Tetrahedron Letters No.33, pp. 2849-2851, 1969. Pergamon Press. Printed in Great Britain.

# THE SYNTHESIS OF DERIVATIVES OF 4-AMINO-3-O-METHYL-2, 4, 6-TRIDEOXY-α-D-RIBO-HEXOPYRANOSE, A COMPONENT OF THE STEROIDAL ALKALOID HOLACURTIN.

J.Hildesheim, S.D.Géro, G.Khuong-Huu and C.Monneret.

Institut de Chimie des Substances Naturelles, C.N.R.S., 91-Gif-sur-Yvette, France.

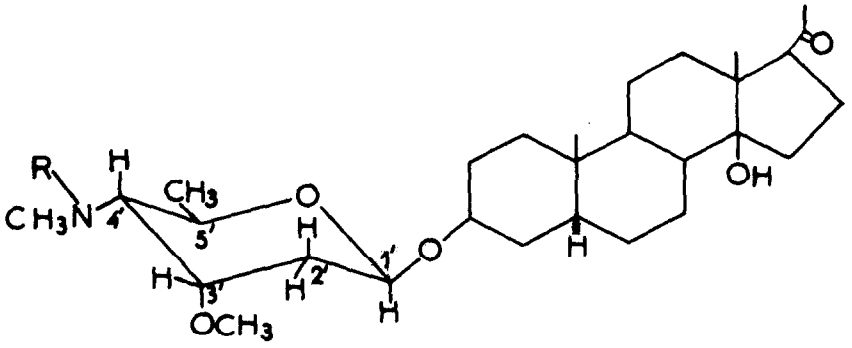
(Received in UK 2 June 1969; accepted for publication 16 June 1969)

Holacurtin[1], a glyco-steroidal alkaloid, has been shown to be 1 on the basis of chemical degradation, N.M.R. and mass spectral data. Methanolysis of its N-acetyl derivative 2 liberated a mixture of methyl glycosides 13 which were shown to be methyl 4-acetamido-4-methylamino-3-O-methyl-2, 4, 6-trideoxy-αβ-D-ribo-hexopyranoside 13. We report in this communication the synthesis of the α-anomer 10, which corroborates the structure and stereochemistry previously assigned to the carbohydrate component of holacurtin.

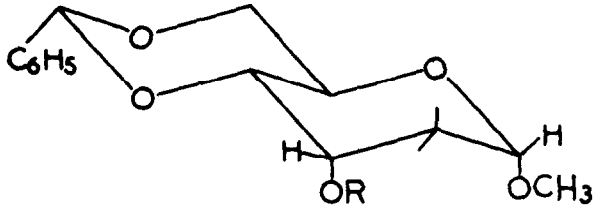
Methyl 4, 6-O-benzylidene-2-deoxy-α-D-ribo-hexopyranoside[2, 3] 3 was used as starting material for the synthesis of the carbohydrate component of the holacurtin. Compound 3 was obtained via a four step reaction sequence by standard procedures from methyl α-D-glucopyranoside. Treatment of 3 with dimethyl sulphate and sodium hydroxide in tetrahydrofuran gave methyl 4, 6-O-benzylidene-2-deoxy-3-O-methyl-α-D-ribo-hexopyranoside 4, m.p. 99-100°, $[\alpha]_D$ + 125°, in 90% yield. Removal of the 4, 6-O-benzylidene protecting group from 4 was achieved without difficulty by hydrogenolysis, using 5% palladium on charcoal. The resulting syrupy diol[4] 5 $[\alpha]_D$ + 190°, homogenous on TLC, was converted to its di-O-toluene-p-sulphonate[5] 6, m.p. 90-91°, $[\alpha]_D$ + 103°. Treatment of the di-O-sulphonate 6, with lithium aluminium hydride in tetrahydrofuran at 0° gave the crystalline methyl 2, 6-dideoxy-3-O-methyl-4-O-toluene-p-sulphonyl-α-D-ribo-hexopyranoside 7, m.p., 83-84°, $[\alpha]_D$ +153, 8°, in 82% yield.

Introduction of the required nitrogen function with D-ribo-hexopyranoside configuration 10 was achieved by double inversion at C-4.

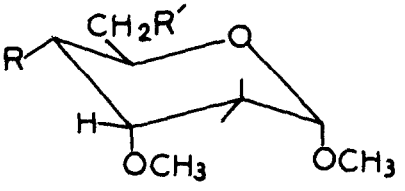
Thus, compound 7 underwent a bimolecular replacement reaction with sodium benzoate in dimethylformamide to give, by inversion of configuration at C-4, the syrupy 4-O-benzoate 11, in 40% yield. Catalytic debenzoylation of 11, using methanolic sodium methoxide, followed by toluene-p-sulphonylation gave the crystalline, methyl 2, 6-dideoxy-3-O-methyl-4-O-toluene-p-sulphonyl-α-D-xylo-hexopyranoside 12, m.p. 89-90°, $[\alpha]_D$ +78°. Its N.M.R. and mass spectra were fully consistent with structure 12 and were different in physical and chromatographic properties from its diastereomer 7.



