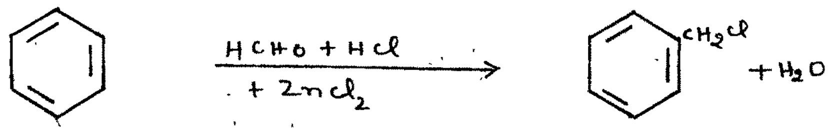
Part IV

THEORETICAL

Chloromethylation of some Chromones and Flavones

The replacement of a hydrogen atom (generally of an aromatic compound) by a chloromethyl group, $-CH_2Cl$, in a single operation is known as chloromethylation. The reaction is usually carried out by the condensation of formaldehyde with aromatic compounds in presence of hydrochloric acid.



A survey of the work done on the chloromethylation of aromatic compounds till 1942 was made by Fuson and McKeever (Organic Reactions, Vol. I, John Wiley and Sons, New York, 1942, p. 63).

This reaction is of synthetic importance because of the ease with which the chlorine atom in chloromethyl group undergoes substitution reactions with various reagents. Alcohols result when such compounds are hydrolysed by heating with water as such or under pressure. Alcohols can be prepared indirectly through the saponification of acetic acid esters obtained from the interaction of chloromethylated compound with acetic acid in presence of fused sodium acetate. Many alcohols with various functional groups have been prepared by this method. Chloromethyl derivatives can be converted to cyanomethyl derivatives, which in their turn on hydrolysis give acetic acid derivatives.

The chloromethyl derivatives on reduction gives methyl derivatives. On Sommelet reaction i.e. heating with hexamin the chloromethyl group is replaced by the formyl group.

Mannich bases which are substances of potential therapeutic value are obtained from the chloromethyl derivatives on condensation with various secondary amines such as dimethylamine, diethylamine, morpholine etc.

Application of the reaction

Aromatic hydrocarbons such as benzene, naphthalene, anthracene, phenanthrene, diphenyl and many of their derivatives have been successfully chloromethylated. Highly alkylated homologues react rapidly in the absence of catalysts. Thus Nauta and Dienske (Rec. Trav. Chim., 1936, 55, 1000 ; C.A. 1937, 31, 1776) chloromethylated mesitylene without using any catalyst and obtained the mono- as well as the dichloromethyl derivatives. Braun and Nells (Ber., 1934, 67, 1094) chloromethylated m-xylene and obtained the dichloromethyl derivative. Chloromethylation of alkyl derivatives give the para-substituted derivatives (with respect to the alkyl group) in good yield, but a small amount of the ortho chloromethyl derivative is also obtained. A second chloromethyl group can usually be introduced and sometimes excellent yield of the dichloromethyl derivative is obtained.

Halogens and nitro group in the aromatic ring have a retarding influence on the rate of the reaction. Stephen et al., (J. Chem. Soc., 1920, 117, 510) found that nitrobenzene and ortho and para-nitrotoluenes give chloromethyl derivatives but in low yield. Substances such as ortho and para-chloronitrobenzenes and p-dichlorobenzene do not react at all. The presence of alkyl groups in the nucleus however counteracts the influence of these substituents. Vavon et al. (Bull. Soc. Chim., 1936, 6, 1025) got the chloromethyl derivative on chloromethylation of bromomesitylene. Fuson and McKeever (J. Amer. Chem. Soc., 1940, 62, 784) found that benzophenone does not undergo chloromethylation at all. Stephen et al. (loc. cit.) failed to chloromethylate anthraquinone. Here also the presence of alkyl groups in the nucleus counteracts this influence. Thus Fuson and McKeever (loc. cit.) chloromethylated acetomesitylene and obtained α^3-chloroacetoisodurene successfully.

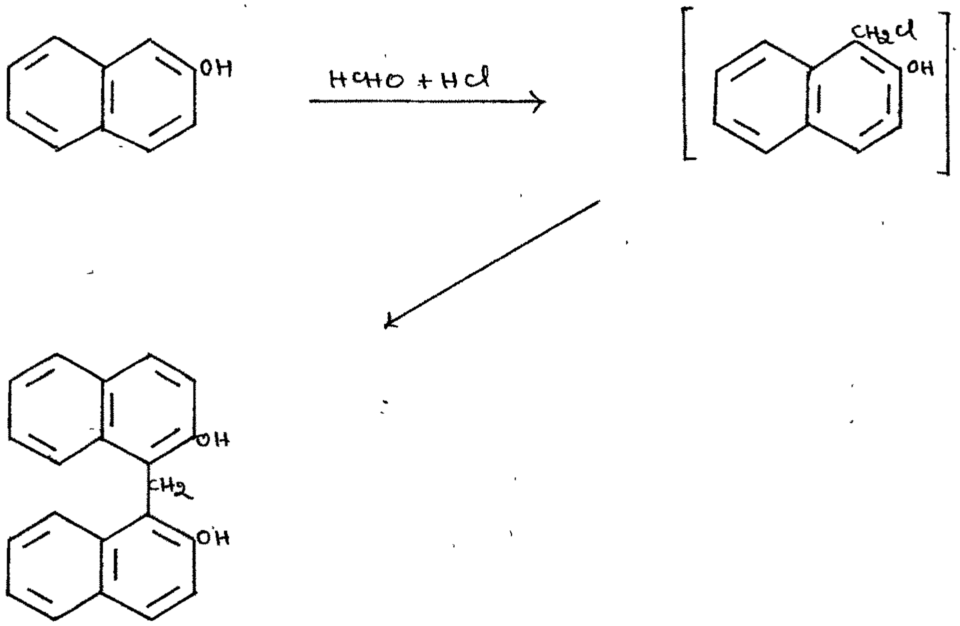
Hydroxy groups in the nucleus greatly promote the rate of reaction and the reaction proceeds vigorously giving polymeric products. A suitable device to avoid polymeric product in the case of phenols is to convert them to esters by treatment with ethyl chlorocarbonate. Ethyl arylcarbonates undergo smooth chloromethylation (Sommelet et al., Compt. rend., 1933, 197, 256 ; 1934, 198, 2256). The activating influence of hydroxy groups may be sufficiently attenuated by de-activating groups such as nitro-, carboxy-, or acetyl- to make a smooth reaction possible. Stoermer and Behn

(Ber., 1901, 34, 2455) successfully chloromethylated o-nitrophenol. Buehler (J. Tennessee Acad. Sci., 1947, 22, 303 ; C.A. 1948, 42, 2244) chloromethylated salicylic acid and obtained the 5-chloromethyl product in good yield.

Phenol ethers react smoothly. Phenol ethers and other phenolic compounds containing an aldehyde group also react in a satisfactory manner.

Aromatic amines react vigorously but the complex condensation products are invariably the result of the reaction and it has not been possible to isolate simple chloromethyl derivatives from these compounds (Wagner, J. Amer. Chem. Soc., 1933, 55, 724).

In chloromethylation, the most important side reaction is the formation of the diaryl methane derivatives. Highly reactive compounds tend to yield this type of products

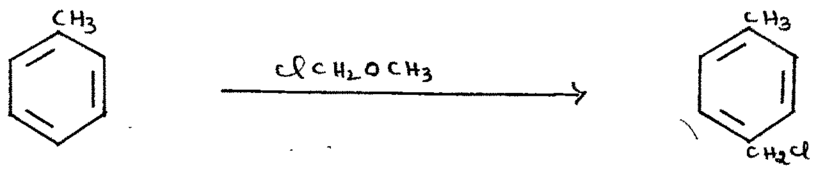


and sometimes the isolation of the intermediate chloromethyl derivative is impossible. Castigloni (Gazz. chim. Ital., 1937, 67, 324; C. A., 1937, 31, 8528) chloromethylated β-naphthol and obtained the corresponding diarylmethane derivative.

