Synthesis of Buchananine, a Novel Pyridine Alkaloid

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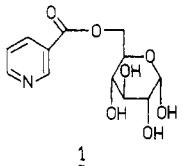
In the past there has been considerable interest in the synthesis of nicotinic esters of alcohols and polyalcohols,[1] and these have been used for enrichment of cereals[2] and for regulation of arterial pressure[3] and cholesterol levels in blood.[4] During the course of a NMR study of the anomeric purity of nicotinic esters of sugars we noted that a novel alkaloid, buchananine, had been isolated[5] from the plant *Cryptolepis buchanani* (which is used[6] in a preparation for treatment of rickets in children). The structure of buchananine, crystallized from aqueous solution, was proposed[5] to be 6-*O*-nicotinyl-α-D-glucopyranose (**1**). Since



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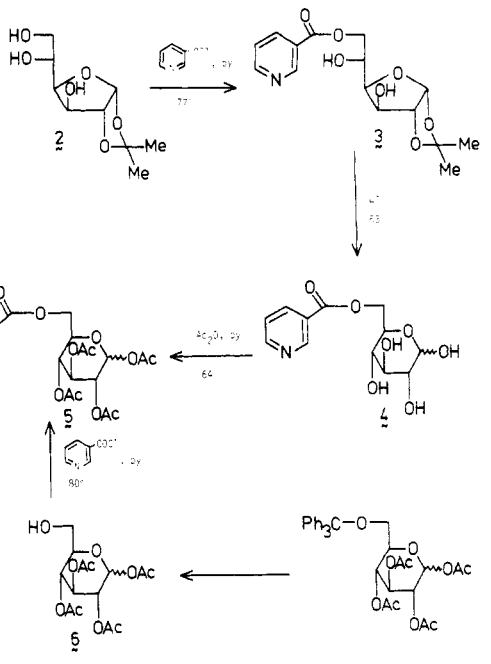
we have observed[7] that pyridines dramatically enhance the rate of mutarotation in certain sugars in water, we were surprised that buchananine could be considered to be the pure α anomer. In the present note we describe a synthesis of buchananine which, in our hands,[8] exists as a mixture of α and β isomers.

1,2-*O*-Isopropylidene-D-glucofuranose (**2**) was treated (Scheme I) with nicotinoyl chloride[2] in pyridine and gave a 77% yield of 1,2-*O*-isopropylidene-6-*O*-nicotinoyl-D-glucofuranose (**3**). Treatment of **3** with 5 N HCl, followed by a bicarbonate workup, then gave 6-*O*-nicotinoyl-D-pyranose (**4**) as a crystalline solid which was shown by 360-MHz NMR in D_2O to be a 40:60 mixture of the α and β isomers (Figure 1).[9]

For confirmation of the structure of our synthetic material, compound **4** was transformed into the corresponding tetraacetate **5** and found to be identical (TLC, IR, NMR) with material obtained by esterification of 1,2,3,4-*O*-tetraacetyl-D-glucopyranose (**6**)[10] with nicotinoyl chloride. The tetraacetates were separated by high-pressure liquid

Scheme I



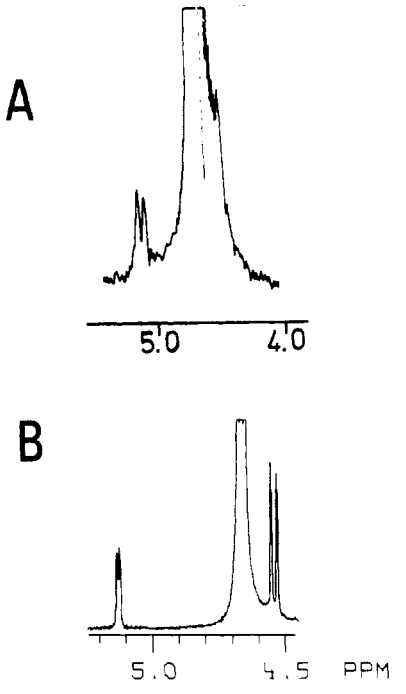
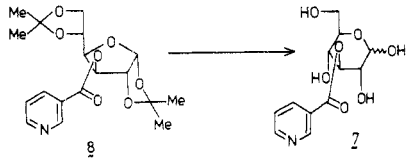


Figure 1. Proton NMR spectra in D_2O of 6-*O*-nicotinoyl-D-glucopyranose (buchananine) (A) at 60 MHz measured on a Varian EM-360 spectrometer and (B) at 360 MHz measured on a Nicolet NT-360 spectrometer. Comparison of the spectra (cf. ref 5) shows that the resonances associated with the β isomer (δ 4.54) are hidden beneath the water peak at 60 MHz (A) but are clearly visible at 360 MHz (B) using the same sample.

chromatography (high-pressure LC) into the α and β forms.

