Acid-catalysed Rearrangements of Some Spiro cyclopropyl Ketones

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The acid-catalysed ring opening of spiro-cyclopropyl ketones having a phenyl substituent at the 2-position of the cyclopropane ring occurred with cleavage of the C(1)–C(2) bond whether or not this was the small-ring bond more overlapped with a *p*-orbital of the carbonyl group.

THE rearrangement of cyclopropyl ketones in rigid systems by photoexcitation [1] or electron addition [2] is normally under stereoelectronic control; the cyclopropane bond cleaved is that which is better placed to overlap with a *p*-orbital of the carbonyl carbon atom. Similar control has been expected [3] in the acid-catalysed rearrangement of these ketones. The results, however, have been few and contradictory. The acid-catalysed hydrolysis [4] of lumicholestenone (I), for example, resulted in the breaking of the less overlapped bond, as shown, whereas in the similar hydrolysis [5] of dihydrolumisantonin (II) the more overlapped bond was cleaved. Bellamy and Whitham [3a] found that the reaction of 3-methylcar-4-en-2-one (III) with acetic anhydride in sulphuric acid also resulted in cleavage of the more overlapped bond.

The bulk of the evidence [3,6] appears to show, however, that either of the suitably placed cyclopropane bonds has sufficient overlap in the transition state, so that the direction of ring opening is determined, as originally proposed by Walborsky and Plonsker,[6a] mainly by the ability of the substituents on the two carbon atoms at the 'back' of the cyclopropane ring to delocalise a positive charge.

We have examined the acid-catalysed ring opening of the diastereoisomers of some spiro-cyclopropyl derivatives [7] (IV) of chromanone in which there are considerable differences in the degrees of overlap of the less overlapped bond (l) and the more overlapped bond (m) with a *p*-orbital of the carbonyl carbon atom. The rearrangements were carried out by use of toluene-*p*-sulphonic acid in refluxing ethanol and/or methanol. The substrates and their products are given in Table 1. The relevant signals in the n.m.r. spectra of the rearrangements products are given in Table 2.

In all cases the cyclopropyl ketones rearranged with ring opening towards the more stable carbonium ion. This was expected of the *trans,cis*- and *cis,cis*-isomers,†

TABLE 1

Acid-catalysed rearrangement of cyclopropyl ketones

Substrate	Solv.	Products
trans,trans-2,2′-Diphenylchroman-3-spirocyclopropan-4-one (V)	EtOH	(2*SR*,3*SR*)-*trans*-3-[(2*RS*)-2-Ethoxy-2-phenylethyl]flavanone (VI; R = Et)
	MeOH	(2*SR*,3*SR*)-*trans*-3-[(2*RS*)-2-Methoxy-2-phenylethyl]flavanone (VI; R = Me)
trans,trans-2′-Deuterio-2,2′-diphenylchroman-3-spirocyclopropan-4-one (XXI)	EtOH	(2*SR*,3*SR*)-*trans*-3-[(2*RS*)-2-Deuterio-2-ethoxy-2-phenylethyl]-flavanone (XXII; R = Et)
	MeOH	(2*SR*,3*SR*)-*trans*-3-[2*RS*)-2-Deuterio-2-methoxy-2-phenylethyl]-flavanone (XXII; R = Me)
cis,trans-2,2′-Diphenylchroman-3-spirocyclopropan-4-one (VII)	EtOH	(2*SR*,3*SR*)-*trans*-3-[(2*RS*)-2-ethoxy-2-phenylethyl]flavanone (VIII)
trans,trans-6-Chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one (IX)	MeOH	(2*SR*,3*SR*)-*trans*-6-Chloro-3-[(2*RS*)-2-methoxy-2-phenylethyl]-2-methylchromanone (X) and the (3*RS*)-*cis*-isomer (XI)
trans,cis-6-Chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one (XII)	MeOH	(2*SR*,3*SR*)-*trans*-6-Chloro-3-[(2*SR*)-2-methoxy-2-phenylethyl]-2-methylchromanone (XIII) and the (3*RS*)-*cis*-isomer (XIV)
Mixture of *cis,trans*- [(XV) 71%] and *cis,cis*- [(XVI) 29%] 6-chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one	MeOH	(XIII) 43% (XIV) 28% (X) 13% (XI) 16%
trans-2′-Phenylchroman-3-spirocyclopropan-4-one (XVII)	MeOH	(3*SR*)-3-[(2*RS*)-2-Methoxy-2-phenylethyl]chromanone (XVIII; R = Me) and the (3*RS*)-isomer (XIX; R = Me)
	EtOH	(3*SR*)-3-[(2*RS*)-Ethoxy-2-phenylethyl]chromanone (XVIII; R = Et) and the (3*RS*)-isomer (XIX; R = Et)
cis-2′-Phenylchroman-3-spirocyclopropan-4-one (XX)	MeOH	(XVIII; R = Me) and (XIX); R = Me)
	EtOH	(XVIII; R = Et) and (XIX; R = Et)

