Synthesis of 3,6-Dihydro-2*H*-pyrans and Pent-2-ene-1,5-diols from αβ-Unsaturated Ketones *via* Cyclopropyl Epoxides

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Cyclopropyl epoxides, formed directly from αβ-unsaturated ketones by reaction with dimethyloxosulphonium methylide or, better, from cyclopropyl ketones by reaction with dimethylsulphonium methylide, are converted, under acidic conditions, into pent-2-ene-1,5-diols and 3,6-dihydro-2*H*-pyrans.

We recently reported [1] that 2-arylcyclopropyl epoxides (III), synthesised from the corresponding cyclopropyl ketones (II) by reaction with dimethylsulphonium methylide (DMSM), readily rearrange to 2-aryl-3,6-dihydro-2*H*-pyrans (IV). We now report the preparation of these dihydropyrans by the reaction of dimethyloxosulphonium methylide (DMOSM) with αβ-unsaturated ketones (I) and by the acid-catalysed cyclisation of pent-2-ene-1,5-diols (V).

Chalcone (1g), one of the first compounds used by Corey and Chaykovsky [2] in their study of DMOSM, was found by them to yield a cyclopropyl ketone rather than a vinyl epoxide. It has now been observed that chalcones (Ia—d), when treated with more than 2 mol. equiv. of DMOSM, form isomeric pairs of cyclopropyl epoxides (IIIa—d) similar to those previously reported [1] from the reactions of cyclopropyl ketones with DMSM. In the present reaction the immediate formation of the cyclopropyl ketone intermediate (II) was observed by t.l.c.; it was followed by a slow (*ca.* 24 h) further reaction.

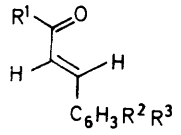
Simple work-up of these reactions by dilution with water and extraction with ether, gave the cyclopropyl epoxide isomers (IIIa—d). Because of the sensitivity of these epoxides to traces of acid, no attempt was made to characterise them other than to obtain their n.m.r. spectra. When chromatographed on silica gel they rearranged, as expected, to 3,6-dihydro-2*H*-pyrans (IVa—d) but, in contrast to the reactions [1] of similar compounds with toluene-4-sulphonic acid, other products were obtained.

Also formed were significant quantities of pent-2-ene-1,5-diols (Va—d), presumably by the hydration of an intermediate homoallylic cation (VI). The formation of these diols (V) is of interest in that the pent-2-ene-1,5-diol structure is one of the principal characteristics of many prostaglandins. Indeed Just and his co-workers [3] have isolated a small amount (2%) of prostaglandin $PGF_{1\alpha}$ methyl ester (VIII) from the formolysis of a cyclopropyl epoxide (VII).

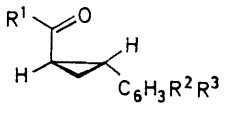
To take advantage of the more effective epoxidising ability of DMSM, we decided to carry out the reaction in two stages by first converting the αβ-unsaturated ketones

[1] J. A. Donnelly, J. G. Hoey, S. O'Brien, and J. O'Grady, *J.C.S. Perkin I*, 1973, 2030.
[2] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87**, 1353.
[3] G. Just, C. Simonovitch, F. H. Lincoln, W. P. Schneider, U. Axen, G. B. Spero, and J. E. Pike, *J. Amer. Chem. Soc.*, 1969, **91**, 5364.

(Ia and c—g) into the corresponding cyclopropyl ketones (IIa and c—g) and then, using DMSM, forming the



(I)



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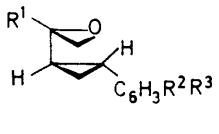
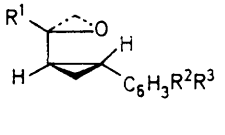
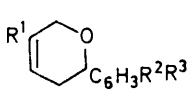
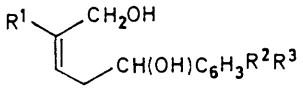


(III)





(IV)

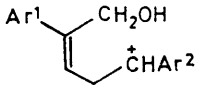


(V)

a; R^1 = Ph, R^2 = 2-OMe, R^3 = H
b; R^1 = Ph, R^2 R^3 = 3,4-OCH_2O-
c; R^1 = Ph, R^2 = 4-OMe, R^3 = H
d; R^1 = 4-MeC_6H_4, R^2 = 4-OMe, R^3 = H
e; R^1 = 4-$MeOC_6H_4$, R^2 = 4-OMe, R^3 = H
f; R^1 = 4-$MeOC_6H_4$, R^2 = R^3 = H
g; R^1 = Ph, R^2 = R^3 = H
h; R^1 = Me, R^2 = 4-OMe, R^3 = H

cyclopropyl epoxides (IIIa and c—g) for reaction on silica gel. It was found that the overall increases in the yields of dihydropyrans (IVa and c—g) and diols (Va and c—g) justified the extra operation.

