Halogenation of Isoflavones Using Thionyl and Sulphuryl Chlorides

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The reactions of thionyl and sulphuryl chlorides on isoflavones have been found to give a number of new chloroisoflavones and isoflavanones, whose structures have been elucidated on the basis of their spectral analytical data.

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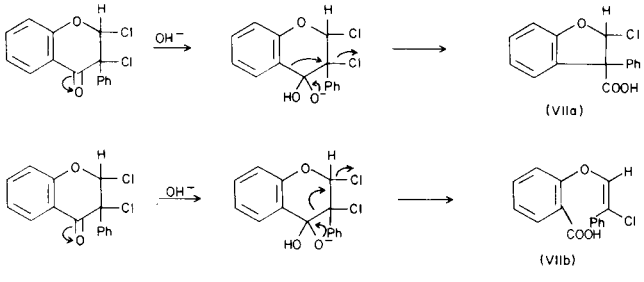
The interesting results obtained concerning the reaction of flavones with thionyl and sulphuryl chlorides (1), prompted us to extend the application of the action of these reagents to isoflavones.

Isoflavone (I) does not react with thionyl chloride in benzene when refluxed for 15 hours. Addition of a large excess of the reagent and refluxing for 30 hours also quantitatively yields the original compound. 7-Hydroxyisoflavone (II) reacted with thionyl chloride in benzene to give 7-chloroisoflavone (III), which was found to be identical with the sample prepared as described in the literature (2). 7-Methoxyisoflavone (IV) when refluxed with thionyl chloride in benzene gave 6-chloro-7-methoxyisoflavone (V). Spectral data for V is described in the Experimental. It is seen from the above reactions that the pyrone ring of isoflavone is not affected by thionyl chloride. However, when I was refluxed with sulphuryl chloride in carbon tetrachloride for 15 hours, a colourless compound was obtained which was assigned the structure 2,3-dichloroisoflavanone (VI). Its ir spectrum (potassium bromide) showed a band at 1695 cm^{-1} (>C=O), while the nmr (deuteriochloroform) gave the following signals: δ 6.34 (1H, s, C_2H), 6.9-8.3 (9H, m, aromatic).

The structure of VI was confirmed by hydrolysis with 1% alcoholic potassium hydroxide, when a chlorocarboxylic acid having the molecular composition $C_{15}H_{11}ClO_3$ (M^+ 274) was obtained. The latter could have one of the two possible structues VIIa or VIIb, formed as indicated below. The ir spectrum (potassium bromide)



showed bands at 2678, 2612 cm^{-1} (-OH of -COOH), 1706, 1253 cm^{-1} (>C=O of -COOH), 1641 cm^{-1} (C=C), 1607, 1581, 1489 cm^{-1} (aromatic) and 1284, 1167 and 1112 cm^{-1} (aryl ether).

The H^1-nmr (270 MHz) (deuteriochloroform) showed a sharp singlet at δ 7.025, integrating for one proton, which was attributed to the =CH proton. The C^{13}-nmr (deuteriochloroform) spectrum of the hydrolysis product confirmed its structure as VIIb. In this spectrum no chemical shifts were observed up to δ 118 ppm. In structure VIIb, the carboxylic group is attached to the aromatic ring and was observed as a signal at δ 170.67. The signal for =C-H was obtained at δ 138.31.

Refluxing 7-hydroxyisoflavone (II) with sulphuryl chloride in carbontetrachloride for 15 hours afforded two compounds, which were separated by column chromatography over aluminia. Elution with petroleum ether (40-60°)-benzene (3:2) yielded a colourless solid found to be 2,3,6,8-tetrachloro-7-hydroxyisoflavanone (VIII). The second compound eluted with petroleum ether (40-60°)-benzene (3:17) was assigned the structure as 6,8-dichloro-7-hydroxyisoflavone (IX) since its ir spectrum (potassium bromide) showed the carbonyl band at 1640 cm^{-1} suggesting an α,β-unsaturated ketone structure. Also, its nmr spectrum (deuteriochloroform) showed the C_2 proton as a signal at δ 7.5.

A similar reaction of 7-methoxyisoflavone (III) with sulphuryl chloride followed by column chromatography gave two compounds: 2,3,6,8-tetrachloro-7-methoxyisoflavanone (X) and 2,3,8-trichloro-7-methoxyisoflavanone (XI). The structures of X and XI were assigned on the basis of analytical and spectral evidence.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer spectrophotometer and the nmr spectra were determined on a Varian 90 MHz spectrometer with TMS as the internal standard. The homogeneity of the compounds was ascertained by tlc on silica gel-G plates. Neutral alumina was used for column chromatography.

Reaction of II with Thionyl Chloride.