Role of catalysts, solvents and temperature in chloromethylation

There are a variety of techniques reported in the literature for chloromethylation. It is normally achieved by using formalin. Formaldehyde may be added as formalin (40 %) or it may be generated in the reaction mixture by depolymerisation of paraformaldehyde. Paraformaldehyde is preferred as it can be weighed accurately and is most suitable whenever anhydrous conditions are to be maintained. Blank (Bull. Soc. Chim., 1923, 33, 318) introduced the chloromethyl group into an aromatic hydrocarbons by means of a mixture of formalin and anhydrous zinc chloride. Catalyst may or may not be required. Catalysts which have been reported to be very useful are zinc chloride and acetic acid. Many other catalysts such as sulphuric acid, phosphoric acid and aluminium chloride are also used, though these catalysts tend to favour the formation of diaryl methane derivatives. Fieser and Seligman (J. Amer. Chem. Soc., 1935, 57, 942) found that the yield of the chloromethyl product was increased three fold when a little anhydrous aluminium chloride was used with fused zinc chloride in the chloromethylation of p-bromotoluene. Sommelet (Compt. rend., 1913, 157, 1443) used stannic chloride with success with compounds which normally resist chloromethylation. For liquids no diluent is required. For solids which do not dissolve in hydrochloric acid, a solvent is used. Acetic acid, carbon disulphide, ethylene dichloride and benzene are the common solvents used in chloromethylation. Rate of reaction also depends upon the temperature of reaction and a variety of reaction temperatures are used depending on the type of the compound to be chloromethylated. Highly reactive compounds react at 0° while temperatures of 60-70° are much favoured for less reactive compounds. Sometimes reactions are carried out at 140° under pressure.

Chloromethyl ether ($CH_3O.CH_2Cl$) or dichloromethyl ether ($ClCH_2{\cdot}O{\cdot}CH_2Cl$) have been also successfully used in chloromethylation. The reaction often proceeds smoothly in the absence of a catalyst. Stannic chloride may be used as a catalyst with less reactive compounds. Carbon disulphide or other indifferent solvents may be used as diluents. The chloromethyl ether is mostly used in excess. The reaction usually proceeds without hydrochloric acid.



Vavon et al. (Bull. Soc. Chim., 1939, 6, 1025) studied the effect of substitutents on the ease of chloromethylation of benzene by chloromethyl ether in the absence of a catalyst. They found that the rate is increased by $-CH_3$; $-C_2H_5-$, $-C_3H_7-$, $-OCH_3$, and reduced by -Cl, -Br, -I, $-CH_2Cl$, -COOH and $-NO_2$ groups.

Weisler and Chechak (U.S.P.2486542 ; C.A. 1950, 44, 2037) found that an aromatic compound containing one or two aromatic rings can be chloromethylated and the chloromethyl group can be simultaneously reduced if stannous chloride is added to the reaction mixture.

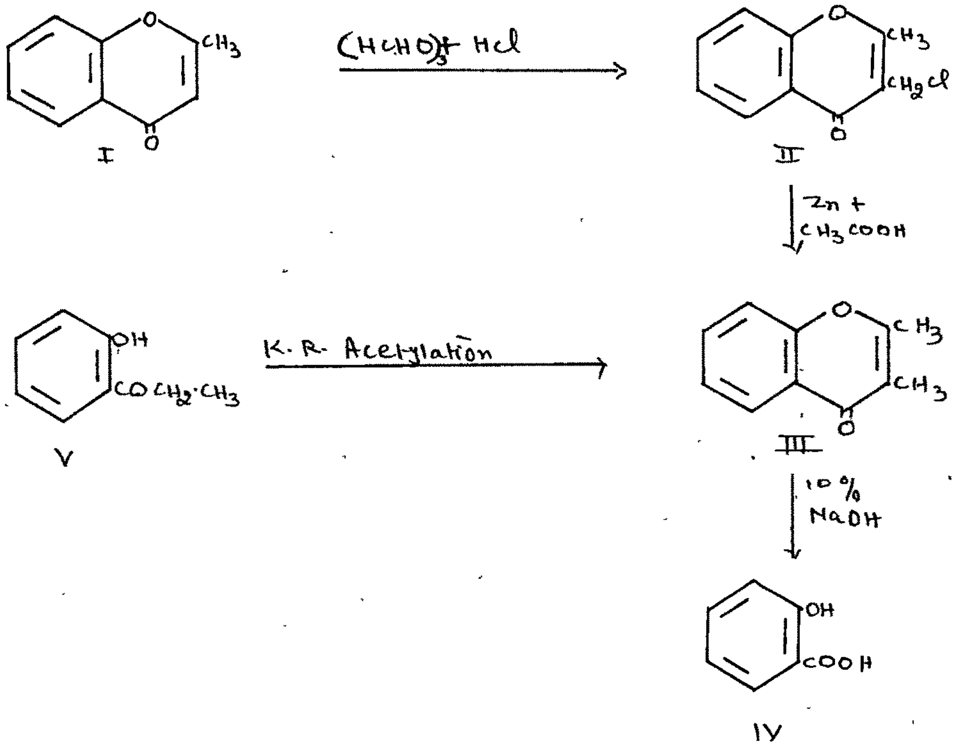
Chloromethylation of chromones and flavones

Nakamura and Matsura (J. Pharm. Soc., Japan, 1953, 73, 481) chloromethylated acacetin 7-methyl ether and obtained the 8-chloromethyl derivative and another isomer to which no definite structure was assigned. Da Re and co-workers (Ann. Chim., (Rome), 1956, 46, 904 ; Arzneimittel- Forsch, 1960, 10, 800 ; C.A. 1961, 55, 5477) chloromethylated 7-methoxy-2,3-dimethylchromone, 7-methoxy-3-methylflavone and 7-methoxy-3-ethylflavone and obtained the 8-chloromethyl derivatives in all cases. A few chloromethyl derivatives have been prepared by other methods. For example, Alexander Schonberg et al. (J. Amer. Chem. Soc., 1955, 77, 1019) treated khellol with thionyl chloride and obtained the 2-chloromethyl derivative and Da Re et al. (Ann. Chim., Rome, 1956, 46, 910) obtained 6-chloromethyl derivatives from 6-hydroxymethyl 2,3-dimethylchromone and 6-hydroxymethyl-3-methylflavone by treatment with zinc chloride and hydrochloric acid. Further, Offe (Ber., 1938, 71B, 1837) chlorinated 2-methylchromone with manganese dioxide and hydrochloric acid and reported to have obtained the 2-chloromethyl derivative.

The chloromethylation of 2-methylchromone, flavone, 7-methoxy-2-methylchromone and 7-methoxyflavone has now been studied and the structures of the compounds obtained established.

Chloromethylation of 2-methylchromone

2-Methylchromone (I) on chloromethylation with even three moles of paraformaldehyde and hydrogen chloride at 85-90° gave only the original chromone. However, on chloromethylation with four moles of paraformaldehyde it gave a monochloromethyl derivative which was reduced with zinc dust and aqueous acetic acid to the corresponding methyl derivative. The reduction product on alkaline hydrolysis gave salicylic

