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# NEW ROUTE TO HIGHER SUGARS

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**Abstract**—A novel general route to higher aldoses is proposed involving transformation of the starting monosaccharide to *trans*-2,3-dehydro-2,3-dideoxyaldonic acid, or to its ester, by Knoevenagel-Doebner condensation or Wittig reaction, followed by double bond hydroxylation to give higher aldonic acids. The acids obtained are reduced to the corresponding aldoses by conventional methods.

ALTHOUGH higher sugars[1-2] are of considerable interest for biochemical investigations, the compounds are difficult to obtain from natural sources—only three bacterial[3-5] and one plant[6] aldoheptose having been isolated up to the date. The existing synthetic routes to higher aldoses depend on elongation of the carbon chain by one carbon atom at a time. Hence, even the most effective, like Kiliani–E. Fisher[7] or Sowden–H. Fisher[8] methods are tedious if the carbon chain is to be elongated by several atoms.

The new route to higher aldoses involves addition of a two carbon atom unit to the sugar chain. The method is based on transformation of the starting monosaccharide to the *trans*-2,3-dehydro-2,3-dideoxyaldonic acid or to its ester, followed by hydroxylation to a higher aldonic acid, which is subsequently reduced to the higher aldose according to the standard procedure.[9]


R = monosaccharide residue; R′ = H or $C_2H_5$

*The synthesis of* trans-2,3-*dehydro*-2,3-*dideoxy-aldonic acids*

The unsaturated aldonic acids may be regarded as key intermediates. After several synthetic attempts, the new methods based on the Knoevenagel-Doebner condensation or the Wittig reaction make them now readily available.

*Knoevenagel–Doebner condensation.* The initial modification of the route to *trans*-2,3-dehydro-2,3-dideoxyaldonic acids involves condensation of alkylidene derivatives of monosaccharides (al-form) with malonic acid under the conditions of Knoevenagel–Doebner; the synthesis was accomplished with several monosaccharides[10,11] and resulted in 60–70% yields of unsaturated aldonic acids. The corresponding data

[1] J. M. Webber, *Adv. Carbohydrate Chem.* **17**, 15 (1962).
[2] D. A. L. Davies, *Adv. Carbohydrate Chem.* **15**, 271 (1960).
[3] M. V. Slein and G. W. Schnell, *Proc. Soc. Exptl. Biol.* **82**, 734 (1953).
[4] W. Weidel, *Z. Physiol. Chem.* **299**, 253 (1955).
[5] A. P. MacLennan and D. A. L. Davies, *Biochem. J.* **66**, 562 (1957).
[6] H. H. Sephton and N. K. Richtmyer, *J. Org. Chem.* **28**, 1691 (1963).
[7] C. S. Hudson, *Adv. Carbohydrate Chem.* **1**, 1 (1945).
[8] J. C. Sowden, *Adv. Carbohydrate Chem.* **6**, 291 (1951).
[9] N. K. Kochetkov and B. A. Dmitriev, *Chem. and Ind.* 2147 (1962).
[10] N. K. Kochetkov and B. A. Dmitriev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 1262 (1962).
[11] N. K. Kochetkov and B. A. Dmitriev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* in press.

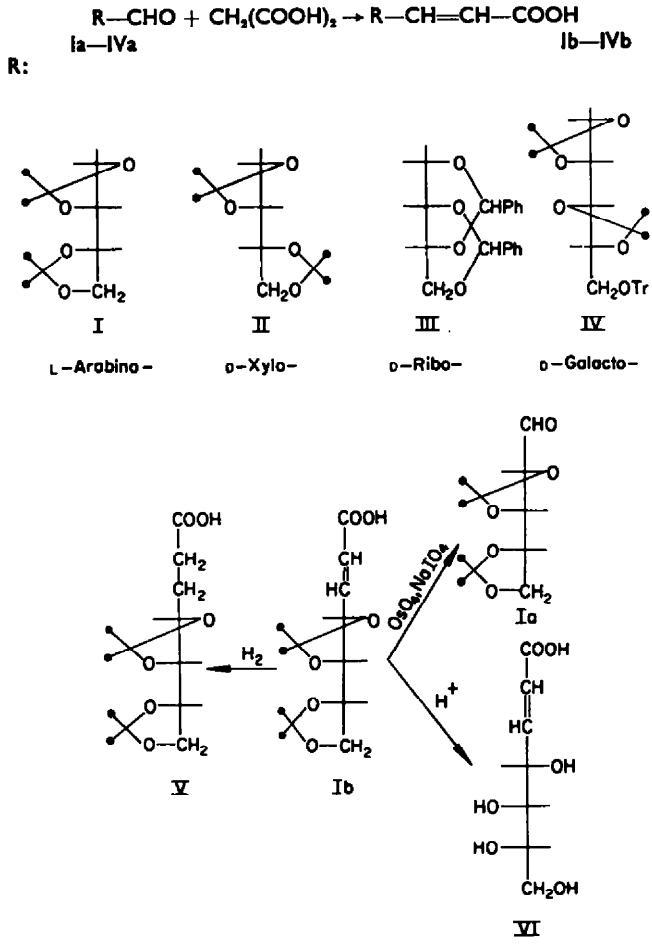



TABLE 1. ALKYLIDENE DERIVATIVES OF *trans*-2,3-DEHYDRO-2,3-DIDEOXY-ALDONIC ACIDS, Ib–IVb (DRY PYRIDINE, 1% PIPERDINE, 100°, 0·5–1 HR)

| Monosaccharide residue; brutto-formula | Yield % | M.p. | $[\alpha]_D$ (*c*, solvent, temp) | Analyses Found | Analyses (required) |
|---|---|---|---|---|---|
| | | | | C% | H% |
| 4,5;6,7-Di-O-isopropylidene-L-arabino-$C_{12}H_{20}O_6$ | 63·5 | 128–(from heptane) | −8·95° (2·01,MeOH,24) | 57·40<br>57·30<br>(57·34) | 7·50<br>7·48<br>(7·40) |
| 4,5;6,7-Di-O-isopropylidene-D-xylo-$C_{12}H_{20}O_6$ | 65 | syrup | — | — | — |
| 4,6;5,7-Di-O-benzylidene-D-ribo-$C_{21}H_{20}O_6$ | 75 | 220 (from ethanol) | −111·4° (1·61, dioxane, 20) | 68·65<br>68·46<br>(68·47) | 5·54<br>5·48<br>(5·47) |
| 4·5;6·7-Di-O-isopropylidene-8-O-trityl-D-galacto-$C_{32}H_{36}O_7$ | 70 | 149–151 (from heptane) | −11·1° (0·76, benzene, 18) | 73·18<br>73·03<br>(72·78) | 6·97<br>6·76<br>(6·66) |

are given in Table 1. The structure of the compounds obtained was proved chemically using the acid with L-arabino-configuration (Ib).[10]

