

Methanolysis of 3,4-Dihalogenochromans and 1,2-Dihalogenotetralins

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Rates and activation parameters have been obtained for the methanolysis of *trans*-3*eq*,4*eq*-dihalogeno-2,2-dimethylchromans, *trans*-3*ax*,4*ax*-dihalogenochromans, and 1,2-dihalogenotetralins in methanol-acetone. The structures of the dihalogeno-compounds were deduced by n.m.r. measurements. The reactions involve a carbonium ion intermediate, the mechanism being dependent on steric and neighbouring-group effects. The results are similar to those for the hydrolysis of *trans*-3*eq*,4*eq*-dihalogeno-2,2-dimethylchromans.

It has been demonstrated that the methanolysis of all the dihalogeno-compounds described in ref. 1 and in the present paper involves the replacement of the chlorine or bromine atom in the 4-position (1-position for tetralins).

EXPERIMENTAL

Materials.—Commercial acetone was purified² and stored over calcium sulphate. Before use, it was refluxed for 24 h over the drying agent and fractionated (b.p. 56.5–57°).³ AnalaR methanol was treated by Lund and Bjerrum's method;⁴ the distillate had b.p. 64–65°. A standard solution of dihalogeno-compound in acetone (10 ml) was added to methanol (90 ml) at room temperature for runs at 20° or above, or to methanol (90 ml) at the temperature of the thermostat bath for runs below 20°.

3,4-Dibromochroman⁵ was recrystallised from light petroleum (b.p. 100–120°); m.p. 127–128°. 3,4-Dichlorochroman⁶ was recrystallised from light petroleum (b.p. 40–60°); m.p. 89–90°. 3,4-Dibromo-2,2-dimethylchroman¹ was recrystallised from light petroleum (b.p. 40–60°); m.p. 81–82°. 3,4-Dichloro-2,2-dimethylchroman⁷ was recrystallised from light petroleum (b.p. <40°); m.p. 59–60°. 1,2-Dibromotetralin⁸ was recrystallised

from light petroleum (b.p. 40–60°); m.p. 71–72°. 1,2-Dichlorotetralin⁹ was recrystallised from light petroleum (b.p. <40°); m.p. 39–40°. The mixed dihalogeno-compounds were prepared from the appropriate *cis*- or *trans*-halogenohydrins and an equimolar proportion of a phosphorus halide,¹⁰ as follows.

(i) The chlorohydrin (0.06 mol), phosphorus tribromide (0.06 mol), and benzene (250 ml) were stirred for 15 h. Removal of the solvent and recrystallisation from a suitable solvent gave the bromochloro-derivative [Table 1, (i)].

(ii) The bromohydrin (0.06 mol) in benzene (150 ml) was added slowly to a solution of phosphorus pentachloride (0.06 mol) in benzene (100 ml). After stirring for 15 h the bromochloro-derivative [Table 1 (ii)] was obtained as in (i).

Halogenohydrins.—*trans*-3-Bromochroman-4-ol,⁵ *trans*-3-chlorochroman-4-ol,⁶ *trans*-3-bromo-2,2-dimethylchroman-4-ol,¹ *trans*-3-chloro-2,2-dimethylchroman-4-ol,⁷ *trans*-2-bromotetralin-1-ol,⁹ and *trans*-2-chlorotetralin-1-ol¹¹ were prepared by hydrolysis of the corresponding dihalogeno-compounds with aqueous acetone. *cis*-3-Bromochroman-4-ol and *cis*-3-chlorochroman-4-ol were obtained by treating 3-bromochroman-4-one and 3-chlorochroman-4-one with sodium borohydride.⁶ Similarly *cis*-2-bromotetralin-

⁶ W. D. Cotterill, J. Cottam, and R. Livingstone, *J. Chem. Soc. (C)*, 1970, 1006.

⁷ J. Cottam, R. Livingstone, and S. Morris, *J. Chem. Soc.*, 1965, 5266.

⁸ F. Strauss and L. Lemmel, *Ber.*, 1913, **46**, 232.

⁹ J. V. Braun and G. Kirschbaum, *Ber.*, 1921, **54**, 597.

