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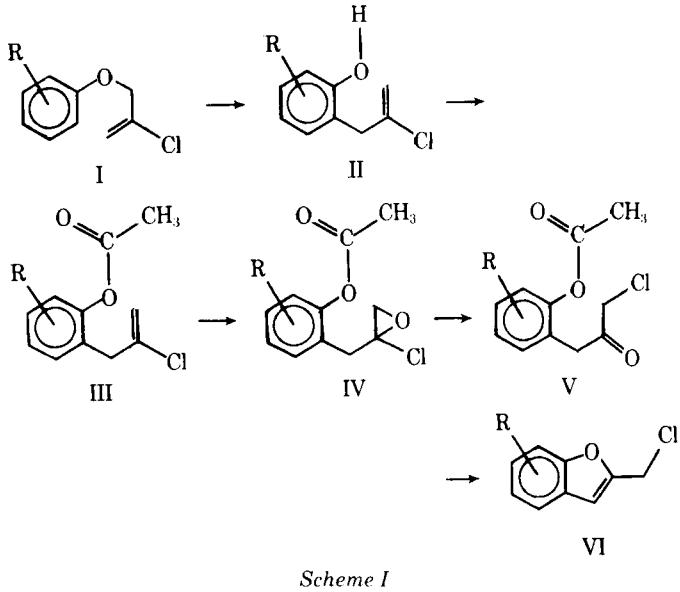
Abstract □ 2-Chloromethylbenzo[*b*]furans were prepared in high overall yield from the corresponding chloroethylphenyl ethers through chloroepoxide and α-chlorophenylacetone intermediates.

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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Table I—Yields, Physical Properties, and Microanalytical Data [a]

Compound	R	Melting or Boiling Point (Recrystallization Solvent)	Yield, %	Molecular Formula	Analysis, %	Calc.	Found
IIIa	4-Cl	90°/0.20 torr	98	$C_{11}H_{10}Cl_2O_2$	C	53.90	53.82
					H	4.11	4.12
					Cl	28.93	28.81
IIIb	6-Cl	89°/0.25 torr	96	$C_{11}H_{10}Cl_2O_2$	C	53.90	53.97
					H	4.11	4.13
					Cl	28.93	28.83
IIIc	4-OCH_3	100°/0.90 torr	100	$C_{12}H_{13}ClO_3$	C	59.88	59.91
					H	5.44	5.49
					Cl	14.73	14.84
IIId	6-OCH_3	95°/1.00 torr	98	$C_{12}H_{13}ClO_3$	C	59.88	59.87
					H	5.44	5.47
					Cl	14.73	14.83
IIIe	6-CH_3	80°/0.15 torr	99	$C_{12}H_{13}ClO_2$	C	64.15	64.08
					H	5.83	5.88
					Cl	15.78	15.81
Va	4-Cl	98–100° (Carbon tetrachloride–hexane)	70[b]	$C_{11}H_{10}Cl_2O_3$	C	50.60	50.56
					H	3.86	3.87
					Cl	27.16	27.14
Vb	6-Cl	91–93° (Carbon tetrachloride–hexane)	75[b]	$C_{11}H_{10}Cl_2O_3$	C	50.60	50.66
					H	3.86	3.87
					Cl	27.16	27.09
Vc	4-OCH_3	104.5–105° (Methylene chloride–petroleum ether)	81[b]	$C_{12}H_{13}ClO_4$	C	56.15	56.16
					H	5.11	5.15
					Cl	13.81	13.74
Vd	6-OCH_3	85–86° (Carbon tetrachloride–petroleum ether)	60[b]	$C_{12}H_{13}ClO_4$	C	56.15	56.07
					H	5.11	5.13
					Cl	13.81	13.88
Ve	6-CH_3	94–95° (Carbon tetrachloride)	95[b]	$C_{12}H_{13}ClO_3$	C	59.88	59.65
					H	5.44	5.49
					Cl	14.73	14.64
VIa	5-Cl	54–55° (Hexane)	99	$C_9H_6Cl_2O$	C	53.77	53.74
					H	3.01	3.06
					Cl	35.27	35.16
VIb	7-Cl	84–86° (Methylene chloride–petroleum ether)	99	$C_9H_6Cl_2O$	C	53.77	53.70
					H	3.01	2.99
					Cl	35.27	37.18

[a] IR, UV, and NMR data are consistent with the reported structures and are similar to data reported under *Experimental*. [b] The yield of V is based on III (*i.e.*, on the two-step conversion).

to stand (neat) at room temperature for several days; this reaction was accelerated markedly by a trace of anhydrous hydrogen chloride. The phenylacetone derivatives (V) are potentially useful intermediates in the synthesis of substituted phenethylamines and phenpropylamines.

