The Synthesis of Methyl β-D-Lyxofuranoside Derivatives bearing a Fused Oxazoline Ring†‡

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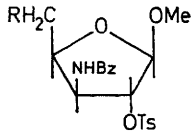
Methyl β-D-lyxofuranoside derivatives bearing a fused oxazoline ring have been synthesised by two routes: (*a*) from the appropriate *trans*-benzamido–sulphonyloxy-system or (*b*) from *N*-benzoylepimines by rearrangement.

CONTINUING our studies on the synthesis of nitrogen-containing furanosides, we have now prepared some oxazoline derivatives; such compounds should be readily convertible into *cis*-amino-alcohols.

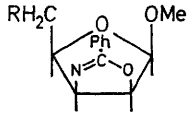
Two routes are available for the synthesis of the required compounds: (i) rearrangement of the appropriate *N*-aroylepimine and (ii) ring-closure of a *trans*-acylamino–sulphonate system. Rearrangements of the former type in alicyclic systems have been studied extensively,[1-7] but similar rearrangements in carbohydrates have only been investigated in the case of pyranoside derivatives.[8] Similarly, the second route has only been studied with respect to pyranoside systems; either oxazolines or *N*-aroylepimines may be produced. Such reactions have been recently reviewed by Goodman.[9]

Initially we investigated the possibility of direct conversion of the *trans*-benzamido–sulphonyloxy-system into the *cis*-benzamido-alcohol by use of sodium fluoride in *NN*-dimethylformamide. However, when methyl 3,5-dibenzamido-3,5-dideoxy-2-*O*-*p*-tolylsulphonyl-β-D-xylofuranoside (1) was treated with this reagent at 150° for 3 hr. it was converted into a new compound, of lower R_F value (t.l.c.), shown to be methyl 5-benzamido-2,3,5-trideoxy-2,3-(2-phenyl-1-oxa-3-azaprop-2-eno)-β-D-lyxofuranoside (5), *m/e* 352 (M^+), $\nu_{max.}$ 1656s (oxazoline C=N) cm.$^{-1}$.

Similarly, methyl 3-benzamido-3-deoxy-2-*O*-*p*-tolylsulphonyl-β-D-xylofuranoside (2) gave methyl 2,3-dideoxy-2,3-(2-phenyl-1-oxa-3-azaprop-2-eno)-β-D-lyxofuranoside (6) in 70% yield. Oxazolines are usually prepared by treatment of a *trans*-acylamino–sulphonyloxy-system with a weak base; this method has now been used for the preparation of the related 5-deoxy- and 5-*O*-benzoyl-oxazolines (7) and (8) from the corresponding *trans*-benzamido–*p*-tolylsulphonyloxy-systems, namely methyl 3-benzamido-3,5-dideoxy-2-*O*-*p*-tolylsulphonyl-β-D-xylofuranoside (3) and methyl 5-*O*-benzoyl-3-benzamido-3-deoxy-2-*O*-*p*-tolylsulphonyl-β-D-xylofuranoside (4). In none of the ring-closure reactions was any of the corresponding 2,3-*N*-benzoylepimino-2,3-dideoxy-compound detected by t.l.c.; these



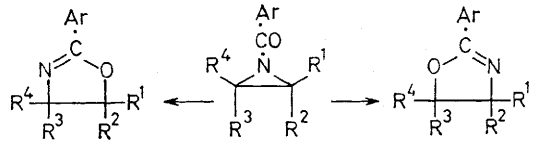
(1) R = NHBz
(2) R = OH
(3) R = H
(4) R = OBz



(5) R = NHBz
(6) R = OH
(7) R = H
(8) R = OBz

furanoside compounds thus differ from their pyranoside counterparts.

As already mentioned, *N*-aroylepimines undergo rearrangement on treatment with nucleophilic reagents, such as sodium iodide in aprotic solvents, to give oxazolines. In the case of unsymmetrical epimines, such as those on a sugar or a steroid ring, either of two oxazolines may be formed (see Scheme), depending on



which C–N bond is broken. In the cases reported so far for steroid[10] and pyranoside[8] systems, only one oxazoline resulted.[11] The systems studied were conformationally rigid and, if the mechanism involves opening by iodide ion followed by ring-closure,[1] then the product is the expected one (*i.e.* that formed from the predicted diaxial intermediate).

The furanoside epimines at present under investigation are known to open predominantly at C-3 when

† For a preliminary report of part of this work, see *Compt. rend.*, 1968, **267***C*, 980.

