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Reactions of Some Spiro Chromenes with Bromine and Chlorine

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The addition of halogens and hydrolysis of some 2,2'-spiro-2-cycloalkyl chromenes have been investigated and the effects of the size of the spiro-annelated on the chemistry of spiro chromenes are described.

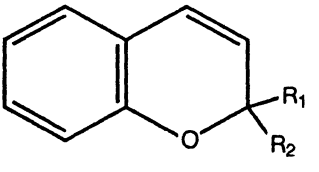
INTRODUCTION

The synthesis and chemistry of 2,2-dimethyl chromenes have been studied extensively[1]. The considerable interest of the spirobenzopyrans is due to the tendency of the ring opening to give coloured compounds on exposure to light or heat such as spiro (benzopyranindolines) and spiro (bichromenes)[2,3], as well as analgesics, antidepressants, antianxietal, antihypertensive and hypoglycemic agents[1].

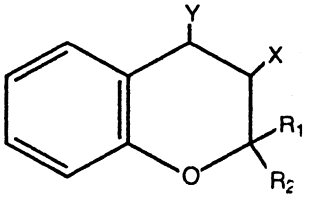
The effects of substituents on the aromatic ring of the chromenes have also been investigated[4]. The unsymmetrically 2,'2-disubstitute compounds have received some attention possibly due to their absence in the nature[5].

The routes to spiro chromenes have been reviewed[6], but, in general, it can be prepared by a modified Claisen rearrangement by the reaction of the appropriate phenol with propargyl alcohol derivatives.[7]

In the present paper the author reported the reaction of some spiro chromenes and the effects of the size of the spiro-annelated on the chemistry of spiro chromenes.

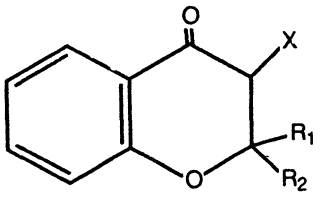


(1)



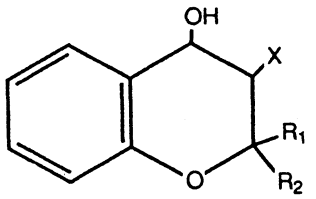
(2)

Fig. 1



(4)

X = Y = Cl , Br



(3)

R1 + R2 = Cyclopentane
R1 + R2 = Cyclohexane
R1 + R2 = Cycloheptane

Fig. 1 (Contd.)

EXPERIMENTAL

^{1}H NMR spectra were obtained with a Perkin-Elmer R32 spectrometer (90 Hz) for solutions in $CDCl_3$, chemical shifts were reported as d-values, in ppm downfield from the internal stander tetra-methyl silane (TMS).

General method of preparation of 3,4-dihalogeno chromenes

A solution of halogen (0.01 mol) in chloroform (10 cm^3) was added dropwise to a stirred solution of a chromene (0.01 mole) in chloroform (10 cm^3), maintained at 0–5°C. After 30 min. the solvent was removed from the pale orange solution without allowing the temperature of the solution to exceed 40°C. The residual brown oil was crystallised to yield the 3,4-dihalogen chromene.

The following compounds were synthesised in this method: *(Cyclopentane)-2,2'-Spiro-3, 4-dibromochromene (2a)* as colourless needles from petroleum ether (b.pt. 40–60°C), m.pt. 37–39°C, 38%, NMR 6.64–7.55 (aromatic); 5.64 (1 H, d, J 4 Hz, 4–H); 7.72 (1 H, d, J 4 Hz, 3–H); 1.40–2.3 (cyclopentane).

(Cyclohexane)-2,2'-spiro-3,4-dibromochromene (2b): as colourless crystals from petroleum (b.pt. 60–80°C), m.pt. 87–89°C, 90%, NMR 6.75–7.62 (aromatic); 5.7 (1 H, d, J 6 Hz, 4–H); 4.6 (1 H, d, J 6 Hz, 3–H); 0.9–2.22 (cyclohexane).

(Cycloheptane)-2,2'-spiro-3,4-dibromochromene (2c): as colourless needles from petroleum ether (b.pt. 40–60°C), m.pt. 90–91°C, 40%, 3, NMR 6.65–7.55 (aromatic); 5.5 (1 H, d, J 8 Hz, 4–H); 4.5 (1 H, d, J 8 Hz, 3–H); 1.2–2.6 (cycloheptane).