The pent-2-ene-1,5-diols (Va and c—g) were dehydrated and cyclised to the corresponding 3,6-dihydro-2*H*-pyrans (IVa and c—g) by treatment with toluene-4-sulphonic acid. The diols with 4-methoxyphenyl



(IX)

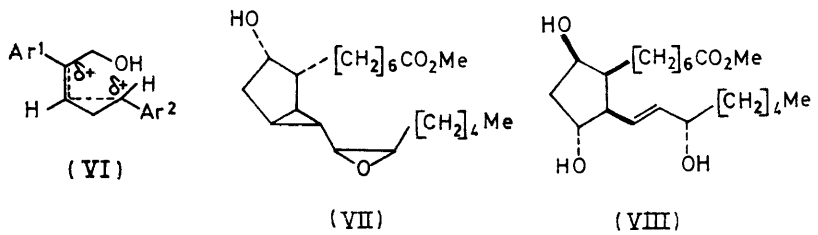
substituents in the 5-position were noticeably quicker to cyclise than the 5-phenyl-substituted diols, probably reflecting the greater ease of producing the carbocation (IX) from the former.

As might be expected, the phenyl substituent on the heterocyclic ring is not vital for the formation either of dihydropyrans or diols. *trans*-1-Acetyl-2-(4-methoxyphenyl)cyclopropane (IIh) was converted by DMSM and silica gel into 3,6-dihydro-2-(4-methoxyphenyl)-5-methyl-2*H*-pyran (IVh) and 5-(4-methoxyphenyl)-2-methylpent-2-ene-1,5-diol (Vh). The n.m.r. spectrum of the crude product, at high sensitivity, showed a double doublet centred at τ 0·11, suggesting the presence of traces of isomers of 2-[2-(4-methoxyphenyl)cyclopropyl]propanal (X), the products of a more usual epoxide rearrangement.[4]

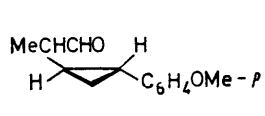
The cyclopropyl epoxides least prone to intramolecular rearrangement to dihydropyran [the diphenyl substituted compounds (IIIg)] were treated with dilute hydrochloric acid in aqueous dioxan in an attempt to increase the yield of the diol (Vg) and to replace silica gel by a more usual hydrolytic reagent. The overall yield (66%) of dihydropyran plus pent-2-ene was similar to that obtained (68%) using silica gel but the yield of pent-2-ene-1,5-diol (Vg) decreased from 50 to 42%. A better yield (67%) of an intermolecular reaction product, 5-methoxy-2,5-diphenylpent-2-en-1-ol (XI), was obtained when the cyclopropyl epoxides (IIIg) were treated with toluene-4-sulphonic acid in aqueous methanol. Similar concomitant openings of both rings have previously been reported.[1,5,6]

EXPERIMENTAL

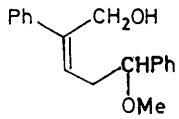
The n.m.r. spectra were measured with a Perkin-Elmer R12 spectrometer at 60 MHz for solutions in deuteriochloroform with tetramethylsilane as internal reference. M.p.s were obtained with a Kofler hot-stage apparatus.



(VI) (VII) (VIII)



(X)



(XI)

The experimental details particular to each substrate are given in the Table; the n.m.r. spectral and analytical data for new compounds are listed in Supplementary Publication No. SUP 21003 (3 pp.).* DMOSM [2] was employed as previously described.[7] The reactions with DMSM [2] were

* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1973, Index issue.

[4] A. Rosowsky in ' Heterocyclic Compounds with Three- and Four-membered Rings,' ed. A. Weissberger, Interscience, New York, 1964, p. 231.

