

CHROMONES

Part IV. Nitration of 5-Hydroxychromone Derivatives and Their Methyl Ethers

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IN continuation of the work earlier reported on nitration of chromones,¹ nitration of 5-hydroxy-2-methylchromone, 5-hydroxy-flavone and their methyl ethers has now been investigated and the constitution of the products established.

Nitration of 5-hydroxy-2-methylchromone (I, R = H, R₁ = Me) with nitric acid (d. 1.42) in acetic acid or concentrated sulphuric acid at 0° gave a mononitro derivative, m.p. 218°. On alkaline hydrolysis it furnished 2:6-dihydroxy-3-nitroacetophenone (II). As is obvious, the constitution of the mononitro derivative could not be determined by alkaline degradation as both the 6-nitro (V, R = H, R₁ = Me) and 8-nitro (III, R = H, R₁ = Me) chromones would yield a 4-nitroresorcinol derivative.

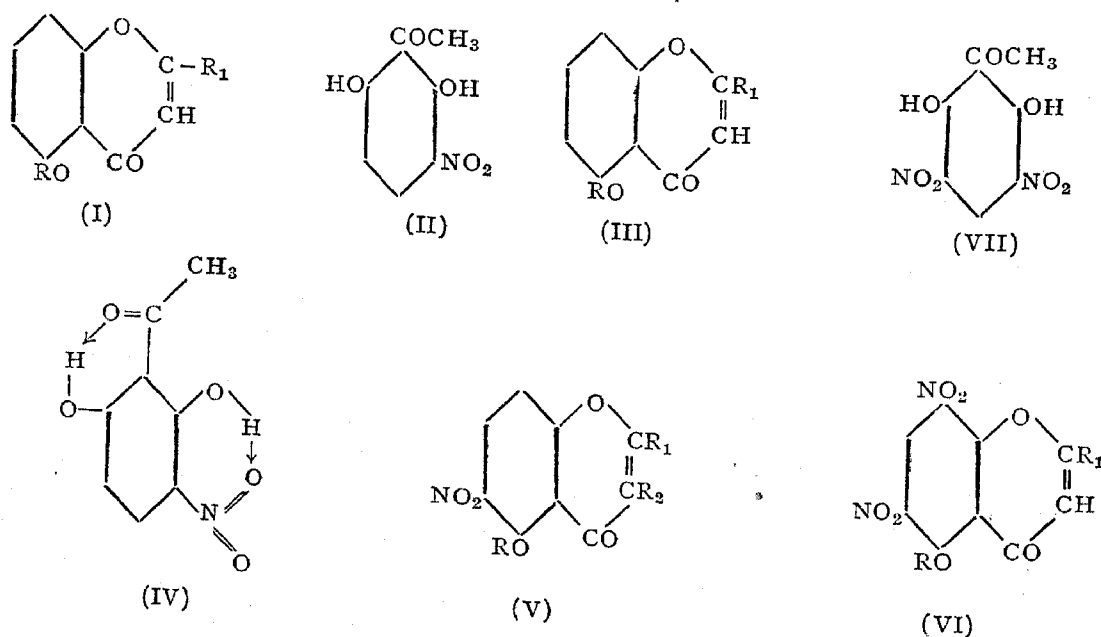
5-Hydroxy-2-methyl-6-nitrochromone (m.p. 161°) has been recently synthesised by Naik and Thakor,² by Kostanecki-Robinson acetylation of 2:6-dihydroxy-3-nitroacetophenone (II). As stated by them, due to its doubly chelated structure, this compound (IV) could be expected to give a 6-nitrochromone derivative (V, R = H; R₁ = Me). Hence, the mononitro product, m.p. 218°, must be 5-hydroxy-2-methyl-8-nitrochromone (III, R = H, R₁ = Me).

It is interesting to note that while 5-hydroxy-2-methyl-6-nitrochromone (V, R = H, R₁ = Me), like simple 5-hydroxy-2-methyl-chromone,³ on alkaline degradation underwent ketone splitting to give 4-nitroresorcinol presumably through the corresponding γ -resorcylic acid derivative,² in the present case the 8-nitro isomer (III, R = H, R₁ = Me) on hydrolysis furnished 2:6-dihydroxy-3-nitroacetophenone (II).