‡ Part XXV in the series 'Nitrogen-containing Carbohydrate Derivatives,' by R. D. Guthrie and co-workers; Part XXIV, *J. Chem. Soc.* (*C*), 1970, 1385.

[1] H. W. Heine, *Angew. Chem. Internat. Edn.*, 1962, **1**, 528.

[2] P. E. Fanta, 'Heterocyclic Compounds with Three- and Four-Membered Rings,' vol. 19, part I, ed. A. Weissberger, Interscience, New York, 1964, pp. 524—575.

[3] H. W. Heine, M. E. Fetter, and E. Nicholson, *J. Amer. Chem. Soc.*, 1959, **81**, 2202; H. W. Heine, *ibid.*, 1961, **83**, 2570; H. W. Heine, *J. Org. Chem.*, 1966, **31**, 2662.

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[6] P. E. Fanta and E. N. Walsh, *J. Org. Chem.*, 1965, **30**, 3574; 1966, **31**, 59.

[7] R. Thrum and A. R. Day, *J. Medicin. Chem.*, 1965, **8**, 107.

[8] R. D. Guthrie and Z. M. El Shafei, *J. Chem. Soc.* (*C*), 1970, 843.

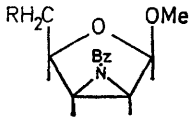
[9] L. Goodman, *Adv. Carbohydrate Chem.*, 1967, **22**, 109.

[10] G. Drefahl, K. Ponsold, and D. Klemm, *J. prakt. Chem.*, 1968, **38**, 168.

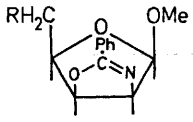
[11] Methyl 2,3-*N*-aroylepimino-4,6-*O*-benzylidene-2,3-dideoxy-α-D-allopyranosides differ from other six-membered ring systems studied in that two oxazolines result from rearrangement with sodium iodide (Z. M. El Shafei and R. D. Guthrie, unpublished work).

treated with azide ion,[12] and so it was predicted that one oxazoline would be formed predominantly, if not exclusively. Indeed, when methyl 5-benzamido-2,3-*N*-benzoylepimino-2,3-dideoxy-β-D-lyxofuranoside (9) was refluxed with an excess of sodium iodide in acetonitrile, t.l.c. showed complete disappearance of the starting material after 18 hr. and the formation of two new products, visually estimated to be in the ratio of *ca.* 25 : 1. The minor product was shown by t.l.c. to be identical with the C(3)–N oxazoline (5). The major compound, obtained in 95% yield, was identified as an oxazoline by its spectral properties (mass, n.m.r., and i.r. spectra) and elemental analysis, and was therefore assigned the C(2)–N structure (12). Similarly, methyl 2,3-*N*-benzoylepimino-2,3-dideoxy-β-D-lyxofuranoside (10) gave two oxazolines, one (70%) shown to be the C(2)–N isomer (13) and the other (*ca.* 10% by t.l.c.) to be the C(3)–N isomer (6) (by t.l.c.).

When methyl 2,3-*N*-benzoylepimino-2,3,5-trideoxy-β-D-lyxofuranoside (11) was treated in a similar manner, the selectivity of the attack by iodide ion was considerably less than that observed in the cases already described. Two products were isolated, in the ratio of 2 : 1. The minor product was identical with the C(3)–N oxazoline (7) already prepared; the major product had properties consistent with an oxazoline structure and it was therefore assumed to be the C(2)–N isomer (14). The lack of selectivity of opening of (11) is presumed to be due to the change from the electron-withdrawing benzamido- or hydroxy-group [in (9) and (10)] to a hydrogen atom (11).



(9) R = NHBz
(10) R = OH
(11) R = H



(12) R = NHBz
(13) R = OH
(14) R = H

EXPERIMENTAL

Solvents were evaporated *in vacuo* with a bath temperature of less than 50°. T.l.c. and preparative layer chromatography (p.l.c.) were carried out with silica gel. New compounds had i.r. and n.m.r. spectra consistent with the assigned structures. Rotations quoted are for solutions in chloroform.

