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A NEW ROUTE TO BRANCHED-CHAIN SUGARS BY APPLICATION OF THE NITROMETHANE METHOD TO KETOSES

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The current literature reveals a considerable interest in the chemical synthesis of various branched-chain carbohydrates (1). Several methods for such synthesis have been developed (1-4) which utilise oxo-sugars as intermediates. The classical sugar dialdehyde-nitromethane route (5) for the synthesis of amino sugars, has been modified (6) by using nitroethane to give branched-chain deoxy amino sugars where branching is on the carbon bearing the amino group. A branched-chain can also be introduced on a carbon not bearing the amino group (7). In addition, a recent method (8) describes the synthesis of branched-chain deoxy sugars containing a nitrile or an amino group on the branched chain.

We wish to report now on the application of the nitromethane method (5) to oxo-sugars to give a novel class of branched-chain sugars having a nitro group. These can be readily converted to branched-chain deoxy sugars containing a nitro or amino group on the branched chain.

The procedure used is the following. To a stirred solution of 5 mmoles of 1,2-O-isopropylidene-5-O-triphenylmethyl-α-D-*erythro*-pentofuranos-3-ulose (I) (9) in 15 ml of nitromethane, cooled in a dry ice bath below -20°, was added dropwise over 5 minutes, a suspension of 6 mmoles of sodium hydride in 15 ml of nitromethane. After stirring at room temperature for 1 hr, the mixture was neutralized dropwise with glacial acetic acid. The solvent was evaporated under vacuum, water added to the residue and the mixture extracted with chloroform. Usual work up of the chloroform solution gave compound III,* mp. 120-121.5°, in 76% yield. The 60 MHz n.m.r. spectrum shows the following proton signals : τ^{CDCl_3} 3.98 (1H, doublet), $J_{1,2}$ 4.0 Hz (H-1); 5.13 (1H, doublet) (H-2); 5.88 (1H, triplet), $J_{4,5}$ 5 Hz (H-4); 6.68 (2H, multiplet) (H-5);

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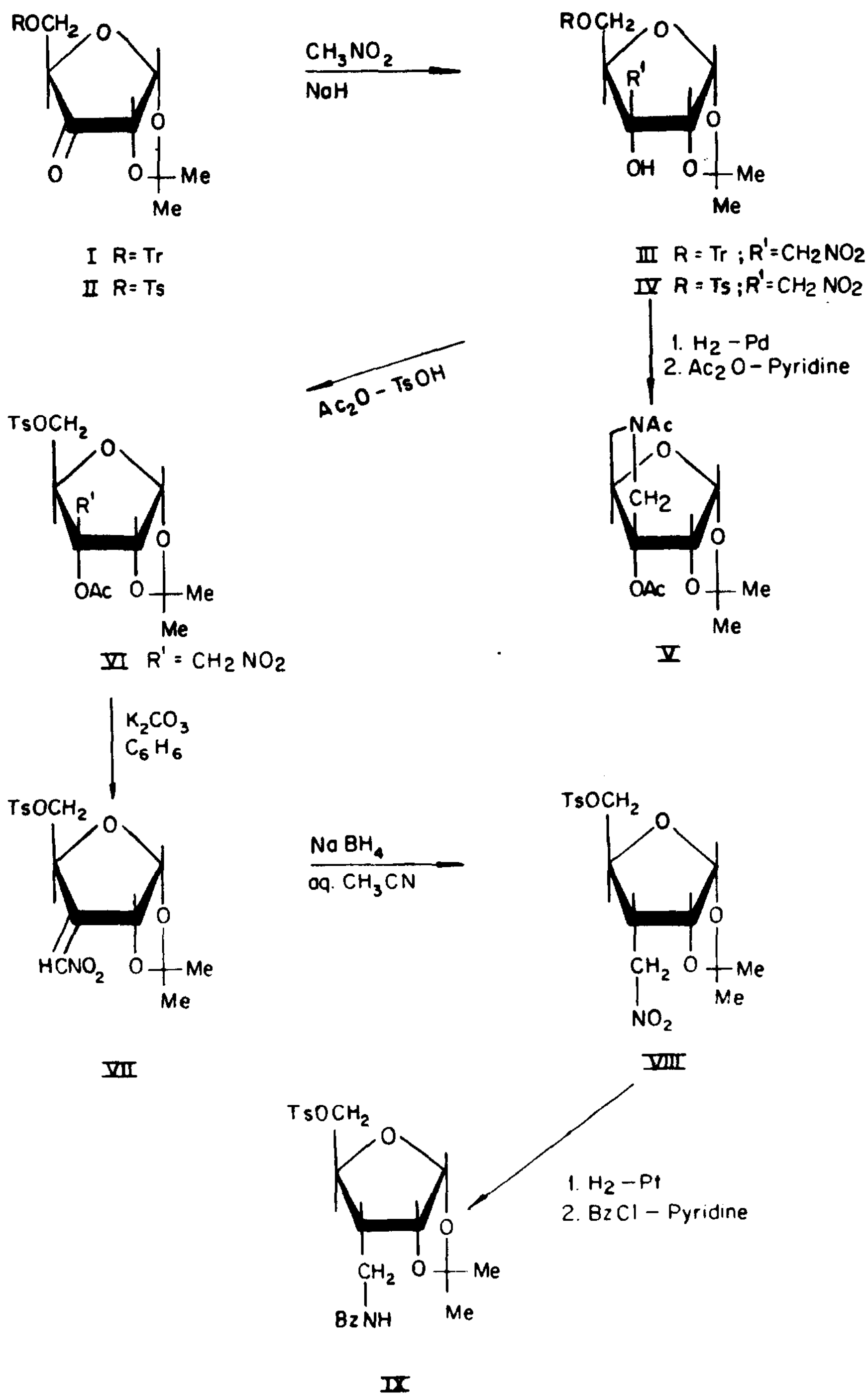
* All new compounds were homogeneous on tlc and gave satisfactory elemental analyses and infrared spectra. Each compound gave a peak in its mass spectrum at M^+-15 (loss of CH_3), except for III which gave m/e 491.