The acid (Ib) is monocarboxylic as revealed by potentiometric titration data, and in accord with the mol. wt. The IR spectrum contains carboxyl (1729, 2650 $cm^{-1}$) and conjugated trans-double bond (988, 1667 $cm^{-1}$) bands. Compound Ib consumes one mole of hydrogen in the presence of Pd–$BaSO_4$ to give the dideoxy acid (V). The position of the double bond was confirmed by periodate oxidation in the presence of osmium tetraoxide and resulted in the starting al-form (Ia).

TABLE 2. *trans*-2,3-DEHYDRO-2,3-DIDEOXY-ALDONIC ACIDS (VI–VIII) (50% $CH_3COOH$, 100°, 30 MIN)

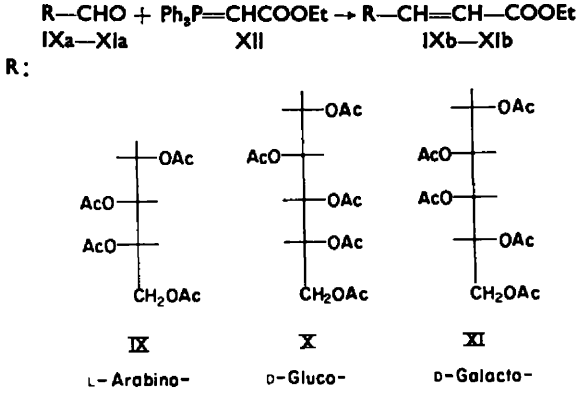
| Configuration | Brutto-formula | M.p. (from ethanol) $R_f$ (system) | $[\alpha]_D^{20}$ ($c$, water) | Analyses Found C% | (required) H% |
|---|---|---|---|---|---|
| L-Arabino-(VI) | $C_7H_{12}O_6$ | 175<br>0·31 (E) | −18·3°<br>(0·87) | 43·72<br>43·61<br>(43·75) | 6·25<br>6·39<br>(6·29) |
| D-Xylo-*(VII) | $C_7H_{12}O_6$ | Amorf.<br>0·31 (E) | −15·8°<br>(1·01, pyridine) | 43·64<br>43·52<br>(43·75) | 6·41<br>6·39<br>(6·29) |
| D-Galacto-(VIII) | $C_8H_{14}O_7$ | 203–205<br>0·40 (H) | −19·4°<br>(0·98) | 43·13<br>(43·24) | 6·57<br>(6·35) |

* The acid VII was isolated from the hydrolysate of IIb by adsorbtion on Dowex I × 8 ($CH_3COO^-$) and subsequent elution with acetic acid.

The unsaturated acids (Ib–IVb) when heated in 50% acetic acid readily split off the alkylidene group to give the corresponding unprotected acids.[10,11]

This route to unsaturated aldonic acids is limited to the availability of the starting alkylidene derivatives of al-form of hexoses.

*Wittig reaction.* Although the reaction with 2,3-O-isopropylidene-D-glyceric aldehyde[12] is known, the Wittig reaction has hitherto not been applied to carbohydrates but after elaborating several modifications of unsaturated aldonic acids synthesis,[13,14] these intermediates are now readily available.




[12] R. Kuhn and R. Brossmer, *Angew. Chem.* **14**, 252 (1952).
[13] N. K. Kochetkov and B. A. Dmitriev, *Chem. and Ind.* 864 (1963).
[14] N. K. Kochetkov and B. A. Dmitriev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* in press.

The al-form acetates of monosaccharides particularly, L-arabinose (IXa), D-glucose (Xa) and D-galactose (XIa) acetates, react smoothly with carboethoxymethylenetriphenylphosphorane (XII) to give ca. 80% yields of unsaturated ethyl aldonates (IXb–XIb; Table 3). The structure of the compounds was confirmed by their IR spectra.

This novel approach to unsaturated aldonates can be applied to any unprotected monosaccharide as starting compounds, the need for protected al-forms having been overcome.[15]

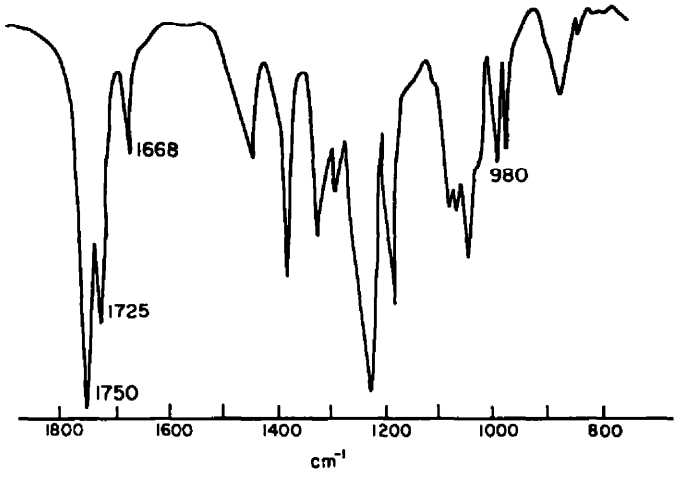



FIG. 1. IR-spectrum of ethyl *trans*-2,3-dehydro-2,3-dideoxy-4,5,6,7-tetra-O-acetyl-L-arabinoheptonate IXb (KBr disk). The spectra of Xb and XIb are similar to that of IXb.