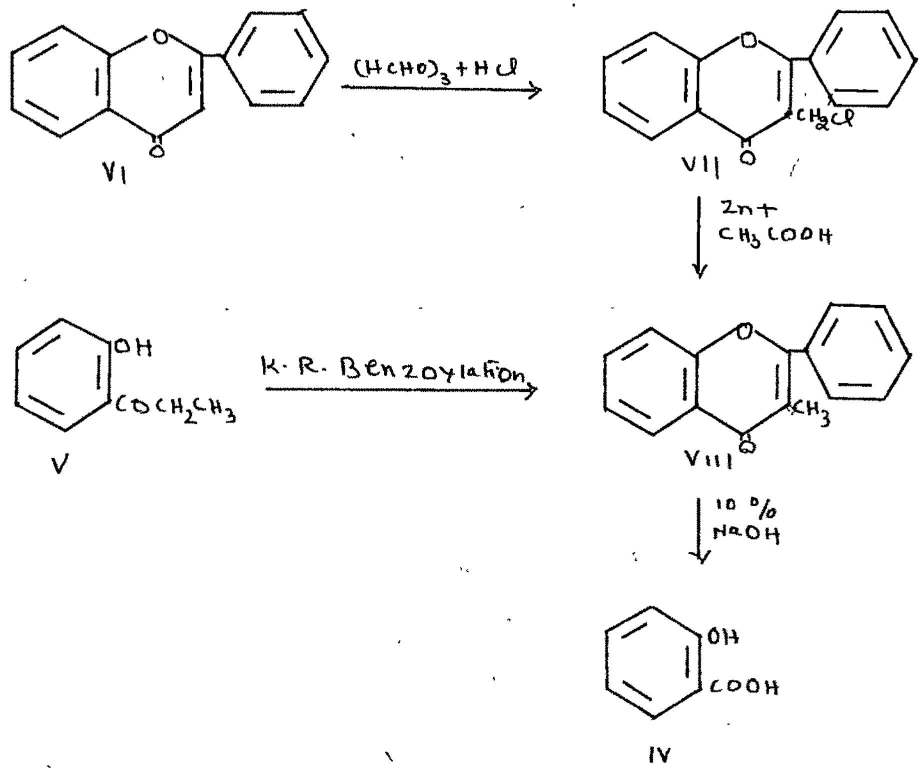


acid (IV) indicating that the chloromethyl group had not entered the benzonoid part of the molecule. Further, the reduction product was found to be identical with 2,3-dimethylchromone (III) obtained by the Kostanecki-Robinson acetylation of o-hydroxypropiophenone (V) (Robertson, Sandrock and Hendry, J. Chem. Soc., 1931, 2426): The chloromethyl derivative is therefore assigned 2-methyl-3-chloromethylchromone structure (II).

No higher chloromethyl derivative could be obtained on chloromethylation of 2-methylchromone or 2-methyl-3-chloromethylchromone even with a large excess of paraformaldehyde. Catalysts like phosphoric acid or sulphuric acid did not improve the yield.

Chloromethylation of flavone

Flavone (VI) on chloromethylation with less than four moles of paraformaldehyde and hydrogen chloride gave only the original flavone, but with four moles of paraformaldehyde,



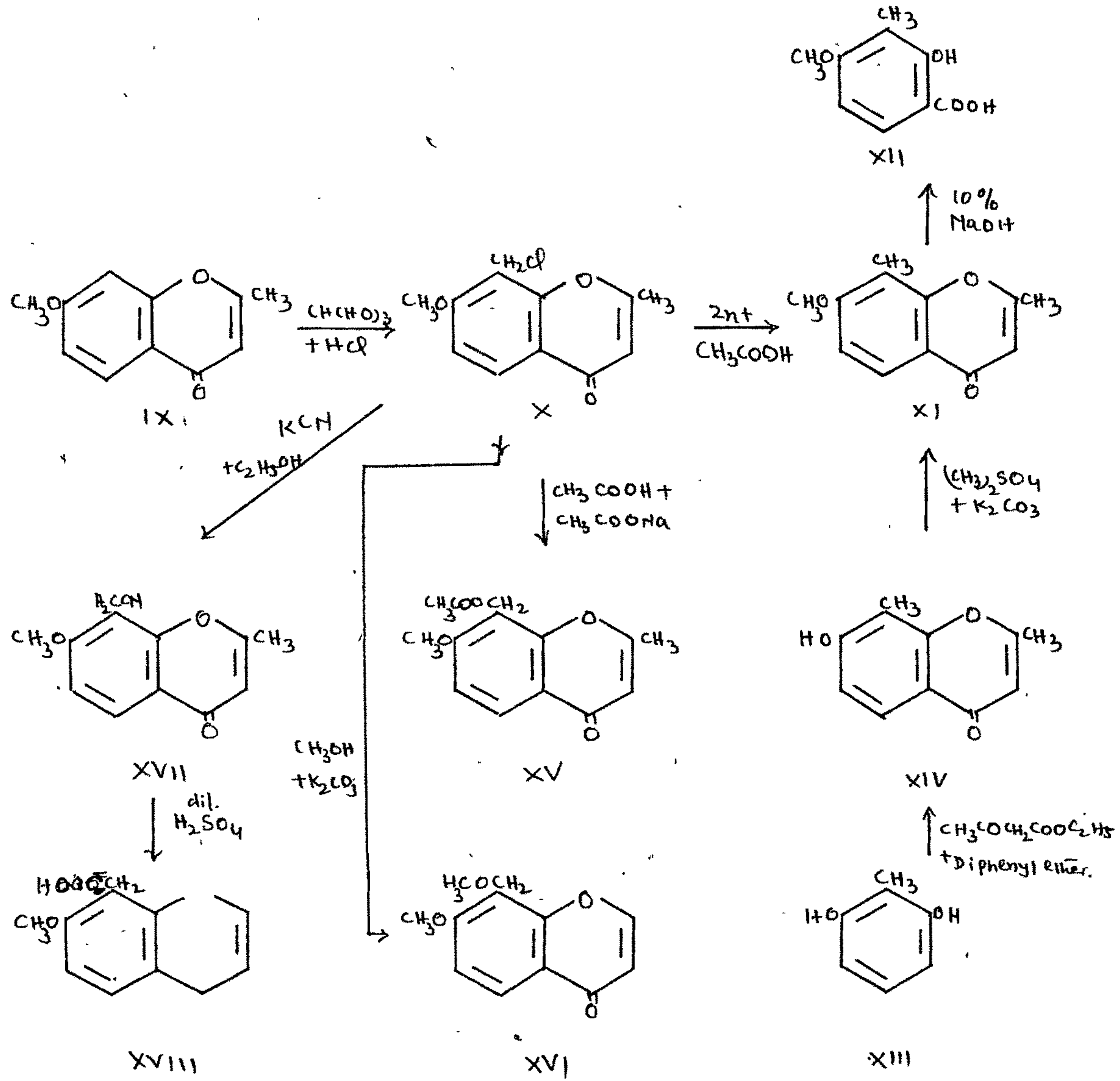
it gave a monochloromethyl derivative which on reduction with zinc dust and aqueous acetic acid gave the methyl derivative which on hydrolysis with alkali yielded salicylic acid (IV). Further, the reduction product was found to be identical on direct comparison with an authentic specimen of 3-methylflavone (VIII) prepared from o-hydroxypropiophenone (V) by the Kostanecki Robinson benzoylation (Wheeler et al., J. Chem. Soc., 1950, 1252). The chloromethyl derivative has therefore been assigned the 3-chloromethylflavone (VII) structure.

Chloromethylation of 7-methoxy-2-methylchromone

7-Methoxy-2-methylchromone (IX) on chloromethylation with one or two moles of paraformaldehyde and hydrogen chloride at 90-95° did not give any chloromethyl derivative, only the original chromone was recovered unchanged. With three moles of paraformaldehyde it gave the monochloromethyl derivative which was reduced with zinc dust and acetic acid. The reduced product was found to be identical on direct comparison with 7-methoxy-2,8-dimethylchromone (XI) obtained by the methylation of 7-hydroxy-2,8-dimethylchromone (XIV) synthesised by refluxing 2-methylresorcinol (XIII) with ethyl acetoacetate in diphenyl ether according to the method of Desai, Trivedi and Sethna (J. M. S. University of Baroda, 1955, IV-2, 1). The reduced product on hydrolysis with alkali gave an acid which was found to be identical on direct comparison with 2-hydroxy-3-methyl-4-methoxybenzoic acid (XII) obtained by the alkaline hydrolysis of 7-methoxy-2,3,8-

trimethylchromone according to Da Re and Verlicchi (Ann. Chim., Rome, 1956, 46, 904). The chloromethyl derivative was therefore 7-methoxy-8-chloromethyl-2-methylchromone (X).