Sharma and co-workers[5] claimed that the natural sample of buchananine was the α anomer (**1**) on the basis of a 60-MHz NMR spectrum in D_2O (C_1-H, δ 5.32, $J_{1,2}$ = 3.5 Hz).[11] A spectrum of our synthetic material **4** at 60 MHz

(1) Forlano, E. A.; Deferrari, J. O.; Cadenas, R. A. *Carbohydr. Res.* **1972**, *21*, 484–486.
(2) Badgett, C. O.; Woodward, C. F. *J. Am. Chem. Soc.* **1947**, *69*, 2907.
(3) Mercier, J.; Gavend, M.; Van Luv, V.; Dessaigne, S. *Congr. Union Ther. Int.*, [*C. R.*], *8th* **1963**, 361.
(4) Dorner, G.; Fischer, F. W. *Arzenmittel. Forsch.* **1961**, *11*, 110–113.
(5) Dutta, S. K.; Sharma, B. N.; Sharma, P. V. *Phytochemistry* **1978**, *17*, 2047–2048.
(6) Chopra, R. N.; Nayar, S. L.; Chopra, I. C. In "Glossary of Indian Medicinal Plants"; CSIR Publications: New Delhi, India, 1956; p 82.
(7) Smith, K. M.; Somanathan, R.; Tabba, H. D.; Minch, M, to be published.
(8) Attempts to secure a comparison sample of natural buchananine have so far been unsuccessful.
(9) Using a similar method we have synthesized the 3-nicotinoyl-D-glucopyranose **7** from 1,2,5,6-*O*-diisopropylidene-D-glucofuranose.



8 **7**

(10) Whistler, R. L.; Doner, L. W.; Kosik, M. *Meth. Carbohydr. Chem.* **1972**, *6*, 411.

(11) The chemical shifts reported by Dutta et al.[5] for the pyridine protons in buchananine (9.33, 9.20–9.0, 8.18 ppm) are to lower field than those observed in our synthetic material (see Experimental Section); these shifts are more characteristic of a pyridinium species and correlate well with the shifts we have observed for buchananine hydrochloride [δ 9.30 (1 H, s, C_2ArH), 9.07 (1 H, d, C_6ArH), 8.96 (1 H, d, C_4ArH), 8.18 (1 H, dd, C_5ArH); with water line reference at 4.76 ppm].

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also gave the same impression, but at 100 or 360 MHz (Figure 1) it is clear that a mixture is present. This is as might be expected since we have noted[7] that addition of methyl nicotinate to pure β-D-glucose in D_2O accelerates the rate of mutarotation at least twofold. Thus, buchananine might be expected to catalyze its own mutarotation. On the basis of the above observations we conclude that buchananine as described by Sharma and co-workers[5] exists as a mixture of α and β isomers, though, of course, we cannot comment upon its precise identity in nature.

Experimental Section

Melting points were measured on a hot-stage apparatus and are uncorrected. With the exception of the 60-MHz spectrum shown in Figure 1A, all NMR spectra were run at 360 MHz, using a Nicolet NT-360 spectrometer. Ultraviolet spectra were measured on a Cary 15 spectrophotometer, and infrared spectra were determined on a Beckman IR8. Optical rotations were recorded on a Jasco DIP-180 automatic polarimeter. High-pressure LC was performed on a Waters Associates instrument consisting of a Model 6000A solvent delivery system, U6K injector, and a Perkin-Elmer LC55B variable-wavelength detector connected to an external strip recorder. The detector was set at 215 nm and a normal phase column (Waters Associates) packed with μPorasil was used for separations, eluting with ethyl acetate/cyclohexane (2:3).

1,2-*O*-Isopropylidene-6-*O*-nicotinoyl-D-glucofuranose (3). To a solution of 220 mg (1×10^{-3} mol) of 1,2-*O*-isopropylidene-D-glucofuranose (**2**) (Aldrich) in 5 mL of dry pyridine was added 177 mg (1×10^{-3} mol) of nicotinoyl chloride hydrochloride, and the mixture was stirred overnight at ambient temperature. The solution was then poured into water and extracted into butanol. Washing of the organic phase with water and saturated aqueous sodium bicarbonate, followed by drying (anhydrous $MgSO_4$) and evaporation to dryness, gave a crystalline solid (250 mg, 77%): mp 134–136 °C; $[\alpha]^{20}_D$ +4.5° (*c* 4.3, EtOH); mass spectrum, *m/e* (%) 325 (3, M^+), 310 (100); IR (Nujol) 3500 (OH), 1690 (CO), 1600 (Ar) cm^{-1}; UV (EtOH) 257 nm (ε 70000), 262 (72000), 269 (56000); ^1H NMR (CD_3OD) δ 9.21 (1 H, d, *J* = 1.4 Hz, C_2ArH), 8.78 (1 H, dd, *J* = 1.65, 6.0 Hz, C_6ArH), 8.40 (1 H, dt, *J* = 1.9, 8.0 Hz, C_4ArH), 7.60 (1 H, m, C_5ArH), 5.93 (1 H, d, *J* = 3.6 Hz, $C_1'H$), 4.28 (3 H, m, sugar H), 1.47, 1.33 (each 3 H, s, CMe_2).

