Carbohydrate Research, 100 (1982) c1–c4
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

Preliminary communication

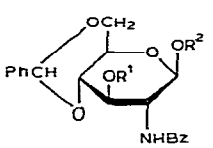
Phenyloxazoline derivatives of 2-amino-2-deoxy-D-glucopyranose*

ROY GIGG** AND ROBERT CONANT
Laboratory of Lipid and General Chemistry, National Institute for Medical Research, Mill Hill, London NW7 1AA (Great Britain)

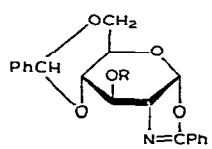
(Received June 17th, 1981; accepted for publication, June 22nd, 1981)

Methyloxazoline derivatives of amino sugars have recently been used extensively[1–9] for the preparation of 2-acetamido-2-deoxy-β-D-hexopyranosides, although much of the early work on such oxazoline derivatives involved phenyloxazolines[10]. Several general methods[10] are available for the preparation of the oxazolines proceeding (*a*) from 2-acylamino-2-deoxyglycosyl chlorides with silver salts[11] or with halide-ion participation[4,12] in the presence of base, (*b*) from β-1-acetates[6,13,14], (*c*) from prop-1-enyl β-glycosides[15], and (*d*) from methyl glycosides by acetolysis[16].

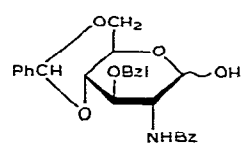
The availability[17] of *O*-substituted prop-1-enyl 2-benzamido-2-deoxy-β-D-glucopyranosides allowed the method of Anderson and his co-workers[15] for the preparation of the phenyloxazolines to be used. Thus, the phenyloxazoline **5** {m.p. 161–163°, $[\alpha]_D^{21}$ +104° (*c* 1, chloroform)} was readily prepared from the prop-1-enyl glycoside **1**[17]. Isomerisation of the alcohol **2**[17] with potassium *tert*-butoxide in dimethyl sulphoxide gave the prop-1-enyl glycoside **3**, which was converted into the acetate **4**. Compound **4** was converted by Anderson's procedure into the phenyloxazoline **6** which, on basic hydrolysis, gave the phenyloxazoline **7** {m.p. 241–243°, $[\alpha]_D^{38}$ +161° (*c* 1, chloroform)}. This oxazoline can be protected at position **3** by various groups.



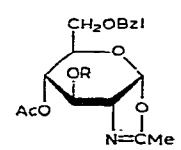
1 R^1 = Bzl, R^2 = —CH=CHMe
2 R^1 = H, R^2 = —CH_2CH=CH_2
3 R^1 = H, R^2 = —CH=CHMe
4 R^1 = Ac, R^2 = —CH=CHMe



5 R = Bzl
6 R = Ac
7 R = H



8



9
R = —CH_2CH=CHMe

*Phenyloxazoline Derivatives of Amino Sugars, Part 4. For Part 3, see ref. 23. These results were presented at the 1st European Symposium on Carbohydrates and Glycoconjugates, Vienna, Austria, Sept. 14–17, 1981.

**To whom correspondence should be directed.

For the preparation of other phenyloxazolines containing allyl protecting-groups, we considered that the Anderson procedure might be unsuitable, since we have shown[18] that mercuric chloride can form addition compounds with the allyl group. We have therefore devised a new route to phenyloxazolines which should also be suitable for the preparation of methyloxazolines. Subsequently, Durette and Meitzner[2] have used the Anderson procedure to prepare the oxazoline **9** (containing a but-2-enyl group) from the corresponding prop-1-enyl β-glycoside and obtained a 50% yield after purification by h.p.l.c.

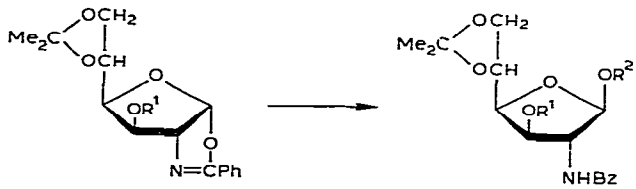
In the new procedure, the phenyloxazolines were prepared from the free sugars, which are readily available from the prop-1-enyl α- or β-glycosides. We reasoned that mesylation of a protected 2-benzamido-2-deoxyhexopyranose, in the presence of halide ion, would give initially some β-1-methanesulphonate, which would be rapidly converted into the phenyloxazoline by neighbouring-group participation, and some α-1-methanesulphonate, which would be displaced by halide ion to give the β-1-halide which would again give the phenyloxazoline by neighbouring-group participation.