[5] A. B. Turner, R. E. Lutz, N. S. McFarlane, and D. W. Boykin, *J. Org. Chem.*, 1971, **36**, 1107.

[6] T. Shono, I. Nishiguchi, A. Oku, and R. Oda, *Nippon Kagaku Zasshi*, 1969, **90**, 907.

[7] P. Bennett, J. A. Donnelly, D. C. Meaney, and P. O'Boyle, *J.C.S. Perkin I*, 1972, 1554.

Substrate	(g)	Reagent(s) (mol. equiv.)		Time at room temp. (h)	Time at reflux (h)	Purification [a]	Products [b]	Yield (mg)	M.p. (°C)	(solvent) [c]
(Ia)	1	DMOSM	3·5	0·5		P	(IVa) *	50	112—113	(E)
							(Va) *	115	83—84	(CB)
							(IIa) *	780	42—50	(E)
(Ib)	0·7	DMOSM	5·5	14		P	(IVb) *	230	157—158	(E)
							(Vb) *	130	69—70	(CB)
(Ic)	1	DMOSM	3	33		C	(IVc) [d]	341	149—150	
							(Vc) *	64	*e*	
(Id)	1	DMOSM	3	13		C	(IVd) [d]	247	128—129	
							(Vd) *	84	*e*	
(IIa)	1	DMSM	1·1	6		P	(IVa)	256	112—113	
							(Va)	353	83—84	
							(IIa)	340		
(IIc) [f]	1	DMSM	1·3	2·5		P	(IVc) [d]	707	149—150	
							(Vc)	182	*e*	
(IId) [d]	1	DMSM	1·2	3		P	(IVd)	628	128—129	
							(Vd)	126	*e*	
(IIe) [d]	1	DMSM	1·2	4		P	(IVe) [d]	587	160—162	
							(Ve) *	238	*e*	
(IIf) [f]	1	DMSM	1·1	3		P	(IVf) *	163	121—123	(M)
							(Vf) *	341	*e*	
							(IIf)	313	41—42	
(IIg) [g]	1	DMSM	1·2	2·5		P	(IVg) [d]	176	108—110	
							(Vg) *	535	*e*	
(IIIg) [d]	0·097	*h*		72	4	P	(IVg) [d]	23	108—110	
							(Vg)	44	*e*	
(IIIg) [d]	0·098	*i*		3		P	(XI) *	75	*e*	
(IIh) [j]	1	DMSM	1·4	3		P	(IVh) *	218	*e*	
							(Vh) *	433	*e*	
							(IIh)	121		
(Va)	0·163	*k*		24	5		(IVa)	53	112—113	
							(Va)	81	83—84	
(Vc)	0·032	*k*		12			(IVc) [d]	27	149—150	
(Vd)	0·037	*k*		12			(IVd)	32	128—129	
(Ve)	0·028	*k*		12			(IVe) [d]	21	160—162	
(Vf)	0·051	*k*		24	12		(IVf)	23	121—123	
							(Vf)	16	*e*	
(Vg)	0·152	*k*		6	44		(IVg) [d]	86	108—110	
							(Vg)	33	*e*	

[a] P = P.l.c. on silica gel; C = column chromatography on silica gel. [b] New compounds are marked with an asterisk. [c] E = Ethanol; CB = cyclohexane–benzene; M = methanol. [d] Ref. 1. [e] Oil. [f] Ref. 5. [g] Ref. 2. [h] Dissolved in dioxan (4 ml) and aqueous hydrochloric acid (10%; 1 ml). [i] Dissolved with toluene-*p*-sulphonic acid (trace) in methanol (4 ml) and water (1 ml). [j] T. R. L. Johnson and L. A. Jones, *J. Chem. and Eng. Data*, 1971, **16**, 112. [k] Dissolved with toluene-*p*-sulphonic acid (trace) in chloroform (5 ml).

carried out in an inert atmosphere by adding the methylide in dimethyl sulphoxide (DMSO) to a solution of the ketone in DMSO maintained as near as possible to its freezing point during the addition. The cyclopropyl epoxide mixtures showed the previously described [1] characteristic n.m.r. signals at τ 7·0—7·5.

All reactions were worked-up by dilution with water and extraction with ether; the solvent was removed on a rotatory evaporator at room temperature after the solution had been washed with water and dried over anhydrous sodium sulphate.

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