Anal. Calcd for $C_{15}H_{19}NO_7$: C, 55.38; H, 5.84; N, 4.30. Found: C, 55.38; H, 5.86; N, 4.22.

6-*O*-Nicotinoyl-D-glucopyranose (4). 1,2-*O*-Isopropylidene-6-*O*-nicotinoyl-D-glucofuranose (**3**, 200 mg, 0.6×10^{-3} mol) was stirred in 2 mL of 5 N hydrochloric acid for 4 h at ambient temperature. Solid sodium carbonate was added to neutralize the solution and the water was removed under reduced pressure to give a residue which was triturated with ethyl acetate and then absolute ethanol. Removal of the ethanol gave a solid which was crystallized from aqueous methanol to give the product (92 mg, 53%): mp 136–140 °C; $[\alpha]^{20}_D$ +38° (*c* 3.08, H_2O); IR (Nujol) 3300 (OH), 1730 (CO), 1600 (Ar) cm^{-1}; UV (EtOH) 257 nm (ε 35300), 262 (38600), 269 (30000); ^1H NMR (D_2O) δ 8.80 (1 H, s, C_2ArH), 8.47 (1 H, d, *J* = 4.81 Hz, C_6ArH), 8.11 (1 H, dd, *J* = 1.66, 7.96 Hz, C_4ArH), 7.38 (1 H, m, C_5ArH), 5.12 (<1 H, d, *J* = 3.56 Hz, $C_1'H$, α isomer), 4.54 (<1 H, d, *J* = 7.87 Hz, $C_1'H$, β isomer), 3.75 (1 H, m, sugar H), 3.62 (1 H, m, sugar H), 3.35 (1 H, m, sugar H), 3.15 (1 H, t, *J* = 7.92 Hz, $C_2'H$).[11]

1,2,3,4-*O*-Tetraacetyl-6-*O*-nicotinoyl-D-glucopyranose (5). 6-*O*-Nicotinoyl-D-glucopyranose (**4**, 250 mg) was acetylated by using 2 mL of acetic anhydride in 2 mL of pyridine at ambient temperature for 3 h. Workup with aqueous sodium bicarbonate gave an oil (415 mg, 64%) which was separated by high-pressure LC (μPorasil column, elution with ethyl acetate/cyclohexane, 2:3) into the α and β isomers. **β-Isomer**: mp 136–139 °C; mass spectrum, *m/e* 454 ($M^+ + 1$, 100%); ^1H NMR ($CDCl_3$) δ 9.16 (1 H, s, C_2ArH), 8.80 (1 H, d, *J* = 4.42 Hz, C_6ArH), 8.22 (1 H, dd, *J* = 1.67, 8.0 Hz, C_4ArH), 7.41 (1 H, m, C_5ArH), 5.97 (1 H, d, 8.2 Hz, $C_1'H$, 5.42 (2 H, m, sugar H), 5.21 (1 H, t, *J* = 8.0 Hz, sugar H), 4.22 (1 H, dd, *J* = 2.0, 12.0 Hz, $C_6'H$), 4.04 (1 H, m, $C_5'H$), 2.13, 2.04, 1.92 (3 H, s, 6 H, s, and 3 H, s, 4 COMe).

Anal. Calcd for $C_{20}H_{23}NO_{11}$: C, 52.98; H, 5.07; N, 3.09. Found: C, 52.96; H, 5.23; N, 2.93.

α-Isomer: mp 135–138 °C; ^1H NMR ($CDCl_3$) δ 6.35 (1 H, d, *J* = 3.5 Hz, $C_1'H$).

