Studies on the Synthesis of Heterocyclic Compounds. XVI. Cleavage of 1,3-Benzodioxoles and -Benzoxathioles by Sodium Iodide-Acyl Chloride

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The cleavage reaction of ethereal and thioethereal bonds with sodium iodide and acyl chloride has been studied. In all the 1,3-benzodioxoles and -benzoxathioles studied, the opening of the heterocyclic ring with formation of 1,2-diacetoxybenzene or 2-hydroxythiophenol diacetic ester and *gem*-diiodoalkanes and iodoalkenes has been observed. The structure of newly prepared compounds has been determined by analytical and spectroscopic data or comparison with authentic samples.

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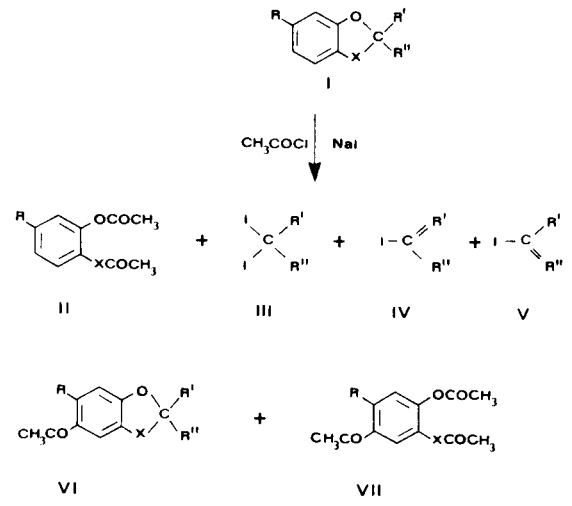
Our continuing interest in the cleavage of ethereal and thioethereal bonds [1] has led us to experiment with the reagent sodium iodide-acyl chloride, which has been shown to be very effective in the ether cleavage affording the corresponding esters and iodides without Lewis acids as the catalyst [2-4].

Our intention was to establish the scope of this reagent in causing ethereal bond cleavage in 1,3-benzodioxole and -benzoxathiole systems under milder conditions than those previously observed, in order to study the possibility of using it as an alternative method of synthesis of the *gem*-diiodoalkanes and -cycloalkanes.

The cleavage reactions were carried out with acyl iodide, prepared *in situ* from sodium iodide and acyl chloride, to which an acetonitrile solution of 1,3-benzodioxole or -benzoxathiole derivative was added. Using 1,3-benzodioxole derivatives, the cleavage reaction could be completed simply by stirring at room temperature, whereas

Scheme



a) X = O; R' = R" = H; R = H

b) X = O; R' = R" = CH_3; R = H

c) X = O; R' = CH_3; R" = C_2H_5; R = H

d) X = O; R' = CH_3; R" = CH_2-C_6H_5; R = H

e) X = O; R' = R" = iC_3H_7; R = H

f) X = O; R' R" = $-(CH_2)_4-$; R = H

g) X = O; R' R" = $-(CH_2)_5-$; R = H

h) X = O; R' = R" = H; R = CHO

i) X = S; R' = R" = R = H

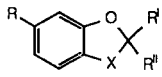
l) X = S; R' = R" = CH_3; R = H

m) X = S; R' R" = $-(CH_2)_4-$; R = H

n) X = S; R' R" = $-(CH_2)_5-$; R = H

Table I

Action of Sodium Iodide-Acyl Chloride on 1,3-Benzodioxoles and -Benzoxathioles



Starting Material		Reaction Time	% Products			
X = O	% Cleavage	hours [a]	II	III	IV + V	VI
R = R^I = R^{II} = H (Ia)	90	6	43	40	-	traces
R = H R^I = R^{II} = CH_3 (Ib)	85	10	40	35	-	traces
R = H R^I = CH_3 R^{II} = C_2H_5 (Ic)	80	12	38	18	19	5
R = H R^I = CH_3 R^{II} = CH_2-C_6H_5 (Id)	82	14	38	15	18	10
R = H R^I = R^{II} = i-C_3H_7 (Ie)	traces	24	-	-	-	20
R = H R^I R^{II} = $(CH_2)_4$ (If)	82	20	40	20	15	8
R = H R^I R^{II} = $(CH_2)_5$ (Ig)	75	24	35	17	12	12
R = CHO R^I = R^{II} = H (Ih)	84	15	40	38	-	-
X = S						
R = R^I = R^{II} = H (Ii)	85	12	42	42	-	-
R = H R^I = R^{II} = CH_3 (Il)	85	24	38	36	-	traces
R = H R^I R^{II} = $(CH_2)_4$ (Im)	80	24	35	25	8	8
R = H R^I R^{II} = $(CH_2)_5$ (In)	76	24	35	20	6	10

[a] All the cleavage reactions of the 1,3-benzodioxole derivatives were performed in acetonitrile at room temperature, while those of 1,3-benzoxathioles were performed at reflux temperature.

