranosid-4-yl)theophylline derivatives. Some mechanistic features of this 1,4-rearrangement followed by solvolysis are discussed, and a rationalization of the formation of the C-4′ derivatives in the fusion reaction of 2-acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol with theophylline is offered.

INTRODUCTION

In the preceding paper[1], it was shown that the fusion reaction of 2-acetamido-3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (**1**) with theophylline in the presence of boron trifluoride etherate, conducted for 2 h at 85–90°, afforded several nucleosidic products which belong to two different classes. They were identified as: (*a*) 2′,3′-unsaturated nucleosides with the base linked at C-1′, and (*b*) 2′,3′-unsaturated nucleosides having the base attached at C-4′ and a methoxyl group glycosylically bonded. For the sake of brevity, the products in the first group were named 7-C-1′-theophylline derivatives, and those in the second group, 7-C-4′-theophylline derivatives. As the products in the second group were not formed in the fusions of shorter reaction-time, they were regarded as being secondary products.

It has already been demonstrated that some glycosylically non-nitrogeneous, unsaturated nucleosides structurally related to the first group are liable to further transformation. Under conditions similar to those used in their preparation, it was claimed[2,3] that these compounds rearrange into 1′,2′-unsaturated nucleosides through an allylic shift of the base to C-3′.

---

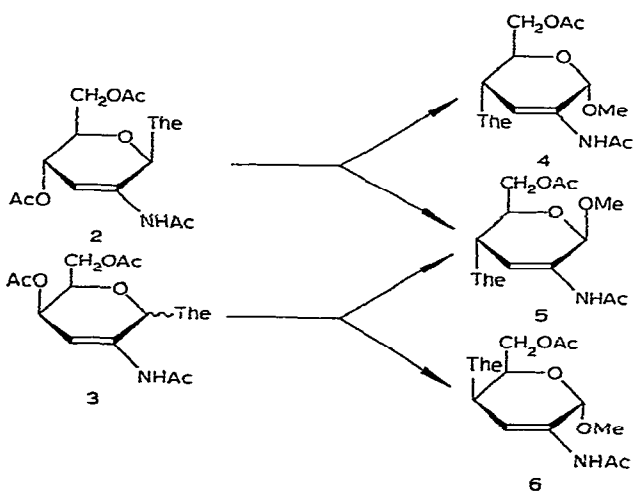
*Unsaturated Amino Sugars in the Preparation of a New Type of Nucleoside, Part II. For Part I, see ref. 1.

**Present address: Referral Centre of the University of Zagreb, P.O. Box 327, 41001 Zagreb, Yugoslavia.

In order to acquire a better understanding of the mode of formation of the 7-C-4′-theophylline derivatives, an investigation of the rearrangement of pure samples of some 7-C-1′-theophylline derivatives was undertaken. The results, and a mechanistic basis for rationalizing this diverse behavior, are now presented.

