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Reactions of substituted thioflavones and 2-methyl-thiochromone with thionyl and sulphuryl chlorides

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Abstract. The reactions of 6- and 8-methylthioflavones and 2-methyl-thiochromone with thionyl and sulphuryl chlorides have been studied. The structures of all the compounds obtained have been established on the basis of spectral analytical data.

Keywords. Chlorothioflavones ; chlorothiochromones ; thionyl ; sulphuryl chlorides.

1. Introduction

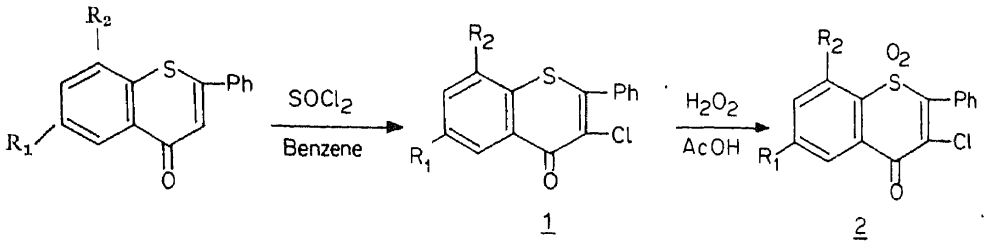
In a previous communication (Merchant *et al* 1979) the action of thionyl and sulphuryl chlorides on thioflavones yielding chlorothioflavone and chlorothioflavanones was reported. The importance of some thiochromone and halothiochromone derivatives as antifungal and antiviral agents (Nishio *et al* 1972; Meiji Confectionary Co., 1972) as well as their usefulness as agricultural bactericides and fungicides (Nishio *et al* 1972; Matsumoto *et al* 1975) prompted us to undertake the synthesis of new halothiochromone derivatives.

2. Results and discussion

6-Methylthioflavone (Bossert 1964) was refluxed with thionyl chloride in benzene for 20 hr to give a colourless crystalline solid which was assigned the structure as 3-chloro-6-methylthioflavone (Ia). Its IR (KBr) spectrum showed the carbonyl frequency at 1630 cm^{-1}, while its NMR ($CDCl_3$) spectrum showed the absence of the C_3 proton.

Refluxing 8-methylthioflavone with thionyl chloride in benzene for 20 hr. yielded 3-chloro-8-methylthioflavone (Ib) as colourless needles. The IR (KBr) spectrum of Ib showed a band at 1610 cm^{-1} for the carbonyl group while no signal was seen for the C_3 proton in the NMR spectrum. Reduction in the time of heating led to a decrease in the yields of the chloro-compounds.

The chlorosulphides Ia and Ib were oxidised with hydrogen peroxide in acetic acid to give 3-chloro-6-methylthioflavone-1, 1-dioxide (2a) and 3-chloro-8-methylthioflavone-1, 1-dioxide (2b) respectively.



1 2

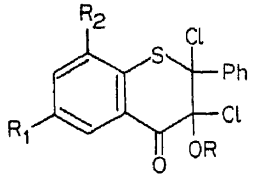
6-methylthioflavone : $R_1 = Me$; $R_2 = H$ a : $R_1 = Me$; $R_2 = H$

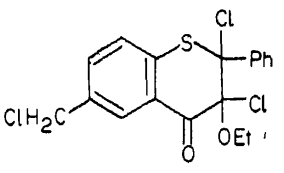
8-methylthioflavone : $R_1 = H$; $R_2 = Me$ b : $R_1 = H$; $R_2 = Me$

Treating 2-methylthiochromone with thionyl chloride in benzene at 0°, 30° or at reflux temperature gave a black sticky mass from which no single compound could be isolated.

