# CHAPTER II

# IODINATION OF SOME FLAVONES AND FLAVANONES

## CHAPTER II

## THEORETICAL

### Iodination of some flavones and flavanones

In the review of the work done on the halogenation of flavones and flavanones, it has been seen that the iodination of flavones and flavanones has not been studied systematically except by Shah and Sethna (1) who, in this laboratory, carried out the systematic iodination of 5-hydroxy and 7-hydroxyflavone and obtained different iodo derivatives. The structures have been assigned on the basis of the hydrolysis to phenolic iodo acids and iodo ketones of known structures or to which the structures have been definitely assigned.

A few iodoflavones have been synthesised by other methods. Mulchandani and Shah (2) synthesised 6-iodoflavone and 6-iodo-4'-methoxyflavone by dehydrogenation of the corresponding flavanones with selenium dioxide and 6-iodo-3',4'-methylenedioxyflavone from 2'-hydroxy-5'-iodo-3,4-methylenedioxychalcone by treatment with selenium dioxide. They also obtained 6-iodo-3-hydroxyflavone from 2'-hydroxy-5'-iodochalcone by treatment with alkaline hydrogen peroxide. Chen and Yang (3) prepared 3'-iodo- and 4'-iodoflavone by dehydrogenation of the corresponding flavanone with N-bromosuccinimide. Chen and Chang (4) synthesised 6-iodo-4'-methoxy-3-hydroxyflavone from 2'-hydroxy-5'-iodo-4-methoxychalcone by alkaline hydrogen peroxide treatment. The same authors (5) obtained 7-iodoflavone (i) from 2'-hydroxy-4'-iodochalcone by treating with selenium dioxide and (ii) by the dehydrogenation of 7-iodoflavanone obtained from 2'-hydroxy-4'-iodochalcone with N-bromosuccinimide. 7-Iodo-4'-methoxyflavone was obtained from 2'-hydroxy-4'-iodo-4-methoxychalcone by treatment with selenium dioxide. 7-Iodo-3-hydroxyflavone and 7-iodo-4'-methoxy-3-hydroxyflavone were obtained from the corresponding chalcones by alkaline hydrogen peroxide treatment.

Jurd (6) reported the synthesis of 7-hydroxy-8-iodoflavone, 3'-iodo-4'-methoxyflavone and 7,4'-dimethoxy-8-iodoflavone by the cyclisation of the β-diketones obtained by the Baker-Venkataraman transformation of the iodo-o-benzoyloxyacetophenones.

A few workers have also reported the preparation of iodoflavanones. Seshadri et al.(7) reported the 3-iodo derivatives of 5-hydroxy-7,4'-dimethoxy-,5,7-dimethoxy-, and 5-hydroxy-7,3',4'-trimethoxyflavanone . The 3-iodo derivatives of the above flavanones were converted into the corresponding flavone derivatives by the treatment of potassium acetate and acetic acid. Wheeler et al.(8) [illegible] iodinated 5,7-3',4'-tetramethoxy and 5-hydroxy-7,3',4'-trimethoxyflavanone with silver acetate and iodine and obtained the 3-iodo derivatives .Kulkarni et al.(9) iodinated 5,7-3',4'-tetramethoxyflavanone with iodine and silver acetate.

Wadodkar (10) prepared 3-iodo derivatives of the following flavanones by treating them with iodine monochloride in acetic acid: 6-Methyl-$4'$-methoxy-, 6-methyl-$3',4'$-methylenedioxy-, 7-methyl-$4'$-methoxy-, 6-methyl-8-bromo-$4'$-methoxy-, 6-nitro-7-hydroxy-$4'$-methoxy- and 6-bromo-7-hydroxy-$4'$-methoxyflavanone. All the above 3-iodo derivatives were converted into the corresponding flavone derivatives by treating with silver acetate and acetic acid.

The present work is a continuation of the work going on in this laboratory on the study of iodination of flavones. The objectives have been mainly to study the pattern of substitution in flavones and flavanones and to utilise the iodo derivatives for further synthetical work such as the synthesis of biflavonyls, and cyano flavanes.

The iodination of flavones and flavanones has been studied with three different iodinating agents: (i) iodine and iodic acid, (ii) iodine and ammonia and (iii) iodine monochloride.

The iodination is assumed to take place according to the following equations :

( i ) With iodine and iodic acid :

$$5RH + 4I + HIO_3 \longrightarrow 5\ RI + 3\ H_2O$$

(ii ) With iodine and ammonia :

$$3I_2 + NH_3 \longrightarrow NI_3 + 3HI$$

$$3RH + NI_3 \longrightarrow 3RI + NH_3$$

(iii) With iodine monochloride :

$$RH + ICl \longrightarrow RI + HCl$$

Iodination with iodine and iodic acid was found to be quite smooth and better yields were obtained in this method in most of the cases than in the other two methods and therefore the iodination has been studied mainly with iodine and iodic acid.

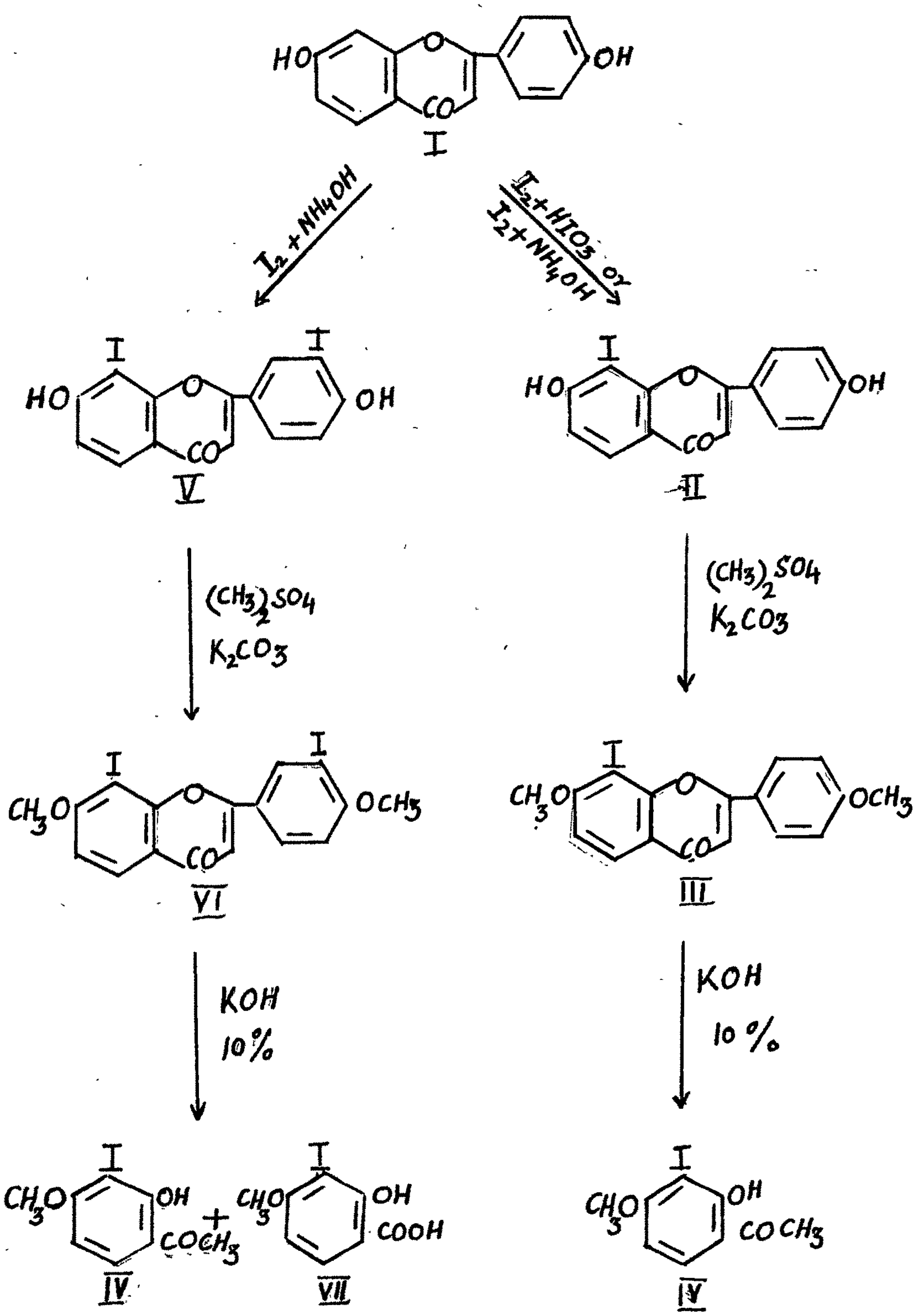
Iodination of 7,4'-dihydroxyflavone, 7-hydroxy-4'-methoxyflavone, 7,4'-dimethoxyflavone, 5,7-dihydroxyflavone, 6-hydroxyflavone, simple flavanone, 7-hydroxyflavanone, 7-hydroxy-4'-methoxyflavanone and 4'-hydroxyflavanone has now been studied and the structures of the iodo compounds obtained have been established.

