CHAPTER III

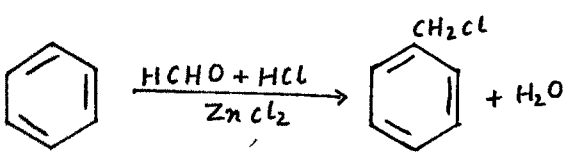
CHLOROMETHYLATION OF SOME FLAVONES AND FLAVANONES

CHAPTER III

T H E O R E T I C A L

Chloromethylation of some flavones and flavanones

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 generally carried out by the condensation of formaldehyde with an aromatic compound in the presence of hydrochloric acid. Some times a catalyst such as zinc chloride is used.



A survey of chloromethylation of aromatic compounds upto 1941 has been made by Fuson and McKeever (1) and some of the more recent work has been reviewed by Olah and Tolgyesi (2) in a recent monograph on Friedel-Crafts and Related Reactions.

The reaction is of synthetic importance because of the ease with which the chlorine atom in chloromethyl group undergoes substitution reactions with various reagents, for example, the chlorine of the chloromethyl group can be replaced by a hydroxy, cyano, methoxy, acetoxy or other groups by treating it with appropriate reagents.

Further, on Sommelet reaction the chloromethyl group can be replaced by the formyl group. On oxidation the chloromethyl derivative is readily converted into the corresponding acid and on reduction it gives rise to the methyl derivative.

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

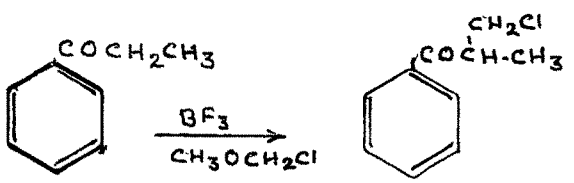
Application of the reaction :

Chloromethylation is generally applicable to aromatic hydrocarbons ; though the application to the aliphatic compounds is not uncommon. Aromatic hydrocarbons such as benzene, naphthalene, anthracene, phenanthrene, diphenyl and many of their derivatives have been successfully chloromethylated. Substituents such as hydroxyl, alkyl and alkoxy accelerate the reaction and the reaction proceeds even in the absence of a catalyst to form the mono-or di(chloromethyl) derivative in good yield. The reactivity increases rapidly with electropositive substituents. Highly alkylated homologues react rapidly in the absence of a catalyst. Thus Nauta and Dienske (3) chloromethylated mesitylene without using any catalyst and obtained the mono as well as dichloromethyl derivative. Braun and Nelles (4) chloromethylated m-xylene and obtained the dichloromethyl

derivative. Chloromethylation of a monoalkyl benzene derivative gives a higher percentage of para isomer (with respect to the alkyl group) than the ortho isomer. A second chloromethyl group usually can be introduced some-times in excellent yield. An electro-negative group in the benzene ring deactivates the molecule. Stephen et al. (5) found that nitrobenzene and ortho and para nitrotoluenes gave chloromethyl derivatives but in low yield. Similarly the presence of a halogen atom in the nucleus retards the reaction, but, by using drastic methods the yield can be increased. Substances such as ortho and para-chloronitrobenzenes and para-dichlorobenzene do not react at all. The presence of alkyl groups in the nucleus however counteracts the influence of these substituents. Vavon et al. (6) got the chloromethyl derivative on chloromethylation of bromositylene. Wakae et al. (7) chloromethylated 2-ethoxy and 3-ethoxynitrobenzenes and obtained the monochloromethyl derivatives. Buc (8) prepared the 6-chloro-methyl derivative from 2-nitro-4-chlorotoluene.

Ketones are generally unreactive. Fuson and McKeever (9) found that benzophenone cannot be chloromethylated, but Balani and Sethna (10) have successfully chloromethylated 4-hydroxy-benzophenone and its methyl ether. Stephen et al. (5) failed to chloromethylate anthraquinone. Here also the presence of an alkyl group in the nucleus counteracts this

influence. Thus Fuson and McKeever (9) chloromethylated acetomesitylene and obtained α^3-chloroacetoisodurene successfully. In aromatic ketones such as resacetophenone the chloromethyl group may enter either ~~in~~ the side chain or the nucleus as observed by Tilichenko et al. (11) and Chaikovskaya (12). Thus β-chloromethyl ketone was obtained on chloromethylation of ethyl phenyl ketone with CH_3OCH_2Cl in the presence of BF_3 as a catalyst.



However, in the case of o-hydroxyphenyl ethyl ketone the chloromethyl group entered only the nucleus as seen by Da Re et al. (13).

Aromatic amines react vigorously but complex condensation products are invariably the result of the reaction and it has not been possible to isolate simple chloromethyl derivatives from these compounds, as observed by Wagner (14).

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 products in the case of phenols is to convert them to esters by treatment with ethyl chlorocarbonate. Ethyl arylcarbonates undergo smooth chloromethylation,

as observed by Sommelét et al. (15). The activating influence of hydroxy groups may be sufficiently moderated by deactivating groups such as nitro, carboxy-, or acetyl- to make a smooth reaction possible. Stoermer and Bohn (16) successfully chloromethylated o-nitrophenol. Buchler (17) chloromethylated salicylic acid and obtained the 5-chloromethyl product in good yield. Polyhydric phenols have not been successfully chloromethylated so far. Attempts to chloromethylate resorcinol and hydroquinone met with failure.

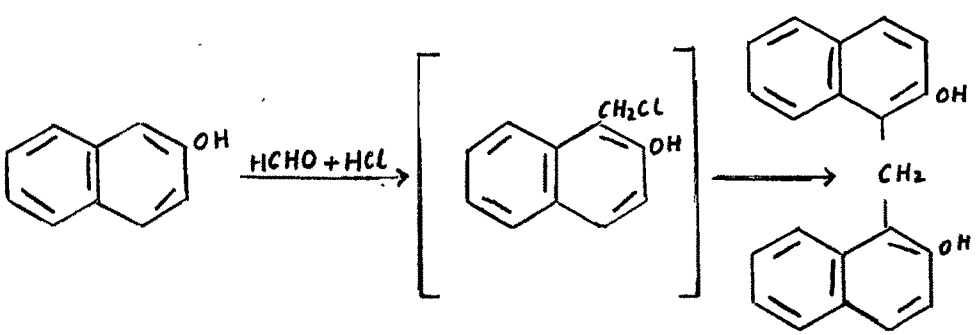
Phenol ethers react smoothly. Phenol ethers and other phenolic compounds containing an aldehyde group also react in a satisfactory manner.

Mndzhoyan and Aroyan (18) studied the effects of the alkoxy groups in chloromethylation. They chloromethylated anisole, phenetole, isopropyloxy benzene and butyloxybenzene and they found that the yield decreases according to the bulk of the group. While they could isolate the dichloromethyl derivative of anisole in 90 % yield, the butyloxybenzene gave only 48 % di-chloromethyl derivative. Profft and Drux (19) have also studied the chloromethylation of alkoxybenzenes. They could get the monochloromethyl derivative of phenetole in 71 % yield, the amyloxybenzene gave only 59 % monochloromethyl derivative.

