CHROMONES

Part I. Nitration of Some 7-Hydroxychromones and Their Methyl Ethers

By A. M. Mehta, G. V. Jadhav and R. C. Shah, F.A.Sc.

(Organic Chemistry Laboratory, Royal Institute of Science, Bombay)

Received October 28, 1948

No systematic study of the nitration of chromones appears to have been made so far, although a few nitrochromones have been prepared by direct nitration of some of the naturally occurring flavones like chrysin,[1] apigenin,[2] quercetin pentamethyl ether,[3] luteolin tetramethyl ether and morin pentamethyl ether.[4] Two other attempts at nitration of chromones are due to Simonis who succeeded in preparing 6-nitro-2: 3-dimethylchromone[5] and 6-nitro-2: 3: 5: 7-tetramethylchromone.[6] Bogert and Marcus[7] in their attempts to nitrate flavone failed to isolate any pure nitro-compound, a mixture of 2'-, 3'-, and 4'-nitroflavones being obtained.

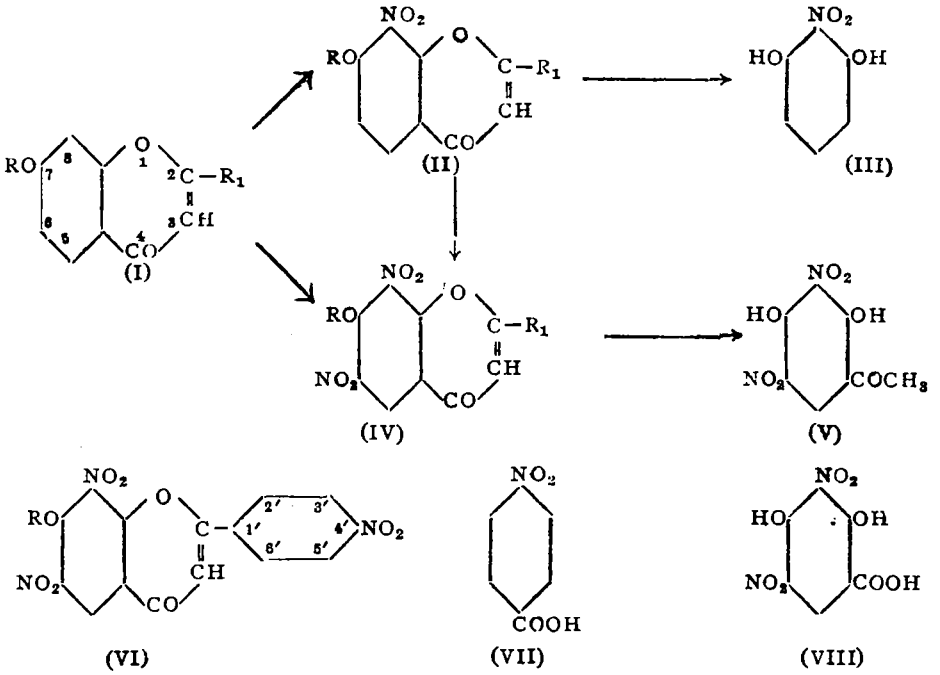
As a part of a comprehensive and systematic study on substitution in chromones, in the present investigation nitration of 7-hydroxy-2-methylchromone (I: R = H; $R_1 = CH_3$), 7-hydroxy flavone (I: R = H; R_1 = Ph) and their methyl ethers has been carried out under various conditions.

7-Hydroxy-2-methylchromone (I: R = H; $R_1 = CH_3$) at 0° C. with nitric acid (d. 1·42) in concentrated sulphuric acid gave a mono-nitro derivative which, on hydrolysis, yielded 2-nitro resorcinol (III) and was therefore 7-hydroxy-8-nitro-2-methylchromone (II: R = H; $R_1 = CH_3$). The methyl ether of I (R = $R_1 = CH_3$) also gave 8-nitro derivative as the product was identical with the methyl ether of the nitro-hydroxy compound. In the latter case, it may be pointed out that the usual methods of methylation, namely, with dimethyl sulphate and alkali in cold or with methyl iodide in presence of anhydrous potassium carbonate in acetone proved unsuccessful. Recourse was therefore taken to a method using dry sodium salt of the hydroxychromone with dimethyl sulphate in toluene, which gave good results with all the nitro-hydroxy compounds.

