Nitrogen-containing Carbohydrate Derivatives. Part XXIII.[1] Some Ring-opening Reactions of Methyl 2,3-*N*-Aroylepimino-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranosides

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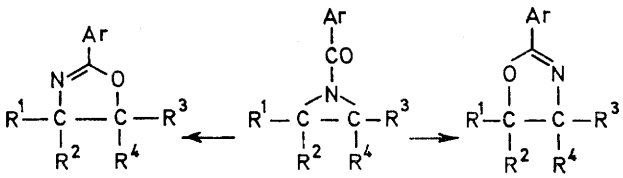
Reaction of methyl 2,3-*N*-aroylepimino-4,6-*O*-benzylidene-α-D-mannosides (1) with sodium iodide in *NN*-dimethylformamide gave only the 2-*N*-3-*O*-oxazolines. Reaction with thiocyanate ion, however, gave no oxazolines but instead the methyl 2-arylamido-4,6-*O*-benzylidene-3-deoxy-3-thiocyanato-α-D-altrosides, which were desulphurised to give the appropriate 2,3-dideoxy-2-arylamido-derivatives.

THE ring-opening reactions of 2,3-epiminoglycopyranosides show some unusual features,[2-5] particularly those compounds in the *allo*-series. In this paper a study of the action of iodide ion and of thiocyanate ion on the *N*-aroylmannosides (1) is described.

The isomerisation of aroylaziridines into 2-aryl-2-oxazolines by nucleophilic reagents such as iodide, thiocyanate, and azide ions is well known.[6-12] It has been shown that the *N*-benzoylepiminomannoside (1a) on treatment with sodium azide in boiling dimethylformamide gives a mixture of methyl 3-azido-2-benzamido-4,6-*O*-benzylidene-2 3-dideoxy-α-D-altroside and methyl 4,6-*O*-benzylidene-2,3-dideoxy-3,2-(2-phenyl-1-oxa-3-azaprop-2-eno)-α-D-mannoside (2a);[3] that is, there is competition between ' normal ' opening by the azide ion to give *trans*-diaxial product, and isomerisation to



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oxazoline. Few studies have been made on unsymmetrical aziridines, which in theory could give rise to two isomeric oxazolines (Scheme). A preliminary

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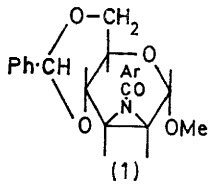
communication [13] on the rearrangement of some furanoside 2,3-*N*-aroylepimines with iodide ion reported that a mixture of both possible products was formed, whereas a similar rearrangement of a 2,3-*N*-benzoylepiminosteroid [14] gave only one oxazoline.

Treatment of the *N*-benzoylepiminomannoside (1a) with sodium iodide in boiling dimethylformamide afforded the corresponding oxazoline (2a). Similarly, *N*-*p*-nitrobenzoyl- (1b) and *N*-anisoyle-piminomannoside (1c) gave methyl 4,6-*O*-benzylidene-2,3-dideoxy-3,2-(2-*p*-nitrophenyl- and methyl 4,6-*O*-benzylidene-2,3-dideoxy-3,2-(2-*p*-methoxyphenyl-1-oxa-3-azaprop-2-eno)-α-D-mannoside (2b) and (2c), respectively. The *p*-nitrobenzoyl derivative (1b) was the most reactive of all (30



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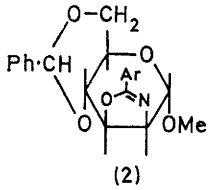

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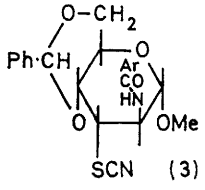

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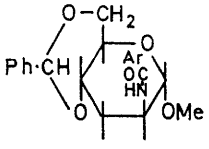

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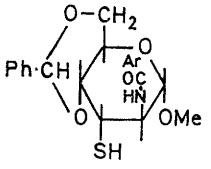

Ar = *p* MeO·C$_6$H$_4$ (5)

For (1)—(4)
a; Ar = Ph
b; Ar = *p*-O$_2$N·C$_6$H$_4$
c; Ar = *p*-MeO·C$_6$H$_4$

min.) whereas the anisoyl derivative (1c) came intermediate in reactivity (4 hr.). As judged by t.l.c. only one product was formed in each of these reactions.

