Synthesis and Reactions of Some Spiro[2*H*-chromen-2,1′-cycloalkanes]

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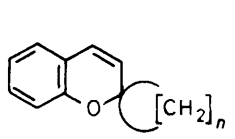
Spiro[2*H*-chromen-2,1′-cyclopentane] and the analogous cyclohexane and cycloheptane compounds have been prepared from the corresponding cycloalkanones. Reactions of the chromens with halogens and some chemistry of the derived products are described. The dehalogenation of an α-bromoketone by sodium borohydride in boiling methanol is reported. 3,4-Epoxyspiro[chroman-2,1′-cycloalkanes] have been obtained and ring-opened. The effects of the size of the spiro-annelated ring are minimal.

Our studies of the chemistry of 2*H*-1-benzopyrans or 2*H*-chromens have centred around the influence which substituents in the aromatic ring have on reactions of the double bond in the pyran moiety.[1,2] Despite a recent indication that the chromen ring system is not necessary for antijuvenile hormone activity,[3] interest is still maintained in the precocenes [4] and recently an attempt has been made to correlate the ^{13}C chemical shift of the C-3 and C-4 atoms in chromens with precocene-like activity.[5] Our attention is currently focused on the effects of variation in the substituents present at C-2 and some results of our investigations into the synthesis and chemistry of a series of chromens having a cycloalkane ring spiro-annelated at the 2-position (1) are now reported.

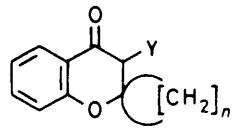
Routes to chromens from aromatic precursors have been reviewed,[6] but, in general, these are unsuitable for the synthesis of those heterocycles bearing a 2-spiro-substituent, although spiro[2*H*-1-benzopyranindolines], of interest because of their photochromic [7] or thermochromic [8] properties, have been obtained directly from salicylaldehyde and alkylidene-2-indolines in ethanol [9] or dimethylformamide.[10] The availability of spiro[chroman-2,1′-cycloalkan]-4-ones (2; Y = H) from 2-hydroxyacetophenone and a cycloalkanone *via* the enamine [11] prompted their use as sources of the chromens. Reduction with sodium borohydride proceeded without the complications encountered by others in similar reactions [12,13] and dehydration of the resulting spiro-substituted chroman-4-ols (4; Y = H) with anhydrous copper(II) sulphate afforded the title compounds (1) in isolated yields of *ca.* 50% from the cycloalkanone.

The singlet near δ 2.7 arising from the C-3 protons in the chromanones (Table) is shifted upfield in the chromanols and, since the two protons are no longer equivalent, the signal is more complex. Coupling with the hydroxylic proton is not observed and the multiplet overlaps with the alicyclic signals. The signal from 4-H appears as a triplet in the cyclopentane derivative (4a), but four peaks are visible in the spectra of the other two chromanols (4b, c). It thus appears that the size of the cycloalkyl ring causes small variations in the interactions between the protons at C-3 and C-4.

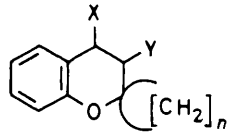
The spiro-chromens reacted with bromine and with chlorine to give the 3,4-dihalogenospiro[chroman-2,1′-cycloalkanes] (3) which underwent nucleophilic attack by water to yield the corresponding 3-halogenochroman-4-ols (4; Y = Br or Cl). The exclusive displacement of the halogen atom at C-4 is to be expected if the reaction proceeds *via* a carbocation mechanism, as has been proposed for the related 3,4-dihalogeno-2,2-dimethylchromans,[14] because of the stabilisation of the intermediate benzylic cation. The bromohydrins were also obtained directly from the chromens by reaction with *N*-bromosuccinimide in moist dimethyl sulphoxide,[15] but attempts to prepare the chlorohydrins using *N*-chlorosuccinimide failed. Conversion of the halohydrins into the 3,4-epoxyspiro[chroman-2,1′-cycloalkanes] (5) on treatment with



