Rearrangement of Cyclopropyl Epoxides to 3,6-Dihydro-2*H*-pyrans

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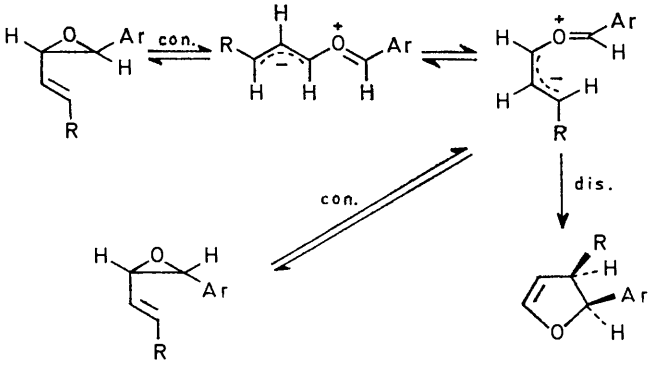
Aryl-substituted cyclopropyl epoxides rearrange to 3,6-dihydro-2*H*-pyrans. This new rearrangement is related to that of vinyl epoxides to dihydrofurans but occurs under much milder conditions, probably by way of a homoallyl cation resulting from opening of the epoxide ring by adventitious acid catalysis. It provides a relatively simple procedure for the synthesis of 2-aryl-3,6-dihydro-2*H*-pyrans.

THE vinyl-epoxide-to-dihydrofuran thermal rearrangement (Scheme 1) is considered by Paladini and Chuche [1] to proceed by way of a carbonyl ylide intermediate rather than through the diradical route (Scheme 2) indicated [2] for the corresponding vinylcyclopropane-to-

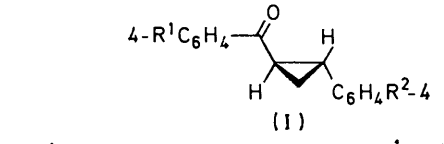


SCHEME 1

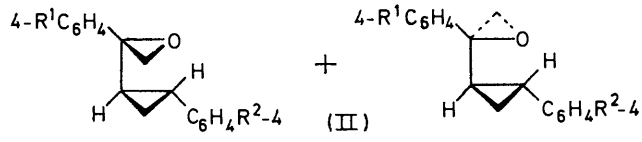
SCHEME 2

cyclopentene rearrangement. Both these reaction pathways have been favoured over the alternative 1,3-sigmatropic mechanisms available. As a result of our interest [3] in the chemistry of reactive centres adjacent to a cyclopropane ring, we undertook [4] a study of cyclopropyl epoxides. These are related to the aforementioned systems by virtue of the partial double bond character of cyclopropanes. Having contiguous cyclopropane and epoxide rings, they were readily available from the corresponding cyclopropyl ketones by reaction with dimethylsulphonium methylide. *trans*-1-Benzoyl-2-(4-methoxyphenyl)cyclopropane (Ia) gave a mixture of the two cyclopropyl epoxide isomers (IIa). These epoxides were sensitive (see Table) and it was impossible to separate them. The n.m.r. spectrum of the mixture, especially in the τ 7 region, was entirely compatible with this structural assignment. Newman has recently reported [5] that a similar reaction involving griseofulvin and dimethylsulphoxonium methylide yields a single cyclopropyl epoxide (III). In the present case, the epoxidic ring proton signals appear as a sextet, the low-field doublet of each isomer coinciding. An analysis of these signals indicates an isomer ratio of approximately 63 : 37, with the epoxide protons of the major component having chemical shifts of τ 7·00 and 7·10 and the minor component 7·00 and 7·15.