A mixture of the free sugar[17] **8** (1 g, 2.1 mmol), tetraethylammonium bromide (1 g, 4.8 mmol), 2,6-dimethylpyridine (10 mL, 86 mmol), and dichloromethane (25 mL) was stirred at 0°, and a solution of methanesulphonyl chloride (1 mL, 12.8 mmol) in dichloromethane (5 mL) was added. After 1 h, **8** had almost completely dissolved; after 2.5 h at 0°, triethylamine (5 mL, 36 mmol) was added followed by the dropwise addition of water (5 mL). The solution was stirred for 5 min and diluted with water (30 mL), and the dichloromethane layer was separated, washed with water, and dried (K_2CO_3). Evaporation of the solvents gave a crystalline product which was recrystallised from ethanol (containing a little triethylamine) to give the phenyloxazoline **5** (85% yield), identical with the material prepared by the Anderson procedure.

In considering the use of these phenyloxazolines for coupling reactions, to give β-glycosides, we were conscious of the acid-lability of the benzylidene group, which might be a complicating factor in the conventional method of coupling using acidic catalysts[10,12] in the presence of an aglycon. Although aglycons containing benzylidene groups have been used in this acid-catalysed coupling[19,20], the yields obtained[20] with 1,3-*O*-benzylideneglycerol were 31–36% and this low yield may have been due to isomerisation of the glycerol derivative to a mixture of 1,2-*O*- and 1,3-*O*-benzylideneglycerol which would be expected to occur under acidic conditions[21]. The optimum conditions for the use of *p*-toluenesulphonic acid as a catalyst have been considered by Anderson and his co-workers[1], and they consider that the ratio of *p*-toluenesulphonic acid to oxazoline may be an important parameter. The oxazolines are basic and form salts with the acid catalysts, but the mixture will become acidic when the oxazolines have reacted. In the early experiments of Micheel and his co-workers[22], silver carbonate and Drierite were added to overcome this problem.

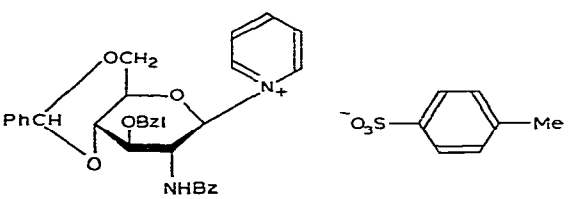
We have shown[23] that the phenyloxazolines **10** can be converted into the simple

glycosides **11** by treatment with a large excess of boiling alcohol in the presence of pyridinium *p*-toluenesulphonate without affecting the isopropylidene group. This occurs because the oxazoline is a stronger base than pyridine and is therefore protonated, with subsequent ring opening by the nucleophilic alcohol. We therefore attempted to apply this reaction to the phenyloxazoline **5**.

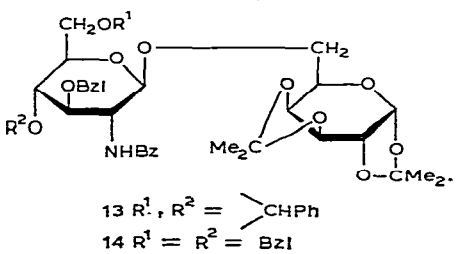


10 11

When a mixture of **5** (1 mmol), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1.1 mmol), *p*-toluenesulphonic acid (8 mmol), and pyridine (100 mmol) was kept at 50° for 2 h, t.l.c. showed the absence of **5**. The product was recrystallised from ethyl acetate to give the pyridinium derivative **12** {m.p. 174–177° (dec.), $[\alpha]_D^{27}$ −18° (*c* 0.5, chloroform)} in 80% yield. It is interesting to compare this result with that of Salo and Fletcher[24], where *N*-acylenamines were prepared from oxazolines by the action of *p*-toluenesulphonic acid in tetramethylurea at 100°, and the result of Wolfrom and Winkley[25], who prepared a nucleoside derivative of 2-acetamido-2-deoxy-D-glucofuranose by fusing a methyloxazoline with 2,6-dichloropurine in the presence of *p*-toluenesulphonic acid.



12



However, when a mixture of **5** (1 mmol), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1.1 mmol), 2,6-dimethylpyridinium *p*-toluenesulphonate (0.8 mmol), 2,6-dimethylpyridine (2 drops), and dry acetonitrile (10 mL) was heated under reflux for 18 h, the glycoside **13** {m.p. 252–256°, $[\alpha]_D^{23}$ −34° (*c* 1, chloroform)} was obtained in 80% yield after crystallisation. The corresponding benzyl derivative **14** {m.p. 170–173°, $[\alpha]_D^{23}$ −25° (*c* 2, chloroform)} was also prepared from prop-1-enyl 2-benzamido-3,4,6-tri-*O*-benzyl-2-deoxy-β-D-glucopyranoside[26] *via* the phenyloxazoline (prepared by the Anderson procedure) and the 2,6-dimethylpyridinium *p*-toluenesulphonate procedure. Thus it appears that hindered, weak-base salts of

strong acids are also suitable catalysts for glycosidation by the oxazoline method and these may prevent some of the problems associated with the use of free acids. 2,6-Dimethylpyridinium *p*-toluenesulphonate is a crystalline, apparently non-hygroscopic compound that is readily prepared by dissolving *p*-toluenesulphonic acid monohydrate (1 g) in hot 2,6-dimethylpyridine (20 mL), cooling to room temperature, and filtering off the crystals which are then washed with ether and dried.