¹ R. Livingstone, *J. Chem. Soc.*, 1962, 76.

² A. I. Vogel, 'A Text Book of Practical Organic Chemistry,' Longmans, Green, London, 1956, p. 171.

³ 'Organic Solvents,' ed. A. Weissberger, Interscience, New York, 1955.

⁴ Ref. 2, p. 169.

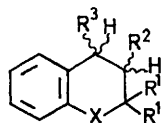
⁵ P. Maitte, *Ann. Chim. (France)*, 1954, **9**, 431.

¹⁰ A. G. Pinkus and P. G. Waldrep, *J. Org. Chem.*, 1959, **24**, 1012; W. Gerrard, *J. Chem. Soc.*, 1945, 848.

¹¹ M. Mousseron-Canet, *Bull. Soc. chim. France*, 1956, 1551.

1-ol and *cis*-2-chlorotetralin-1-ol were prepared by reduction of the corresponding 2-halogeno-1-ketones.

TABLE 1



X	R ¹	R ²	R ³	B.p. of solvent light petroleum (°C)	Yield (%)	M.p. (°C)	C	Found (%)			
								H	Br	Cl	
(a) Bromo-chloro compounds											
(i)	O	Me	Cl	Br	<40	74 *	53-54	48.1	4.6	29.5	12.3 a
	O	H	Cl	Br	40-60	83, * 74 †	117-118	43.7	3.3	32.0	14.2 b
	CH ₃	H	Cl	Br	40-60	78, * 63 †	57-58	48.6	4.2	32.9	14.3 c
(ii)	O	Me	Br	Cl	40-60	64 *	84-85	47.8	5.0	30.0	12.4 a
	O	H	Br	Cl	80-100	60, * 57 †	95.5-96.5	43.8	3.4	33.4	13.9 b
	CH ₃	H	Br	Cl	<40	51, * 45 †	56-57	49.1	4.3	32.2	14.3 c
(b) Dihalogeno-compounds prepared by methods (i) and (ii)											
	O	Me	Br	Br	40-60	73 *	81-82 d				
	O	Me	Cl	Cl	<40	60 *	59-60 e				
	O	H	Br	Br	100-120	71, * 74 †	127-128 f				
	CH ₃	H	Br	Br	40-60	84, * 78 †	71-72 g				
	CH ₃	H	Cl	Cl	<40	64, * 49 †	39-40 h				

* From *trans*-halogenohydrin. † From *cis*-halogenohydrin.

a C₁₁H₁₃BrClO requires C, 48.0; H, 4.4; Br, 29.1; Cl, 12.9%. b C₉H₉BrClO requires C, 43.5; H, 3.2; Br, 32.6; Cl, 14.3%. c C₁₀H₁₀BrClO requires C, 48.7; H, 4.1; Br, 32.8; Cl, 14.4%. d Ref. 1. e Ref. 7. f Ref. 5. g Ref. 8. h Ref. 9.

Reactions were followed to 70% completion in most cases except for the slower runs, and the rate coefficient was not affected by the volume of space above the solution. All rate constants had coefficients of variation of less than 3%.

The apparent activation energy was calculated by the method of least squares and is shown in Table 4 together with the least squares coefficients *a* and *b*. Also shown is *k*₁ at 293.2 K from which the free energy of activation, Δ*G*^{*}, at 293.2 K, can be calculated for each compound from the equation:¹³

$$\Delta G^* = 19.151T \log kT/h - 19.151T \log k_1$$

(*k* = Boltzmann constant)

Spectra.—The 60 MHz ¹H n.m.r. spectra were measured on a Varian A60A spectrometer for *ca.* 10% solutions in deuteriochloroform, with tetramethylsilane as internal reference.