When the nitration was carried out at 100° with nitric acid (d. 1.42) in acetic acid, a dinitro derivative, m.p. 204-05° was obtained. The same product was also obtained on nitration of 5-hydroxy-2-methyl-6-nitrochromone (V, R = H, R₁ = Me) and 5-hydroxy-2-methyl-8-nitrochromone

(III, $R = H$, $R_1 = Me$) and on alkaline hydrolysis it furnished 2:6-dihydroxy-3:5-dinitroacetophenone (VII). The product was, therefore, 5-hydroxy-2-methyl-6:8-dinitrochromone (VI, $R = H$, $R_1 = Me$).

The hitherto unknown 5-methoxy-2-methylchromone (I, $R = R_1 = Me$) was prepared by the usual method. On nitration with nitric acid (d. 1.42) and concentrated sulphuric acid at 0° , it gave a mononitro derivative, m.p. 215° . However, 5-hydroxy-2-methyl-8-nitrochromone could not be methylated and the usual methods of demethylation failed in case of this methoxy-nitro derivative. With boiling sodium hydroxide solution it furnished 2-acetyl-4-nitroresorcinol, demethylation and degradation occurring simultaneously. On keeping it with aqueous sodium hydroxide at room temperature (30°) however, 5-hydroxy-2-methyl-8-nitrochromone (III, $R = H$, $R_1 = Me$) was obtained. Demethylation also occurred with boiling alcoholic potassium hydroxide. Hence the product was 5-methoxy-2-methyl-8-nitrochromone (III, $R = R_1 = Me$). Thus, during alkaline hydrolysis, presumably demethylation precedes degradation.



Further nitration of 5-methoxy-2-methyl-8-nitrochromone, with nitric acid (d. 1.42) and sulphuric acid at room temperature (30°) furnished 5-hydroxy-2-methyl-6:8-dinitrochromone, demethylation occurring simultaneously. This further indicates the labile nature of the methoxy group in these nitrochromones.

5-Hydroxyflavone (I, $R = H$, $R_1 = Ph$) when treated with nitric acid (d. 1.42) in sulphuric acid at 0° afforded a mononitro derivative, m.p.

225–26°, which on alkaline hydrolysis gave 2:6-dihydroxy-3-nitroacetophenone (II). It has been assigned the constitution, 5-hydroxy-8-nitroflavone (III, $R = H$, $R_1 = Ph$), as it was different from 5-hydroxy-6-nitroflavone (V, $R = H$, $R_1 = Ph$), m.p. 209°, obtained by Naik and Thakor² on Kostanecki-Robinson benzoylation of 2:6-dihydroxy-3-nitroacetophenone (II) and subsequent hydrolysis of 5-hydroxy-3-benzoyl-6-nitroflavone obtained.

Nitration of the flavone (I, $R = H$, $R_1 = Ph$) at 100° afforded a dinitro derivative, 5-hydroxy-6:8-dinitroflavone, m.p. 253–54° (V, $R = H$, $R_1 = Ph$). It was also obtained on further nitration of 5-hydroxy-6-nitroflavone (V, $R = H$, $R_1 = Ph$) and 5-hydroxy-8-nitroflavone (III, $R = H$, $R_1 = Ph$) and on hydrolysis gave 2:6-dihydroxy-3:5-dinitroacetophenone (VII).

6-Methoxyflavone (I, $R = Me$, $R_1 = Ph$) on nitration with nitric acid (d. 1.42) and sulphuric acid at 0° afforded a dinitro derivative. On hydrolysis with aqueous sodium hydroxide, 2:6-dihydroxy-3-nitroacetophenone (II) was obtained, indicating only one nitro group in the benzene ring. Attempt to isolate any mononitrobenzoic acid, which may be formed as one of the products of hydrolysis, if the other nitro group is in the phenyl ring, proved futile. It could not be demethylated under the usual conditions, adopted in previous cases. The constitution of this compound thus could not be established. However, the nitro group in the benzene ring may be considered to be in 8-position rather than 6- from analogy with 5-methoxy-2-methylchromone. Tentatively the structure has been assigned as 5-methoxy-8: (?) -dinitroflavone.