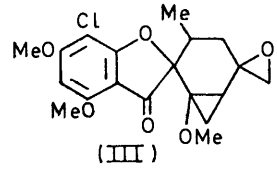
A novel rearrangement was observed when these epoxides were heated, neat or in toluene, at 100° for 10—15 min. 3,6-Dihydro-2-(4-methoxyphenyl)-5-phenyl-2*H*-pyran (IVa) was formed quantitatively. The epoxides (IIb and c), derived from *trans*-1-(4-methoxybenzoyl)- (Ib) and *trans*-1-(4-methylbenzoyl- 2-(4-methoxyphenyl)cyclopropane (Ic), were similarly reactive



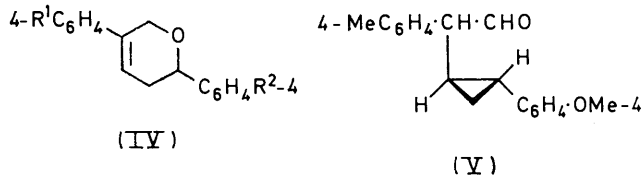
(I)



(II)



(III)



(IV) (V)

a; R^1 = H, R^2 = OMe b; R^1 = R^2 = OMe

c; R^1 = Me, R^2 = OMe d; R^1 = R^2 = H

(see Table), forming 3,6-dihydro-2,5-bis-(4-methoxyphenyl)-2*H*-pyran (IVb) and 3,6-dihydro-2-(4-methoxyphenyl)-5-(4-methylphenyl)-2*H*-pyran (IVc), respectively. The n.m.r. spectrum of the crude product from the latter reaction, at high sensitivity, showed two

[1] J. C. Paladini and J. Chuche, *Tetrahedron Letters*, 1971, 4383.
[2] P. H. Mazzocchi and H. J. Tamburin, *J. Amer. Chem. Soc.*, 1970, **92**, 7220, and references therein.
[3] P. Bennett, J. A. Donnelly, D. C. Meaney, and P. O'Boyle, *J.C.S. Perkin I*, 1972, 2982; 1973, 688.
[4] J. A. Donnelly, P. Bennett, S. O'Brien, and J. O'Grady, *Chem. and Ind.*, 1972, 500.
[5] H. Newman, *J. Org. Chem.*, 1971, **36**, 2375; see also W. Kirmse and B. Kornrumph, *Angew. Chem. Internat. Edn.*, 1969, **8**, 75.

doublets at τ 0·27 and 0·33, suggesting the presence of traces of isomers of 2-[2-(4-methoxyphenyl)cyclopropyl]-2-(4-methylphenyl)acetaldehyde (V), the products of a common epoxide rearrangement.[6]

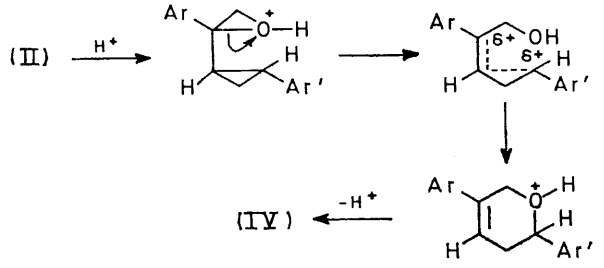
Although the most likely mechanism (Scheme 3) for the present rearrangement involves adventitious acid-catalysed opening of the epoxide ring, followed by might substantiate such a process in an otherwise suitably substituted analogue.

In any case, the rate of reaction appears to be too dependent[7] on the cyclopropyl substituent for such a concerted process. Thus, the replacement of the 4-methoxyphenyl substituent by phenyl slowed the rearrangement by at least a factor of 80. The

