Homoallylic Rearrangement of Spiro Cyclopropyl Carbinols

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Analogues of chroman-3-spirocyclopropan-4-one, on reduction by sodium borohydride gave, as major product, the chroman-4-ol resulting from hydride attack on the more hindered side of the carbonyl group. The chroman-4-ols were stereoselectively rearranged by acid catalysts to 3-substituted 2*H*-chromens.

THE course of the acid-catalysed homoallylic rearrangement of cyclopropyl carbinols is dependent [1] on substitution pattern, acid strength, and solvent. The high stereoselectivity of the reaction for the formation of diastereoisomers of some spiro cyclopropyl carbinols [*e.g.* (V)—(VIII)] related to chroman-4-ol, in which the relatively rigid system imposes restrictions on the conformations of possible intermediates.

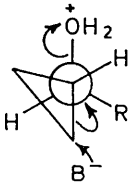
TABLE 1

Reactions of cyclopropyl ketones

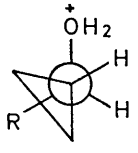
Substrate	Amount (g)	Reagent	Products	Amount (g)	M.p. (°C)	Solvent [a]
trans,trans-6-Chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one (III)	0·50	$NaBH_4$	trans,trans,cis-6-*Chloro*-2-*methyl*-2′-*phenylchroman*-3-*spirocyclopropan*-4-*ol* (V)	0·13	113—114	40—60 [b]
			and its trans,trans,trans-*isomer* (VI)	0·07	137—138	80—100 [b]
trans,trans-6-Chloro-2-methyl-2′-phenylchroman-2-spirocyclopropan-4-one (III)	0·50	PhMgBr	trans,trans-6-*Chloro*-2-*methyl*-2′,4-*diphenylchroman*-3-*spirocyclopropan*-4-*ol* (XXII)	0·38	170—172	Ligroin
trans,cis-6-Chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one (IV)	0·50	$NaBH_4$	trans,cis,trans-6-*Chloro*-2-*methyl*-2′-*phenylchroman*-3-*spirocyclopropan*-4-*ol* (VII)	0·23		
			and its trans,cis,cis-*isomer* (VIII)	0·18		
trans-2′-Phenylchroman-3-spirocyclopropan-4-one (IX)	1·00	$NaBH_4$	trans,cis-2′-*Phenylchroman*-3-*spirocyclopropan*-4-*ol* (X)	0·48	92—93	60—80 [b]
			and its trans,trans-*isomer* (XI)	0·26	109—111	60—80 [b]
trans-2′-Phenylchroman-3-spirocyclopropan-4-one (IX)	1·90	PhMgBr	trans-2′,4-*Diphenylchroman*-3-*spirocyclopropan*-4-*ol* (XXIII)	1·50	99—101	60—80 [b]
trans-2′-Deuterio-2′-phenylchroman-3-spirocyclopropan-4-one, $[^2H_\alpha]$-(IX)	1·00	$LiAlH_4$	trans,cis-2′-*Deuterio*-2′-*phenylchroman*-3-*spirocyclopropan*-4-*ol* $[^2H_\alpha]$-(IX)	0·50	92—93	60—80 [b]
			and its trans,trans-*isomer*, $[^2H_\alpha]$-(XI)	0·28	108—110	60—80 [b]
trans-2′-Deuterio-2′-phenylchroman-3-spirocyclopropan-4-one, $[^2H_\alpha]$-(IX)	1·90	PhMgBr	trans-2′-*Deuterio*-2′,4-*diphenylchroman*-3-*spirocyclopropan*-4-*ol*, $[^2H]_\alpha$-(XXIII)	1·60	99—101	60—80 [b]
cis-2′-Phenylchroman-3-spirocyclopropan-4-one (XXa)	0·30	$NaBH_4$	cis-2′-*Phenylchroman*-3-*spirocyclopropan*-4-*ol* (XXI)	0·23	102—103	60—80 [b]
trans,trans-2′-(4-Methoxyphenyl)-2-phenylchroman-3-spirocyclopropan-4-one (XXb)	1·00	$NaBH_4$	trans,trans,cis-2′-(4-*Methoxyphenyl*)-2-*phenylchroman*-3-*spirocyclopropan*-4-*ol* (XIIIb)	0·65	123—134	EtOH
			and its trans,trans,trans-*isomer* (XIVb)	0·20	142—143	EtOH
trans,trans-2,2′-Diphenylchroman-3-spirocyclopropan-4-one (XIIa)	2·50	PhMgBr	trans,trans-2,2′,4-*Triphenylchroman*-3-*spirocyclopropan*-4-*ol* (XXIV)	2·14	143—144	EtOH–H_2O

[a] Solvent of crystallisation. [b] Light petroleum of this boiling range.

trans-olefins has been explained [2] on the basis of the lesser degree of non-bonded interaction in one (I) of the



(I)



(II)

conformations [(I) and (II)] leading to concerted *anti*-elimination. We have studied the rearrangement of the

† In this paper, stereochemical prefixes refer, first, to the relative configurations of the side-chain aromatic substituent and the carbonyl group, secondly, to those of the 2-substituent and the cyclopropyl methylene group, and thirdly, to those of the 4-hydroxy-group and the cyclopropyl methylene group.

