Synthesis of 1-*O*-(2′-Acetoxy)benzoyl-α-D-2-deoxyglucopyranose, a Novel Aspirin Prodrug

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Abstract □ The synthesis and characterization of 1-*O*-(2′-acetoxy)-benzoyl-α-D-2-deoxyglucopyranose, a novel aspirin prodrug, are described. 3,4,6-Tri-*O*-benzyl-α-D-2-deoxyglucopyranose was synthesized by methylating the anomeric hydroxyl group of 2-deoxyglucose, benzylating the 3-, 4-, and 6-hydroxy functional groups, and cleaving hydrolytically the anomeric methyl group. Reaction of the tribenzylated sugar with the acid chloride of aspirin and subsequent hydrogenolysis of the benzyl groups resulted in the prodrug, mp 128°. The compound was further characterized by elemental analysis and PMR and ^{13}C-NMR spectroscopy. *In vitro*, the compound cleaved to aspirin with a half-life of 7 min at 37°. Prodrug cleavage was independent of pH over the pH 3–9 range.

Keyphrases □ 1-*O*-(2′-Acetoxy)benzoyl -α-D- 2-deoxyglucopyranose —aspirin prodrug, synthesis □ Aspirin prodrugs—synthesis of 1-*O*-(2′-acetoxy)benzoyl-α-D-2-deoxyglucopyranose □ Prodrugs—aspirin, synthesis of 1-*O*-(2′-acetoxy)benzoyl-α-D-2-deoxyglucopyranose

Aspirin, probably the most widely used drug in the world, is a potent, effective, and low cost medicament. However, it produces occult GI blood loss in a large percentage of patients (1–6). Studies have also shown that gastric irritation is a local effect (6) of contact of the mucosa with the highly acidic aspirin particles or the saturated solution surrounding those particles. Although GI bleeding can be prevented by administration of aspirin in a highly buffered solution (7), the high sodium content of such buffered products makes their chronic use impractical (6).

Previous communications showed that the acylal derivative 1-ethoxy(ethyl-2-acetoxy)benzoate is an oily, insoluble compound which cleaves very rapidly, generating aspirin (8), and that the acylal 1-*O*-(2′-acetoxy)benzoyl-α-D-glucopyranose is a more soluble, crystalline compound which only slowly generates aspirin in solution (9).

The present report describes the synthesis of the prodrug 1-*O*-(2′-acetoxy)benzoyl-α-D-2-deoxyglucopyranose (V), a crystalline compound that cleaves to aspirin *in vitro* in a reaction that is independent of pH; it has a half-life of 7 min at 37° (10). The prodrug, a neutral compound, should generate a nonirritating aspirin solution upon contact with the gastric milieu.

EXPERIMENTAL

Materials—The following materials were reagent grade or equivalent: methanol, sodium carbonate, acetone, absolute ethanol, ethyl acetate, potassium hydroxide, dry dioxane, dry pyridine, ethyl ether, sodium sulfate, acetic acid, sulfuric acid, dichloromethane, sodium bicarbonate, palladium-on-carbon, petroleum ether, and chloroform. 2-Deoxyglucose[1] and *o*-acetylsalicyloyl chloride[2] were used as received. Benzyl chloride[2] was redistilled at 175 ± 0.5°.

Synthesis—The general procedure for the synthesis of the prodrug (V) was a modification of that of Glaudemans and Fletcher (11).

α-Methyl-2-deoxyglucopyranose (I)—A solution of the starting material, 2-deoxyglucose (15 g, 0.09 mole), in 2% methanolic hydrochloric acid (540 ml) was warmed to 40° and shaken for 1 hr. After cooling to 20°, the mixture was stirred with excess sodium carbonate (32 g) for 15 min. After filtration, the solvent was removed under reduced pressure to give an oil containing a small amount of white solid.

The oil was dissolved in acetone (750 ml) and, after filtration and solvent removal, crystallized from 5 ml of ethanol at −5°. The crystalline material (I) was recovered by filtration and washed with cold (−5°) ethyl acetate. The yield was 10 g (61%), mp 91–92°[3] [lit. (12) mp 91–92°]; NMR[4] (dimethyl sulfoxide-d_6): δ 4.1–4.8 (m, 3H, OH), 3.1–4.1 (m, 9H, 3-6-H's, 1-H, OCH_3), and 1.1–2.3 (m, 2H, 2-H's).

*α-Methyl-3,4,6-tri-*O*-benzyl-2-deoxy-D-glucopyranose (II)*—Nine grams (0.05 mole) of I was added to a suspension of finely powdered potassium hydroxide (44.8 g) in dry dioxane (110 ml), and the mixture was warmed to reflux. As soon as reflux was smooth, colorless benzyl chloride (62 ml) was added dropwise over 45 min. After an additional 40 min of refluxing, the dioxane was distilled off during 3 hr. After cooling, the residue was diluted to 350 ml with water and extracted with ether.