The n.m.r. spectra of the three oxazolines showed a marked downfield shift of the 1-H signal, presumably due to the presence of the neighbouring 2-aryloxazoline group. The signal occurred at τ 4·72—4·78 as a sharp singlet; the corresponding signal for the epimine precursors occurred at τ *ca.* 5·0 and for 2-amino-2-deoxy-altroside derivatives at τ *ca.* 5·40.

These isomerisations into oxazolines do not require the presence of a nucleophile. When aroylepiminomannosides were refluxed in dimethylformamide alone, the corresponding oxazolines were obtained, but in a lower yield than if iodide ion was present. Traces of other compounds were formed in these reactions (t.l.c.). The order of reactivity in this case was *p*-nitrobenzoyl > benzoyl > anisoyl. Pyrolytic isomerisation of aroylaziridines has been reported to form either *N*-allyl amides or 2-oxazolines.[6,7]

Although the thiocyanate ion is known to cause isomerisation of aroylaziridines into oxazolines,[6] it behaved differently towards *N*-aroylepiminomannosides, causing fission of the epimino-ring similar to that occurring [15] with the corresponding epoxide. Treatment of (1a) with sodium thiocyanate in boiling dioxan afforded methyl 2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-3-thiocyanato-α-D-altroside (3a), the expected product from diaxial ring-opening at C-3 (*cf.* opening of the epoxide [15]). The 1-H signal (τ 5·39) was a singlet characteristic of α-altropyranosides. The structure was confirmed by desulphurisation of (3a) with Raney nickel to give methyl 2-benzamido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*ribo*-hexopyranoside (4a); the n.m.r. spectrum showed the expected methylene multiplet at τ 7·85, but showed no change in the 1-H signal compared with that signal for (3a). Thus the methylene group is at C-3. Similarly, *N*-*p*-nitrobenzoylepiminomannoside (1b) gave methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*p*-nitrobenzamido-3-thiocyanato-α-D-altroside (3b), which upon desulphurisation afforded methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*p*-nitrobenzamido-α-D-*ribo*-hexopyranoside (4b). T.l.c. showed that only one product was formed in these reactions.

However, the *N*-anisoylepiminomannoside (1c) under similar conditions gave the expected methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*p*-methoxybenzamido-3-thiocyanato-α-D-altroside (3c), which gradually changed into methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*p*-methoxybenzamido-3-thio-α-D-altroside (5), so that after 12 hr. complete transformation had occurred. It could be shown (t.l.c.) at any stage that both of the two compounds (3c) and (5) were present in ratios approximately proportional to the reaction time. Why (3c) should differ from (3a) and (3b) in the reaction with thiocyanate ion is not at all clear.

General comments on these reactions and on other ring-opening reactions of epimino-sugars will be made in a subsequent paper.

The *N*-2,4-dinitrophenyl group is a useful blocking group for amino-sugars, and may be hydrolysed off by an ion exchange resin (OH form).[16,17] Application of this procedure to *N*-dinitrophenylepimino-mannoside and -alloside was unsuccessful; complete decomposition occurred.

