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REACTION OF SUBSTITUTED FLAVONES WITH THIONYL AND SULPHURYL CHLORIDES

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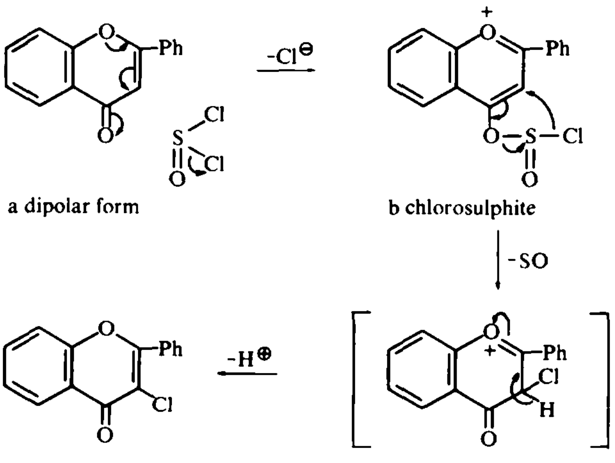
Abstract—Thionyl chloride reacts with 6-methyl- and 7-methoxyflavones to yield the 3-chloro derivatives in both cases. Reaction of the above flavones with sulphuryl chloride gives two compounds with the former flavone and 4 compounds with the latter. All the structures have been established on the basis of spectral data and the hydrolysis products.

IN OUR preliminary communication[1,2] we reported the reaction of thionyl chloride ($SOCl_2$) and sulphuryl chloride (SO_2Cl_2) with flavone to yield 3-chloroflavone with the former and 2,3,3-trichloroflavanone with the latter reagent.

While SO_2Cl_2 is a well known chlorinating agent, $SOCl_2$ does not always behave as one and we suggest the following mechanism for the formation of 3-chloroflavone from the reaction of thionyl chloride with flavone.



The dipolar form (a) reacts with $SOCl_2$ forming the chlorosulphite b, from which c is formed by extrusion of sulphur monoxide, known to be in equilibrium with SO_2 and elemental sulphur.[3,4] Neutralization of the positive charge on c leads to the 3-chloroflavone d.

The present paper also gives a detailed account of our work on the reaction of the above reagents with 6-methyl- and 7-methoxy-flavones which give some very interesting results.

6-Methylflavone[5] on reaction with excess of $SOCl_2$ at the reflux temperature of C_6H_6 afforded (4%) the expected 3-chloro-6-methyl flavone (I), whose structure is consistent with spectral, analytical and chemical properties: IR (nujol) 1670 (CO) (1645 cm^{-1} in original flavone) 1620, 1570, 1490, 820, 770, 700 (aromatic), 645 (C—Cl) cm^{-1}. Hydrolysis of I with 1% alcoholic KOH gave 2-benzoyl-5-methylcoumaranone (Ia), whose structure was established on the basis of its spectral data and by the colouration (olive green) with alcoholic $FeCl_3$, IR (nujol) 1615 (CO-hydrogen bonded), 1560, 1530, 910, 800, 785, 685 (aromatic) cm^{-1}.

When 6-methylflavone was treated with excess of SO_2Cl_2 in CCl_4, two products were obtained, and separated by fractional crystallisation from EtOH. The less soluble was assigned as 3-chloro-6-dichloromethylflavone (II) on the basis of its analysis, spectra and chemical properties. The IR spectra showed bands at $\nu_{(nujol)}$ 1645 (CO), 1615, 1560, 1495, 770, 740, 700 (aromatic), 645 (C—Cl) cm^{-1} whereas the NMR ($CDCl_3$) spectrum showed signals at : δ 8·38 (H_5, 1H, d, $J = 2{\cdot}5$ c/s; δ 8·01 (H_7, 2′, 6′, 3H, b.m.); δ 7·65 (H_8, 3′,4′,5′,4H, b.m.); δ 6·85 (1H, S, $CHCl_2$). A comparison of the NMR of II with that of 6-methylflavone showed the disappearance of the Me protons at δ 2·44, as well as the H_3 proton at δ 6·78, which confirmed the structure II. Further, when II was hydrolysed with 1% alcoholic KOH, two compounds were isolated which were separated by column chromatography (silica gel). The first eluted with C_6H_6 was found to be 3-chloro-6-formylflavone (IIa) on the basis of its IR spectrum (nujol): 1695 (CO of CHO), 1660 (CO of flavone), 1610, 1565, 1495, 760, 690 (aromatic), 655 (C—Cl) cm^{-1}. The presence of a formyl group in IIa was further confirmed by the preparation of a 2,4-dinitrophenylhydrazone.