DISCUSSION

Dreiding models of 3,4-dihalogenochromans give information corresponding to that reported for the related 2,2-dimethyl derivatives.¹⁴ The ¹H n.m.r. spectra of the 3,4-disubstituted chromans were used to determine the configurations of the substituents at C-3 and C-4.¹⁴

TABLE 2

Methanolysis products

Dihalogeno compound				Product				Yield (%)	M.p. (°C)	Found (%)			Molecular formula	Requires (%)		
X	R ¹	R ²	R ³	X	R ¹	R ²	R ³			C	H	Br		Cl	C	H
O	Me	Br	Br	O	Me	Br	OMe	93.1	74 †							
O	Me	Cl	Cl	O	Me	Cl	OMe	93.8	71-73 †	63.6	6.5	15.0	C ₁₂ H ₁₆ ClO ₂	63.6	6.6	15.7
O	Me	Br	Cl	O	Me	Br	OMe	93.7	74 †							
O	Me	Cl	Br	O	Me	Cl	OMe	93.5	71-73 †	63.7	6.6	15.6	C ₁₂ H ₁₆ ClO ₂	63.6	6.6	15.7
O	H	Br	Br	O	H	Br	OMe	92.2		49.5	4.5	33.1	C ₁₀ H ₁₁ BrO ₂	49.4	4.5	32.9
O	H	Cl	Cl	O	H	Cl	OMe	93.6		60.7	5.6	17.9	C ₁₀ H ₁₁ ClO ₂	60.5	5.6	17.9
O	H	Br	Cl	O	H	Br	OMe	91.8		49.4	4.6	32.7	C ₁₀ H ₁₁ BrO ₂	49.4	4.5	32.9
O	H	Cl	Br	O	H	Cl	OMe	92.2		60.5	5.9	17.9	C ₁₀ H ₁₁ ClO ₂	60.5	5.6	17.9
CH ₃	H	Br	Br	CH ₃	H	Br	OMe	94.1		55.0	5.5	33.6	C ₁₁ H ₁₃ BrO	54.8	5.4	33.1
CH ₃	H	Cl	Cl	CH ₃	H	Cl	OMe	95.5		66.6	6.6	18.1	C ₁₁ H ₁₃ ClO	67.2	6.7	18.0
CH ₃	H	Br	Cl	CH ₃	H	Br	OMe	93.8								
CH ₃	H	Cl	Br	CH ₃	H	Cl	OMe	91.5								

* For formula see Table 1. † Mixed m.p. 74°.

Product Analysis.—The dihalogeno-compounds and anhydrous methanol were boiled for 20 h. After removal of the solvent the product was chromatographed on alumina from ether-light petroleum (b.p. 80-100°) (1:4) to give as sole product the 4-methoxy- or the 1-methoxy-derivative from the chromans and the tetralins, respectively (Table 2).

Kinetic Measurements.—Rates of liberation of protons were measured at temperatures controlled to ±0.1°. A sampling procedure was used below 25° and a sealed-tube technique at higher temperatures. Samples (5.0 ml) were quenched in ice-cold acetone (150 ml) and titrated for acid (lacmoid indicator). Blank experiments showed that the quenching was efficient, that the reaction was irreversible, and that only one halogen atom was displaced. First-order rate constants were calculated (Table 3). Calculated and experimental 'infinity' values agreed to within experimental error.

Initial concentrations of organic halide were usually *ca.* 0.06M. All runs were performed in duplicate and the rate constant was tested for significance by the 't' test.¹²

¹² M. Moroney, 'Facts from Figures,' Penguin, London, 1960, p. 371.

¹³ E. Grunwald and J. E. Leffler, 'Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963.

¹⁴ R. Binns, W. D. Cotterill, and R. Livingstone, *J. Chem. Soc.*, 1965, 5049.

The values 175, 65, 55, and 55° of the torsion angle between H_C and H_X in structures (Ia), (Ib), (IIa), and (IIb), respectively, are those obtained from the models for the structures which are estimated to have the least

TABLE 3

Rate constants for the methanolysis of 3,4-dihalogenochromans and 1,2-dihalogenotetralins