Table II

Compound	Molecular formula	Analysis % Calcd./Found C	H
2-Methyl-2-benzyl-1,3-benzodioxole (**Id**)	$C_{15}H_{14}O_2$	79.62 79.60	6.24 6.25
3,4-Diacetoxybenzaldehyde (**IIh**)	$C_{11}H_{10}O_5$	59.46 59.41	4.54 4.53
2-Methyl-2-ethyl-5-acetyl-1,3-benzodioxole (**VIc**)	$C_{12}H_{14}O_3$	69.88 69.85	6.84 6.83
2-Methyl-2-benzyl-5-acetyl-1,3-benzodioxole (**VId**)	$C_{17}H_{16}O_3$	76.10 76.05	6.01 6.02
5-Acetilspiro[1,3-benzodioxa-2,1'-ciclopentane] (**VIf**)	$C_{13}H_{14}O_3$	71.54 71.48	6.47 6.47
5-Acetylspiro[1,3-benzodioxa-2,1'-ciclohexane] (**VIg**)	$C_{14}H_{16}O_3$	72.39 72.35	6.94 6.93

when using the corresponding benzoxathiole derivatives the reaction had to be refluxed. As a first step the cleavage occurs by formation of oxonium salts [1,5] successively leading to the corresponding esters and the alkyl and alkenyl iodides (Scheme). In contrast with earlier studies, this ether-cleaving reagent was successfully applied to aromatic systems containing formyl and hydroxyl functions in addition to the benzodioxole group [5] (Table 1).

In contrast with our observations using other reagents, cleavage of both the C-O and C-S linkages always occurred. In fact the reaction proceeded rapidly with formation of the following mixture: 1,2-diacetoxybenzene, in good yields even after a few hours; *gem*-diiodoalkane which, due to loss of hydrogen iodide, decreased progressively on increasing the reaction times; and consequent formation of

iodoalkenes and polymeric mixtures. In all cases small amounts of 5-acetyl derivatives, which became significant only when R′ and R″ were sterically demanding, were always observed. Compounds **VII**, which always formed in very low yields, was pointed out by spectrometric methods or by comparison with authentic samples [6].

The course of the cleavage reactions was monitored by isolating small samples from the reaction mixture at regular intervals and analyzing them by glc and hplc in comparison with authentic samples prepared otherwise.

This cleavage system of ethereal bonds suggests that this reaction could be used in preparing macrocyclic derivatives which would be an improvement over previous methods using tin and antimony intermediates [7]. Work is under way to confirm and ascertain the generality of this process.

EXPERIMENTAL

The ir spectra were recorded on a Perkin-Elmer model 157 G spectrophotometer. Samples were examined as potassium bromide pellets or as thin films in the case of liquids; absorption frequencies are quoted in reciprocal centimeters. The nmr spectra were determined on a Varian EM 360 L spectrometer and chemical shifts were measured in ppm (δ) using tetramethylsilane as the internal standard. The mass spectra were run on a VG ZAB-2F instrument operating at 70 eV (200 μA). Merck silica gel (70-230 mesh) were used for column chromatography. The glc analyses were performed on a Perkin-Elmer 881 instrument equipped with an SE-30 column (2m × 0.5 cm, 5% chromosorb W 60/80). The hplc analyses were performed on a Perkin-Elmer series 4 liquid chromatograph. A Perkin-Elmer C_{18} column (250 × 4.6 mm id) was used; mobile phase 50:50 methanol-water; flow-rate: 1 ml minute $^{-1}$; detector UV/Visible Perkin-Elmer LC 85B; λ = 254 nm). Boiling points were uncorrected and obtained from distillation or by means of a boiling point apparatus. Melting points were determined on an Electrothermal melting point apparatus and were uncorrected. Microanalyses for CHN were carried out on a Carlo Erba model 1106 Elemental Analyzer.

Starting Materials.

The following compounds were prepared as described previously: 1,3-benzodioxole [8], 2,2-dimethyl-1,3-benzodioxole [9,10], 2-methyl-2-ethyl-1,3-benzodioxole [10], spiro[1,3-benzodioxa-2,1′-cyclopentane] [9,10], spiro[1,3-benzodioxa-2,1′-cyclohexane] [9,10] 2,2-diisopropyl-1,3-benzodioxole [11], 1,3-benzoxathiole [12], 2,2-dimethyl-1,3-benzoxathiole [12,13], spiro[1,3-benzoxathiole-2,1′-cyclopentane] [12,13], spiro[1,3-benzodioxa-2,1′-cyclohexane] [12,13], 2-hydroxythiophenol [14].