When the nitration of 7-hydroxy-2-methylchromone was carried out at room temperature (30° C.) using fuming nitric acid in concentrated sulphuric acid a di-nitro-product was obtained, which was also obtained on further nitration of the above mono-nitro-hydroxychromone. It was found to be 7-hydroxy-6: 8-dinitro-2-methylchromone (IV; R = H; $R_1 = CH_3$

as on alkaline degradation it furnished 3: 5-dinitroresacetophenone (V). It is interesting to note that while the 8-nitro compound underwent hydrolysis giving presumably a resorcylic acid derivative which on subsequent decarboxylation gave 2-nitroresorcinol, the 6: 8-dinitro-derivative, like 7-hydroxychromones,[8] gave the usual resacetophenone derivative. The methyl ether of the dinitro product (IV: R = R_1 = CH_3) was found to be identical with the dinitro product obtained by direct nitration of 7-methoxy-2-methylchromone.

All attempts to get higher nitro-derivatives proved unsuccessful, resulting in rupture of the pyrone ring. If nitration was attempted in acetic acid 3: 5-dinitro-β-resorcylic acid (VIII) was obtained, while in presence of sulphuric acid splitting took a different course giving 3: 5-dinitroresacetophenone (V).



The nitration of 7-hydroxyflavone (I: R = H; R_1 = Ph) took a similar course and furnished 8-nitro- and 6: 8-dinitro-7-hydroxyflavones (II: R = H; R_1 = Ph and IV: R = H; R_1 = Ph respectively) as was shown by their degradation products which were identified as 2-nitroresorcinol (III) and 3: 5-dinitro resacetophenone (V) respectively. When heated on a steam-bath with concentrated nitric acid (d. 1·42) it also furnished a trinitro-derivative which on hydrolysis gave *p*-nitrobenzoic acid (VII), indicating

that further nitration has taken place in 4′-position. As the trinitro derivative could also be obtained by further nitration of 7-hydroxy-6: 8-dinitroflavone, the structure was assigned as 7-hydroxy-6: 8: 4′-trinitroflavone (VI). Attempts to further nitrate the compound only resulted in rupture of the γ-pyrone ring, *p*-nitrobenzoic being isolated. As before, the mono- and di-nitro-derivatives of 7-methoxy flavone (I: R = CH_3; R_1 = Ph) were found to be identical with the methyl ethers of the corresponding hydroxynitroflavones, showing that they underwent similar substitution.

The marked reactivity of the 8-position in 7-hydroxychromones has been observed before and is evident from the formation of the 8-aldehyde by the action of formylating agents on 7-hydroxy-3-methoxyflavone.[9] It is the 8-position which is involved in the Fries migration of 7-acetoxy-2-methylchromone[10] and in the Claisen transformation of the alkyl ethers of 7-hydroxyflavone and 7-hydroxy-2-methyl-3-methoxychromone.[11] The results of the present study are in line with the above observations demonstrating the Mills-Nixon effect in 7-hydroxychromones.[12]

Experimental

7-Hydroxy-8-nitro-2-methylchromone

7-Hydroxy-2-methylchromone,[13] m.p. 249° C. (1 g.) in concentrated sulphuric acid (5 c.c.) was treated with nitric acid (d. 1·42; 5 c.c.) at 0° C. gradually with stirring. After standing at 0° C. for 4 hours the contents were poured over crushed ice and the yellow solid collected and washed. On crystallisation from alcohol it yielded dark yellow rhombic plates, m.p. 268° C. (Found: N, 6·5. $C_{10}H_7O_5N$ requires N, 6·3 per cent.). Soluble in alcohol ether and benzene and gave reddish brown coloration with alcoholic ferric chloride. *Acetyl* derivative, light brown needles from alcohol, m.p. 164° C. (Found: N, 5·5. $C_{12}H_9O_6N$ requires N, 5·3 per cent.).