Aromatic compounds with more than one ether group react vigorously as expected. Melnikov and Parilutskaya (20) have isolated mono as well as

di(chloromethyl) derivatives of alkoxy derivatives of hydroquinone. However, the dimethyl ethers of resorcinol and catechol did not give pure products on chloromethylation. Negative groups in the polyalkoxy benzenes retard the reaction considerably giving rise to chloromethyl derivatives in a satisfactory manner. Quelet (21) chloromethylated 3,4-dimethoxy bromobenzene and obtained 2-bromo-4,5-dimethoxy benzylchloride. Mathai and Sethna (22) studied the chloromethylation of negatively substituted resorcinols.

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. Castiglioni (23) chloromethylated β-naphthol and obtained the corresponding diarylmethane derivative.

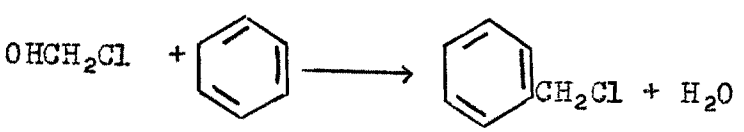


Mechanism :

The various views on the mechanism of chloromethylation have been reviewed by Olah and Tolgyesi (2) and the salient points are given below.

The exact mechanism of the chloromethylation of aromatic compounds with formaldehyde and hydrogen chloride has not yet been established. The intermediate formation of chloromethanol ($ClCH_2OH$) has been suggested and the

$$CH_2O \ (aq) + HCl \longrightarrow HOCH_2Cl$$



same mechanism may hold good when the reaction is carried out with chloromethyl ether. But the evidence for the formation of the chloromethanol has not been found. Probably the Cl-C bond in the chloromethanol would be immediately hydrolysed in the aqueous media. It is probable that the reaction proceeds through a protonated formaldehyde or involves the formaldehyde-Lewis acid halide complex, as a reactive carbonium ion type reagent.

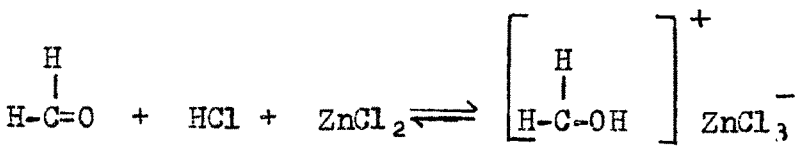
Ogata (24) studied the rate of the chloromethylation of mesitylene with formalin in aqueous acetic acid and concluded that the protonated formaldehyde was the attacking species under the conditions employed(hydroxylic solvent) and the hydroxymethyl and chloromethyl derivatives were in a mobile equilibrium.

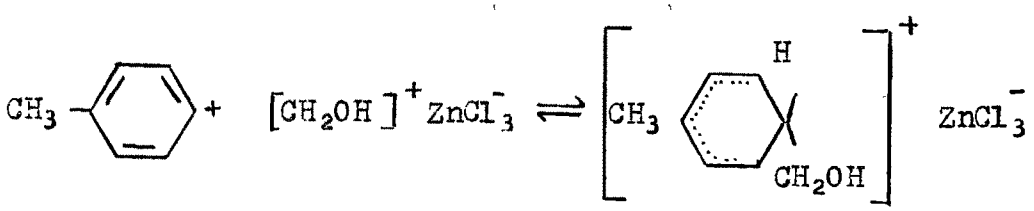
$$CH_2O + H^+ \rightleftharpoons {}^{+}CH_2OH$$

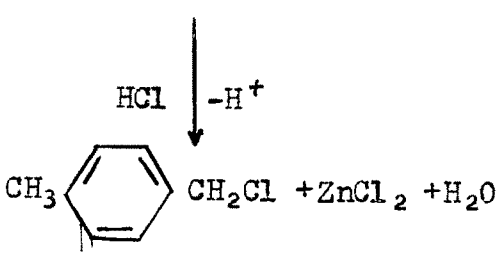
$$ArH + {}^{+}CH_2OH \longrightarrow ArCH_2OH + H^+$$

$$ArCH_2OH + HCl \rightleftharpoons ArCH_2Cl + H_2O$$

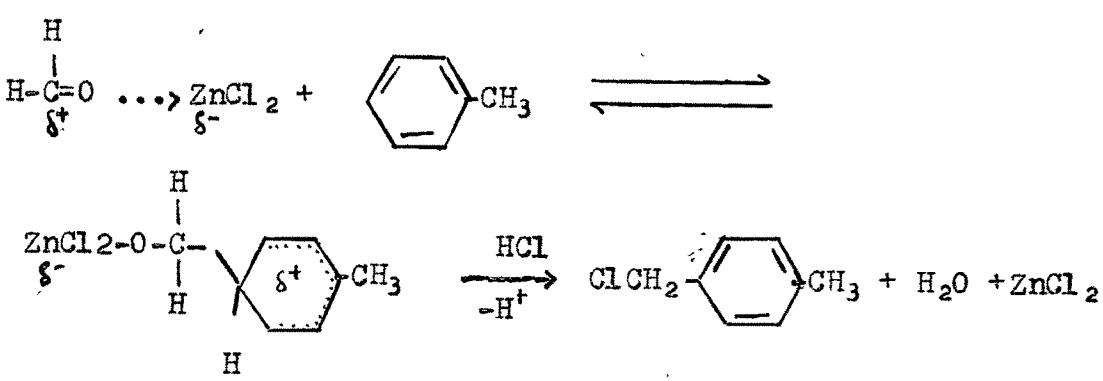
The same mechanism involving zinc chloride and hydrochloric acid as the catalysts can be written as follows :







or :



If the reaction involves the formation of a relatively stable carbonium ion, $HOCH_2^+$, the possible resonance with $H\overset{+}{O} = CH_2$ would be expected to greatly stabilize the intermediate ion and to facilitate its formation.

Nazarov and Semenovsky (25) studied the mechanism of the halomethylation and came to the conclusion that the active intermediate is the hydroxymethyl cation ($[CH_2OH]^+$), and not the chloromethyl cation ($[CH_2Cl]^+$) suggested by Wichterle and Cerny (26).

Another strong argument, in favour of the hydroxymethylation mechanism of halomethylation, lies in the fact that chloromethylation gives the same isomer distribution as bromomethylation for a number of aromatics (42,43). This indicates a common attacking species in both reactions. If halomethylation proceeded with the participation of halomethyl ions, then on steric grounds, the bromomethylation of toluene, ethylbenzene, and cumene should result in the formation of less ortho- and more para-isomer than the chloromethylation.

The hydroxymethyl-ion mechanism of halomethylation is further supported by the work of Wadane, Trogus and Hess (44) who established the following equilibria in acedic media, indicating the presence of the hydroxymethyl cation :

pH	Equilibrium
below 2.6	$H_2C(OH)_2 \rightleftharpoons H_2C^+-OH + \bar{O}H$
2.6-4.5	$H_2C(OH_2) \rightleftharpoons H_2C^+-\bar{O} + \bar{O}H + \overset{+}{H}$
above 4.5	$H_2C(OH)_2 \rightleftharpoons H_2C(OH)\bar{O} + H^+$

The role of catalysts, solvents and temperature in chloromethylation :

There are a variety of techniques reported in the literature on 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 (28) introduced the chloromethyl group into 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 (29) 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 (30) 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 the 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^{o} while temperatures of $60\text{-}70^{o}$ are much favoured for less reactive compounds. Sometimes reactions are carried out at 140^{o} under pressure.