The second compound from hydrolysis eluted with MeOH was found to be 2-benzoyl-5-formylcoumaranone (IIb). Its structure was in agreement with its analytical, spectral data, IR (nujol) 1695 (CO of CHO), 1615 (CO-hydrogen bonded), 1595, 1575, 1540, 765, 710, 685 (aromatic) cm^{-1}, its colouration (green) with alcoholic $FeCl_3$ and solubility in aqueous $NaHCO_3$, indicating the presence of an enolic OH group.

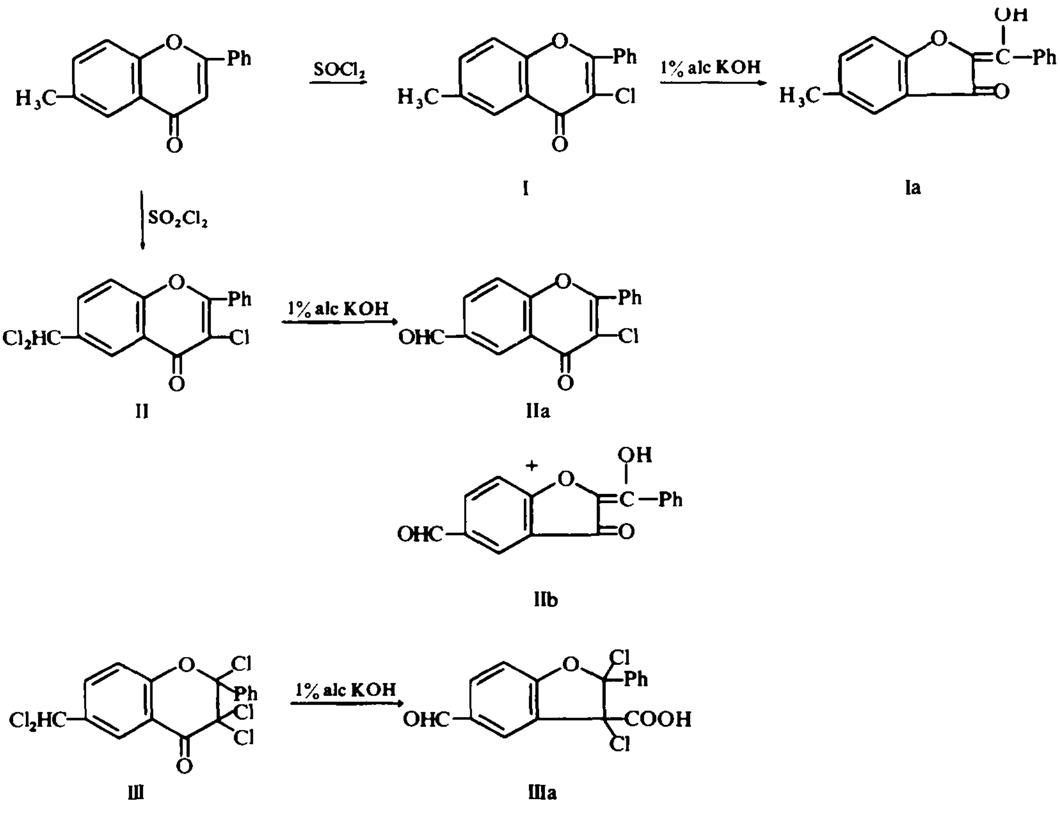
The second compound obtained by the reaction of 6-methyl flavone with SO_2Cl_2 (6%) was found to be 6-dichloromethyl-2,3,3-trichloroflavanone (III), the structure of which was in agreement with its spectra and chemical properties: IR (nujol): 1725[2] (CO), 1615, 1595, 1495, 740 (aromatic), 640 (C—Cl) cm^{-1}; NMR ($CDCl_3$) δ 8·28 (H_5, 1H, d, $J = 2{\cdot}5$ c/s); δ 8·03 (H_7, 2′,6′,3H, b.m.); δ 7·51 (5H, b.m.); δ 6·81 (1H, S, $CHCl_2$). A comparison of the NMR of III with that of 6-methylflavone also showed the disappearance of the Me and H_3 protons. Refluxing III with 1% alcoholic alkali yielded an acid which from analogy with our previous observations[2] was assigned the structure as 3-carboxy-2,3-dichloro-5-formyl-2-phenyl-2,3-dihydrobenzofuran (IIIa). This structure was supported by the formation of a 2,4-D.N.P. as well as its IR (nujol): 3200 (broad OH of COOH), 1685 (CO of COOH), 1605, 1540, 1495, 790, 775, 700 (aromatic), 640 (C—Cl) cm^{-1}.