(1)



(2) Y = Br, Cl, or H



(3) X = Y = Br or Cl

(4) X = OH; Y = Br, Cl, or H

(5) XY = O

(6) X = Cl, OH, or H; Y = OH

base confirmed the anti-periplanar relationship of the 3- and 4-substituents [16] expected from the mechanistic course of the addition reactions to the chromens. The ease of formation of the epoxides contrasts with the difficulty encountered in the synthesis of precocene I epoxide,[1,17] which has been proposed as the species responsible for antijuvenile hormone activity of precocenes.[18]

The n.m.r. spectra (Table) of the dihalogenochromans show two features of interest. The coupling constants, $J_{3,4}$, which are smaller than those in the parent chromens in keeping with the increase in length of the 3–4 bond,[19] are consistently higher for the chloro-compounds than the corresponding bromo-derivatives. This is in agreement with data for the related compounds derived from 2*H*-chromen itself,[20] but differs from the reported values for the analogous 2,2-dimethylchroman derivatives.[14] It is also noteworthy that the size of the spiro-annelated ring at C-2 influences the value of the coupling constant; $J_{3,4}$ increases with increasing ring size and this feature is also evident in the 3-halogenochroman-4-ols. The variation in *J* values for these compounds reflects the ease with which the dihedral angle between C-3 and C-4 may be altered by external factors because of the flexibility of the heterocyclic ring. Thus, changes in the size of the halogen substituents and variations in the extent of 1,3-interactions between the protons at C-3 and C-2′ may be the causes of the differences in the coupling constants. No such variation in $J_{3,4}$ is apparent in the spectra of the epoxides and it appears that the rigidity imposed on the system by the 3-membered ring is sufficient to resist the relatively minor changes associated with 1,3-interactions.

Ring opening of the epoxides with lithium aluminium hydride afforded the chroman-3-ols (6; X = H). Their n.m.r. spectra show differences from those of the chroman-4-ols. The signal from 3-H is now downfield of that arising from the protons at C-4. The latter signal is separated from the alicyclic multiplet and the whole appears as a distorted ABX system.

Dry hydrogen chloride converts the epoxychromans into the 4-chlorochroman-3-ols (6; X = Cl), although the cycloheptane derivative could not be purified. The chemical shifts of 3-H and 4-H are more widely separated in these chlorohydrins than in the isomeric 3-chlorochroman-4-ols (4; Y = Cl) and $J_{3,4}$ is 4 Hz whereas in the latter $J_{3,4}$ is 8—10 Hz.

The addition of water to the epoxides was achieved on activated alumina as described by Posner [21] and led to the *trans*-diols (6; X = OH); $J_{3,4}$ is 9 Hz implying *trans*-diaxial geometry. In confirmation, $J_{3,4}$ for the *cis*-diol, prepared directly from the chromen using potassium permanganate, is 4 Hz.

3-Bromospiro[chroman-2,1′-cycloalkan]-4-ones (2; Y = Br) were obtained both by the oxidation of the corresponding 3-bromochroman-4-ols with chromium trioxide and by direct bromination of the chroman-4-ones.[22] Only the oxidative route was applied to the synthesis of the 3-chloroketones (2; Y = Cl). The expected downfield shift of 3-H is observed in all cases upon introduction of the halogen atom.

The conversion of the bromochromanones (2d—f) to the *cis*-bromohydrins was attempted under a variety of conditions. In boiling methanol solution, sodium borohydride yielded the chroman-4-one as the major product; n.m.r. spectroscopic examination of the crude reaction product also indicated the presence of *cis*-bromohydrin ($J_{3,4}$ 4 Hz) together with unchanged starting material. However, after 24 h, the chromanone (2; Y = H) was the only product. At 0 °C, although some chromanone was formed, the main product was the bromohydrin, but its isolation from the crude product was not accomplished. Dehalogenation by sodium borohydride has been reported previously [23] but not under such mild conditions.