6-Methylthioflavone was refluxed with sulphuryl chloride in carbon tetrachloride for 15 hr to give a sticky solid. Boiling the latter with methanol yielded a solid which was separated into three compounds by chromatography over alumina. Elution with hexane-benzene (9 : 1) first afforded a colourless solid which was assigned the structure as 2, 3, 7-trichloro-3-methoxy-6-methylthioflavanone (3a) on the basis of NMR spectral data. The second compound was also eluted with hexane-benzene (9 : 1) and identified as 2, 3-dichloro-3-methoxy-6-methylthioflavanone (3b) on the evidence obtained from the NMR spectrum. Elution with hexane-benzene (3 : 7) afforded a third compound which was assigned the structure as 3, 7-dichloro-6-methylthioflavone (3c) which is fully consistent with its spectral and analytical data discussed later.

Refluxing 6-methylthioflavone with sulphuryl chloride in carbon tetrachloride and boiling the resulting sticky material with ethanol afforded a colourless solid. Chromatography of the latter over alumina yielded three compounds 2, 3, 7-trichloro-3-ethoxy-6-methylthioflavanone (4a), 2, 3-dichloro-3-ethoxy-6-methylthioflavanone (4b) and 2, 3-dichloro-6-chloromethyl-3-ethoxythioflavanone (4c) which were eluted with hexane-benzene (2 : 3) hexane-benzene (3 : 2) and chloroform respectively. Structures of 4*a*, 4*b* and 4*c* were assigned on the basis of their spectral data.





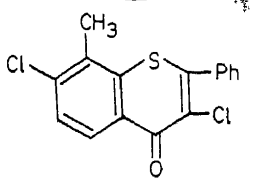
4c

3b : R = Me; R_1 = Me; R_2 = H

4b : R = Et; R_1 = Me; R_2 = H

5 : R = Me; R_1 = H; R_2 = Me

6a : R = Et; R_1 = H; R_2 = Me

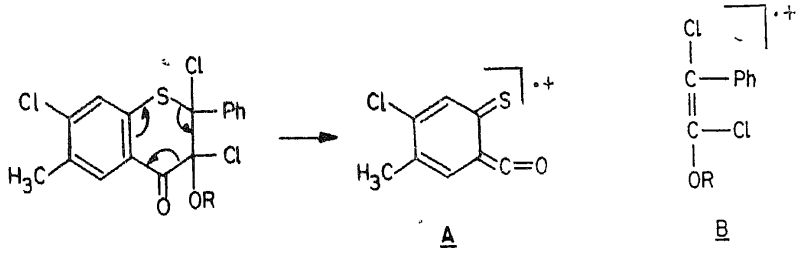


6b

Refluxing 8-methylthioflavone with sulphuryl chloride in carbon tetrachloride and boiling the product with methanol yielded a sticky compound which was chromatographed over alumina. Elution with hexane-benzene (4 : 1) gave a colourless crystalline compound which was assigned the structure as 2, 3-dichloro-3-methoxy-8-methyl-thioflavanone (5). Its NMR ($CDCl_3$) showed singlets at δ 2·35 and δ 3·23 for the methyl and methoxyl protons respectively and a multiplet at δ 6·96–8·06 for the aromatic protons.

Similarly, the sticky product obtained from the reaction of 8-methylthioflavone and sulphuryl chloride on boiling with ethanol gave two compounds which were separated by chromatography over alumina. The first compound eluted with hexane-benzene (2 : 3) was assigned the structure as 2, 3-dichloro-3-ethoxy-8-methylthioflavanone (6a) on the basis of its NMR spectral data. The second compound eluted with hexane-benzene (1 : 9) was assigned the structure as 3, 7-dichloro-8-methylthioflavone (6b) which was fully consistent with its spectral-analytical data.

Attempts to hydrolyse the chlorothioflavanones 3 to 6 with alcoholic potassium hydroxide were unsuccessful and the original compounds were recovered in all cases. Hence the position of the third chlorine atom in 3*a* and 4*a* could not be established by chemical means. However this was determined on the basis of mass and NMR spectral data. In the mass spectrum of 3*a* besides the molecular ion peak at m/e 386; two prominent peaks at m/e 184 and 202 corresponding to fragments A and B respectively were observed. Other peaks were obtained at m/e 351 (loss of Cl), 323 (loss of CO), 287 (loss of Cl), 252 (loss of Cl).