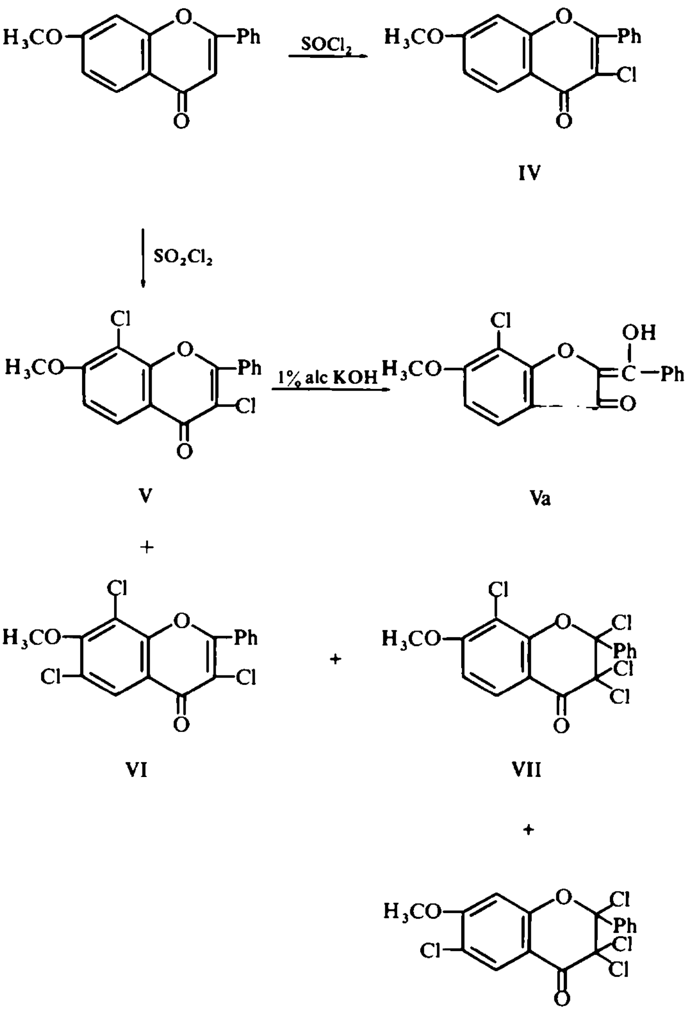
The reaction of 7-methoxyflavone[6] with excess of $SOCl_2$ afforded a single compound which was found to be 3-chloro-7-methoxyflavone (IV); IR (nujol): 1660 (CO), 1605, 1555, 1490, 775, 690 (aromatic) cm^{-1}.

The reaction of 7-methoxyflavone with SO_2Cl_2 in CCl_4 gave four compounds which were separated by PLC followed by fractional crystallisation. The first compound was assigned the structure 3,8-dichloro-7-methoxyflavone (V), (R_f value in C_6H_6 0·22). This structure is in full agreement with its spectral-analytical data and chemical properties IR (nujol) 1665 (CO), 1615, 1610, 1590, 1490, 820, 780, 770, 690 (aromatic), 635 (C—Cl) cm^{-1}, NMR ($CDCl_3$), δ 8·43 (H_5, 1H, d, $J = 8{\cdot}5$ c/s, 2·5 c/s);

