Carbohydrate Research, 44 (1975) C18–C21

Preliminary communication

Chemistry of the glycosidic linkage. 2-Alkoxy-3-(*p*-nitrobenzoyl)-2-phenyl-4,5-[α-D-glucopyrano]-2-oxazolidines, a new class of carbohydrate 1,2-orthoacid derivative*

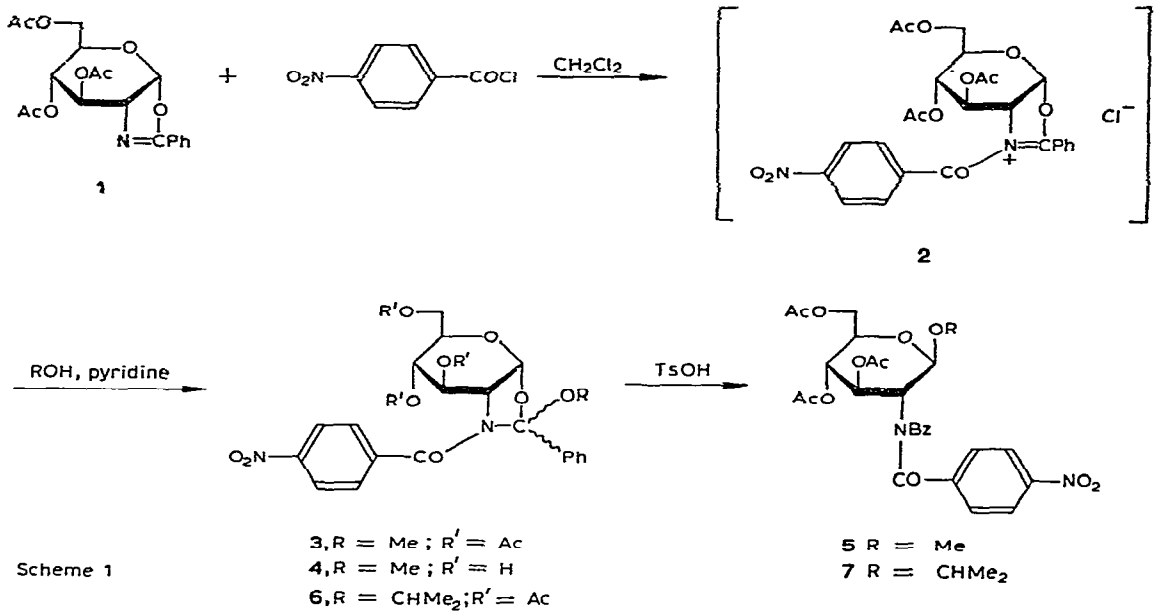
STEPHEN HANESSIAN, GIUSEPPE CASSINELLI†, and MICHAEL CASEY
Department of Chemistry, University of Montreal, Montreal, Quebec H3C 3V1 (Canada)
(Received October 3rd, 1975; accepted for publication, October 8th, 1975)

The so-called oxazoline method[1] has been extensively used in recent years in the synthesis of 1,2-*trans*-glycosides of 2-acylamido-2-deoxyhexopyranosides. The method is characterized by high yields, and is applicable to the synthesis of disaccharides and oligosaccharides[2–7]. Mechanistically, it is related to the orthoester method of glycoside synthesis[8], in that the reactive intermediate which undergoes nucleophilic attack at the anomeric carbon atom is presumed to be the protonated, 1,2-oxazolinium ion[1], as compared to a 1,2-acyloxonium ion[8].

In this paper we describe the synthesis, and acid-catalyzed rearrangements, of oxazolidine derivatives incorporating the 2-amino-2-deoxy-D-glucose structure of the general type shown in Scheme 1.