TABLE 3. FULL ACETATES OF ETHYL *trans*-2,3-DEHYDRO-2,3-DIDEOXYALDONATES, IXb–XIb

| Monosaccharide residue, brutto formula | Yield % | M.p. (from ethanol), $R_f$ | $[\alpha]_D^{20}$ ($c$, $CHCl_3$) | Analyses Found (required) C% | H% |
|---|---|---|---|---|---|
| 4,5,6,7-Tetra-O-acetyl-L-arabino-$C_{17}H_{24}O_{10}$ | 75 | 83–84<br>0·7 ($SiO_2$) | −35·9°<br>(5·8) | 52·71<br>52·75<br>(52·57) | 6·17<br>6·21<br>(6·23) |
| 4,5,6,7,8-Penta-O-acetyl-D-gluco-$C_{20}H_{28}O_{12}$ | 84 | 127–129<br>0·67 ($SiO_2$) | +19·1°<br>(4·5) | 52·38<br>52·38<br>(52·17) | 6·16<br>6·17<br>(6·13) |
| 4,5,6,7,8-Penta-acetyl-D-galacto-$C_{20}H_{28}O_{12}$ | 77·5 | 161<br>0·65 ($SiO_2$) | +11·25°<br>(4·27) | 52·26<br>51·98<br>(52·17) | 6·00<br>6·13<br>(6·13) |

The unprotected monosaccharides (D-arabinose, D-ribose, D-glucose, D-galactose, D-glycero-D-guloheptose) give good yields of the corresponding unsaturated ethyl aldonates (Table 4).

[15] N. K. Kochetkov and B. A. Dmitriev, *Dokl. Akad. Nauk SSSR* **151**, 106 (1963).

$$R{-}CHO + Ph_3P{=}CHCOOEt \rightarrow R\text{-}CH{=}CH{-}COOEt$$
XII

R:

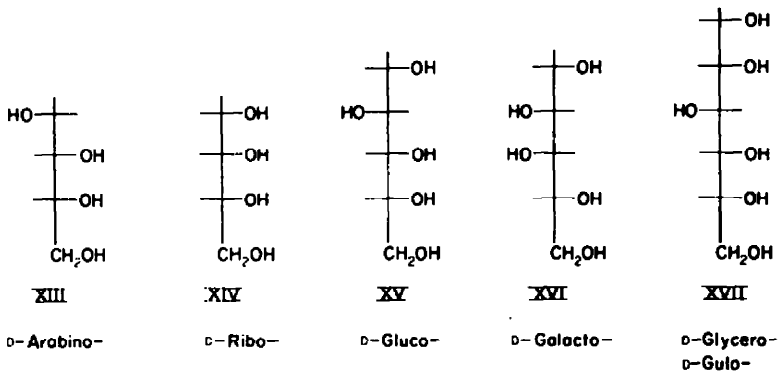
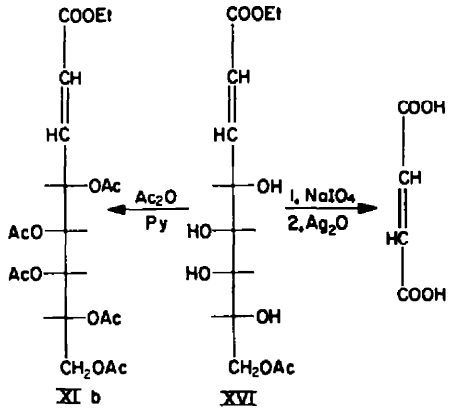



TABLE 4. ETHYL *trans*-2,3-DEHYDRO-2,3-DIDEOXY-ALDONATES, XIII–XVII (90°, DIMETHYLFORMAMIDE, 3–4 HR)

| Configuration. Brutto-formula | Yield % | $R_f$ (E) | M.p. (solvent) | $[\alpha]_D^{20}$ | Analyses Found (required) C% | H% |
|---|---|---|---|---|---|---|
| D-Arabino- $C_9H_{16}O_6$ | 60·5 | 0·52 | 133–135 $CH_3COOC_2H_5$ | +14·45° (2·97, water) | 48·90 48·95 (49·09) | 7·25 7·37 (7·32) |
| D-Ribo- $C_9H_{16}O_6$ | 45·5 | 0·67 | 61–64 $CH_3COOC_2H_5$ | −21·0° (4·3, $CH_3COOH$) | 48·91 48·95 (49·09) | 7·34 7·35 (7·32) |
| D-Gluco- $C_{10}H_{18}O_7$ | 46·5 | 0·59 | 115–116 $CH_3COOC_2H_5$- $CH_3OH$; 4:1 | −11·6° (4·64, $CH_3COOH$) | 47·98 48·01 (47·99) | 7·28 7·28 (7·25) |
| D-Galacto- $C_{10}H_{18}O_7$ | 43 | 0·62 | 158–159 EtOAc–alc. | −12·6° (4·11, water) | 48·17; 47·90 (47·99) | 7·30; 7·30 (7·25) |
| D-Glycero- D-gulo- $C_{11}H_{20}O_8$ | 31·5 | 0·51 | 108–110 MeOH–EtOAc | −24·5° (2·65, AcOH) | 47·07; 47·32 (47·12) | 7·31; 7·06 (7·19) |

The structure of the unsaturated esters was proved via the reactions of ethyl *trans*-2,3-dehydro-2,3-dideoxy-D-galactooctonate (XVI).[11]

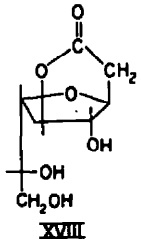
The product of acetylation of XVI is identical with the acetate (XIb) obtained previously from the al-form of acetate (XIa). It appears, that the Wittig reaction with unprotected monosaccharides always results in considerable amounts of carbohydrate by-products having no double bonds. From the reaction with D-galactose, this by-product was isolated in a crystalline form. The IR spectrum (1734, 3300 $cm^{-1}$), analysis for labile hydrogen (three hydroxyls) and lead tetraacetate oxidation suggest




XI b XVI

structure XVIII[14] for this compound. Apparently other monosaccharides form analogous by-products, also having a five- or six-membered anhydrocycle, and, if stereochemically possible, a five- or six-membered lactone cycle.

In order to eliminate the formation of by-products, the cyclic sugar acetates with open glycosidic centres can be used as starting compounds. The acetyl group protecting the hydroxyl at $C_4$ prevents intramolecular cyclisation, and, formation of the




XVIII

by-products. Thus the condensation of α,D-galactose tetraacetate[16] with phosphorane (XII) gives after additional acetylation XIb identical with the unsaturated acetate obtained by the Wittig reaction from al-D-galactose penta-O-acetate.

As three methods have now become available for the synthesis of unsaturated aldonic acids, this class of compounds must gain more general importance in carbohydrate synthetic chemistry.

