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The Stereochemistry and Reactions of some 3,4-Disubstituted Chromans

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Hydrolysis of *trans*-3,4-dihalogenochromans yielded *trans*-3-halogeno-4-hydroxychromans; borohydride reduction of 3-halogenochroman-4-ones gave *cis*-3-halogeno-4-hydroxychromans. The ¹H n.m.r. coupling constants of these compounds showed that the hetero-ring exists in the half-chair conformation, with both substituents axial in the *trans*-isomer, and that the most stable conformation of the *cis*-isomer is that in which the 4-substituent is pseudo-axial.

CHROMEN ^{1,2} reacted with chlorine and bromine in carbon tetrachloride to give 3,4-dichloro-and 3,4-dibromo-chroman,^{1,3} (Ia) and (Ib) respectively. Both 3,4-dihalogenochromans were hydrolysed in aqueous acetone to give the corresponding 3-halogeno-4-hydroxychromans, (Ic) and (Id), which on treatment with potassium hydroxide in ether gave 3,4-epoxychroman

¹ P. Maitte, Ann. Chim. (France), 1954, 9, 431.

² W. E. Parham and L. D. Huestis, J. Amer. Chem. Soc., 1962, 84, 813.

(II). The stereochemical preference for the formation of epoxide by dehydrohalogenation of 1,2-halogeno-hydrins is that the two interacting groups should be anti-periplanar.⁴ This suggests that these 3-halogeno-4-hydroxychromans (Ic) and (Id) possess a *trans*-configuration.

The ¹H n.m.r. spectral parameters (Table) of the ³ R. Binns, W. D. Cotterill, and R. Livingstone, J. Chem. Soc., 1965, 5049.

Soc., 1965, 5049. ⁴ N. A. LeBel and R. F. Czaja, J. Org. Chem., 1961, **26**, 4768. 3,4-dihalogenochromans (Ia and b) and the 4-acetoxy-3-halogenochromans (Ie and f) [obtained by acetylation of the corresponding 4-hydroxy-3-halogenochromans



(Ic and d)] revealed that their structures are closely related and they will be considered as a group. The

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equation ⁸ indicates that the C(3)-H_C bond bisects the C-2 methylene system, and that in the proposed halfchair conformation H_0 is equatorial. The 3ax-halogeno-substituent is antiperiplanar to H_A , and the observation that ${}^{3}J_{\rm BC} \simeq 2 \times {}^{3}J_{\rm AC}$ is therefore ascribed to the electronegativity effect 9 of the 3ax-substituent; no modification to the half-chair geometry of the heteroring is thus required.

The signal of 2-axial proton (H_A) lies at lower field than that of the 2-equatorial proton (H_B) for compounds (Ia, b, e, and f). This reversal of the normal order may be explained by that fact that in the diaxial conformation the 3-axial halogeno-group has a much stronger deshielding effect 10 on proton H_A (dihedral angle $\phi = 180^{\circ}$) than on proton H_B ($\phi = 60^{\circ}$). The 3,4-dihalogenochromans and their hydrolysis products exist predominantly in the trans-diaxial conformation (Ia, b, c, and d) because the corresponding diequatorial conformation (Ia', b', c', and d') is destabilised by dipole-dipole repulsion between the 3eq- and 4eqsubstituents, and by repulsion between the 4eq-substituent and the *peri*-hydrogen. The hydrolysis of the trans-3,4-dihalogenochromans (Ia) and (Ib) proceeds with retention of configuration owing to the effect of the neighbouring 3-halogeno-substituent.¹¹

N.m.r. spectral parameters of cis- and trans-3,4-di-substituted chromans

	δ (p.p.m.)				Coupling constants (Hz)					
Compound	Hx	HB	HA	HB	$J_{\rm cx}$	³ Jac	³ Јвс	⁴ J _{BX}	² <i>J</i> AB	Solvent
(Ī) a	5.12	4.44	4.65	4.25	3.0	1.5	3.0	1.7	12.1	[² H]Chloroform
b	5.18	4.11	4.51	3.83	$2 \cdot 5$	1.6	2.5	$2 \cdot 1$	12.9	Benzene
e	5.86	4.55	4.46	4.37	$3 \cdot 2$	1.4	3.8	1.3	12.5	Acetone
f	6.21	4.62	4.47	4.38	$3 \cdot 4$	1.6	3.9	$1 \cdot 2$	12.7	Pyridine
(III) c	6.30	4.97	4.35	4.60	3.8	7.6	$2 \cdot 5$	0.9	11.6	² H _a]Dimethyl sulphoxide
`´d	6.23	5.01	4.37	4.63	$3 \cdot 8$	8.3	$2 \cdot 4$	0.9	11.9	^{[2} H ₆]Dimethyl sulphoxide
Spectra recorded at both 60 and 100 MHz.										

