Journal of Medicinal and Pharmaceutical Chemistry

VOL. 2, No. 2 (1960)

Antituberculosis Agents—VI.[1] Streptidine-oxyethyl β-D-glucopyranoside

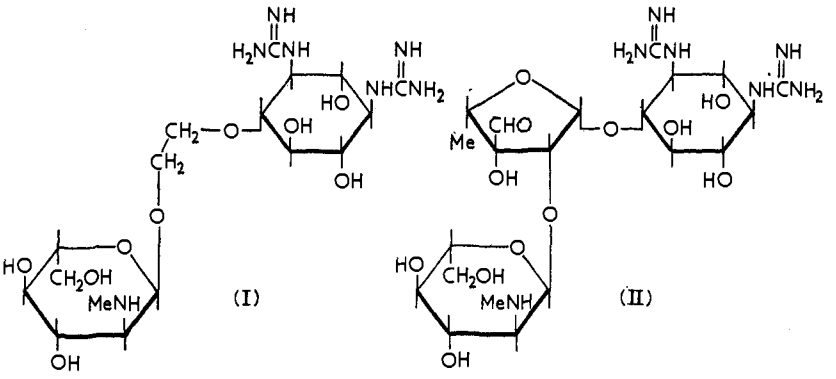
A. M. COMRIE, H. C. MITAL and J. B. STENLAKE, *The School of Pharmacy, The Royal College of Science and Technology, Glasgow*

In Part V[1] we described the preparation of a series of streptidine-, strepturea- and streptamine-β-glucosides and -β-glucosaminides. Concurrently with this work we also considered the preparation of other streptomycin analogues such as streptidine-oxyethyl-2-*N*-methylamino-2-deoxy-α-L-glucopyranoside (I), which bears a formal resemblance to streptomycin (II). We now report the synthesis of streptidine-oxyethyl β-D-glucopyranoside (III; R = H) which has been prepared as a model compound for these studies.

In preliminary experiments 2-chloroethyl-tetra-*O*-acetyl-β-D-glucopyranoside[2] and 2-bromoethyl-tetra-*O*-acetyl-β-D-glucopyranoside,[4] prepared from acetobromoglucose and the corresponding ethylenehalohydrin, failed to yield any condensed product in reactions with a model compound, cyclohexanol. This can be attributed to the lower reactivity of the alkyl halides compared with the halogen at the reducing carbon of *O*-acetylglycosyl halides.

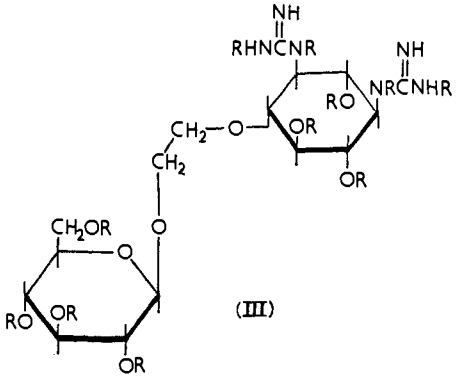
Attention was then turned to the use of the tosyloxy group, which is known to be replaceable in ether formation by methoxy[3] and benzylphenoxy[4] radicals using sodium hydride and other condensing agents. The required condensation can be approached in two ways, using the tosyl ester of either hepta-acetylstreptidine or 2-hydroxyethyl-tetra-*O*-acetyl-β-D-glucopyranoside as intermediate. The greater reactivity of primary alcohol tosylates compared with secondary alcohol tosylates[5, 6] in such condensations favoured the choice of the latter intermediate.

2-Hydroxyethyl-tetra-*O*-acetyl-β-D-glucopyranoside (IV; R = H), prepared from acetobromoglucose and ethylene glycol by the method of Fischer and Fischer,[7] was condensed with *p*-toluenesulphonyl chloride in dry pyridine at 0° to yield 2-toluene-*p*-sulphonyloxyethyl-tetra-*O*-acetyl-β-D-glucopyranoside (IV; R = Ts). Reaction of the product with hepta-acetylstreptidine

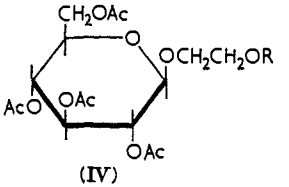


(I)

(II)



(III)



(IV)

dihydrobromide[1] in the presence of sodium hydride[4] was considered unworkable, as the alkaline conditions would favour deacetylation of the reactants and hence coupling at alternative positions of the streptidine nucleus. Similarly direct condensation of the reactants with excess of the alcohol as solvent[3] is only appropriate where this is a liquid at moderate temperatures. However, ether formation has been observed as a side reaction in the preparation of some sulphonic esters, such reactions being favoured under rather drastic or prolonged reaction conditions.[8] Likewise, intramolecular formation of a cyclic ether 3,6-anhydro-1,2-*O*-isopropylidene-5-*O*-tosyl-D-glucose has also been shown to occur when 1,2-*O*-isopropylidene-D-glucofuranose is treated with excess *p*-toluenesulphonyl chloride in boiling pyridine–chloroform for eight

hours, whereas reaction at 40° is normal and leads to the formation of 1,2-*O*-isopropylidene-3,5,6-tri-*O*-tosyl-D-glucofuranose.[9, 10] The required condensation was therefore attempted under similar conditions.