*The synthesis of higher aldonic acids*

The *trans*-2,3-dehydro-2,3-dideoxyaldonic acids (or esters) may be transformed to the corresponding higher aldonic acids by double bond hydroxylation. Investigation of *cis*-hydroxylation with osmium tetraoxide in the presence of a number of oxidants reveals that the most effective oxidant for alkylidene unsaturated aldonic acid hydroxylation is iodic acid; the reaction proceeding very readily and resulting also in removal of the protective groupings.[17]

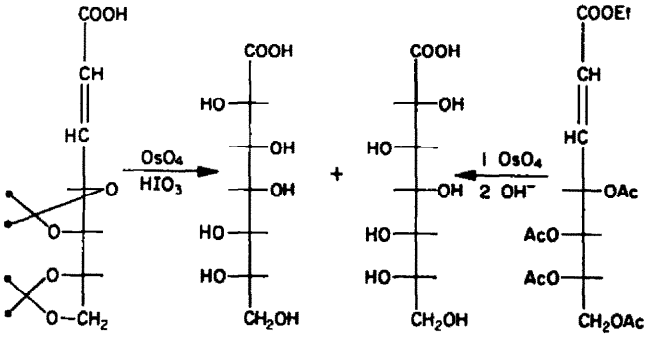
For the hydroxylation of acetylated esters[14] and free unsaturated acids,[11] the use

[16] B. Helferich and R. Steinpreis, *Chem. Ber.* **91**, 1794 (1958).

[17] N. K. Kochetkov and B. A. Dmitriev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 669 (1964).

of potassium chlorate and acetic acid is recommended while for the unsaturated esters, obtained by the Wittig reaction from unprotected monosaccharides, chloric acid is preferred. The use of the latter as oxidant for regenerating $OsO_4$ during double bond hydroxylation is most convenient.

In all cases, the hydroxylation is partly stereospecific, this specifity being due to the polyhdyroxylic residue. For example, hydroxylation of acid (Ib) with iodic acid as oxidant results in L-glycero-L-galacto-(XIX) and L-glycero-L-idoheptonic (XXI) acids in a ratio of 55:30.




I b XIX XXI IX b

(ethyl ester XX) (γ-lactone XXII)

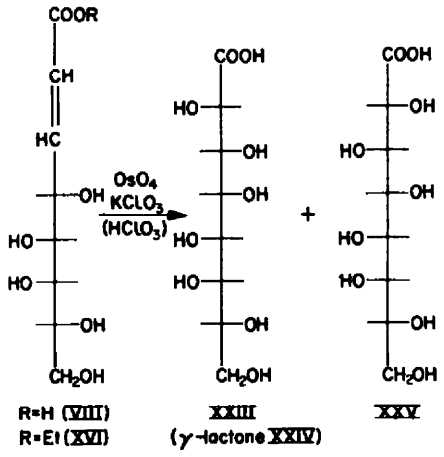
The isomeric acids may be separated as cadmium salts: cadmium L-glycero-L-galactoheptonate is practically insoluble in water,[18] whereas the readily soluble cadmium aldonates, having the ido-configuration, form crystalline double salts with cadmium bromide.[19] Hydroxylation of the unsaturated acid (Ib) proceeds smoothly and the transformation of the alkylidene derivatives, obtained by the Knoevenagel–Doebner condensation can be effected without difficulty to yield both possible isomers. For hydroxylation of ethyl *trans*-2,3-dehydro-2,3-dideoxy-4,5,6,7-tetra-O-acetyl-L-arabino-heptonate (IXb) a $KClO_3$–$CH_3COOH$ mixture was used. The modification using iodic acid is less convenient as the isolation of the reaction product is complicated by the presence of free iodine and strong mineral acid. After removing inorganic salts, the product is saponified by alkali and the L-glycero-L-galacto-isomer (XIX) isolated from the mixture of heptonic acids as the insoluble cadmium salt in a 45% yield. As the hydroxylation of the ester (IXb) was performed in order to prove the structure of the products of the Wittig reaction with al-forms of monosaccharides, the second isomer was not isolated in a pure state.

Hydroxylation of the unsaturated octonic acid (VIII) having the D-galacto-configuration or its ethyl ester (XVI) results in the formation of the D-threo-L-galacto-isomer (XXIII) as major product of the reaction.

The hydroxylation conditions for the acid (VIII) were such that the acid (XXIII) with the D-threo-L-galacto-configuration crystallises from the reaction mixture, hence

[18] W. St. Smith, *Liebig's Ann.* **272**, 182 (1892).

[19] J. W. Pratt, N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.* **75**, 4503 (1953).




it is known, that the compound is only sparingly soluble in water.[20] Hydroxylation in the presence of iodic acid is inconvenient, as the presence of mineral acids causes lactonisation of the octonic acids obtained, thus complicating their isolation. For this reason, potassium chlorate in the presence of acetic acid is used. With this reagent the acid (XXIII) precipitates from the reaction mixture (yield 57%). The D-threo-L-ido-isomer (XXV) remaining in the mother liquor may be isolated in a 26% yield and characterised as a crystalline double salt with cadmium bromide.

Hydroxylation of the ethyl ester (XVI) in aqueous ethanol in the presence of chloric acid proceeds readily, and the D-threo-L-galacto-isomer precipitates from the reaction mixture. However, the product obtained appeared chromatographically unhomogenous and contains $\gamma$-lactone (1770 $cm^{-1}$) and ester (1728 $cm^{-1}$) bands in the IR spectrum. For separation of the isomeric acids (XXIII and XXV), the mixture after hydroxylation is treated, after demineralisation, with $Cd(OH)_2$ to precipitate the cadmium salt of XXIII, and the mother liquor treated with $CdBr_2$ to precipitate the isomer (XXV). As in the case of the acid (VIII), the hydroxylation of the ester (XVI) results in a marked predominance of the D-threo-L-galacto-isomer.

*The preparation of higher aldoses*

Aldonic acids are usually reduced to the corresponding aldoses as their esters or lactones. The reduction is effected with 2·5% sodium amalgam[21] or sodium borohydride[22] under carefully controlled conditions at pH 3–3·5, maintained by continuous addition of acid or by buffering the solution.[23] Both procedures are inconvenient, in the first, it is necessary to use special equipment whereas in the second, the isolation of the reaction product is complicated by the presence of a large excess of inorganic material. A new procedure,[24,25] uses a 10-fold excess of strong cation exchanger in the $H^+$-form (KU-2, Amberlite IR-120). This simple method enables effective control of pH during reduction with sodium amalgam or complex hydrides.