Authentic Samples.

Cathecol, dibromomethane, acetone, 2-butanone, phenylacetone, 2,4-dimethyl-3-pentanone, cyclohexanone, cyclopentanone, diiodomethane, 2,2-diiodopropane, acetyl chloride, piperonal, as well as all the solvents were commercial products and were used without further purification; 2-iodobutene-2 [15], 2-iodobutene-1 [15], 2,2-diiodobutane [15], 2-iodo-3-phenylpropene [15], 1-phenyl-2-iodopropene [15], 1-phenyl-2,2-diiodopropane [15], 1-iodocyclopentene [15], 1,1-diiodocyclopentane [15], 1-iodocyclohexene [15], 1,1-diiodocyclohexane [15], 5-acetyl-1,3-benzodioxole [11], 2,2-dimethyl-5-acetyl-1,3-benzodioxole [11], 2,2-diisopropyl-5-acetyl-1,3-benzodioxole [11], 5-acetyl-1,3-benzoxathiole [16], 2,2-dimethyl-5-acetyl-1,3-benzoxathiole [1], 5-acetylspiro[1,3-benzoxathiole-2,1′-cyclopentane] [1], 5-acetylspiro [1,3-benzoxathiole-2,1′-cyclohexane] [1], 1,2-diacetoxybenzene [17], 2-hydroxythiophenoldiacetic ester [7] were prepared according to literature procedures.

Compounds **Id**, **IIh** and **VIc,d,f,g** were prepared by the following methods.

2-Methyl-2-benzyl-1,3-benzodioxole **Id**.

A benzene (200 ml) solution of cathecol (0.1 mole) and 2,4-dimethyl-3-pentanone (0.1 mole) was heated under reflux for 24 hours in the presence of a trace of *p*-toluenesulphonic acid. Water, formed in the reaction was removed azeotropically using a Dean-Stark apparatus. The reaction mixture was evaporated and the residue, redissolved in ether, was washed with 2*N* sodium hydroxide, and water. The organic layer, dried over anhydrous sodium sulphate, was evaporated and the residue distilled under reduced pressure to give **Id** as a yellow oil, bp 129-130° (1 mm); n_D^{24} 1.5473; ir (film): 3040, 3020, 2920, 1620, 1600, 1480, 1450, 1375, 1360, 1310, 1230, 1180, 1110, 1100, 1060, 1000, 950, 900, 835, 805, 730, 690 cm^{-1}; nmr (deuteriochloroform): δ 7.25 (s, 5H aromatic), 6.53 (s, 4H aromatic), 3.10 (s, CH_2, 2H) and 1.54 ppm (s, CH_3, 3H).

3,4-Diacetoxybenzaldehyde (**IIh**).

To a stirred mixture of 5,4-dihydroxybenzaldehyde (10 mmoles) and pyridine (10 mmoles) in 30 ml of benzene at room temperature, a solution of acetyl chloride (25 mmoles) in 5 ml of benzene was added dropwise. The reaction mixture was stirred and refluxed for several hours, then cooled and the solvent evaporated in vacuum. The crude residue was purified by eluting through a silica gel column using a 3:1 mixture of petroleum ether-diethyl ether as eluent to give a white powder, yield 45%; mp 83-85°; ir (potassium bromide): 3040, 2900, 2830, 1770, 1690, 1600, 1490, 1450, 1420, 1365, 1250, 1200, 1160, 1100, 1000, 890, 850, 830 cm^{-1}; nmr (deuteriochloroform): δ 9.76 (s, CHO, 1H deuterium oxide exchanged), 7.38-6.93 (m, 3H aromatic) and 2.2 ppm (s, $2CH_3$, 6H).

2-Methyl-2-ethyl-5-acetyl-1,3-benzodioxole (**VIc**).

A cooled solution of acetyl chloride (10 mmoles) in dry 1,2-dichloroethane (10 ml) was added dropwise at 0° to a solution of 2-methyl-2-ethyl-1,3-benzodioxole (**Ic**) (10 mmoles) and aluminium chloride (10 mmoles) in dry 1,2-dichloroethane (30 ml). After 3 hours at 0° the mixture was decomposed by shaking with ice and dilute hydrochloric acid for 1 hour. The organic layer was washed in 10% sodium hydroxide, in water, then dried over anhydrous sodium sulphate and evaporated. The residue was chromatographed on a silica gel column using petroleum ether-diethyl ether (5:1) to give **VIc** as a white solid (45% yield), mp 30-31°; ir (potassium bromide): 2960, 2920, 1670, 1600, 1485, 1440, 1360, 1270, 1250, 1175, 1040, 1020, 915, 850, 810 cm^{-1}; nmr (deuteriochloroform): δ 7.58-6.66 (m, 3H aromatic), 2.43 (s, CO-CH_3, 3H), 2.12-1.75 (q, CH_2, 2H), 1.6 (s, CH_3, 3H) and 1.05-0.83 ppm (t, CH_2-CH_3, 3H).