The 8-chloromethyl derivative (X) was converted into 8-acetoxymethyl derivative (XV) by heating with glacial acetic acid and fused sodium acetate and into the 8-methoxymethyl derivative (XVI) by heating with absolute methyl alcohol in presence of anhydrous potassium carbonate. The Sommelet reaction on the chloromethyl derivative (X) gave



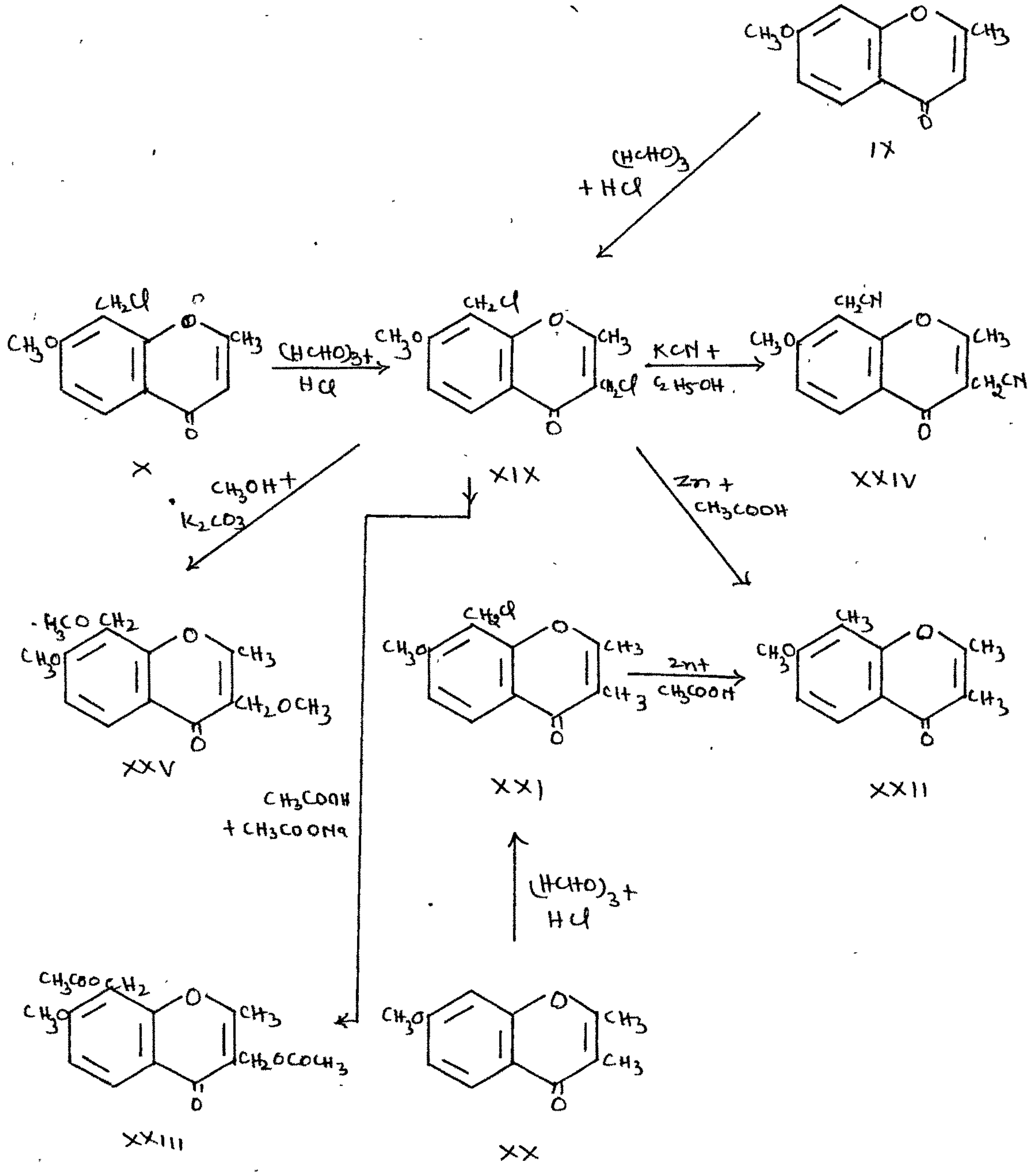
an unworkable product. On treatment with aqueous potassium cyanide the chloromethyl derivative (X) gave the 8-cyanomethyl derivative (XVII) which on hydrolysis with dilute sulphuric acid gave 7-methoxy-2-methylchromone-8-acetic acid (XVIII).

Further chloromethylation of 7-methoxy-8-chloromethyl-2-methylchromone (X) in glacial acetic acid with 5 moles or excess of paraformaldehyde gave a dichloromethyl derivative. On reduction it gave a product which was found on direct comparison to be 7-methoxy-2,3,8-trimethylchromone (XXII). This was prepared for comparison by the reduction of the 8-chloromethyl derivative (XXI) obtained from the chloromethylation of 7-methoxy-2,3-dimethylchromone (XX) according to Da Re et al. (loc. cit.). The reduced product gave 2-hydroxy-3-methyl-4-methoxybenzoic acid on alkaline hydrolysis. The dichloromethyl derivative was therefore 7-methoxy-3,8-dichloromethyl-2-methylchromone (XIX).

7-Methoxy-2-methylchromone (IX) on chloromethylation with 5 moles of excess of paraformaldehyde gave the same dichloromethyl derivative (XIX). No trichloromethyl derivative could be obtained on chloromethylation of 7-methoxy-2-methylchromone (IX) or 7-methoxy-3,8-dichloromethyl-2-methylchromone (XIX) even with a large excess of paraformaldehyde.

The 3,8-dichloromethyl derivative (XIX) was converted into the corresponding diacetoxymethyl- (XXIII) ;

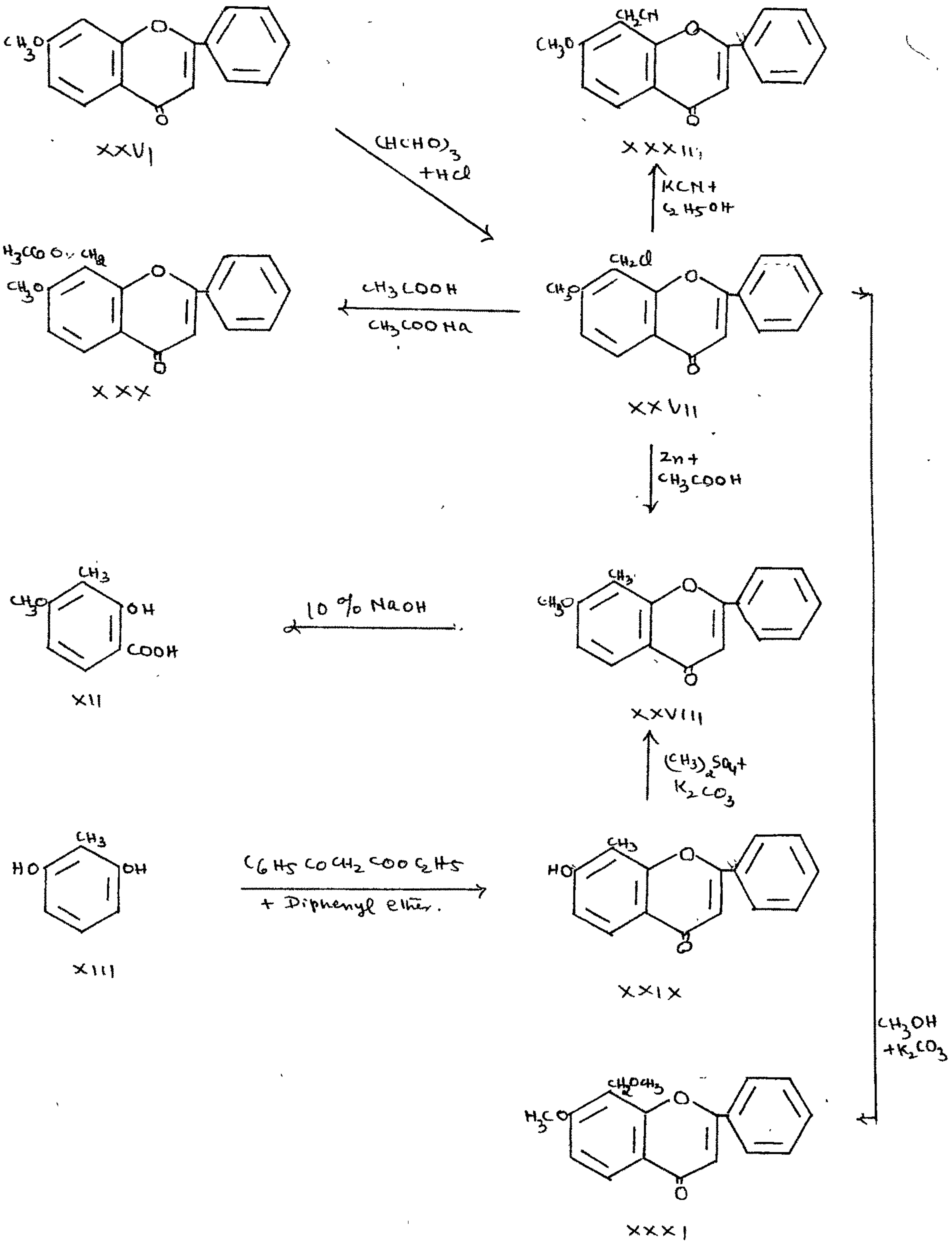
dicyanomethyl (XXIV) and dimethoxymethyl- (XXV) derivatives by the procedure described before.