Chloromethyl ether (CH_3OCH_2Cl) or dichloromethyl ether ($ClCH_2\text{-}O\text{-}CH_2Cl$) 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.

Weisler and Chechak (31) 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 flavones and flavanones

Nakamura and Matsura (32) 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 (32,33) chloromethylated 7-methoxy-3-methylflavone and 7-methoxy-3-ethylflavone and obtained 8-chloromethyl derivative in both the cases. In this laboratory, Shah and Sethna (34) chloromethylated simple flavone and obtained 3-chloromethylflavone. The same authors also chloromethylated 7-methoxyflavone and obtained 8-chloromethyl and 3,8-dichloromethyl derivatives. A few chloromethyl derivatives of flavones have been prepared by other methods. For example, Schonberg et al. (35) treated Khellol with thionyl chloride and obtained the 2-chloromethyl derivative. Da Re et al. (33) obtained 6-chloromethyl derivative from 6-hydroxymethyl-3-methylflavone by treatment with zinc chloride and hydrochloric acid. Matsuka (36) chloromethylated simple and 5,7-dimethyl-4'-methoxyflavanone with chloromethyl ether in acetic acid and obtained chloromethyl derivative in each case but they have not proved the structures. This appears to be the only instance in literature of chloromethylation of flavanones.

In the present work the chloromethylation of 7-hydroxyflavone, 6-hydroxy and 6-methoxyflavone, simple flavanone and 7-methoxyflavanone has been carried out.

Some of the chloromethyl derivatives have been further converted into Mannich bases by reaction with secondary amines such as dimethylamine and morpholine. Da Re et al. (33) prepared Mannich bases from 7-methoxy-3-ethyl-8-chloromethylflavone by reacting with various organic bases such as dimethylamine, diethylamine, piperidine and morpholine.

Some of them have been found to have good Central Nervous System stimulant activity.

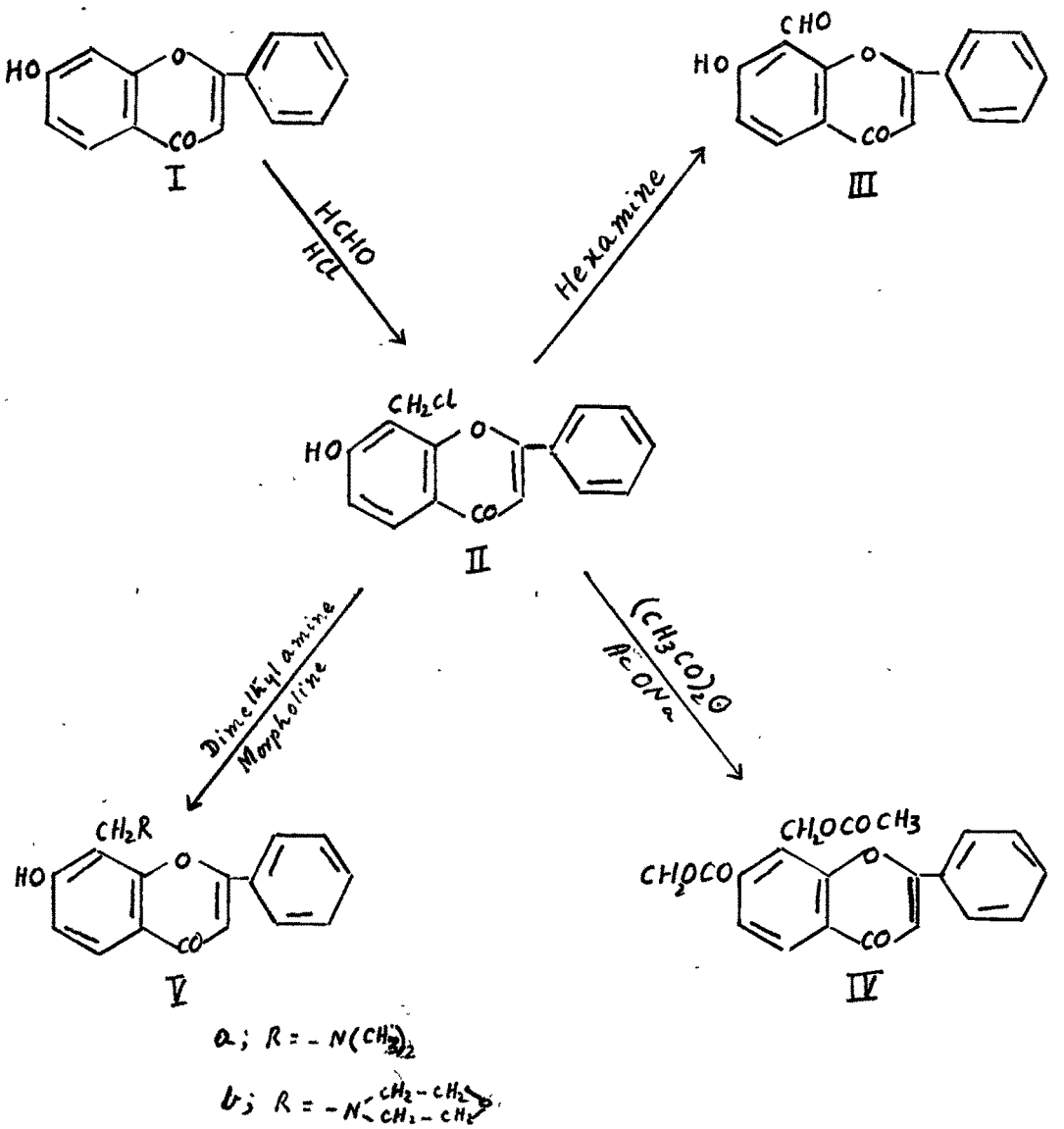
The chloromethyl derivatives have also been subjected to Sommelet reaction to get the corresponding formyl derivatives and also to the action of sodium acetate and acetic anhydride to convert them into the acetoxymethyl derivatives.

Chloromethylation of 7-hydroxyflavone

7-Hydroxyflavone (I) did not undergo chloromethylation with either two or three moles of paraformaldehyde and hydrochloric acid at 90-95°. However, with four moles of paraformaldehyde it gave a monochloromethyl derivative. On heating with hexamine in acetic acid it gave the known 7-hydroxy-8-formyl-flavone (III) (37) as seen by direct comparison with an authentic specimen. 7-Hydroxy-8-chloromethylflavone (II) structure has therefore been assigned to the chloromethyl derivative. On heating with acetic anhydride and fused sodium acetate the chloromethyl derivative gave 7-acetoxy-8-acetoxymethyl flavone (IV)

and with dimethylamine and morpholine the corresponding Mannich bases (V a,b).

No di(chloromethyl) derivative could be isolated even with excess of paraformaldehyde.