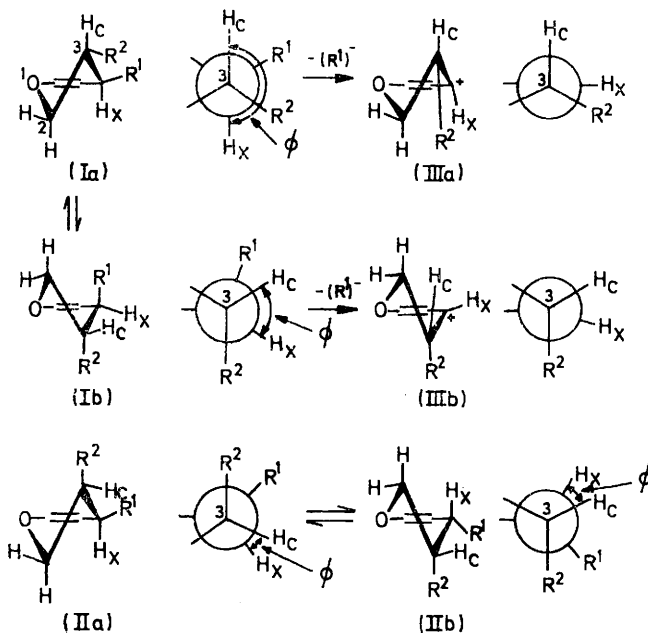
Compound	10 ⁶ k ₁ /s ⁻¹ (T/K)		
3,4-Dibromo-2,2-dimethylchroman	6.12 (263.4)	31.4 (273.7)	64.2 (278.3)
3,4-Dichloro-2,2-dimethylchroman	1.57 (298.1)	3.37 (304.0)	10.2 (312.9)
3-Chloro-4-bromo-2,2-dimethylchroman	4.50 (283.6)	17.0 (292.8)	34.7 (298.2)
3-Bromo-4-chloro-2,2-dimethylchroman	4.11 (283.7)	15.1 (293.7)	4.42 (302.6)
3,4-Dibromochroman	2.98 (283.6)	12.5 (293.6)	25.6 (298.8)
3,4-Dichlorochroman	3.99 (318.6)	7.01 (323.4)	18.8 (333.0)
4-Bromo-3-chlorochroman	4.00 (300.3)	6.86 (304.1)	25.1 (313.8)
3-Bromo-4-chlorochroman	3.71 (301.5)	5.05 (304.0)	15.8 (313.2)
1,2-Dibromotetralin	7.06 (313.9)	20.8 (322.6)	34.5 (327.5)
1,2-Dichlorotetralin	0.412 (323.5)	1.29 (332.7)	2.53 (338.2)
1-Bromo-2-chlorotetralin	3.13 (322.6)	12.4 (333.6)	35.7 (342.0)
2-Bromo-1-chlorotetralin	2.46 (323.4)	8.36 (333.6)	16.1 (338.8)

TABLE 4

Values of a and b in $\log k_1 = a + b/T$ and of E and ΔG^* for the methanolysis of 3,4-dihalogeno-2,2-dimethylchromans, 3,4-dihalogenochromans, and 1,2-dihalogenotetralins

Compound	$E/kJ\ mol^{-1}$	$10^6 k_1/s^{-1}$	a	$-b$
3,4-Dibromo-2,2-dimethylchroman	95.7 ± 1.7	5190	14.8	4996.7
3,4-Dichloro-2,2-dimethylchroman	97.9 ± 1.4	8.13	12.4	5115.3
4-Bromo-3-chloro-2,2-dimethylchroman	98.5 ± 1.8	177	13.8	5142.4
3-Bromo-4-chloro-2,2-dimethylchroman	89.4 ± 2.3	141	12.1	4669.2
3,4-Dibromochroman	100.0 ± 2.5	119	13.9	5213.7
3,4-Dichlorochroman	94.6 ± 1.7	1.85	11.1	4932.3
4-Bromo-3-chlorochroman	106.7 ± 1.3	14.2	14.2	5578.5
3-Bromo-4-chlorochroman	97.5 ± 1.1	12.3	12.5	5094.6
1,2-Dibromotetralin	100.0 ± 2.0	4.8	12.5	5214.4
1,2-Dichlorotetralin	112.5 ± 0.9	0.0547	12.8	5876.5
2-Bromo-1-chlorotetralin	115.0 ± 1.7	0.428	14.1	5998.0
1-Bromo-2-chlorotetralin	110.9 ± 1.2	0.348	13.3	5801.9

combined angle and eclipsing strain in the pyran ring. [Because of the flexibility of this ring the C(3)-C(4) torsion angle may be varied without undue strain.] These angles give theoretical coupling constants of