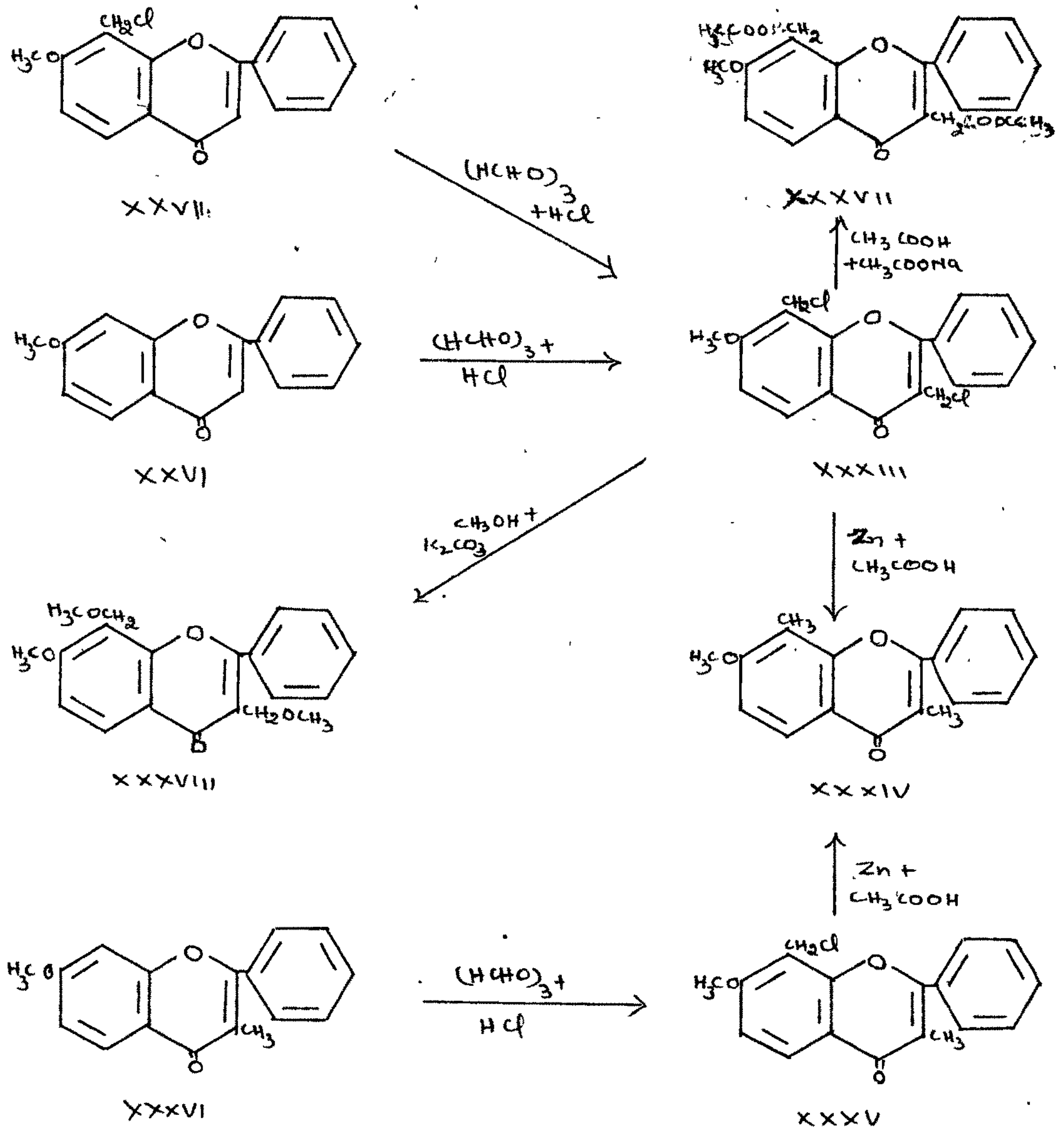
Chloromethylation of 7-methoxyflavone

7-Methoxyflavone (XXVI) did not undergo chloromethylation with one or two moles of paraformaldehyde and hydrogen chloride. However, with three moles of paraformaldehyde it gave the monochloromethyl derivative. Its reduction with zinc dust and dilute acetic acid yielded a product which on treatment with alkali gave 2-hydroxy-3-methyl-4-methoxybenzoic acid (XII) (Da Re et al., loc.cit.) indicating that the chloromethyl group must have entered the 8-position of the molecule. This was confirmed when the reduction product was found to be identical with 7-methoxy-8-methylflavone (XXVIII) obtained by methylation of 7-hydroxy-8-methylflavone (XXIX) synthesised by refluxing 2-methylresorcinol (XIII) with ethyl benzoylacetate in diphenyl ether according to the procedure described by Desai, Trivedi and Sethna (loc. cit.). The chloromethyl derivatives was therefore 7-methoxy-8-chloromethylflavone (XXVII).

The above 8-chloromethyl flavone (XXVII) was converted into the corresponding acetoxymethyl- (XXX), methoxymethyl- (XXXI) and cyanomethyl- (XXXII) derivatives by procedures described before.


CH3O
XXVI
(HCHO)3 +HCl
CH2CN
CH3O
XXXIII
KCN+ C2H5OH
H3CCOO·CH2
CH3O
XXX
CH3COOH
CH3COONa
CH2Cl
CH3O
XXVII
Zn+ CH3COOH
CH3
CH3O
OH
COOH
XII
10 % NaOH
CH3
CH3O
XXVIII
(CH3)2SO4+ K2CO3
CH3
HO
OH
XIII
C6H5COCH2COOC2H5
+ Diphenyl ether.
CH3
HO
XXIX
CH3OH +K2CO3
CH2OCH3
H3CO
XXXI

7-Methoxy-8-chloromethylflavone (XXVII) on chloromethylation with 5 moles or excess of paraformaldehyde yielded a dichloromethyl derivative. On reduction with zinc dust and aqueous acetic acid it gave a product which on treatment with alkali gave 2-hydroxy-3-methyl-4-methoxybenzoic acid (XII) which indicated that the second chloromethyl group had entered the pyrone part of the molecule. That the chloromethylation product was 7-methoxy-3,8-dichloromethylflavone



(XXXIII) was proved by establishing the identity of the reduced product with an authentic specimen of 7-methoxy-3,8-dimethylflavone (XXXIV) prepared according to Da Re and Verlicchi (loc. cit.) by the reduction of 7-methoxy-8-chloromethyl-3-methylflavone (XXXVI) .