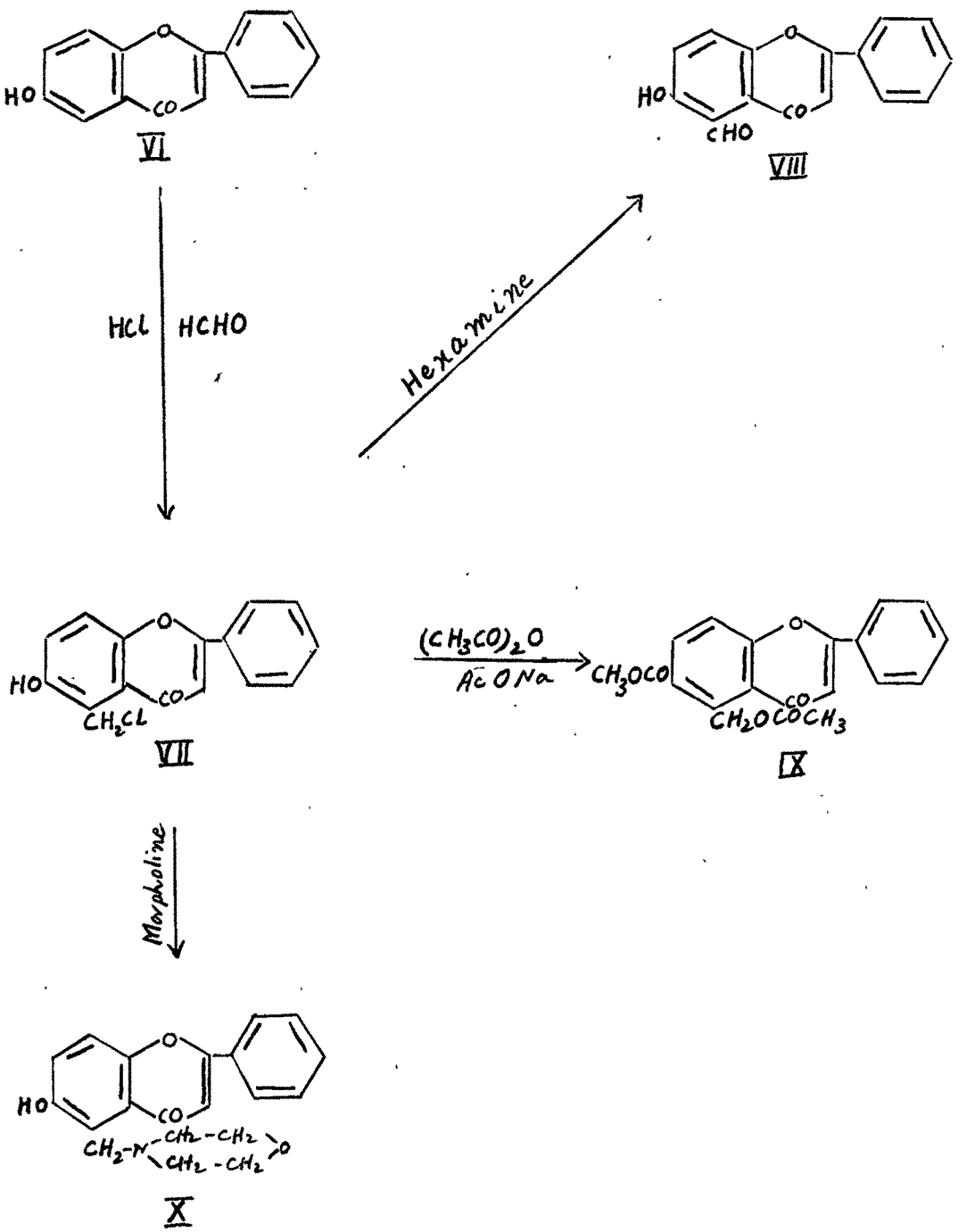
Chloromethylation of 6-hydroxyflavone

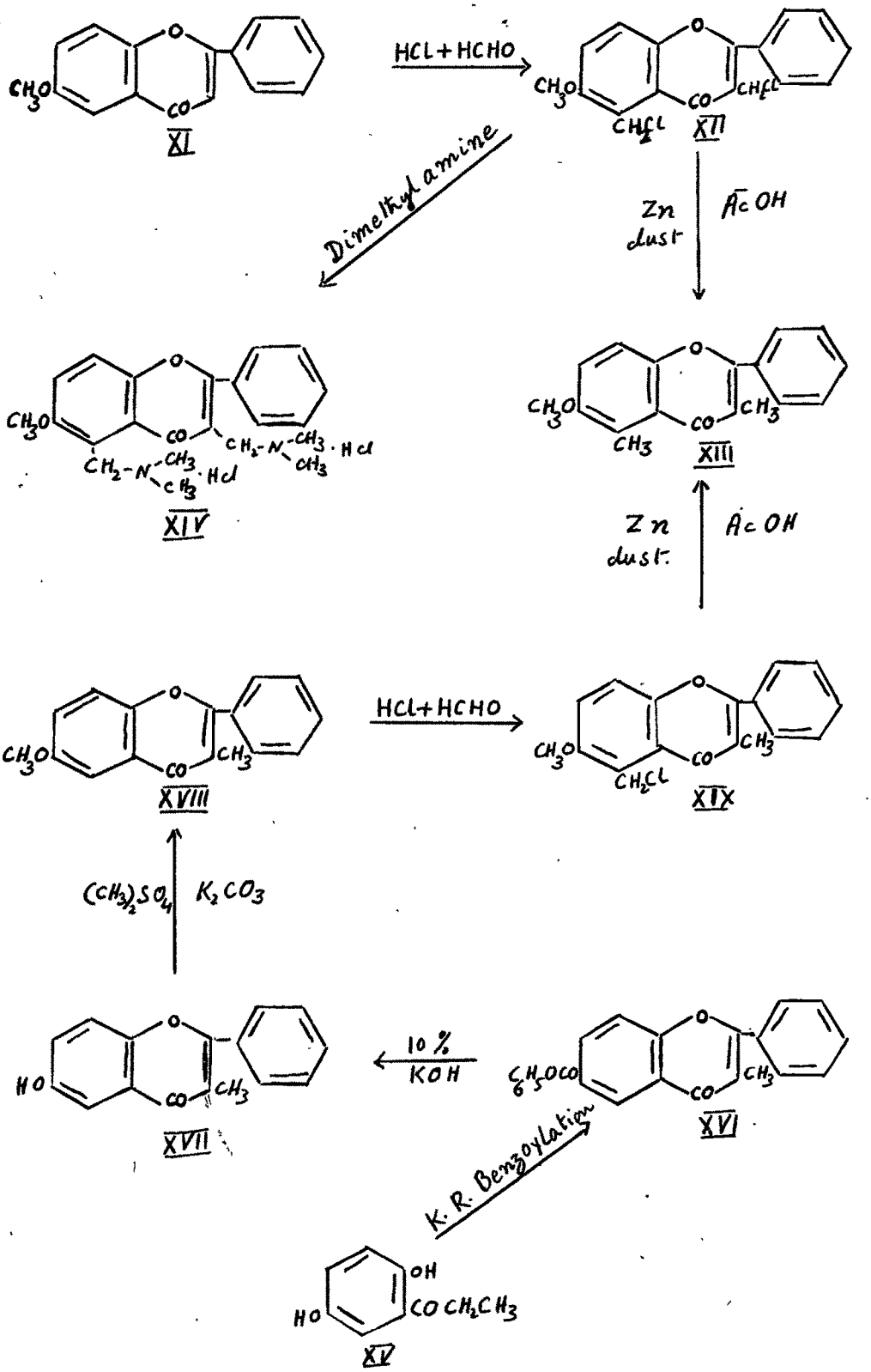
6-Hydroxyflavone (VI) did not undergo chloromethylation with either two or three moles of paraformaldehyde and hydrochloric acid. However, with four moles of paraformaldehyde it gave a monochloromethyl derivative which when heated with hexamine in acetic acid gave the known 6-hydroxy-5-formylflavone (VIII) (38) as seen by direct comparison with an authentic specimen. So the 6-hydroxy-5-chloromethyl flavone (VII) structure has been assigned to the monochloromethyl derivative. On heating with acetic anhydride and fused sodium acetate the monochloromethyl derivative gave 6-acetoxy-5-acetoxymethyl flavone (IX) and with morpholine the corresponding Mannich base (X) was obtained.