[20] V. D. MacKlay, R. M. Hann and C. S. Hudson, *J. Amer. Chem. Soc.* **60**, 1035 (1938).
[21] N. Sperber, H. E. Zaugg and W. M. Sandstrom, *J. Amer. Chem. Soc.* **69**, 915 (1947).
[22] M. L. Wolfrom and H. B. Wood, *J. Amer. Chem. Soc.* **73**, 2933 (1951).
[23] H. S. Isbell, U.S.P. 2632005 (1953); *Chem. Abstr.* **48**, 1434 (1954).
[24] B. A. Dmitriev and N. K. Kochetkov, *Avt. Svid.* 161720 (1964).
[25] N. K. Kochetkov and B. A. Dmitriev, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* in press.

The ester (XX) and lactones (XXII and XXIV) are thus reduced to, L-glycero-L-galacto-heptose (XXVI; the antipod of this sugar recently isolated from gram-negative bacteria[5]), L-glycero-L-idoheptose (XXVII) and D-threo-L-galactooctose (XXVIII; Table 5) respectively.

TABLE 5. REDUCTION OF ALDONIC ACID LACTONES AND ESTERS TO ALDOSES (pH 3–3·5; 5°)

| Starting compound | Aldose | Yield % | $[\alpha]_D$ (*c*, water), $R_f$ | Derivative |
|---|---|---|---|---|
| Ester XX | L-glycero-L-galactoheptose XXVI | 95 | −68·0° (1·2, equil.), 0·13 (E), 0·2 (F) | phenylhydrazone, m.p. 196°; phenylosazone, m.p. 200° |
| Lactone XXII | L-glycero-L-idoheptose XXVII | 95 | +2·2° (5·0, equil.), 0·25 (E) | dibenzyldithioacetale, m.p. 130 |
| Lactone XXIV | D-threo-L galactooctose XXVIII | 55 | −56·2° (0·81, equil.), 0·3 (H) | dibenzyldithioacetale, m.p. 206–207° |

## EXPERIMENTAL

Thin layer chromatography was performed on non-fixed alumina (IV) according to the published procedure;[26] solvent systems: benzene–light petroleum 1:1 (A); benzene (B); $CHCl_3$ (C); $CHCl_3$–MeOH 95:5 (D). Thin-layer chromatography on silicagel G was performed in system D. Alumina of III activity was used for preparative scale column chromatography. Paper chromatography was performed in the Leningrad factory "Goznak" paper by ascending technique in n-butanol–acetic acid–water 4:1:2 (E), n-butanol–ethanol–water 40:12:18 (F), water–water saturated n-butanol (G) n-propanol–acetic acid–water 4:1:2 (H). The same solvent systems were used for cellulose column chromatography. Reducing sugars were detected on chromatograms by *p*-anisidine–$H_3PO_4$; polyhydroxylic compounds by potassium periodate–cuprate;[27] acids by alcoholic solution of bromophenol-blue; lactones and esters by methanolic solution of $NH_2OH$ followed by $FeCl_3$–HCl;[28] unsaturated compounds by neutral solution of $KMnO_4$.

2,3:4,5-*Di*-O-*isopropylidene*-D-*xylose diethyldithioacetale* (XXIX)

D-Xylose diethyldithioacetale[29] (10 g) was added to a cooled (—5°) solution of 1,5 ml $H_2SO_4$ in 100 ml acetone and kept at room temp overnight; the solution was then neutralised with conc. $NH_4OH$, the inorganic precipitate removed by filtration and the solution evaporated to dryness. The syrupy residue was dissolved in hexane–benzene and chromatographed on 300 g $Al_2O_3$ in hexane–benzene with increasing concentration of the latter from 0 to 100% to give XXIX as a colourless syrup (9, 6 g, 73%), b.p. 100–105°/$10^{-3}$ mm Hg (in bath), $[\alpha]_D^{25}$ −51·25° (*c* 2·99, benzene), $n_D^{18}$ 1·4960, $R_f$ 0·8 ($Al_2O_3$, B). (Found: C, 53·4; 53·9; H, 8·2; 8·2; S, 18·9; 19·0; $C_{15}H_{28}O_4S_2$ requires: C, 53·55; H, 8·38; S, 19·07%).

2,3:4,5-*Di*-O-*isopropylidene*-6-O-*trityl*-D-*galactose diethyldithioacetale* (XXX)

D-Galactose diethyldithioacetale[30] (10 g) was treated as above to give an isopropylidene derivative. The crude product (12 g) was treated with a solution of 8·35 g triphenylchlormethane in 50 ml dry pyridine for 35 min at 100°. After evaporation of the mixture, the crystalline residue was washed with alcohol (75 ml) and recrystallised from alcohol to give XXX (10·5 g, 53%), m.p. 117°,

[26] N. K. Kochetkov, B. A. Dmitriev and A. L. Usov, *Dokl. Akad. Nauk SSSR* **143**, 863 (1961).
[27] T. G. Bonner, *Chem. and Ind.* 345 (1960).
[28] Abdel-Akher and M. F. Smith, *J. Amer. Chem. Soc.* **73**, 5859 (1951).
[29] E. Curtis and J. K. N. Jones, *Canad. J. Chem.* **38**, 1305 (1960).
[30] M. L. Wolfrom, *J. Amer. Chem. Soc.* **52**, 2464 (1930).

$[\alpha]_D^{20}$ −52·3° (*c* 2·2, benzene), $R_f$ 0·6 ($Al_2O_3$, A). (Found: C, 69·2; 69·1; H, 7·4; 7·4; S, 10·4; 10·4; $C_{25}H_{44}O_5S_2$ requires: C, 69·04; H, 7·28; S, 10·53%).

2,3;4,5-*Di*-O-*isopropylidene-al*-D-*xylose* (IIa)

To a solution of 3·36 g XXIX in 33 ml acetone, 3 ml water was added and then 5 g yellow HgO followed by 5 g $HgCl_2$ was introduced with vigorous stirring. The mixture was stirred for 3 hr at 55°, filtered and the solution evaporated. The residue was extracted with $CHCl_3$ (3 × 25 ml), the extract filtered and washed with 1N KI solution (2 × 25 ml), water, dried with $MgSO_4$ and evaporated *in vacuo* to give IIa (1·85 g, 80%), $[\alpha]_D^{23}$ −23° (*c*, 3·1, alcohol), $n_D^{17}$ 1·4546, $R_f$ 0·7 ($Al_2O_3$,D); oxime m.p. 89°. Bourne *et al.*[21] give for the L-isomer: $[\alpha]_D^{19}$ +25·6° (*c* 3·2, alcohol), $n_D^{16}$ 1·4545; oxime m.p. 90–91°.