Table. Physical, analytical, and n.m.r. spectral data for spiro-annelated chromens (1), chromanones (2), chromans (3) and (5), and chromanols (4) and (6)

Compound	*n*	X	Y	M.p. (°C) ‡ [b.p. °C/mmHg]	Yield (%)	Found (%) (Required) C	H	Br	Cl	^{1}H N.m.r. data † δ, multiplicity, *J*/Hz 3-H	4-H	OH
(1a)	4			[116/10]	91	84.0 (83.8	7.8 7.6)			5.6, d, 10	6.3, d, 10	
(1b)	5			[124/3]	81	84.2 (84.0	8.3 8.1)			5.6, d, 10	6.25, d, 10	
(1c)	6			[144/8.5]	94	84.1 (84.1	8.2 8.4)			5.6, d, 10	6.25, d, 10	
(2d)	4		Br	70—71 [a]	56	55.5 (55.5	4.7 4.7	28.4 28.4)		4.35, s		
(2e)	5		Br	70—71 [b]	39	56.9 (57.0	5.2 5.1	27.6 27.1)		4.35, s		
(2f)	6		Br	[138/10]	75	58.1 (58.3	5.5 5.5	25.9 25.9)		4.4, s		
(2g)	4		Cl	[105/10]	60	65.8 (66.0	5.4 5.5		15.3 15.0)	4.3, s		
(2h)	5		Cl	[120/11]	63	67.1 (67.1	6.2 6.0		14.0 14.2)	4.25, s		
(2i) *	6		Cl							4.3, s		
(3a)	4	Br	Br	38—39 [c]	82	45.0 (45.1	4.1 4.1	46.4 46.2)		4.7, d, 4	5.65, d, 4	
(3b)	5	Br	Br	89—90 [b]	89	46.8 (46.7	4.5 4.5	44.7 44.4)		4.6, d, 6	5.7, d, 6	
(3c)	6	Br	Br	92—93 [a]	99	48.3 (48.1	4.7 4.8	42.6 42.8)		4.6, d, 8	5.6, d, 8	
(3d)	4	Cl	Cl	55—56 [c]	65	60.5 (60.7	5.4 5.4		27.4 27.6)	4.4, d, 5.5	5.2, d, 5.5	
(3e)	5	Cl	Cl	86—87 [a]	53	62.3 (62.0	5.7 5.9		26.1 26.1)	4.2, d, 7.5	5.2, d, 7.5	
(3f)	6	Cl	Cl	87—88 [c]	72	63.1 (63.2	6.4 6.3		24.9 24.9)	4.2, d, 9.5	5.15, d, 9.5	
(4a)	4	OH		56—57 [b]	76	76.6 (76.4	7.7 7.9)			2.1, m	4.85, t, 7	2.2br, s
(4b)	5	OH		63—64 [c]	86	77.1 (77.0	8.3 8.3)			2.05, m	4.8, m	2.3br, s
(4c)	6	OH		62.5—63.5 [a]	72	77.5 (77.6	8.6 8.6)			2.05, m	4.7, m	2.35br, s
(4d)	4	OH	Br	48—49 [c]	64	55.4 (55.1	5.4 5.3	28.5 28.3)		4.4, d, 8	4.95, dd, 8,[d] 5 [e]	2.6, d, 5 [e]
(4e)	5	OH	Br	109—110 [b]	37	56.8 (56.6	5.7 5.7	26.8 26.9)		4.1, d, 9	4.9, dd, 9,[d] 5 [e]	2.65, d, 5 [e]
(4f)	6	OH	Br	87—88 [b]	72	58.1 (57.9	6.1 6.1	25.4 25.7)		4.1, d, 10	4.85, d, 10	2.65br, s
(4g)	4	OH	Cl	69—70 [c]	58	65.4 (65.4	6.4 6.3		14.9 14.9)	4.1, d, 8	4.75, d, 8	2.8br, s
(4h)	5	OH	Cl	108—109 [b]	68	66.6 (66.5	7.0 6.8		13.8 14.0)	3.9, d, 9	4.8, dd, 9,[d] 5 [e]	2.7, d, 5 [e]