δ 8·11 ($H_{2'}$, 6', 2H, b.m.); δ 7·66 ($H_{3'}$, 4', 5', 3H, b.m.); δ 7·23 (H_6, 1H, d, $J = 8{\cdot}5$ c/s); δ 4·1 (3H, S, OCH_3). The shifting of the carbonyl frequency from 1645 cm^{-1} (in 7-methoxyflavone) to 1665 cm^{-1} in V is an indication that the H_3 proton is chlorinated. A comparison of the NMR of V with that of 7-methoxyflavone showed the disappearance of the H_3, and H_8 protons, indicating replacement by chlorine. Further, in the NMR of V the H_5 and H_6 protons clearly show an orthocoupling suggesting that the H_5 and H_6 protons are free. In order to confirm the structure, V was refluxed with 1% alcoholic KOH when the expected 2-benzoyl-7-chloro-6-methoxycoumaranone (Va) was obtained. This structure (Va) was supported by an olive green colouration with alcoholic $FeCl_3$ and IR (nujol): 1620 (CO, hydrogen bonded), 1600, 1570, 1490, 760 (aromatic) cm^{-1}.

The second compound obtained above was found to be 7-methoxy-3,6,8-trichloroflavone (VI) (R_f value in C_6H_6 0·62). The suggested structure was in agreement with its spectral data, IR (nujol): 1665 (CO), 1600, 1585, 1545, 1490, 770, 760, 690 (aromatic) cm^{-1}, NMR ($CDCl_3$) δ 8·20 (H_5, 1H, s); δ 8·03 ($H_{2'}$, 6', 2H, b.m.); δ 7·56 ($H_{3'}$, 4', 5', 3H, b.m.); δ 4·05 (3H, s, OCH_3). The shifting of the carbonyl frequency from 1645 cm^{-1} (in 7-methoxyflavone) to 1665 cm^{-1} in VI indicated that the H_3 proton was chlorinated. Also a comparison of the NMR of VI with that of 7-methoxyflavone showed the disappearance of H_3, H_6 and H_8 protons while the H_5 proton appeared as a singlet.





IV

V

Va

VI

VII

VIII

The third compound was found to be 2,3,3,8-tetrachloro-7-methoxy-flavanone (VII) (R_f value in C_6H_6 0·88). Its structure was supported by spectral, analytical data, IR (nujol): 1725 (CO), 1600, 1560, 1490, 820, 790, 770, 700, 690 (aromatic), 635 (C—Cl) cm^{-1}, NMR ($CDCl_3$); δ 8·25 (H_5, 1H, d, J = 8·5 c/s); δ 8·21 ($H_{2'}$, 6', 2H, b.m.); 7·50 ($H_{3'}$, 4', 5', 3H, b.m.); δ 7·05 (H_6, 1H, d, J = 8·5 c/s); δ 4·10 (3H, S, OCH_3). The shifting of the carbonyl frequency from 1645 cm^{-1} (in 7-methoxy flavone) to 1725 cm^{-1} (in VII) was suggestive of the 2,3,3-trichloroflavanone structure. In the NMR spectrum of VII, the H_3 and H_8 protons disappeared while H_5 and H_6 protons appeared in the spectrum as a doublet and were orthocoupled.

The fourth compound obtained from 7-methoxyflavone was found to be 7-methoxy-2,3,3,6-tetrachloroflavanone (VIII) (R_f value C_6H_6 0·95). The suggested structure was in agreement with its spectra, IR (nujol): 1720 (CO), 1600, 1495, 780, 740, 690 (aromatic). 635 (C—Cl) cm^{-1}, NMR ($CDCl_3$), δ 8·1 (H_5, 1H, s); δ 8·00 ($H_{2'}$, 6', 2H, b.m.); δ 7·52 ($H_{3'}$, 4', 5', 3H, b.m.); δ 6·73 (H_8, 1H, s); δ 3·96 (3H, s, OCH_3). Here also, the carbonyl frequency was shifted to 1720 cm^{-1} whereas in the NMR spectrum the disappearance of the H_3 and H_6 protons was observed. The H_5 and H_8 protons appeared as singlets as expected.

