Note

Synthesis of pernicotinic esters of some monosaccharides

E. A. Forlano and J. O. Deferrari
Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires (Argentina)
R. A. Cadenas
Departamento de Química, Facultad de Agronomía y Veterinaria, Universidad de Buenos Aires (Argentina)

(Received November 1st, 1971)

Badgett *et al.*[1,2], searching for insoluble substitutes for niacin to enrich cereals, were the first to prepare nicotinic esters of alcohols and polyalcohols. They synthesized the nicotinates of ethylene glycol, pentaerythritol, inositol, and glycerol by heating the corresponding alcohols with nicotinoyl chloride hydrochloride. Alternatively, by employing a mixture of nicotinic anhydride and pyridine[3], the nicotinates of glycerol and 1,2-*O*-isopropylideneglycerol were obtained.

By analogous procedures, or by esterification with mixtures of calcium nicotinate and chlorosulfonic acid, or with nicotinic acid and phosphoryl chloride, the hexanicotinates of D-glucitol[4] and *myo*-ionisitol[5] were prepared. The ester of the latter was investigated for its effects on arterial pressure[6] and on cholesterol levels in blood[7].

The synthesis of the pentanicotinates of D-glucose and D-galactose was attempted[8] by heating, at 120° in a sealed tube, a mixture of the respective sugar with nicotinoyl chloride and pyridine, and the syrups obtained were crystallized as picrates. Under similar experimental conditions, methyl tetra-*O*-nicotinoyl-α-D-glucopyranoside was also synthesized[8], and its demethylation led to 2,3,4,6-tetra-*O*-nicotinoyl-D-glucose; the former compound has recently been prepared under milder conditions[9]. These derivatives were found to be as effective as niacin for cereal enrichment.

We now report the preparation of the nicotinic esters of D-glucose, D-galactose, D-mannose, L-arabinose, and D-xylose. Charonnat *et al.*[10] have described the synthesis of several polyalcohol nicotinates and of penta-*O*-nicotinoyl-D-glucose; the latter was obtained as a product of m.p. 168°, for which the authors gave only the nitrogen analysis. By modifying the conditions of purification and crystallization, we have prepared this ester in pure state, m.p. 190°. The D-galactose pentanicotinate, described as a syrup[8], was isolated as a pure, amorphous solid.

As direct esterification by the methods used usually affords pyranoid compounds, it is probable that these nicotinates have pyranose structures. The n.m.r. spectra at 60 MHz do not allow an overall analysis of the structures synthesized, because the anomeric proton is the sole discernible proton, but the spectra provided evidence for the anomeric purity of the nicotinates.

The optical rotatory values suggested that the D-glucose, D-galactose and D-xylose nicotinates are of the α anomeric configuration, and this was confirmed by the observed H-1 coupling constants. On the same basis, the D-mannose and L-arabinose nicotinates possess the β anomeric configuration.

EXPERIMENTAL

Evaporations were conducted under diminished pressure, below 60°. Melting points are not corrected. N.m.r. spectra were recorded at 60 MHz with a Varian A-60 n.m.r. spectrometer. Tetramethylsilane (τ 10.00) was used as the internal standard. T.l.c. was performed on Silica Gel G (E. Merck, Darmstadt, Germany) with 17:3 (v/v) benzene–methanol as the mobile phase, zones being detected with 5% sulfuric acid in ethanol and subsequent charring at 120°. All of the purified nicotinates showed only one component by t.l.c.

Nicotinoyl chloride hydrochloride. — This was prepared according to Badgett and Woodward[1]; m.p. 154°; yield 80%.

General method. — The following general method was applied to each sugar. Nicotinoyl chloride hydrochloride (8 g) was dissolved in a mixture of anhydrous pyridine (8 ml) and ethanol-free chloroform (25 ml), and the powdered sugar (1 g) was added to this solution; the temperature was kept for 5 h at −5 to 0°, with shaking. The solution was kept for 14 h at 0° and 24 h at room temperature, and then successively washed with water (2×20 ml), 10% sodium carbonate solution (2×15 ml), and water (3×20 ml), dried (anhydrous sodium sulfate), and evaporated to dryness. The resulting syrup was dried for 48 h in a vacuum desiccator. The technique then applied to each particular sugar was as follows.

*Penta-*O*-nicotinoyl-α-D-glucopyranose.* — For this ester, the procedure just described was actually conducted at room temperature. The final syrup obtained was dissolved in 60% ethanol (25 ml), and the solution was poured into ice–water (500 ml). The resulting powder was washed with cold, 60% ethanol, and dried in a vacuum desiccator; yield 3.9 g (99%). The product was recrystallized from 30% ethanol, giving crystals of m.p. 189–190°, $[\alpha]_D^{19}$ +133° (*c* 0.24, chloroform). N.m.r. spectrum: H-1 doublet at τ 3.02, $J_{1,2}$ 3.5 Hz.