Treatment of Va or Vb with hot concentrated hydrochloric acid resulted in facile cyclization to VIa or VIb, respectively. Excessive decomposition accompanied attempted cyclization of Vc–Ve.

EXPERIMENTAL

Table I summarizes the yields, physical properties, and microanalyses for the compounds prepared[1]. Scheme I illustrates the steps in the synthesis.

2-(2′-Chloroprop-2-enyl)-4-chlorophenyl Acetate (IIIa)—A solution of IIa (6.09 g, 0.03 mole) and acetic anhydride (10 ml) in anhydrous pyridine (30 ml) was stirred magnetically and allowed to stand for 12 hr at room temperature. The pyridine and excess anhydride were removed *in vacuo*, and the residue was distilled to yield IIIa (7.21 g, 98%), bp 90°/0.20 torr; IR: 2899, 1757, 1634, 1475, 1427, 1404, 1366, 1190 (br), 1164, 1043, 1009, 943, 909, and 890 cm^{-1}; NMR: δ 2.25 (s, 3H), 3.59 (s, 2H), 5.29 (d, J = 13 Hz, 2H), and 7.08–7.60 (m, 3H); UV: λ_{max} 228 (Σ 3170) and 278 (55) nm.

2-(3′-Chloropropan-2′-one)-4-chlorophenyl Acetate (Va)—A stirred solution of IIIa (30 g, 0.115 mole) and *m*-chloroperbenzoic acid (85%, 36 g) in methylene chloride (300 ml) was allowed to stand at room temperature for 9 days. It was then concentrated to dryness *in vacuo*, and the residue was dissolved in ether (200 ml). The ethereal solution was washed successively with saturated aqueous sodium carbonate solution (200 ml), water (200 ml), and 10% aqueous hydrochloric acid (200 ml); the solution was dried over sodium sulfate and concentrated *in vacuo*.

The residual acid catalyzed the conversion of IVa to Va; the reaction was monitored by TLC (silica gel, methylene chloride); after several days, none of the chloroepoxide remained. The product was crystallized from carbon tetrachloride–hexane to yield 21 g (70%) of Va, mp 98–100°; IR: 2907, 1761, 1718, 1481, 1368, 1196, 1163, 1111, 1009, and 881 cm^{-1}; NMR: δ 2.27 (s, 3H), 3.78 (s, 2H), 4.07 (s, 2H), and 6.93–7.43 (m, 3H); UV: λ_{max} 226 (Σ 3260), 270 (550), and 278 (520) nm.

2-Chloromethyl-5-chlorobenzo[*b*]furan (VIa)—A vigorously stirred solution of Va (2.0 g, 7.66 mmoles) in concentrated hydrochloric acid (60 ml) was heated at 90° for 1 hr, and the cooled solution then was extracted with chloroform (3 × 60 ml). The chloroform solution was washed with water (100 ml), dried over sodium sulfate, and concentrated *in vacuo* to give 1.53 g (99%) of VIa, mp 53–55°. Crystallization from hexane at −78° gave VIa, mp 54–55°; IR: 2941, 1855, 1730, 1610, 1577, 1460, 1445, 1429, 1314, 1272, 1263, 1192, 1130, 1064, 961, 925, 889, 870, 833, 719, and 698 cm^{-1}; NMR: δ 4.52 (s, 2H), 6.51 (s, 1H), and 7.13–7.40 (m, 3H); UV: λ_{max} 215 (Σ 19,600), 256 (13,700), 288 (3460), and 298 (2990) nm.

[1] Melting points (uncorrected) were determined in an open capillary with a Thomas–Hoover Unimelt apparatus. IR spectra were determined for carbon tetrachloride solutions (unless otherwise specified) with a Perkin-Elmer 237 spectrophotometer. UV data were determined for 95% ethanol solutions with a Beckman DB-G spectrophotometer. NMR spectra were determined with a Varian T-60 spectrometer for carbon tetrachloride solutions (unless otherwise specified) containing ~1% tetramethylsilane as the internal standard. Microanalyses were performed by Atlantic Microlab, Atlanta, Ga.

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