On the Reaction of α-(2-Hydroxyphenoxy)alkylketones with Dimethylsulphoxonium Methylide. A Novel Route to 2-Substituted-2,3-dihydro-2-hydroxymethyl-1,4-benzodioxins

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A new route to 2-substituted-2,3-dihydro-2-hydroxymethyl-1,4-benzodioxins **3** based on the reaction of α-(2-hydroxyphenoxy)alkylketones **1** with dimethylsulphoxonium methylide in dimethylsulphoxide is reported. Besides the desired compounds **3**, the isomeric 2*H*-3,4-dihydro-1,5-benzodioxepines **4** were also isolated, generally as minor products. The concurrent formation of **3** and **4** has been interpreted as occurring through the intermediate oxiranes **2**, which can undergo intramolecular nucleophilic attack at either of the carbon atoms of the epoxy ring.

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The synthesis of 2-substituted-2,3-dihydro-2-hydroxymethyl-1,4-benzodioxins **3** can be achieved through nucleophilic addition of catechol to 2-substituted-1-chloro-2,3-epoxypropanes under alkaline conditions [1,2]. This method, however, is rather unsatisfactory, since preparation of the epoxides generally involves a multistep process. Furthermore, if substituted catechol derivatives are employed, mixtures of regioisomers may be formed [1]. We now wish to report a new route to compounds **3** (see Scheme) based on the reaction of α-(2-hydroxyphenoxy)-alkylketones **1** with dimethylsulphoxonium methylide (DMSOM) in dimethylsulphoxide (DMSO), which avoids some of the previous drawbacks. Moreover the present method allows the preparation of new compounds **3** with an extra substituent in 3 position, which are not easily achievable otherwise.

Results and Discussion.

The starting ketones **1** (Table 1) were readily prepared by reacting catechol, or a substituted catechol, with the proper α-haloketone in acetone in the presence of potassium carbonate. The ^{1}H-nmr studies showed that these compounds exist in dimethylsulphoxide-d_6 as mixtures of cyclic hemiketal **1'** and **1"** and open-chain keto **1** forms in equilibrium (see Table 2 and Experimental).

The reaction of compounds **1** with DMSOM, obtained *in situ* from trimethylsulphoxonium iodide and sodium hydride according to Corey [3], was performed in DMSO at room temperature.

Table 1

Yields and Physical Data for Compounds **1**

Compound	R^1	R^2	R^3	Yield (%)	Mp (°C) (Solvent)	IR, cm^{-1} [a]	Molecular formula	Analysis Calcd. (Found) C%	H%
1a	Me	H	H	64	98-100 (*n*-hexane)	3200 (ν OH)	$C_9H_{10}O_3$	65.05 (65.01)	6.07 (5.98)
1b	Me	Me	H	59	75-77 (*n*-hexane-benzene 30:1)	3500, 3440, 3150 (ν OH)	$C_{10}H_{12}O_3$	66.65 (66.38)	6.71 (6.81)
1c	Ph	H	H	42	110-113 [b] (isopropyl ether)	3400 (ν OH)	$C_{14}H_{12}O_3$	73.67 (73.59)	5.30 (5.23)
1d	Ph	Me	H	61	69-72 (*n*-hexane)	3540-3450 (ν OH)	$C_{15}H_{14}O_3$	74.36 (74.41)	5.83 (5.82)
1e	Et	H	H	78	58-60 (*n*-hexane)	3400 (ν OH), 1730 (ν C=O)	$C_{10}H_{12}O_3$	66.65 (66.95)	6.71 (6.73)
1f	Me	H	Cl	90	79-81 (*n*-hexane-benzene 1:9)	3240 (broad, ν OH)	$C_9H_9ClO_3$	53.88 (53.81)	4.52 (4.40)

[a] Spectra recorded in nujol mull; only some diagnostic signals are reported. [b] Lit [5], bp 89-90°/0.2 mm.

