Tetrahedron Letters No.6, pp. 289-293, 1964. Pergamon Press Ltd.
Printed in Great Britain.

NEW SYNTHESIS OF GLYCOSIDES

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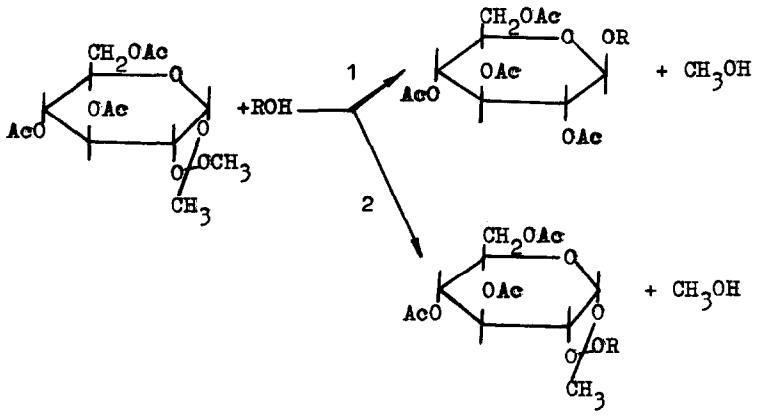
(Received 23 December 1963)

THE development of general methods for preparation of glycosides is one of the acute problems of carbohydrate synthetic chemistry. All of the now existing methods leading to glycosides with complex aglycones including oligosaccharides are based on the long known Koenigs-Knorr reaction /1,2/. The complicated nature of this reaction brings about low yields and difficulties during isolation. Numerous attempts to make the method more reliable were practically unsuccessful. Hence, it seemed advisible to look for principally novel approaches.

We have found acetylated monosaccharide 1,2-alkylorthoacetates to react with alcohols in the presence of catalytic amounts of $HgBr_2$ and toluenesulphonic acid (or sometimes in the absence of the latter) resulting in good yields of acetylated 1,2-trans-glycosides or of isomeric orthoesters, depending on the reaction conditions.



3,4,6-Tri-O-acetyl-1,2-O-(methylorthoacetyl)-α-D--glucopyranose (I) and cholesterol (II) when boiled in nitromethane in the presence of 0.001 moles $HgBr_2$ and 0.00075 moles p-toluenesulphonic acid per mole of (I) afforded 3,4,6-tri-O-acetyl-1,2-O-(cholesterylorthoacetyl)--α-D-glucopyranose (III), 26%, m.p.98-102° (dec.) (from methanol), $[\alpha]_D$-2° ± 2°(in $CHCl_3$) (Found: C 68.69, H 9.01; $C_{41}H_{64}O_{10}$ requires: C 68.86, H 9.00%) and 2,3,4,6-tetra-O-acetyl-β-cholesteryl-D-glucopyranoside (IV),15%, m.p.156-158° (from methanol), $[\alpha]_D$-27° ± 2°(in $CHCl_3$), no depression of m.p. on admixture with authentic sample (cf. /3/: m.p.157-159°, $[\alpha]_D$-25° in $CHCl_3$). The compounds were isolated from the reaction mixture by adsorption chromatography on neutral alumina (alumina of activity grade III by Brockman and gradient elution with CCl_4 ⟶ ⟶ $CHCl_3$ or C_6H_6 ⟶ $CHCl_3$ were used here and throughout).

The direction of this reaction was completely determined by the amount of $HgBr_2$ added and on the nature of the

solvent. We have succeeded in finding proper conditions to direct the reaction exclusively by pathway (1) or (2).

The use of dichloroethane and addition of minor amounts of $HgBr_2$ (0.001 moles) results in selective formation of orthoester. These conditions when applied to the reaction of I with II resulted in III, 18%, as the only reaction product.

On the other hand, the use of nitromethane and greater amounts of $HgBr_2$ (0.008-0.1 moles) lead to acetylated 1,2-trans-glycopyranosides. This can be examplified by the fact, that I or 3,4,6-tri-O-acetyl-1,2-O-(ethylorthoacetyl)--α-D-glucopyranose (V) when boiled in nitromethane with II in the presence of 0.008 moles $HgBr_2$ and 0.000 25 moles p-toluenesulphonic acid resulted in a 45% yield of IV as the only reaction product.

