2-HYDROXYMETHYL-3,4,5,6,7,8-HEXAHYDRO-2H-1-BENZOPYRAN-5-ONES. AN UNUSUAL CASE OF METHYLENE TRANSFER REACTION FROM SULFUR YLIDES

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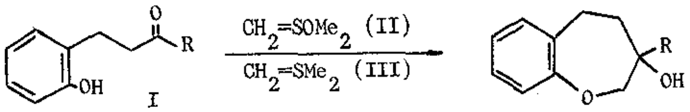
Reaction of dimethylsulfonium and -sulfoxonium methylides with 2-(3'-oxoalkyl)-1,3-cyclohexanediones (VII) or with 2-hydroxy-3,4,5,6,7,8-hexahydro-2H-1-benzopyran-5-ones (VIII) gives the 2-hydroxymethyl-3,4,5,6,7,8-hexahydro-2H-1-benzopyran-5-ones (XII).

Dimethylsulfonium and -sulfoxonium methylides generally react with non-enolizable ketones to give the corresponding epoxides. However, when there are nucleophiles in proximity to the carbonyl involved in the reaction, the final product is no longer the epoxide, but a larger ring formed by participation of the neighboring nucleophile[1]. Many five-membered and some six-membered heterocycles[2,3] have been synthesized from a ketone with a heteroatom nucleophile in the β or γ position. We have recently discovered that seven-membered heterocycles IV can be similarly prepared from 2-(o-hydroxyphenyl)alkyl ketones (I)[4] :

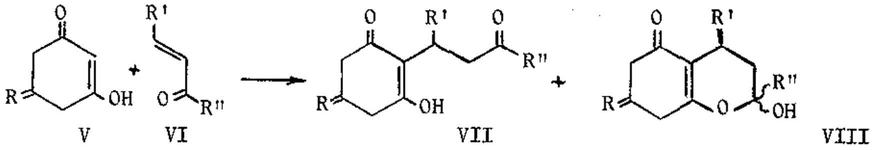


I

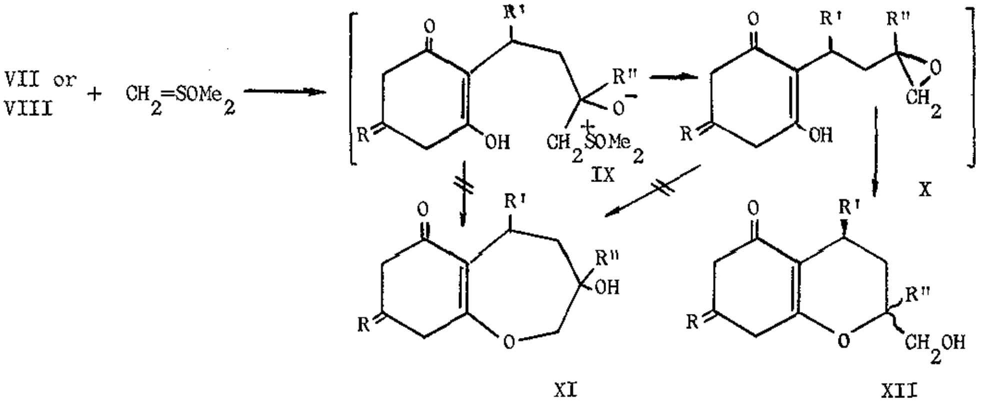
IV

We now report the results of the reaction of these same ylides (II, III) with compounds similar to I, i. e., VII and VIII, in which an enolized β-diketone takes place of the phenolic portion. Starting materials VII and VIII were prepared by the base-catalyzed condensation of α,β- unsaturated ketones VI with cyclohexanediones V.

Both reactants and reaction conditions determine whether the open chain compound VII or the cyclic ketal VIII is isolated.[5-7]

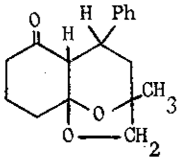


In all cases examined, compounds VII and VIII react readily with dimethyloxosulfonium methylide, in DMSO as well as in THF with no salt dissolved[8], to give exclusively title compounds XII, and none of the expected seven-membered heterocycles XI. Also the most reactive dimethylsulfonium methylide in THF[8] gives similar results; it brings to compounds XII, along with a certain amount of the corresponding methyl ethers. The reaction can be formulated as follows :



Both ketone VII and cyclic ketal VIII react with the ylide to form zwitter ion intermediate IX, which rapidly collapses to epoxide X. Participation of the enolate oxygen, through a six-membered ring transition state, effects ring closure with the simultaneous formation of the hydroxymethyl group. Neither direct displacement of DMSO by the enolate oxygen nor ring opening of the epoxide to give the 3-hydroxy-1-oxepin derivative XI was ever observed[9]. The different behaviour of VII and VIII relative to the aromatic system I may be due to the difference in nucleophilicity of the two oxygens in the intermediates. In the reaction of I, the displacement of DMSO from the intermediate betaine by the phenolic oxygen must be much faster than the formation of the epoxide[4].