2,3;4,5-*Di*-O-*isopropylidene*-6-O-*trityl-al*-D-*galactose* (IVa)

Compound XXX (18·35 g) was treated with HgO (18 g) and $HgCl_2$ (18 g) in acetone–water (385 ml) to give a syrupy IVa (15·6 g, near quantitative), $[\alpha]_D^{20}$ +19·5° (*c* 5·3, $CHCl_3$), $R_f$ 0·7 ($Al_2O_3$,D).

*Condensation of alkylidene derivatives of al-form of monoses* (Ia–IVa) *with malonic acid*

*Synthesis of unsaturated acids* (Ib–IVb). A solution of the alkylidene derivative (Ia–IVa; 0·04 moles) and malonic acid (0·045 moles) in dry pyridine in the presence of a few drops of piperidine was heated for 0·5 1 hr at 100°. The mixture was left overnight at room temp, then evaporated to dryness and the residue recrystallised from an appropriative solvent. The results of condensation and properties of the compounds obtained are listed in Table 1.

*Reactions of* trans-2,3-*dehydro*-2,3-*dideoxy*-4,5;6,7-*di*-O-*isopropylidene*-L-*arabinoheptonic acid* (Ib)

*Hydrogenation* of 300 mg Ib in 10 ml alcohol in the presence of 10% Pd–$BaSO_4$ was accomplished in 15 min at room temp and normal press. to give 300 mg dideoxy acid (V) as a syrup, $[\alpha]_D^{20}$ −25·65° (*c* 2·22, methanol), $n_D^{16}$ 1·4569; anilide[10] m.p. 100–101° (from water–ethanol 8:2), $[\alpha]_D^{23}$ −19·4° (*c* 1·03, alcohol). (Found: C, 65·2; 65·2; H, 7·9; 7·9; $C_{18}H_{27}NO_6$ requires: C, 65·31; H, 7·79%).

*Oxidative cleavage.* A catalytic amount of $OsO_4$ was added to the solution of 250 mg Ib in 5 ml 75% dioxane. After the appearance of a black colour the mixture was treated with 460 mg $NaIO_4$ with stirring. After 30 min, 10 ml water was added and the mixture extracted with $CHCl_3$ (3 × 10 ml); the extract washed with dil. $Na_2S_2O_3$aq, water, dried with $MgSO_4$ and evaporated to give Ia (200 mg, 95%), $R_f$ 0·6 ($Al_2O_3$,D); *p*-nitrophenylhydrazone m.p. 132° (from EtOH–water 2:3) identical with an authentic sample.

*Preparation of unsubstituted* trans-2,3-*dehydro*-2,3-*dideoxyaldonic acids* (VI–VIII)

The alkylidene derivatives of acids Ib, IIb and IVb were heated with 25–30 vol 50% acetic acid for 30 min on a boiling water bath. The solution was cooled, treated with charcoal, if necessary, filtered and evaporated to dryness. The results of the hydrolysis and properties of the acids obtained are listed in Table 2.

*Synthesis of acetates of al-form of monosaccharides* (IXa–XIa)

Compounds IXa–XIa were prepared in nearly quantitative yields by treatment of the corresponding diethyldithioacetales with $HgCl_2$–HgO in water–acetone as described for the synthesis of IIa and IVa: IXa, m.p. 111–113° (from acetone–ether–light petroleum 1:1:1), $R_f$ 0·6 ($Al_2O_3$,D); Wolfrom *et al.* give[22]: 113–115°; Xa, syrup, $R_f$ 0·5 ($SiO_2$,D); XIa, m.p. 119–120° (from acetone–ether–light petroleum 1:1:1), $R_f$ 0·35 ($SiO_2$,D); Wolfrom *et al.*[20] give: m.p. 120–121°.

*Condensation of acetates of al-form of monosaccharides* (Xa–XIa) *with carbethoxymethylenetriphenylphosphorane* (XII)

*Synthesis of acetates of* trans-2,3-*dehydro*-2,3-*dideoxyaldonic acid esters* (IXb–XIb). A solution of 0·01 mole IXa–XIa was refluxed with phosphorane (XII;[23] 0·011 mole) in 30 ml dry benzene for

[21] E. J. Bourne and G. P. McSweney, *J. Chem. Soc.* 3113 (1952).
[22] M. L. Wolfrom and M. R. Newlin, *J. Amer. Chem. Soc.* **52**, 3619 (1930).
[23] O. Isler *et al.*, *Helv. Chim. Acta* **40**, 1242 (1957).

1·5 hr. After evaporation to dryness, the residue was recrystallised from EtOH to give esters IVb–XIb. Additional portions of IXb–XIb were isolated from the mother liquors by column chromatography on $Al_2O_3$ in benzene–$CHCl_3$. The results of condensation are listed in Table 3.

*Condensation of unprotected monosaccharides with phosphorane* (XII)

*Synthesis of* trans-2,3-*dehydro*-2,3-*dideoxyaldonic acid esters* (XIII–XVII). A solution of the monosaccharide (0·05 moles) in dimethylformamide (40 ml) was heated with phosphorane (XII; 1·5–3 fold excess) for 4 hr at 90°. The solution was evaporated to dryness, the residue treated with water (50 ml), the precipitate filtered off, washed with water and the combined filtrate and washings extracted with $CHCl_3$ (3 × 25 ml), treated with charcoal and evaporated to dryness. The residue was chromatographed on a cellulose column in solvent system G (for ester XVII was used system F), the fractions containing unsaturated esters XIII–XVII were evaporated, the residue dissolved in water, treated with charcoal, evaporated and dried *in vacuo* over $P_2O_5$. The yields and properties of the esters synthesised are listed in Table 4.

*Reactions of ethyl* trans-2,3-*dehydro*-2,3-*dideoxy*-D-*galactooctonate* (XVI)

*Acetylation* of XVI with acetic anhydride–pyridine yielded the pentaacetate of XVI, m.p. 160° (from EtOH), $[\alpha]_D^{20}$ +11·5° (*c*, 4·2, $CHCl_3$), identical with an authentic sample.