Cyclopropyl epoxide	Reaction conditions	Product	M.p. (°C) (solvent) [a]	Amount (mg) of substrate	Yield (mg) of product [b]	Analysis (%)	λmax. (MeOH) (log ε)	τ Values
(IIa) R¹ = H, R² = OMe	1, Neat at 100° for 10 min	3,6-*Dihydro*-2-(4-*methoxyphenyl*)-5-*phenyl*-2H-*pyran* (IVa)	149—150 MeOH	84	67	Formula: $C_{18}H_{18}O_2$	229 (4·19)	3·55—3·87 (m, 4-H)
	2, In toluene at 100° for 15 min			89	75	Found: C, 81·3; H, 6·6	243s (4·14)	5·17—5·57 (m 2-H, 2 × 6-H)
	3, In aqueous dioxan (80%), containing a trace of *p*-TSA [c] at room temp.; immediate reaction			78	65	Required: C, 81·2; H, 6·8		6·16 (s, OMe)
	4, In aqueous methanol (80%), containing a trace of *p*-TSA [c] at room temp.; immediate reaction			74	59			7·30—7·70 (m, 2 × 3-H)
	5, In $CDCl_3$ at 35° for 12 h [d]							
(IIb) R¹ = R² = OMe	1, Neat at room temp. overnight	3,6-*Dihydro*-2,5-*bis*-(4-*methoxyphenyl*)-2H-*pyran* (IVb)	160—162 MeOH	993	331 [e]	Formula: $C_{19}H_{20}O_3$	229 (4·00)	3·58—3·88 (m, 4-H)
	2, In dried Et_2O containing a trace of *p*-TSA [c] at room temp. for 3 h			91	85	Found: C, 77·1; H, 7·0	256 (4·27)	5·17—5·54 (m, 2-H, 2 × 6-H)
	3, In $CDCl_3$ at 35° for 24 h [d]					Required: C, 77·0; H, 6·8		6·14 (s, 2 × OMe)
								7·28—7·47 (m, 2 × 3-H)
(IIc) R¹ = Me, R² = OMe	1, Neat at 100° for 10 min	3,6-*Dihydro*-2-(4-*methoxyphenyl*)-5-(4-*methylphenyl*)-2H-*pyran* (IVc)	128—129 MeOH	88	74 [f]	Formula: $C_{19}H_{20}O_2$	227 (4·23)	3·61—3·86 (m, 4-H)
	2, Neat at room temp. for 3 days			84	21 [e]	Found: C, 81·5; H, 7·1	247 (4·24)	5·16—5·57 (m, 2-H, 2 × 6-H)
	3, Neat at room temp. for 3 days in dark			93	16 [e]	Required: C, 81·4; H, 7·2		6·19 (s, OMe)
	4, In toluene at 100° for 15 min			92	78 [f]			7·36—7·75 (m, 2 × 3-H)
	5, In dried benzene, containing a trace of *p*-TSA [c] at room temp. overnight			165	138			7·64 (s, Me)
	6, In $(CD_3)_2SO$ at 35° for 15 min [d]							
	7, In $CDCl_3$ at 35° for 36 h							
	8, In dried Et_2O or dried benzene at room temp. for 3 days and for 12 h respectively	Substrate (IIc)						
(IId) R¹ = R² = H	1, Neat at 100° for 36 h	3,6-*Dihydro*-2,5-*diphenyl*-2H-*pyran* (IVd)	108—109 MeOH	83	54	Formula: $C_{17}H_{16}O$	244 (4·08)	3·61—3·89 (m, 4-H)
	2, Neat at 200° for 1 h			96	41	Found: C, 86·3; H, 6·8		5·20—5·56 (m, 2-H, 2 × 6-H)
	3, In refluxing toluene for 21 h			103	84	Required: C, 86·4; H, 6·8		7·38—7·71 (m, 2 × 3-H)
	4, In refluxing Me_2SO for 3 h			92	68			
	5, In CH_2Cl_2 containing CDI_2 (0·05 g) at room temp. for 3 days and then under reflux for 4 h			95	78			
	6, In boron trifluoride–ether at 0° for 10 min			57	46			
	7, In $CDCl_3$ containing a trace of *p*-TSA [c] at 35° for 12 h [d]							
	8, In benzene, chloroform, methanol, or aqueous dioxan (80%) at room temp. overnight	Substrate (IId)						
(VI)	1, Neat at 200° for 2 h [d]	2-Cyclopropyl-2-phenylacetaldehyde (VII)	(138—139 for 2,4-DNP deriv.*)					
	2 In refluxing toluene for 20 h	Substrate (VI)						

[a] Crystallisation solvent. [b] Unless otherwise stated these are the sole reaction products as shown by n.m.r. spectroscopy and thin layer chromatography of the crude reaction products. [c] Toluene-4-sulphonic acid. [d] Small scale reaction. [e] Remaining material was substrate. [f] N.m.r. spectrum of crude product, at high sensitivity, indicated the presence also of isomers of 2-[2-(4-methoxyphenyl)cyclopropyl]-2-(4-methylphenyl)acetaldehyde (V).