No di(chloromethyl) derivative could be isolated even with excess of paraformaldehyde. When zinc chloride was used a complex compound was obtained.

Chloromethylation of 6-methoxyflavone

6-Methoxyflavone (XI) did not undergo chloromethylation with four moles or less than four moles of paraformaldehyde even at 90-95°. With one mole of paraformaldehyde and hydrogen chloride in presence of anhydrous zinc chloride a complex compound with zinc chloride was obtained. This was seen by the fact that the same product was obtained when the reaction was repeated


HO
CO
VI
HCl HCHO
Hexamine
HO
CHO
CO
VIII
HO
CO
CH2Cl
VII
(CH3CO)2O
AcONa
CH3OCO
CO
CH2OCOCH3
IX
Morpholine
HO
CO
CH2-N
CH2-CH2
CH2-CH2
O
X


HCl + HCHO
Dimethyl amine
Zn dust
AcOH
Zn dust
AcOH
HCl + HCHO
(CH3)2SO4
K2CO3
10 %
KOH
K. R. Benzoylation

without adding paraformaldehyde.

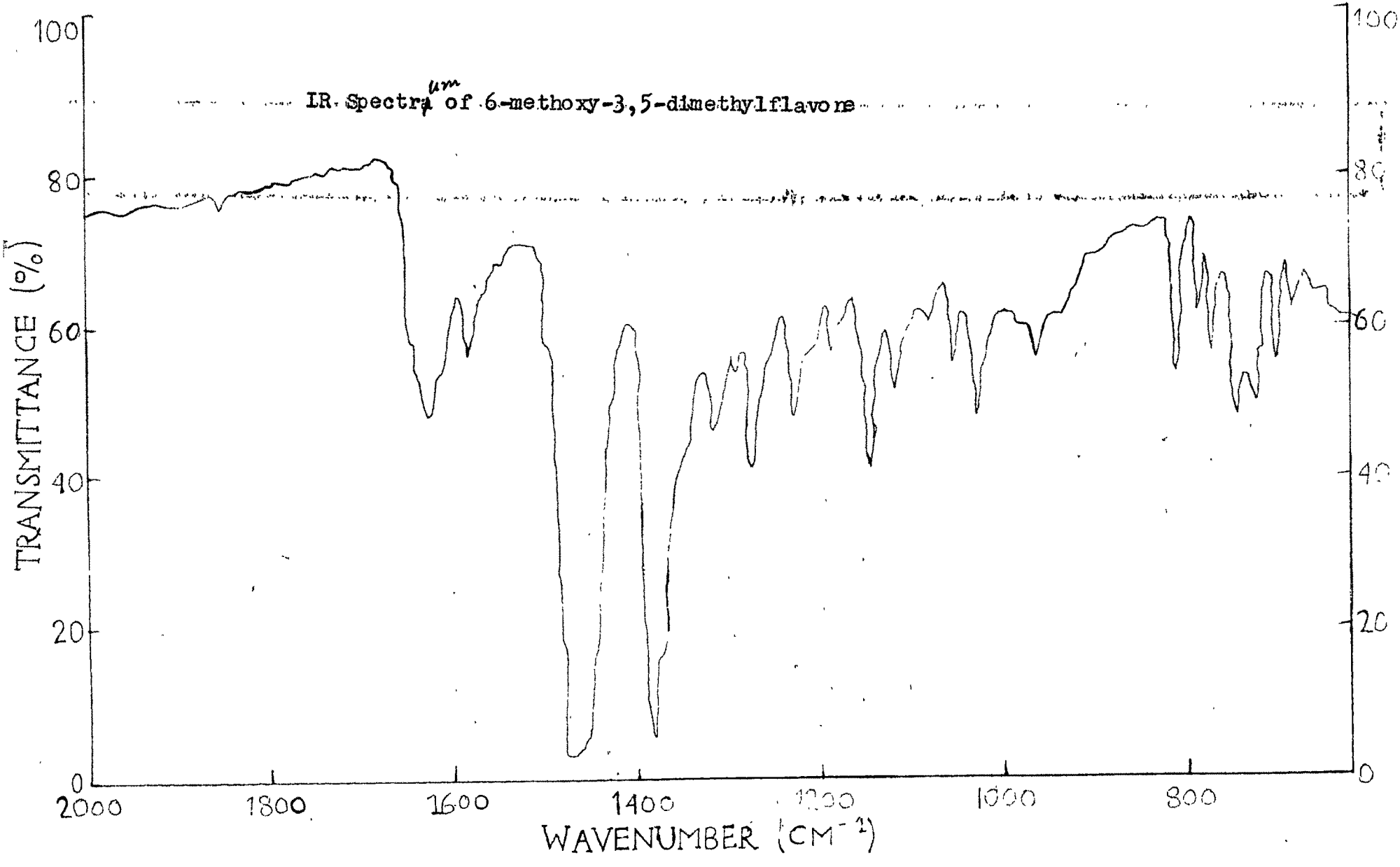
On chloromethylation with excess (8 moles) of paraformaldehyde 6-methoxyflavone (XI) gave a di-(chloromethyl) derivative which on reduction gave a product m.p. 136°. This was identical with the product obtained on the reduction of the monochloromethyl derivative formed on chloromethylation of 6-methoxy-3-methylflavone (XVIII) which is hitherto unknown and was prepared through the Kostanecki-Robinson benzoylation of Quinpropiophenone (XV). Therefore, one of the chloromethyl group must have entered the 3-position. The di(chloromethyl) derivative has been assigned the 6-methoxy-3,5-di(chloromethyl) flavone (XII) structure.

It has not been possible to get the NMR data.

The IR spectra for the dimethyl derivative and for 6-methoxyflavone have been obtained (Fig. 1 and 2 respectively) The sharp band at 810 cm^{-1} in the spectrum of the dimethyl derivative points to the presence of a 1,2,3,4-tetra substituted benzene ring. If the second methyl group had been in the 7-position it would have given a band at about 870 cm^{-1} showing the presence of a 1,2,3,4,5-penta substituted benzene ring but this band is absent. This data therefore lends support to the 3,5-di(chloromethyl) structure.