Scheme

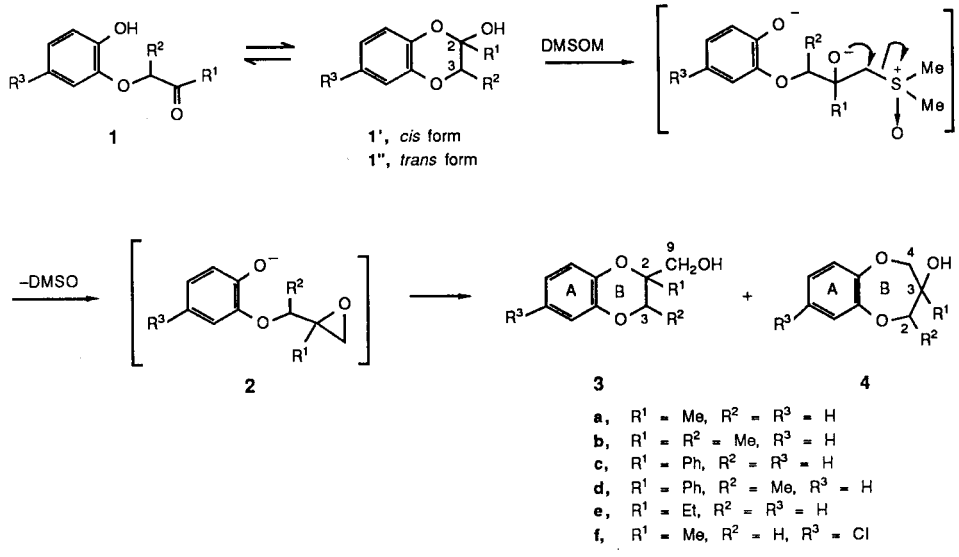

Table 2

^{1}H-NMR Chemical Shifts (δ, ppm) for Compounds **1** in DMSO-d_6

1a	(open form, < 5%): 9.05 (s, OH, 1H), 6.8-7.0 (m, aromatic, 4H), 4.73 (s, CH_2, 2H), 2.17 (s, $COCH_3$, 3H);
1'a	(closed form, > 95%): 6.92 (s, OH-2, 1H), 6.8-7.0 (m, aromatic, 4H), 3.97 and 3.85 (d, H_Z3, 2H, $J_{3a,3b}$ = 11.0 Hz), 1.44 (s, Me-2, 3H)
1'b	(*cis* closed form, 75%): 6.7-6.9 (m, aromatic, 4H), 6.76 (d, OH-2, 1H, $J_{OH\text{-}2,3}$ = 1.2 Hz), 3.92 (dq, H-3, 1H, $J_{3,OH\text{-}2}$ = 1.2 and $J_{3,Me\text{-}3}$ = 6.4 Hz), 1.43 (s, Me-2,3H), 1.30 (d, Me-3,3H, $J_{Me\text{-}3,3}$ = 6.4 (Hz);
1'c	(*closed* form, *ca.* 100%): 6.8-7.6 (m, aromatic, 9H), 7.5 (s, OH-2, 1H), 4.11 and 3.92 (d, H_Z3, 2H, $J_{3a,3b}$ = 11.0 Hz).
1d	(open form, 2%): 9.01 (s, OH, 1H), 8.08 and 6.7-7.6 (m, aromatic, 9H), 5.83 (q, CH, 1H, $J_{CH,\,Me}$ = 6.7 Hz), 1.53 (d, Me, 3H, $J_{Me,CH}$ = 6.7 Hz);
1'd	(*cis* closed form, 80%): 6.7-7.6 (m, aromatic, 9H), 7.36 (d, OH-2, 1H, $J_{OH\text{-}2,3}$ = 1.5 Hz), 4.10 (dq, H-3, 1H, $J_{3,OH\text{-}2}$ = 1.5 and $J_{3,Me\text{-}3}$ = 6.3 Hz), 1.06 (d, Me-3, 3H, $J_{Me\text{-}3,3}$ = 6.3 Hz);
1"d	(*trans* closed form, 18%): 6.7-7.6 (m, aromatic, 9H), 7.39 (s, OH-2, 1H), 4.38 (q, H-3, 1H, $J_{3,Me\text{-}3}$ = 6.5 Hz), 0.89 (d, Me-3, 3H, $J_{Me\text{-}3,3}$ = 6.5 Hz)
1e	(open form, < 5%): 9.02 (s, OH, 1H), 6.8-7.0 (m, aromatic, 4H), 4.74 (s, OCH_2, 2H), 2.56 (q, $COCH_2$, 2H, $J_{CH_2,Me}$ = 7.5 Hz), 0.97 (t, Me, 3H, J_{Me,CH_2} = 7.5 Hz);
1'e	(closed form, > 95%): 6.8-7.0 (m, aromatic, 4H), 6.70 (s, OH-2, 1H), 3.97 and 3.88 (d, H_Z3,2H, $J_{3a,3b}$ = 11.0 Hz), 1.76 and 1.71 (m, CH_Z2,2H), 0.95 (t, Me, 3H, $J_{Me,CH_2\text{-}2}$ = 7.5 Hz)
1f	(open form, < 5%): 9.32 (s, OH, 1H), 6.8-7.0 (m, aromatic, 3H), 4.82 (s, CH_2, 2H), 2.17 (s, COMe, 3H);
1'f	(closed form, > 95%): 7.02 (s, OH-2, 1H), 6.8-7.0 (m, aromatic, 3H), 4.01 and 3.87 (d, H_Z3,2H, $J_{3a,3b}$ = 11.0 Hz), 1.45 (s, Me-2, 3H)