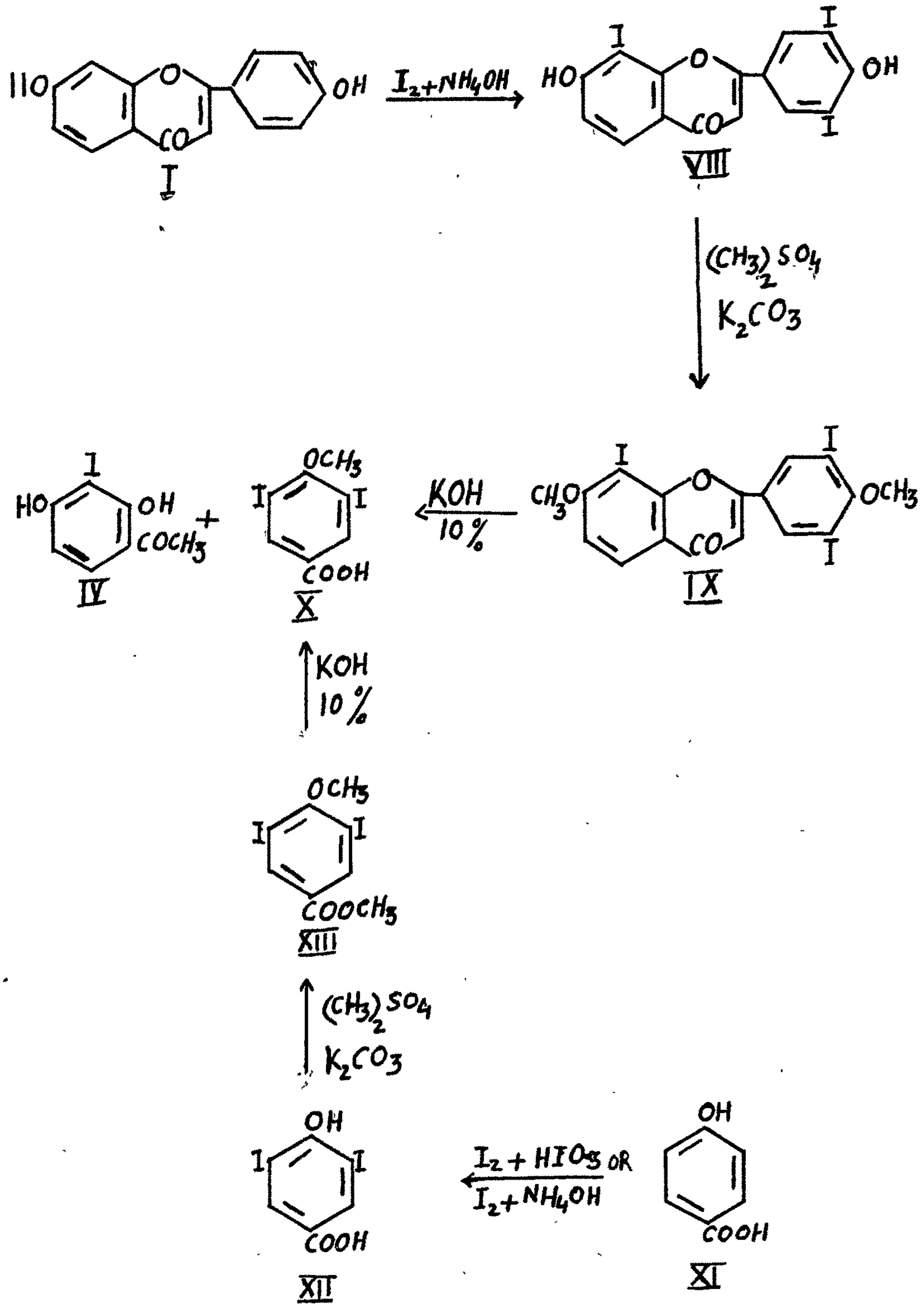
### Iodination of 7,4'-dihydroxyflavone

7,4'-Dihydroxyflavone (I) on iodination with theoretical amounts of iodine and iodic acid gave a mono iodo derivative. Its dimethyl ether on hydrolysis gave the known 2-hydroxy-3-iodo-4-methoxyacetophenone (IV) (1). Therefore the mono iodo flavone has been assigned the 8-iodo structure (II).

7,4'-Dihydroxyflavone on iodination with one mole of iodine and ammonia gave the same iodo derivative (II) in good yield.