Hydrolysis of 7-Hydroxy-8-nitro-2-methylchromone

The solution of the chromone (1 g.) in caustic soda (4 per cent.; 25 c.c.) was heated on a steam-bath for 2 hours, cooled and acidified. It was extracted with ether, the extract washed and dried and ether removed. The oily residue with a smell resembling that of *o*-nitrophenol was crystallised from aqueous alcohol in orange prisms, m.p. 84° C. It did not depress the melting point of an authentic sample of 2-nitroresorcinol, m.p. 84° C., prepared by the method of Hodgson and Dyson.[14]

7-Methoxy-8-nitro-2-methylchromone

7-Methoxy-2-methylchromone[13] was prepared from 7-hydroxy-2-methylchromone (1 g.) by methylation with methyl iodide (5 g.) and potassium

carbonate in dry acetone (50 c.c.). The mixture was refluxed for 24 hours, acetone removed and diluted with water. The light brown solid was washed with dilute alkali and crystallised from dilute alcohol, white needles, m.p. 112° C. Kostanecki and Rozycki[13] give m.p. 113° C. It was dissolved in concentrated sulphuric acid (5 c.c.) and nitrated with nitric acid (d. 1·42; 5 c.c.) at 0° C. After keeping for two hours it was worked up as before when the nitro compound separated as white plates from alcohol, m.p. 211° C. (Found: N, 6·2. $C_{11}H_9O_5N$ requires N, 6·0 per cent.). It did not depress the melting point of the methyl ether of 7-hydroxy-8-nitro-2-methylchromone prepared as below.

7-Hydroxy-8-nitro-2-methylchromone (1·5 g.) was suspended in absolute alcohol (20 c.c.) and caustic soda solution (25 per cent.; 1 c.c.) added and stirred. After two hours in a refrigerator the orange-yellow sodium salt was collected, washed with absolute alcohol and dried at 120° C. for 4–5 hours. It (1 g.) was heated with dry toluene (15 c.c.) and freshly distilled dimethyl sulphate (5 c.c.) on an oil-bath at 120° C. for 4 hours. After steam-distillation the remaining solution was filtered hot. The crystals which separated on standing, collected washed with dilute alkali and crystallised from alcohol, tiny white plates, m.p. 211° C.

7-Hydroxy-6: 8-dinitro-2-methylchromone

7-Hydroxy-2-methylchromone (1 g.) in concentrated sulphuric acid (10 c.c.) at 0° C. was treated with nitric acid (d. 1·5; 5 c.c.) slowly with stirring, the temperature being maintained below 10° C. The mixture was left at room temperature (30° C.) and the next day worked up as before. After three crystallisations from alcohol the dinitro compound was obtained in yellow plates, m.p. 233° C. (Found: N, 10·3. $C_{10}H_6O_7N_2$ requires N, 10·5 per cent.). Dissolves in soda bicarb. and gives reddish brown coloration with alcoholic ferric chloride.

The same 7-hydroxy-6: 8-dinitro-2-methylchromone was obtained on further nitration of 7-hydroxy-8-nitrochromone with concentrated sulphuric and fuming nitric acid (d. 1·5; 5 c.c.) at 30° C.

Hydrolysis of 7-Hydroxy-6: 8-dinitro-2-methylchromone

The dinitrochromone (1 g.) was hydrolysed by heating its solution in caustic soda (4 per cent.; 20 c.c.) on a steam-bath for two hours. The light brown substance obtained on cooling and acidification, after three crystallisations from alcohol, gave pale yellow tiny crystals, m.p. 167° C. More of the same compound was obtained on extraction of the filtrate with ether. It did not depress the melting point of 3: 5-dinitroresacetophenone prepared as below.

