

## Chloromethylation of Some Flavones and Flavanones

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7-Hydroxy- and 6-hydroxyflavone have been chloromethylated and the structures of the mono-chloromethyl derivatives proved by converting them into the known formyl derivatives by Sommelet reaction. Similarly simple- and 7-methoxyflavanone have been chloromethylated and the structures of the monomethyl derivatives proved by reduction to the methyl derivatives and converting these methyl derivatives into flavones of known structures.

Shah and Sethna<sup>1</sup> studied the chloromethylation of 7-methoxyflavone. The work has now been extended to other flavones and flavanones.

7-Hydroxyflavone with four moles of paraformaldehyde and hydrogen chloride gave a monochloromethyl derivative to which the 8-chloromethyl structure has been assigned as on treatment with hexamine it gave the known 7-hydroxy-8-formylflavone<sup>2</sup>. 6-Hydroxyflavone on similar chloromethylation gave the 5-chloromethyl derivative which on heating with hexamine gave the known 6-hydroxy-5-formylflavone<sup>3</sup>. No di(chloromethyl) derivative could be obtained even with excess of the reagents from either of the above flavones.

Matsuka<sup>4</sup> chloromethylated simple flavanone and 5, 7-dimethoxy-4'-methylflavone but did not assign any definite structure to the chloromethyl derivatives. No other work on chloromethylation of flavanone appears to have been reported.

Simple flavanone on chloromethylation afforded the 3-chloromethyl derivative which on reduction with zinc and acetic acid and dehydrogenation with selenium dioxide gave the known 3-methylflavone<sup>5</sup>. 7-Methoxyflavanone on chloromethylation furnished the 8-chloromethyl derivative which on reduction and dehydrogenation gave the known 7-methoxy-8-methylflavone<sup>6</sup>.

Some of the chloromethyl derivatives have been converted into the corresponding acetoxy methyl derivatives by reacting with sodium acetate and acetic anhydride and into Mannich bases by reaction with dimethyl amine and morpholine.

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## EXPERIMENTAL\*

*7-Hydroxy-8-chloromethylflavone* : 7-Hydroxyflavone (2.38 g.) was dissolved in acetic acid (80%; 75 ml.) and paraformaldehyde (1.20 g.) added. The solution was maintained at 90–95° and hydrogen chloride gas passed until a shining crystalline product separated (1.5 hr.). The reaction mixture was cooled when more product separated which was recrystallised from dioxane m.p. 215° (decomp.); yield 1.0 g. (Found : C, 67.15; H, 3.92; Cl, 12.22%.  $C_{16}H_{11}O_3Cl$  requires C, 67.00; H, 3.84; Cl, 12.39%).

*7-Hydroxy-8-formylflavone* : The above chloromethyl derivative (1.0 g.) was mixed with hexamine (1.0 g.) and glacial acetic acid (10 ml.) and the reaction mixture was refluxed for 1 hr. The separated complex was collected and decomposed by refluxing for half an hour with hydrochloric acid (20 ml; 50%) and then crystallised from acetic acid. The m.p. and the mixed m.p. with an authentic specimen was 223°.

*7-Acetoxy-8-acetoxymethylflavone* : The above chloromethyl derivative (0.5 g.) was refluxed with acetic anhydride (10 ml.) and fused sodium acetate (0.5 g.) for 1 hr. The reaction mixture was poured into ice cold water and stirred for half an hour. The separated product crystallised from alcohol, m.p. 185–86°. (Found : C, 68.36; H, 4.40.  $C_{20}H_{16}O_6$  requires C, 68.19; H, 4.54%).

*7-Hydroxy-8-dimethylaminomethylflavone* : Dimethylamine (3 ml.; 40%) was added to 7-hydroxy-8-chloromethylflavone (1.0 g.) in alcohol (30 ml.) and the reaction mixture was heated on a steam bath for 6 hr. The residue obtained on removal of alcohol was treated with dil. hydrochloric acid and filtered. The filtrate was neutralised with sodium bicarbonate solution and the product obtained crystallised from alcohol, m.p. 184°. (Found : N, 4.18.  $C_{18}H_{17}O_3N$  requires N, 4.72%).

*7-Hydroxy-8-morpholinomethylflavone* : Morpholine (3 ml.) was added to the above chloromethyl derivative (1.0 g.) in alcohol (30 ml.) and on working up the reaction mixture as described above the product was obtained which crystallised from alcohol, m.p. 208°. (Found : N, 4.08.  $C_{20}H_{19}O_4N$  requires N, 4.15%).

*6-Hydroxy-5-chloromethylflavone* : HCl gas was passed through a mixture of 6-hydroxyflavone (1.19 g.), paraformaldehyde (1.4 g.) in acetic acid (80%; 60 ml.) at room temperature for 4 hr. The chloromethyl derivative which separated on cooling the reaction mixture was collected and crystallised from toluene m.p. 210° (decomp.) yield 0.5 g. (Found : C, 66.80; H, 3.52; Cl, 12.69.  $C_{16}H_{11}O_3Cl$  requires C, 67.00; H, 3.84; Cl, 12.39%).