Methyl 5-Benzamido-2,3,5-dideoxy-2,3-(2-phenyl-1-oxa-3-azaprop-2-eno)-β-D-lyxofuranoside (5).—Methyl 3,5-dibenzamido-3,5-dideoxy-2-*O*-*p*-tolylsulphonyl-β-D-xylofuranoside (1) (0·46 g.) and sodium fluoride (0·2 g.) in dimethylformamide (5 ml.) were heated with stirring at 150° for 3 hr. The cooled mixture was partitioned between water and chloroform. The chloroform layer was washed, dried, and concentrated to a syrup. T.l.c. (ethyl acetate) showed only one spot (R_F 0·65). The product crystallised and yielded the *oxazoline* (5) (0·22 g., 72%), m.p. 204—206° (from ethyl acetate–light petroleum), $[\alpha]_D^{22}$ −188° (*c* 0·4) (Found: C, 67·8; H, 6·0; N, 7·85. $C_{20}H_{20}N_2O_4$ requires C, 68·2; H, 5·7; N, 8·0%).

Methyl 3-Benzamido-3-deoxy-2-O-p-tolylsulphonyl-β-D-xylofuranoside (2).—Methyl 3-azido-3-deoxy-2-*O*-*p*-tolylsulphonyl-β-D-xylofuranoside (0·3 g.) was reduced with hydrogen over Adams catalyst (0·1 g.) in methanol (10 ml.) for 1·5 hr. The solution was evaporated to 2 ml. and benzoic anhydride (0·23 g.) was added. The mixture was set aside overnight at room temperature, then evaporated, and the residual syrup was stirred for 2 hr. with excess of sodium hydrogen carbonate. Work-up as in the preceding experiment gave the *amide* (2) (0·3 g.) (82%), m.p. 119—122°, $[\alpha]_D^{21}$ +27° (*c* 0·33) (Found: C, 56·6; H, 5·5; N, 3·2; S, 7·55. $C_{20}H_{23}NO_7S$ requires C, 57·0; H, 5·5; N, 3·3; S, 7·6%).

Methyl 2,3-Dideoxy-2,3-(2-phenyl-1-oxa-3-azaprop-2-eno)-β-D-lyxofuranoside (6).—Compound (2) (0·2 g.) and sodium fluoride (0·1 g.) were heated with stirring in dimethylformamide (2·5 ml.) at 150° for 4 hr. Work-up as described for the oxazoline (5) gave a crude product, which was chromatographed on silica gel (10 g.); elution with ethyl acetate gave an homogeneous syrup (70%) [t.l.c. (ethyl acetate) R_F 0·4], which yielded the *oxazoline* (6), m.p. 114—115° (from ethyl acetate–light petroleum), $[\alpha]_D^{23}$ −100° (*c* 0·47) (Found: C, 58·4; H, 6·2; N, 5·5. $C_{13}H_{15}NO_4,H_2O$ requires C, 58·4; H, 6·4; N, 5·2%).

Methyl 5-Benzamido-2,3,5-trideoxy-3,2-(2-phenyl-1-oxa-3-azaprop-2-eno)-β-D-lyxofuranoside (12).—A solution of 5-benzamido-2,3-*N*-benzoylepimino-2,3-dideoxy-β-D-lyxofuranoside (9) (0·71 g.) and sodium iodide (3·7 g.) in acetonitrile (90 ml.) was refluxed overnight. The solvent was evaporated off and the residue was partitioned between chloroform and water. The chloroform layer was washed, dried, and evaporated to leave a solid which yielded the *oxazoline* (12) (95%), homogeneous by t.l.c. (ethyl acetate), R_F 0·3, m.p. 213—215° (from ethyl acetate–light petroleum), $[\alpha]_D^{24}$ −131° (*c* 0·42) (Found: C, 67·8; H, 5·7; N, 8·0. $C_{20}H_{20}N_2O_4$ requires C, 68·2; H, 5·7; N, 7·95%). T.l.c. of the crude product showed the presence of (12) and (5) in the ratio of *ca.* 25 : 1.

Methyl 2,3-Dideoxy-3,2-(2-phenyl-1-oxa-3-azaprop-2-eno)-β-D-lyxofuranoside (13).—A solution of 2,3-benzoylepimino-2,3-dideoxy-β-D-lyxofuranoside (10) (60 mg.) and sodium iodide (300 mg.) in acetonitrile (6 ml.) was refluxed overnight. The mixture was treated in the same way as that from compound (9) to yield the crystalline *oxazoline* (13) (42 mg., 70%), m.p. 151—153° (from ethyl acetate–light petroleum), $[\alpha]_D^{23}$ −52·3° (*c* 0·42) (Found: C, 62·7; H, 5·9; N, 5·5. $C_{13}H_{15}NO_4$ requires C, 62·6; H, 6·1; N, 5·6%).

T.l.c. (ethyl acetate) of the crude product showed essentially two spots, R_F 0·2 and 0·45, corresponding to (13) and (6) (comparison with authentic samples).