(Cyclopentane)-2,2'-spiro-3,4-dichlorochromene (2d): as colourless needles from petroleum ether (30–40°C), m.pt. 56–57°C, 60%, NMR 6.65–7.5 (aromatic); 5.25 (1 H, d, J 5.5 Hz, 4–H); 4.4 (1 H, d, 5.5 Hz, 3–H); 1.4–2.27 (cyclopentane).

(Cyclohexane)-2,2'-spiro-3,4-dichlorochromene (2e): as colourless needles

from petroleum ether (b.pt. 40–60°C), m.p. 88°C, 50%, NMR 6.72–7.55 (aromatic); 5.2 (1 H, d, J 7.5 Hz, 4–H); 4.2 (1 H, d, J 7.5 Hz, 3–H); 1.1–2.25 (cyclohexane).

(Cycloheptane)-2,2'-spiro-3,4-dichlorochromene (2f): as colourless needles from light petroleum ether (b.pt. 30–40°C), m.pt. 87°C, 70%, NMR 6.7–7.55 (aromatic); 5.15 (1 H, d, J 9 Hz, 4–H); 4.2 (1 H, d, J 9 Hz, 3–H); 1.2–2.42 (cycloheptane).

General methods of preparation of 3-halogenochroman-4-ols:

A mixture of a 3,4-halogenochromene (0.01 mol) and water (25 cm^3) in acetone (25 cm^3) was boiled under reflux for 12 hrs. The cooled reaction mixture was poured into water and extracted with ether, dried over Na_2SO_4. Removal of the ether gave the halogenochroman-4-ol as a crude.

(Cyclopentane)-2,2'-spiro-3-bromochroman-4-ol (3a): as colourless prisms from light petroleum (b.pt. 30–40°C), m.pt. 47–49°C, 63%, NMR 6.72–7.55 (aromatic); 4.9 (1 H, dd, J 8 Hz, 4–H); 4.35 (1 H, d, J 8 Hz, 3–H); 2.55 (1 H, d, J 5 Hz, OH); 1.55–2.45 (cyclopentane).

(Cyclohexane)-2,2'-spiro-3-bromochroman-4-ol (3b): as colourless prisms from pertroleum ether (b.pt. 60–80°C), m.pt. 110–111°C, 34%, NMR 6.65–7.57 (aromatic); 4.95 (1 H, dd, J 9 Hz, 4–H); 4.1 (1 H, d, J 9 Hz, 3–H); 2.65 (1 H, d, J 5 Hz, OH); 0.9–2.32 (cyclohexane).

(Cycloheptane)-2,2'-spiro-3-bromochroman-4-ol (3c): as colourless prisms from light petroleum (b.pt. 30–40°C), m.pt. 88°C, 69%, NMR 6.7–7.6 (aromatic); 4.49 (1 H, dd, J 10 Hz, H–4); 4.1 (1 H, d, J 10 Hz, H–3); 3.65, (1 H, s, OH); 1.3–2.9 (cycloheptane).

(Cyclopentane)-2,2'-spiro-3-chlorochroman-4-ol (3d): as colourless crystals from petroleum ether (b.pt. 30–40°C), m.pt. 70–71°C, 57%, NMR 6.65–7.55 (aromatic); 4.75 (1 H, d, J 18 Hz, 4-H); 4.15 (1 H, d, J 18 Hz, 3-H) 2.75 (1 H, s, OH); 1.55–2.30 (cyclopentane).

(Cyclohexane)-2,2'-spiro-3-chlorochroman-4-ol (3e): as colourless crystals from petroleum (b.pt. 60–80°C), m.pt. 108–109°C, 71%, NMR 6.7–7.6 (aromatic); 4.8 (1 H, dd, J 9 Hz, 4-H); 3.9 (1 H, d, J 9 Hz, 3-H); 2.65 (1 H, d, J 5 Hz, OH); 1.0–2.4 (cyclohexane).

(Cycloheptane)-2,2'-spiro-3-chlorochroman-4-ol (3f): as colourless prisms from light petroleum (b.pt. 30–40°C), m.pt. 62–63°C, 82%, NMR 6.65–7.55 (aromatic); 4.75 (1 H, dd J 10 Hz, 4-H); 3.95 (1 H, d, J 10 Hz, 3–H); 2.65 (1 H, d, J 5 Hz, OH); 0.7–2.3 (cycloheptane).

General method of preparation of 3-halogeno chroman-4-ones

A mixture of a 3-halogenochroman-4-ol (0.015 mol) and chromium trioxide solution (9.0 cm^3) was maintained at 55–60°C for 2 hrs and then poured into water. The solution was extracted with ether and washed with sodium hydrogen carbonate solution until neutralised, and dried over (Na_2SO_4); evaporation of the solvent left 3-halogenochroman-4-one.

