Anomalous Sodium Dithionite Reduction of a 1-[2-(3-Indolyl)-ethyl]-pyridinium Bromide

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The sodium dithionite reduction of 1-[2-(3-indolyl)ethyl]-3-methoxycarbonylpyridinium salts to the corresponding 1,4-dihydropyridine derivatives, followed by acid-induced cyclization to indoloquinolizine systems, has proven to be very useful in the preparation of several indole alkaloid models of the vallesiachotamine type.[1-8] In some cases, however, this reaction sequence leads to low yields and/or anomalous products.[6,8]

We now describe a case in which the side reactions of the reduction play the predominant role. When the salt *1* was treated with sodium dithionite in the presence of sodium hydrogen carbonate in aqueous methanol the main products isolated were the tetrahydropyridine derivatives *2* and *3*.

The formation of compounds *2* and *3* can be rationalized as shown in Scheme 1. The removal of the acidic proton in the 4-position of the salt *1* by sodium hydrogen carbonate leads to the conjugated system *4*, which can then be reduced to *2*. If, however, the carbonyl group in *4* first undergoes nucleophilic attack by MeO^-, followed by opening of the lactone ring, then the allylic alcohol derivative *5* would result. The latter could then undergo allylic cleavage (*cf.* hydrogenolysis) and reduction to give *3*. We reject the possibility that the lactone ring is first cleaved followed by esterification since esterification under the conditions used (*vide supra*) seems unlikely to us.

Conjugated systems such as *4* have previously been proposed to rationalize low yields and anomalous results in palladium catalyzed hydrogenations of some 3-acetylpyridine *N*-alkyl salts in the presence of triethylamine.[9-12]

Experimental. The IR spectra were recorded with a Perkin-Elmer 257 spectrophotometer, the ^1H NMR spectra with the I.E.F. 240 (240 MHz) instrument of Institut d'Electronique Fondamentale d'Orsay[13] and the mass spectra with an A.E.I. MS-50 mass spectrometer at 70 eV, using direct sample insertion into the ion source, whose temperature was 150 – 160 °C.

General procedure. Sodium dithionite (300 mg) was added in small portions during 0.5 h to a stirred solution of the pyridinium salt *1*[10] (100 mg) and $NaHCO_3$ (400 mg) in aqueous MeOH (20 ml; MeOH – H_2O, 1:2) under argon. The mixture was stirred for 12 h, water was added and the mixture was extracted several times with CH_2Cl_2. The extracts were washed with water, dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue was fractionated by preparative layer chromatography (silica gel, neutral).

Tetrahydropyridine 2. Viscous oil, yield 20 mg. IR (film): ν C=O 1665 (s) cm^{-1}. ^1H NMR (240 MHz, $CDCl_3$): δ 0.96 (3 H, t, J 8 Hz, $-CH_2-CH_3$), 1.76 (2 H, m, $-CH_2-CH_3$), 4.12 (1 H, dd, J_1 10 Hz, J_2 2 Hz, H of CH_2O), 4.36 (1 H, dd, J_1 10 Hz, J_2 2 Hz, H of CH_2O), 6.96 (1 H, d, J 1 Hz, indolyl α-H), 7.60 (1 H, d, J 2 Hz, C-2-H), 8.10 (1 H, br s, NH). MS [IP 70 eV; *m/e* (% rel. int.)]: 324 (28) ($C_{20}H_{24}N_2O_2$), 194 (100) (*cf.* Ref. 10).

Tetrahydropyridine 3. Viscous oil, yield 10 mg. IR (film): ν C=O 1665 (s) cm^{-1}. ^1H NMR (240 MHz, $CDCl_3$): δ 0.86 (3 H, t def., $-CH_2-CH_3$), 1.06 (3 H, d, J 8 Hz, $-CH-CH_3$), 3.64 (3 H, s, $-COOCH_3$), 6.96 (1 H, d, J 1 Hz, indolyl α-H), 7.36 (1 H, d, J 2 Hz, C-2-H), 8.06 (1 H, br s, NH). MS [IP 70 eV; *m/e* (% rel. int.)]: 340 (30) ($C_{21}H_{28}N_2O_2$), 210 (100).