† Stereochemical prefixes refer, firstly, to the relative configurations of the side-chain phenyl ring and the carbonyl group, and, secondly, to those of the 2-substituent and the cyclopropane methylene group.

[1] W. G. Dauben, L. Schutte, R. E. Wolf, and E. J. Deviny, *J. Org. Chem.*, 1969, **34**, 2512; W. G. Dauben and G. W. Shaffer, *Tetrahedron Letters*, 1967, 4415.

[2] W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, 1966, **31**, 3794; T. Norin, *Acta Chem. Scand.*, 1965, **19**, 1289.

[3] (*a*) A. J. Bellamy and G. H. Whitham, *Tetrahedron*, 1968, **24**, 247; (*b*) F. Fringuelli and A. Taticchi, *J. Chem. Soc.* (*C*), 1971, 297.

[4] B. A. Shoulders, W. W. Kwie, W. Klyne, and P. D. Gardner, *Tetrahedron*, 1965, **21**, 2973.

[5] D. H. R. Barton, P. de Mayo, and M. Shafiq, *J. Chem. Soc.*, 1958, 140.

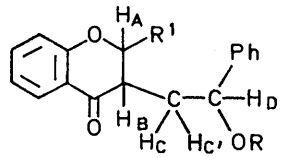
[6] (*a*) H. M. Walborsky and L. Plonsker, *J. Amer. Chem. Soc.*, 1961, **83**, 2138; (*b*) C. U. Pittman and S. P. McManus, *ibid.*, 1969, **91**, 5915.

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

as breakage of their more overlapped cyclopropane bond coincides with rearrangement towards the benzylic carbon atom. This coincidence also occurs in the *cis,trans*-isomers because of the preferred [7] equatorial

