

Chromones and Flavones. Part IV*. Chloromethylation of Some Chromones and Flavones

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Flavone and 2-methylchromone on chloromethylation afford the 3-chloromethyl derivatives. 7-Methoxy-2-methylchromone and 7-methoxyflavone afford similarly the 8-chloromethyl and the 3,8-dichloromethyl derivatives. The structures have been proved by reduction to the corresponding methyl derivatives which have been compared with the authentic specimens.

Nakamura and Matsura¹ chloromethylated acacetin 7-methyl ether and Da Re and co-workers² chloromethylated 7-methoxy-2,3-dimethylchromone, 7-methoxy-3-methylflavone, and 7-methoxy-3-ethylflavone. In all the cases the 8-chloromethyl derivatives were obtained. No other work on chloromethylation of chromones and flavones appears to have been reported.

2-Methylchromone and flavone on chloromethylation with paraformaldehyde and hydrogen chloride gave the 3-chloromethyl derivatives. These were reduced to the corresponding 3-methyl derivatives which were directly compared with authentic specimens. No dichloromethyl derivatives could be prepared even with excess of paraformaldehyde and a catalyst, such as zinc chloride.

7-Methoxy-2-methylchromone and 7-methoxyflavone on a similar chloromethylation with paraformaldehyde gave the 8-chloromethyl derivatives. On reduction they gave the corresponding 8-methyl derivatives, identical with the methylation products of 7-hydroxy-2,8-dimethylchromone and 7-hydroxy-8-methylflavone, which were synthesised by refluxing 2-methylresorcinol with ethyl acetoacetate and ethyl benzoylacetate respectively in boiling diphenyl ether, according to the procedure of Desai *et al.*³ Further chloromethylation of the 8-chloromethyl derivatives or chloromethylation of 7-methoxy-2-methylchromone and 7-methoxyflavone with excess of paraformaldehyde furnished the 3,8-dichloromethyl derivatives. On reduction these furnished the corresponding methyl derivatives which were directly compared with the authentic specimens.

No trichloromethyl derivative could be obtained. Some of the above chloromethyl derivatives have been converted into the methoxymethyl, acetoxymethyl, and cyanomethyl derivatives.

*Part III, *J. Chem. Soc.*, 1961, 2663.

1. *J. Pharm. Soc., Japan*, 1953, 73, 481.

2. *Ann. Chim., Rome*, 1956, 46, 904; *Arzneimittel Forsch.*, 1960, 10, 800.

3. *J. M. S. University, Baroda*, 1955, IV-2, 1.

*EXPERIMENTAL

2-Methyl-3-chloromethylchromone.—A mixture of 2-methylchromone (1.6 g.) in acetic acid (20 ml, 80%) and paraformaldehyde (4.0 g.) was saturated with HCl at 85-90° for 6 hrs. The product, obtained on dilution, crystallised from petroleum ether in colorless needles (58%), m.p. 103-104°. (Found: C, 63.54; H, 3.83; Cl, 16.92. $C_{11}H_9O_2Cl$ requires C, 63.31; H, 4.31; Cl, 17.02%).

The chloromethyl derivative (0.5 g.) in acetic acid (20 ml, 80%) was reduced with zinc dust (1 g.) at 60°. The product crystallised from dilute acetic acid in colorless needles; m.p. and mixed m.p. with 2,3-dimethylchromone⁴, 96-97°.

3-Chloromethylflavone, obtained as above by passing hydrogen chloride in a mixture of flavone (2.22 g.) and paraformaldehyde (5 g.) in acetic acid (25 ml, 80%) at 85-90° for 5 hrs., crystallised from 1:1 mixture of benzene-petroleum ether (b.p. 60-80°) in colorless needles (58%), m.p. 156°. (Found: C, 71.56; H, 3.52; Cl, 13.61. $C_{16}H_{11}O_2Cl$ requires C, 71.00; H, 4.06; Cl, 13.12%).

The chloromethyl derivative was reduced with zinc dust and dilute acetic acid. It was crystallised from dilute ethanol in white needles; m.p. and mixed m.p. with 3-methylflavone⁵, 72-73°.