*6-Hydroxy-5-formylflavone* : This was prepared from the above chloromethyl derivative as before, crystallised from acetic acid. The m.p. and mixed m.p. with an authentic specimen was 221°.

*The acetoxymethyl derivative* : It was prepared from the chloromethyl derivative as described above and crystallised from alcohol, m.p. 214°. (Found : C, 68.33; H, 4.82.  $C_{20}H_{16}O_6$  requires C, 68.19; H, 4.54%).

\* All the m.p.s. are uncorrected.

*6-Hydroxy-5-morpholinomethylflavone* : Prepared as described above was crystallised from alcohol, m.p. 192°. (Found : N, 4.18.  $C_{20}H_{19}O_4N$  requires N, 4.15%).

*3-Chloromethylflavanone* : Flavanone (1.0 g.) was dissolved in glacial acetic acid (10 ml.) and paraformaldehyde (4.5 g.) added. The reaction mixture was kept on a steam bath and HCl gas passed for 3 hr. The reaction mixture was then left overnight in refrigerator. The product obtained was crystallised from benzene and petroleum ether mixture, m.p. 137°. Matsuka<sup>4</sup> prepared the same compound with chloromethyl ether and reported the same m.p. (Found : C, 70.24; H, 4.52; Cl, 12.73.  $C_{16}H_{13}O_2Cl$  requires C, 70.46; H, 4.77; Cl, 13.02%).

*3-Methylflavanone* : The above chloromethyl derivative was dissolved in acetic acid and slowly added to a mixture of zinc dust (2.0 g.) and glacial acetic acid (5 ml.) with stirring. The stirring was continued for half an hour more and then heated on a steam bath for 1 hr. more. The reaction mixture was diluted with ice cold water and left overnight. The product separated was crystallised from alcohol. (Found : C, 80.76; H, 5.82.  $C_{16}H_{14}O_2$  requires C, 80.64; H, 5.92%).

*3-Methylflavone* : The above methyl derivative (1.0 g.) was dissolved in amyl alcohol (10 ml.) and selenium dioxide (2.0 g.) added. The reaction mixture was heated in an oil bath at 145° for 8 hr. The reaction mixture was filtered and diluted with petroleum ether and left overnight in a refrigerator. The product obtained crystallised from alcohol. M.P. and mixed m.p. with 3-methylflavone<sup>5</sup> was 73°.

*7-Methoxy-8-chloromethylflavanone* : Paraformaldehyde (2.0 g.) was added to glacial acetic acid (10 ml.) and HCl gas passed till all paraformaldehyde dissolved and a clear solution was obtained. To this clear solution 7-methoxyflavanone (1.0 g.) was added, and the reaction mixture left overnight in a refrigerator. The solid which separated was crystallised from benzene and petroleum ether mixture, m.p. 149°. Yield 0.6 g. (Found : C, 67.28; H, 5.19; Cl, 11.88;  $C_{17}H_{15}O_3Cl$  requires C, 67.44; H, 4.96; Cl, 11.73%).

*7-Methoxy-8-methylflavanone* : The above chloromethyl derivative (1.0 g.) dissolved in glacial acetic acid (10 ml.) and zinc dust (2.0 g.) added. The reaction mixture was kept overnight at room temperature. Next day it was filtered and diluted with ice cold water. The solid which separated was crystallised from benzene, m.p. 130°. (Found : C, 76.55; H, 5.80.  $C_{17}H_{16}O_3$  requires C, 76.10; H, 6.01%).

*7-methoxy-8-methylflavone* : This was prepared from the above flavanone derivative as before and was crystallised from alcohol. The m.p. and mixed m.p. with an authentic specimen was 171°.

*7-Methoxy-8-acetoxymethylflavanone* : The above chloromethyl derivative (0.5 g.) was dissolved in glacial acetic acid (10 ml.) and fused sodium acetate (0.5 g.) added. On working up the reaction mixture as usual the product was obtained which crystallised from alcohol, m.p. 91°. (Found : C, 72.14; H, 5.82.  $C_{19}H_{18}O_5$  requires C, 72.24; H, 6.00%).

*7-Methoxy-8-dimethylaminomethylflavanone hydrochloride* : Dimethylamine (3 ml.; 40%) was added to the above chloromethyl derivative in alcohol (30 ml.) and the reaction mixture heated on a steam bath for 6 hr. The residue obtained on removal of alcohol was treated with dilute hydrochloric acid and filtered. The filtrate on neutralization with sodium

hydroxide solution gave an oily product which was extracted with ether. The ether extract was dried over fused calcium chloride and HCl gas was passed through it till a solid separated. This was collected and crystallised from alcohol ether mixture, m.p. 140°. (Found : N, 3.90 Cl, 9.80.  $C_{19}H_{22}NO_3Cl$  requires N, 3.69; Cl, 9.35%).

*7-methoxy-8-morphinomethylflavanone* : This was prepared from the above chloromethyl derivative as before and crystallised from benzene and petroleum ether. M. p. 149–50°. (Found : N, 4.34.  $C_{21}H_{23}O_4N$  requires N, 3.97%).

Thanks are due to Professor Suresh Sethna for his kind interest in the work.

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*Received September 9, 1968.*