TABLE 2

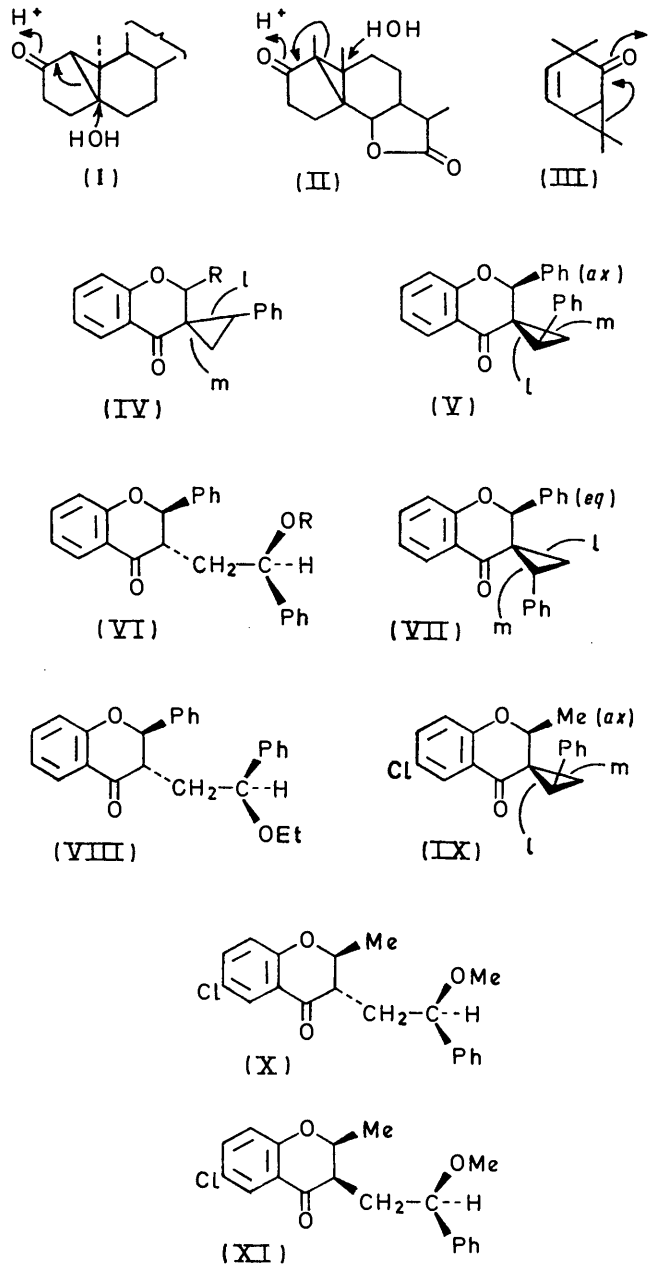
N.m.r. spectra of rearrangement products (τ values; J in Hz)



Compound	H	τ (J)
(VI; R = Et)	A	4·70 (12·0)
	B	6·66—7·17
	C	7·46—7·93
	C′	8·26—8·69
	D	5·85 (6·6, 7·4)
	CH_3	8·95 (6·3)
	$O{\cdot}CH_3$	6·81 (6·3)
(XXII; R = Et)	A	4·74 (11·7)
	B	6·68—7·18
	C	7·70 (5·7, 14·6)
	C′	8·49 (6·1, 14·6)
	CH_3	8·95 (6·3)
	$O{\cdot}CH_3$	6·83 (6·3)
(VI; R = Me)	A	4·74 (11·9)
	B	6·76—7·15
	C	7·38—7·84
	C′	8·25—8·70
	D	6·01 (6·2, 8·0)
	$O{\cdot}CH_3$	6·96
(XXII; R = Me)	A	4·75 (11·3)
	B	6·74—7·15
	C	7·67 (4·7, 14·2)
	C′	8·44 (9·5, 15·1)
	$O{\cdot}CH_3$	6·97
(VIII)	A	4·67 (10·1)
	B	6·40—6·90
	C, C′	7·86—8·36
	D	5·63 (4·4, 8·8)
	CH_3	8·90 (6·7)
	$O{\cdot}CH_2$	6·74 (6·7)
(X)	A	5·42 (6·6, 8·4)
	B	7·29—7·61
	C, C′	7·70—8·07
	D	5·59 (5·4, 6·6)
	CH_3	8·53 (6·6)
	$O{\cdot}CH_3$	6·82
(XI)	A	5·25 (3·9, 6·6)
	B	6·78—7·00
	C, C′	8·02—8·22
	D	5·76 (5·1, 6·9)
	CH_3	8·62 (6·6)
	$O{\cdot}CH_3$	6·78
(XIII)	A	5·55 (6·6, 12·6)
	B	6·93—7·27
	C, C′	7·89—8·11
	D	5·66 (6·6, 6·6)
	CH_3	8·50 (6·6)
	$O{\cdot}CH_3$	6·78
(XIV)	A	5·40 (3·0, 6·6)
	B	7·18—7·47
	C, C′	7·58—8·31
	D	5·73 (6·6, 6·6)
	CH_3	8·68 (6·6)
	$O{\cdot}CH_3$	6·87

conformation of the 2-substituent. But in the *trans,-trans*-isomers, the two likely controlling factors are in opposition. The structure of the rearrangement products shows, however, that the more important factor in the direction of ring opening is the ability of the substituent to delocalise a positive charge rather than the relative degrees of overlap between the small-ring bonds and an adjacent *p*-orbital.