Table (*continued*)

Compound	*n*	X	Y	M.p. (°C) ‡ [b.p. °C/mmHg]	Yield (%)	Found (%) (Required) C	H	Cl	^{1}H N.m.r. data † δ, multiplicity, *J*/Hz 3-H	4-H	OH
(4i)	6	OH	Cl	62—63 [c]	91	67.7 (67.5	7.0 7.1	13.1 13.3)	3.9, d, 10	4.7, dd, 10,[d] 5 [e]	2.6, d, 5 [e]
(5a)	4	-O-		40—41 [a]	84	77.0 (77.2	7.0 6.9)		3.5, d, 4.5	3.85, d, 4.5	
(5b)	5	-O-		80—82 [c]	82	77.5 (77.7	7.4 7.5)		3.4, d, 4.5	3.8, d, 4.5	
(5c)	6	-O-		[148/10]	81	78.0 (78.3	7.9 7.8)		3.5, d, 4.5	3.85, d, 4.5	
(6a)	4		OH	94—95 [c]	91	76.7 (76.4	8.0 7.9)		3.75, t, 5	2.45—3.25, m	2.15, s
(6b)	5		OH	96—98 [b]	95	77.0 (77.0	8.3 8.3)		3.7, t, 5	2.45—3.25, m	2.1, s
(6c)	6		OH	101—102 [b]	83	77.5 (77.6	8.4 8.6)		3.75, t, 5	2.45—3.25, m	2.0, s
(6d)	4	Cl	OH	93—94 [a]	68	65.5 (65.4	6.4 6.3	14.8 14.9)	5.3, d, 4	3.9, d, 4	2.4, s
(6e)	5	Cl	OH	95—97 [c]	30	66.6 (66.5	6.8 6.8	14.3 14.0)	5.4, d, 4	3.9, d, 4	2.4, s
(6f)	4	OH	OH	128 [a]	58	70.7 (70.9	7.3 7.3)		3.8, dd, 9, 5	4.6, t, 7	3.35, dd, 7,5
(6g)	5	OH	OH	139—140 [a]	69	71.8 (71.8	7.9 7.7)		3.5, d, 9	4.6, d, 9	3.6br, s

* (2i) Was isolated as the 2,4-dinitrophenylhydrazone, m.p. 156—157 °C, from butanol (Found: C, 56.5; H, 4.5; Cl, 8.0; N, 12.6. $C_{21}H_{21}ClN_4O_5$ requires C, 56.3; H, 4.4; Cl, 7.8; N, 12.8%). † The alicyclic multiplet occurs in the range δ 0.9—2.4 and the aromatic peaks between δ 6.5—8.0 for all compounds. ‡ Solids crystallised from: [a] light petroleum (b.p. 40—60 °C); [b] light petroleum (b.p. 60—80 °C); [c] light petroleum (b.p. 30—40 °C); [d] $J_{3,4}$. [e] $J_{4,OH}$.

Although we have not attempted to examine the generality of this reaction, 2,2-dimethylchroman-4-one results from the borohydride reduction of the corresponding 3-bromo-compound in methanol. This contrasts with the reduction of 3-bromochroman-4-one to the *cis*-bromohydrin.[24] The reduction of the spiro-bromoketones with lithium aluminium hydride yields some *trans*-bromohydrin in addition to the compounds formed above with sodium borohydride. These results provide further evidence of the complexity of the reduction of bromochromanones first noted in the attempted dehalogenation by zinc and acetic acid.[2]

Experimental

^{1}H N.m.r. spectra were obtained with a Perkin-Elmer R12B spectrometer for solutions in deuteriochloroform. General procedures for syntheses of the dihalogenochromans (3a—f), halogenochromanols (4d—i), epoxychromans (5a—c), chroman-3-ols (6a—e), and halogenochroman-4-ones (2d—i) have been described,[2] and the synthesis of the chroman-4-ones (2a, b) derived from cyclopentanone and cyclohexanone has been reported.[11] Physical data for these compounds are presented in the Table.

