Novel Synthesis of 3-Hydroxy-2,3,4,5-tetrahydro-1-benzo-oxepins by Cyclization of 2-(*o*-Hydroxyphenyl)alkyl Ketones with Dimethyloxosulphonium Methylide

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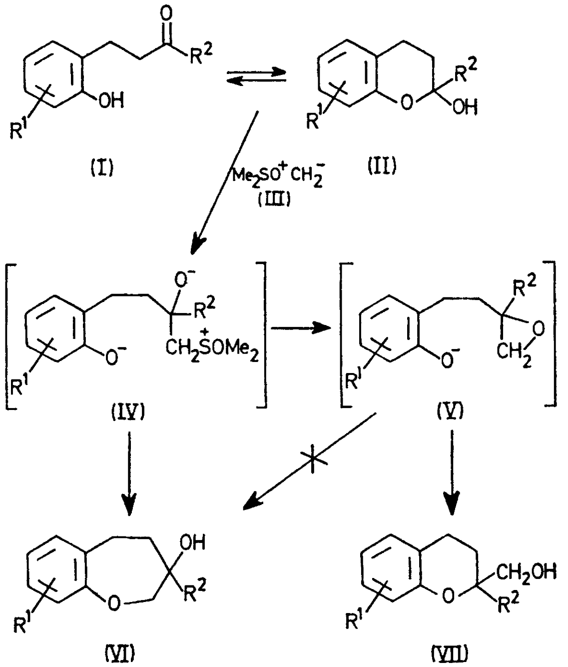
Summary Reaction of dimethyloxosulphonium methylide with 2-(*o*-hydroxyphenyl)alkyl ketones (I) in Me_2SO or tetrahydrofuran (THF) gives the 3-hydroxy-2,3,4,5-tetrahydro-1-benzo-oxepins (VI a—e) in high yields; the corresponding 4,5-dihydro- and 2,5-dihydro-1-benzo-oxepins, (VIII) and (IX), respectively, are obtained from (VIc) by acid treatment or by acetylation and pyrolysis.

In nature, suitably substituted phenols can cyclize to form benzofuran, benzopyran (chromans), or 1-benzo-oxepin (homocromans) rings, depending on whether the phenolic oxygen atom attacks C-2, C-3, or the end of the isoprene chain. Of these, the 1-benzo-oxepins are the least commonly occurring compounds, and so the least studied from the synthetic point of view.[1,2]



SCHEME

TABLE[a]

Compound	R¹	R²	Yield/%	M.p./°C
(VIa)	H	Me	92	liquid
(VIb)	H	Et	87	liquid
(VIc)	H	Ph	90 (5)	123
(VId)	5-OH	Me	78	204—205
(VIe)	3-OMe	Ph	95 (2)	134—135

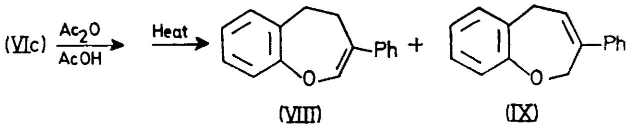
[a] Satisfactory analyses were obtained for all new compounds. The yields of the isomer (VII) are reported in parentheses.

During a study of annulation reactions involving sulphur ylides to form oxygen heterocycles,† we discovered a new and simple synthetic route to the 1-benzo-oxepins. The starting materials for this synthesis, 2-(*o*-hydroxyphenyl)-alkyl ketones (I) or the isomeric 2-chromanols (II), are readily available from the controlled catalytic reduction of *o*-hydroxybenzylidene ketones or from the condensation of vinyl ketones with hydroquinones.[3]

Compounds (I) and (II) react readily with dimethyloxosulphoxonium methylide (III) to give the title compounds (VIa—e) in high yields. An equimolar mixture of (I) or (II) and (III) in Me$_2$SO or THF[4] was either left under nitrogen at room temperature for 24 h or heated to 50—60 °C for a few hours. The reaction was monitored by t.l.c. Following the usual work-up, the crude product was purified either by crystallization (benzene-hexane) or by chromatography on silica gel when the major product, 3-hydroxy-2,3,4,5-tetrahydro-1-benzo-oxepin (VI), was eluted first (hexane–ether, 90:10), followed by 2-hydroxymethyl chroman (VII) (hexane–ether, 80:20).

The reaction mechanism for the formation of (VI) and (VII) is given in the Scheme and the yields and m.p.s. of the products are summarised in the Table. Compound (III) reacts with (I) or (II) to give (IV) which gives (VI) directly by elimination of Me$_2$SO upon attack of the phenolic oxygen. Alternatively, (IV) can form the epoxide (V) which, on nucleophilic attack of the phenolic oxygen on the epoxide quaternary carbon, gives (VII). Compounds such as (V) have been reported[5] to rearrange exclusively to derivatives like (VII) in both acid and basic media.

Structure assignments for (VI) and (VII), and thus for (V), were primarily based on n.m.r. spectroscopic analyses. In the spectra of (VIc) and (VIIc) (CDCl$_3$) the two protons of the methylene group introduced into the molecule appear as an AB system: (VIc), δ 3·87 (H$_A$), 4·80 (H$_B$), J_{AB} 13 Hz; and (VIIc) δ 3·73 (H$_A$), 3·85 (H$_B$), J_{AB} 12 Hz (C*H*$_2$OH, H$_A$ and H$_B$ are diastereotopic). Upon acetylation of (VIIc), CH$_2$OAc appears as a singlet at δ 4·36 (2H), as would be expected for the acetate of a primary alcohol



Compounds (VIc), when either warmed in the presence of HClO$_4$ or acetylated and pyrolysed, furnished the olefins (VIII) and (IX), thus confirming the structure ascribed; (VIII): 75%, liquid, δ (CDCl$_3$) 6·87 (t, =C*H*O, ^4J 1·2 Hz), and (IX): 15%, δ (CDCl$_3$) 6·10 (=C*H*, ^3J 5·5 and ^4J 1·8 Hz).

(*Received*, 28*th June* 1976; *Com.* 722.)

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† For the syntheses of benzofurans, chromans, and rotenoids by this route see B. Holt and P. A. Lowe, *Tetrahedron Letters*, 1966, 683; M. C. Sacquet, B. Graffe, and P. Maitte, *ibid.*, 1972, 4453; P. Bravo, G. Gaudiano, and C. Ticozzi, *Gazzetta*, 1973, **103**, 95; L. Crombie, P. W. Freemenn, and D. A. Whiting, *J.C.S. Perkin I*, 1973, 1277.

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[5] M. F. Grundon and H. M. Okely, *J.C.S. Perkin I*, 1975, 150.