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SYNTHESIS OF CHLORPROPAMIDE-N^1-(2, 3, 4, 6-TETRA-O-ACETYL-β-D-GLUCURONIDE) UNDER PHASE TRANSFER CATALYZED CONDITION

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ABSTRACT

Chlorpropamide-N^1-peracetyl glucoside was synthesized by a phase transfer catalysed method. The synthetic product was analysed by spectroscopic techniques (NMR and MS).

Introduction

Chlorpropamide (Diabinese, Melitase) a potential member of sulphonylurea group, is best known as an oral hypoglycaemic agent that achieves its therapeutic action by stimulating the biosynthesis and release of insulin by the failing pancreas. It also boosts vasopressin secretion in individuals with pituitary form of diabetes insipidus (Lamer J. 1985; Crossland J. 1980).

Most drugs and xenobiotics that make their way into human body, result in the formation of conjugates, as a path-way of their Phase-II metabolism, with the indigenous substances like glucuronic acid, glucose, glycine and sulphates. Their aqueous solubility make them easily excretable through the urine (Dutton G.J. 1980; Gorrod et al 1978).

N-Glucuronides and glucosides of sulphonamides, which are somewhat structurally related to chlorpropamide, have been reported along with other drugs (Bridges et al 1969; Kadlubar et al 1977; Wooley et al 1979; Nielsen P. 1973; Paulson G.D. et al 1981; Gicra D.D. et. al (1982) but the precise structural evidence of their proposed conjugates, has not been supported by the modem spectroscopic technique like NMR and mass spectrometery. synthesis of such required authetic conjugates in a pure state seems to be the major problem. The present work describes successfully the synthesis of N^1-peracetyl glucoside of chlorpropamide, by using a reported method (Dess D. et al 1981). The synthetic product was then characterized by ^{1}HNMR and mass spectrometry (El).

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Materials and Methods

Chlorpropamide-N^1-(2, 3, 4, 6-tetra-O-acetyl-β-D-glucoside) was synthesized, using a reported method (Dess D. et al 1981) by dissolving chlorpropamide (0.55g, 0.002 mole) and benzyltriethyl-ammonium bromide (0.28g, 0.002 mole) in aqueous sodium hydroxide (1.25M, 2 ml). The resulting solution was added to a solution a-acetobromoglucopyranose (2, 3, 4, 6-tetra-O-acetyl-α-D-glucopyranoside bromide) (0.41g, 0.001 mole) in chloroform (5ml). The mixture was stirred vigorously and heated under reflux (3h). After cooling, water (10 ml) was added. The organic layer was separated and washed twice with aqueous sodium hydroxide (1.25M, 3 ml) and dried (sodium sulphate). Gummy material was obtained after removing the solvent. Recrystallization from methanol/water (1:3) yielded the colourless product (0.48g, 42%), m.p. 53-56°.

Results

The NMR (proton) analysis of the resulting synthetic product, which was recorded at 80- MHz FT, on a Bruker model WP 80 SY spectrometer gave the following data: δ ($CDCl_3$,): 0.9 (3H, t); 1.3-1.6 (213, m); 1.95 (6H, s); 2.0 (6H, s); 3.15 (2H, q); 3.8-4.1 (3H, m); 4.9-5.15 (3H, m); 5.8 OH, (1H, d, J= 9 Hz); 7.5 (2H, d, J = 10Hz); 7.8 (2H, d, J = 10Hz); 7.9 (1H, s).

Mass spectra, recorded with VG-Analytical ZAB-1F, with electron impact mode of ionization, gave the following data: Mz (%): 564 (M + 1 – C_3H_7 5), 504 (564-OAc, 10), 444 (504-OAc, 5), 402 (45), 384 (444-OAc, 40), 373 (6), 360 (13), 331 (19), 277 (7), 197 (4), 169 (27), 157 (6), 139 (5), 127 (10), 111 (20), 98 (22), 81 (14), 69 (5), 56 (7), (AC, 100).

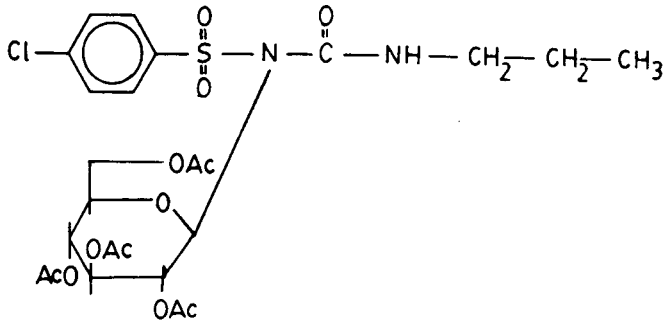

Fig. 1: Chlorpropasnide-N^1-(2, 3, 4, 6-tetra-O-acety1-β-D-glucuside).

Discussion

The synthesis of glucosides and glucuronides (protected and unprotected) of drugs containing nitrogen and other compounds have previous been reported (Paulson G.D. et al 1981; Giera D.D. et al 1982; Tank B.K. et al 1979; Al-Sharif M.A.M. 1982; Soine W.H. et al 1984; Berrang B. et al 1975) but the used methods have generally resulted in rather low yields of the desired products. The results indicate that the adopted method (Doss D. et al 1981) used for the synthesis of chlorpropamide-N^1-peracetyl glucoside is advantageous from the reported methods as it involves a simple phase transfer catalysed technique, where the 2, 3, 4, 6-tetra-O-acetyl-α-D-glucopyranoside bromide is held in the organic phase, which somewhat protects it from the premature attack by the alkali, the nitrogen anion (-N-) a nucleophile is generated by dissolving chlorpropamide in a slight excess of aqueous alkali; this will then attack, nucleophilically, the a-acetobromoglucoside (bromide being a good leaving group) when the two reacting agents arc brought into intimate contact by the influence of benzyltriethylammonium bromide (a phase transfer catalyst) at the interface of two solvents. The reaction product will be lipophilic, and so will be predominantly distributed in the chloroform, an organic phase and will consequently be protected from hydrolysis by the residual alkali. thus this simple phase transfer catalysed method, without involving complex separation techniques, was found to give excellent yields of the required peracetyl-N^1-glucoside conjugate of the desired drug.

The stereochemistry of the linkage at the peracetyle glucoside would be expected to be p, if the attack on the a-acetoglucopyranoside bromide by the chlorpropamide nitrogen anion, acting as nucleophile, had followed the SN2 mechanism. Evidence to the β-linkage was obtained from the proton NMR analysis of the anomeric proton, which showed a doublet at δ 5.8 with J = 9Hz; these values are consistent with the expected and reported β-glucoside linkage (Soine W.H. et at 1984).

M-Glucuronide (protected) of th*e* same drug was also synthesized (Ahmad B. et al.) to prove the authentity of the conjugated metabolite.

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