Methyl 2,3,5-Trideoxy-2,3-(2-phenyl-1-oxa-3-azaprop-2-eno)-β-D-lyxofuranoside (7).—Methyl 3-benzamido-3,5-dideoxy-2-*O*-*p*-tolylsulphonyl-β-D-xylofuranoside (3) (0·26 g.) in a solution of sodium (0·17 g.) in absolute ethanol (25 ml.) was refluxed for 0·5 hr. The mixture was allowed to cool to room temperature, neutralised with solid carbon dioxide, and then evaporated to dryness. The residue was partitioned between water (25 ml.) and chloroform (25 ml.), and the chloroform solution was washed with water and evaporated to leave a crystalline solid. This gave the *oxazoline* (7) (0·13 g., 87%), m.p. 85—86° (from ether–light petroleum); $[\alpha]_D^{25}$ −66·4° (*c* 1·1), *m/e* 233 (M^+),

[12] J. Hildesheim, J. Cleophax, A. M. Sepulchre, and S. D. Gero, *Carbohydrate Res.*, 1969, **9**, 315.

202 (M — CH_3O), 117 (M — C_7H_5NO), and 105 (C_7H_5O) (Found: C, 67·3; H, 6·8; N, 6·0. $C_{13}H_{15}NO_3$ requires C, 66·9; H, 6·5; N, 6·0%).

Methyl 2,3,5-*Trideoxy*-3,2-(2-*phenyl*-1-*oxa*-3-*azaprop*-2-*eno*)-β-D-*lyxofuranoside* (14).—A solution of methyl 2,3-benzoylepimino-2,3,5-trideoxy-β-D-lyxofuranoside (11) (0·57 g.) and sodium iodide (5·0 g.) in acetonitrile (25 ml.) was refluxed for 18 hr. The dark red solution was allowed to cool and evaporated to dryness, and the residue was partitioned between water (25 ml.) and chloroform (25 ml.). The chloroform layer was washed with water and evaporated to leave a yellowish-brown syrup (0·47 g.) which slowly crystallised. P.l.c. (ether) gave two components: methyl 2,3,5-trideoxy-2,3-(2-phenyl-1-oxa-3-aza-prop-2-eno)-β-D-lyxofuranoside (7) (0·17 g., 29%), identical with the sample obtained before, and *methyl* 2,3,5-*trideoxy*-3,2-(2-*phenyl*-1-*oxa*-3-*azaprop*-2-*eno*)-β-D-*lyxofuranoside* (14) (0·25 g., 44%), m.p. 109—110° $[\alpha]_D^{25}$ −21·2° (*c* 1·6), *m/e* 233 (M^+), 202 (M — CH_3O), 117 (M — C_7H_5NO), and 105 (C_7H_5O) (Found: C, 66·6; H, 6·5; N, 6·1. $C_{13}H_{15}NO_3$ requires: C, 66·9; H, 6·5; N, 6·0%).

Methyl 5-O-*Benzoyl*-2,3-*dideoxy*-2,3-(2-*phenyl*-1-*oxa*-3-*azaprop*-2-*eno*)-β-D-*lyxofuranoside* (8).—Methyl 3-benzamido-5-*O*-benzoyl-3-deoxy-2-*O*-*p*-tolylsulphonyl-β-D-xylofuranoside (4) (0·9 g.) in a solution of sodium (0·33 g.) in absolute ethanol (50 ml.) was refluxed for 0·5 hr. The solution was allowed to cool to room temperature, neutralised with solid carbon dioxide, and extracted with chloroform (2 × 25 ml.). The chloroform solution was washed with water, dried, and evaporated to leave a syrup, which was dissolved in dry pyridine (10 ml.). Benzoyl chloride (2·0 ml.) was added and the mixture was left at room temperature overnight; water (2 ml.) was then added, and after a further 0·5 hr. the mixture was poured into rapidly stirred ice–water (100 ml.). A white solid which separated was filtered off, washed with water, and recrystallised twice from methanol to give the *oxazoline* (8) (0·43 g., 64%), m.p. 141—142°, $[\alpha]_D^{25}$ −40·6° (*c* 1·0), *m/e* 353 (M^+), 322 (M — CH_3O), 248 (M — C_7H_5O), 218 (M — $C_8H_7O_2$), and 105 (C_7H_5O) (Found: C, 67·5; H, 5·6; N, 4·0. $C_{20}H_{19}NO_5$ requires C, 67·9; H, 5·4; N, 3·9%).

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