On iodination with two moles of iodine and ammonia it gave a di-iodo derivative the methyl ether of which, on alkaline hydrolysis yielded the known products: 2-hydroxy-3-iodo-4-methoxyacetophenone (IV) and 2-hydroxy-3-iodo-4-methoxybenzoic acid (VII) (1) indicating that one of the two iodine atoms was in the 8-position. The other fragment


HO
OH
CO
I
I₂+NH₄OH
I₂+HIO₃ or
I₂+NH₄OH
I
I
HO
OH
CO
V
I
HO
OH
CO
II
(CH₃)₂SO₄
K₂CO₃
(CH₃)₂SO₄
K₂CO₃
I
I
CH₃O
OCH₃
CO
VI
I
CH₃O
OCH₃
CO
III
KOH
10%
KOH
10 %
I
CH₃O
OH
COCH₃
IV
+
I
CH₃O
OH
COOH
VII
I
CH₃O
OH
COCH₃
IV


I
I₂+NH₄OH
VIII
(CH₃)₂SO₄
K₂CO₃
IX
KOH
10%
X
IV
KOH
10%
XIII
(CH₃)₂SO₄
K₂CO₃
XII
I₂ + HIO₃ OR
I₂+NH₄OH
XI

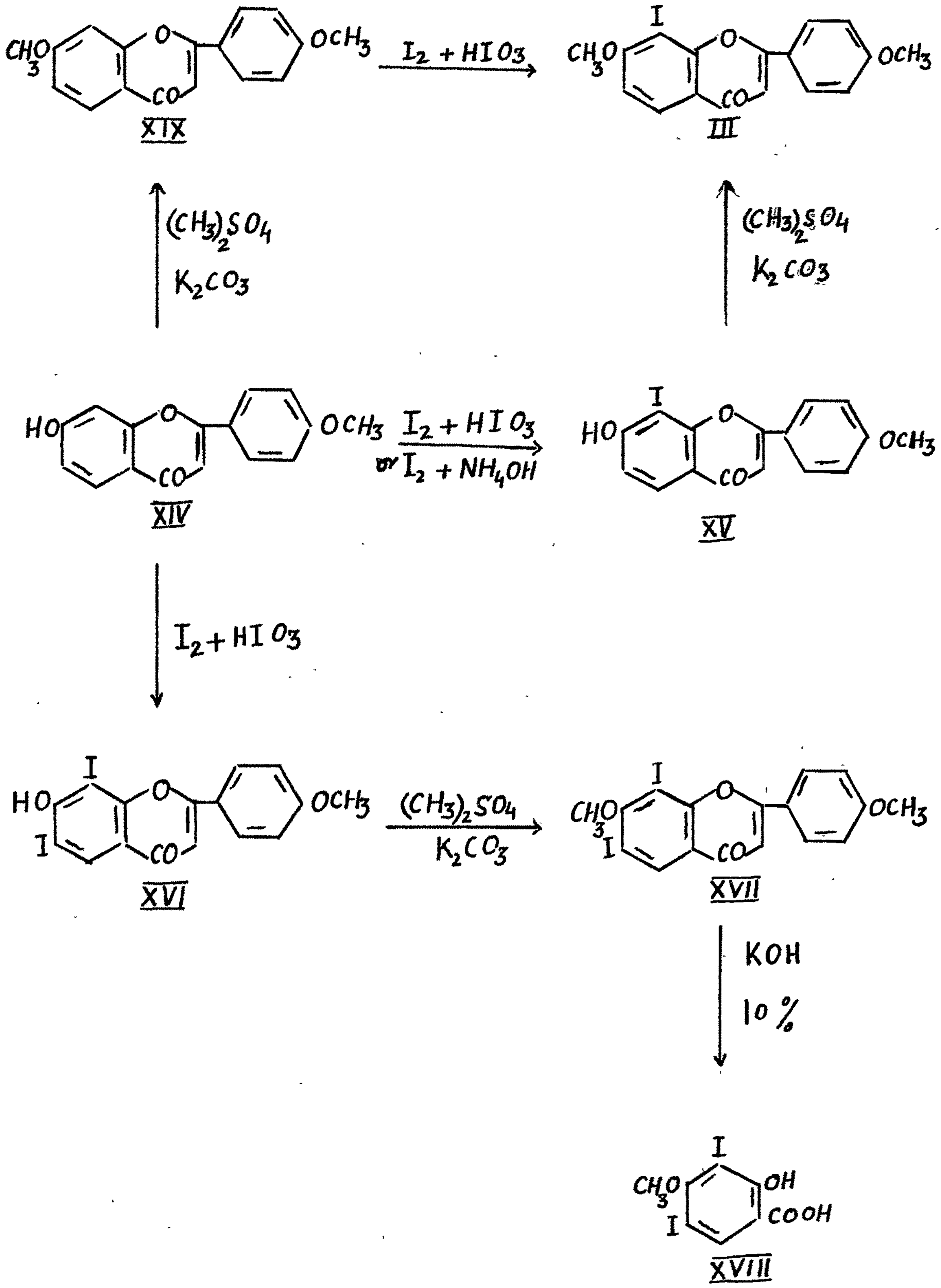
containing the side phenyl nucleus could not be isolated from the reaction mixture after the hydrolysis. The 7,4'-dihydroxy-8,3'-di-iodoflavone (V) structure has been tentatively assigned to the di-iodo derivative. This is also supported by the results obtained with 3 moles of iodine and ammonia described below.

With three moles of iodine and ammonia 7,4'-dihydroxyflavone (I) gave a tri-iodo derivative the methyl ether of which on hydrolysis yielded 2-hydroxy-3-iodo-4-methoxyacetophenone (IV) (1) and 3,5-di-iodo-4-methoxybenzoic acid (X). The latter was synthesised for comparison by iodination of 4-hydroxybenzoic acid (XI) followed by simultaneous methylation and esterification and subsequent hydrolysis of the ester formed. The tri-iodo derivative was therefore, 7,4'-dihydroxy-8,3',5'-tri-iodoflavone (VIII)

## Iodination of 7-hydroxy-4'-methoxyflavone

7-Hydroxy-4'-methoxyflavone (XIV) on iodination with theoretical amounts of iodine and iodic acid and iodine and ammonia gave a mono iodo derivative. Its methyl ether was found to be identical with 7,4'-dimethoxy-8-iodoflavone (III) described above. Therefore the mono iodoflavone was the-8-iodoflavone derivative (XV).

On iodination with twice the theoretical amounts of iodine and iodic acid 7-hydroxy-4'-methoxyflavone (XIV) gave only the same 8-iodo derivative but in better yield. On iodination with three times the amounts of iodine and iodic acid it gave a di-iodo derivative the methyl ether of which on alkaline hydrolysis gave the known


CH3O
OCH3
XIX
I2 + HIO3
I
CH3O
OCH3
III
(CH3)2SO4
K2CO3
(CH3)2SO4
K2CO3
HO
OCH3
XIV
I2 + HIO3
or I2 + NH4OH
I
HO
OCH3
XV
I2 + HIO3
I
HO
I
OCH3
XVI
(CH3)2SO4
K2CO3
I
CH3O
I
OCH3
XVII
KOH
10 %
I
CH3O
I
OH
COOH
XVIII

2-hydroxy-4-methoxy-3,5-di-iodobenzoic acid (XVIII) (1). The di-iodo derivative has therefore been assigned the 6,8-di-iodo structure (XVI).

No tri-iodoflavone could be obtained even on iodination with large excess of the iodinating agents.

7-Hydroxy-4'-methoxyflavone (XIV) on iodination with iodine and ammonia gave the 8-iodo derivative (XV) in good yield. No higher iodo derivative could be obtained even with excess of iodine and ammonia.

### Iodination of 7,4'-dimethoxyflavone

7,4'-Dimethoxyflavone (XIX) did not undergo iodination with theoretical amounts of iodine and iodic acid but on iodination with eight times the theoretical amounts of iodine and iodic acid it provided a mono iodo derivative which was found to be identical with 7,4'-dimethoxy-8-iodoflavone (III) as seen by direct comparison.