EXPERIMENTAL

Rotations were measured for solutions in chloroform. Where possible, compounds were identified by mixed m.p. and by i.r. spectroscopy: new compounds had i.r. and n.m.r. spectra consistent with the assigned structures. T.l.c. was performed with silica gel G (Merck) in ether–

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chloroform (1 : 1) unless otherwise stated. *NN*-Dimethylformamide will be referred to as DMF. Raney nickel was prepared by the method of Dominguez and his co-workers.[18]

Methyl 4,6-O-*Benzylidene*-2,3-*dideoxy*-2,3-p-*nitrobenzoylepimino*-α-D-*mannoside* (1b).—The epiminomannoside [19] (3 g.) in dry pyridine (15 ml.) was treated with *p*-nitrobenzoyl chloride (4 g.), and the mixture was kept for 2 hr. at room temperature. It was poured on crushed ice, and the product gave the *title compound* (75%), m.p. 168—169° (from ethanol–acetone), $[\alpha]_D^{23}$ −26·3° (*c* 1·0) (Found: C, 61·4; H, 4·8; N, 7·2. $C_{21}H_{20}N_2O_7$ requires C, 61·2; H, 4·9; N, 6·8%).

Methyl 2,3-*Anisoylepimino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannoside* (1c).—The epiminomannoside [19] (5 g.) in dry pyridine (25 ml.) was treated with freshly prepared anisoyl chloride (5 g.) and the product was worked up as in the previous experiment. Crystallisation from ethanol gave the *title compound* (80%), m.p. 185—186°, $[\alpha]_D^{23}$ −29·8° (*c* 0·95) (Found: C, 66·4; H, 5·8; N, 3·6. $C_{22}H_{23}NO_6$ requires C, 66·5; H, 5·8; N, 3·5%).

Isomerisation by Iodide Ion.—(a) *Methyl* 2,3-*benzoylepimino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannoside*. (i) The *N*-benzoylepiminomannoside [19] (1 g.) in DMF (25 ml.) was treated with sodium iodide (2 g.), and the mixture was boiled under reflux for 12 hr. T.l.c. then showed complete disappearance of the starting compound. The mixture was poured on crushed ice, and the solid obtained was filtered off, washed, and dried. Crystallisation from ethanol–water afforded methyl 4,6-*O*-benzylidene-2,3-dideoxy-3,2-(2-phenyl-1-oxa-3-azaprop-2-eno)-α-D-mannoside (2a) (75%), m.p. 150—151° $[\alpha]_D^{23}$ −73° (*c* 1·0) (lit.,[20] m.p. 147—148°, $[\alpha]_D$ −67°; lit.,[3] 148—149° $[\alpha]_D^{21}$ −65·6°) (Found: C, 68·5; H, 5·6; N, 3·9. Calc. for $C_{21}H_{21}NO_5$: C, 68·7; H, 5·8; N, 3·8%).

(ii) The *N*-benzoylepiminomannoside (200 mg.) in DMF (5 ml.) was boiled under reflux for 22 hr. Evaporation, extraction with chloroform, and evaporation of the extract afforded the same product (2a) (40%), m.p. and mixed m.p. 150—151°.

(b) *Methyl* 4,6-O-*benzylidene*-2,3-*dideoxy*-2,3-p-*nitrobenzoylepimino*-α-D-*mannoside*. (*i*) The *N*-*p*-nitrobenzoylepiminomannoside (1 g.) was treated as in (a) (i); complete reaction occurred in 30 min. When poured on crushed ice the mixture gave a solid, which afforded *methyl* 4,6-O-*benzylidene*-2,3-*dideoxy*-3,2-(2-p-*nitrophenyl*-1-*oxa*-3-*azaprop*-2-*eno*)-α-D-*mannoside* (2b) (70%), m.p. 226—227° (from ethanol–acetone), $[\alpha]_D^{23}$ −76·3° (*c* 0·8) (Found: C, 60·9; H, 4·7; N, 7·0. $C_{21}H_{20}N_2O_7$ requires C, 61·2; H, 4·9; N, 6·8%).

(ii) The *N*-*p*-nitrobenzoylepiminomannoside (1b) (200 mg.) in DMF (5 ml.) was boiled under reflux for 4 hr. Evaporation, extraction with chloroform, and evaporation of the extract afforded the same product (2b) (38%), m.p. and mixed m.p. 226°.

