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A NOVEL PROCEDURE FOR THE SYNTHESIS OF 1',2'-*cis* NUCLEOSIDES

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Some substituted groups at C-2 in the pyranose ring have influence not only on the optical rotation (1-4) but also on the anomeric configuration of the pyranoses (5-9). 3,4,6-Tri-*O*-acetyl-2-*O*-trichloroacetyl-β-D- (5), 3,4,6-tri-*O*-acetyl-2-*O*-nitro-β-D- (6), and 3,4,6-tri-*O*-acetyl-β-D- (7) glucopyranosyl halides were prepared and used for the syntheses of the anomeric mixture of *O*-glucosides and of the α-D-glucose derivatives by the Koenigs-Knorr reaction. It is of interest to use these compounds for the synthesis of 1',2'-*cis* nucleosides. We have found that trihalogenoacetyl derivatives of glucosyl halides were superior to the acetyl derivatives for the preparation of 1',2'-*cis* nucleosides under the conditions of the Koenigs-Knorr reaction. The yields of 1',2'-*cis* nucleosides obtained by the present procedure were relatively higher than those by the other procedures (8). Moreover, α-D-glucopyranosyltheophylline was successfully synthesized according to the present procedure. This communication describes some typical results of our experiments.

A mixture of 3,4,6-tri-O-acetyl-2-O-trichloroacetyl-β-D-glucopyranosyl chloride (I) (5.0 mmoles), 6-benzamidopurine (5.0 mmoles), mercuric cyanide (II) (1.4 g.) and anhydrous calcium sulfate (III) (3.0 g.) was dissolved in nitromethane (9) (IV) (50 ml.). The mixture was refluxed for 4-7 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The syrupy product was deacylated in methanol saturated with ammonia according to the usual procedure. The product was passed through a Dowex-50(H^+) column and the column was eluted with 1 N NH_4OH. The fractions which showed positive UV absorption were collected and concentrated to produce an amorphous residue, yield 1.0 g. (64%). Paper chromatographic examination and n.m.r. spectrum of the product showed the presence of α- and β-D-glucopyranosyladenines. Both the anomers were separated by the preparative paper chromatography as described in our previous paper (8). α-D-Glucopyranosyladenine: yield 0.5-0.6 g. (32-38%); syrup; $[\alpha]_D^{14}$ ca. +95° (c 0.6, water); Rf 0.13 (10); $\lambda_{max}^{H_2O}$ 259 mμ; n.m.r. (11) δ 6.35 (doublet, H-1', $J_{1',2'}$, 4.0 c.p.s.), and 8.08 and 8.43 (H-2 and 8). β-D-Glucopyranosyladenine: yield 0.2 g. (13%); m.p. 206°; $[\alpha]_D^{25}$ -6° (c 0.5, water); Rf 0.10; $\lambda_{max}^{H_2O}$ 259 mμ; n.m.r. δ 5.63 (doublet, H-1', $J_{1',2'}$, 9.0 c.p.s.), and 8.04 and 8.30 (H-2 and 8).

A mixture of I (5.0 mmoles), theophylline (5.0 mmoles), II (1.4 g.) and III (2.0 g.) was similarly treated as described above. The isolation and separation of the anomeric mixture were carried out by the preparative paper chromatography. α-D-Glucopyranosyltheophylline: yield 0.07 g. (4%); m.p. 228-229°;

$[\alpha]_{\underline{D}}^{15.5}$ +189° (c 0.9, water); Rf 0.27; $\lambda_{max}^{H_2O}$ 275 mμ (ε_{max} 9.4 X 10^3); n.m.r. δ 3.35 and 3.54 (Me-N-1 and 3), 6.67 (doublet, H-1', $J_{1',2'}$ 5.0 c.p.s.), and 8.45 (H-8); ν_{max}^{Nujol} 3240-3260 (OH), 1705 (C=O), 860 (equatorial C-H deformation-vibration at C-1') $cm.^{-1}$; o.r.d. (c 0.7, water) $[\phi]_{700}$ +440°, $[\phi]_{600}$ +611°, $[\phi]_{500}$ +929°, $[\phi]_{400}$ +1640°, $[\phi]_{350}$ +2350°, and $[\phi]_{300}$ +4500°. β-D-Glucopyranosyltheophylline: yield 0.1 g. (6%); m.p. 266-268°; $[\alpha]_{\underline{D}}^{15.5}$ -2.3° (c 0.9, water); $\lambda_{max}^{H_2O}$ 275 mμ (ε_{max} 8.8 X 10^3); n.m.r. δ 3.35 and 3.54 (Me-N-1 and 3), 5.88 (doublet, H-1', $J_{1',2'}$ 8.8 c.p.s.), and 8.33 (H-8). The i.r. spectrum of the β-D-anomer was identical with that of an authentic sample of 7-β-D-glucopyranosyltheophylline (12).

The procedure was found to be applicable to the synthesis of other 1',2'-cis nucleosides. The details will be reported elsewhere.

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10. The paper chromatographic examination was carried out on Toyo Roshi No. 51 filter paper by the descending technique, using 1-butanol-water (86:14, v/v) as developing solvent.

11. The n.m.r. spectra were recorded at 60 Mc. with a Varian A-60 spectrometer at its normal operating temperature, and chemical shifts in the n.m.r. spectra were expressed on δ scale in p.p.m. down field displacement from sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard.

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