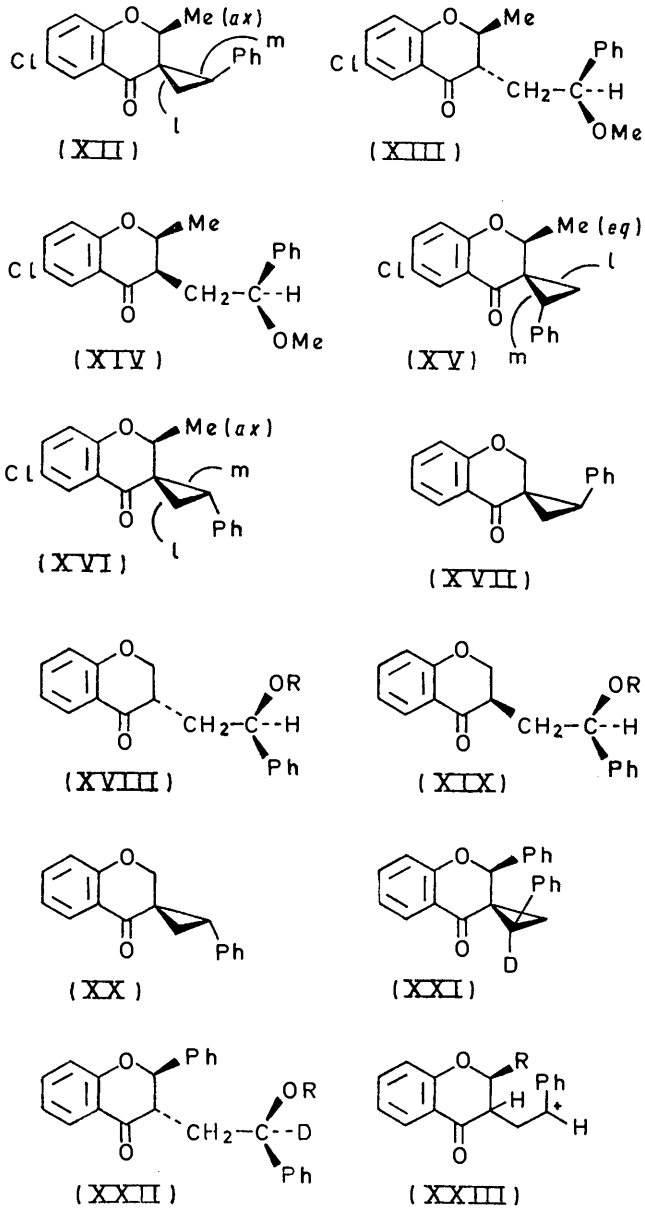
The formation by *trans,trans*-2,2′-diphenylchroman-3-spirocyclopropan-4-one (V) of a different *trans*-3-ethylflavanone from that formed by its *cis,trans*-isomer (VII) is consistent with concerted solvent attack and



ring opening. This phenomenon, which was noted by Stork and Gregson [8] for aryl participation in cyclopropyl ketone rearrangements, is more fully observed

[8] G. Stork and M. Gregson, *J. Amer. Chem. Soc.*, 1969, **91**, 2373.