A B

3a : R = −Me

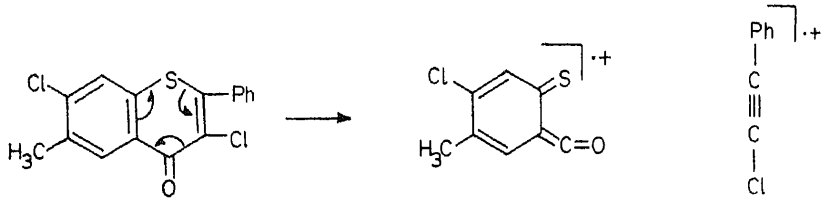
4a : R = − Et

The above fragmentation pattern is in full agreement with that reported for thioflavone derivatives (Schumann *et al* 1969) and proves that the third chlorine atom is in ring A. The NMR spectrum of 3a showed a singlet at δ 7·86 corresponding to the C_5 proton and a four proton multiplet at δ 7·26–7·43 for the $C_{8'}$, $C_{3'}$, $C_{4'}$ and $C_{5'}$ protons. The C_2, and C_6, protons are shifted downfield and appear as a multiplet as δ 7·56–7·73 probably due to the proximity of the chlorine atom at C_2 (Merchant *et al* 1978). Hence the third chlorine atom must be at position 7 or ortho to the methyl group.

In the case of 4*a*, the mass spectrum showed the molecular ion peak at m/e 400; the fragments A and B at m/e 184 and 216 and other peaks at m/e 365 (loss of Cl) 330 (loss of Cl), 302 (loss of CO), and 295 (M–3Cl) showing that the third chlorine atom is in ring A. In the NMR spectrum of 4*a* the C_5 proton appeared as a

singlet at δ 7·86; the C_8, $C_{3'}$, $C_{4'}$ and $C_{5'}$ protons were seen as a four-proton multiplet at δ 7·2–7·43 while the $C_{2'}$ and $C_{6'}$ protons appeared as a multiplet shifted downfield to δ 7·5–7·76 as in the case of 3*a*. Therefore in 4*a* also the third chlorine atom is at position –7.

The structures of 3*c* and 6*b* were assigned on the basis of their spectral data as follows : Their IR (KBr) spectra showed carbonyl bands at 1630 and 1635 cm^{-1} respectively suggesting α-halo, α, β-unsaturated ketone structures. The mass spectrum of 3*c* showed the molecular ion peak at m/e 320; fragments A′ and B′ at m/e 184 and 136 respectively and other peaks at m/e 285 (loss of Cl) 257 (loss of CO) and 251 (M–2Cl).

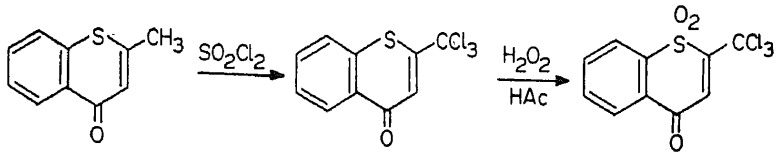


3*c* A′ B′

The NMR spectrum of 3*c* showed the C_5 proton as a singlet at δ 8·26 and the remaining aromatic protons as a singlet at δ 7·4. The second chlorine atom is probably at C_7 as no ortho coupling is seen for the C_7 and C_8 protons.

In the NMR spectrum of 6*b* the C_5 proton appears in the form of an AB pattern at δ 8·33 showing that positions 5 and 6 are unsubstituted. The remaining aromatic protons appear as a six-proton signal at δ 7·26–7·42. Therefore the second chlorine atom must be at position –7.