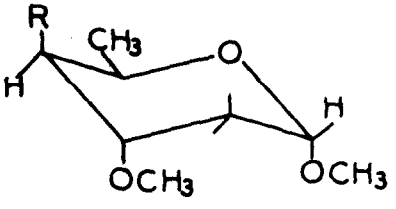
1 R=H
2 R=COCH$_3$



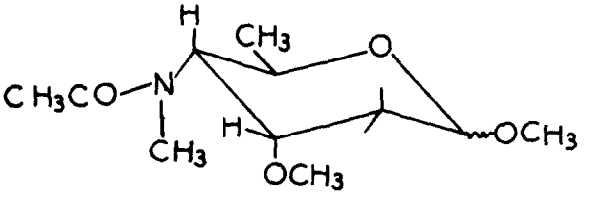
3 R=H
4 R=CH$_3$



5 R=R′=OH
6 R=R′=OTS
7 R=OTs; R′=H
8 R=N$_3$; R′=H
9 R=NHCOCH$_3$; R′=H
10 R=NCH$_3$COCH$_3$; R′=H



11 R=OBz
12 R=OTs



13

When 12 was heated with sodium azide in dimethylformamide at 140° over 2 hours, the methyl 4-azido-2, 4, 6-trideoxy-3-O-methyl-α-D-ribo-hexopyranoside 8 formed, could not be isolated, due to its volatility. Catalytic reduction of the crude azide 8, using $PtO_2$ catalyst, followed by in situ N-acetylation (methanol-acetic anhydride) yielded the crystalline methyl 4-acetamido-2, 4, 6-trideoxy-3-O-methyl-α-D-ribo-hexopyranoside 9, m.p. 154-156°, $[\alpha]_D$ + 205°. The over all yield of 9 from methyl 2, 6-dideoxy-3-O-methyl-4-O-toluene-p-sulphonyl-α-D-xylo-hexopyranoside 12 was 32%. Treatment of the 4-acetamide 9 with methyl iodide-sodium hydride-dimethylformamide[7, 8] afforded methyl-4-acetamido-4-methylamino-3-O-methyl-2, 4, 6-trideoxy-α-D-ribo-hexopyranoside 10, m.p. 80-82°, $[\alpha]_D$ + 273°, in quantitative yield. Methanolysis of 10 afforded the mixture of anomers 13, which on TLC[8] and two dimensional TLC[8] was indistinguishable from the glycosides obtained by methanolysis of N-acetyl holocurtin 2, kindly provided by Dr. Goutarel. The mass spectra of the synthetic and naturally derived methyl 4-acetamido-4-methylamino-3-O-methyl-2, 4, 6-trideoxy-α-D-ribo-hexopyranoside were superposable.

This synthesis, by an unambigous pathway, therefore confirms the structure and stereochemistry previously allotted to the carbohydrate moiety of the glyco-steroidal alkaloid 1 by physical methods[1].

A second related glyco-steroidal alkaloid "mitiphylline"[9] has also recently been shown to contain this sugar 13.

1. M.M.Janot, Ph.Devissaguet, Q.Khuong-Huu, J.Parello, N.G.Bisset and R.Goutarel, C.R.Acad.Sci., 266, Ser.C., 388 (1968).

2. A.Rosenthal and P.Catsoulacos, Canad.J.Chem., 46, 2868 (1968).

3. A.C.Richardson, Carbohydrate Res., 4, 422 (1967).

4. R.Jeanloz, D.A.Prins and T.Reichstein, Helv.Chim.Acta, 29, 371 (1946).

5. D.A.Prins, Helv.Chim.Acta, 29, 378 (1946).

6. J.S.Brimacombe, O.A.Ching and M.Stacey, J.Chem.Soc., Ser.C, 197 (1969).

7. J.Coggins and L.Benoiton, Abstr.of Papers, Biol.18, 156th ACS National Meeting, Atlantic City, 1968.
D.W.Thomas, unpublished results.

8. Solvents for TLC and two-dimensional TLC: a) ethyl acetate-hexane (95:5),
b) ether-methanol (98:2).

9. M.M.Janot, M.Lebœuf, A.Cavé, R.O.B.Wijesekera and R.Goutarel, C.R.Acad.Sci., 267, Ser.C, 1050 (1968).

Acknowledgment - The authors wish to express their sincere gratitude to Professor E.Lederer for the constant encouragement with which he supported this work. Thanks are due to Dr.R.Goutarel for fruitful discussions.

This work has been supported by a research grant from the Délégation Générale à la Recherche Scientifique et Technique auprès du Premier Ministre, n°67-0192.