Since benzamido derivatives can be converted[27] into acetamido and other acylamino derivatives, the application of phenyloxazoline derivatives (which usually have a greater tendency to crystallise than the corresponding acetamido derivatives) may be useful in the preparation of biologically important carbohydrate derivatives.

REFERENCES

1 M. A. Nashed, M. Kiso, C. W. Slife, and L. Anderson, *Carbohydr. Res.*, 90 (1981) 71–82.
2 P. L. Durette and E. P. Meitzner, *Carbohydr. Res.*, 89 (1981) 279–288.
3 J. Alais and A. Veyrières, *J. Chem. Soc., Perkin Trans. 1*, (1981) 377–381.
4 C. D. Warren, M. A. E. Shaban, and R. W. Jeanloz, *Carbohydr. Res.*, 59 (1977) 427–448.
5 C. D. Warren, R. W. Jeanloz, and G. Strecker, *Carbohydr. Res.*, 71 (1979) c5–c8.
6 P. Rollin and P. Sinaÿ, *J. Chem. Soc., Perkin Trans. 1*, (1977) 2513–2517.
7 C. D. Warren, C. Augé, M. L. Laver, S. Suzuki, D. Power, and R. W. Jeanloz, *Carbohydr. Res.*, 82 (1980) 71–83.
8 C. Augé, C. D. Warren, R. W. Jeanloz, M. Kiso, and L. Anderson, *Carbohydr. Res.*, 82 (1980) 85–95.
9 K. L. Matta and J. J. Barlow, *Carbohydr. Res.*, 53 (1977) 47–56.
10 For reviews, see S. E. Zurabyan and A. Ya. Khorlin, *Russ. Chem. Rev.*, 43 (1974) 887–904; H. El Khadem, *Adv. Carbohydr. Chem. Biochem.*, 25 (1970) 351–405.
11 A. Ya. Khorlin, M. I. Shul'man, S. E. Zurabyan, I. M. Privalova, and Yu. L. Kopaevich, *Izv. Akad. Nauk SSSR, Ser. Khim*, (1968) 2094–2098; S. E. Zurabyan, T. P. Volosyuk, and A. Ya. Khorlin, *Carbohydr. Res.*, 9 (1969) 215–220.
12 R. U. Lemieux and H. Driguez, *J. Am. Chem. Soc.*, 97 (1975) 4063–4069.
13 K. L. Matta and J. J. Barlow, *Carbohydr. Res.*, 51 (1976) 215–222.
14 M. Kiso, H. Nishiguchi, and A. Hasegawa, *Carbohydr. Res.*, 82 (1980) c13–c15.
15 M. A. Nashed, C. W. Slife, M. Kiso, and L. Anderson, *Carbohydr. Res.*, 58 (1977) c13–c16; 82 (1980) 237–252; M. A. Nashed, *ibid.*, 71 (1979) 299–304.
16 R. W. Jeanloz, E. Walker, and P. Sinaÿ, *Carbohydr. Res.*, 6 (1968) 184–195; S. S. Rana, J. J. Barlow, and K. L. Matta, *Carbohydr. Res.*, 91 (1981) 149–157.
17 R. Gigg and R. Conant, *Carbohydr. Res.*, 100 (1982) 441–444.
18 R. Gigg and C. D. Warren, *J. Chem. Soc., C*, (1968) 1903–1911.
19 T. S. Antonenko, S. E. Zurabyan, and A. Ya. Khorlin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1970) 1153–1155.
20 S. E. Zurabyan, T. S. Antonenko, and A. Ya. Khorlin, *Carbohydr. Res.*, 15 (1970) 21–27.
21 N. Baggett, J. M. Duxbury, A. B. Foster, and J. M. Webber, *Carbohydr. Res.*, 2 (1966) 216–223.
22 F. Micheel and H. Köchling, *Chem. Ber.*, 91 (1958) 673–676; F. Micheel and E. Drescher, *ibid.*, 91 (1958) 670–672.
23 R. Gigg and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, (1977) 2006–2014.
24 W. L. Salo and H. G. Fletcher, Jr., *J. Org. Chem.*, 34 (1969) 3189–3191.
25 M. L. Wolfrom and M. W. Winkley, *J. Org. Chem.*, 31 (1966) 3711–3713.
26 P. A. Gent, R. Gigg, and R. Conant, *J. Chem. Soc., Perkin Trans. 1*, (1972) 1535–1542.
27 R. Gigg and R. Conant, *Carbohydr. Res.*, 100 (1982) c5–c9.