ROCH2
O
Me
Me
I R= Tr
II R= Ts
CH3NO2
NaH
ROCH2
R'
OH
III R = Tr ; R'=CH2NO2
IV R = Ts ; R'=CH2NO2
1. H2 - Pd
2. Ac2O - Pyridine
Ac2O - TsOH
TsOCH2
OAc
VI R' = CH2NO2
NAc
CH2
V
K2CO3
C6H6
HCNO2
VII
NaBH4
aq. CH3CN
CH2
NO2
VIII
1. H2 - Pt
2. BzCl - Pyridine
BzNH
IX

6.83 (1H, singlet lost on addition of D_2O) (OH); an AB system centered at 5.59, $J_{a,b}$ 12.5 Hz (methylene protons a and b on C-1'); two singlets of 3 protons each at 8.40 and 8.60 (isopropylidene methyl groups).

Similar treatment of crude II (10) with nitromethane afforded IV, mp. 131.5-132°, in 45% overall yield. The 60 MHz n.m.r. spectrum shows the following proton signals : τ^{CDCl_3} 4.20 (1H, doublet), $J_{1,2}$ 4.0 Hz (H-1); 4.90 (1H, doublet) (H-2); 5.81 (3H, multiplet) (H-4 and H-5); an AB system centered at 5.46, $J_{a,b}$ 12.5 (methylene protons a and b on C-1'); 6.67 (1H, singlet lost on addition of D_2O) (OH). That IV had indeed the *ribo* configuration was deduced from the following evidence. Reduction over palladium on charcoal and subsequent acetylation (Ac_2O-C_5H_5N) gave compound V, mp. 173-174°, in 43% yield. $\nu_{max}^{CHCl_3}$: 1745 (ester C = O), 1640 cm^{-1} (amide C = O). The n.m.r. spectrum at ambient probe temperature in $CDCl_3$ shows the presence of two isomers, but in DMSO-d_6 at 100° only one isomer is seen. Such isomerism, due to restricted rotation about the C-N bond, is expected from carbohydrates containing a ring nitrogen (12).

Acetylation of IV with acetic anhydride and toluenesulfonic acid at room temperature for 4.5 hr gave the acetate VI as an oil in 90% yield. Satisfactory elemental analysis was not obtained due to instability, but an accurate mass determination on the base peak, [M^+-15 (loss of CH_3)], in the mass spectrum of a freshly prepared sample gave 430.079; calcd. for $C_{17}H_{20}NO_{10}S$: 430.080.

Treatment of acetate VI with 0.5 molar excess of anhydrous K_2CO_3 (13) in dry benzene for 4.5 hr at ambient temperature gave the nitro-olefin VII as an oil which showed two spots on tlc, presumably the *cis* and *trans* isomers. The mixture was directly reduced with $NaBH_4$ in aqueous acetonitrile (14) to give a 58% overall yield of the deoxy sugar VIII, mp. 96-97°, after recrystallization from MeOH-H_2O. The configuration at C-3 was deduced from the 100 MHz n.m.r. spectrum; this shows : τ^{CDCl_3} 4.24 (1H, doublet), $J_{1,2}$ 4.0 Hz (H-1); 5.22 (1H, triplet) $J_{2,3}$ 4.1 Hz (H-2). The H-2 signal is a triplet showing that H-2 is also coupled to H-3, and since there is no coupling between H-3 and H-2 in 1,2-*O*-isopropylidene-α-*D*-xylofuranose, C-3 must have the deoxy *ribo* configuration (8).

Reduction of VIII over platinum and subsequent benzoylation of the amine gave compound IX, mp. 146-147°, in 78% yield. The 100 MHz n.m.r. spectrum of VIII again confirmed the deoxy *ribo* configuration at C-3 : τ^{CDCl_3} 4.30 (1H, doublet), $J_{1,2}$ 4.0 Hz (H-1); 5.31 (1H, triplet), $J_{2,3}$ 4.1 Hz (H-2).

The route IV ⟶ VIII presents the synthesis of a branched-chain deoxy sugar from a branched-chain hydroxy sugar with inversion at the branched point.

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