intramolecular attack on the resulting homoallyl cation, thorough washing of the solvent and the glassware with alkali had no apparent effect on the reaction. An



SCHEME 3

alternative possibility is a $[_\sigma 2_s + _\sigma 2_a]$ thermal rearrangement. The involvement of the heteroatom would, however, preclude any stereochemical consequences that epoxides (IId) resulting from the reaction of *trans*-1-benzoyl-2-phenylcyclopropane (Id) with dimethylsulphonium methylide rearranged to 3,6-dihydro-2,5-diphenyl-2*H*-pyran (IVd) in 21 h. Removal of the substituent on the cyclopropane ring resulted in complete suppression of the rearrangement: 1-cyclopropyl-1-phenyloxiran (VI) was unreactive under the usual conditions but when heated neat at 200° it underwent the more common epoxide reaction, and rearranged[8] to 2-cyclopropyl-2-phenylacetaldehyde (VII). These substituent effects are more characteristic of an acid-catalysed mechanism (Scheme 3) than of a concerted one.

Not surprisingly, therefore, treatment of the aryl-cyclopropyl epoxides (IIa—d) with traces of toluene-4-sulphonic acid in various solvents resulted in the rapid formation of the corresponding 3,6-dihydro-2*H*-pyrans (IVa—d) under very mild conditions (see Table). This is probably the most useful method[9] available at present

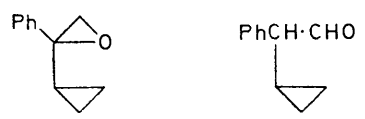
[6] A. Rosowsky in 'Heterocyclic Compounds with Three- and Four-Membered Rings,' ed. A. Weissberger, Interscience, New York, 1964, p. 231.

[7] S. J. Rhoads in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1963, p. 655.

[8] *Cf.* Y. Shono, I. Nishiguchi, A. Oku, and R. Oda, *Tetrahedron Letters*, 1967, 517.

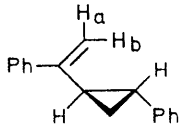
[9] See, for example, V. I. Nikitin and V. K. Sidorenko, *Zhur. org. Khim.*, 1966, **2**, 1734 (*Chem. Abs.*, 1967, **66**, 55363).

for synthesising 2-aryl-3,6-dihydro-2*H*-pyrans. Kapps and Kirmse,[10] in synthesising unsubstituted cyclopropyloxiran, obtained 3,6-dihydro-2*H*-pyran as a minor (7%)

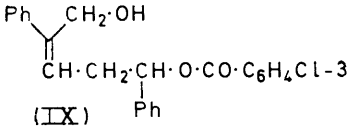


(VI)

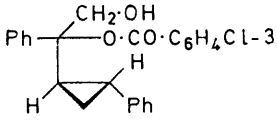
(VII)



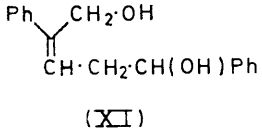
(VIII)



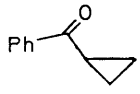
(IX)



(X)

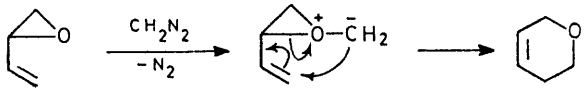


(XI)



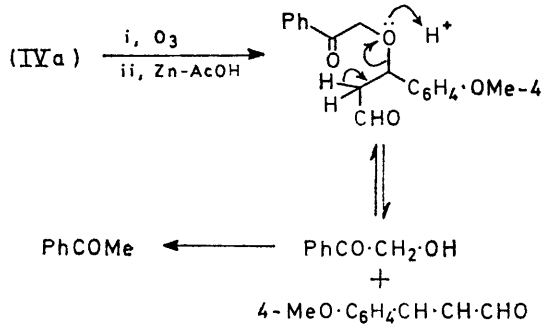
(XII)

product; probably by the mechanism shown (Scheme 4) and not *via* the cyclopropyl epoxide.