As outlined in the Scheme, besides the desired 2,3-dihydro-1,4-benzodioxins **3**, the isomeric 2*H*-3,4-dihydro-1,5-benzodioxepins **4** were also isolated. The yield and the product distribution, reported in Table 3, show that the benzodioxin derivatives **3** are always the main products, except for the reaction of ketone **1d**, which afforded predominantly the corresponding benzodioxepin **4d**.

Noticeably only one of the two possible diastereoisomeric racemates of the benzodioxins **3b** and **3d** has been obtained [4]. Separation of the target compounds **3** from the isomeric benzodioxepins **4** was generally accomplished by treatment of the crude reaction mixture with *p*-toluenesulphonyl chloride. The tosylates of the primary alcohols **3** were thus obtained as the only products, and easily puri-

Table 3

Yields and Physical Data for Compounds **3** and **4**

Substrate	Products	R^1	R^2	R^3	Yield [a] (%)	benzodioxin [b] benzodioxepin	Mp (°C) or bp (°C/mm) (solvent)	Molecular formula	Analysis Calcd. (Found) C%	H%
	3a	Me	H	H			64-66 [c] (ligroin)	$C_{10}H_{12}O_3$		
1a					64	2:1				
	4a	Me	H	H			73-75 [c] (ligroin)	$C_{10}H_{12}O_3$		
	3b [d]	Me	Me	H			89-91 (*n*-hexane-benzene 9:1)	$C_{11}H_{14}O_3$	68.02 (67.90)	7.27 (7.35)
1b					65	3:2				
	4b [e]	Me	Me	H			180-190/0.2	$C_{11}H_{14}O_3$	68.02 (67.81)	7.27 (7.35)
	3c [f]	Ph	H	H			82-84 (*n*-hexane-benzene 9:1)	$C_{15}H_{14}O_3$	74.36 (74.19)	5.83 (5.91)
1c					95	2:1				
	4c	Ph	H	H			190-200/0.8	$C_{15}H_{14}O_3$	74.36 (74.49)	5.83 (6.01)
	3d [g]	Ph	Me	H			115-117 (ethanol)	$C_{16}H_{16}O_3$	74.98 (74.79)	6.29 (6.32)
1d					90	3:7				
	4d [h]	Ph	Me	H			104-106 (ethanol)	$C_{16}H_{16}O_3$	74.98 (74.70)	6.29 (6.19)
	3e	Et	H	H			160-170/0.8 [c]	$C_{11}H_{14}O_3$		
1e					95	4:3				
	4e	Et	H	H			170-175/1.5 [c]	$C_{11}H_{14}O_3$		
	3f	Me	H	Cl			74-76 [c] (*n*-hexane)	$C_{10}H_{11}ClO_3$		
1f					46	7:3				
	4f	Me	H	Cl			160-170/1.5	$C_{10}H_{11}ClO_3$	55.95 (56.09)	5.17 (5.01)