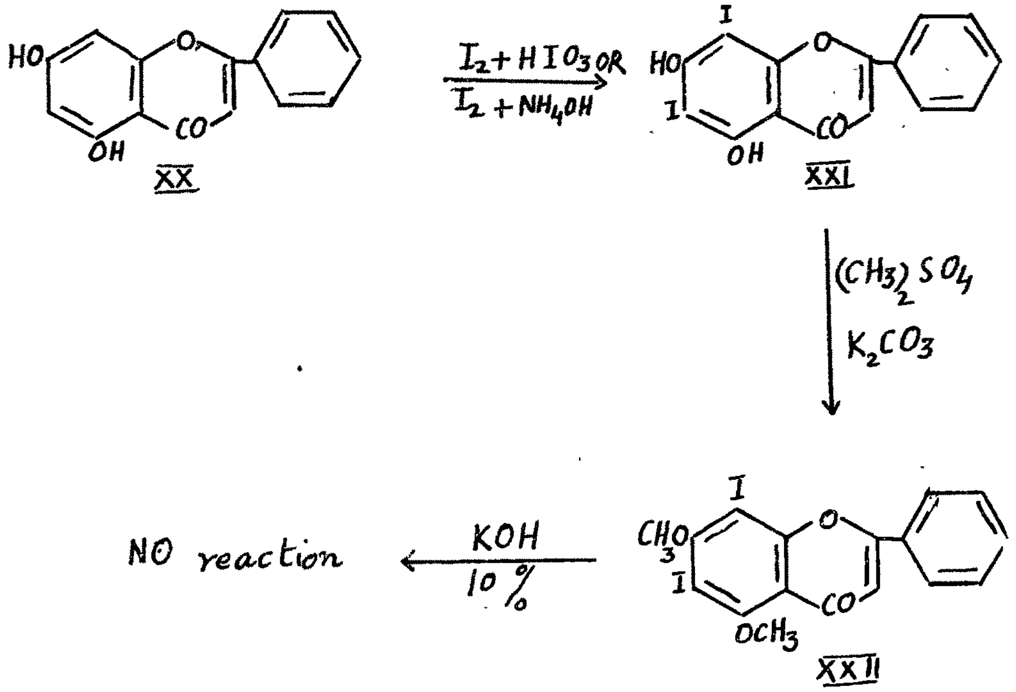
No di-iodo derivative could be obtained.

### Iodination of 5,7-dihydroxyflavone

5,7-Dihydroxyflavone (XX) on iodination with iodine and iodic acid directly gave a di-iodo derivative. No mono iodo derivative could be isolated. Its methyl ether did not provide a coumarone derivative on heating with alkali. Therefore, there was no iodine in the 3 position (11). 5,7-Dihydroxy-6,8-di-iodoflavone (XXI) structure has, therefore, been tentatively assigned to the compound. It remained unchanged on boiling with alkali.

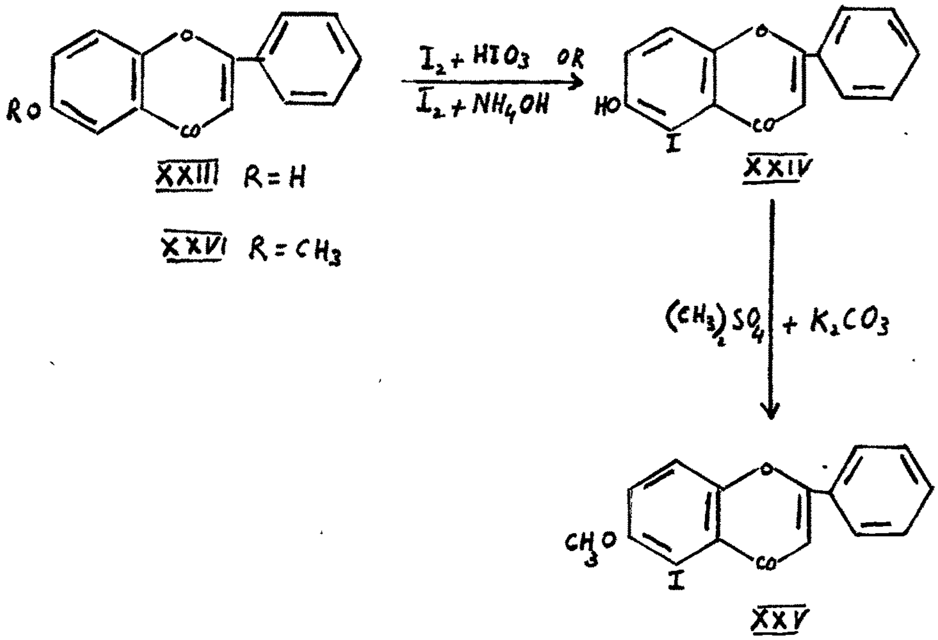
With twice the theoretical amounts of iodine and iodic acid the same di-iodoflavone was obtained in good yield. No tri-iodoflavone could be obtained even with a large excess of the iodinating agents.

The same di-iodoflavone was obtained with iodine and ammonia.



## Iodination of 6-hydroxyflavone

6-Hydroxyflavone (XXIII) on iodination with theoretical amounts of iodine and iodic acid provided a mono iodo derivative to which the 5-iodo-6-hydroxyflavone (XXIV) structure has been tentatively assigned in view of the results obtained by Iyer and Venkataraman (13) in the coupling of 6-hydroxyflavone with diazotised aniline. Attempts to synthesise 5-iodo-6-hydroxyflavone from the known 5-amino-6-hydroxyflavone (13) by diazotization and Sandmayer's reaction failed as on diazotization the diazonium oxide separated out as insoluble product as observed by the


RO
XXIII R = H
XXVI R = CH3
I2 + HIO3 OR
I2 + NH4OH
HO
I
XXIV
(CH3)2SO4 + K2CO3
CH3O
I
XXV
CO

previous workers (13).