SCHEME 4

The 3,6-dihydro-2*H*-pyran structure of the products follows from the fact that the rearrangement product (IVa) of the original cyclopropyl epoxides (IIa) is unchanged by refluxing aqueous dioxan–hydrochloric



SCHEME 5

acid, forms a stable dibromide, has the characteristic styrene absorption at 243 nm (log ε 4·14) in the near u.v., and, on ozonolysis, yields acetophenone and 4-methoxycinnamaldehyde. In this last reaction (Scheme 5), the initial keto-aldehydic product presumably undergoes a reverse Michael-type reaction to give 2-hydroxyacetophenone and 4-methoxycinnamaldehyde. 2-Hydroxyacetophenone was reduced, as expected,[11] to acetophenone in the presence of zinc and acetic acid. The n.m.r. spectra of 3,6-dihydro-2*H*-pyrans at 60 MHz are not sufficiently resolved to give unambiguous support to the proposed structures. In confirmation of the epoxidic nature of the substrate cyclopropanes (II), when *trans*-1-phenyl-1-(2-phenylcyclopropyl)ethylene (VIII) was epoxidised with 3-chloroperbenzoic acid, one of the products was 3,6-dihydro-2,5-diphenyl-2*H*-pyran (IVd). Also isolated were the two esters [8] [(IX and (X)] of 3-chlorobenzoic acid, 2,5-diphenylpent-2-ene-1,5-diol (XI), and *trans*-1-benzoyl-2-phenylcyclopropane (Ia).

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. U.v. spectra were taken with a Perkin-Elmer 124 spectrometer.

The cyclopropyl ketones were prepared by the general method given [12] previously. Three [(Ia), (Id), and (XII)] have already been reported.[8,13] *trans*-4,4′-Dimethoxychalcone [14] (3·0 g) gave trans-1-(4-*methoxybenzoyl*)-2-(4-*methoxyphenyl*)*cyclopropane* (Ib) (2·9 g), m.p. 49—50° [light petroleum (b.p. 60—80°)] (Found: C, 76·6; H, 6·2. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%). *trans*-4-Methoxy-4′-methylchalcone [15] (7·56 g) gave trans-2-(4-*methoxyphenyl*)-1-(4-*methylbenzoyl*)*cyclopropane* (Ic) (7·61 g), m.p. 56—58° (ethanol) (Found: C, 81·4; H, 6·5. $C_{18}H_{18}O_2$ requires C, 81·2; H, 6·8%).

The cyclopropyl epoxides (IIa—d) and (VI) were synthesised from the appropriate cyclopropyl ketones and dimethylsulphonium methylide by the method described by Corey and Chaykovsky [16] except that dimethyl sulphoxide alone was used as solvent and the reactions were carried out at *ca.* 13° for the first 10 min, then at ambient temperature for 2—4 h. The details of the reactions carried out with these compounds are given in the Table.

Addition of bromine (0·06 g) to a solution of 3,6-dihydro-2-(4-methoxyphenyl)-5-phenyl-2*H*-pyran (IVa) (0·10 g) in chloroform (10 ml) gave 4,5-*dibromotetrahydro*-2-(4-*methoxyphenyl*)-5-*phenylpyran* (0·1 g), m.p. 137—138° (methanol) (Found: C, 51·0; H, 4·2; Br, 37·8. $C_{18}H_{18}Br_2O_2$ requires C, 50·7; H, 4·2; Br, 37·5%).

3,6-Dihydro-2-(4-methoxyphenyl)-5-phenyl-2*H*-pyran (IVa) (0·418 g) was ozonised [17] in chloroform–acetic acid at −10°. After treatment with zinc dust for 3 h, the product was filtered, washed with water, and fractionated by preparative layer chromatography to give acetophenone (0·062 g) [2,4-dinitrophenylhydrazone, m.p. 240—242° (lit.,[18] 237°)], and 4-methoxycinnamaldehyde (0·056 g), m.p. 59—60° (hexane) (lit.,[19] 58°).