Anal. Calc. for $C_{36}H_{27}N_5O_{11}$: C, 61.27; H, 3.84; N, 9.92. Found: C, 61.24; H, 3.89; N, 10.30.

*Penta-*O*-nicotinoyl-β-D-mannopyranose.* — The syrup was dissolved in 50% ethanol, and the solution was poured into ice–water (500 ml). The white powder resulting was filtered off, washed with cold, 50% ethanol, and dried; yield 3.3 g (88%) of crude product, m.p. 40–50°. This was dissolved in hot acetone, and the solution was diluted slowly with ethyl ether to turbidity; the solution was kept overnight at room temperature, and then in a refrigerator. After three similar purifications, needles were obtained; m.p. 132–133°, $[\alpha]_D^{25}$ −82.4° (*c* 1.3, chloroform) N.m.r. spectrum: H-1 doublet at τ 3.53, $J_{1,2}$ 0.5 Hz.

Anal. Calc. for $C_{36}H_{27}N_5O_{11}$: C, 61.27; H, 3.84; N, 9.92. Found: C, 61.60; H, 3.64; N, 9.88.

*Penta-*O*-nicotinoyl-α-*D*-galactopyranose.* — The dried, final syrup was dissolved in hot ethanol, and the solution was decolorized and poured into ice–water (500 ml). The powder obtained was dissolved in hot, light petroleum (b.p. 60–80°), and the solution was slowly cooled to room temperature; yield 3.4 g (88%) of an amorphous solid that, after three similar treatments with light petroleum, had m.p. 88–110°, $[\alpha]_D^{27}$ +172° (*c* 0.6, chloroform). Chromatography on a column of Silica Gel (Davison) did not afford a crystalline product. N.m.r. spectrum: H-1 doublet, at τ 2.94, $J_{1,2}$ 3 Hz.

Anal. Calc. for $C_{36}H_{27}N_5O_{11}$: C, 61.27; H, 3.84; N, 9.92. Found: C, 60.81; H, 3.90; N, 10.16.

*Tetra-*O*-nicotinoyl-β-*L*-arabinopyranose.* — The dried syrup was dissolved in hot, 13% ethanol (400 ml). On cooling to room temperature, a syrup separated out that became powdery on scratching; yield 3 g (76%), m.p. 88–95°. Recrystallization of 1 g from 10% ethanol (500 ml) gave needles (0.8 g), m.p. 90–96°, $[\alpha]_D^{25}$ +323° (*c* 1.1, chloroform). N.m.r. spectrum: H-1 singlet at τ 3.10.

Anal. Calc. for $C_{29}H_{22}N_4O_9$: C, 61.05; H, 3.89; N, 9.82. Found: C, 60.95; H, 3,95; N, 9.50.

*Tetra-*O*-nicotinoyl-α-*D*-xylopyranose.* — The syrup was dissolved in boiling 20% ethanol (320 ml) and, on cooling, long prisms were obtained; yield 3.0 g (79%), m.p. 157°; $[\alpha]_D^{28}$ +150° (*c* 1.3, chloroform). N.m.r. spectrum: H-1 doublet at τ 3.12, $J_{1,2}$ 3.5 Hz.

Anal. Calc. for $C_{29}H_{22}N_4O_9$: C, 61.05; H, 3.89; N, 9.82. Found: C, 61.37; H, 4.20; N, 9.84.

ACKNOWLEDGMENT

We thank the Consejo Nacional de Investigaciones Científicas y Técnicas de Argentina for a scholarship (to E. A. F.).

REFERENCES

1 C. O. Badgett and C. F. Woodward, *J. Amer. Chem. Soc.*, 69 (1947) 2907.

2 C. O. Badgett, R. C. Provost, C. L. Ogg, and C. F. Woodward, *J. Amer. Chem. Soc.*, 67 (1945) 1135.

3 C. O. Badgett, *J. Amer. Chem. Soc.*, 69 (1947) 2231.

4 G. Di Paco and S. C. Tauro, French Pat. 1,629; *Chem. Abstr.*, 59 (1963) 4027.

5 T. Gono and Y. Nakjima, Jap. Pat. 18,098 (1965); *Chem. Abstr.*, 64 (1966) 800.

6 J. Mercier, M. Gavend, V. Van Luu, and S. Dessaigne, *Congr. Union Therap. Intern., 8th, Brussels*, (1963) 361.

7 G. Dorner and F. W. Fischer, *Arzneimittel-Forsch.*, 11 (1961) 110.

8 F. M. Strong, L. Lutwak, and M. A. Farooqee, *Arch. Biochem.*, 18 (1948) 297.

9 I. M. Sarkar and J. C. Arthur, Jr., *Carbohyd. Res.*, 6 (1968) 207.

10 R. Charonnat, M. Harispe, M. V. Harispe, and L. Chevillard, *Bull. Soc. Chim. Fr.*, (1948) 1014.