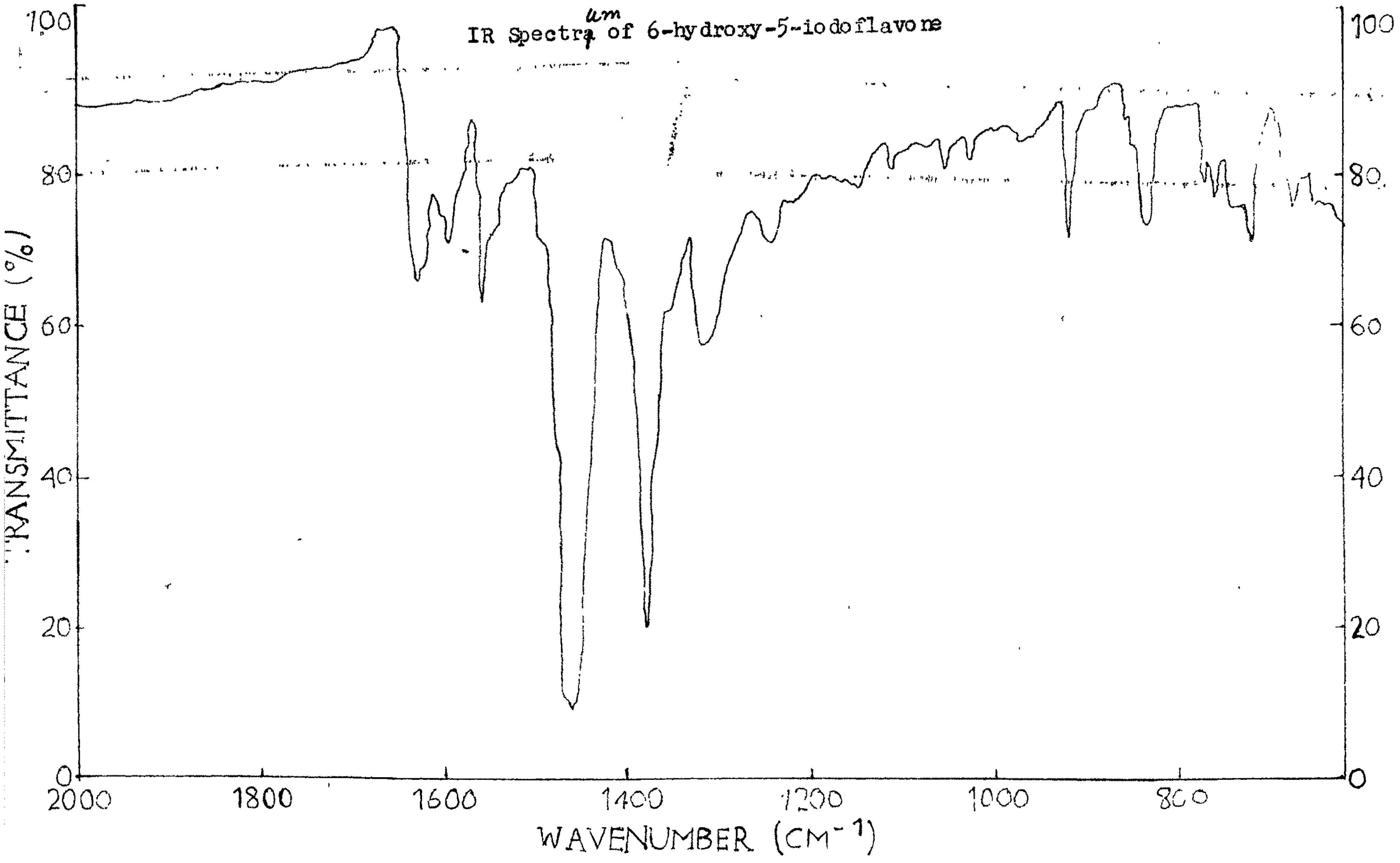
A satisfactory NMR spectrum of the iodo derivative could not be obtained on account of the sparing solubility of the iodo derivative in the usual solvents such as $CDCl_3$.

The IR spectra for 6-hydroxyflavone and the mono-iodo derivative were obtained (Fig. 2 and 1 respectively). The iodo derivative shows a band at 835 $cm^{-1}$ which suggests that there is a 1, 2,3,4-tetra substituted benzene ring. If the iodine had been in the 7-position the band would have appeared at about 860 $cm^{-1}$ indicating the presence of 1,2,4,5-tetra substituted benzene ring. The author however realises that a definite conclusion can be reached only from satisfactory NMR spectrum.

No di-iodo derivative could be obtained even with a large excess of iodine and iodic adid. With iodine and ammonia the same mono iodo derivative was obtained.

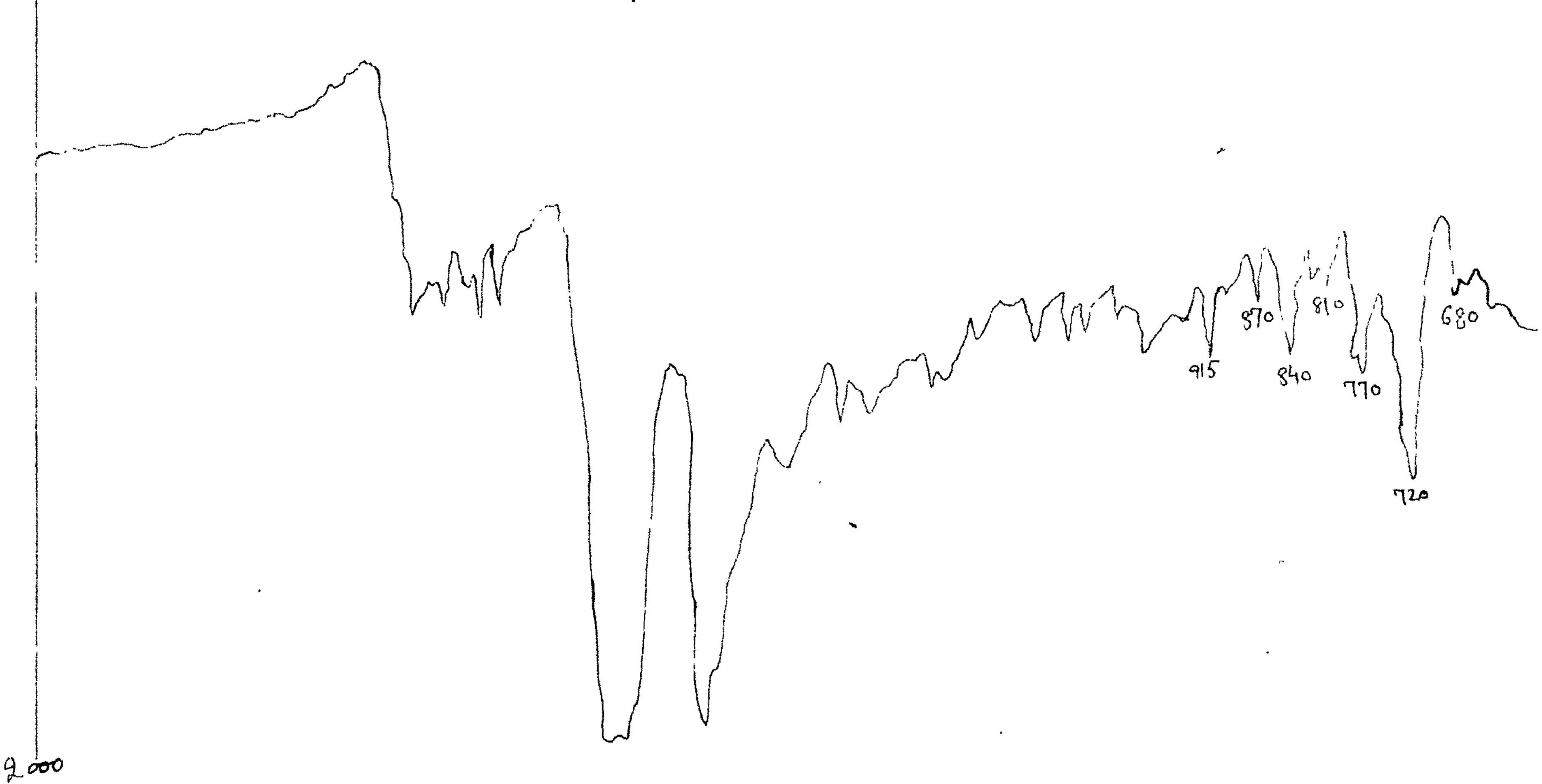
### Attempted iodination of 6-methoxyflavone and 7,8-dihydroxyflavone

Both the flavones were subjected to the action of iodine and iodic acid and iodine and ammonia under varying conditions of time, temperature and quantities. No iodo derivative could be isolated even with a large excess of the iodinating agents. Iodination of 6-methoxyflavone was also tried with iodine monochloride but it did not succeed.