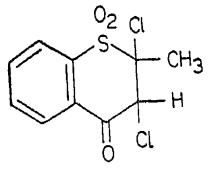
2-Methylthiochromone (C) when refluxed with sulphuryl chloride in carbon tetrachloride afforded a colourless solid assigned the structure as 2-trichloromethyl thiochromone (7). Its IR (KBr) spectrum showed a band for the carbonyl group at 1635 cm^{-1} while its NMR ($CDCl_3$) spectrum showed a singlet at δ 7·2 for the C_3–proton and a multiplet at δ 7·3–8·36 for the aromatic protons. Oxidation of 7 with hydrogen peroxide and acetic acid yielded the corresponding sulphone (8).



7 8

When 2-methylthiochromone-1, 1-dioxide was refluxed with sulphuryl chloride in carbon tetrachloride for 15 hr a colourless solid was obtained which was assigned the structure as 2, 3-dichloro-2-methyl-thiochromanone-1, 1-dioxide (9). Its IR (KBr) spectrum showed a band for the carbonyl group at 1675 cm^{-1} suggesting a thiochromanone structure. The NMR ($CDCl_3$) showed a split signal at δ 2·33–2·53 for the methyl protons. The split and the downfield shift could be attri-

buted to the proximity of the sulphone group and the chlorine atom at the C_2 position. The C_3-proton appeared as a singlet at δ 6·43 and the aromatic protons appeared as a four-proton multiplet at δ 7·46–8·20.



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3. Experimental

All melting points reported here are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer. The NMR spectra were recorded on a Varian 90 MHz spectrometer. Chemical shifts are quoted in δ values relative to tetramethylsilane (TMS) as internal standard. Spectra discussed in the text have not been included here. The homogeneity of compounds was ascertained by TLC on silica gel G plates. The spots were developed in an iodine chamber. Neutral alumina was used for column chromatography.

3.1. *Reaction of methylthioflavones with thionyl chloride in benzene*

To a solution of the methylthioflavone (0·5 g) in dry benzene (5 ml) was added thionyl chloride (5 ml). The mixture was refluxed on a water bath with additions of thionyl chloride at 5 hr intervals for a period of 20 hr. The excess thionyl chloride was removed under vacuum by reported additions of dry benzene and the compound obtained purified by column chromatography over alumina.

1a : 3-chloro-6-methylthioflavone (250 mg), m.p. 135–37° (petrol ether 60–80°). NMR (DMSO-d_6) 2·42 (3H, S, – CH_3), 7·4–8·4 (8H, m, ar). (Found C, 67·1; H, 4·2. $C_{16}H_{11}OSCl$ requires C, 67·1; H, 3·9%).

2a : 3-chloro-8-methylthioflavone (250 mg), m.p. 152–54° (hexane). NMR ($CDCl_3$) 2·46 (3H, S, – CH_3), 7·26–8·5 (8H, m, ar.). (Found C, 67·0; H, 4·1. $C_{16}H_{11}OSCl$ requires C, 67·1; H, 3·9%).

3.2. *Oxidation of halothioflavones* 1*a and* 2*a*

A mixture of the halothioflavone (100 mg), hydrogen peroxide (3 ml) and acetic acid (6 ml) were heated under reflux for 3 hr. The reaction mixture was diluted with water when a solid separated which was filtered, dried and crystallised.

1b : 3-chloro-6-methyl thioflavone-1, 1-dioxide (40 mg), m.p. 234–35° (benzene). (Found C, 60·3; H, 3·4. $C_{16}H_{11}O_3SCl$ requires C, 60·3; H, 3·4%).

2b : 3-chloro-8-methyl thioflavone-1, 1-dioxide (40 mg), m.p. 143–45° (acetic acid). (Found C, 60·1; H, 3·5. $C_{16}H_{11}O_3SCl$ requires C, 60·1; H, 3·4%).