*Oxidative cleavage.* A solution of XVI (100 mg) in water (5 ml) was treated with $NaIO_4$ (400 mg) for 2 hr, then KOHaq (280 mg in 10 ml water) and $Aq_2O$ (580 mg) were added. The mixture was stirred for 12 hr, the precipitate filtered off, the filtrate acidified with $H_2SO_4$ and extracted with ethyl acetate (3 × 5 ml). Evaporation of the extract gave 40 mg fumaric acid identical with an authentic sample.

2-*Deoxy*-3,6-*anhydro*-D-*glycero*-L-*glucooctono*-δ-*lactone* (XVIII)

A. The reaction mixture obtained from D-galactose with phosphorane (XII) was separated by cellulose column chromatography resulting in the unsaturated ester (XVI) and lactone (XVIII), the yield of the latter was 49·5%, m.p. 89–91° (from ethyl acetate–methanol, 4:1), $[\alpha]_D^{16}$ +28·3° (*c* 3·16), $CH_3COOH$), $R_f$ 0·4 (E); IR spectrum (in vaseline oil): 3300 $cm^{-1}$ (hydroxyl), 1734 $cm^{-1}$ (δ-lactone). (Found: C, 47·4; 47·3; H, 5·9; 5·9; $H_{act}$ 1·4; 1·5; $C_8H_{12}O_6$ requires: C, 47·26; H, 5·92; $H_{act}$ 1·48%).

B. The ester (XVI; 10 mg) in dimethylformamide (1 ml) was heated at 90° with phosphorane (XII; 10 mg) and triphenylphosphine oxide (10 mg) for 4 hr. Paper chromatographic examination of the reaction mixture in system E gave an intensive spot of lactone XVIII ($R_f$ 0·4) besides the starting material ($R_f$ 0·6).

*Oxidation of the lactone* (XVIII) *with lead tetraacetate*

In the oxidation of XVIII with lead tetraacetate,[24] 1 mole lactone consumed 1·12 moles oxidant during 9 hr; the formaldehyde formed was identified as the dimedone derivative identical with an authentic sample.

*Condensation of* 2,3,4,6-*tetra*-O-*acetyl*-α-D-*galactose*

Tetra-O-acetyl-α-D-galactose[16] (0·2 g) and phosphorane (XII; 0·2 g) in abs. benzene (4 ml) were refluxed for 9 hr. The reaction mixture was evaporated to dryness, the residue dissolved in 1 ml acetic anhydride, 1 ml pyridine was added and the mixture left overnight. After evaporation of the solution, 10 ml water was added and the crystalline precipitate filtered off, dried over $P_2O_5$ and recrystallised from alcohol. The ester obtained (0·22 g, 82%) was identical with an authentic sample (XIb).

*Hydroxylation of* trans-2,3-*dehydro*-2,3-*dideoxy*-4,5;6,7-*di*-O-*isopropylidene*-L-*arabinoheptonic acid* (Ib)

A solution of acid (Ib; 5·23 g) in n-propanol (35 ml) was treated with water (12·5 ml) and a catalytic amount of $OsO_4$. A solution of $HIO_3$ (3·38 g) in water (22·5 ml) was added to the reaction mixture after the formation of a black colour and then left overnight. Propanol and iodine were

[24] A. S. Perlin, *Methods in Carbohydrate Chemistry* Vol. I; p. 427. N.Y. and London (1962).

evaporated *in vacuo* with addition of water until the disappearance of colour, the solution was then diluted to 200 ml with water and passed through a column with 25 ml Amberite IRA-400 ($CH_3COO^-$). The elution was performed with increasing concentration of aqueous acetic acid in water (linear gradient, 3–30%, total volume 400 ml), fraction volume 13 ml. Combined fractions 1–10 were heated 1 hr on a boiling water bath and evaporated *in vacuo* to dryness, yielding 5 g of a mixture of heptonic acids (XIX and XXI) and their lactones. This mixture was dissolved in water (300 ml) and boiled with excess $Cd(OH)_2$ for 30 min. The hot solution was neutralized with gaseous $CO_2$ and quickly filtered. On cooling to the room temp, crystalline cadmium L-glycero-L-galactoheptonate (3 g; yield 55·5%) was obtained. The mother liquor was evaporated to dryness, the residue dissolved in 50 ml water, the solution filtered, evaporated *in vacuo* and the residue (2·5 g) dissolved in 30 ml water; 1·5 g $CdBr_2$ was added and the solution evaporated to dryness. The crystalline material was dissolved by heating in 60 ml water; 60 ml alcohol was added, the hot solution filtered and on cooling the filtrate, 2·37 g of a double salt of cadmium L-glycero-L-idoheptonate with $CdBr_2$ was obtained in crystalline form, yield 29·5%.

*Hydroxylation of ethyl* trans-2,3-*dehydro*-2,3-*dideoxy*-4,5,6,7-*tetra*-O-*acetyl*-L-*arabinoheptonate* (IXb)

A solution of the ethyl ester (IXb; 1·9 g) in dioxame (25 ml) was treated with water (5 ml) and a catalytic amount of $OsO_4$. After the appearance of a black colour, 0·6 g $KClO_3$ in 7 ml water was added followed by the addition of 10 ml dioxane and 1 ml acetic acid. The mixture was left for 2 days at room temp, then evaporated to dryness *in vacuo* and the solid residue extracted with $CHCl_3$ (3 × 15 ml). The extract was washed with water, dried with $Na_2SO_4$ and evaporated yielding 2·3 g hydroxylation products. This residue was dissolved in 50 ml MeOH, 30 ml water was added and the hot solution treated slowly with a solution of 1·7 g KOH in 10 ml water. The mixture was refluxed for 5 min, cooled, 50 ml of water added and the MeOH evaporated. The aqueous solution obtained was passed through a column with Amberlite IR-120 ($H^+$) and after evaporation of the eluate 1·1 g heptonic acids (XIX and XXI) was obtained as a mixture, from which 0·62 g cadmium-L-glycero-L-galactoheptonate was isolated according to the procedure above, yield 45%.