3 : 5-Dinitroresacetophenone

3 : 5-Dinitroresacetophenone does not appear to have been prepared by direct nitration of resacetophenone. Adams[15] isolated it in an attempt to nitrate 4-O-acetylresacetophenone. In the present case it was prepared by direct nitration of resacetophenone as follows.

Resacetophenone (5 g.) was dissolved in acetic acid (20 c.c.) and nitric acid (d. 1·42; 15 c.c.) was slowly added. After the vigorous reaction subsided, it was heated on a steam-bath for 15 minutes and poured on crushed ice. 3 : 5-Dinitroresacetophenone that separated was crystallised from alcohol several times when yellow crystals, m.p. 167° C., were obtained. Adams [15] gives the same melting point.

7-Methoxy-6 : 8-dinitro-2-methylchromone

7-Methoxy-2-methylchromone was nitrated under identical conditions used for the dinitro of the hydroxychromone when 7-methoxy-6 : 8-dinitrochromone separated on diluting the reaction mixture with water. It was obtained first from hot water and then from alcohol in long rectangular plates, m.p. 114° C. (Found: N, 10·2. $C_{11}H_8O_7N_2$ requires N, 10·0 per cent.). It did not depress the melting point of the methyl ether of the dinitro-hydroxychromone prepared as below.

A solution of sodium hydroxide (25 per cent; 2 c.c.) was added to 7-hydroxy-6 : 8-dinitro-2-methylchromone (2 g.) suspended in alcohol (25·30 c.c.). On standing the yellow sodium salt separated which was collected and dried as before. The sodium salt (1 g.), dimethyl sulphate (5 c.c.) and toluene (15 c.c.) were refluxed on an oil-bath at 125° C. for 24 hours, and worked up as before. It crystallised from alcohol, white plates, m.p. 114° C.

Action of nitric acid on 7-Hydroxy-2-methylchromone at 100° C.

7-Hydroxy-2-methylchromone (1 g.) in acetic acid (10 c.c.) was heated with nitric acid (d. 1·42; 5 c.c.) on a water-bath for 4 hours and worked up as before when a nitro-acid, m.p. 205° C., was obtained which was identified as 3 : 5-dinitro-β-resorcylic acid.[16]

If however the experiment was repeated in concentrated sulphuric cid (10 c.c.) with concentrated nitric acid (d. 1·42; 5 c.c.) or fuming nitric acid (5 c.c.), the product was found to be 3 : 5-dinitroresacetophenone, m.p. 167° C.

Similar results were obtained on attempting to further nitrate 7-hydroxy-6 : 8-dinitro-2-methylchromone.

7-Hydroxy-8-nitroflavone

7-Hydroxyflavone,[17] m.p. 240° C. (1 g.) was added in very small amounts to a cooled mixture of concentrated sulphuric acid (5 c.c.) and nitric acid (d. 1·42; 5 c.c.) with stirring. After leaving at room temperature overnight, it was poured into ice-cold water, the solid collected and washed. It was boiled with little alcohol (10 c.c.), collected and crystallised from a mixture of pyridine and acetic acid, tiny crystals, m.p. 300° C. (approx.) (Found: N, 4·8. $C_{15}H_9O_5N$ requires N, 4·9 per cent.). Faint coloration with alcoholic ferric chloride. *Acetyl* derivative, light brown needles from acetic acid, m.p. 256°–57° C. (Found: N, 4·5. $C_{17}H_{11}O_6N$ requires N, 4·3 per cent.).

Hydrolysis of 7-Hydroxy-8-nitroflavone

The nitroflavone (1 g.) in caustic soda (4 per cent.; 25 c.c.) was refluxed for 3 hours. It was cooled and filtered and the filtrate shaken with ether. The residue after removal of ether was dissolved in water and steam-distilled. The distillate extracted with ether, the extract dried and ether removed. The residue was crystallised from alcohol (50%) when orange crystals of 2-nitroresorcinol m.p. 84° C. were obtained.