The ether portions were dried and, after filtration, evaporated at reduced pressure to give an oil. The oil was subjected to vacuum distillation (bath temperature of 200°, 0.4 mm Hg). The oily product (II) remained in the distillation vessel in ~100% yield; NMR ($CDCl_3$): δ 6.7–7.7 (m, 15H, ArH), 4.2–5.0 (m, 7H, ring-CH_2–, 1-H), 3.3–4.2 (m, 5H, 3-6-H's), 3.2 (s, 3H, OCH_3), and 1.4–2.5 (m, 2H, 2-H's).

*3,4,6-Tri-*O*-benzyl-α-D-2-deoxyglucopyranose (III)*—Compound II (22.3 g, 0.05 mole) was dissolved in hot (70°) acetic acid, slowly treated with hot (70°) 1 *M* H_2SO_4, and stirred at 70° for 1 hr. The reaction mixture was slowly added to cold water (3 liters, 10°), stirred for 2 hr, and kept at 10° for 24 hr. The product (III) was recovered by filtration and washed with methanol. The yield was 14 g (65%), mp 96–97°; NMR ($CDCl_3$): δ 6.7–7.7 (m, 15H, ArH), 5.1–5.4 (s, 1H, 1-H), 4.2–5.1 (m, 6, H ring-CH_2–), 3.2–4.2 (m, 6H, 3-6-H's, 1-OH), and 1.4–2.5 (m, 2H, 2-H's).

1-O-(2′-Acetoxy)benzoyl -3,4,6- tri-O-benzyl-α-D-2-deoxyglucopyranose (IV)—A solution of III (13.7 g, 0.032 mole) in dichloromethane (130 ml) was treated with a solution of *O*-acetylsalicyloyl chloride (6.93 g, 0.035 mole) and pyridine (2.8 ml) in dichloromethane (50 ml) and

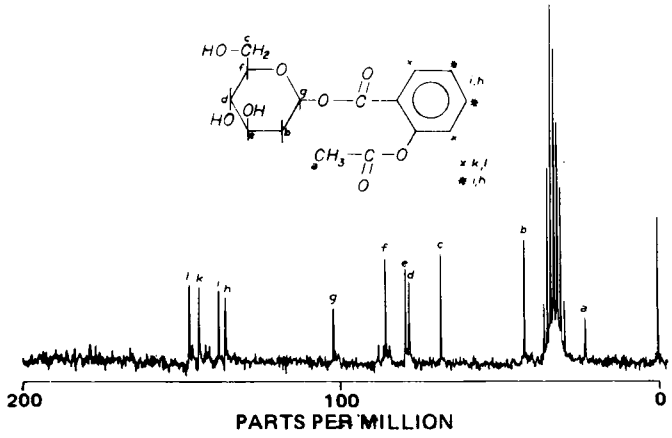

Figure 1—^{13}C-*NMR spectrum of 1-*O*-(2′-acetoxy)benzoyl-α-D-2-deoxyglucopyranose in acetone-*d_6.

[1] Sigma Chemical Co., St. Louis, Mo.
[2] Aldrich Chemical Co.

[3] All melting points were obtained using a Hoover Uni-melt capillary apparatus and are uncorrected.
[4] PMR spectra were obtained using a Varian EM-360 spectrophotometer with tetramethylsilane as the internal reference.

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stirred at 20° for 23 hr. Then 100 g of ice was added, and the mixture was left for an additional 1 hr. The dichloromethane layer was separated and washed with water, 3 *N* H_2SO_4, water, and a saturated solution of sodium bicarbonate. It then was dried and evaporated under reduced pressure to yield an oil.

The crude product separated as a waxy solid from a solution of the oil in methanol (200 ml). Recrystallization from ethanol gave IV (4.7 g, 25%); NMR ($CDCl_3$): δ 6.7–8.0 (m, 19H, ArH), 5.8 (d, 1H, 1-H), 4.4–4.9 (m, 6H, ring-CH_2–), 3.4–3.9 (m, 5H, 3-6-H's), and 1.0–2.5 (m, 5H, 2-H, –$OCOCH_3$). The ^{13}C-NMR[5] (deuterochloroform) was also consistent with the structure of IV.