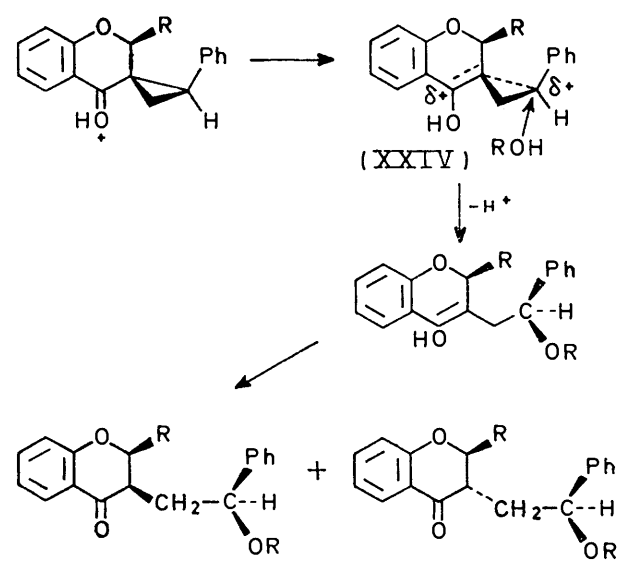
in the rearrangements of the 2-methylchroman-3-spirocyclopropan-4-ones [(IX), (XII), (XV), and (XVI)]; all four isomers were rearranged and each produced a pair of epimers. The products from the *trans,trans*-isomer (IX) were identical with those from the *cis,cis*-isomer * (XVI), as would be expected from concerted solvent attack and ring opening. Similarly, the products from the *trans,cis*-isomer (XII) were identical



with those from the *cis,trans*-isomer * (XV). In assigning stereochemistry to the rearrangement products (Table 1) it has been assumed that inversion of configuration occurred at the benzylic cyclopropane carbon atom.

* The *cis,trans*- and *cis,cis*-isomers were available in quantity only as a mixture but the distribution of the rearrangement products from this mixture is in accord (see Table 1) with these conclusions.

One might reasonably consider that the acid-catalysed rearrangement of cyclopropyl ketones generally proceeds by protonation of the carbonyl oxygen atom with the subsequent formation of a cyclopropylmethyl cation. Many structures have been considered [9] for this cation to accommodate various modes of electron delocalisation. Roberts has recently proposed [10] that the mode of electron delocalisation varies with the nature of the solvent and that for nucleophilic solvents, such as ethanol and methanol, the homoallyl structure



SCHEME 1

SCHEME 2

[*e.g.* (XXIV)] is favoured. Accordingly, the rearrangement of the chroman-3-spirocyclopropan-4-ones, as exemplified by the *trans,cis*-isomers, is shown in Scheme 1.

The recent work of Pittman and McManus [6b] introduces the possibility that these rearrangements proceed, as in Scheme 2, by protonation of the cyclopropane ring followed by cyclic oxonium ion formation. If so, in the present work the opening of the three-membered ring

[9] P. Schleyer and G. W. Van Dine, *J. Amer. Chem. Soc.*, 1966, **88**, 2321.
[10] D. D. Roberts, *J. Org. Chem.*, 1966, **31**, 2000.

and its attack by the carbonyl group must be synchronous, as must the attack by solvent and the opening of the heterocyclic ring at a later stage.

The present cyclopropyl ketone substrates are not suitable for distinguishing between the cyclopropylmethyl cation and the cyclic oxonium ion mechanisms except insofar as the rate studies of Pittman and McManus [6b] for the generation of cyclic oxonium ions might suggest that where the cyclopropane ring can open to leave a particularly stable carbonium ion, such as the benzyl ion [*e.g.* (XXIII)], ring opening would precede attack by the carbonyl group and would, almost certainly, preclude the observed stereospecificity.

EXPERIMENTAL

The n.m.r. spectra were measured with a Varian HR60A or 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.