The yield of the dichloromethyl derivative was improved by using catalysts such as phosphoric acid and zinc chloride.

No trichloromethyl derivative was obtained on reaction even with a large excess of paraformaldehyde from either 7-methoxyflavone (XXVI) or 7-methoxy-3,8-dichloromethylflavone (XXXIII).

The dichloromethyl derivative (XXXIII) was converted into the corresponding diacetoxy- (XXXVII) and the dimethoxymethyl- (XXXVIII) derivatives.

EXPERIMENTAL

Chloromethylation of 2-methylchromone : 3-chloromethyl-2-methylchromone

(i) 2-Methylchromone (1.6 g. ; 0.01 mole) was dissolved in acetic acid (5.0 ml.) and water (10 ml.) and paraformaldehyde (1.2 g. ; 0.04 mole) were added. Hydrogen chloride was passed through the reaction mixture maintained at 85-90° for 6 hr. The reaction mixture was cooled and diluted with excess of cold water and the separated shining product was collected and dried. It crystallised from petroleum ether (b.p. 60-80°) in colourless stout needles, m.p. 103-104°. Yield 0.8 g.

(ii) The chloromethyl derivative was obtained in better yield (1.1 g.) by saturating the reaction mixture containing 2-methylchromone (1.6 g. ; 0.01 mole) and paraformaldehyde (4.0 g.) with hydrogen chloride gas at 75-80° for 4 hr. Addition of catalysts such as phosphoric acid or sulphuric acid did not improve the yield.

Analysis :

4.622 mg. of the substance gave 10.762 mg. of carbon dioxide and 1.580 mg. of water.

12.292 mg. of the same substance gave 8.406 mg. of silver chloride.

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 %.

2,3-Dimethylchromone

The above chloromethyl derivative (0.5 g.) in acetic acid (5 ml.) was added slowly to a mixture of zinc dust (2.0 g.), acetic acid (5 ml.) and water (1 ml.). The reaction mixture was then heated at 75-80° on a water bath for 2 hr. and diluted with water and the solution was extracted with ether. The residue, obtained after the removal of ether, crystallised from very dilute alcohol in rhombic plates. M.P. and mixed m.p. with 2,3-dimethylchromone was 96-97°. ~~Wheeler~~ Robertson et al. (loc. cit.) give the same m.p.

The above chromone (0.3 g.) was refluxed with sodium hydroxide solution (10 % ; 20 ml.) for 3 hr. and the reaction mixture was acidified. The product obtained after extraction with ether was crystallised from hot water. M.P. and mixed m.p. with salicyclic acid was 159°.

Chloromethylation of flavone : 3-chloromethylflavone

Flavone (2.22 g. ; 0.01 mole) was dissolved in glacial acetic acid (10 ml.) and water (50 ml.) and paraformaldehyde (1.2 g. ; 0.04 mole) were added. The solution was maintained at 85-90° and hydrogen chloride was passed for 5 hr. The shining product which separated on cooling the reaction mixture was collected, dried and crystallised from benzene and petroleum ether (b.p. 60-80°) mixture in colourless needles, m.p. 153°. Yield 1.3 g.

The above chloromethyl derivative was obtained in a better yield (1.6 g.) by carrying out the reaction with excess of paraformaldehyde (5.0 g.) under the same conditions.

Analysis :

4.814 mg. of the substance gave 12.624 mg. of carbon dioxide and 1.516 mg. of water.

13.500 mg. of the same substance gave 7.426 mg. of silver chloride.

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 %.

3-Methylflavone

The above chloromethyl derivative (0.6 g.) was reduced by slow addition of its acetic acid solution (10 ml.) to a stirred mixture of zinc (2.0 g.), acetic acid (5 ml.) and water (1.20 ml.) at room temperature during half an hour. The reaction mixture was then heated on a water bath maintained at 75-80° for further half an hour and then diluted with water. It was kept in a refrigerator over-night and next day the separated pasty product was repeatedly crystallised from dilute alcohol when colourless needles were obtained. M.P. and mixed m.p. with 3-methylflavone was 72-73°. Wheeler et al. (loc. cit.) give the same m.p.

The above flavone (0.3 g.) was refluxed with sodium hydroxide solution (10 % ; 20 ml.) for 2 hr. On working up the reaction mixture as before salicylic acid was obtained.

Chloromethylation of 7-methoxy-2-methylchromone : 7-Methoxy-8-chloromethyl-2-methylchromone

7-Methoxy-2-methylchromone (1.9 g. ; 0.01 mole) was dissolved in glacial acetic acid (30 ml.) and paraformaldehyde (0.9 g.) was added. The solution was maintained at 75-80° and hydrogen chloride was passed for 8 hr. The cooled reaction mixture on dilution with cold water yielded a pasty product which solidified on keeping in a refrigerator over-night. It crystallised from benzene, petroleum ether (b.p. 60-80°) mixture in colourless needles, m.p. 153°. Yield 0.3 g.

The residue after the removal of the solvent from the mother liquor, on extraction with hot water gave the original 7-methoxy-2-methylchromone m.p. 110°.

The above chloromethyl derivative was obtained in a better yield (0.8 g.) by carrying out the reaction for 1 hr. at 75-80° in presence of zinc chloride (2 g.) and paraformaldehyde (3 g.)

Analysis :

4.292 mg. of the substance gave 9.472 mg. of carbon dioxide and 1.772 mg. of water.

17.28 mg. of the same substance gave 10.32 mg. of silver chloride.

Found : C = 60.23 % ; H = 4.62 % ; Cl = 14.78 %.

$C_{12}H_{11}O_3Cl$ requires : C = 60.39 % ; H = 4.61 % ; Cl = 14.88 %.

7-Methoxy-2,8-dimethylchromone

The above chloromethyl derivative (0.5 g.) was reduced as before by slowly adding its acetic acid solution to a mixture of zinc dust (2 g.), acetic acid (10 ml.)

and water (2 ml.). The product which separated on dilution of the reaction mixture crystallised from dilute ethyl alcohol in colourless needles, m.p. and mixed m.p. with 7-methoxy-2,8-dimethyl-chromone synthesised as described below was 140°.

7-Hydroxy-2,8-dimethylchromone

2-Methylresorcinol (2.48 g. ; 0.02 mole) and ethyl acetoacetate (2.6 g. ; 0.03 mole) were added to dry diphenyl ether (20 ml.) and the reaction mixture refluxed with a short air condenser for 2 hr. After cooling the reaction mixture, diphenyl ether was removed by steam distillation. The pasty solid obtained solidified on repeated washings with petroleum ether (b.p. 60-80°). The reddish brown residue crystallised from dilute ethyl alcohol in buff coloured needles, m.p. 258°. yield 1·8g. Dann et al. (Ann., 1954, 587, 16) synthesised this compound by the condensation of 2-methylresorcinol with cis-β-chlorocrotonate in presence of hydrofluoric acid and treatment of the product formed with alkali. Yield 1.8 g.

Analysis :

4.370 mg. of the substance gave 11.154 mg. of carbon dioxide and 2.150 mg. of water.

Found : C = 69.64 % ; H = 5.50 %.

$C_{11}H_{10}O_3$ requires : C = 69.47 % ; H = 5.26 %.

The methyl ether

The above hydroxychromone (0.5 g.) was refluxed in acetone solution with dimethyl sulphate (0.5 ml.) in presence of anhydrous potassium carbonate (2 g.) for 1 hr. The product obtained on removal of acetone solidified after treatment with dilute alkali. It crystallised from dilute alcohol in colourless needles, m.p. 140°.

<u>Analysis</u> :

4.46 mg. of the substance gave 11.524 mg. of carbon dioxide and 2.346 mg. of water.

Found : C = 70.48 % ; H = 5.88 %.

$C_{12}H_{12}O_3$ requires : C = 70.58 % ; H = 5.88 %.