Reduction of Cyclopropyl Ketones.—The carbinols were obtained (Table 1) by the reduction of the corresponding ketones [3] with sodium borohydride.[4] Thus, *trans,trans*-6-chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one † (III) gave two isomeric alcohols in the ratio 1·9 : 1·0. Spectroscopically, there is but one notable difference between these alcohols: the 4-H of the major product is magnetically deshielded, by 0·83

[1] For leading references see M. Julia and C. Descoins, *Bull. Soc. chim. France*, 1970, 1822; S. Sarel, J. Yovell, and M. Sarel-Imber, *Angew. Chem. Internat. Edn.*, 1968, **7**, 577.

[2] S. F. Brady, M. A. Ilton, and W. S. Johnson, *J. Amer. Chem. Soc.*, 1968, **90**, 2882.

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

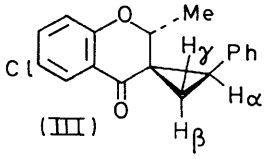
[4] *Cf.* W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc.* (*C*), 1967, 485; S. P. Acharya and H. C. Brown, *J. Amer. Chem. Soc.*, 1967; **89**, 1925; N. A. Lebel and R. N. Liesemer, *ibid.*, 1965, **87**, 4301.

p.p.m., relative to that of the minor product. Dreiding models show that, to avoid severe non-bonded interaction with the side-chain phenyl substituent, the 2-Me group is in the axial conformation in both carbinols and that the major difference between the 4-protons is their relative proximity to the 2-Me group and the consequent change in the extent of their van der Waals deshielding by this group.

The 4-H and the 2-Me group in configuration (V) are approximately 1 Å apart and are well within the distance required [5] for effective mutual deshielding. Because it has the more deshielded 4-H we believe that the major product has this configuration and was formed by attack by the complex hydride from the more hindered side of the ketone, giving the thermodynamically more stable alcohol. The minor product then has the alternative configuration (VI). The n.m.r. spectra of the carbinols are given in a Supplementary Publication (see Experimental section).

Reduction of *trans,cis*-6-chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one (IV) gave a different pair of isomeric alcohols. Again the 4-H of the major product was magnetically deshielded (by 0·80 p.p.m.) relative to that of the minor product. The products have been assigned, therefore, the structures (VII) and (VIII), respectively.

In accord with the foregoing interpretation of the chemical shifts of the 4-H, in the carbinols without a 2-Me substituent, *i.e.* those [(X) and (XI)] obtained by the reduction of *trans*-2′-phenylchroman-3-spirocyclopropan-4-one (IX), the chemical shifts of the 4-protons in both isomers are similar and occur at the higher field [τ *ca.* 5·95; *cf.* 5·93—6·01 and 5·13—5·18 for the 2-Me analogues (VI) and (VIII), and (V) and (VII)].



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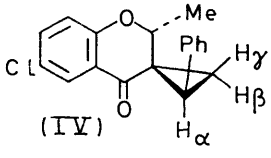

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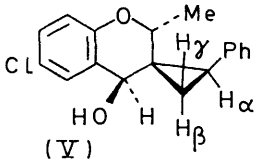

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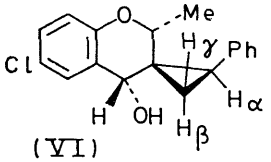

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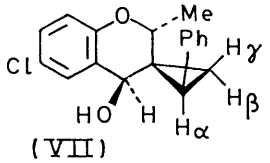

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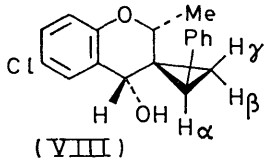
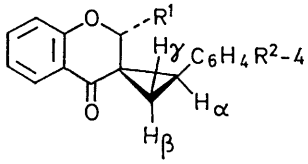
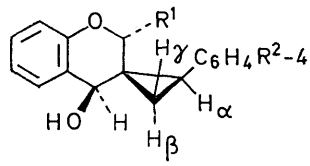