(c) *Methyl* 2,3-*anisoylepimino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannoside*. (i) The *N*-anisoylepiminomannoside (1c) (1 g.) was treated as in (a) (i); 4 hr. were necessary for complete reaction. The mixture, when poured on crushed ice, afforded a solid, which gave *methyl* 4,6-O-*benzylidene*-2,3-*dideoxy*-3,2-(2-p-*methoxyphenyl*-1-*oxa*-3-*azaprop*-2-*eno*)-α-D-*mannoside* (2c) (85%), m.p. 183—184° (from ethanol–water), $[\alpha]_D^{23}$ −83·2 (*c* 0·95) (Found: C, 66·8; H, 6·0; N, 3·5. $C_{22}H_{23}NO_6$ requires C, 66·5; H, 5·8; N, 3·5%).

(ii) The *N*-anisoylepiminomannoside (1c) (200 mg.) in DMF (5 ml.) was boiled under reflux for 25 hr. Work-up as in (b) (ii) gave the product (2c) (20%), m.p. and mixed m.p. 183°.

Fission by Thiocyanate.—(a) *Methyl* 2,3-*benzoylepimino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannoside*. The *N*-benzoylepiminomannoside (1a) (1 g.) in dioxan (70 ml.) was treated with sodium thiocyanate (1·5 g.) and boiled under reflux for 10 hr. When poured on crushed ice the mixture gave a brown solid, which afforded *methyl* 2-*benzamido*-4,6-O-*benzylidene*-2,3-*dideoxy*-3-*thiocyanato*-α-D-*altroside* (3a) (75%), m.p. 163—165° (from methanol–water) (Found: C, 59·6; H, 5·3; N, 6·4; S, 7·4. $C_{22}H_{22}N_2O_6S,H_2O$ requires C, 59·4; H, 5·4; N, 6·3; S, 7·2%).

A well stirred mixture of (3a) (0·9 g.), Raney nickel (*c* 9 g.), and ethanol (50 ml.) was boiled under reflux for 5 hr. Filtration through Celite and evaporation of the solvent gave a syrup. Preparative t.l.c. then afforded *methyl* 2-*benzamido*-4,6-O-*benzylidene*-2,3-*benzylidene*-2,3-*dideoxy*-α-D-ribo-*hexopyranoside* (4a) (65%) as a glass, $[\alpha]_D^{22}$ +12·3° (*c* 0·99) (Found: C, 68·6; H, 6·3; N, 3·8. $C_{21}H_{20}NO_5$ requires C, 68·3; H, 6·3; N, 3·8%).

(b) *Methyl* 4,6-O-*benzylidene*-2,3-*dideoxy*-2,3-p-*nitrobenzoylepimino*-α-D-*mannoside*. The *N*-*p*-nitrobenzoylepiminomannoside (1b) (1 g.) and sodium thiocyanate (1·5 g.) in dioxan (80 ml.) were boiled under reflux for 4 hr. The mixture was poured on crushed ice and kept overnight in the refrigerator to give a solid. This was purified by preparative t.l.c. (in 5% methanol–chloroform) and then recrystallised from methanol–acetone to give *methyl* 4,6-O-*benzylidene*-2,3-*dideoxy*-2-p-*nitrobenzamido*-3-*thiocyanato*-α-D-*altroside* (3b) (72%), m.p. 223—224° (decomp.), $[\alpha]_D^{23}$ −62·1° (*c* 0·95) (Found: C, 55·9; H, 4·7; N, 9·0. $C_{22}H_{21}N_3O_7S$ requires C, 56·0; H, 4·5; N, 8·9%).

A well stirred mixture of the thiocyanato-compound (3b) (0·6 g.), Raney nickel (*ca.* 5 g.), and ethanol (50 ml.) was boiled under reflux for 4 hr. and filtered through Celite. Evaporation of the solvent gave a syrup which was purified by preparative t.l.c. and recrystallised from ether to give *methyl* 4,6-O-*benzylidene*-2,3-*dideoxy*-2-p-*nitrobenzamido*-α-D-ribo-*hexopyranoside* (4b) (50%), m.p. 167—169°, $[\alpha]_D^{25}$ +44·4° (*c* 1·0) (Found: N, 6·7; 6·9. $C_{21}H_{22}N_2O_7$ requires N, 6·8%).