2-Methyl-2-benzyl-5-acetyl-1,3-benzodioxole (**VId**).

This compound was prepared under the previously described conditions for **VIc** as a white crystalline solid (65% yield), mp 73-74°; ir (potassium bromide): 2930, 1670, 1600, 1495, 1445, 1385, 1355, 1330, 1290, 1260, 1240, 1190, 1140, 1110, 1080, 1035, 1020, 960, 910, 870, 850, 805 cm^{-1}; nmr (deuteriochloroform): δ 7.50-6.61 (m, 3H aromatic), 7.23 (s, 5H aromatic), 3.10 (s, CH_2, 2H), 2.43 (s, $COCH_3$, 3H) and 1.55 ppm (s, $2CH_3$, 6H).

5-Acetylspiro[1,3-benzodioxa-2,1′-cyclopentane] (**VIf**).

This compound was obtained under the previously described conditions for **VIc** in a yield of 50%; mp 32-33°; ir (potassium bromide): 2980, 2930, 1680, 1610, 1500, 1450, 1370, 1340, 1280, 1260, 1205, 1120, 1090, 1045, 1020, 960, 905, 850, 820 cm^{-1}; nmr (deuteriochloroform): δ 7.60-6.63 (m, 3H aromatic), 2.46 (s, CO-CH_3, 3H) and 2.10-1.80 ppm (m, $(CH_2)_4$, 8H).

5-Acetylspiro[1,3-benzodioxa-2,1′-cyclohexane] (**VIg**).

This compound was obtained as a light yellow solid (55% yield); mp 46-47°; ir (potassium bromide): 2950, 2850, 1675, 1605, 1580, 1500, 1450, 1355, 1290, 1265, 1150, 1130, 1070, 970, 915, 850, 810 cm^{-1}; nmr (deuteriochloroform): δ 7.56-6.69 (m, 3H aromatic), 2.50 (s, CH_3, 3H) and 1.97-1.57 ppm (m, $(CH_2)_5$, 10H).

Cleavage of 1,3-Benzodioxole (**Ia**).

To a stirred acetonitrile (10 ml) mixture of 1,3-benzodioxole (10

mmoles) and sodium iodide (25 mmoles) cooled in an ice-water bath, a solution of acetyl chloride (20 mmoles) in 10 ml of acetonitrile was added. After six hours of stirring the reaction mixture was quenched by addition of aqueous sodium bisulphite. The resulting mixture was extracted with ether and the ethereal layer washed with 3*N* hydrochloric acid, 5% sodium carbonate solution, and water consecutively. It was then dried over anhydrous potassium carbonate. The ether was evaporated and the crude reaction mixture distilled under reduced pressure and purified by column chromatography on silica gel using petroleum ether-diethyl ether (5:1) to give a mixture of 1,2-diacetoxybenzene (**IIa**) (43% yield) and diiodomethane (**IIIa**) (40% yield). The cleavage reactions of **Ib-g** were performed under the previously described conditions for **Ia**. The obtained products are summarized in Table I.

Cleavage of 1,3-benzoxathiole (**1i**).

To a stirred acetonitrile (10 ml) mixture of 1,3-benzoxathiole (10 mmoles) and sodium iodide (25 mmoles) cooled in an ice-water bath, a solution of acetyl chloride (20 mmoles) in 10 ml of acetonitrile was added. Then the reaction mixture was heated under reflux for 12 hours and afterwards it was quenched by addition of aqueous sodium bisulphite. The resulting mixture was extracted with ether and the ethereal layer washed with 3*N* hydrochloric acid, 5% sodium carbonate solution, and water consecutively. It was then dried over anhydrous potassium carbonate. The ether was evaporated and the crude reaction mixture distilled under reduced pressure and purified by column chromatography on silica gel using petroleum ether-diethyl ether (5:1) to give a mixture of 2-hydroxythiophenoldiacetic ester (**IIi**) (42% yield) and diiodomethane (**IIIi**) (42% yield).

The cleavage reactions of **1l-n** were performed under the previously described conditions for **1i**. The obtained products are summarized in Table I.

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