(VIII)

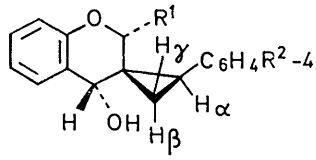
In contrast, the n.m.r. signal of the 4-H of the major product from the sodium borohydride reduction of the flavan-4-one derivative, *trans,trans*-2′-(4-methoxyphenyl)-2-phenylchroman-3-spirocyclopropan-4-one (XIIb), occurs *upfield* of that of the minor product. In this case, however, the axial 2-phenyl substituent is in a position to shield the 4-H in configuration (XIIIb) relative to that in configuration (XIVb) (estimated



(IX) $R^1 = R^2 = H$
(XII) a; R^1 = Ph, R^2 = H
b; R^1 = Ph, R^2 = OMe



(X) $R^1 = R^2 = H$
(XIII) a; R^1 = Ph, R^2 = H
b; R^1 = Ph, R^2 = OMe



(XI) $R^1 = R^2 = H$
(XIV) a; R^1 = Ph, R^2 = H
b; R^1 = Ph, R^2 = OMe

shielding [6] 0·3 p.p.m.; observed 0·5 p.p.m.) and, despite the large increase in hindrance by the axial 2-phenyl group, complex hydride attack probably again occurs preferentially from the more hindered side.

Acid-catalysed Rearrangement of Cyclopropyl Carbinols.—It was impossible in many cases to separate sufficient of the components of the alcohol mixtures without decomposition. Consequently, the acid-catalysed rearrangements were carried out on the isomer mixtures after preliminary experiments had shown that product compositions were not related to the proportions of the isomeric constituents. Two acid catalysts were used; hydrated toluene-4-sulphonic acid (in benzene) and acetic acid. The results are summarised in Table 2. The rearrangements of the carbinols (V)—(VIII) related to 6-chloro-2-methylchroman-4-one, may be taken as typical.

The mixture of *trans,trans,cis*- (V) (66%) and *trans,trans,trans*- (VI) (34%) 6-chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-ol rearranged in acetic acid to give the diastereoisomers [(XVIII) and (XIX)] of 3-(2-acetoxy-2-phenylethyl)-6-chloro-2-methyl-2*H*-chromen in the ratio *ca.* 80 : 20. The large degree of stereoselectivity might be attributed [2] to concerted ring-opening and loss of water but as neither of the starting alcohols is free to approach the *trans*-coplanar conformation (I) preferred for such a process and only the minor alcohol can adopt a *cis*-coplanar conformation, we believe that the stereoselectivity results from the formation by both isomers of the homoallyl cation (XVII), followed by *trans*-opening of the ring by solvent from the least hindered side with consequent inversion of configuration at C-2′.

The same products, but in approximately inverse

[5] L. M. Jackman and S. Sternhell, 'Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 1969, p. 71.

[6] C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, 1958, **29**, 1012.

ratio (15 : 85) were obtained from the rearrangement of a mixture of *trans,cis,trans*- (VII) (57%) and *trans,cis,cis*- (VIII) (43%) 6-chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-ol. This result is in accord with the foregoing rationalisation of the stereoselectivity of these reactions.

The ketones *cis,trans*- (XV) and *cis,cis*- (XVI) 6-chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one, available [3] only as a 48 : 52 mixture, were reduced with sodium borohydride, and the resulting alcohols, on (see Table 2). Also, substantial quantities of 3-(2-styryl)-2*H*-chromen [(XXV) and (XXVII)] were isolated. Indeed, this was the only type of product isolated from the 2-phenylchroman-4-ols (XIII) and (XIV).

EXPERIMENTAL

The n.m.r. spectra were measured at 60 MHz with a Varian HR60A spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal reference. M.p.s were obtained with a Kofler hot-stage apparatus.

