Synthesis of Nitrofurantoin-N-Peracetyl Glucoside Under Phase Transfer Catalysed Conditions.

*B. AHMAD AND J.W. POWELL

Department of Pharmaceutical Chemistry, The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, U.K.

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Summary: Nitrofurantoin-N-(2,3,4,6-tetra-O-acetyl-β-D-glucoside) was synthesized under phase transfer catalysed conditions, it was then characterized by NMR (proton) and Mass spectrometry (EI) for the Phase-II metabolic study of Nitrofurantoin.

Introduction

Nitrofurantoin, a synthetic nitrofuran is a broad-spectrum antibacterial agent that is being employed for the prevention and treatment of urinary tract infections [1].

Glucosides and glucuronide conjugates are formed in the Phase-II metabolism of most drugs and xenobiotics that make their way into the human body. Their aqueous solubility make them easily excretable [2,3].

N-Glucoside conjugates of barbiturates, sulphonamides and other drugs have been reported on several occasions [4-10] but the evidence for the precise structure of the proposed conjugates has not been supported by the modern spectroscopic techniques like NMR and Mass spectrometry. Difficulty in synthesizing such required authentic conugates in a pure state seems to be a major problem. The present work describes the successful synthesis of Nitrofurantoin-N-glucoside (protected) by adaptation of the published method [11] of Dess group. The synthetic product was characterized by NMR (proton) and mass spectrometry (EI).

Materials and Method

Synthesis of N-Glucoside (protected)

Nitrofurantoin-N-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucoside) was synthesized, using the approach of Dess *et. al.* [11] by dissolving nitrofurantoin (0.47 g, 0.002 mole) and benzyltriethylammonium bromide (0.28 g, 0.002 mole) in aqueous sodium hydroxide (1.25 M, 2 ml). The resulting solution was added to a solution of α-aceto-bromoglucose (2,3,4,6-tetra-*O*-acetyl-α-*D*-glucopyranoside bromide) (0.41 g, 0.001 mole) in chloroform(5 ml). The mixture was stirred vigorously and heated under reflux (3h). After cooling, water (10 ml) was added. The chloroform layer was separated and washed twice with aqueous sodium hydroxide (1.25 M, 3 ml) and dried (Na_2SO_4). The solvent was removed yielding a yellow gummy material. Separation by PLC with methanol/chloroform (5:95 v/v) as solvent yielded the product (0.5g, 50%), m.p. 70-73° (fig. 1).

Results

NMR(Proton) Analysis

The proton NMR, which was recorded at 80 MHz FT on a Bruker Model WP 80 SY spectrometer, showed the following characteristic peaks of the desired product: δ ($CDCl_3$): 1.9 (6H, s); 2.0 (6H, s); 3.9- 4.25 (5H, m); 4.8-5.5 (3H, m): 5.9 (1H, d, J = 8 Hz); 7.05 (1H, d, J = 2 Hz); 7.4 (1H, d, J = 2 Hz): 7.95 (1H, s).

Mass Spectral Analysis(EI)

Mass Spectra (EI) was measured with a VG-Analytical ZAB-1F operating in EI mode, and the following data were obtained: m/z (%): 431 [M + 2-$C_5H_3N_2O_3$,15), 371 (431-OAc, 17), 357 (431 - CH_2OAC,11), 331 (peracetyl sugar, 50), 250(5), 237 (4), 208 (7) 195 (6), 169(8), 157(7), 140(5), 129(6), 115(13), 98(19), 81(7), 73 (-CH_2OAc, 6), 43 (Ac, 100).

*Present Address:
Department of Pharmacy, Bahauddin Zakariya University, Multan, Pakistan.

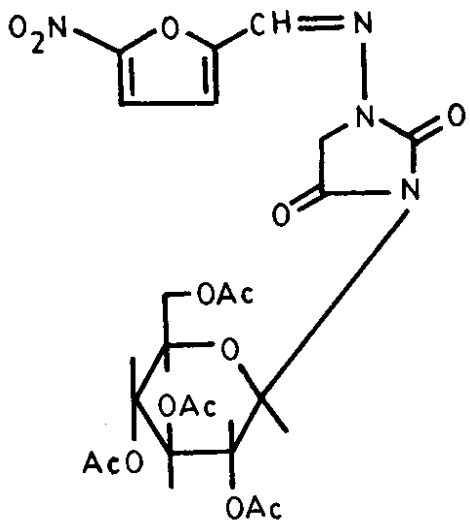

Fig.1: Nitrofurantoin-N-(2,3,4,-6-tetra-O-acetyl-β-D-glucoside).

Discussion

Although the synthesis of peracetyl glucosides and glucuronides of nitrogenous drugs and other compounds have been reported, e.g. [4-10, 12-15] but the methods used have generally resulted in rather low yields of the desired products. The Dees method [11] which was adopted for the synthesis of Nitrofurantoin peracetyl-N-glucoside seems advantageous from the previous methods, as it involves a simple phase transfer catalysed technique, in which the α-aceto-bromo sugar is held in the organic phase, which somewhat protects it from the premature attack by the aqueous alkali: Nitrofurantoin is dissolved in a slight excess of aqueous alkali, which serves to generate the -N-anion; this will then attack, nucleophilically, the α-acetobromoglucoside when the two reactants are brought into intimate contact by the influence of a phase transfer catalyst (e.g. benzyl-triethylammonium bromide) at the interface. Evidently the reaction product will be lipophilic, and so will be predominantly distributed in the organic phase and will consequently be protected from hydrolysis by the residual alkali. Thus this simple phase transfer catalysed method was found to give excellent yields of the required protected glucoside conjugated.

The stereochemistry of the linkage at the peracetyl glucoside would be expected to be β, if the attack by the nitrofurantoin nitrogen anion on the α-acetobromoglucopyranose (bromide being a good leaving group) had followed the SN_2 mechanism. Evidence for the β-linkage was obtained from the NMR (proton) analysis of the anomeric proton, which showed a doublet at δ 5.9 with J = 8 Hz; these values are consistent with the expected and reported β-glucoside linkage [14]. The N-glucuronide (protected) of the same drug was also synthesized [16].

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