[a] Calculated on the crude reaction product as a mixture of **3** and **4**. [b] Determined by glc. [c] In accordance to the reference [1]. [d] One racemate; tosylate, mp 129-131° (ethanol). [e] Mixture of the two diastereoisomeric racemates **4b** and **4b'** in 1:1 ratio. [f] Tosylate, mp 96-98° (ethanol). [g] One racemate; tosylate, mp 132-134° (ethanol). [h] The crude reaction product was a mixture of the two diastereoisomeric racemates **4d** and **4d'** in 6:1 ratio; only racemate **4d** was isolated in pure state by cristallization.

Table 4

^{1}H-NMR Chemical Shifts (δ, ppm) of Compounds **3** in DMSO-d_6

Proton [a]	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**
H-3A	4.09	4.08	4.74	4.86	4.09	4.12
H-3B	3.89		4.32		3.93	3.93
H-9A	3.47	3.48	3.71	3.85	3.46	3.48
H-9B	3.39	3.44	3.64	3.63	3.46	3.41
Me-2	1.22	1.27				1.23
Me-3		1.26		1.28		
Et-2					1.64	
					0.90	
Ph-2			7.2-7.5	7.2-7.5		
OH-9	5.12	4.94	5.29	5.04	5.05	5.15

[a] The ring A protons resonate at 6.7-7.1 ppm.

fied by crystallization. Their alkaline hydrolysis gave pure compounds **3**.

The ^{1}H-nmr spectra of the two series of compounds **3** and **4** were fully consistent with the proposed structures. Specifically, the spectra of compounds **3** revealed the presence of an ABX spin system due to C(9)H_2OH grouping ($^2J_{AB}$ = 11.2-11.8, $^3J_{AX}$ = 5.3-5.5, and $^3J_{BX}$ = 5.5-6.4 Hz), whereas the spectra of compounds **4** exhibited an AB spin system ($^2J_{AB}$ = 11.5-12.5 Hz) and a broad singlet attributable to H_2-4 and OH-3, respectively. These findings are indicative of the presence of a 2-hydroxymethylene dihydrodioxin ring B, and of a 3-hydroxydihydrodioxepin ring B, respectively. The ^{1}H-nmr parameters of compounds **3** and **4** are collected in Tables 4 and 5.

The formation of **3** and **4** may be interpreted as depicted in the Scheme. The first step is a nucleophilic attack of the ylide on the carbonyl of **1**, followed by, or con-

Table 5

^{1}H-NMR Chemical Shifts (δ, ppm) for Compounds **4** in DMSO-d_6

Proton [a]	**4a**	**4b**	**4b'** [b]	**4c**	**4d**	**4d'** [c]	**4e**	**4f**
H-2A	3.92	4.08	4.13	4.30	4.56	4.52	4.00	3.94
H-2B	3.92			4.19			3.91	3.94
H-4A	3.92	4.04	3.99	4.30	4.25	4.48	4.00	3.94
H-4B	3.92	3.85	3.88	4.19	4.14	4.10	3.91	3.94
Me-2		1.25	1.25		1.07	0.89		
Me-3	1.19	1.18	1.06					1.19
Et-3							1.56 0.91	
Ph-3				7.3-7.6	7.2-7.7	7.2-7.7		
OH-3	5.18	4.93	5.11	6.00	5.70	5.95	5.03	5.23

[a] The ring A protons resonate at 6.7-7.1 ppm. [b] Diastereoisomeric racemate of **4b**. [c] Diastereoisomeric racemate of **4d**.

certed with, the ring closure to afford epoxides **2** with DMSO elimination. The same intermediates have been previously hypothesized in the synthesis of compounds **3**, starting from catechol and 2-substituted-1-chloro-2,3-epoxypropanes [1].