significant features from the coupling constant data are that ${}^{3}J_{CA}$, ${}^{3}J_{CB}$, and ${}^{3}J_{CX}$ are small (3-4 Hz), ${}^{4}J_{\text{BX}}$ is ca. 1.5 Hz, and ${}^{4}J_{\text{AX}}$ is ca. 0. Dreiding models showed that, with the hetero-ring in the half-chair conformation and with proton H_X pseudo-equatorial [see (Ia)], protons H_B and H_X lie close to a planar zig-zag orientation for which ${}^{4}J$ coupling is a maximum,⁵ and H_A and H_X are unfavourably situated for ⁴*J* coupling. The alternative 'sofa' conformation does not have the correct geometry for ${}^{4}J$ coupling and this structure will not be considered further. (Bolger and his co-workers 6,7 concluded from ${}^{3}J$ coupling evidence, that the heteroring in a number of substituted flavans probably adopted the half-chair conformation.)

The observed coupling constants between the C-2 methylene protons and proton $H_{\rm C}$ are small (${}^3J_{\rm BC} \approx$ $2 \times {}^{3}J_{A0} \approx 3-4$ Hz) and application of the Karplus

- ⁵ M. Barfield, J. Chem. Phys., 1964, **41**, 3825. ⁶ B. J. Bolger, A. Hirwe, K. G. Marathe, E. M. Philbin, M. A. Vickars, and C. P. Lillya, *Tetrahedron*, 1966, **22**, 621.
- ⁷ B. J. Bolger, K. G. Marathe, E. M. Philbin, T. S. Wheeler, and C. P. Lillya, *Tetrahedron*, 1967, 23, 341.
 - M. Karplus, J. Amer. Chem. Soc., 1963, 85, 2870.
 - ⁹ H. Booth, Tetrahedron Letters, 1965, 411.

The cis-3-halogeno-4-hydroxychromans (IIIa) and (IIIb) were obtained by reduction with sodium borohydride of the corresponding 3-halogenochroman-4ones 12 (IVb) and (IVc). The cis-configuration was assigned on the basis of the ¹H n.m.r. coupling constants of the acetoxy-derivatives (Table) and the fact that dehydrohalogenation with potassium hydroxide gave chroman-4-one (IVa).

The ¹H n.m.r. coupling constants (${}^{3}J_{AO} \approx 8$, ${}^{3}J_{BO} \approx$ 2.5 Hz) between proton H₀ and the C-2 methylene protons of the cis-4-acetoxy-3-halogenochromans (IIIc and d), suggest that H₀ has an axial orientation and that it lies outside the angle made by the methylene protons.^{8,13} The ${}^{4}J_{BX}$ coupling is still appreciable (0.9 Hz), so that H_x must prefer a pseudoequatorial orientation. These preferred orientations for H_0 and H_X prove that the compounds possess a *cis*-configuration and that the

- ¹⁰ R. F. Zurcher, Progr. N.M.R. Spectroscopy, 1967, 2, 241. ¹¹ S. Winstein, E. Grunwald, and L. L. Ingraham, J. Amer. Chem. Soc., 1948, 70, 821.
- 12 J. Colonge and A. Guyot, Bull. Soc. chim. France, 1958, 325.
- ¹³ R. J. Abraham and J. S. E. Holker, J. Chem. Soc., 1963, 806.