IR Spectr~~a~~um of 6-hydroxy-5-iodoflavone

[Fig 1]

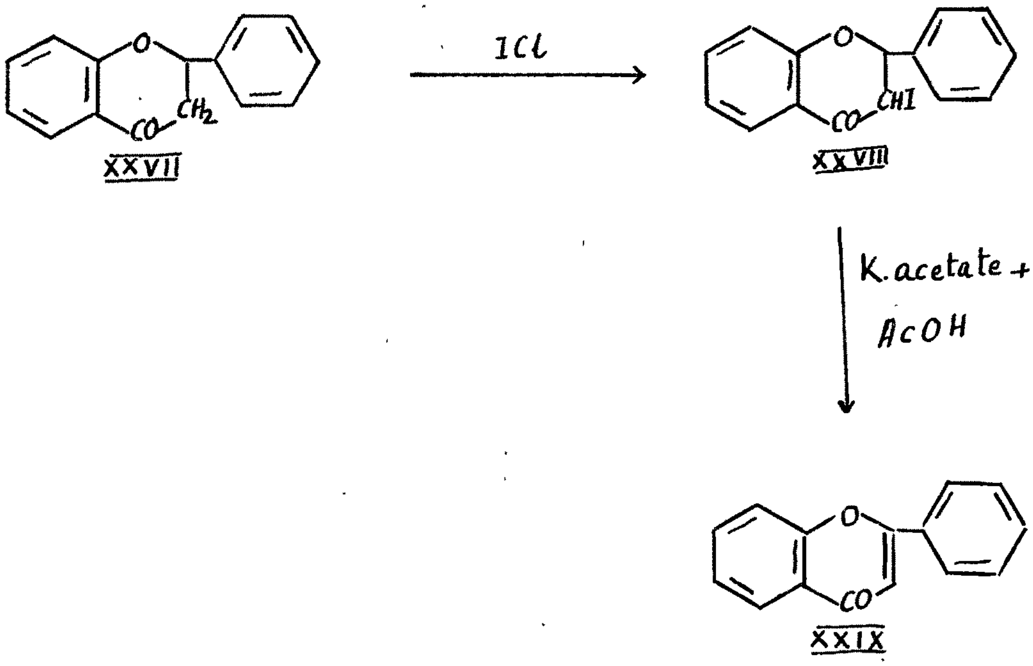
IR Spectr$\overset{um}{a}$ of 6-hydroxyflavone



[Fig 2]

## Iodination of simple flavanone

Simple flavanone (XXVII) could not be iodinated even with excess of iodine and iodic acid and iodine and ammonia. However, on iodination with 4 moles of iodine monochloride it yielded a mono iodo derivative in poor yield. On refluxing with potassium acetate and acetic acid it furnished the simple flavone (XXIX). The mono-iodo derivative was, therefore, 3-iodoflavanone (XXVIII). No higher iodo derivative could be obtained.



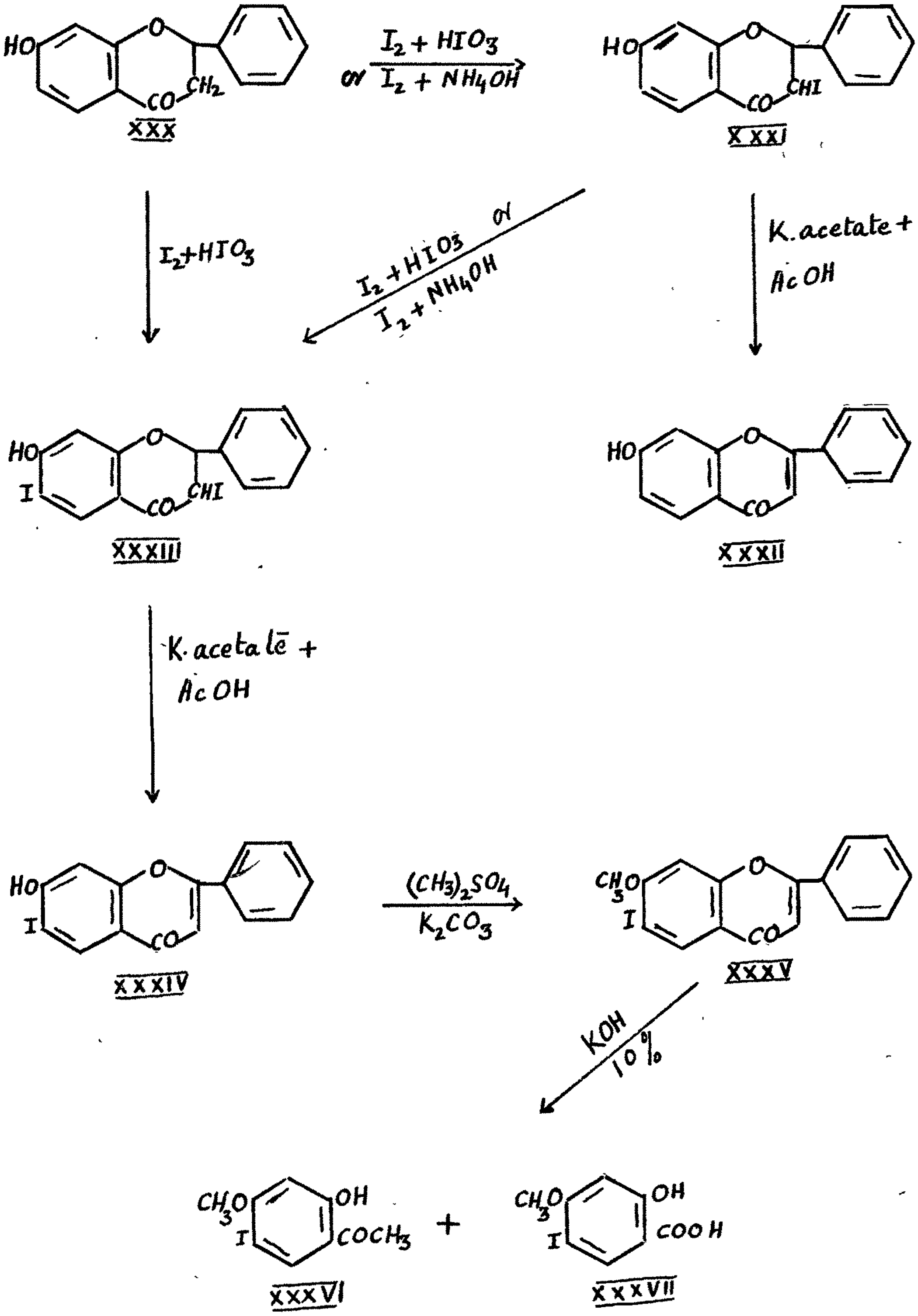
XXVII

XXVIII

XXIX

## Iodination of 7-hydroxyflavanone

7-Hydroxyflavanone (XXX) on iodination with theoretical amounts of iodine and iodic acid gave a mono-iodo derivative which on refluxing with potassium acetate and acetic acid gave 7-hydroxyflavone (XXXII). The 3-iodo structure (XXXI) has, therefore, been assigned to this product.