TABLE 3

Reactions of cyclopropyl ketones with toluene-*p*-sulphonic acid (*p*-TSA) in alcohol

Substrates	Amount	Time (h)	Products	M.p. (°C) (solvent)	Yield (g)	Formula	Found (%) Required (%) C	H
(V)	0·5 g	24	(VI; R = Et)	106—107 (P)	0·39	$C_{25}H_{24}O_3$	80·5	6·7
EtOH	50 ml						80·6	6·5
p-TSA	0·7 g						80·6	6·5
(V)	1·0 g	24	(VI; R = Me)	104—105 (P′)	0·66	$C_{24}H_{22}O_3$	80·4	6·4
MeOH	100 ml						80·4	6·2
p-TSA	1·0 g							
(XXI)	0·1 g	24	(XXII; R = Et)	106—107 (P)	0·036			
EtOH	25 ml							
p-TSA	0·1 g							
(XXI)	0·08 g	24	(XXII; R = Me)	104—105 (P′)	0·04			
MeOH	50 ml							
p-TSA	0·08 g							
(VII)	0·15 g	24	(VIII)	94 (A)	0·09	$C_{25}H_{24}O_3$	80·8	6·8
EtOH	15 ml						80·6	6·5
p-TSA	0·15 g							
(IX)	0·5 g	24	(X) and	82·5—83·5 (E)	0·184	$C_{19}H_{19}ClO_3$	69·2	6·0
MeOH	50 ml						69·0	5·8
p-TSA	0·5 g		(XI) and	74—75 (E)	0·115	$C_{10}H_{19}ClO_3$	69·2	5·9
			(IX)	114—115	0·13		69·0	5·8
(XII)	0·25 g	25	(XIII) and	58—59 (E)	0·075	$C_{19}H_{19}ClO_3$	68·7	5·8
MeOH	25 ml						69·0	5·8
p-TSA	0·25 g		(XIV) and	75—76 (E)	0·065	$C_{19}H_{19}ClO_3$	69·3	5·8
							69·0	5·8
			(XII)	95	0·03			
Mixture of	0·45 g	24	(XIII) and	58—59	0·146			
(XV) (71%) [a] and								
(XVI) (29%)			(XIV) and	75—76	0·094			
MeOH	50 ml							
p-TSA	0·45 g		(X) and	82—83	0·044			
			(XI)	74—75	0·056			
(XVII)	0·5 g	27·5	(XVIII; R = Me) and	Oil [b]	0·46	$C_{18}H_{18}O_3$	76·8	6·5
MeOH	50 ml		(XIX; R = Me)				76·6	6·4
p-TSA	0·5 g							
(XVII)	0·5 g	36	(XVIII; R = Et) and	Oil [b]	0·5	$C_{19}H_{20}O_3$	76·5	7·0
EtOH	50 ml		(XIX; R = Et)				77·0	6·8
p-TSA	0·5 g							
(XX)	0·1 g	41·5	(XVIII; R = Me) and	Oil [b]	0·8			
MeOH	10 ml		(XIX; R = Me)					
p-TSA	0·1 g							
(XX)	0·33 g	45	(XVIII; R = Et) and	Oil [b]	0·25			
EtOH	33 ml		(XIX; R = Et)					
p-TSA	0·33 g							

[a] P = Light petroleum (b.p. 60—80°); P′ = light petroleum (b.p. 40—60°); E = ethanol; A = aqueous ethanol.

[b] Determined by n.m.r. spectroscopy. [b] The components of these mixtures were inseparable. Their n.m.r. spectra are not inconsistent with the assigned structures. The products from the reactions in methanol show a pair of methoxy-signals, of approximately equal intensity, at τ 6·76 and 6·78, suggesting approximately 1 : 1 mixtures of two components. The products from the reactions in ethanol show a pair of methylene quartets at τ 6·71 and 6·73 and a pair of methyl triplets at τ 8·91 and 8·92; the symmetry of these multiplets again suggests approximately 1 : 1 mixtures of two components.

The rearrangements were carried out (details in Table 3) by refluxing an alcoholic solution of the cyclopropyl ketone for the stated length of time and then doubling the volume of the solution with water. The volume was then halved by evaporation under reduced pressure and the solution was extracted with ether. These extracts were subjected to preparative layer chromatography.

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