Alkaline hydrolysis of 7-methoxy-2,8-dimethylchromone : 2-hydroxy-3-methyl-4-methoxybenzoic acid

7-Methoxy-2,8-dimethylchromone (0.3 g.) was refluxed with sodium hydroxide solution (10 % ; 20 ml.) for 3 hr. and then acidified. The product crystallised from dilute ethyl alcohol in colourless needles. M.P. and mixed m.p. with 2-hydroxy-3-methyl-4-methoxybenzoic acid prepared according to Da Re et al. (loc. cit.) was 214°.

7-Methoxy-8-acetoxymethyl-2-methylchromone

7-Methoxy-8-chloromethyl-2-methylchromone (0.5 g.) was refluxed with freshly fused and powdered sodium acetate (3 g.) in glacial acetic acid (2 ml.) for 3 hr. The product obtained on dilution of the reaction mixture with water crystallised from benzene and petroleum ether (b.p. 60-80°) mixture in colourless needles, m.p. 162°. Some decomposition was observed during crystallisation from aqueous solvents.

Analysis :

4.302 mg. of the substance gave 10.176 mg. of carbon dioxide and 2.154 mg. of water.

Found : C = 64.46 % ; H = 5.59 %.

$C_{14}H_{14}O_5$ requires : C = 64.11 % ; H = 5.38 %.

7-Methoxy-8-methoxymethyl-2-methylchromone

It was prepared by refluxing the chloromethyl derivative (0.5 g.) with absolute methyl alcohol (10 ml.) in presence of anhydrous potassium carbonate (1 g.) for 1 hr. The product obtained on dilution of the reaction mixture crystallised from benzene in colourless needles, m.p. 132-133°

Analysis :

3.510 mg. of the substance gave 8.518 mg. of carbon dioxide and 1.842 mg. of water.

Found : C = 66.23 % ; H = 5.87 %.

$C_{13}H_{14}O_4$ requires : C = 66.65 % ; H = 6.02 %.

Attempted Sommelet reaction

The chloromethyl derivative (0.5 g.) was dissolved in chloroform (15 ml.) and refluxed with hexamin (0.5 g.) for 2 hr. The separated complex was hydrolysed with 80 % acetic acid (20 ml.) by refluxing for 2 hr. No definite product could be isolated. Hydrolysis of the complex product with dilute hydrochloric acid also failed.

7-Methoxy-8-cyanomethyl-2-methylchromone

The alcoholic solution of the chloromethyl derivative (0.5 g.) was refluxed with potassium cyanide (0.5 g.) in water (2 ml.) for half an hour on a steam bath. The reaction mixture on dilution yielded a solid which crystallised from dilute acetic acid in colourless needles, m.p. 170°.

Analysis :

4.554 mg. of the substance gave 11.296 mg. of carbon dioxide and 2.02 mg. of water.

6.712 mg. of the same substance gave 0.39 ml. of nitrogen at 39° and 753 mm.

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 %.

Chloromethylation of 7-methoxy-8-chloromethyl-2-methylchromone : 7-Methoxy-3,8-dichloromethyl-2-methylchromone

7-Methoxy-8-chloromethyl-2-methylchromone (1.2 g. ; 0.005 mole) was dissolved in glacial acetic acid (25 ml.) and paraformaldehyde (0.75 g. ; 0.025 mole) was added. Hydrogen chloride was passed through the reaction mixture for 6 hr. at 75-80°. The product obtained on dilution of the reaction mixture with water crystallised from benzene and petroleum ether (b.p. 60-80°) mixture in colourless needles, m.p. 204°. Yield 0.8 g.

The same dichloromethyl derivative was also obtained when 7-methoxy-2-methylchromone (1.9 g. ; 0.01 mole) was chloromethylated with paraformaldehyde (5 g.) by passing the hydrogen chloride for 2 hr. at 85-90°. Yield 1. 0 g.

Analysis :

4.196 mg. of the substance gave 8.414 mg. of carbon dioxide and 1.582 mg. of water.

20.30 mg. of the same substance gave 19.72 mg. of silver chloride.

Found : C = 54.72 % ; H = 4.22 % ; Cl = 24.04 %.

$C_{13}H_{12}O_3Cl$ requires : C = 54.35 % ; H = 4.18 % ; Cl = 24.47 %.

7-Methoxy-2,3,8-trimethylchromone

The above dichloromethyl derivative (0.5 g.) was reduced with zinc dust (2 g.) and acetic acid (10 ml.) and water (2 ml.) as usual. The separated product on dilution of the reaction mixture with water crystallised from dilute alcohol in colourless needles, m.p. and mixed m.p. with 7-methoxy-2,3,8-trimethylchromone (Da Re et al. loc. cit.) was 149-150°.

Analysis :

4.82 mg. of the substance gave 12.880 mg. of carbon dioxide and 2.684 mg. of water.

Found : C = 71.22 % ; H = 6.23 %.

$C_{13}H_{14}O_3$ requires : C = 71.54 % ; H = 6.47 %.

The above reduction product (0.4 g.) when refluxed with sodium hydroxide solution (10 % ; 20 ml.) for 3 hr. gave 2-hydroxy- 3-methyl-4-methoxybenzoic acid described before.

7-Methoxy-3,8-diacetoxymethyl-2-methylchromone

7-Methoxy-3,8-dichloromethyl-2-methylchromone (0.3 g.) was refluxed in glacial acetic acid (10 ml.) in presence of fused sodium acetate (2 g.) for 1 hr. The product obtained crystallised from benzene and petroleum ether (b.p. 60-80°) mixture in colourless needles, m.p. 159°.

Analysis :

4.892 mg. of the substance gave 10.974 mg. of carbon dioxide and 2.352 mg. of water.

Found : C = 61.21 % ; H = 5.38 %.

$C_{17}H_{18}O_7$ requires : C = 61.07 % ; H = 5.43 %.

7-Methoxy-3,8-dimethoxymethyl-2-methylchromone

It was prepared by refluxing the dichloromethyl derivative (0.5 g.) in absolute methyl alcohol (20.0 ml.) in presence of anhydrous potassium carbonate (1 g.). The product obtained crystallised from benzene and petroleum ether (b.p. 60-80°) mixture in colourless needles, m.p. 142°.

Analysis :

4.606 mg. of the substance gave 10.938 mg. of carbon dioxide and 2.572 mg. of water.

Found : C = 64.80 % ; H = 6.25 %.

$C_{15}H_{18}O_5$ requires : C = 64.73 % ; H = 6.52 % .

7-Methoxy-3,8-dicyanomethyl-2-methylchromone

It was prepared by refluxing the dichloromethyl derivative (0.5 g.) in ethyl alcohol (2.0 ml.) with potassium cyanide (1 g.) in water (2 ml.) for 1 hr. on a steam bath. The product crystallised in colourless needles from dilute acetic acid, m.p. 173°.

Analysis :

4.230 mg. of the same substance gave 10.450 mg. of carbon dioxide and 1.840 mg. of water.

6.224 mg. of the same substance gave 0.613 mg. of nitrogen at 41° and 753 mm.

Found : C = 67.42 % ; H = 4.87 % ; N = 10.60 %.

$C_{15}H_{12}O_3N_2$ requires : C = 67.15 % ; H = 4.51 % ; N = 10.44 %.

<u>Chloromethylation of 7-methoxyflavone</u> : <u>7-Methoxy-8-chloromethylflavone</u>

7-Methoxyflavone (2.52 g. ; 0.01 mole) was dissolved in acetic acid (25 ml.) and water (2.0 ml.) and paraformaldehyde (0.9 g. ; 0.03 mole) was added. The reaction mixture was then kept at 75-80° and saturated with hydrogen chloride for 5 hr. The reaction mixture was cooled and diluted with excess of cold water and the separated product crystallised from benzene and petroleum ether (b.p. 60-80°)mixture in colourless needles, m.p. 227°. Yield 0.9 g.

The use of zinc chloride (1 g.) as a catalyst in the above reaction improved the yield (1.2 g.)