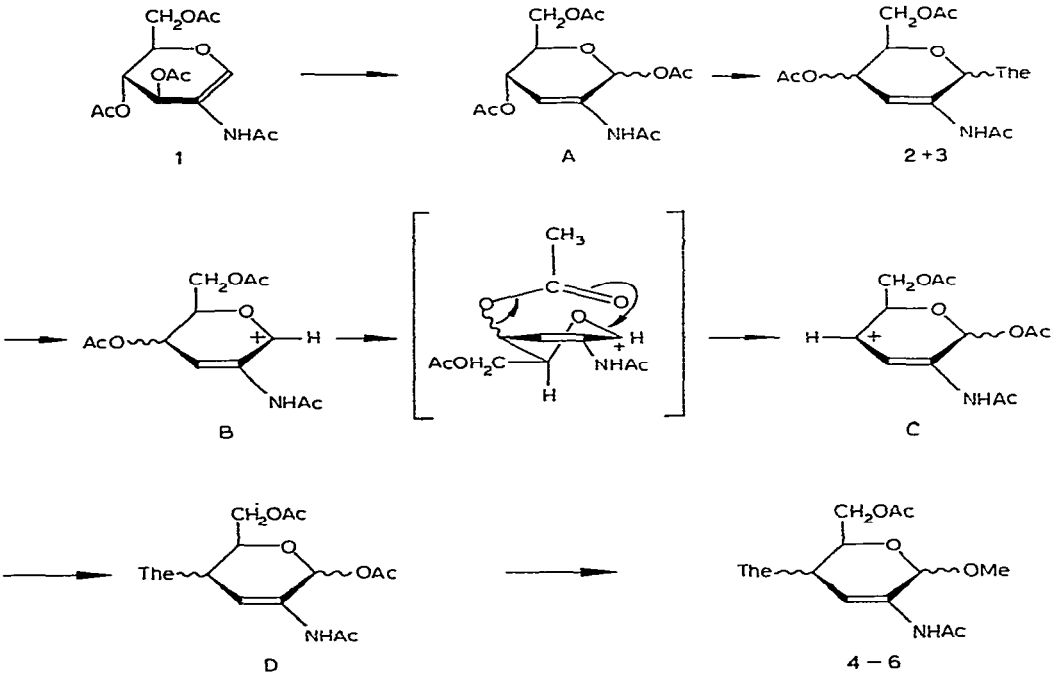
RESULTS AND DISCUSSION

Treatment of 7-(2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enopyranosyl)theophylline (**2**) with boron trifluoride etherate at the fusion temperature (200°) led to decomposition of the nucleoside, and to isolation of the free base and several, carbohydrate-degradation products. Therefore, compound **2** was subjected to a reaction with boron trifluoride etherate in boiling methanol. This reaction afforded two products, namely, 7-(methyl 2-acetamido-6-*O*-acetyl-2,3,4-trideoxy-α-D-*erythro*-hex-2-enopyranosid-4-yl)theophylline (**4**) and its β anomer (**5**) in 58 and 35% yield, respectively. Under the same conditions, treatment of the anomeric mixture 7-(2-acetamido-4,6-di-*O*-acetyl-2,3-dideoxy-α,β-D-*threo*-hex-2-enopyranosyl)theophylline (**3**) gave 7-(methyl 2-acetamido-6-*O*-acetyl-2,3,4-trideoxy-α-D-*threo*-hex-2-enopyranosid-4-yl)theophylline (**6**) as the major product (54% yield). In addition, compound **5** (12%) and free theophylline were formed. Compounds **4**–**6** obtained in this way proved to be indistinguishable from those prepared by the fusion method[1]. The structures of **5** and **6** were unambiguously determined by X-ray crystallographic analysis[4,5].



When product 7 (a mixture analogous in composition to 3, but each component having a free 4′-hydroxyl group[1]) was treated in the same way, no rearrangement occurred: 30% of unchanged 7 was recovered, and theophylline was isolated in 48% yield. This behavior indicates that the presence of an acetoxyl group at C-4′ is an indispensable requirement for the rearrangement.

In view of these experiments, the following mechanism for the formation of the 7-C-4′-theophylline derivatives **4–6** in the fusion reaction from **1** may be proposed.



Scheme 1

First, the formation of the 7-C-1′-theophylline derivatives **2** and **3** will be discussed. The initial step is the allylic rearrangement of **1**, in agreement with the known suggestion on the reactivity of glycals in general[6–8]. Direct proof for the formation of such an intermediate A was now obtained: when the 2-(*N*-acetylacetamido) derivative[9,10] of **1** was used as the starting, unsaturated amino sugar in the fusion reaction, the same products, **2** and **3**, were eventually obtained, again showing[11] that one *N*-acetyl group is selectively removed during the fusion. In addition, 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose[12], the stable intermediate, was isolated in a substantial proportion (31%), thus confirming the proposed structure of intermediate A.

The formation of the 7-C-1′-theophylline derivatives therefore occurs by a simple mechanism, the 1-acetoxyl group being displaced by the nucleophile. The most common product to be expected[7,8,13,14] in such a reaction, namely, the α-D-*erythro*

derivative, has never been recognized in this case; instead, the β-D-*erythro* isomer (**2**) is formed, accompanied by an inseparable mixture of both D-*threo* anomers (**3**). The isomerization at C-4 was earlier observed[15,16] in such allylic rearrangements. However, the fact that the α-D-*erythro* derivative was not found among the products appears to lack a satisfactory explanation.