Reactions between hepta-acetylstreptidine dihydrobromide[1] and 2-toluene-*p*-sulphonyloxyethyl-tetra-*O*-acetyl-β-D-glucopyranoside were examined in *N*,*N*-dimethylformamide in the presence of Drierite to ensure freedom from moisture, and silver oxide to remove hydrogen bromide and neutralise the liberated *p*-toluenesulphonic acid. Removal of the latter is important to inhibit deacetylation[11] of the reactants and reaction products. After a series of pilot experiments, the reaction conducted at 95° for 8 h yielded undeca-acetylstreptidine-oxyethyl β-D-glucopyranoside (III; R = Ac), which on deacetylation with methanolic ammonia gave the required streptidine-oxyethyl β-D-glucopyranoside (III; R = H).

We are indebted to Glaxo Laboratories Ltd., for investigation of the tuberculostatic activity of streptidine-oxyethyl β-D-glucopyranoside against *Mycobacterium tuberculosis* (human strain 666) in Dubos liquid medium. The results recorded in Table I show it to be even less active than streptidine-β-D-glucopyranoside. This confirms the conclusion reached in Part V[1], that although the streptidine fragment of streptomycin is essential for activity, this is also dependent on the retention of the streptose moiety of the molecule.

Experimental*†

2-Hydroxyethyl tetra-O-*acetyl*-β-D-*glucopyranoside*, was prepared from acetobromoglucose by the method of Fischer and Fischer;[7] yield 46 per cent, m.p. 100–102°, $[\alpha]_D^{19} - 26°$ (*c*, 0·88 in $CHCl_3$). Fischer and Fischer give m.p. 101–103°, $[\alpha]_D^{16} - 26°$.

2-Toluene-p-*sulphonyloxyethyl tetra*-O-*acetyl*-β-D-*glucopyranoside*. 2-Hydroxyethyl tetra-*O*-acetyl-β-D-glucopyranoside (3·03 g, 0·0078 mole) was dissolved in dry pyridine (3 ml) and cooled in ice. A solution of dry toluene-*p*-sulphonyl chloride[12] (1·63 g, 0·0085 mole) in dry pyridine (3 ml) was added slowly, and the solution

* Analyses by Miss M. Buchanan, Mr. W. McCorkindale and Dr. A. C. Syme of this College and by Drs. Weiler and Strauss, Oxford.

† Melting points are uncorrected.

maintained at 0° for 2½ h. Ice-cooled water (60 drops) was stirred in over a period of 15 min followed by a further addition of cold water (50 ml). The precipitate was washed with cold water (2 × 20 ml), dried and crystallised from dry ether (200 ml) to yield colourless needles of *2-toluene*-p-*sulphonyloxyethyl tetra*-O-*acetyl*-β-D-*glucopyranoside*, (2·298 g, 54·5 per cent), m.p. 109–110°, $[\alpha]_D^{18}$ −13·1° (*c*, 2·0 in $CHCl_3$), max. 225 mμ (ε, 5950), 262 mμ (ε, 297·5) in ethanol.

Anal. Calcd. for $C_{23}H_{30}O_{13}S$: C, 50·5; H, 5·5; S, 5·9. Found: C, 50·4; H, 5·6; S, 5·4.

4-{1,3-Bis (diacetylguanidino)-2,5,6-tri-acetoxycyclohexyl}-oxyethyl tetra-O-*acetyl*-β-D-*glucopyranoside*, (*undeca-acetylstreptidine-oxyethyl* β-D-*glucopyranoside*). Hepta-acetylstreptidine dihydrobromide (2·185 g, 0·003 mole) was dissolved in *N*,*N*-dimethylformamide (10 ml) in a flask wrapped in black paper. The solution was kept *in vacuo* (0·2 mm) for 15 min. Drierite (3·01 g), and silver oxide (2·5 g), were added and the mixture stirred for 30 min. 2-Toluene-*p*-sulphonyloxyethyl tetra-*O*-acetyl-β-D-glucopyranoside (1·515 g, 0·0029 mole) was added in two portions with a 30-min interval. The mixture was stirred at 95° for 8 h. The solvent was evaporated leaving a viscous residue, which was triturated and extracted with dry ether (5 × 20 ml). The ether-insoluble residue was dissolved in absolute chloroform (5 × 10 ml), the solution treated with hydrogen sulphide, and filtered. The filtrate was concentrated *in vacuo* to *ca.* 10 ml and poured slowly into dry ether (100 ml). The tan-coloured precipitate was dissolved in acetone (100 ml), the solution filtered, decolourised with charcoal (0·3 g), and poured slowly into dry ether (100 ml), yielding 1·38 g of amorphous product, m.p. 168–171° (d., micro-block).