Thus in 5-hydroxy-chromones, as would be expected, positions '6' and '8' are reactive. The nitration first takes place in the 8-position. It may be noted that on Fries rearrangement of 5-acetochromone derivatives the migration occurs to the 6-position.⁴ Analogous behaviour has been observed in the coumarin series. Thus while Fries transformation of 5-acyloxy-coumarins furnishes 6-acyl derivatives,⁵ nitration leads to 8-nitrocoumarins.⁶

EXPERIMENTAL

Nitration of 5-Hydroxy-2-methylchromone (I, $R = H$, $R_1 = Me$) at 0°:
5-Hydroxy-2-methyl-8-nitrochromone (III, $R = H$, $R_1 = Me$)

5-Hydroxy-2-methylchromone,⁷ m.p. 92° (1.0 g.) in acetic acid (10.0 c.c.) was treated with nitric acid (d. 1.42; 5.0 c.c.) at 0° and the mixture kept at that temperature for 2 hours. On dilution a brownish yellow precipitate was obtained and was crystallised from acetic acid in almost colourless plates,

m.p. 218° (Found: N, 6.5. $C_{10}H_7O_5N$ requires N, 6.3%). 5-Hydroxy-2-methyl-8-nitrochromone (III, $R = H$, $R_1 = Me$) is sparingly soluble in alcohol and difficultly in benzene and ether. It gives dark red coloration with alcoholic ferric chloride. It is sparingly soluble in sodium hydroxide, insoluble yellow sodium salt separating out. Acetyl derivative separated as colourless needles from alcohol, m.p. 196–97° (Found: N, 5.5. $C_{12}H_9O_6N$ requires N, 5.3%).

The same mononitro compound was obtained when the nitration was carried out with nitric acid (d. 1.42; 5.0 c.c.) in concentrated sulphuric acid (10 c.c.) at 0°.

Attempts to methylate the compound with sodium hydroxide-dimethyl sulphate or methyl iodide-potassium carbonate (acetone) met with failures; similar also was the result when its sodium salt and dimethyl sulphate were refluxed in toluene or nitrobenzene.

Hydrolysis of 5-Hydroxy-2-methyl-8-nitrochromone (III, $R = H$, $R_1 = CH_3$):
2:6-Dihydroxy-3-nitroacetophenone (II)

5-Hydroxy-2-methyl-8-nitrochromone (1.0 g.) was boiled with sodium hydroxide solution (6%; 25 c.c.) for 2 hours, cooled and acidified. The brown solid obtained on standing was collected and crystallised from dilute alcohol (50%) in yellow needles, m.p. 119°. Mixed melting point with an authentic specimen of 2:6-dihydroxy-3-nitroacetophenone (II)⁸ was not lowered.

Nitration of 5-Hydroxy-2-methylchromone (I, $R = H$, $R_1 = Me$) at 100° :
5-Hydroxy-2-methyl-6:8-dinitrochromone (VI, $R = H$, $R_1 = Me$)

A mixture of 5-hydroxy-2-methylchromone (0.5 g.), acetic acid (10.0 c.c.) and nitric acid (d. 1.42; 5.0 c.c.) was heated on a steam-bath for half an hour and cooled. The yellow solid obtained on dilution was crystallised from acetic acid, yellow needles, m.p. 204–05° (Found: N, 10.3. $C_{10}H_6O_7N_2$ requires N, 10.5%). It is sparingly soluble in benzene and alcohol. It gives red coloration with alcoholic ferric chloride and is insoluble in alkali, the insoluble sodium salt separating out. Acetyl derivative was obtained in needles from alcohol, m.p. 155° (Found: N, 9.3. $C_{12}H_7O_8N_2$ requires N, 9.1%). Attempts at methylation of the product proved fruitless.

5-Hydroxy-2-methyl-6:8-dinitrochromone (VI, $R = H$, $R_1 = Me$) was also obtained on nitration of 5-hydroxy-2-methyl-6-nitrochromone² (V, $R = H$, $R_1 = Me$) (0.5 g.) in acetic acid (10.0 c.c.) and nitric acid (d. 1.42; 5.0 c.c.) or 5-hydroxy-2-methyl-8-nitrochromone (III, $R = H$, $R_1 = Me$) (0.5 g.) in

acetic acid (10.0 c.c.) and nitric acid (d. 1.42; 5.0 c.c.) on a steam-bath for half an hour.