7-Methoxy-8-chloromethyl-2-methylchromone, obtained from 7-methoxy-2-methylchromone (1.9 g.) in glacial acetic acid (30 ml), paraformaldehyde (3 g.), and zinc chloride (2 g.) by passing hydrogen chloride for 1 hr. at 75-80°, gave lustrous needles (33%) from benzene-petroleum ether mixture, m.p. 153°. (Found: C, 60.23; H, 4.62; Cl, 14.78. $C_{22}H_{11}O_3Cl$ requires C, 60.39; H, 4.61; Cl, 14.88%).

7-Hydroxy-2,8-dimethylchromone.—2-Methylresorcinol (2.48 g.) and ethyl acetoacetate (2.6 g.) were refluxed in diphenyl ether (20 ml) for 2 hrs. The product, obtained on removal of diphenyl ether by steam distillation, crystallised from dilute ethanol in buff needles (42%), m.p. 258°. Dann *et al.*⁶, who prepared it by condensing 2-methylresorcinol with *cis*- β -chlorocrotonate recorded the same m.p. (Found: C, 69.64; H, 5.50. Calc. for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26%).

The *methyl ether* was prepared by refluxing the above chromone (0.5 g.) in acetone with dimethyl sulphate (1 ml) in presence of anhydrous potassium carbonate (2 g.) for 2 hrs. It was crystallised from dilute ethanol in colorless needles; m.p. and mixed m.p. with the product obtained from the reduction of 7-methoxy-8-chloromethyl-2-methylchromone with zinc dust and dilute acetic acid, 144-45°. (Found: C, 70.48; H, 5.88. $C_{12}H_{12}O_3$ requires C, 70.58; H, 5.88%).

7-Methoxy-8-acetoxymethyl-2-methylchromone, prepared by refluxing the chloromethyl product (0.5 g.) in glacial acetic acid (15 ml) and fused sodium acetate (2 g.) for 2 hrs., gave colorless needles from a mixture of benzene-petroleum ether, m.p. 168°. (Found: C, 64.46; H, 5.59. $C_{14}H_{14}O_5$ requires C, 64.11; H, 5.38%).

* All melting points are uncorrected.

4. Robertson *et al.*, *J. Chem. Soc.*, 1931, 2426.

5. Wheeler *et al.*, *ibid.*, 1950, 1252.

6. *Annalen*, 1954, 587, 16.

Methoxy-8-cyanomethyl-2-methylchromone, prepared by refluxing the chloromethyl derivative (0.5 g.) in ethanol (20 ml) with aqueous potassium cyanide (1 g.), afforded colorless needles from ethanol, m.p. 174-75°. (Found: C, 67.70; H, 4.96; N, 6.29. $C_{13}H_{11}O_3N$ requires C, 68.11; H, 4.84; N, 6.11%).

7-Methoxy-3,8-dichloromethyl-2-methylchromone was prepared by further chloromethylation of the 8-chloromethyl derivative (1.2 g.) in glacial acetic acid (25 ml) with paraformaldehyde (0.75 g.) by passing HCl for 6 hrs. at 75-80°. It crystallised from benzene-petroleum ether mixture in colorless needles (35%), m.p. 206-207°. (Found: C, 54.72; H, 4.22; Cl, 24.04. $C_{13}H_{12}O_3Cl_2$ requires C, 54.35; H, 4.18; Cl, 24.47%).

The same dichloromethyl derivative was obtained from 7-methoxy-2-methylchromone (1.9 g.) by chloromethylation with paraformaldehyde (5 g.) and HCl at 85-90° for 4 hrs.

The above chloromethyl derivative was reduced with zinc dust and dilute acetic acid as before and crystallised from dilute ethanol in colorless needles, m.p. 149-50°; mixed m.p. with 7-methoxy-2,3,8-trimethylchromone, prepared according to Da Re and co-workers², was not depressed.

The *diacetoxyethyl* derivative, prepared as usual, crystallised from benzene in colorless needles, m.p. 160-61°. (Found: C, 61.21; H, 5.38. $C_{17}H_{16}O_7$ requires C, 61.07; H, 5.43%).

The *dimethoxyethyl* derivative was prepared by refluxing the dichloromethyl derivative (0.5 g.) with methanol (20 ml) in presence of anhydrous potassium carbonate (2 g.) for 2 hrs. The residue after removal of the solvent crystallised from benzene in colorless needles, m.p. 142°. (Found: C, 64.80; H, 6.25. $C_{15}H_{16}O_5$ requires C, 64.73; H, 6.52%).