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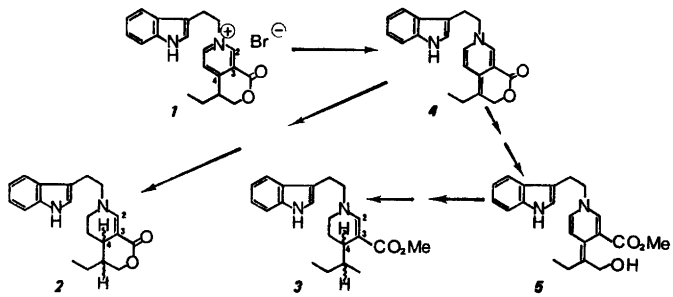

Scheme 1.

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Facile Synthesis of Aryl β-D-Mannopyranosides

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The preparation of β-D-mannopyranosides is a long-standing problem in carbohydrate chemistry.[1–6] It is important that efficient routes to these glycosides are found: β-D-mannopyranose units are widespread in oligo- and polysaccharide sequences of natural origin and their synthesis may be required in various biological contexts. 4-Nitrophenyl β-D-mannopyranoside is useful for linking β-D-mannopyranose units to proteins; after the reduction of the nitro to an amino group, this can be joined to proteins in several ways.[7] Various aryl β-D-mannopyranosides are useful in the assay of β-D-mannopyranosidases.

We have briefly described new methods for the synthesis of alkyl and aryl β-D-mannopyranosides as well as of a disaccharide containing β-D-mannopyranose units.[8,9] The key compound, 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranose is obtained in a 55 % crystalline yield from D-mannose without resorting to the use of chromatography, by means of cyclohexylidenation of D-mannose under kinetic control.[8,9] We have now explored the scope of this methodology for the preparation of aryl β-D-mannopyranosides.

2,3:4,6-Di-*O*-cyclohexylidene-α-D-mannopyranose, diethyl azodicarboxylate, triphenylphosphine and a phenol were allowed to react in toluene at room temperature. The reaction product was purified by means of silica gel column chromatography. Results are shown in Table 1. The results in Table 2 indicate that the α/β ratio of anomers obtained in the reaction increases with solvent polarity. The cyclohexylidene groups were removed with acid under mild conditions.

Experimental. General methods were the same as those described before.[10]

Glycosylation procedure. Diethyl azodicarboxylate (0.40 g, 2.3 mmol) in dry toluene (2.5 ml) was added to a stirred solution of 2,3:4,6-di-*O*-cyclohexylidene-α-D-mannopyranose (0.50 g, 1.5 mmol), triphenylphosphine (0.55 g, 2.1 mmol) and the phenol (2.1 mmol) in dry toluene (10 ml) at room temperature. The reaction was monitored by TLC (solvent, Table 1). When the reaction was complete, the solution was concentrated and the β-D-mannopyranoside derivative was obtained in a pure state by means of silica gel column chromatography.

3-Nitrophenyl β-D-mannopyranoside (11). A solution of *1* (510 mg, 1.1 mmol) in 80 % aqueous acetic acid (15 ml) was heated for 1 h at 100 °C. Concentration and crystallization from acetone yielded *11* (200 mg, 60 %) m.p. 73–75 °C $[\alpha]_D^{20}$ −69° (*c* 0.7, H_2O).

4-Nitrophenyl β-D-mannopyranoside (12). A solution of *3* (480 mg, 1.0 mmol) in 80 % aqueous acetic acid (15 ml) was heated for 1 h at 100 °C. Concentration and crystallization from water yielded *12* (180 mg, 58 %) m.p. 205–207 °C, $[\alpha]_D^{20}$ −108° (*c* 1, H_2O).[2,3,9,11]

Phenyl 2,3,4,6-tetra-O-acetyl-β-D-mannopyranoside (13). A solution of *5* (450 mg, 1.1 mmol) in 90 % aqueous trifluoroacetic acid (5 ml) was kept for 30 min at 0 °C. The solution was concentrated and the residue treated with acetic anhydride (2 ml) in pyridine (3 ml) for 15 min at 100 °C. Concentration and crystallization from ethanol yielded *13* (232 mg, 49 %) m.p. 163–165 °C, $[\alpha]_D^{20}$ −61° (*c* 0.8, $CHCl_3$). Anal: $C_{20}H_{24}O_{10}$: C, H.

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