The availability, by the method now described, of a new type[10] of "orthoamide" derivative** unveils a novel and unique facet in the chemistry of carbohydrate oxazoline derivatives that has both practical and mechanistic significance. The synthetic approach to this type of compound was based on the rationale that the nitrogen atom in such 2,4,6-trisubstituted, Δ^2-oxazoline derivatives as **1** should exhibit considerable reactivity toward electrophilic reagents[11]. Indeed, treatment of **1** (refs. 1 and 12) with *p*-nitrobenzoyl chloride (1 equiv.) in the minimal volume of dichloromethane during 1–2 days at 25°, followed by addition of pyridine (2 equivs.) and an excess of methanol (100 equiv.) and keeping for 2 h at 25°, gave a mixture containing the oxazolidine derivative **3** (70%), methyl 3,4,6-tri-*O*-acetyl-2-[*N*-benzoyl-*N*-(*p*-nitrobenzoyl)amino]-2-deoxy-β-D-glucopyranoside (**5**; ~20%), and traces of minor components. Treatment of the mixture with 0.01M sodium methoxide in methanol during 1 h at 25°, followed by chromatography on

*Part of a series on "Preparative and exploratory carbohydrate chemistry".
†On leave from the Farmitalia Research Laboratories, Milan, Italy, 1974–1975.
**The term "orthoamide" is used for the sake of convenience, in view of the general structural relationship of these derivatives to the 1,2-orthoesters. According to DeWolfe, "an orthoamide is a substance having three nitrogen atoms bonded to an orthoacyl carbon"; see ref. 9.



Scheme 1

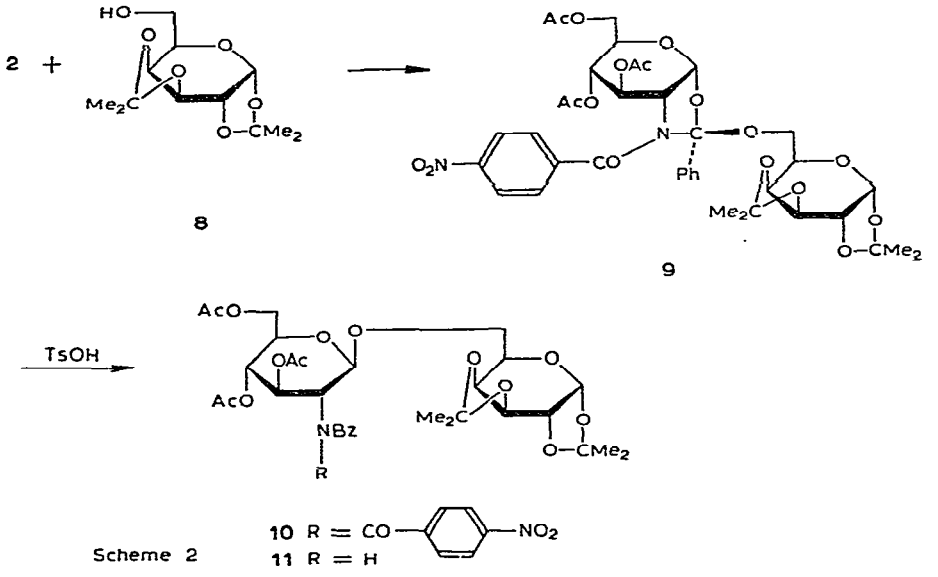
silica gel with 1:24 EtOAc–benzene, gave the oxazolidine derivative **4** in 60% overall yield (based on the starting oxazoline), as an amorphous solid consisting of an ~1:2 *endo–exo* mixture of diastereoisomers, m.p. 130–132°, $[\alpha]_D^{23}$ +88° (*c* 1.7, chloroform), and the known methyl 2-benzamido-2-deoxy-β-D-glucopyranoside[1(c)]. Acetylation of **4** with Ac_2O–pyridine at 25° gave the triacetate **3** as an amorphous solid (92%); m.p. 120–122°, $[\alpha]_D^{23}$ +132° (*c* 1, chloroform)[13]; n.m.r. data (60 MHz, $CDCl_3$): δ 3.43 (3 H,OCH_3); (pyridine-d_5): δ 3.50 and 3.43 (3 H,OCH_3).