The above dinitrochromone (VI, $R = H$, $R_1 = Me$) (1.0 g.) on hydrolysis with boiling sodium hydroxide solution (2 N; 20 c.c.) for 4 hours furnished 2:6-dihydroxy-3:5-dinitroacetophenone⁸ (VII), crystallised from dilute alcohol, m.p. and mixed m.p. 104°.

2:6-Dihydroxy-3:5-dinitroacetophenone (VII)

It was prepared by nitration of 2-acetylresorcinol by slightly modifying the method of Naik and Jadhav.⁹

Nitric acid (1.42 d.; 10.0 c.c.) was added dropwise with stirring to a solution of 2-acetylresorcinol (2.0 g.) in glacial acetic acid (20.0 c.c.) cooled to 5°. It was then kept at that temperature for 2 hours with occasional shaking. Steam was passed to remove any mononitro derivative. The residual liquid on cooling gave yellow crystals of 2:6-dihydroxy-3:5-dinitroacetophenone (VII). The mother-liquor on ether extraction gave a further quantity of the same. It was crystallised from boiling water in shining yellow needles, m.p. 104–05° (1.4 g.).

5-Methoxy-2-methylchromone (I, $R = R_1 = Me$)

5-Hydroxy-2-methylchromone (1.0 g.), dry potassium carbonate (5.0 g.), methyl iodide (4.0 c.c.) and dry acetone (50 c.c.) were refluxed on a warm water-bath for 24 hours. More methyl iodide (4.0 c.c.) was added and the mixture refluxed for further 24 hours. After filtering off the solid, acetone was removed and the mixture diluted with water. The oil that separated was washed with dilute sodium hydroxide solution and taken up in ether. On removing ether after drying, an oil was obtained which solidified on keeping in a desiccator under vacuum for 24 hours. It was crystallised from alcohol (95%) in colourless cubes, m.p. 102–03° (Found: C, 69.0; H, 5.3. $C_{11}H_{10}O_3$ requires C, 69.4; H, 5.2%). It does not give any coloration with alcoholic ferric chloride solution.

*Nitration of 5-Methoxy-2-methylchromone (I, $R = R_1 = Me$) at 0° :
5-Methoxy-2-methyl-8-nitrochromone (III, $R = R_1 = Me$)*

5-Methoxy-2-methylchromone (1.0 g.) was cooled externally to 0°, and a cooled mixture of concentrated sulphuric acid (5.0 c.c.) and nitric acid (d. 1.42; 5.0 c.c.) was added gradually with stirring. The mixture was left at 0° for one and half hours, poured into crushed ice, and the nitro compound that separated was collected, washed and crystallised from acetic acid in soft pale yellow plates, m.p. 215° (Found: N, 6.2. $C_{11}H_9O_5N$

requires N, 6.0%). Mixed m.p. with 5-hydroxy-2-methyl-8-nitrochromone was considerably depressed. It does not give any coloration with alcoholic ferric chloride solution. It gives no coloration with alkali, but turns yellow on keeping with it. Attempts to further nitrate the chromone (III, $R = R_1 = \text{Me}$) with nitric acid (d. 1.42) in acetic acid at 0°, 30° or 100° met with failures.

The nitrochromone (0.5 g.) was boiled with sodium hydroxide solution (10%; 10 c.c.) on a wire-gauze for about an hour when the whole of it went into solution. It was cooled and acidified and the product crystallised from alcohol (95%) in pale yellow needles, m.p. and mixed m.p. with 2:6-dihydroxy-3-nitroacetophenone (II), 119°.

Attempts at demethylating the nitrochromone with hydriodic acid in acetic anhydride or anhydrous aluminium chloride in nitrobenzene did not furnish any definite product. However, demethylation could be effected with aqueous or alcoholic alkali. The nitrochromone (0.5 g.) was refluxed with alcoholic potassium hydroxide on a warm water-bath for half an hour. Alcohol was removed and the yellow salt that remained was acidified and crystallised from acetic acid when 5-hydroxy-2-methyl-8-nitrochromone (III, $R = \text{H}$, $R_1 = \text{Me}$), m.p. and mixed m.p. 218°, was obtained. The same product was also obtained along with some 2:6-dihydroxy-3-nitroacetophenone when the nitrochromone (0.2 g.) was kept with sodium hydroxide solution (10%; 20 c.c.) at room temperature for 72 hours.