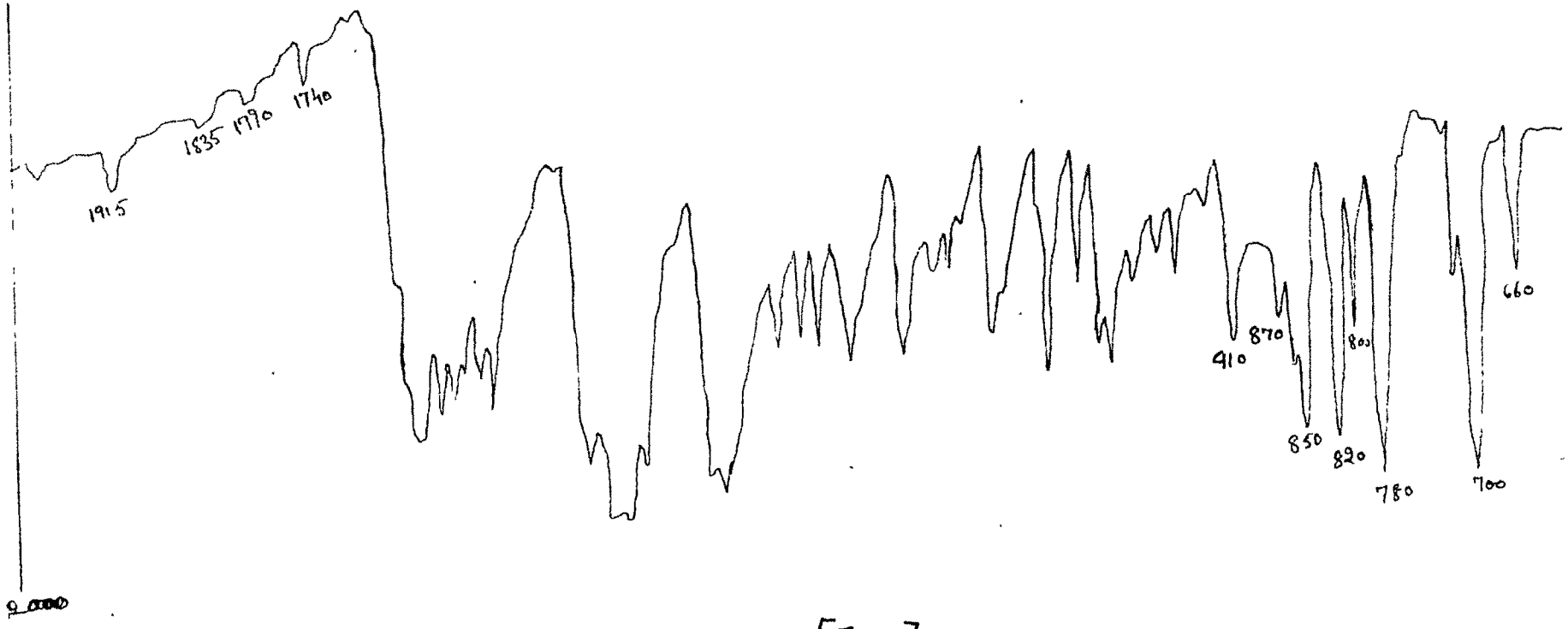
On heating with dimethylamine the di(chloromethyl) derivative gave the corresponding Mannich base (XIV).

No trichloromethyl derivative could be obtained on chloromethylation of 6-methoxyflavone (XI) or


IR Spectrum of 6-methoxy-3,5-dimethylflavone
TRANSMITTANCE (%)
WAVENUMBER (CM⁻¹)
100
80
60
40
20
0
2000
1800
1600
1400
1200
1000
800

[Fig 1]

IR Spectrum of 6-methoxyflavone



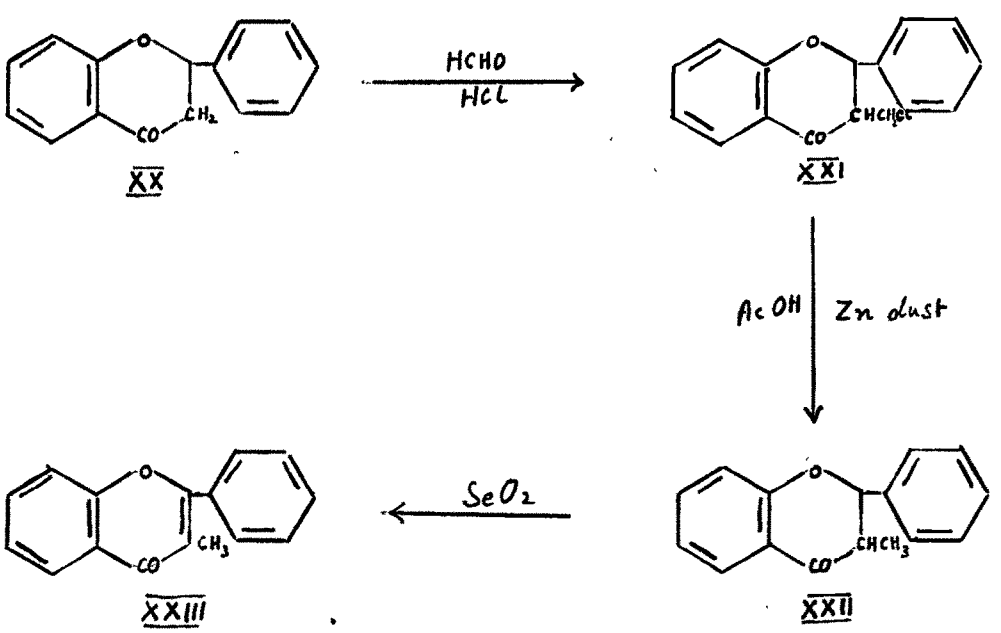
[Fig 2]

6-methoxy-3,5-di(chloromethyl)flavone even with large excess of paraformaldehyde.

Chloromethylation of simple flavanone

As the structure of the monochloromethyl derivative obtained from simple flavanone has not been proved (see page669) it was thought of repeating the work to definitely establish the structure.

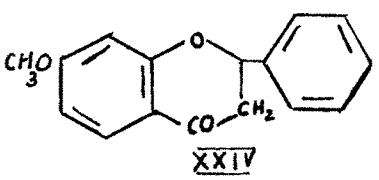
Simple flavanone (XX) on chloromethylation in glacial acetic acid with excess of paraformaldehyde and hydrochloric acid at 90-95° gave a monochloromethyl derivative in very poor yield. The monochloromethyl derivative on reduction with zinc dust and acetic acid yielded a product which on treatment with selenium dioxide gave the known 3-methylflavone (XXIII) (40). Therefore the monochloromethyl derivative was 3-chloromethyl flavanone (XXI) and the reduced product was 3-methylflavanone (XXII).



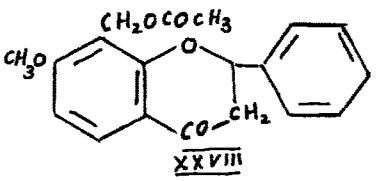
Chloromethylation of 7-methoxyflavanone

7-Methoxyflavanone (XXIV) on chloromethylation in acetic acid with one mole of paraformaldehyde gave a monochloromethyl derivative which on reduction with zinc dust and acetic acid gave a product which on treatment with selenium dioxide gave the known 7-methoxy-8-methylflavone (XXVII) (41) as seen by direct comparison with an authentic specimen. The chloromethyl derivative was, therefore, 7-methoxy-8-chloromethylflavanone (XXV) and the reduced product was 7-methoxy-8-methylflavanone (XXVI). 7-Methoxy-8-chloromethylflavanone was converted into the corresponding acetoxy methyl derivative by refluxing with sodium acetate and acetic acid and into the corresponding Mannich bases (XXIX a,b) on reaction with dimethylamine and morpholine.