TABLE 2

Acid-catalysed rearrangements of cyclopropyl carbinols

Substrate	Amount (g)	Reagents	Products	Amount (g)
trans,trans-6-Chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one (III)	0·50	(i) $NaBH_4$ (ii) AcOH	3-(2-*Acetoxy*-2-*phenylethyl*)-6-*chloro*-2-*methyl*-2H-*chromen*, (2*SR*,2′*RS*) (XVIII; R = Ac)	0·32
			and (2*SR*,2′*SR*) (XIX; R = Ac)	<0·08 [a]
trans,trans-6-Chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one (III)	0·40	(i) $NaBH_4$ (ii) TsOH	6-*Chloro*-2-*methyl*-3-(2-*styryl*)-2H-*chromen* (XXV), m.p. 80—81°	0·14
			6-*Chloro*-3-(2-*hydroxy*-2-*phenylethyl*)-2-*methyl*-2H-*chromen*, (2*SR*,2′*RS*) (XVIII; R = H)	0·10
			and (2*SR*,2′*SR*) (XIX; R = H)	<0·02 [a]
trans,cis-6-Chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one (IV)	0·25	(i) $NaBH_4$ (ii) AcOH	3-(2-Acetoxy-2-phenylethyl)-6-chloro-2-methyl-2*H*-chromen, (2*SR*,2′*SR*) (XIX; R = Ac)	0·21
			and (2*SR*,2′*RS*) (XVIII; R = Ac)	<0·04
trans,cis-6-Chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one (IV)	0·25	(i) $NaBH_4$ (ii) TsOH	6-Chloro-2-methyl-3-(2-styryl)-2*H*-chromen (XXV)	0·03
			6-chloro-3-(2-hydroxy-2-phenylethyl)-2-methyl-2*H*-chromen, (2*SR*,2′*SR*) (XIX; R = H),	0·08
			and (2*SR*,2′*RS*) (XVIII; R = H)	<0·02
Mixture of *cis,trans*- (XV) (48%) and cis,cis- (XVI) (52%) 6-chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one	0·34	(i) $NaBH_4$ (ii) AcOH	3-(2-Acetoxy-2-phenylethyl)-6-chloro-2-methyl-2*H*-chromen, (2*SR*,2′*RS*) (XVIII; R = Ac)	0·14
			and (2*SR*,2′*SR*) (XIX; R = Ac)	0·11
Mixture of *cis,trans*- (XV) (48%) and cis,cis- (XVI) (52%) 6-chloro-2-methyl-2′-phenylchroman-3-spirocyclopropan-4-one	0·18	(i) $NaBH_4$ (ii) TsOH	6-Chloro-2-methyl-3-(2-styryl)-2*H*-chromen (XXV),	0·02
			6-chloro-3-(2-hydroxy-2-phenylethyl)-2-methyl-2*H*-chromen, (2*SR*,2′*RS*) (XVIII; R = H),	0·04
			and (2*SR*,2′*SR*) (XIX; R = H)	0·03
trans-2′-Phenylchroman-3-spirocyclopropan-4-one (IX)	1·00	(i) $NaBH_4$ (ii) AcOH	3-(2-*Acetoxy*-2-*phenylethyl*)-2H-*chromen* (XXVI; R^1 = H, R^2 = Ac), m.p. 65—66°	0·66
trans-2′-Phenylchroman-3-spirocyclopropan-4-one (IX)	0·35	(i) $NaBH_4$ (ii) TsOH	3-(2-*Styryl*)-2H-*chromen* [b] (XXVII; R = H), m.p. 123—124°	0·03
			and 3-(2-*hydroxy*-2-*phenylethyl*)*chromen* (XXVI; R^1 = R^2 = H)	
cis-2′-Phenylchroman-3-spirocyclopropan-4-one (XXa)	0·13	(i) $NaBH_4$ (ii) AcOH	3-(2-Acetoxy-2-phenylethyl)-2*H*-chromen (XXVI; R^1 = H, R^2 = Ac)	0·08
cis-2′-Phenylchroman-3-spirocyclopropan-4-one (XXa)	0·20	(i) $NaBH_4$ (ii) TsOH	3-(2-Styryl)-2*H*-chromen (XXVII; R = H)	0·02
			and 3-(2-hydroxy-2-phenylethyl)-2*H*-chromen (XXVI; R^1 = R^2 = H)	0·05
trans,trans-2,2′-Diphenylchroman-3-spirocyclopropan-4-one (XIIa)	1·00	(i) $NaBH_4$ (ii) AcOH	3-(2-*Acetoxy*-2-*phenylethyl*)*flav*-3-*ene*, (2*SR*,2′*RS*) (XXVI; R^1 = Ph, R^2 = Ac), m.p. 97—98°	0·72
trans,trans-2,2′-Diphenylchroman-3-spirocyclopropan-4-one (XIIa)	1·00	(i) $NaBH_4$ (ii) TsOH	3-(2-*Styryl*)*flav*-3-*ene* (XXVII; R = Ph), m.p. 138—139°	0·94
trans,cis-2,2′-Diphenylchroman-3-spirocyclopropan-4-one (XXIX)	0·07	(i) $NaBH_4$ (ii) AcOH	3-(2-*Acetoxy*-2-*phenylethyl*)*flav*-3-*ene*, (2*SR*,2′*SR*) (XXVIII), m.p. 88—89°	0·06
cis,trans-2,2′-Diphenylchroman-3-spirocyclopropan-4-one (XXb)	0·25	(i) $NaBH_4$ (ii) AcOH	3-(2-Acetoxy-2-phenylethyl)flav-3-ene (2*SR*,2′*SR*) (XXVIII)	0·20
cis,trans-2,2′-Diphenylchroman-3-spirocyclopropan-4-one (XXb)	0·25	(i) $NaBH_4$ (ii) TsOH	3-(2-Styryl)flav-3-ene (XXVII; R = Ph)	0·15