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most stable half-chair conformation is that of 4axacetoxy-3eq-halogenochroman (IIIc and IIId). By assuming that ${}^{3}J_{AaxCax}$ is 10.5 Hz and ${}^{3}J_{AeqCeq}$ 1.5 Hz (ref. 6) the position of the conformational equilibria may be calculated. Thus 68% (ΔG 0.45 k.cal./mole) of



cis-4-acetoxy-3-bromo-chroman exists in the conformation in which the acetoxy-group occupies a pseudoaxial position. The free-energy difference between the two conformations of these cis-isomers is probably due to the destabilisation of (IIIc') and (IIId') by steric repulsion between the *peri*-hydrogen and the 4eq-acetoxy-group, and by dipole-dipole repulsion between the 3ax-halogeno-substituent and the ring oxygen [there will also be some dipole-dipole stabilisation of the other conformations (IIIc and d)]. The signal of the 2eq-proton (H_B) lies at lower field than that of the 2ax-proton (H_A) ; this is the order normally observed ¹⁴ in 'cyclohexane systems and it is to be expected, since in the major conformation the 3eq-halogeno-group lies between the C-2 geminal protons (ϕ 60°), thus shielding both protons equally. The differential shielding is now due to the anisotropy effect of the C(3)-C(4) bond.¹⁰

EXPERIMENTAL

The n.m.r. spectra were obtained with Varian A60A and HA100 spectrometers for *ca.* 10% solutions in the named solvents (Table). The spectra were analysed as ABMX systems and the solvents were chosen to give the largest chemical shift differences. The errors in coupling constant values are <0.3 Hz. and in the chemical shifts are <0.02 p.p.m.

M.p.s were determined with a Kofler hot-stage apparatus. The acetates were prepared in the cold by use of acetic anhydride-pyridine.

3,4-Dichlorochroman (Ia).—Chlorine from potassium permanganate (2.45 g.) and hydrochloric acid (16.5 ml.) was passed slowly into a solution of chromene (5.0 g.) in carbon tetrachloride (100 ml.) at 0°. Evaporation and crystallisation from light petroleum (b.p. $80-100^{\circ}$) gave 3,4-dichlorochroman (3.3 g., 43%) as plates, m.p. $89-90^{\circ}$ (Found: C, 53.0; H, 4.0; Cl, 34.7. C₉H₈Cl₂O requires C, 53.2; H, 3.9; Cl, 35.0%).

3,4-Dibromochroman (Ib).—Bromine (7.65 g.) in carbon tetrachloride (50 ml.) was added to chromene (6.3 g.) in carbon tetrachloride (50 ml.). Evaporation and crystallisation from light petroleum (b.p. $100-120^{\circ}$) gave 3,4-dibromochroman (13.1 g., 94%), m.p. $127-128^{\circ}$ (lit.,¹ 124°).

Trans-3-Halogeno-4-hydroxychromans.—The 3,4-dihalogenochroman (10.0 g.), acetone (100 ml.), and water (30—40 ml.) were boiled for 24 hr. Pouring into water, isolation with ether, and crystallisation from a suitable solvent gave the trans-3-halogeno-4-hydroxychroman.

(i) Trans-3-Chloro-4-hydroxychroman (Ic) (82%) had m.p. 106—107° [from light petroleum (b.p. 60—80°)] (Found: C, 58·7; H, 4·9; Cl, 18·8. $C_9H_9ClO_2$ requires C, 58·55; H, 4·9; Cl, 19·2%); acetate (Ie), m.p. 74°, [from light petroleum (b.p. <40°)] (Found: C, 58·1; H, 4·8; Cl, 15·5. $C_{11}H_{11}ClO_3$ requires C, 58·2; H, 4·9; Cl, 15·7%).

(ii) trans-3-Bromo-4-hydroxychroman (Id) (91.5%) gave needles, m.p. 107—108° [from light petroleum (b.p. 80—100°)] (Found: C, 47.4; H, 4.2. $C_9H_9BrO_2$ requires C, 47.2; H, 3.9%); acetate (If), m.p. 62° [from light petroleum (b.p. 40—60°)] (Found: C, 49.0; H, 4.1; Br, 29.95. $C_{11}H_{11}BrO_3$ requires C, 48.7; H, 4.1; Br, 29.5%).

3-Chlorochroman-4-one (IVb).—(a) Chroman-4-one (4.8 g.), sulphuryl chloride (1.7 ml.), and chloroform (30 ml.) were boiled for 2.5 hr. Evaporation and crystallisation from benzene-light petroleum (b.p. 40—60°) gave 3chlorochroman-4-one (4.2 g., 71%), as plates, m.p. 59.5— 60.5° (Found: C, 59.2; H, 3.7; Cl, 18.9. $C_9H_7ClO_2$ requires C, 59.2; H, 3.8; Cl, 19.45%).