EXPERIMENTAL

3-*Chloro-6-methylflavone* I. To a soln of 6-methylflavone (500 mg) in dry C_6H_6 (5 ml) $SOCl_2$ (5 ml) was added and the mixture refluxed. After 5 hr, more $SOCl_2$ (5 ml) was added. In all $SOCl_2$ (15 ml) was added and the mixture refluxed for 15 hr. $SOCl_2$ was removed under vacuum, and the solid mass obtained, dissolved in EtOH and cooled, when colourless needles (20 mg) separated, recrystallised from EtOH (charcoal) m.p. 135°. (Found: C, 70·80; H, 4·13; Cl, 13·30. Calc. for $C_{16}H_{11}O_2Cl$: C, 70·97; H, 4·06; Cl, 13·12%).

2-*Benzoyl-5-methylcoumaranone* Ia. To a soln of I (200 mg) in EtOH (10 ml) was added 1% alcoholic KOH (14 ml) and the mixture refluxed for 4 hr. After cooling and acidified with HCl, the mix was diluted with H_2O and cooled when a yellow mass separated. Filtering, washing with H_2O, and recrystallisation from EtOH–H_2O gave fine yellow needles (120 mg), m.p. 113–114° (lit.[7] m.p. 112°). (Found: C, 76·40; H, 5·05. Calc. for $C_{16}H_{12}O_3$: C, 76·19; H, 4·76%).

3-*Chloro-6-dichloromethylflavone* II. 6-Methylflavone (1 g) dissolved in dry CCl_4 (10 ml) was added to SO_2Cl_2 (20 ml) and the mixture refluxed for 15 hr. SO_2Cl_2 was removed under vacuum by repeated addition of CCl_4. The thick liquid obtained was dissolved in EtOH and allowed to cool when a white solid (400 mg) separated. It was recrystallised from EtOH as white silky needles, m.p. 182–183°. (Found: C, 56·90; H, 2·51; Cl, 31·5. Calc. for $C_{16}H_9O_2Cl$ C, 56·53; H, 2·65; Cl, 31·23%).

The mother liquor of the above was concentrated and kept in a refrigerator when III separated as yellow needles, m.p. 111–115°. Repeated crystallisation from EtOH (charcoal) afforded colourless needles, 100 mg m.p. 138–139°. (Found: C, 47·29; H, 2·35; Cl, 43·1. Calc. for $C_{16}H_9O_2Cl_5$: C, 47·08; H, 2·20; Cl, 43·38%).

3-*Chloro-6-formylflavone* IIa. To a soln of II (200 mg) in EtOH (10 ml) was added 1% alcoholic KOH (14 ml) and the mixture refluxed for 4 hr. Then cooled, acidified with HCl, diluted with H_2O till turbidity obtained and cooled when yellow product separated. TLC (silica gel; 2% MeOH in C_6H_6) showed two compounds, separated by column chromatography (silica gel). IIa was eluted with C_6H_6 as a white solid, and crystallised from C_6H_6-pet. ether, as white silky needles, (80 mg) m.p. 198°. (Found: C, 67·50; H, 3·33; Cl, 12·10. Calc. for $C_{16}H_9O_3Cl$: C, 67·60; H, 3·16; Cl, 12·32%). (2,4-D.N.P. m.p. 322°. (Found: N, 12·10. Calc. for $C_{22}H_{13}O_6N_4$: N, 12·06%).

The second compound eluted with MeOH was treated with $NaHCO_3$aq soln and filtered. The filtrate on acidification gave a yellow solid (30 mg) crystallised from EtOH–H_2O as fine yellow needles (IIb), m.p. 145°. (Found: C, 72·54; H, 3·97. Calc. for $C_{16}H_{10}O_4$: C, 72·14; H, 3·70%). It gave an olive green colouration with alcoholic $FeCl_3$.

3-*Carboxy-2,3-dichloro-5-formyl-2-phenyl-2,3-dihydrobenzofuran* IIIa. A soln of III (200 mg) in EtOH (10 ml) was added to 1% alcoholic KOH soln (14 ml) and the mixture refluxed for 4 hr. Then cooled, acidified with HCl, diluted with H_2O and cooled. The solid which separated was filtered, washed with H_2O treated with $NaHCO_3$aq, and filtered. The filtrate was acidified with HCl, the white solid which separated was filtered and washed with H_2O. Crystals from C_6H_6-pet. ether as white needles, (30 mg) m.p. 181°. (Found: C, 57·20; H, 3·1; Cl, 21·20. Calc. for $C_{16}H_{10}O_4Cl_2$: C, 56·97; H, 2·96; Cl, 21·06%). 2,4-D.N.P.: m.p. 248–249°.