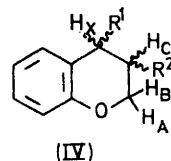
Conformations of the heterocyclic ring of *cis*- (II) and *trans*-3,4-disubstituted chromans (I), with Newman projection formulae for the C(3)-C(4) bonds

7.4 (Ia), 2.0 (Ib), and 3.3 Hz (IIa and b). These values, when compared with those obtained experimentally (Table 5), show that, in all the 3,4-dihalogenochromans and 3-halogeno-4-methoxychromans studied, the most probable configuration is that with the 3- and 4-substituents *trans* and axial (Ib), except in the case of the 2,2-dimethyl derivatives when they are *trans* and equatorial¹⁴ (Table 5).

Effect of Various Groups on the Mechanism of Methanolysis.—The effects of (a) neighbouring phenylene group, (b) neighbouring halogen, and (c) oxygen are the same as for the hydrolysis of 2,2-dimethyl-3,4-dihalogenochromans.¹⁴

TABLE 5

Chemical shifts and coupling constants for the hydrogen atoms in 3,4-disubstituted chromans (IV)



Reactants: R¹ = Br or Cl, R² = Br or Cl
Products: R¹ = Me, R² = Br or Cl

Substituents R ¹ R ²	δ				J/Hz				
	H_X	H_C	H_A	H_B	$^3J_{CX}$	$^3J_{AC}$	$^3J_{BC}$	$^4J_{BX}$	$^3J_{AB}$
Br Br	5.18	4.11	4.51	3.83	2.5	1.6	2.5	2.7	12.9
Cl Cl	5.12	4.44	4.65	4.25	3.0	1.5	3.0	1.7	12.1
OMe Br	4.33	4.25	4.28	4.23					12.3
OMe Cl	4.71	4.33	4.29	4.16					12.7
OMe Br	4.70	4.19	(Me)	(Me)	7.5				
OMe Cl	4.53	4.13	(Me)	(Me)	7.8				

Comparison of the rate coefficients for the methanolysis of 3,4-dihalogenochromans shows that $k_1(\text{dibromo})/k_1(\text{dichloro})$ is approximately twice $k_1(\text{bromo})/k_1(\text{chloro})$ for the methanolysis of some monohalogeno-compounds.¹⁵ Similar results are obtained for the 1,2-dihalogenotetralins. It has been shown previously¹⁴ that $k_1(\text{dibromo})/k_1(\text{dichloro})$ for the hydrolysis of 3,4-dihalogeno-2,2-dimethylchromans is *ca.* seven times greater than $k_1(\text{bromo})/k_1(\text{chloro})$ for the hydrolysis of some monohalogeno-compounds.¹⁵ Comparison of the rate coefficients for methanolysis of dihalogeno-2,2-dimethylchromans with those for methanolysis of some monohalogeno-compounds shows that $k_1(\text{dibromo})/k_1(\text{dichloro})$ is *ca.* ten times greater than $k_1(\text{bromo})/k_1(\text{chloro})$. An explanation has already been given for such differences;¹⁴ the extra increase in the case of the 2,2-dimethyl compounds may be cited as evidence for the repulsion between the 2*ax*-methyl and the 4*ax*-halogen, which would increase the rate of ionisation.¹⁴

Variation in Activation Energy.—Values of E are presented in Table 4. All the rate constants are subject to errors of 1–3%. Under these conditions the errors involved in the calculation of E are *ca.* 900 J mol⁻¹.

Comparison of the kinetics of methanolysis of *trans*-1,2-dihalogenotetralins and 3,4-dihalogenochromans indicates that the difference in the rates of methanolysis of compounds with identical neighbouring and leaving groups is the same for each pair of compounds. We conclude that the two sets of compounds are solvolysed by similar mechanisms, and the difference in rates of methanolysis can be attributed to the larger resonance energy and torsional strain of the chroman derivatives.

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¹⁵ See, for example, C. R. Cowie, H. J. M. Fitches, and G. Kohnstam, *J. Chem. Soc.*, 1963, 1585, for various pairs in acetone solvents.