(c) *Methyl* 2,3-*anisoylepimino*-4,6-O-*benzylidene*-2,3-*dideoxy*-α-D-*mannoside*. (i) The *N*-anisoylepiminomannoside (1c) (1 g.) in dioxan (70 ml.) was treated with sodium thiocyanate (1·5 g.) and boiled under reflux. During the first 2 hr., t.l.c. showed a spot at R_F 0·33, but after that another spot, at R_F 0·13, started to appear. Refluxing was continued for 6 hr., during which time t.l.c. showed the gradual increase of the latter compound. The mixture was then poured on crushed ice, and the solid obtained was subjected to preparative t.l.c.

From the band at R_F 0·13 a solid was isolated which gave *methyl* 4,6-O-*benzylidene*-2-*deoxy*-2-p-*methoxybenzamido*-3-*thio*-α-D-*altroside* (5) (20%), m.p. 155—157° (decomp.) (from acetone–water) $[\alpha]_D^{23}$ −50·8° (*c* 0·65) (Found: C, 59·0; H, 6·0; N, 2·8; S, 7·0. $C_{22}H_{25}NO_6S,H_2O$ requires C, 58·8; H, 6·1; N, 3·1; S, 7·1%).

[18] X. A. Dominguez, I. C. Lopez, and R. Franco, *J. Org. Chem.*, 1961, **26**, 1625.

[19] R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 1963, 5288.

[20] D. H. Buss, L. Hough, and A. C. Richardson, *J. Chem. Soc.*, 1963, 5295.

From the band at R_F 0·33, a solid was isolated which gave *methyl* 4,6-O-*benzylidene*-2,3-*dideoxy*-2-p-*methoxybenzamido*-3-*thiocyanato*-α-D-*altroside* (3c) (55%), m.p. 219—220° (*decomp.*) (from methanol–water), $[\alpha]_D^{23}$ +83·5° (*c* 0·85) (Found: C, 60·3; H, 5·1; N, 6·1. $C_{23}H_{27}N_2O_6S$ requires C, 60·5; H, 5·3; N, 6·1%).

From the band at R_F 0·6, a solid was isolated which gave starting material (15%), m.p. 185—186° (from ethanol).

(ii) The reaction was repeated under the same conditions as in (i); the thiocyanato-compound (3c) was again the only product for the first 2 hr., after which the mercapto-compound (5) started to appear. Further refluxing showed the gradual increase of (5) with the concomitant decrease of (3c); after 12 hr., (5) was the only product.

Methyl 4,6-O-*Benzylidene*-2,3-*dideoxy*-2,3-(2,4-*dinitrophenylepimino*)-α-D-*mannoside*.—The epiminomannoside (1 g.) in DMF (10 ml.) was vigorously stirred with 2,4-dinitrofluorobenzene (0·8 g.) and sodium hydrogen carbonate (2 g.) for 20 hr. at room temperature. The product was poured on crushed ice and sodium chloride (5 g.) was added; the yellow solid produced was filtered off, washed well with water, and dried. Recrystallisation from propan-2-ol gave the *title compound* (90%), m.p. 179—180°, $[\alpha]_D^{23}$ +13·3° (*c* 0·9) (Found: C, 56·0; H, 4·2; N, 9·5. $C_{20}H_{19}N_3O_8$ requires C, 55·9; H, 4·5; N, 9·8%).

Attempted Hydrolysis with Alkaline Resin.—*N*-(2,4-Dinitrophenyl)epiminomannoside (or -alloside [3]) (200 mg.) was dissolved in acetone–water (2 : 1 v/v; 10 ml.) and Amberlite IRA-400 (OH) resin (9 g.) was added; the mixture was shaken for 4 days at room temperature. Evaporation of the filtrate to dryness, during which an ester smell was detected, gave no recognisable products.

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