Structure assignement of the reaction products XII was based on analytical and spectroscopic data. A strong carbonyl absorption at 1600-1610 cm^{-1}, characteristic of a substituted α,β-unsaturated ketone[10], and a hydroxyl band at 3430-3490 cm^{-1} rule out any open chain form. NMR data (in $CDCl_3$ or DMSO) unambiguously distinguish between the two possible cyclic forms. The new methylene group appears as an AB system centered at $\approx 3.5\,\delta$ (the two protons are diastereotopic). A fairly marked broadening of the signals due to further coupling was often noted, and could be removed by exchange with D_2O. Upon acetylation, one observes, in addition to a variation in the magnetic nonequivalence of the protons, a low field shift of both protons of approximately 0.5 ppm (typical values for primary acetates), while the remaining signals are nearly unaffected. For all new compounds, mass spectra show a common fragmentation pattern : in addition to the molecular ion, there are ions corresponding to the loss of H_2O, of CH_2OH, and of CH_2OH and H_2 (the latter leads to a stable pyrilium ion). Starting materials and reaction products are reported in the table. The only side-product of this reaction was XIII (5% yields)[11], resulting from the addition of the hydroxide of the CH_2OH to the cojugate double bond.



XIII

M.p. : 192-194 from acetone; IR (nujol): 1710 cm^{-1}
NMR ($CDCl_3$): $C\underline{H}_2O$, AB system; H_A, 3.44; H_B, 4.04; J_{AB} = 7.5 Hz; H_4, 3.50 (multiplet); H_5, 2.95 δ, d, J_{H_5,H_4} = 11 Hz.

TABLE*

Compound	R	R'	R"	Yields %	M.p., °C	Solvent	Reactants	
XIIa	H	H	Me	92	88-89	Ethyl acetate	VIIa	II
XIIa	H	H	Me	55 (33)§	"	"	VIIa	III
XIIb	Me	H	Me	95	99-100	Benzene-hexane	VIIb	II
XIIb	Me	H	Me	70 (15)§	"	"	VIIb	III
XIIc	Me	H	Ph	55	78	Hexane	VIIc	II
XIId[12]	H	Ph	Me	45	148-150	Acetone	VIIId	II
XIIe	H	Ph	Me	45	126-128	Acetone	VIIId	II
XIIf	Me	Ph	Me	90	201	Acetone	VIIIf	II

* Satisfactory elementary analyses were obtained for all new compounds.
§ Yields of methyl ether of XII (see reference 13)

References and Footnotes

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5 VIIa and VIIb were obtained by following the procedure described for similar compounds by S. Ramachandran and M. S. Newman, Organic Syntheses, 1961, 41, 38, and by J. W. Patterson, Jr, and W. Reusch, Synthesis, 1971, 155.

6 VIIc was obtained refluxing cyclohexane-1,3-dione and -dimethylamino propiophenone in benzene-pyridine, following the procedure of K. Balasubramanian, J. P. John, and S. Swaminathan, Synthesis, 1974, 51.

7 VIIId and VIIIf were obtained as described by H. Stetter and M. Coenen, Ber., 1954, 87, 869.

8 E. J. Corey and M. Chaikovsky, J. Am. Chem. Soc., 1965, 87, 134.

9 Some epoxides like X but possessing an aromatic ring (phenol or 2-quinolone epoxides) have also been reported to rearrange exclusively to six-membered ring compounds like XII; M. F. Grundon and M. H. Okely, J. Chem. Soc., Perkin I, 1975, 150.

10 For example $-CO-\overset{|}{C}=\overset{|}{C}-OMe$ in compounds obtained from VIIa,b by O-methylation show a IR band at 1620 cm^{-1}.

11 XIII was isolated from the crude by silica gel chromatography. It was eluted first by hexane/ethyl acetate 90/10; XIId and XIIe followed in the order when a 70/30 hexane/ethyl acetate mixture was used.

12 XIId and XIIe are <u>cis</u> <u>trans</u> isomer, NMR spectra analysis did not allow to establish which is which.

13 Oils; IR (nujol): 1650, 1620, 1390, 1110 cm^{-1}; NMR ($CDCl_3$): $C\underline{H}_2O$, AB system centered at 3.35 and $C\underline{H}_3O$, singlet at 3.38 δ; MS: M^+, 210 and 238, and ($M^+ - C_2H_6O$), 164 and 192 m/e respectively.

Received, 23rd August, 1976