1,2,3,4-*O*-Tetraacetyl-6-*O*-nicotinoyl-β-D-glucopyranose Methiodide. 1,2,3,4-*O*-Tetraacetyl-6-*O*-nicotinoyl-β-D-glucopyranose (**5**, 20 mg) was stirred with 1 mL of methyl iodide in 2 mL of dry acetonitrile for 18 h at ambient temperature. Evaporation of the solvent gave a yellow solid which was recrystallized from ethyl acetate/ether to give the methiodide hydrate (18 mg, 66%): mp 196–198 °C; ^1H NMR (CD_3OD) δ 9.58 (1 H, s, C_2ArH), 9.17 (1 H, d, *J* = 6.1 Hz, C_6ArH), 9.09 (1 H, d, *J* = 8.0 Hz, C_4ArH), 8.29 (1 H, m, C_5ArH), 5.95 (1 H, d, *J* = 8.0 Hz, $C_1'H$), 5.63 (1 H, t, *J* = 9.4 Hz, sugar H), 5.47 (1 H, t, *J* = 9.5 Hz, sugar H), 5.24 (1 H, t, *J* = 8.7 Hz, sugar H), 4.56 (3 H, s, ^+NMe), 4.40 (2 H, m, $C_6'H$), 4.26 (1 H, m, $C_5'H$), 2.16, 2.11, 2.10, 1.98 (each 3 H, s, 4 COMe).

Anal. Calcd for $C_{21}H_{26}INO_{11}\cdot H_2O$ (hygroscopic): C, 41.10; H, 4.56; N, 2.28. Found: C, 41.25; H, 4.23; N, 2.16.

1,2,3,4-*O*-Tetraacetyl-6-*O*-nicotinoyl-D-glucopyranose (5) (from 1,2,3,4-*O*-Tetraacetyl-D-glucopyranose, 6). To a solution of 800 mg (2.2×10^{-3} mol) of 1,2,3,4-*O*-tetraacetyl-D-glucopyranose[10] (**6**) in 5 mL of dry pyridine was added 177 mg (2.2×10^{-3} mol) of nicotinoyl chloride, and the mixture was stirred at ambient temperature for 18 h. An aqueous sodium bicarbonate workup gave an oil (760 mg, 80%) for which the IR, NMR, high-pressure LC, and TLC were identical with those reported above for the material synthesized from 6-*O*-nicotinoyl-D-glucopyranose (**4**).

3-*O*-Nicotinoyl-1,2,5,6-diisopropylidene-D-glucofuranose (8). This compound was synthesized from 1,2,5,6-diisopropylidene-D-glucofuranose, using the method described for the preparation of compound (**3**), and was isolated as an oil: NMR ($CDCl_3$) δ 9.86 (1 H, d, *J* = 1.4 Hz, C_2ArH), 8.78 (1 H, dd, *J* = 1.18, 4.66 Hz, C_6ArH), 8.26 (1 H, dt, *J* = 8.0, 1.18 Hz, C_4ArH), 7.39 (1 H, m, C_5ArH), 5.93 (1 H, d, *J* = 3.67 Hz, $C_1'H$), 5.49 (1 H, d, *J* = 2.71 Hz, sugar H), 4.61 (1 H, d, *J* = 3.69 Hz, sugar H), 4.30 (2 H, m, sugar H), 4.05 (2 H, m, sugar H), 1.52, 1.38, 1.29, and 1.23 (each 3 H, s, 2 CMe_2).

3-*O*-Nicotinoyl-D-glucopyranose (7). This compound was obtained from the foregoing diacetonide, using 5 N HCl, as described above: ^1H NMR (D_2O) δ 8.86 (1 H, s, C_2ArH), 8.54 (1 H, d, *J* = 4.21 Hz, C_6ArH), 8.17 (1 H, d, *J* = 7.93 Hz, C_4ArH), 7.46 (1 H, m, C_5ArH), 5.18 (<1 H, d, *J* = 3.7 Hz, $C_1'H$, α-isomer), 4.60 (<1 H, d, *J* = 8.7 Hz, $C_1'H$ β-isomer), 3.75 (1 H, m, sugar H), 3.40 (1 H, m, sugar H), 3.20 (1 H, t, *J* = 8.7 Hz, sugar H).

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Conversion of Pyrimidine Nucleoside 2',3'-Orthoacetates into Pyrimidine 2'-Azido-2'-deoxynucleosides

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Among the nucleoside antibiotics produced by microorganisms only three are known to possess aminodeoxyribofuranose structures, puromycin,[1] 3'-amino-3'-deoxyadenosine,[1] and 2'-amino-2'-deoxyguanosine.[2] The last is the only known occurrence of 2'-amino-2'-deoxy-

(1) R. J. Suhadolnik, "Nucleoside Antibiotics", Wiley-Interscience, New York, 1970.
(2) T. Nakanishi, T. Iida, F. Tomita, and A. Furuya, *Chem. Pharm. Bull.*, **24**, 2955 (1976).

0022-3263/80/1945-5000$01.00/0