Nitration of 5-Methoxy-2-methyl-8-nitrochromone (III, $R = R_1 = \text{Me}$) at 28–30°: 5-Hydroxy-2-methyl-6:8-dinitrochromone (VI, $R = \text{H}$, $R_1 = \text{Me}$)

The nitrochromone (III, $R = R_1 = \text{Me}$) (0.5 g.) at 0° (external) was treated with a cooled mixture of concentrated sulphuric acid (5.0 c.c.) and nitric acid (d. 1.42; 5.0 c.c.). It was kept at room temperature (28–30°) for 20 hours and then poured into crushed ice. The yellow solid obtained was crystallised from acetic acid, and was identified as 5-hydroxy-2-methyl-6:8-dinitrochromone (VI, $R = \text{H}$, $R_1 = \text{Me}$), m.p. and mixed m.p. 204–05°.

5-Hydroxyflavone (I, $R = \text{H}$, $R_1 = \text{Ph}$)

It was prepared by the general method given by Virkar.¹⁰

2:6-Dibenzoyloxyacetophenone,¹¹ m.p. 105° (7.0 g.), was added to pulverised sodium (0.46 g.) in dry toluene (30 c.c.) and the mixture was heated at 130° for 8 hours. The separated sodium salt was collected and washed thoroughly with benzene. It was acidified with dilute acetic acid. 5-Hydroxy-3-benzoylflavone obtained was crystallised from glacial acetic

acid in yellow shining needles, m.p. 175°. Baker¹¹ had used anhydrous potassium carbonate and gives m.p. 177°; Sugasawa¹² gives m.p. 173–74°.

The debenzoylation could best be effected according to the method of Rajagopalan, Rao and Seshadri.¹³ The above 3-benzoylflavone was gently refluxed with aqueous alcoholic sodium carbonate (5.0%; 200 c.c.) for 2 hours. The alcohol was removed under reduced pressure, the residue acidified and the brown solid crystallised from alcohol in pale yellow needles, m.p. 157° (2.0 g.). Sugasawa¹² gives m.p. 156–57°.

Nitration of 5-Hydroxyflavone (I, R = H, R₁ = Ph) at 0°: 5-Hydroxy-8-nitroflavone (III, R = H, R₁ = Ph)

5-Hydroxyflavone (0.5 g.) was treated with a mixture of sulphuric acid (5.0 c.c.) and nitric acid (d. 1.42; 5.0 c.c.) at 0° and left at that temperature for an hour. After working up as usual, the *nitroflavone* obtained was crystallised from acetic acid as fine crystals, which shrank at 200 and m.p. 225° (Found: N, 4.8. C₁₅H₉O₅N requires N, 4.9%). Mixed melting point with 5-hydroxy-6-nitroflavone (m.p. 209°) was considerably depressed. It gives red coloration with alcoholic ferric chloride. It dissolves in sodium hydroxide on warming giving a yellow solution. It is sparingly soluble in hot alcohol and insoluble in ether and benzene. All attempts at its methylation were unsuccessful. *Acetyl* derivative, crystallised from alcohol, m.p. 239° (Found: N, 4.5. C₁₇H₁₁O₆N requires N, 4.3%).

It was hydrolysed with sodium hydroxide solution (2 N) as usual when 2: 6-dihydroxy-3-nitroacetophenone (II), m.p. 119°, was obtained.

Nitration of 5-Hydroxyflavone (I, R = H, R₁ = Ph) at 100°: 5-Hydroxy-6: 8-dinitroflavone (VI, R = H, R₁ = Ph)

5-Hydroxyflavone (0.5 g.) in acetic acid (5.0 c.c.) was gradually treated with nitric acid (d. 1.42; 50 c.c.) when after about 5 minutes the mononitro derivative (III, R = H, R₁ = Ph) separated. The mixture was heated on a steam-bath for 15 minutes, when the mononitro product went in solution and the *dinitroflavone* (VI, R = H, R₁ = Ph) separated in tiny canary yellow plates, recrystallised from acetic acid, m.p. 253–54° (Found: N, 8.8. C₁₅H₈O₇N₂ requires N, 8.5%). It is sparingly soluble in boiling alcohol, insoluble in ether and benzene and easily soluble in acetic acid and acetone. It gives red coloration with alcoholic ferric chloride. With aqueous sodium hydroxide it gives an orange-yellow solution, while the sodium salt gets precipitated. *Acetyl* derivative, crystallised from acetic acid, m.p. 264–65° (Found: N, 7.8. C₁₇H₁₀O₈N₂ requires N, 7.6%).