Anal. Calcd. for $C_{38}H_{54}N_6O_{21}$: N, 9·0. Found: 9·5.

Further purification by chromatography on Silene EF and Celite[13] (5:1) in various solvents, failed to improve the above constants; neither could crystallization be achieved, and the product was used without further treatment in the next experiment.

4-{1,3-Diguanidino-2,5,6-trihydroxycyclohexyl} oxyethyl β-D-*glucopyranoside*, (*streptidine-oxyethyl* β-D-*glucopyranoside.*) Undeca-acetylstreptidine-oxyethyl β-D-glucopyranoside (1·05 g) was

Table I. Inhibition of *M. tuberculosis* (human strain 666) in Dubos Liquid Medium after incubation at 37° for 14 days

	Concentration μg/ml											
	100	50	25	12·5	6·25	3·12	1·58	0·78	0·4	0·2	0·1	0·05
Streptomycin (II)	—	—	—	—	—	—	—	—	—	—	++	++
Streptidine-β-D-glucopyranoside[1]	—	—	+	++	++	++	++	++	++	++	++	++
Streptidine-oxyethyl β-D-glucopyranoside (III)	++	++	++	++	++	++	++	++	++	++	++	++

deacetylated with dry methanolic ammonia as described for the preparation of streptidine β-D-glucopyranoside,[1] to yield *streptidine-oxyethyl* β-D-*glucopyranoside* (0·41 g, 75 per cent), m.p. 160–162° (d.), $[\alpha]_D^{22} - 18°$ (*c*, 2·7 in water).

Anal. Calcd. for $C_{16}H_{32}N_6O_{10}.H_2O$: C, 39·5; H, 7·0; N, 17·3. Found: C, 39·8; H, 6·2; N, 16·4.

Dihydrochloride, m.p. 190–192° (d.).

Anal. Calcd. for $C_{16}H_{32}N_6O_{10}.2HCl$: N, 15·5. Found: N, 15·6.

Dihelianthate, m.p. 240–243° (d., micro-block).

Anal. Calcd. for $C_{44}H_{64}N_{12}O_{16}S_2.2H_2O$: C, 47·3; H, 6·1; N, 15·1; S, 5·7. Found: C, 46·6; H, 5·9; N, 15·5; S, 6·1.

Tuberculostatic Activity

The compounds were dissolved in water (1,000 μg/ml) the solutions diluted in Dubos liquid medium, and the dilutions innoculated with *M. tuberculosis* (human strain 666). The results recorded after 14 days incubation at 37° C, are shown in Table I.

Summary. Streptidine-oxyethyl β-D-glucopyranoside has been prepared and shown to be inactive against *M. tuberculosis* (human strain 666) in Dubos liquid medium at a concentration of 100 μg/ml. This confirms earlier conclusions that the streptose–aldehydic function is essential for activity in this series.

Acknowledgements. The bacteriological testing was carried out by Glaxo Laboratories Ltd., whom we wish to thank for a generous gift of streptomycin and dihydrostreptomycin, and also for a maintainance grant to one of us (H.C.M.).

(*Received 4 December, 1959*)

References

[1] Part V, Comrie, A. M., Mital, H. C. and Stenlake, J. B. This Journal, **2**, 153 (1960)

[2] Coles, H. W., Dodds, M. L. and Bergeim, F. H. *J. Amer. chem. Soc.*, **60**, 1020 (1938)

[3] Heyl, F. W., Herr, M. E. and Centrollella, A. P. *J. Amer. chem. Soc.*, **71**, 247 (1949)

[4] Wheatley, W. B., Fitzgibbon, W. E., Cheney, L. C., and Binkley, S. B. *J. Amer. chem. Soc.*, **72**, 1655 (1950)

[5] Tipson, R. S., Clapp, M. A., and Cretcher, L. H. *J. org. Chem.*, **12**, 133 (1947)
[6] Wiggins, L. F. and Wood, D. J. C. *J. chem. Soc.*, 1180 (1951)
[7] Fischer, E. and Fischer, H. *Ber. dtsch. chem. Ges.*, **43**, 2521 (1910)
[8] Ferns, J. and Lapworth, A. *J. chem. Soc.*, 273 (1912)
[9] Ohle, H. and Dickhäuser, E. *Ber. dtsch. chem. Ges.*, **58**, 2593 (1925)
[10] Ohle, H., Vargha, L. and Erlbach, H. *Ber. dtsch. chem. Ges.*, **61**, 1211 (1928)
[11] Freudenberg, K. *Liebigs Ann.*, **433**, 230 (1923)
[12] Tipson, R. S. *J. org. Chem.*, **9**, 235 (1944)
[13] Wolfrom, M. L., Cron, M. J., DeWalt, W. and Husband, R. M. *J. Amer. chem. Soc.*, **76**, 3675 (1954)