Oxiranes **2** could not be isolated, but they were sufficiently stable to be detected as intermediates when the reactions between **1a** or **1c** and DMSOM were followed by ^{1}H-nmr spectroscopy (see Experimental). The build-up and the disappearance of a characteristic AB spin system (^2J = 5 Hz) at δ 2.80 and 2.66 for **2a** and 3.26 and 2.84 for **2c** due to the geminally coupled oxirane protons gave experimental evidence. The final intramolecular attack by the phenolate anion can eventually occur at either of the epoxy carbon atoms leading to **3** and **4**, respectively. The data reported in Table 2 show that such attack occurred predominantly at the more substituted carbon atom of the oxirane ring, the 6-exo process being favoured according to Baldwin rules [6]. The different regio-selectivities observed with the methyl substituted ketones **1b** and **1d** (7-endo process favoured) might by explained in terms of a more difficult attainment of collinearity of the phenolate anion with the oxirane C-O bond, which must be broken in the formation of the six-membered ring [7,8].

The present method of synthesis of 2,3-dihydro-1,4-benzodioxin derivatives **3** represents an useful alternative particularly in the preparation of monosubstituted compounds as indicated by the reaction of 3-(4-chloro-2-hydroxyphenoxy)propan-2-one **1f**, which afforded only the regio isomer **3f**.

EXPERIMENTAL

Melting points were obtained in open capillary tubes on a Büchi apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 257 spectrophotometer. The ^{1}H-nmr spectra were recorded on a Bruker CXP 300 spectrometer operating at 300.13 MHz. Chemical shifts are in ppm relative to TMS (δ 0.00) as the internal standard. NOe difference spectra were obtained by alternatively subtracting right off-resonance free induction decays (fids) from right on-resonance induced fids. The composition of the reaction mixtures was calculated by glc or by using nmr integration technique.

α-(2-Hydroxyphenoxy)alkylketones **1**.

General Procedure.

To a mixture of catechol (0.1 mole) and potassium carbonate (0.1 mole) in 100 ml of acetone, 0.09 mole of α-bromoketone (or, in the case of **1a** and **1b**, 0.09 mole of α-chloroketone and 0.09 mole of potassium iodide) were added. After heating at reflux for 12-24 hours, the reaction mixture was cooled, filtered and evaporated to dryness. The residue was partitioned between methylene chloride and water. The organic layer was separated and repeatedly washed with water. After drying over sodium sulphate and evaporation to dryness, the residue was crystallized from the proper solvent (Table 1). In the case of **1b**, **1d** and **1g** the residue was preliminary purified by distillation *in vacuo* (bp 140-160°/0.4 mm, 135-150°/0.4 mm and 185-205°/0.8 mm, respectively). The ^{1}H-nmr studies indicated that these compounds exist in dimethylsulphoxide-d_6 as mixtures of open-chain keto **1** and *cis* and *trans* cyclic hemiketal forms **1'** and **1"** in equilibrium. Thus, for instance, the ^{1}H-nmr spectrum of **1d** exhibited signals attributable to an equilibrium mixture of open **1d** and *cis* and *trans* **1'd** and **1"d**, the three isomers being present in a *ca.* 2:80:18 ratio.

Different ratios of the three prototropic forms were observed for the other α-(2-hydroxyphenoxy)alkylketones **1**, the cyclic forms being always the preferred ones (see Table 2). In the *cis* tautomers **1'b** and **1'd** H-3 showed a ω-type long-range coupling constant of 1.2 and 1.5 Hz, respectively, with OH-2, which suggests *trans* orientation for H-3 and OH-2.

Reaction of α-(2-Hydroxyphenoxy)alkylketones **1** with DMSOM.

General Procedure.

A solution of ketone **1** (0.1 mole) in 300 ml of dimethylsulphoxide was added dropwise to DMSOM (0.2 mole) prepared from 45 g (0.2 mole) of trimethylsulphoxonium iodide and 6 g (0.2 mole) of 80% dispersion of sodium hydride in mineral oil in 500 ml of dimethylsulphoxide according to the literature [2]. After stirring at room temperature under nitrogen

for 4-6 hours, the mixture was poured on ice, the *p*H adjusted to 4-7 with hydrochloric acid (1:1) and the resulting precipitate extracted with methylene chloride. The collected organic layers were washed with 5% aqueous sodium hydroxide, dried over sodium sulphate and evaporated to dryness to give a mixture of compounds **3** and **4**. The yield and the distribution of the products are reported in Table 3.