Spiro[*chroman*-2,1′-*cycloheptan*]-4-*one* (2c).—A solution of 2-hydroxyacetophenone (68 g), cycloheptanone (61.6 g), and pyrrolidine (10 g) in toluene (150 cm^3) was kept at room temperature overnight and subsequently boiled under reflux for 5 h with separation of the water produced. The cold solution was poured into water and the organic layer was separated and washed successively with dilute hydrochloric acid, aqueous sodium hydroxide, and water. Removal of the dried (Na_2SO_4) solvent and distillation of the residual red oil gave the *chromanone* (67%), b.p. 160 °C at 8.5 mmHg as a yellow oil (Found: C, 78.1; H, 7.8. $C_{15}H_{18}O_2$ requires C, 78.3; H, 7.8%).

The 2,4-*dinitrophenylhydrazone*, m.p. 194—195 °C, was crystallised from butanol (Found: C, 61.6; H, 5.3; N, 13.4. $C_{21}H_{22}N_4O_5$ requires C, 61.5; H, 5.4; N, 13.7%).

Spiro[*chroman*-2,1′-*cycloalkan*]-4-*ols* (4a—c).—Sodium borohydride (5 g) was added in small portions during 30 min to a solution of the spiro[chroman-2,1′-cycloalkan]-4-one (15 g) in methanol (100 cm^3). After being boiled for 2 h, the mixture was poured into water and the product was isolated with ether and purified by distillation and subsequent crystallisation.

Spiro[*chromen*-2,1′-*cycloalkanes*] (1a—c).—Freshly dehydrated copper(II) sulphate (6.0 g) was added portionwise to the pre-heated chroman-4-ol (10.5 g). A vigorous reaction ensued, which was completed by maintaining the mixture at boiling point for a further 10 min. The chromen was extracted into chloroform and distilled.

3-*Bromospiro*[*chroman*-2,1′-*cycloalkan*]-4-*ols* (4d—f).—A stirred solution of the chromen (2.5 g) and water (1.0 g) in dimethyl sulphoxide (25 cm^3) was maintained at 0—5 °C whilst *N*-bromosuccinimide (4.5 g) was added during 30 min. After a further 1 h, water was added and the product was isolated with ether and crystallised.

3-*Bromospiro*[*chroman*-2,1′-*cycloalkan*]-4-*ones* (2d—f).—A solution of bromine (6.0 g) in carbon tetrachloride (10 cm^3) was added during 30 min to a solution of spiro[chroman-2,1′-cycloalkan]-4-one (8.5 g) in carbon tetrachloride (80 cm^3); the solution was then stirred for 4 h at room temperature and then at *ca.* 60 °C for 30 min. The solvent was removed and the residual brown oil was purified by column chromatography and distillation or crystallisation.

trans-*Spiro*[*chroman*-2,1′-*cycloalkan*]-3,4-*diols* (6f, g).—Water (3 cm^3) was added to a slurry of alumina (75 g; Woelm N Super 1 grade) and ether (200 cm^3). After 10 min, the

epoxychroman (2.0 g) was added and the mixture was stirred for 72 h. The organic material was isolated from the alumina with methanol (100 cm^3) and was crystallised.

cis-*Spiro*[*chroman*-2,1′-*cyclopentan*]-3,4-*diol*.—A solution of potassium permanganate (1.6 g) in water (50 cm^3) was added dropwise during 15 min to a stirred, cooled solution of spiro-[chromen-2,1′-cyclopentane] (3.0 g), sodium hydroxide (1 cm^3; 25%), crushed ice (25 g), and t-butyl alcohol (50 cm^3). The solution was stirred for a further 15 min after the addition was complete, the temperature being maintained <15 °C. The solution was then heated almost to boiling and the manganese dioxide filtered off; the filtrate was then concentrated to *ca.* 30 cm^3 and extracted with chloroform (3 × 10 cm^3). Removal of the dried (Na_2SO_4) solvent yielded a brown oil which solidified with time and upon recrystallisation from light petroleum (b.p. 60—80 °C) produced crystals of cis-*spiro*-[*chroman*-2,1′-*cyclopentan*]-3,4-*diol* (28%), m.p. 102—103 °C (Found: C, 70.9; H, 7.3. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%).