3-*Chloro-7-methoxyflavone* IV. $SOCl_2$ (5 ml) was added to a soln of 7-methoxyflavone (500 mg) in dry C_6H_6 (7 ml) and the mixture refluxed for 15 hr with addition of $SOCl_2$ (5 ml) at 5 hr intervals (total 15 ml). $SOCl_2$ was removed under vacuum and the solid obtained dissolved in EtOH. H_2O was added till turbidity obtained, and kept in a refrigerator. The white globules which separated were purified by column chromatography (silica gel). The fraction eluting with C_6H_6 was crystallised from C_6H_6-pet. ether as white globules, (50 mg) m.p. 119–120°. (Found: C, 67·00; H, 3·71; Cl, 11·98. Calc. for $C_{16}H_{11}O_3Cl$: C, 67·48; H, 3·86; Cl, 12·04%).

3,8-*Dichloro-7-methoxyflavone* (V). 7-Methoxyflavone (500 mg) was dissolved in dry CCl_4 (5 ml). SO_2Cl_2 (10 ml) was added, the mixture refluxed for 15 hr and the SO_2Cl_2 removed under vacuum. The residue obtained was dissolved in EtOH (50 ml) and cooled when white needles separated out. It was purified by PLC (silica gel) R_f 0·22 (C_6H_6). Compound extracted with $CHCl_3$ and the solid obtained after removal of solvent was crystallised from EtOH as white needles, 80 mg, m.p. 208. (Found: C, 60·05; H, 3·50; Cl, 22·00. Calc. for $C_{16}H_{11}O_3Cl_2$: C, 59·81; H, 3·11; Cl, 22·11%).

Mother liquor of above was concentrated and kept in a refrigerator when a solid separated. TLC showed four compounds having R_f 0·22 identical with above compound (V); 0·62 (VI); 0·88 (VII); 0·95 (VIII) (C_6H_6), which were separated by a PLC (silica gel in C_6H_6). The portion of silica gel corresponding to R_f (0·62) was removed and extracted with $CHCl_3$. Removal of solvent gave VI (20 mg) crystallised from EtOH–EtOAc as white needles, m.p. 192°. (Found: C, 54·30; H, 3·03; Cl, 29·49. Calc. for $C_{16}H_9O_3Cl_3$: C, 54·00; H, 2·59; Cl, 29·67%).

The portion of the silica gel corresponding to the two R_f values (0·88 and 0·95) was together extracted with $CHCl_3$. Removal of $CHCl_3$ gave an oil, dissolved in EtOH, and cooled when VII (30 mg) separated as a colourless solid. It recrystallised from EtOH as colourless cubes, m.p. 169°. (Found: C, 49·10; H, 3·00; Cl, 36·40. Calc. for $C_{16}H_{10}O_3Cl_4$: C, 48·97; H, 2·55; Cl, 36·22%).

The mother liquor from above was concentrated, cooled and colourless stout needles of VIII (20 mg) separated, purified by recrystallisation, m.p. 204°. (Found: C, 49·00; H, 2·83; Cl, 36·40. Calc. for $C_{16}H_{10}O_3Cl_4$: C, 48·97; H, 2·55; Cl, 36·22%).

2-*Benzoyl-7-chloro-6-methoxycoumaranone* Va. To a soln of V (100 mg) in EtOH (5 ml) was added 1% alcoholic KOH (7 ml) and the mixture refluxed for 4 hr. After cooling it was acidified with HCl, diluted with H_2O and kept in a refrigerator when a yellow compound separated, filtered, washed with H_2O and treated with $NaHCO_3$aq and filtered. The yellow solid obtained on acidification of the filtrate was crystallised from aqueous EtOH as fine yellow needles, 60 mg, m.p. 142°. (Found: C, 63·40; H, 3·92; Cl, 11·71. Calc. for $C_{16}H_{11}O_4Cl$: C, 63·47; H, 3·63; Cl, 11·73%).

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