To a solution of 7-hydroxyisoflavone (0.5 g.) in dry benzene (5 ml.) were added six 5 ml. portions of thionyl chloride at 5 hour intervals and the whole refluxed for 30 hours. Thionyl chloride was removed under vacuum by repeated additions of dry benzene to yield III as a colourless solid (350 mg.), which was crystallised from ethanol, m.p. 144-145°; ir (potassium bromide): 1640 cm^{-1}; nmr (deuteriochloroform): δ 7.92 (1H, s, C_2H), 7.2-7.6 (6H, m, Ar.), 8.2 (1H, d, C_5H).

Anal. Calcd. for $C_{15}H_9ClO_2$: C, 70.3; H, 3.5. Found: C, 69.9; H, 3.7.

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Reaction of IV with Thionyl Chloride.

A similar reaction of thionyl chloride on IV followed by removal of the excess reagent yielded V as colourless needles (300 mg.), m.p. 208-210°, crystallized from benzene; ir (potassium bromide): 1640 cm^{-1}; nmr (deuteriochloroform): δ 4.0 (3H, s, $-OCH_3$), 6.9 (1H, s, Ar.), 7.2-7.6 (5H, m, Ar.), 7.93 (1H, s, C_2H), 8.28 (1H, s, C_5H).

Anal. Calcd. for $C_{16}H_{11}ClO_3$: C, 67.1; H, 3.8. Found: C, 67.1; H, 4.0.

Reaction of I with Sulphuryl Chloride.

Isoflavone (1 g.) was dissolved in carbon tetrachloride (10 ml.) and sulphuryl chloride (20 ml.) was added. The reaction mixture was refluxed for 15 hours and sulphuryl chloride removed completely under vacuum to give VI on crystallisation from methanol (yield 600 mg.), m.p. 136-138°.

Anal. Calcd. for $C_{15}H_{10}Cl_2O_2$: C, 61.4; H, 3.4. Found: C, 61.0; H, 3.7.

Reaction of II with Sulphuryl Chloride.

Similarly, the reaction of II with sulphuryl chloride followed by the usual work up and chromatography over alumina gave VIII and IX. Compound VIII was eluted with petroleum ether (40-60°):benzene (3:2), crystallised from benzene-hexane mixture, m.p. 194-196° (yield 250 mg.); ir (potassium bromide): 3560, 1690 cm^{-1}; nmr (deuteriochloroform): δ 6.5 (1H, s, C_2H), 7.2-8.2 (6H, m, Ar.).

Anal. Calcd. for $C_{15}H_8Cl_4O_3$: C, 47.6; H, 2.1. Found: C, 47.4; H, 2.4.

Further elution with petroleum ether (40-60°):benzene (3:17) yielded IX (300 mg.) on crystallisation from benzene, m.p. 215-217°; ir (potassium bromide): 3320, 1640 cm^{-1}; nmr (deuteriochloroform): δ 7.5 (1H, s, C_2H), 7.53-7.9 (5H, m, Ar.), 8.1 (1H, s, C_5H).

Anal. Calcd. for $C_{15}H_{10}Cl_2O_3$: C, 58.3; H, 3.3. Found: C, 58.7; H, 3.6.

Reaction of IV with Sulphuryl Chloride.

The reaction of IV with sulphuryl chloride, after removal of the excess sulphuryl chloride and chromatography over alumina gave X eluted with hexane:benzene (49:1) and crystallised from petroleum-ether (100-120°), m.p. 165-167° (yield 200 mg.); ir (potassium bromide): 1720 cm^{-1}; nmr (deuteriochloroform): δ 3.96 (3H, s, $-OCH_3$), 6.38 (1H, s, C_2H), 7.20-7.66 (5H, m, Ar.), 7.98 (1H, s, C_5H).

Anal. Calcd. for $C_{16}H_{10}Cl_4O_3$: C, 49.0; H, 2.5. Found: C, 49.4; H, 2.6.

Compound XI was eluted with hexane:benene (7:3) as a colourless solid crystallised from benzene-hexane mixture, m.p. 175-177° (yield 150 mg.); ir (potassium bromide): 1695 cm^{-1}; nmr (deuteriochloroform): δ 3.93 (3H, s, $-OCH_3$), 6.4 (1H, s, C_2H), 6.6-8.0 (7H, m, Ar.).

Anal. Calcd. for $C_{16}H_{11}Cl_3O_3$: C, 53.7; H, 3.1. Found: C, 53.3; H, 3.4.

Hydrolysis of 2,3-Dichloroisoflavanone (VI).

A mixture of VI (100 mg.), ethanol (5 ml.) and alcoholic potassium hydroxide (7 ml., 1%) was refluxed for 4 hours. The reaction mixture was cooled, diluted with water and acidified with dilute hydrochloric acid to give VIIb (40 mg.) crystallised from hexane m.p. 98-100°.

Anal. Calcd. for $C_{15}H_{11}ClO_3$: C, 65.5; H, 4.0. Found: C, 65.4; H, 3.8.

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