The *dicyanomethyl* derivative, prepared as usual, crystallised from dilute acetic acid in colorless needles, m.p. 176-78°. (Found: C, 67.42; H, 4.87; N, 10.6. $C_{15}H_{12}O_3N_2$ requires C, 67.15; H, 4.51; N, 10.44%).

7-Methoxy-8-chloromethylflavone.—A mixture of 7-methoxyflavone (2.52 g.) in acetic acid (30 ml, 80%), paraformaldehyde (0.9 g.), and zinc chloride (2 g.) was treated with HCl at 75-80° for 5 hrs. The product obtained on working up as before crystallised in colorless needles (30%) from benzene-petroleum ether mixture, m.p. 227°. (Found: C, 67.98; H, 4.32; Cl, 12.30. $C_{17}H_{13}O_3Cl$ requires C, 67.88; H, 4.32; Cl, 11.81%).

7-Hydroxy-8-methylflavone.—A mixture of 2-methylresorcinol (2.48 g.) and ethyl benzoylacetate (5.8 g.) was refluxed in diphenyl ether (20 ml) for 2 hrs. The product, obtained on removal of diphenyl ether by steam distillation, crystallised from ethanol in needles (40%), m.p. 255-57°. Rangaswami and Seshadri⁷, who prepared it by the Kostanecki-Robinson benzoylation of 3-methylresacetophenone, recorded the same m.p. (Found: C, 76.46; H, 4.82. Calc. for $C_{16}H_{12}O_3$: C, 76.12; H, 4.80%).

The *methyl ether*, prepared as before, crystallised from dilute ethanol in colorless needles, m.p. and mixed m.p. with the product obtained on reduction of 7-methoxy-8-

chloromethylflavone with zinc dust and dilute acetic acid, 175-76°. (Found: C, 76.55; H, 4.97. $C_{17}H_{14}O_3$ requires C, 76.87; H, 5.30%).

The *acetoxyethyl* derivative, prepared as before, crystallised from benzene-petroleum ether mixture in colorless needles, m.p. 184-85°. (Found: C, 70.06; H, 5.07. $C_{18}H_{16}O_5$ requires C, 70.36; H, 4.98%).

The *methoxymethyl* derivative, prepared as before, crystallised from benzene-petroleum ether mixture in colorless needles, m.p. 214-15°. (Found: C, 72.49; H, 5.40. $C_{18}H_{16}O_4$ requires C, 72.96; H, 5.44%).

The *cyanomethyl* derivative, prepared as before, crystallised from dilute ethanol in colorless needles, m.p. 222-23°. (Found: C, 74.24; H, 4.78; N, 4.95. $C_{18}H_{15}O_3N$ requires C, 74.21; H, 4.50; N, 4.81%).

7-Methoxyflavone-8-acetic Acid.—The above cyanomethyl derivative on hydrolysis with 50% H_2SO_4 by gently refluxing for 2 hrs. gave the acetic acid derivative which crystallised from dilute acetic acid in colorless needles, m.p. 258-59°. (Found: C, 69.81; H, 4.20. $C_{18}H_{14}O_5$ requires C, 69.67; H, 4.55%).

7-Methoxy-3,8-dichloromethylflavone, obtained by further chloromethylation of the 8-chloromethyl derivative (1.5 g.) in glacial acetic acid (40 ml, 80%) with paraformaldehyde (0.75 g.) and hydrogen chloride at 75-80° for 6 hrs., crystallised from benzene-petroleum ether mixture in colorless needles (23%), m.p. 184°. (Found: C, 61.70; H, 3.88; Cl, 20.06. $C_{18}H_{14}O_3Cl_2$ requires C, 61.84; H, 4.01; Cl, 20.34%).

The same dichloromethyl derivative was also obtained from 7-methoxyflavone (2.5 g.) and paraformaldehyde (1.5 g.) by passing HCl gas as above; yield 20%. There was no significant improvement in the yield when the reaction was repeated using zinc chloride as a catalyst.

The dichloromethyl derivative, on reduction with zinc dust and dilute acetic acid as before, gave a product which crystallised from dilute ethanol in colorless needles; m.p. and mixed m.p. with an authentic specimen prepared according to Da Re and co-workers⁶, 139-41°.

The *dimethoxymethyl* derivative, prepared as before, crystallised from benzene-petroleum ether mixture in colorless needles, m.p. 157-58°. (Found: C, 70.63; H, 5.90. $C_{20}H_{20}O_5$ requires C, 70.57; H, 5.92%).