In the interconversion of the 7-C-1′-theophylline derivatives into the corresponding 7-C-4′-theophylline derivatives **4–6**, a 1,4-rearrangement may be envisaged as operative. Boron trifluoride, a strong Lewis acid, with the assistance of the endocyclic double bond, could give rise to the formation of the carbonium ion B. Then, the acetoxyl group might migrate to C-1, creating the carbonium ion C. As already noted, the presence of a good leaving-group at C-4 is essential. With a compound containing a free 4-hydroxyl group, such as **7**, the reaction does not proceed. In a further step, through nucleophilic attack of the base on the carbonium ion C, an intermediate D could be produced. Regardless of the fine details of the mechanism of formation of D, it seems necessary to assume that the structure of the final products in the fusion reaction is that depicted in D. In the course of the processing, D could be transformed, through solvolysis, into the stable glycosides which are then isolated. The products **4–6** were obtained when a methanol-containing solvent mixture was used as an eluant for column chromatography. When ethanol was applied, formation of the corresponding ethyl glycosides, was observed[1].

It might be assumed that the deliberate rearrangement of pure compounds **2** and **3** with boron trifluoride etherate in methanol occurs by a similar, or the same, mechanism. The fact that the products obtained on such treatment are the α and β anomers of the D-*erythro* and D-*threo* configurations supports the suggestion of the formation of ions B and C.

It may be relevant at this point to contrast the rearrangement of the present compounds with that of closely related (but glycosylically non-nitrogeneous) acetylated, unsaturated nucleosides[2,3]. In fact, compounds **2** and **3** could, theoretically, be rearranged through an allylic shift, to produce 1′,2′-unsaturated nucleosides having the base linked at C-3′. On the other hand, acetylated, glycosylically non-nitrogeneous, unsaturated nucleosides having the base at C-1′, could be transformed through a 1,4-rearrangement, as herein described, into the isomeric 7-C-4′-nucleosides. However, if it is accepted that compounds **2** and **3** undergo a 1,4 rearrangement, whereas the glycosylically non-nitrogeneous nucleosides are rearranged through an allylic mechanism[2,3], the question is whether such diverse behavior could be attributed to the presence of the 2-acetamido group. In the present state of our knowledge, it appears that additional speculation is not justified.

EXPERIMENTAL

General methods. — T.l.c. was conducted on plates (5 × 10 cm) of silica gel F 254 (E. Merck) in the following solvent-systems: *A*, 9 : 1 ether–methanol; and *B*, 12 : 1 chloroform–methanol, the ratios being v/v. The components were detected under

u.v. light, or by spraying with 10% sulfuric acid and heating. Column chromatography was performed on silica gel (E. Merck; 0.05–0.20-mm particle size) with the solvent system specified. The n.m.r. spectra were recorded at 60 MHz with an EM-360 spectrometer, for solutions in chloroform-*d*.

Treatment of **2** *with boron trifluoride etherate in methanol.* — To a solution of **2** (180 mg) in methanol (50 mL) was added boron trifluoride etherate (2 drops), and the mixture was boiled under reflux for 90 min, cooled, concentrated *in vacuo* to ~25 mL, and kept overnight in a refrigerator. Crystals which precipitated were filtered off: 56 mg (35%), m.p. 242–244°, $[\alpha]_D$ −71.8° (*c* 0.5, pyridine). I.r. and n.m.r. spectra identified it as *7-(methyl 2-acetamido-6-*O*-acetyl-2,3,4-trideoxy-β-*D-erythro-*hex-2-enopyranosid-4-yl)theophylline* (**5**).

The mother liquor was evaporated to dryness, and the residue was dissolved in chloroform (60 mL). The solution was successively washed with saturated aqueous sodium hydrogencarbonate (twice) and water, dried (Na_2SO_4), and evaporated *in vacuo*. The dry, semicrystalline residue (74 mg, 46%) was found (by its n.m.r. spectrum) to be *7-(methyl 2-acetamido-6-*O*-acetyl-2,3,4-trideoxy-α-*D-erythro-*hex-2-enopyranosid-4-yl)theophylline* (**4**). On trituration of a sample with methanol, it crystallized: m.p. 192–193°, mixed m.p. with an authentic sample[1] of **4**, undepressed.

Treatment of **3** *with boron trifluoride etherate in methanol.* — A solution of **3** (320 mg) in methanol (10 mL) containing boron trifluoride etherate (3 drops) was boiled under reflux for 15 min. On cooling, prismatic crystals of **5** were deposited: 36 mg (12%), m.p. 247–248°; mixed m.p. with an authentic sample[1] was undepressed, and the i.r. spectrum was identical with that of **5**.