HO
CO
CH₂
XXX
I₂ + HIO₃
or I₂ + NH₄OH
HO
CO
CHI
XXXI
I₂+HIO₃
I₂ + HIO₃ or
I₂ + NH₄OH
K. acetate +
AcOH
HO
I
CO
CHI
XXXIII
HO
CO
XXXII
K. acetate +
AcOH
HO
I
CO
XXXIV
(CH₃)₂SO₄
K₂CO₃
CH₃O
I
CO
XXXV
KOH
10%
CH₃O
I
OH
COCH₃
XXXVI
+
CH₃O
I
OH
COOH
XXXVII

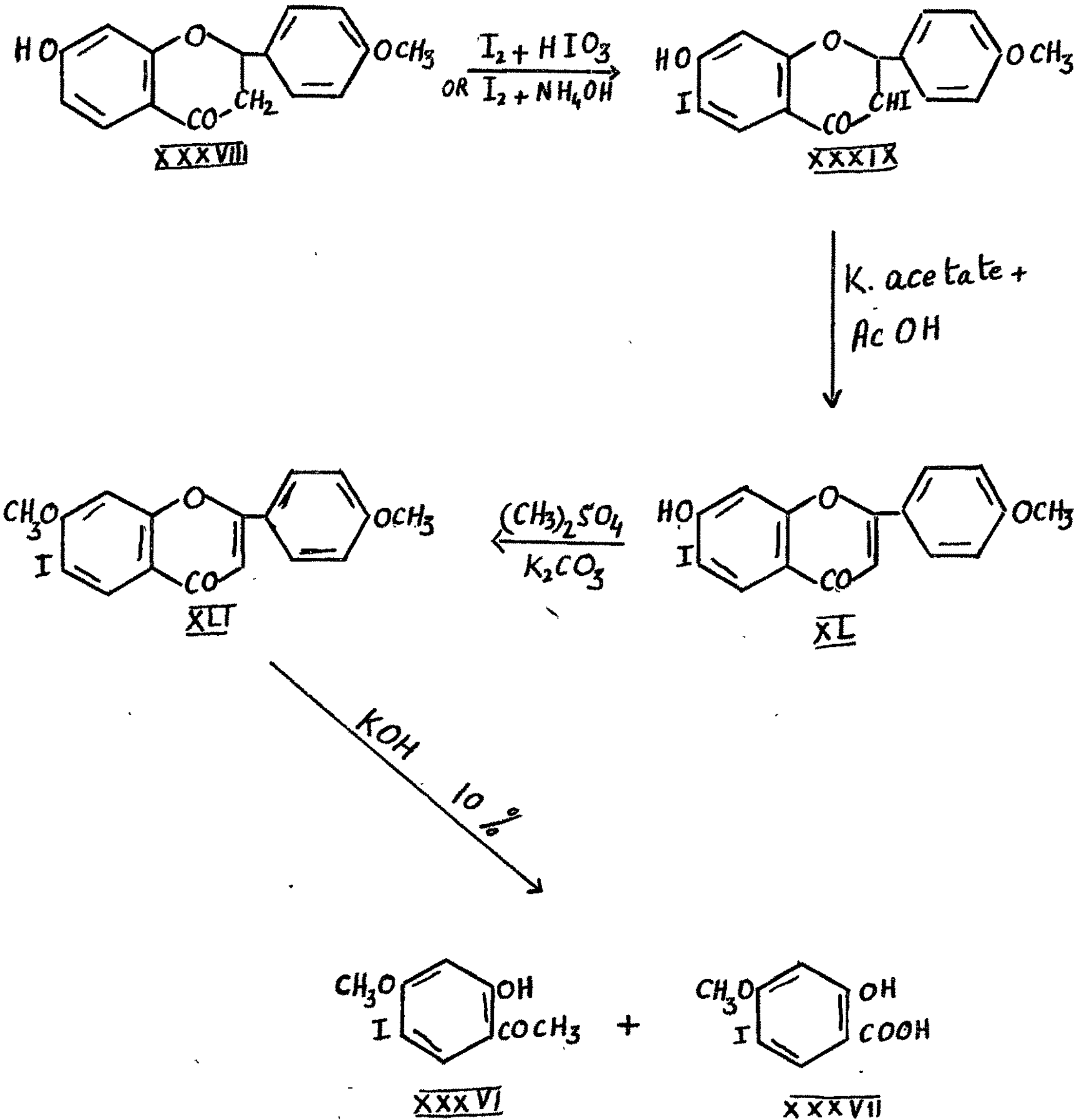
On iodination with twice the theoretical amounts of iodine and iodic acid 7-hydroxyflavanone (XXX) gave a di-iodo derivative which on refluxing with potassium acetate and acetic acid gave a mono-iodo derivative the methyl ether of which on hydrolysis with alcoholic potash gave the known 2-hydroxy-4-methoxy-5-iodoacetophenone (XXXVI) and 2-hydroxy-4-methoxy-5-iodobenzoic acid (XXXVII) (1). Therefore, the di-iodo derivative of flavanone was 7-hydroxy-3,6-di-iodoflavanone (XXXIII) and the mono-iodo derivative was 7-hydroxy-6-iodoflavone having m.p. 294° which was different from 7-hydroxy-8-iodoflavone, m.p. 230° as reported by Shah and Sethna (1).

7-Hydroxy-3-iodoflavanone (XXXI) on further iodination with theoretical amounts of iodine and iodic acid gave the same 7-hydroxy-3,6-di-iodoflavanone (XXXIII).

7-Hydroxyflavanone (XXX) on iodination with iodine and ammonia in molecular proportion gave the 3-iodo derivative (XXXI) and with twice the amounts of iodine and ammonia it gave the 3,6-di-iodoflavanone (XXXIII) described above.