(Cyclopentane)-2,2'-spiro-3-bromochroman-4-one (4a): as colourless needles from petroleum ether (b.pt. 40–60°C), m.pt. 69°C, 62%, NMR 6.85–8.05 (aromatic); 4.3 (1 H, s, 3-H); 1.65–2.55 (cyclopentane).

(Cyclohexane)-2,2'-spiro-3-bromochroman-4-one (4b): as colourless needles from petrolum ether (b.pt. 60–80°C), m.pt. 73°C, 43%, NMR 6.85–8.05 (aromatic); 4.35 (1 H, s, 3-H); 1.2–2.5 (cyclohexane).

(Cycloheptane)-2,2'-spiro-3-bromochroman-4-one (4c): as a pale yellow liquid, b.pt. 135°C, 65%, NMR 6.8–8.1 (aromatic); 4.4 (1 H, s, 3-H); 0.9–2.55 (cycloheptane).

(Cyclopentane)-2,2'-spiro-3-chlorochroman-4-one (4d): as a pale yellow oil, b.pt. 105°C, 55%, NMR 6.7–7.95 (aromatic); 4.3 (1 H, s, 3-H); 1.55–2.45 (cyclopentane).

(Cyclohexane)-2,2'-spiro-3-chlorochroman-4-one (4e): as a pale yellow oil, b.pt. 119°C, 40%, NMR 6.75–8.0 (aromatic); 4.25 (1 H, s, 3-H); 0.7–2.4 (cyclohexane).

(Cycloheptane)-2,2'-spiro-3-chlorochroman-4-one (4f): as a bright red plate from petroleum ether, m.pt. 155°C, 95%, NMR 6.7–8.0 (aromatic); 4.3 (1 H, s, 3-H); 0.8–2.45 (cycloheptane).

RESULTS AND DISCUSSION

Addition of bromine or chlorine in chloroform gave the respective 3,4-dihalogen-2,2'-spiro-2'-cycloalkane chromene derivative. No evidence of halogen substitution in the aromatic ring was obtained compared with early work using 2.2-dimethylchromene[8]. The reactions involve a carbonium ion intermediate, the mechanism being dependent on steric and neighbouring group effects[9], which can stabilise a positive charge C-4 in the transition state.

The NMR spectra of the halogenation products show the difference in size and electronegativity of chlorine and bromine wihich are shifted slightly upfield position in the addition of bromine than in the corresponding chlorine and J values of 3,4-dichloro derivatives are larger than J values of 3,4-dibromochromanes.

These compounds show the effect of the ring size of the C-2 spiro annulation. The coupling constant is increase with increasing ring size of the spiro-substituent (Table 1).

TABLE 1
THE COUPLING CONSTANT OF 4-H, 3-H

3,4-dibromo-		3,4-dichloro-		
J 3–H	J 4–H	J 3–H	J 4–H	2-substituent
4 Hz	4 Hz	5.5 Hz	5.5 Hz	cyclopentane
6 Hz	6 Hz	6.5 Hz	6.5 Hz	cyclohexane
8 Hz	8 Hz	8 Hz	8 Hz	cycloheptane

3,4-Dihalogen-2,2′-spirochromenes underwent nucleophilic attack when treated by water in acetone. It has been demonstrated that the hydrolysis of 3,4-dichloro and 3,4-dibromo-2,2-dimethyl chromene involved the replacement of the chlorine or bromine atom in the 4-position and the substitution of the second chlorine or bromine atom required much more forcing conditions[10]. The NMR of the hydrolysis products show that aromatic multiplet is unaffected by the introduction of a hydroxy group at C-4 in place of a halogen atom.

The resonance of the C-3 and C-4 protons undergoes significant changes from those exhibited in the dihalogenochromene. The replacement of a halogen by less electronegative OH group shows the upfield shift of both signals. The 4-H signal is shifted further upfield than the 3-H signal; both of these signals are lower field in the 3-bromine than in the corresponding 3-chlorine. The 4-OH proton signal of 3-halogenochroman-4-ol appears as doublet, the coupling constant of 5 Hz is unaffected by the nature of the halogen or by substitution elsewhere in the molecule.

2,2′-Spiro-2-cycloalkyl-3-halogenochroman-4-ones were prepared by oxidation of the halogeno hydrins with solution of chromium trioxide in acetic acid. The NMR analysis shows the effects of the halogen at C-3 with deshielding of the proton and appears as a singlet at approximately d 4.2–4.3 depending on the size of the cycloalkanes.

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