The filtrate was evaporated to a foam (256 mg) which, on t.l.c. in solvent *A* proved to be a mixture of theophylline and a u.v.-positive spot of a component moving slightly more slowly. A solution of the residue in chloroform was successively washed with saturated aqueous sodium hydrogencarbonate and water (to remove free theophylline), dried (Na_2SO_4), and evaporated *in vacuo*, to give a semicrystalline residue (162 mg, 54%) whose n.m.r. spectrum identified it as *7-(methyl 2-acetamido-6-*O*-acetyl-2,3,4-trideoxy-α-*D-threo-*hex-2-enopyranosid-4-yl)theophylline* (**6**). The crude product was chromatographed on a column of silica gel with solvent *B*. Fractions containing homogeneous material afforded, after evaporation of the solvent, crystalline **6**: m.p. 219–220°, mixed m.p. with an authentic sample[1], undepressed.

Treatment of **7** *with boron trifluoride etherate in methanol.* — A solution of **7** (95 mg) in methanol was treated with boron trifluoride etherate, and processed as already described. The crude product was separated on a column of silica gel with solvent *B*. Two groups of crystals were obtained: 20 mg (48%) and 28 mg (30%), which were, on the basis of their n.m.r. spectra and chromatographic behavior, identified as theophylline and unchanged **7**, respectively.

ACKNOWLEDGMENTS

The author is indebted to B. Mulac, M.Sc., for helpful discussion, and to Mr.

B. Danilov, B.Sc., for assistance in the synthetic part of this study. This work was initiated by a grant from the U.S.–Yugoslav Joint Board on Scientific and Technological Cooperation (National Institutes of Health, Bethesda, Md., Agreement No. 02-010-1), and was supported, in part, by a grant from the Research Council of Croatia.

REFERENCES

1 N. PRAVDIĆ AND B. DANILOV, *Carbohydr. Res.*, 97 (1981) 31–44.
2 R. J. FERRIER AND M. M. PONPIPOM, *J. Chem. Soc., C*, (1971) 553–559.
3 M. FUERTES, G. GARCIA-MUNOZ, R. MADRONERO, AND M. STUD, *J. Heterocycl. Chem.*, 8 (1971) 261–264.
4 B. KOJIĆ-PRODIĆ, E. COFFOU, AND Ž. RUŽIĆ-TOROŠ, *Acta Crystallogr., Sect. B*, 35 (1979) 1166–1170.
5 B. KOJIĆ-PRODIĆ, *Acta Crystallogr., Sect. B*, 35 (1979) 1162–1166.
6 R. J. FERRIER, *Adv. Carbohydr. Chem.*, 20 (1965) 67–137.
7 R. J. FERRIER AND N. PRASAD, *J. Chem. Soc., C*, (1969) 570–575.
8 N. PRAVDIĆ, B. ŽIDOVEC, AND H. G. FLETCHER, JR., *Croat. Chem. Acta*, 42 (1970) 523–533.
9 N. PRAVDIĆ AND H. G. FLETCHER, JR., *J. Org. Chem.*, 32 (1967) 1806–1810.
10 N. PRAVDIĆ, I. FRANJIĆ-MIHALIĆ, AND B. DANILOV, *Carbohydr. Res.*, 45 (1975) 302–306.
11 N. PRAVDIĆ AND I. FRANJIĆ-MIHALIĆ, *Carbohydr. Res.*, 62 (1978) 301–312.
12 N. PRAVDIĆ, B. ŽIDOVEC, AND H. G. FLETCHER, JR., *Croat. Chem. Acta*, 45 (1973) 333–342.
13 R. J. FERRIER, *J. Chem. Soc.*, (1964) 5443–5449.
14 K. ONODERA AND T. YAJIMA, *Carbohydr. Res.*, 13 (1970) 97–104.
15 R. U. LEMIEUX, D. R. LINEBACK, M. L. WOLFROM, F. B. MOODY, E. G. WALLACE, AND F. KOMITSKY, JR., *J. Org. Chem.*, 30 (1965) 1092–1096.
16 R. J. FERRIER AND G. H. SANKEY, *J. Chem. Soc., C*, (1966) 2339–2345.