Separation of 2,3-Dihydro-1,4-benzodioxins **3** and 2*H*-3,4-Dihydro-1,5-benzodioxepins **4**.

a) General Procedure.

The crude mixtures of **3** and **4**, with the exception of the mixtures of **3b**, **4b** and **3d**, **4d** (see later), were dissolved in dry pyridine and treated with an equimolar amount of *p*-toluenesulphonyl chloride at 0-5° with stirring. After 24 hours the reaction mixtures were poured on ice and repeatedly extracted with methylene chloride. The collected organic layers were washed with water, dried over sodium sulphate and evaporated to dryness. Fractional crystallization of the residues from ethanol gave the corresponding tosylates of **3**, from which the benzodioxin alcohols were recovered by alkaline hydrolysis with finely powdered potassium hydroxide in *t*-butyl alcohol according to the literature [1]. The ethanolic mother liquors of the tosylates were evaporated to dryness and dissolved in methylene chloride. The solutions were washed with 5% sodium hydroxide and water to neutrality. Drying over sodium sulphate and evaporation of the solvent gave benzodioxepins **4**, which were purified by crystallization or distillation.

Physical and spectral data of compounds **3** and **4** are reported in Tables 3 and 4.

b) Separation of **3b** and **4b**.

The crude mixture was distilled *in vacuo* and the main fraction (135-145°/0.2 mm) was dissolved in benzene and then treated with *n*-hexane. The solid obtained was filtered and crystallized from a mixture of *n*-hexane-benzene (9:1) to give pure crystals of **3b** as one racemic form. The mother liquors were evaporated to dryness and the residue was submitted to the above general method of separation.

c) Separation of **3d** and **4d**.

The crude mixture was dissolved in ethyl alcohol. After 12 hours the solid obtained was filtered and crystallized from ethyl alcohol to give white crystals of **4d** as one racemic form. The mother liquors were evaporated to dryness and the residue was submitted to the above general method of separation. The stereochemistry of compounds **3d** and **4d** was attributed by the following nOe experiments. For compound **3d**, irradiation of Ph-2 enhanced H-3 (19%) and H_2-9 (3 and 0.5%), and irradiation of Me-3 enhanced H-3 (13%) and H_2-9 (4 and 0.5%). For compound **4d**, irradiation of Ph-3 enhanced H-4B (2%), H-2 (15%), Me-2 (<0.5%) and OH-3 (4%). The strong nOes observed between Ph-2 and H-3 in compound **3d**, and between H-2 and Ph-3 in compound **4d**, in conjunction with the small nOes (<0.5%) observed between Ph-2, Me-3 and Ph-3, Me-2, respectively, indicate that in both the compounds the phenyl and methyl groups are *trans*-oriented.

^{1}H-NMR Monitoring of the Reactions of α-(2-Hydroxyphenoxy)alkylketones **1a** and **1c** with DMSOM in Dimethylsulphoxide-d_6.

A solution of 39.6 mg (0.22 mmole) of **1a** in 0.5 ml of dimethylsulphoxide-d_6 and similarly for **1c**, was added to a nmr tube containing a solution of DMSOM in 0.6 ml of dimethylsulphoxide-d_6 obtained from 96.4 mg (0.44 mmole) of trimethylsulphoxonium iodide and 13.2 mg (0.44 mmole) of 80% dispersion of sodium hydride in mineral oil. The upfield shifts [9] ($\Delta\delta$ 0.2-0.8 ppm) exhibited by the aromatic protons of **1a**, and similarly of **1c**, suggested that the reaction proceeded *via* the formation of the sodium phenolate, which, in its turn, reacted with the ylide to give the intermediate oxiranes **2a** and **2c**, respectively. Successively, **2a** and **2c** reacted to afford, each, two new compounds, whose structures were firmly established as **3a**, **4a** and **3c**, **4c** by adding authentical samples.

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