Solvolysis of **4** in 4:1 1,4-dioxane–M hydrochloric acid during 20 h at 25°, or of the product resulting from *p*-nitrobenzoylation (aq. $NaHCO_3$), gave 3,4,6-tri-*O*-acetyl-2-benzamido-2-deoxy-1-*O*-(*p*-nitrobenzoyl)-α-D-glucopyranose* (60%), m.p. 93–94°, $[\alpha]_D^{23}$ +150° (*c* 1, chloroform). Under acid catalysis with TsOH–CH_2Cl_2 at 25°, compound **3** underwent virtually complete rearrangement within a few minutes, to give the crystalline glycoside **5**, m.p. 168–169°, $[\alpha]_D^{23}$ +23° (*c* 1, chloroform); n.m.r. datum: δ 3.53 (OCH_3, s). Compound **5** was independently obtained by *p*-nitrobenzoylation of methyl 3,4,6-tri-*O*-acetyl-2-benzamido-2-deoxy-β-D-glucopyranoside.

The 2-isopropoxyoxazolidine derivative **6** was prepared similarly to **4**, and obtained as an amorphous solid, m.p. 123–125° (dec.), $[\alpha]_D^{23}$ +105° (*c* 1, chloroform). Acid-catalyzed rearrangement of **6** gave the corresponding β-D-glycoside **7** as an amorphous solid (50%), m.p. 140–145° (dec.), $[\alpha]_D^{23}$ +44° (*c* 0.9, chloroform). Compound **7** could also be obtained in 50% yield by treatment of **3** with isopropyl alcohol and *p*-toluenesulfonic acid.

The generality of the method of preparation of oxazolidine derivatives of this

*Crystalline compounds gave correct microanalyses. All compounds exhibited 60-MHz n.m.r.-spectral characteristics that were in accord with their structures.



Scheme 2

type is further demonstrated by the synthesis and rearrangement of the complex "ortho-amide" **9** (see Scheme 2). Treatment of a solution of **1** (1 mmole) in dichloromethane with *p*-nitrobenzoyl chloride (3 mmoles) as already described, followed by the addition of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**8**; 4 mmoles) and pyridine (2 mmoles) and keeping for 2 h at 25°, gave the beautifully crystalline oxazolidine derivative **9** (30%, from benzene), m.p. 183–184°, $[\alpha]_D^{23}$ +46° (*c* 0.6, chloroform). The high crystallinity, and the well resolved signals corresponding to *C*-methyl and *O*-acetyl methyl groups in the n.m.r. spectrum of this compound suggested that it was a pure diastereoisomer, presumably having an *exo* disposition of the D-galactose residue. Compound **9** underwent acid-catalyzed (TsOH in CH_2Cl_2, or benzene) transformation into the corresponding glycoside **10**, which was isolated as a colorless syrup (67%) by chromatography; $[\alpha]_D^{25}$ +28° (*c* 1.5, chloroform). Treatment of **10** with 0.01M sodium methoxide in methanol, followed by acetylation of the resulting product, gave crystalline 1,2:3,4-di-*O*-isopropylidene-6-*O*-(3,4,6-tri-*O*-acetyl-2-benzamido-2-deoxy-β-D-glucopyranosyl)-α-D-galactopyranose (**11**), m.p. 200–201° (from 2-propanol), $[\alpha]_D^{25}$ −47° (*c* 1, chloroform). Compound **11** was identical to a sample prepared by treatment of the oxazoline **1** (1.3 mmoles) with **8** (1.1 mmoles) in the presence of dry *p*-toluenesulfonic acid (6 mg) in benzene for 30 min at 80°. Whereas compound **11** was unaffected by treatment with 0.15M hydrochloric acid in 1,4-dioxane during 24 h, the oxazolidine analog **9** was rapidly degraded within a few hours to the component sugars* in 0.03M hydrochloric acid in 1,4-dioxane. It was stable however, in 4:1 1,4-dioxane–0.5M acetic acid during 24 h at room temperature.