No di(chloromethyl) derivative could be isolated even with excess of paraformaldehyde.



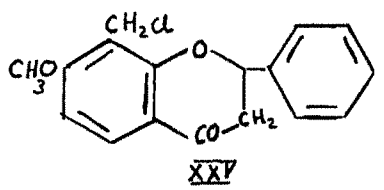
XXIV



XXVIII

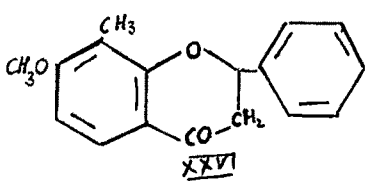
HCl + HCHO

AcOH + AcONa



XXV

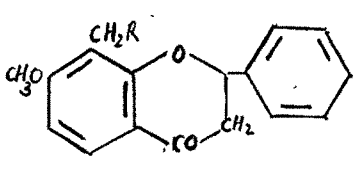
Zn dust / AcOH



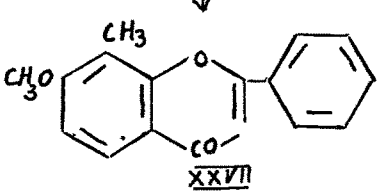
XXVI

Dimethylamine / Morpholine

SeO_2



XXIX



XXVII

a; R = $-N(CH_3)_2 \cdot HCl$

b; R = $-N(CH_2-CH_2)_2O$

EXPERIMENTAL

Chloromethylation of 7-hydroxyflavone : 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 collected, dried and crystallised from dioxan in white needles, m.p. 215° (decomp.). Yield 1.0 g.

The above chloromethyl derivative was obtained in better yield (1.70 g.) by carrying out the reaction with excess of paraformaldehyde (5.0 g.) under the same conditions.

Analysis : 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 %.

No di(chloromethyl) derivative was obtained even with a large excess of paraformaldehyde and zinc chloride.

7-Hydroxy-8-formylflavone

The above chloromethyl derivative (1.0 g.) was dissolved in glacial acetic acid (10.0 ml.) and hexamine (1.0 g.) added. 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 mixed m.p. with 7-hydroxy-8-formylflavone (37) was 223°.

7-Acetoxy-8-acetoxymethylflavone

7-Hydroxy-8-chloromethylflavone (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 in white needles, m.p. 185-86°.

Analysis : Found : C = 68.36 ; H = 4.40 %.
$C_{20}H_{16}O_6$ requires : C = 68.19 ; H = 4.54 %.

7-Hydroxy-8-dimethylaminomethyl-flavone

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 hrs. The residue obtained on removal of alcohol was treated with dilute hydrochloric acid and filtered. The filtrate was neutralized with sodium bicarbonate solution and the product obtained was crystallised from ethyl alcohol in white needles, m.p. 184°.

Analysis : Found : N = 4.18 %.

$C_{18}H_{17}O_3N$ requires : N = 4.72 %.

7-Hydroxy-8-morpholinomethylflavone

Morpholine (3 ml.) was added to 7-hydroxy-8-chloromethylflavone (1.0 g.) in alcohol (30 ml.) and the reaction mixture heated on a steam bath for 6 hrs. The residue obtained on removal of alcohol was treated with dilute hydrochloric acid and filtered. The filtrate was neutralized with sodium bicarbonate solution and the product obtained was crystallised from ethyl alcohol in light brown cubes, m.p. 208°.

Analysis : Found : N = 4.08 %.

$C_{20}H_{19}O_4N$ requires : N = 4.15 %.

Chloromethylation of 6-hydroxyflavone : 6-Hydroxy-5-chloromethylflavone

To 6-Hydroxyflavone (1.19 g.) was dissolved in acetic acid (80 % ; 60 ml.), ~~and~~ paraformaldehyde (1.4 g.) was added and hydrogen chloride gas passed for 4 hrs. The shining product which separated on cooling the reaction mixture was collected, dried and crystallised from toluene in white shining needles, m.p. 210°.

Yield 0.5 g.

Analysis : 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

The above chloromethyl derivative (1.0 g.) was dissolved in glacial acetic acid (10 ml.) and hexamine (1.0 g.) added. The reaction mixture was refluxed for 1 hr. and then poured into ice cold water. The separated complex was refluxed with hydrochloric acid (20 ml. ; 50 %) for half an hour. The residue obtained was crystallised from acetic acid. The m.p. and mixed m.p. with 6-hydroxy-5-formylflavone (38) was 221°.

6-Acetoxy-5-acetoxymethylflavone

6-Hydroxy-5-chloromethylflavone (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 in white needles, m.p. 214°.

Analysis : Found : C = 68.33 ; H = 4.82 %.
$C_{20}H_{16}O_6$ requires : C = 68.19 ; H = 4.54 %.

6-Hydroxy-5-morpholinomethylflavone

Morpholine (3 ml.) was added to 6-hydroxy-5-chloromethylflavone (1.0 g.) in alcohol (30 ml.) and the reaction mixture heated on a steam bath for 6 hrs. The residue obtained on removal of alcohol was treated with dilute hydrochloric acid and filtered. The product obtained on neutralization of the filtrate with

sodium bicarbonate solution crystallized from alcohol in white needles, m.p. 192°.

Analysis : Found : N = 4.18 %.
$C_{20}H_{19}O_4N$ requires : N = 4.15 %.

Chloromethylation of 6-methoxyflavone : 6-Methoxy-3,5-di(chloromethyl)flavone

6-Methoxyflavone (1.26 g.) was dissolved in acetic acid (80 % ; 50 ml.) and paraformaldehyde (4.5 g.) added. The reaction mixture was kept at 90-95° and hydrogen chloride gas passed for 3.5 hrs. The shining crystals obtained on cooling were crystallised from benzene in white needles, m.p. 225°. Yield 0.5 g.

Analysis : Found : C=61.94 ; H=3.82 ; Cl=20.56 %.
$C_{18}H_{14}O_3Cl_2$ requires : C=61.90 ; H=4.01 ; Cl=20.56 %.

6-Methoxy-3,5-dimethylflavone

6-Methoxy-3,5-di(chloromethyl)flavone (0.5 g.) was dissolved in glacial 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. The reaction mixture was then heated on a steam bath for half an hour more. It was then filtered and diluted with ice cold water. The separated product was crystallised from alcohol in white needles, m.p. 135-36°.

Analysis : Found : C = 77.34 ; H = 5.39 %.
$C_{18}H_{16}O_3$ requires : C = 77.12 ; H = 5.75 %.

6-Methoxy-3,5-di-(dimethylaminomethyl)flavone dihydrochloride

Dimethylamine (6 ml. ; 40 %) was added to 6-methoxy-3,5-di(chloromethyl)flavone in alcohol (30 ml.) and the reaction mixture heated on a steam bath for 6 hrs. 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 treated with fused calcium chloride and dry hydrogen chloride gas was passed through the ether extract till a solid product separated. This was filtered and crystallised from alcohol-ether mixture in white needles, m.p. 151°.

Analysis : Found : N = 5.94 ; Cl = 16.27 %.
$C_{22}H_{28}N_2O_3Cl_2$ requires : N = 6.38 ; Cl = 16.17 %.