3.3. *Reaction of* 6- *and* 8-*methyl thioflavones,* 2-*methylthiochromone and* 2-*methylthiochromone*-1, 1-*dioxide with sulphuryl chloride*

A solution of the compound (1 g) in carbon tetrachloride (10 ml) and sulphuryl chloride (20 ml) were refluxed for 15 hr. The excess sulphuryl chloride was

removed under vacuum by repeated additions of carbon tetrachloride. The residual substance was boiled with the appropriate alcohol and the solid obtained chromatographed over alumina.

3a : 2, 3, 7-trichloro-3-methoxy-6-methylthioflavanone (200 mg), m.p. 180–81° (methanol). IR (KBr) γ_{max}: 1700 (>C=O) cm^{-1}. NMR ($CDCl_3$) 2·35 (3H, S, $-CH_3$), 3·23 (3H, S, $-O-CH_3$), 7·26–7·43 (4H, m, H at C_8, $C_{3'}$, $C_{4'}$ and $C_{5'}$) 7·56–7·73 (2H, m, H at $C_{2'}$ and $C_{6'}$), 7·86 (1H, S, H at C_5). (Found C, 52·9, H, 3·2. $C_{17}H_{13}O_2SCl_3$ requires C, 52·6; H, 3·2%).

3b : 2, 3-dichloro-3-methoxy-6-methylthioflavanone (250 mg), m.p. 178–80°. (methanol). IR (KBr) γ_{max}: 1700 (>C=O) cm^{-1}. NMR ($CDCl_3$) 2·35 (3H, S, $-CH_3$), 3·26 (3H, S, $-O-CH_3$), 6·96–7·43 (5H, broad m, H at C_7, C_8, $C_{3'}$, $C_{4'}$ and $C_{5'}$,) 7·50–7·76 (2H, m, H at $C_{2'}$ and $C_{6'}$ 7·93 (1H, S, H at C_5). (Found C, 57·8; H, 4·2. $C_{17}H_{14}O_2SCl_2$ requires C, 57·8; H, 3·9%).

3c : 2, 7-dichloro-6-methylthioflavone (100 mg) m.p. 190–92° (methanol). IR (KBr) γ_{max} 1630 (>C=O) cm^{-1}. NMR ($CDCl_3$) 2·46 (3H, S, $-CH_3$), 7·4 (7H, S, ar.), 8·16 (1H, S, H at C_5). (Found C, 59·5; H, 3·6. $C_{16}H_{10}OSCl_2$ requires C, 59·8; H, 3·1%).

4a : 2, 3, 7-trichloro-3-ethoxy-6-methyl thioflavanone (100 mg), m.p. 145–47° (methanol). IR (KBr) γ_{max}: 1700 (>C=O) cm^{-1}. NMR ($CDCl_3$) 1·03 (3H, t, $-OCH_2-C\underline{H}_3$), 2·36 (3H, S, $-CH_3$), 3·5 (2H, q, $-OC\underline{H}_2CH_3$), 7·20–7·43 (4H, m, H at C_8, $C_{3'}$, C_4, and $C_{5'}$) 7·5–7·76 (2H, m, H at C_2, and C_6) 7·86 (1H, S, H at C_5). (Found C, 53·4; H, 3·4. $C_{18}H_{15}O_2SCl_3$ requires C, 53·8; H, 3·7%).

4b : 2, 3-dichloro-3-ethoxy-6-methylthioflavanone (250 mg), m.p. 226–28° C (benzene). IR (KBr) γ_{max}: 1680 (>C=O) cm^{-1}. NMR ($CDCl_3$) 1·03 (3H, t, $-O-CH_2-C\underline{H}_3$), 2·36 (3H, S, $-CH_3$), 3·5 (2H, q, $-O-C\underline{H}_2-CH_3$), 6·96–7·43 (5H, broad m, H at C_7, C_8, C_3, C_4, and $C_{5'}$) 7·5–7·73 (2H, m, H at C_2, and $C_{6'}$) 7·93 (1H, S, H at C_5). (Found C, 59·1; H, 4·2. $C_{18}H_{16}O_2SCl_2$ requires C, 58·8; H, 4·3%).