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References

1 J. D. Hepworth and R. Livingstone, *J. Chem. Soc. C*, 1966, 2013.
2 J. D. Hepworth, T. K. Jones, and R. Livingstone, *Tetrahedron*, 1981, **37**, 2613.
3 G. Matolcsy, Y. M. Darwish, I. Bélai, L. Varjas, and A. I. Farag, *Z. Naturforsch., Teil A*, 1980, **35**, 1449.
4 F. Camps, J. Coll, A. Messeguer, and M. A. Pericás, *J. Heterocycl. Chem.*, 1980, **17**, 1377; H. Schooneveld, *Experientia*, 1979, **35**, 363.
5 A. P. Ottridge, R. C. Jennings, and G. T. Brooks, *Dev. Endocrinol. (Amsterdam)*, 1981, **15**, 381.
6 L. Merlini, *Adv. Heterocycl. Chem.*, 1975, **18**, 159.
7 R. C. Bertelson in ' Photochromism,' ed. G. H. Brown, Wiley, New York, 1971, p. 49.
8 J. H. Day, *Chem. Rev.*, 1963, **63**, 65.
9 R. Guglielmetti and J. Metzger, *Bull. Soc. Chim. Fr.*, 1967, 2824.
10 A. Hinnen, Fr. Patent, 1970, 2 036 168 (*Chem. Abstr.*, 1971, **75**, 103685.
11 H. J. Kabbé, *Synthesis*, 1978, 886.
12 M. Nakayama, S. Hayashi, M. Tsukayama, T. Horie, and M. Masumura, *Chem. Lett.*, 1975, 55; M. Tsukayama, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1653; A. K. Ganguly, B. S. Joshi, V. N. Kamat, and A. H. Manmade, *Tetrahedron*, 1967, **23**, 4777.
13 M. Tsukayama, T. Sakamoto, T. Horie, M. Masumura, and M. Nakayama, *Heterocycles*, 1981, **16**, 955.
14 R. Binns, W. D. Cotterill, and R. Livingstone, *J. Chem. Soc.*, 1965, 5049.
15 A. W. Langman and D. R. Dalton, *Org. Synth.*, 1979, **59**, 16.
16 N. A. LeBel and R. F. Czaja, *J. Org. Chem.*, 1961, **26**, 4768.
17 R. C. Jennings and A. P. Ottridge, *J. Chem. Soc., Chem. Commun.*, 1979, 920.
18 G. E. Pratt, R. C. Jennings, A. F. Hamnett, and G. T. Brooks, *Nature*, 1980, **284**, 320.
19 M. Karplus, *J. Am. Chem. Soc.*, 1963, **85**, 2870.
20 R. Binns, W. D. Cotterill, I. Derrick, and R. Livingstone, *J. Chem. Soc., Perkin Trans. 2*, 1974, 732.
21 G. H. Posner and D. Z. Rogers, *J. Am. Chem. Soc.*, 1977, **99**, 8208.
22 A. G. Pinkus and R. Gopalan, *J. Chem. Soc., Chem. Commun.*, 1981, 1016 and references therein.
23 R. O. Hutchins, D. Kandasamy, F. Dux, C. A. Maryanoff, D. Rotstein, B. Goldsmith, W. Burgoyne, F. Cistone, J. Dalessandro, and J. Puglis, *J. Org. Chem.*, 1978, **43**, 2259.
24 W. D. Cotterill, J. Cottam, and R. Livingstone, *J. Chem. Soc. C*, 1970, 1006.

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