(b) cis- or trans-3-Chloro-4-hydroxychroman (0.72 g.) and chromium trioxide solution [chromium trioxide (9.5 g.), acetic acid (53 ml.), and water (6.5 ml.)] (2 ml.) were set aside for 2.5 hr. at 70°. Pouring into water, isolation with ether, and crystallisation from benzenelight petroleum (b.p. 40—60°) gave 3-chlorochroman-4-one (0.51 g., 70%), m.p. and mixed m.p. 59—60°.

3-Bromochroman-4-one (IVc).—cis- or trans-3-Bromo-4-hydroxychroman (0.6 g.) and chromium trioxide solution (2 ml.) were set aside for 2 hr. at 70°. Pouring into water and isolation with ether yielded a yellow solid, which gave 3-bromochroman-4-one (0.42 g., 70%), m.p. and mixed m.p. 77—78° (from methanol) (lit.,⁴ 78°).

cis-3-Halogeno-4-hydroxychromans.—Sodium borohydride (1.5—2.0 g.) was added in portions to the 3-halogenochroman-4-one (5 g.) in methanol (35 ml.). After a few hr., water was added to give a solid. Filtration and crystallisation from light petroleum (b.p. 80—100°) gave the cis-3halogeno-4-hydroxychroman.

(i) cis-3-Chloro-4-hydroxychroman (IIIa) (81%) had m.p. 129—129.5° (Found: C, 58.2; H, 4.7; Cl, 19.2. $C_9H_9ClO_2$ requires C, 58.5; H, 4.9; Cl, 19.2%); acetate, m.p. 50° [from light petroleum (b.p. <40°)] (Found: C, 58.4; H, 4.6; Cl, 15.6. $C_{11}H_{11}ClO_3$ requires C, 58.2; H, 4.9; Cl, 15.7%).

(ii) cis-3-Bromo-4-hydroxychroman (IIIb) (70%) had m.p. 109—110° (Found: C, 47.2; H, 4.2; Br, 34.6. $C_9H_9BrO_2$ requires C, 47.2; H, 3.9; Br, 34.9%); acetate, m.p. 65° [from light petroleum (b.p. <40°)] (Found: C, 48.7; H, 4.3; Br, 29.8. $C_{11}H_{11}BrO_3$ requires C, 48.7; H, 4.1; Br, 29.5%).

¹⁴ R. V. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, 1957, **79**, 1005; 1958, **80**, 6098; K. L. Williamson and W. S. Johnson, *ibid.*, 1961, **83**, 4623.

3,4-Epoxychroman (II).—trans-3-Bromo-4-hydroxychroman (4.0 g.), powdered potassium hydroxide (4.0 g.), and ether (100 ml.) were stirred intermittently for 4 days. Filtration and evaporation gave 3,4-epoxychroman (2.5 g., 93%), m.p. 33—34° (Found: C, 72.9; H, 5.5. $C_{9}H_{8}O_{2}$ requires C, 73.0; H, 5.4%).

trans-3-Chloro-4-hydroxychroman (4.0 g.) gave 3,4epoxychroman (2.0 g., 61.5%), m.p. and mixed m.p. 33-34° [from light petroleum (b.p. $<40^{\circ}$)].

Chroman-4-one (IVa).—(a) cis-3-Chloro-4-hydroxychroman (0.85 g.), powdered potassium hydroxide (1.2 g.), and ether (40 ml.) were stirred intermittently for 4 days. Filtration and evaporation gave an oil. Trituration with light petroleum (b.p. $<40^{\circ}$) and filtration yielded starting material (0.42 g.). Evaporation of the filtrate gave chroman-4-one (0.15 g., 44%), m.p. and mixed m.p. 36—39° (lit.,² 39°).

(b) cis-3-Bromo-4-hydroxychroman (8.5 g.), powdered potassium hydroxide (15 g.), and ether (150 ml.) were stirred intermittently for 2 days. Filtration and evaporation gave a solid, which yielded chroman-4-one (3.7 g., 67.4%), m.p. and mixed m.p. $39-39.5^{\circ}$ [from light petroleum (b.p. $40-60^{\circ}$)].

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