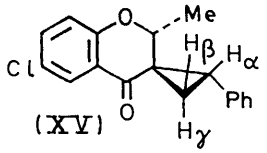
[a] Not isolated but estimated by integration of the n.m.r. spectrum of the crude product. [b] The sole product when the reaction time for rearrangement was increased from 5 to 17 h.

rearrangement with acetic acid, gave the 2*H*-chromen diastereoisomers (XVIII) and (XIX) in the ratio 55 : 45.

The rearrangements of the carbinols with toluene-4-sulphonic acid monohydrate in benzene closely paralleled the acetic acid rearrangements except that hydroxy- rather than acetoxy-2*H*-chromen were formed

The reduction of the chroman-4-ones by sodium borohydride (Table 1) was carried out in standard fashion.[7a] The final methanolic solution was diluted with an equivalent volume of water, reduced to half volume with a rotary evaporator under reduced pressure, and extracted with

[7] L. F. Fieser, 'Organic Experiments,' Heath and Co., Boston, 1966, (*a*) p. 216; (*b*) p. 90.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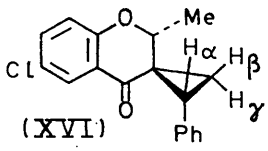
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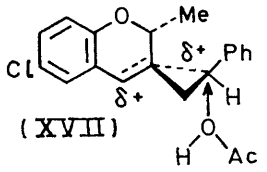
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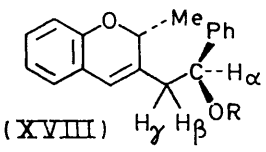
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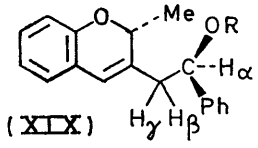
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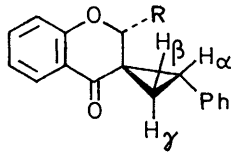
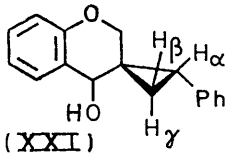
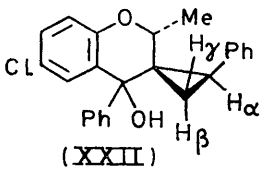
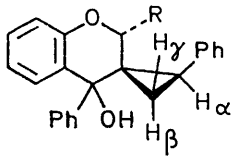
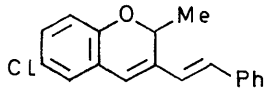

(XX) a; R = H
b; R = Ph

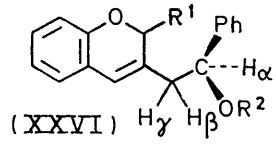

(XXI)

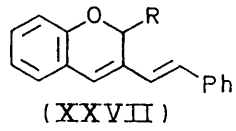

(XXII)

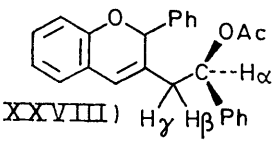

(XXIII) R = H
(XXIV) R = Ph

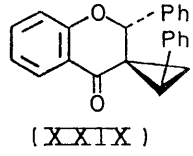
ether. After removal of the ether, the residual oil was resolved into its components by preparative layer chromatography (p.l.c.) on silica gel. A standard method [7b] was also used for chromanol formation by Grignard reaction (Table 1).


(XXV)


(XXVI)


(XXVII)


(XXVIII)


(XXIX)

The rearrangement of chroman-4-ols (Table 2) was carried out by dissolving the unresolved residual oil (see before) from the sodium borohydride reduction of the corresponding chroman-4-ones, in acetic acid (*ca.* 10 ml) and heating the solution on a steam-bath for 30 min. The reaction mixture was then diluted with water, neutralised with aqueous saturated sodium carbonate, and extracted with ether. After removal of the ether, the remaining oil was resolved by p.l.c. on silica gel.

The physical data for all products are given in Supplementary Publication No. SUP 20659 (5 pp.).†

[2/2232 *Received*, 25*th September*, 1972]

† For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20.