1-O-(2′-Acetoxy)benzoyl-α-D-2-deoxyglucopyranose (V)—Compound IV (1 g, 0.002 mole) was dissolved in ethanol (150 ml), and 10% palladium-on-carbon (0.6 g) was added. Hydrogenolysis at 60 psig for 12 hr, filtration, and solvent evaporation at reduced pressure gave an oil. The oil was washed with petroleum ether (50 ml), and it crystallized spontaneously upon the addition of chloroform (15 ml). The yield was 0.52 g (95%), mp 128–129°; NMR (acetone-d_6): δ 7.0–8.2 (m, 4H, ArH), 5.8–5.9 (d, 1H, 1-H), 3.0–4.1 (m, 8H, 3-6-H's, OH's), 2.3 (s, 3H, –$OCOCH_3$), and 1.0–2.3 (m, 2H, 2-H's). The ^{13}C-NMR (acetone-d_6) was also consistent with the structure of V (Fig. 1).

Anal.[6]—Calc. for $C_{15}H_{18}O_8$: C, 55.20; H, 5.57. Found: C, 55.35; H, 5.59.

DISCUSSION

The method described here for Compound V provides a synthetic route for the preparation of acylal prodrugs of aspirin in which the acidic carboxyl function is masked by a sugar molecule. Compound V was characterized by elemental analysis and PMR and ^{13}C-NMR spectroscopy. The ^{13}C-NMR spectrum shown in Fig. 1 is consistent with the assigned structure (V).

Since the regeneration rate of the parent compound from V occurs *in vitro* with a half-life of 7 min at 37° (10) and since preliminary data (9) indicate that the glucose analog hydrolyzes much more slowly, application of the method to other sugars (or other parent drugs) may provide additional useful drug substances.

[5] The ^{13}C-NMR spectra were obtained using a Varian CFT-20 NMR spectrometer.

[6] Elemental analysis was performed by Micro-Analysis, Inc., Wilmington, Del.

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New Compounds: Synthesis of 2-Chloromethylbenzo[*b*]furans

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Received June 20, 1979, from the *Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14260.* Accepted for publication August 8, 1979.

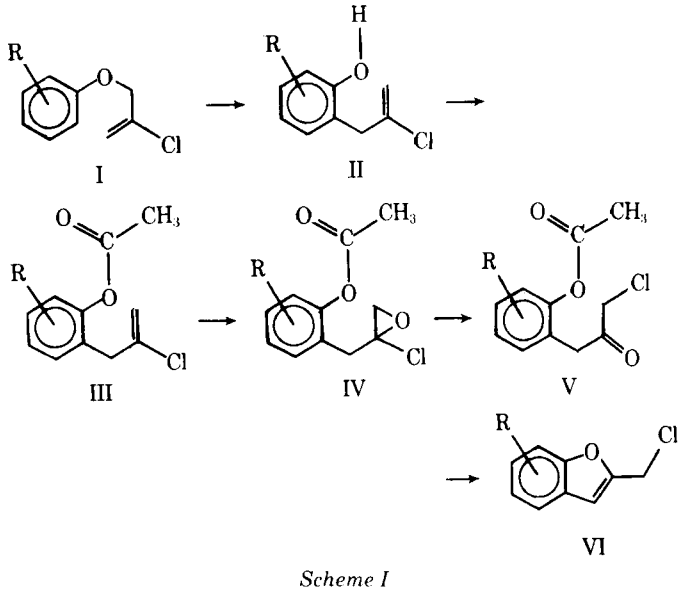
Abstract □ 2-Chloromethylbenzo[*b*]furans were prepared in high overall yield from the corresponding chloroethylphenyl ethers through chloroepoxide and α-chlorophenylacetone intermediates.

Keyphrases □ Benzo[*b*]furans—synthesis of 2-chloromethyl compounds □ 2-Chloromethylbenzo[*b*]furans—synthesis □ Heterocycles—synthesis of 2-chloromethylbenzo[*b*]furans

The benzo[*b*]furan ring system has provided a focus for the development of new agents in several classes, and new synthetic approaches to this heterocyclic system continue to be significant. The synthesis of 2-methylbenzo[*b*]furans from aryl 2-chloroprop-2-enyl ethers was described (1), but low yields were obtained when the starting phenol contained an *o*-chlorine substituent. This report describes an alternative procedure which circumvents this problem and gives a reactive chloromethyl group in the 2-position of the benzo[*b*]furan.

DISCUSSION

The starting phenol was added to a solution of sodium in absolute ethanol. 2,3-Dichloropropene was added, and the mixture was heated under reflux for 24 hr to give the aryl 2-chloroprop-2-enyl ethers (I) in almost quantitative yield. Rearrangement of I to II as described previously (1, 2) and acetylation of II gave III. This acetylation was necessary since the next step, epoxidation, yielded only decomposed material in the presence of the free phenol. Epoxidation of III gave chloroepoxides (IV), usually in crude yields greater than 90%, which were converted directly to the chloroketone (V).



Scheme I

The rearrangement of IV occurred when the chloroepoxide was allowed

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