7-Methoxy-8-nitroflavone

7-Hydroxyflavone (1 g.), anhydrous potassium carbonate (10 g.) and methyl iodide (10 g.) in dry acetone (50 c.c.) were refluxed gently for 24 hours, acetone removed and diluted with water. After washing with caustic soda solution (2 per cent.), the methyl ether was crystallised thrice from alcohol, white needles, m.p. 110° C. Emilewiz and Kostanecki[18] and Turner and Robinson[19] give the same melting point. The methyl ether (1 g.) was added in small amounts to a cooled mixture of concentrated sulphuric acid and nitric acid and left overnight at room temperature. The crude product was boiled with dilute alcohol (50 per cent.; 10 c.c.) and crystallised from acetic acid, white needles, m.p. 300° C. (Found: N, 4·8. $C_{16}H_{11}O_5N$ requires N, 4·7 per cent.). It did not depress the melting point of the methyl ether of hydroxy nitroflavone prepared below.

The dry sodium salt of 7-hydroxy-8-nitroflavone (1 g.), prepared by treating the flavone in alcohol suspension with strong caustic soda solution, dimethyl sulphate (5 c.c.) and dry toluene (15 c.c.) were heated for 6 hours at 125° C. (oil-bath). It was worked up as before and the residue after steam distillation filtered and the solid boiled with caustic soda (2 per cent.) for 15 seconds, washed and crystallised from acetic acid, m.p. 300° C.

7-Hydroxy-6: 8-dinitroflavone

Nitric acid (d. 1·42; 5 c.c.) was added to 7-hydroxyflavone (1 g.) in acetic acid (7 c.c.) and heated on a steam-bath for 20 minutes. The light

yellow needles which separated were collected after cooling and washed with acetic acid, m.p. 288°–89° C. (Found: N, 8·8. $C_{15}H_8O_7N_2$ requires N, 8·5 per cent.).

7-Hydroxy-8-nitroflavone on further nitration with nitric acid in sulphuric acid yielded the same dinitroflavone, m.p. 288°–89° C.

On hydrolysis by refluxing with sodium hydroxide solution (10 per cent.) for about 3 hours yielded 3: 5-dinitro-resacetophenone, m.p. 167° C.

7-Methoxy-6: 8-dinitroflavone

7-Methoxyflavone (1 g.), acetic acid (7 c.c.) and nitric acid (d. 1·42; 5 c.c.) were heated on a steam-bath for 20 minutes and poured into ice-cold water. The product was washed and crystallised from alcohol, m.p. 221° C. (Found: N, 8·1. $C_{10}H_{10}O_7N_2$ requires N, 8·2 per cent.). It did not depress the melting point of the product obtained by methylation of 7-hydroxy-6: 8-dinitroflavone (below).

The sodium salt of 7-hydroxy-6: 8-dinitroflavone prepared as before (0·8 g.) was refluxed with toluene (10 c.c.) and dimethyl sulphate (5 c.c.) at 125° C. for 6 hours. It was worked up as before and the residue after steam distillation suspended in alcohol and caustic soda (few drops of 25 per cent.) added to convert the unreacted hydroxy compound into the sodium salt. The mixture was filtered and washed with cold alcohol. It was then boiled with water to remove the sodium salt, the solution filtered hot and the residue washed with hot water. On crystallisation from alcohol it furnished white needles, m.p. 222° C.

7-Hydroxy-6: 8: 4′-trinitroflavone

7-Hydroxyflavone (1 g.) was added to nitric acid (d. 1·42; 10 c.c.) and heated gently on a steam-bath until the vigorous evolution of the fumes subsided. After half an hour it was poured over crushed ice and the solid crystallised several times from acetic acid when pale yellow needles, m.p. 300°–05° C. were obtained (Found: N, 11·1. $C_{15}H_7O_9N_3$ requires N, 11·3 per cent.).