A solution of n-butyl-lithium in hexane (1·3M; 25 ml)

[10] M. Kapps and W. Kirmse, *Angew. Chem. Internat. Edn.*, 1969, **8**, 75.
[11] M. Smith in ' Reduction,' ed. R. L. Augustine, Dekker, New York, 1968, p. 140.
[12] P. Bennett, J. A. Donnelly, D. C. Meaney, and P. O'Boyle, *J.C.S. Perkin I*, 1972, 1554.
[13] C. Agami and J. Aubouet, *Bull. Soc. chim. France*, 1967, 1391; A. B. Turner, R. E. Lutz, N. S. McFarlane, and D. W. Boykin, *J. Org. Chem.*, 1971, **36**, 1107.
[14] V. Tognazzi, *Gazzetta*, 1924, **54**, 697.
[15] H. Stobbe and K. Bremer, *J. prakt. Chem.*, 1929, **123**, 1.
[16] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1965, **87**, 1353.
[17] J. A. Elvidge and P. G. Sammes, ' A Course in Modern Techniques of Organic Chemistry,' Butterworths, London, 1966, p. 191.
[18] C. F. H. Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955.
[19] M. Scholtz and A. Wiedemann, *Ber.*, 1903, **36**, 845.

was added dropwise, under nitrogen, to methyltriphenylphosphonium bromide (11·9 g) in diethyl ether (200 ml). After 4 h, *trans*-1-benzoyl-2-phenylcyclopropane [13] (7·4 g) in diethyl ether (30 ml) was added slowly. After a further 4 h, the mixture was filtered and the filtrate was chromatographed on a column of silica gel giving trans-1-*phenyl*-1-(2-*phenylcyclopropyl*)*ethylene* (VIII) as an air-sensitive oil (4·93 g) (Found: C, 92·2; H, 7·7. $C_{17}H_{16}$ requires C, 92·7; H, 7·3%), τ 2·3—3·0 (m, aromatic), 4·60 (s, H_a), 4·92 (s, H_b), and 7·7—8·9 (m, cyclopropane).

A suspension in carbon tetrachloride (20 ml) of 3-chloroperbenzoic acid (2·65 g), previously washed with borate–hydrogen chloride buffer solution (pH 8), was added to *trans*-1-phenyl-1-(2-phenylcyclopropyl)ethylene (VIII) (3·0 g) in carbon tetrachloride (50 ml). After 1 h, the solvent was removed and the residue was fractionated on a column of alumina, giving 3,6-dihydro-2,5-diphenyl-2*H*-pyran (IVd) (0·332 g); *trans*-1-benzoyl-2-phenylcyclopropane (Id) (0·200 g); *trans*-1-phenyl-1-(2-phenylcyclopropyl)ethylene (VIII) (0·256 g); 2-*hydroxy*-1-*phenyl*-1-(2-*phenylcyclopropyl*)*ethyl* 3-*chlorobenzoate* (X) (0·550 g), m.p. 109—110° [light petroleum (b.p. 60—80°)] (Found: C, 73·35; H, 5·8; Cl, 9·1. $C_{24}H_{21}ClO_3$ requires C, 73·4; H, 5·4; Cl, 9·0%), τ 2·1—2·9 (m, aromatic), 5·25 (s, CH_2O), 7·20 (s, OH), and 7·6—9·3 (m, cyclopropane); and 5-*hydroxy*-1,4-*diphenylpent*-3-*enyl* 3-*chlorobenzoate* (IX) (0·812 g), an oil (Found: C, 73·0; H, 5·3; Cl, 9·35. $C_{24}H_{21}ClO_3$ requires C, 73·4; H, 5·4; Cl, 9·0%), τ 1·8—2·7 (m, aromatic), 3·80 (t, CH), 4·08 (t, C*H*Ph), 5·50 (s, CH_2O), 6·9—7·3 (m, CH_2), and 8·40 (s, OH); $\lambda_{max.}$ (MeOH) 234 nm (log ε 4·24).

Zinc dust (2 g) was added to a solution of 2-hydroxyacetophenone (1 g) in a mixture (100 ml) of acetic acid and chloroform (50 : 50). After 4 h, the mixture was filtered, washed with water, evaporated to dryness, and fractionated by preparative layer chromatography, yielding acetophenone (0·65 g).

[3/806 *Received*, 16*th April*, 1973]