<u>Analysis</u> :

4.528 mg. of the substance gave 11.280 mg. of carbon dioxide and 1.748 mg. of water.

18.10 mg. of the same substance gave 9.0 mg. of silver chloride.

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 %.

<u>7-Methoxy-8-methylflavone</u>

The above chloromethyl derivative (0.2 g.) was reduced with zinc dust (1 g.) and aqueous acetic acid (10 ml.) as before. The reaction mixture on dilution with water gave a shining product which crystallised in colourless needles from dilute ethyl alcohol. M.P. and mixed m.p. with 7-methoxy-8-methylflavone synthesised as described below was 171°.

7-Hydroxy-8-methylflavone

2-Methylresorcinol (2.48 g. ; 0.02 mole) and ethyl benzoylacetate (5.8 g. ; 0.03 mole)were refluxed in dry diphenyl ether (20 ml.) for 2 hr. The diphenyl ether was removed by steam distillation and the residue was washed with petroleum ether (60-80°) . It was first crystallised from dilute acetic acid and then from ethyl alcohol in needles, m.p. 255-257°. Rangaswami and Seshadri (Proc. Indian Acad. Sci., 1939, 9A, 1) synthesised it from 2,4-dihydroxy-3-methylacetophenone by the Kostanecki-Robinson benzoylation and subsequent debenzoylation with alkali. They give the same m.p.

Analysis :

4.468 mg. of the substance gave 12.518 mg. of carbon dioxide and 1.926 mg. of water.

Found : C = 76.46 % ; H = 4.82 %.

$C_{16}H_{12}O_3$ requires : C = 76.12 % ; H = 4.80 %.

7-Methoxy-8-methylflavone

The above hydroxyflavone (0.3 g.) was refluxed in acetone solution with dimethyl sulphate (0.3 ml.) in presence of anhydrous potassium carbonate (0.6 g.) for 2 hr. The product obtained on removal of acetone crystallised from dilute ethyl alcohol in colourless needles, m.p. 171°.

Analysis :

4.076 mg. of the substance gave 11.434 mg. of carbon dioxide and 1.812 mg. of water.

Found : C = 76.55 % ; H = 4.97 %.

$C_{17}H_{14}O_3$ requires : C = 76.67 % ; H = 5.30 %.

The above reduction product (0.5 g.) when refluxed with sodium hydroxide solution (10 % ; 20 ml.) for 3 hr. and acidified gave 2-hydroxy-3-methyl-4-methoxybenzoic acid.

7-Methoxy-8-acetoxymethylflavone

It was obtained by refluxing the chloromethyl derivative (0.5 g.) with glacial acetic acid (2.0 ml.) and fused sodium acetate (1 g.) for 1 hr. It crystallised from benzene and petroleum ether (b.p. 60-80°) mixture in colourless needles, m.p. 181°.

Analysis :

5.470 mg. of the substance gave 14.042 mg. of carbon dioxide and 2.480 mg. of water.

Found : C = 70.06 % ; H = 5.07 %.

$C_{19}H_{16}O_5$ requires : C = 70.36 % ; H = 4.98 %.

7-Methoxy-8-methoxymethylflavone

It was prepared by refluxing the chloromethyl derivative (0.5 g.) with absolute methyl alcohol (2.0 ml.) and anhydrous potassium carbonate (1 g.) for 1 hr. on a steam bath. It crystallised from benzene and petroleum ether mixture in colourless needles, m.p. 168°.

Analysis :

4.22 mg. of the substance gave 11.208 mg. of carbon dioxide and 2.038 mg. of water.

Found : C = 72.48 % ; H = 5.40 %.

$C_{18}H_{16}O_4$ requires : C = 72.96 % ; H = 5.44 %.

7-Methoxy-8-cyanomethylflavone

It was obtained by refluxing the above chloromethyl derivative (0.5 g.) in ethyl alcohol (2.0 ml.) with potassium cyanide (0.5 g.) in water (2 ml.) for 2 hr. on a steam bath. It crystallised from dilute acetic acid in greenish white needles, m.p. 216°.

Analysis :

4.470 mg. of the substance gave 12.160 mg. of carbon dioxide and 1.910 mg. of water.

9.762 mg. of the same substance gave 0.445 ml. of nitrogen at 40° and 757 mm.

Found : C = 74.24 % ; H = 4.78 % ; N = 4.95 %.

$C_{18}H_{13}O_3N$ requires : C = 74.21 % ; H = 4.50 % ; N = 4.81 %.

7-Methoxyflavone-8-acetic acid

The above cyanomethyl derivative (0.4 g.) was refluxed with sulphuric acid (2 ml.) and water(8 ml.) for 3 hr. The product obtained on dilution of the reaction mixture was purified through dilute sodium bi-carbonate solution. It crystallised from dilute acetic acid in colourless needles, m.p. 253°.

Analysis :

4.734 mg. of the substance gave 12.11 mg. of carbon dioxide and 1.780 mg. of water.

Found : C = 69.81 % ; H = 4.20 %.

$C_{18}H_{14}O_5$ requires : C = 69.67 % ; H = 4.55 %.

Chloromethylation of 7-methoxy-8-chloromethylflavone : 7-Methoxy-3,8-dichloromethylflavone

7-Methoxy-8-chloromethylflavone (1.5 g. ; 0.005 mole) was dissolved in acetic acid (40 ml.) and water (5 ml.) and paraformaldehyde (0.75 g. ; 0.025 mole) was added. The reaction mixture was saturated with hydrogen chloride for 6 hr. at 75-80°. The separated product crystallised from benzene in colourless transparent cubes, m.p. 184°. Yield 0.7 g.

The same dichloromethyl derivative was also obtained when 7-methoxyflavone (2.5 g. ; 0.01 mole) and paraformaldehyde (1.5 g. ; 0.05 mole) were heated with hydrogen chloride for 7 hr at 75-80°.

Analysis :

4.548 mg. of the substance gave 10.282 mg. of carbon dioxide and 1.578 mg. of water.

15.42 mg. of the same substance gave 12.50 mg. of silver chloride.

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 %.

7-Methoxy-3,8-dimethylflavone

The above dichloromethyl derivative (0.5 g.) was reduced by treating its acetic acid solution with zinc dust (2 g.) at 75-80° for 1 hr. On dilution it gave a pasty product which crystallised from dilute alcohol in colourless needles. M.P. and mixed m.p. with 7-methoxy-3,8-dimethylflavone prepared according to Da Re et al. (loc.cit.) was 139-141°.

The above reduction product (0.3 g.) when refluxed with sodium hydroxide solution (10 % ; 20 ml.) for 3 hr. and then acidified gave 2-hydroxy-3-methyl-4-methoxybenzoic acid described before.

7-Methoxy-3,8-diacetoxymethylflavone

It was obtained by refluxing the dichloromethyl derivative (0.5 g.) with acetic acid (15.0 ml.) and fused sodium acetate (2 g.) for 2 hr. It crystallised from benzene and petroleum ether (b.p. 60-80°) mixture in colourless needles, m.p. 145°.

Analysis :

4.056 mg. of the substance gave 9.888 mg. of carbon dioxide and 1.952 mg. of water.

Found : C = 66.53 % ; H = 5.38 %.
$C_{22}H_{20}O_7$ requires : C = 66.66 % ; H = 5.09 %.

7-Methoxy-3,8-dimethoxymethylflavone

It was obtained by refluxing the dichloromethyl derivative (0.5 g.) with absolute methyl alcohol (20 ml.) and anhydrous potassium carbonate (1.0 g.) for 2 hr. It crystallised from benzene and petroleum ether (b.p. 60-80°) mixture in colourless needles, m.p. 157-158°.

Analysis :

5.128 mg. of the substance gave 13.272 mg. of carbon dioxide and 2.706 mg. of water.

Found : C = 70.63 % ; H = 5.90 %.

$C_{20}H_{20}O_5$ requires : C = 70.57 % ; H = 5.92 %.