Chloromethylation of 6-methoxy-3-methylflavone

6-Benzoyloxy-3-methylflavone

Quinpropiophenone (3 g.) was thoroughly mixed with freshly fused and powdered sodium benzoate (3.0 g.) and benzoic anhydride (12.0 g.). The reaction mixture was heated in an oil bath at 185-90° for 8 hrs. with

occasional stirring. The reaction mixture was then treated repeatedly with hot water to remove sodium benzoate and benzoic anhydride and finally washed with sodium bicarbonate solution. The residue obtained was crystallised from acetic acid in white needles, m.p. 142°.

Analysis : Found : C = 77.30 ; H = 4.51 %.
$C_{23}H_{16}O_4$ requires : C = 77.51 ; H = 4.53 %.

6-Hydroxy-3-methylflavone

6-Benzoyloxy-3-methylflavone (1.0 g.) was refluxed with alcoholic potash (10 % ; 20 ml.) on a steam bath for half an hour. The product obtained on acidification with cold dilute hydrochloric acid crystallised from ethyl alcohol in white needles, m.p. 204°.

Analysis : Found : C = 76.16 ; H = 5.25 %.
$C_{16}H_{12}O_3$ requires : C = 76.18 ; H = 4.80 %.

The methyl ether was prepared by refluxing the above flavone (1.0 g.) in dry acetone with dimethyl sulphate (1 ml.) in presence of anhydrous potassium carbonate (2.0 g.) on a steam bath for 8 hrs. The residue after removal of acetone was crystallised from ethyl alcohol in white needles, m.p. 124°.

Analysis : Found : C = 76.31 ; H = 4.88 %.
$C_{17}H_{14}O_3$ requires : C = 76.67 ; H = 5.30 %.

6-Methoxy-5-chloromethyl-3-methylflavone

6-Methoxy-3-methylflavone (1.33 g.) was dissolved in acetic acid (80 % ; 20 ml.) and paraformaldehyde (4.5 g.) (excess) added. The solution was maintained at 90-95° and hydrogen chloride gas passed for 3 hrs. The product which separated on cooling was crystallised from benzene in thick white needles, m.p. 153°. Yield 0.8 g.

Analysis : Found : C=68.93 ; H=5.12 ; Cl=11.53 %.
$C_{18}H_{15}O_3Cl$ requires : C=68.69 ; H=4.77 ; Cl=11.29 %.

6-Methoxy-3,5-dimethylflavone

6-Methoxy-3-methyl-5-chloromethylflavone (0.5 g.) dissolved in glacial acetic acid (10 ml.) was 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 the reaction mixture then heated on a steam bath for half an hour ~~more~~. The product obtained on dilution with ice cold water was crystallised from alcohol. The melting point and mixed m.p. with 6-methoxy-3,5-dimethylflavone described earlier was 136°.

Chloromethylation of simple flavanone : 3-Chloromethylflavanone

Flavanone (1.0 g.) was dissolved in glacial acetic acid (10 ml.) and paraformaldehyde (4.5 g.excess)

added. The reaction mixture was kept on a steam bath and hydrochloric acid gas passed for 3 hrs. The reaction mixture was left overnight in a refrigerator. The product obtained was crystallised from benzene and petroleum ether (b.p. 60-80°) mixture in white needles, m.p. 137°. Matsuoka (36) prepared the same chloromethyl derivative by a different method and reported the same m.p.

Analysis : 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

3-Chloromethylflavanone (1.0 g.) was dissolved in glacial 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 one hour more. The reaction mixture was then filtered and diluted with ice cold water and left overnight in a refrigerator. The product which separated was crystallised from alcohol, m.p. 95°.

Analysis : Found : C = 80.76 ; H = 5.82 %.
$C_{16}H_{14}O_2$ requires : C = 80.64 ; H = 5.92 %.

3-Methylflavone

3-Methylflavanone (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 hrs. The reaction mixture was filtered and diluted with petroleum ether (b.p. 40-60°) and left overnight in a refrigerator. The crystals obtained were filtered and recrystallised from alcohol in white needles, m.p. and mixed m.p. with 3-methylflavone (40) was 73°.

Chloromethylation of 7-methoxyflavanone : 7-Methoxy-8-chloromethylflavanone

7-Methoxyflavanone (1.2 g.) was dissolved in glacial acetic acid (10 ml.), and paraformaldehyde (0.3 g.) was added and hydrogen chloride gas passed for 2 hrs. The reaction mixture was kept overnight in a refrigerator. The product obtained was crystallised from benzene and petroleum ether (b.p. 40-60°) mixture, in white needles, m.p. 149°. Yield 0.4 g.

The same product was obtained in better yield by slightly changing the conditions of the reaction mixture in the following manner.

Paraformaldehyde (2.0 g.) was added to glacial acetic acid (10 ml.) and hydrogen chloride 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 as before. Yield 0.6 g.

Analysis : 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

7-Methoxy-8-chloromethylflavanone (1.0 g.) was 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 in white needles, m.p. 130°.

Analysis : Found : C = 76.55 ; H = 5.80 %.
$C_{17}H_{16}O_3$ requires : C = 76.10 ; H = 6.01 %.

7-Methoxy-8-methylflavone

7-Methoxy-8-methylflavanone (0.8 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 hrs. The reaction mixture was filtered and on cooling the filtrate crystals were obtained which were recrystallised from alcohol in needles, m.p. and mixed m.p. with 7-methoxy-8-methylflavone (41) was 171°.

7-Methoxy-8-acetoxymethylflavanone

7-Methoxy-8-chloromethylflavanone (0.5 g.) was

dissolved in glacial acetic acid (10 ml.) and fused sodium acetate (0.5 g.) added. The reaction mixture was heated on a steam bath for 1 hr. The reaction mixture was then added to ice cold water and the solid which separated was crystallised from alcohol in white needles, m.p. 91°.

Analysis : Found : C = 72.14 ; H = 5.82 %.
$C_{19}H_{18}O_5$ requires : C = 72.24 ; H = 6.02 %.

7-Methoxy-8-dimethylaminomethylflavanone hydrochloride

Dimethylamine (3 ml. ; 40 %) was added to 7-methoxy-8-chloromethylflavanone in alcohol (30 ml.) and the reaction mixture heated on a steam bath for 6 hrs. 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 hydrochloric acid gas was passed through it till a solid separated. This was filtered and crystallised from alcohol- ether mixture in white needles, m.p. 140°.

Analysis : Found : N = 3.90 ; Cl = 9.80 %.
$C_{19}H_{22}NO_3Cl$ requires : N = 3.69 ; Cl = 9.35 %.

7-Methoxy-8-morpholinomethylflavanone

Morpholine (3 ml.) was added to 7-methoxy-8-

chloromethylflavanone (1.0 g.) in alcohol (30 ml.) and the reaction mixture heated on a steam bath for 6 hrs. The residue obtained on removal of alcohol was treated with dilute hydrochloric acid and filtered. The product obtained on neutralization of the filtrate with sodium hydroxide solution crystallised from benzene and petroleum ether (b.p. 40-60°) mixture in yellowish needles, m.p. 149-50°.

Analysis	: Found	: N = 4.34 %.
$C_{21}H_{23}O_4N$	requires	: N = 3.97 %.

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