*Hydroxylation of* trans-2,3-*dehydro*-2,3-*dideoxy*-D-*galactooctonic acid* (VIII)

A solution of VIII (1·34 g) was treated with a small amount of $OsO_4$ and after the appearance of a black colour, a solution of 0·73 g $KClO_3$ in 10 ml water and 1 ml acetic acid was added. The mixture was left 1 day at the room temp and then for 1 day in the refrigerator. The crystalline precipitate was filtered off, washed with 10 ml cold water, MeOH and dried yielding 700 mg of acid XXIII, m.p. 219–220° (dec, from water), $[\alpha]_D^{24}$ +6·1° (*c* 0·52, water). Mackley *et al.*[20] give: m.p. 221° (corr, dec, from water). The mother liquor was washed with $CHCl_3$ (2 × 25 ml) and passed through a column with Amberlite IRA-400($CH_3COO^-$). The column was washed with water until the eluate gave a neutral reaction and was then diluted with acetic acid solution with increasing concentration of $CH_3COOH$ from 5 to 30%, the fraction volume 13 ml. The first aqueous eluate was passed through a column with Amberlite IR-120 ($H^+$) and combined with fractions 2–20 and this solution was evaporated to dryness. The residue obtained was dissolved in 80 ml water, boiled with excess $Cd(OH)_2$ for 20 min, neutralised with gaseous $CO_2$, filtered and left to yield 210 mg crystalline cadmium D-threo-L-galactooctonate monohydrate. (Found: C, 30·2; 30·2; H, 5·1; 5·1; Cd, 17·6; 17·6; $C_{16}H_{30}O_{18}Cd \cdot H_2O$ requires: C, 29·98; H, 5·03; Cd, 17·54%). The overall yield of acid (XXIII) was 57%. The mother liquor after separation of insoluble cadmium salt was evaporated to dryness, the residue dissolved in 10 ml water, $CdBr_2$ (0·5 g) added and the solution evaporated and treated with 25 ml alcohol. The precipitate obtained was filtered off, washed with alcohol and dried over $P_2O_5$ *in vacuo*. The product (700 mg, 26%) was the monohydrate of a double salt of cadmium D-threo-L-idooctonate (acid XXV) with $CdBr_2$, $[\alpha]_D^{17}$ −5·8° (*c* 2·08, 0·2 N HCl). (Found: C, 21·2; 21·1; H, 3·5; 3·6; Cd, 24·1; 24·2; Br, 17·4; 17·5; $C_{16}H_{30}O_{18}Cd \cdot CdBr_2 \cdot H_2O$ requires: C, 21·04; H, 3·53; Cd, 24·62; Br, 17·50%).

*Hydroxylation of ethyl* trans-2,3-*dehydro*-2,3-*dideoxy*-D-*galactooctonate* (XVI)

To a solution of XVI (350 mg) in alcohol (10 ml), water (1 ml) and a small amount of $OsO_4$ were added. The black solution was treated with 8 ml $HClO_3$ solution [obtained by passing 200 mg $KClO_3$ through 1·6 ml cation exchanger KU-2 ($H^+$)]. The mixture was left overnight at room temp

and for 3 hr in a refrigerator, the precipitate obtained (100 mg) was a mixture of the ethyl ester of the acid (XXIII) and its lactone (XXIV). The remaining solution was passed through Amberlite IRA-400 ($CH_3COO^-$) and evaporated to dryness. On treatment of the residue with $Cd(OH)_2$, 70 mg of cadmium D-threo-L-galactooctonate was obtained (acid XXIII). From the mother liquor, 80 mg of a double salt of cadmium D-threo-L-idooctonate (acid XXV) with $CdBr_2$ were isolated, $[\alpha]_D^{17}$ −6° (*c* 3%, 0·2 N HCl).

*Ethyl* L-*glycero*-L-*galactoheptonate* (XX)

A hot solution of Cd salt of the acid (XIX; 2·8 g) in water (250 ml) was saturated with $H_2S$, cooled, shaken with some cellulose powder and filtered through a 2 cm thick cellulose powder layer. The filtrate was evaporated and dried over $P_2O_5$ *in vacuo*. This product (2·07 g) was refluxed with 60 ml 3% gaseous HCl in abs. EtOH for 9 hr and quickly filtered. The crystalline precipitate obtained on cooling was filtered off, washed with ether and dried. The yield of ester (XX) was 1·9 g (75%), m.p. 175° (from alcohol), $[\alpha]_D^{26}$ +18·3° (*c* 3·29, water), $R_f$ 0·36 (E); IR spectrum (in vaseline oil): 1720 $cm^{-1}$ (ester bond). (Found: C, 42·8; 42·8; H, 7·3; 7·1; $C_9H_{16}O_8$ requires: C, 42·52; H, 7·14%).

L-*Glycero*-L-*idoheptono*-γ-*lactone* (XXII)

The double salt of the acid (XXI; 1·8 g) was converted to acid and then to its lactone (XXII) by the method described for the D-isomer.[19] The yield of XXII was 0·84 g (94%), m.p. 150°, $[\alpha]_D^{20}$ +66·1° (*c* 0·2, water, equilibrium), $R_f$ 0·3 (F); IR spectrum: (KBr disk): 1773 $cm^{-1}$ (γ-lactone bond). Pratt *et al.*[19] reported for the D-isomer: m.p. 151–152°, $[\alpha]_D^{20}$ −67·2° (*c* 2, water).

D-*Threo*-L-*galactooctone*-γ-*lactone* (XXIV)

The acid (XXIII; 0·64 g) was transformed into its lactone, yield 0·45 g (78%), m.p. 219–220° (from glacial acetic acid), $[\alpha]_D^{23}$ +63° (*c* 0·8, water), $R_f$ 0·45 (H); IR spectrum (KBr disk): 1770 $cm^{-1}$ (γ-lactone bond). Macklay *et al.*[20] give: m.p. 219–220°, $[\alpha]_D^{20}$ +64·8° (*c* 0·8, water).

*Reduction of ester* (XX) *and of aldonic acid lactones* (XXII *and* XXIV) *to the corresponding aldoses*

A cold solution (5°) of lactone (0·02 mole) or ester in dil. $H_2SO_4$ (pH 3–3·5; 100 ml) was added to 150 ml Amberlite IR-120 ($H^+$) and this mixture was treated with 2·5% sodium amalgam (100 g) with vigorous stirring and cooling (5°). After the reaction was complete (ca. 1 hr), the mixture was decanted from mercury, the ion exchanger was filtered off and washed with 100 ml water. The filtrate after the neutralisation with $BaCO_3$ was evaporated. The results obtained are given in Table 5.