4c : 2, 3-dichloro-6-chloromethyl-3-ethoxythioflavanone (200 mg), m.p. 206–08° (methanol). IR (KBr) γ_{max}: 1690 (>C=O) cm^{-1}. NMR ($CDCl_3$) 1·03 (3H, t, $-O-CH_2-C\underline{H}_3$), 3·5 (2H, q, $-O-C\underline{H}_2-CH_3$), 4·66 (2H, S, $-CH_2-Cl$), 7·06–7·50 (5H, broad m, H at C_7, C_8, $C_{3'}$, C_4, and $C_{5'}$) 7·5–7·7 (2H, m, H at C_2, and $C_{6'}$), 8·1 (1H, S, H at C_5). (Found C 53·9; H, 4·1. $C_{18}H_{15}O_2SCl_3$ requires C, 53·8; H, 3·7%).

5 : 2, 3-dichloro-3-methoxy-8-methylthioflavanone (250 mg), m.p. 154–56° (methanol). IR (KBr) γ_{max}: 1690 (>C=O) cm^{-1}. NMR ($CDCl_3$) 2·36 (3H, S, $-CH_3$), 3·23 (3H, S, $-OCH_3$), 6·96–7·43 (5H, broad m, H at C_6, C_7, C_3, C_4, and $C_{5'}$) 7·56–7·73 (2H, m, H at C_2, and $C_{6'}$) 7·98 (1H, d, H at C_5). (Found C, 57·6; H, 3·6, $C_{17}H_{14}O_2SCl_2$ requires C, 57·7; H, 3·9%).

6a : 2, 3-dichloro-3-ethoxy-8-methylthioflavanone (200 mg); m.p. 106–08° (ethanol) IR (KBr) γ_{max}: 1690 (>C=O) cm^{-1}. NMR ($CDCl_3$) 1·0 (3H, t, $-O-C\underline{H}_2-CH_3$), 2·33 (3H, S, $-CH_3$), 3·46 (2H, q, $-O-C\underline{H}_2-CH_3$) 6·96–7·43 (5H, broad m, H at C_6, C_7, C_3, C_4, and $C_{5'}$) 7·50–7·76 (2H, m, H at C_2, and $C_{6'}$), 7·98 (1H, d, H at C_5). (Found C, 59·3; H, 4·4, $C_{18}H_{16}O_2SCl_2$ requires C, 58·8, H, 4·3%).

6b : 2, 7-dichloro-8-methylthioflavone (75 mg), m.p. 146–48° (ethanol) IR (KBr) γ_{max}: 1635 (>C=O) cm^{-1}. NMR ($CDCl_3$) 2·46 (3H, S, $-CH_3$), 7·26–7·42 (6H, m, ar) 8·33 (1H, d, H at C_5). (Found C, 59·4; H, 3·0, $C_{16}H_{10}OSCl_2$ requires C, 59·8; H, 3·1%).

7 : 2-trichloromethylthiochromone (500 mg) m.p. 145–46° (methanol). (Found C, 43·3; H, 2·6. $C_{10}H_5OSCl_3$ requires C, 42·9; H, 1·8%).

9 : 2,3-dichloro-2-methylthiochromanone-1, 1-dioxide (400 mg) m.p. 125–27° (methanol). (Found C, 43·2; H, 3·3. $C_{10}H_8O_3SCl_2$ requires C, 43·0; H, 3·6%).

3.4. *Oxidation of 2-trichloromethyl thiochromone* (7)

A mixture of 7 (100 mg) hydrogen peroxide (3 ml) and acetic acid (6 ml) were refluxed for 3 hrs, the reaction mixture was cooled and diluted with water. The solid which separated was filtered, dried and crystallised.

8 : 2-Trichloromethyl thiochromone-1, 1-dioxide (50 mg) m.p. = 145–47° (petrol-ether 60–80°). (Found C, 38·7; H, 1·8, $C_{10}H_5O_3SCl$ requires C, 38·5, H, 1·6%).

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