The trinitro derivative could also be prepared by treating 7-hydroxy-6: 8-dinitroflavone with nitric acid (d. 1·42; 10 c.c.) on a steam-bath for half an hour.

Hydrolysis of 7-Hydroxy-6: 8: 4′-trinitroflavone

The trinitroflavone (1 g.) was refluxed with sodium hydroxide solution (2 N.) for 4 hours. On cooling and acidification a yellow substance gradually separated. It was crystallised from acetic acid, tiny yellow needles, m.p.

237° C. It did not depress the melting point of an authentic specimen of para-nitrobenzoic acid. No other product could be isolated in a pure state.

Action of nitric acid on 7-hydroxyflavone on steam-bath

7-Hydroxyflavone (1 g.) in concentrated sulphuric acid (10 c.c.) and nitric acid (d. 1·42; 5 c.c.) were heated on a steam-bath for 4 hours and the reaction mixture worked up as usual when *p*-nitrobenzoic acid, m.p. 237° C., was obtained.

SUMMARY

No systematic study of the nitration of chromones appears to have been carried out previously, though a few naturally occurring flavones have been nitrated. In the present work, nitration of 7-hydroxy-2-methyl-chromone and 7-hydroxyflavone and their methyl ethers has been studied. The mononitro-derivatives have been found to be 8-nitro compounds while the di-derivatives were 6: 8-dinitro products. 7-Hydroxyflavone gave also a trinitro derivative which was found to be 7-hydroxy-6: 8: 4′-trinitroflavone. The constitutions of the nitro compounds were proved by alkaline hydrolysis.

The authors wish to express their thanks to Dr. V. M. Thakor for his keen interest in the work.

REFERENCES

1. Piccard .. *J. Chem. Soc.*, 1873, 1236.
   Darrier .. *Ber.*, 1894, **27**, 21, 1045.
2. Perkin .. *J. Chem. Soc.*, 1900, **77**, 416.
3. Watson .. *Ibid.*, 1914, **105**, 338.
   ——— and Sen .. *Ibid.*, p. 389.
4. Perkin and Watson .. *Ibid.*, 1915, **107**, 198.
5. Petschek and Simonis .. *Ber.*, 1913, **46**, 2014.
6. Simonis and Herovici .. *Ibid.*, 1917, **50**, 787.
7. Bogert and Marcus .. *J. Am. Chem. Soc.*, 1919, **41**. 83.
8. Simonis .. *Ber.*, 1917, **50**, 779.
   Wittig .. *Ibid.*, 1924, **57**, 88.
9. Rangaswami and Seshadri *Proc. Ind. Acad. Sci.*, 1939, **9 A**, 7.
10. Wittig, Bangert and Reichert .. *Ann.*, 1925, **446**, 155.
11. Rangaswami and Seshadri .. *Proc. Ind. Acad. Sci.*, 1939, **9A**, 1.
12. Mills and Nixon .. *J. Chem. Soc.*, 1930, 2510.
    Rangaswami and Seshadri *Proc. Ind. Acad. Sci.*, 1941, **14 A**, 547.
13. Kostanecki and Rozycki .. *Ber.*, 1901, **34**, 102.
14. Hodgson and Dyson .. *J. Chem. Soc.*, 1935, 946.
15. Adams .. *J. Am. Chem. Soc.*, 1919, **41**, 264.
16. Hemmelmayr .. *Monatsh.*, 1905, **26**, 185; 1912, **33**, 971; 1913, 34, 378.
    Einback and Jablonski .. *Ber.*, 1923, **56 B**, 1906.
17. Venkataraman and Robinson .. *J. Chem. Soc.*, 1926, 2345.
18. Emilewiz and Kostanecki *Ber.*, 1899, **32**, 312.
19. Robinson and Turner .. *J. Chem. Soc.*, 1918, **113**, 874.