The same dinitroflavone was also obtained on nitration of 5-hydroxy-6-nitroflavone² (V, R = H, R₁ = Ph) or 5-hydroxy-8-nitroflavone (III, R = H, R₁ = Ph) (0.5 g.) with nitric acid (d. 1.42; 5.0 c.c.) in acetic acid (10 c.c.) on a steam-bath for half an hour.

The dinitroflavone (VI, R = H, R₁ = Ph) (1.0 g.) was hydrolysed by 4 hours boiling with sodium hydroxide solution (2 N, 20 c.c.) when 2:6-dihydroxy-3:5-dinitroacetophenone (VII), m.p. and mixed m.p. 104° was obtained.

Nitration of 5-Methoxyflavone (I, R = Me, R₁ = Ph) at 0°: 5-Methoxy-8: (?) -dinitroflavone

5-Methoxyflavone (0.5 g.) was cooled to 0° (external) and a cooled mixture of sulphuric acid (5 c.c.) and nitric acid (5 c.c.; d. 1.42) was added gradually with stirring. It was kept at 0° for one and half hours and then poured into crushed ice. The nitro compound which separated was filtered, washed and crystallised from acetic acid, m.p. 267°. It analysed for a dinitroflavone derivative (Found: N, 8.4. C₁₆H₁₀O₇N₂ requires N, 8.2%). It did not give any coloration with alcoholic ferric chloride.

The same product was obtained even if the reaction mixture was kept for 20 minutes only. Attempts to get a mononitro derivative by treating the flavone (I, R = Me, R₁ = Ph) with (i) nitric acid (5 c.c.; 1.42) and acetic acid (5 c.c.) at 100° for half an hour or (ii) with fuming nitric acid (5 c.c.) and acetic acid (5 c.c.) at 100° for half an hour were fruitless. The original compound was recovered unaffected.

Attempts to demethylate the dinitroflavone with hydriodic acid and acetic anhydride or anhydrous aluminium chloride in nitrobenzene were unsuccessful. Unlike 5-methoxy-8-nitrochromone, the dinitroflavone remained unaffected when kept with sodium hydroxide solution (10%) for 8 days or refluxed with alcoholic potassium hydroxide solution for 3 hours.

The dinitroflavone (0.5 g.) was refluxed with sodium hydroxide solution (10%; 90 c.c.) for 5 hours, when part of the substance got hydrolysed furnishing 2:6-dihydroxy-3-nitroacetophenone, m.p. and mixed m.p. 116-17°. The rest was recovered unchanged. No other product (nitrobenzoic acid) could be isolated from the reaction mixture.

Attempts to further nitrate this dinitroflavone met with failures.

SUMMARY

In extension of the previous work,¹ nitration of 5-hydroxy-2-methylchromone, 5-hydroxyflavone and their methyl ethers has been investigated.

The mono derivatives from the hydroxychromones have been found to be the 8-nitro compounds, while the di-derivatives were 6:8-dinitro products. The constitutions of the mononitro derivatives have been assigned as they were different from the products, obtained on Kostanecki acylations of 2:6-dihydroxy-3-nitroacetophenone and subsequent deacylation of the 3-acyl derivatives, which would be expected to be the 6-nitro chromones. The constitutions of dinitro derivatives were established by alkaline hydrolysis. 5-Methoxy-2-methylchromone gave 8-nitro derivative, as on demethylation the corresponding hydroxychromone was obtained. On further nitration demethylation occurred furnishing 5-hydroxy-2-methyl-6:8-dinitrochromone. 5-Methoxy-flavone gave a dinitro derivative to which has been provisionally given the structure 5-methoxy-8-(?)-dinitroflavone.

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