The now existing methods for preparation of acetylated monosaccharide alkylorthoacetates start with unstable 1,2--trans-acetylglycosyl halides. We have overcome this disadvantage by developing a new route to orthoesters starting with stable and readily available 1,2-cis-acetylglycosyl halides. The route is based on a modification of Koenigs-Knorr reaction, consisting of use of boiling ethyl acetate as solvent and $PbCO_3$-$CaSO_4$ mixture as hydrogen halide acceptor. Under these conditions, 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide afforded I (isolated by chromatography on alumina), 66%, $[\alpha]_D$ +34° ± 2° (in $CHCl_3$) (Found: C 49.86, H 6.14; $C_{15}H_{22}O_{10}$ requires: C 49.72, H 6.12%) (cf./4/: $[\alpha]_D$ +69°(in $CHCl_3$)) and V (isolated by crystallization from ethanol), 62%, m.p.94-96°, $[\alpha]_D$ +32°±

± 1.5° (in $CHCl_3$) (cf./5/: m.p.97-97.5°, $/\alpha/_D$+31° in $CHCl_3$). Chromatography of the reaction mixture after analogous treatment of 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide afforded 3,4,6-tri-O-acetyl-1,2-O-(ethylorthoacetyl)--α-D-galactopyranose (VI), 58%, syrup, $/\alpha/_D$+78°(in $CHCl_3$) (Found: C 50.88, H 6.42; $C_{16}H_{24}O_{10}$ requires: C 51.05, H 6.42%). Ready availability of the starting orthoesters and the selectivity of the reactions with alcohols enables to claim the route as a convenient method for preparation of 1,2-trans-glycosides.

The new route comprises considerable interest for preparation of disaccharides. Reaction of V with 1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (VII) in nitromethane in the presence of 0.05 moles $HgBr_2$ resulted in a 51% yield of 6-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (isolated by chromatography on alumina), m.p.140-142° (from ether-hexane), $/\alpha/_D$ -54.5° ± 2°(in $CHCl_3$) (Found: C 52.83, H 6.51; $C_{26}H_{38}O_{15}$ requires: C 52.89, H 6.48%) (cf./6/: m.p.141°, $/\alpha/_D$ -52.6° in $Cl_2CHCHCl_2$). Removal of the protective groupings by conventional methods resulted in 6-O-β-D-glucopyranosyl-D-galactose, $/\alpha/_D$+14.0° ± 1.5° (equilibrium, H_2O) (cf./7/: $/\alpha/_D$+13.9° in H_2O at equilibrium). By analogy, VI with VII produce 6-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-1,2:3,4-di-O-isopropylidene--α-D-galactopyranose, 64%, $/\alpha/_D$ -47° ± 2° (in $CHCl_3$) (cf. /6/: m.p.101-102°, $/\alpha/_D$-44.7° in $Cl_2CHCHCl_2$), which on hydrolysis gives rise to 6-O-β-D-galactopyranosyl-D-galactose (purified by partition chromatography), $/\alpha/_D$ +39 ±

± 1° (in H_2O at equilibrium) (Found: C 41.88, H 6.52; $C_{12}H_{22}O_{11}$ requires: C 42.13, H 6.48%) (cf./7/: $[\alpha]_D$ + 34.1° at equilibrium in H_2O).

The scope and the mechanism of the reported useful reaction are now under investigation.

REFERENCES

1. W.L.Evans, D.D.Reynolds, E.A.Talley, Adv.Carbohydr. Chem., 6 271 (1951).
2. R.U.Lemieux, Adv.Carbohydr.Chem., 9 1 (1954).
3. A.J.Khorlin, A.F.Bochkov, L.V.Bakinovsky, N.K.Kochetkov, Dokl.Akad.Nauk SSSR, 143 1119 (1962).
4. R.U.Lemieux, C.Brice, Can.J.Chem., 33 109 (1955).
5. R.U.Lemieux, T.D.Cipera, Can.J.Chem., 34 906 (1956).
6. K.Freudenberg, A.Noe, E.Knopf, Ber., 60, 238 (1927).
7. K.Freudenberg, A.Wolf, E.Knopf, S.Zaheer, Ber.,61 1743 (1928)