The formation of oxazolidine derivatives can best be rationalized by invoking a

*The amino sugar portion was recovered as 3,4,6-tri-*O*-acetyl-2-benzamido-2-deoxy-1-*O*-(*p*-nitrobenzoyl)-α-D-glucopyranose.

kinetically controlled attack of the alcohol on C-2 of the oxazolidinium ion intermediate* 2. The acid-catalyzed rearrangement of the resulting 2-alkoxyoxazolidines into the corresponding glycosides can be explained by accepted mechanisms, and it presumably constitutes a thermodynamically controlled process**. The two reactions are therefore reminiscent of the formation of orthoesters and their rearrangement to glycosides[8]. In the light of these results, it may be pertinent to suggest the formation, in part, of 2-alkoxyoxazolidines as transient intermediates in the acid-catalyzed glycosidation of alkyl(aryl)-glyco[1′,2′:4,5]-2-oxazolines. Finally, it is of interest to point out that the furanoid isomer of **1**, namely 2-phenyl-4,5-(3,5,6-tri-*O*-acetyl-α-D-glucofurano)-2-oxazoline[15], was recovered unchanged when treated with *p*-nitrobenzoyl chloride during 24 h at 25°. This observation suggests the existence of different charge-distributions in the oxazoline rings of the two compounds, reflected in the relative nucleophilicities of the nitrogen atoms***.

ACKNOWLEDGMENTS

We thank the Farmitalia Co., Milan, and the National Research Council of Canada for financial assistance.

REFERENCES

1 (a) F. Micheel and H. Köchling, *Chem. Ber.*, 90 (1957) 1597; (b) 91 (1958) 673–676; (c) 93 (1960) 2372–2377.
2 F. Micheel and E. Drescher, *Chem. Ber.*, 91 (1958) 670–673.
3 S. E. Zurabyan, T. P. Volosyuk, and A. J. Khorlin, *Carbohydr. Res.*, 9 (1969) 215–220; S. E. Zurabyan, T. S. Antonenko, and A. Ya. Khorlin, *ibid.*, 15 (1970) 21–27.
4 S. David and A. Veyrières, *Carbohydr. Res.*, 40 (1975) 23–29.
5 J.-C. Jacquinet, S. E. Zurabyan, and A. Ya. Khorlin, *Carbohydr. Res.*, 32 (1974) 137–143.
6 K. L. Matta, E. A. Johnson, and J. J. Barlow, *Carbohydr. Res.*, 26 (1973) 215–218; K. L. Matta and O. P. Bahl, *ibid.*, 21 (1972) 460–464.
7 R. Iwamoto and Y. Imanaga, *Carbohydr. Res.*, 24 (1972) 133–139.
8 N. K. Kochetkov and A. F. Bochkov, in *Recent Developments in the Chemistry of Natural Products*, Vol. 4, Akademia Kiado', Budapest, 1972, pp. 77–191; G. Wulff and G. Rohle, *Angew. Chem. Int. Ed. Engl.*, 13 (1974) 157–170, and references cited therein.
9 R. H. DeWolfe, *Carboxylic Ortho-Acid Derivatives*, Academic Press, New York, 1970, p. 444.
10 For reviews, see C. V. Pittman, Jr., S. P. McManus, and J. W. Larsen, *Chem. Rev.*, 72 (1972) 357–437; H. El Khadem, *Adv. Carbohydr. Chem. Biochem.*, 25 (1970) 351–404.
11 See, for example, E. M. Fry, *J. Org. Chem.*, 15 (1950) 802–806.
12 N. Pravdić, T. D. Inch, and H. G. Fletcher, Jr., *J. Org. Chem.*, 32 (1967) 1815–1821; see also, T. Osawa, *Chem. Pharm. Bull.*, 8 (1960) 597–601.
13 P. Stockl, H. Honig, and H. Weidmann, *J. Carbohydr. Nucleos. Nucleot.*, 1 (1974) 169–176.
14 S. Hanessian, G. Cassinelli, and M. Casey, to be published.

*In a separate experiment, the salt **2** was treated with *N,N*-dimethylformamide dimethyl acetal as a source of sustained amounts of methoxide ion. Although the yield of oxazolidine derivative **3** remained unchanged, there was no formation of the glycoside **5**.

The formation of the glycoside **5 in the original reaction is most probably due to a competitive attack of methanol on the anomeric carbon atom of the intermediate **2**.

***Undoubtedly, the relative flexibilities of the heterocyclic rings, and related conformational factors, play an important role. The problem is under investigation by the use of ^{13}C nuclear magnetic resonance spectroscopy.