## Iodination of 7-hydroxy-$4'$-methoxyflavanone

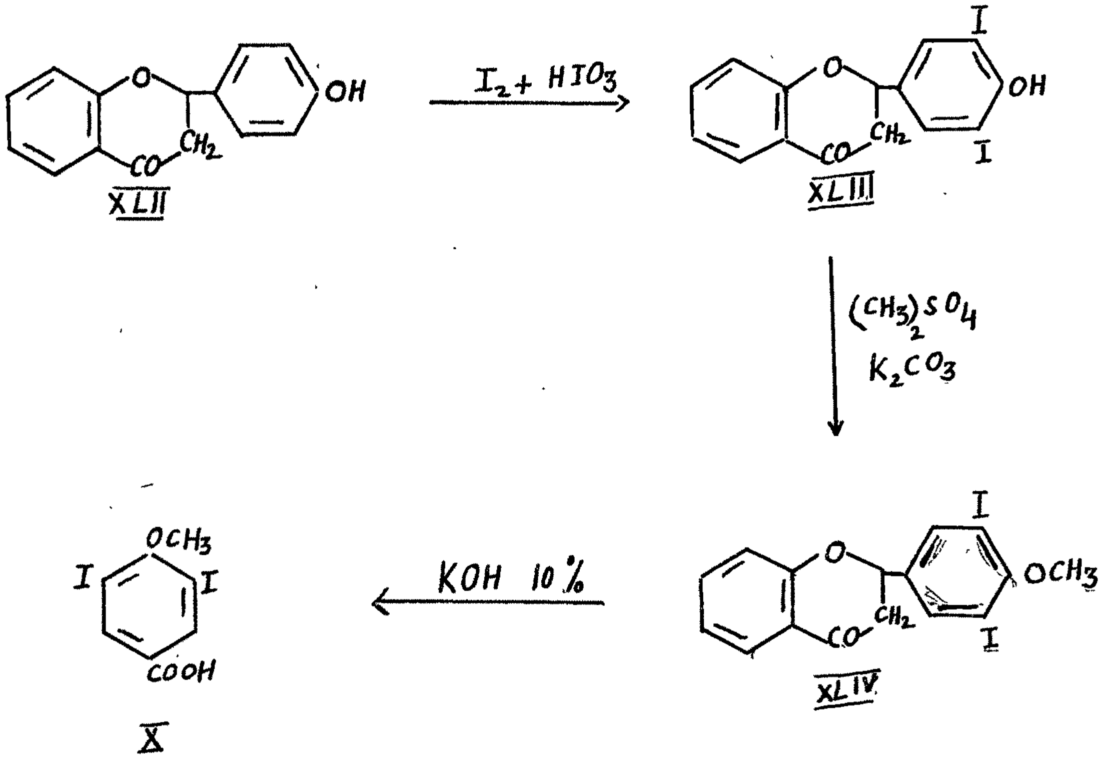
7-Hydroxy-$4'$-methoxyflavanone (XXXVIII) on iodination with theoretical amounts of iodine and iodic acid gave directly a di-iodo derivative. No mono-iodo derivative could be obtained. The di-iodo derivative on refluxing with potassium acetate and acetic acid provided a mono-iodo derivative, the methyl ether of which on hydrolysis with alcoholic potash gave the known 2-hydroxy-4-methoxy-5-iodo acetophenone (XXXVI) and 2-hydroxy-4-methoxy-5-iodobenzoic acid (XXXVII) (1). Therefore, the di-iodo derivative has been assigned the 3,6-di-iodo structure (XXXIX) and the mono-iodo derivative was assigned the 7-hydroxy-4'-methoxy-6-iodoflavone (XL) structure. The same di-iodo derivative was obtained on iodination with iodine and ammonia or with twice the amounts of iodine and iodic acid.



## Iodination of 4'-hydroxyflavanone

4'-Hydroxyflavanone (XLII) on iodination with the theoretical amounts of iodine and iodic acid gave directly a di-iodo derivative. No mono-iodo derivative could be isolated. Its methyl ether on hydrolysis with alcoholic potassium hydroxide gave 3,5-di-iodo-4-methoxybenzoic acid (X) described earlier. The di-iodo derivative was, therefore, 3',5'-di-iodo-4'-hydroxyflavanone (XLIII). Further, on refluxing with potassium acetate and acetic acid no flavone derivative was obtained.

No higher iodo derivative could be obtained even with large excess of the iodinating agents.



## Attempted iodination of 6-hydroxyflavanone

6-Hydroxyflavanone was subjected to the action of iodine and iodic acid. and iodine and ammonia under varying conditions of time, temperature and quantities. No iodo derivative could be obtained. With 4 moles of iodine monochloride a chlorinated product was obtained which has not been investigated further.

## EXPERIMENTAL

### Iodination of 7,4'-dihydroxyflavone : 7,4'-dihydroxy-8-iodoflavone

7,4'-Dihydroxyflavone (1.27 g.) was dissolved in warm alcohol (50 ml.) and iodine crystals (0.5 g.) were added with stirring. Iodic acid (0.3 g.) dissolved in minimum quantity of water was then added to the reaction mixture at room temperature and the stirring continued for 2 hours. The separated product was crystallised from alcohol, m.p. 233° (decomp.) Yield 1 g.

Analysis : Found : I = 33.19 %.
$C_{15}H_9O_4I$ requires : I = 33.42 %.

The same mono iodo derivative was obtained on iodination of 7,4'-dihydroxyflavone (0.5 g.) dissolved in aqueous ammonia (22 % ) as follows: A solution of iodine (0.86 g.) and potassium iodide (1.9 g.) was added drop wise to the stirred ammoniacal solution of flavone at room temperature during half an hour. Finally it was acidified with a cold dilute sulphuric acid. The separated product was crystallised from alcohol.

Iodination with twice the above amounts of iodine (1 g.) and iodic acid (0.6 g.) gave only the same 8-iodo derivative in better yield (1.2 g.).

The dimethyl ether The above iodoflavone (0.5 g.) in acetone was refluxed on a steam bath with dimethyl sulphate ( 1 ml.) in presence of anhydrous potassium carbonate ( 2 g.) for 8 hours. The product obtained on removal of acetone was washed with dilute sodium hydroxide solution and crystallised from alcohol, m.p. 264-65°.

<u>Analysis</u> : Found : C = 49.90 ; H = 3.00 ; I = 31.33 %.

$C_{17}H_{13}O_4I$ requires : C = 49.99 ; H = 3.18 ; I = 31.31 %.

<u>Alkaline hydrolysis of 7,4'-dimethoxy-8-iodoflavone : 2-Hydroxy-3-iodo-4-methoxyacetophenone and 2-hydroxy-3-iodo-4-methoxybenzoic acid</u>

7,4'-Dimethoxy-8-iodoflavone (0.7 g.) was refluxed with aqueous alcoholic potassium hydroxide (10 % ; 30 ml.) for 4 hours. The product obtained on acidification was first treated with sodium bicarbonate solution and the residue treated with sodium hydroxide solution. The sodium bicarbonate extract on acidification gave an iodo acid which crystallised in white needles from dilute ethyl alcohol, m.p. 218°(efferv.) Its alcoholic solution gave a deep red colouration with alcoholic ferric chloride. Mixed m.p. with 2-hydroxy-3-iodo-4-methoxybenzoic acid, prepared according to Shah and Sethna (1), was not depressed.

The sodium hydroxide extract on acidification gave the iodo ketone which crystallised from alcohol in white thick needles, m.p. 152°. Its alcoholic solution gave a deep red colouration with alcoholic ferric chloride.

Mixed m.p. with 2-hydroxy-3-iodo-4-methoxyacetophenone prepared according to Shah and Sethna (1), was not depressed.

### 7,4'-Dihydroxy-8,3'-di-iodoflavone

7,4'-Dihydroxyflavone (0.86 g.) was dissolved in aqueous ammonia (22 % ) and solution of iodine (1.72 g.) and potassium iodide (3.5 g.) was added dropwise to the stirred ammoniacal solution of flavone at room temperature during half an hour. Finally it was acidified with cold dilute sulphuric acid. The separated product was washed and crystallised from acetic acid in light yellow needles, m.p. 254° (decomp.). Yield 0.5 g.

<u>Analysis</u> : Found : I = 50.22 %.

$C_{15}H_8O_4I_2$ requires : I = 50.19 %.

<u>The dimethyl ether</u> ; prepared by refluxing the above iodoflavone (0.5 g.) in acetone on a steam bath with dimethyl sulphate (1 ml.) in the presence of anhydrous potassium carbonate (2 g.) for 8 hours, was crystallised from alcohol in white needles, m.p. 272-73°.

<u>Analysis</u> : Found : C = 38.55 ; H = 2.41 ; I = 47.78 %.

$C_{17}H_{12}O_4I_2$ requires : C = 38.20 ; H = 2.25 ; I = 47.56 %.

### Alkaline hydrolysis of 7,4'-dimethoxy-8,3'-di-iodoflavone : 2-Hydroxy-3-iodo-4-methoxyacetophenone and 2-hydroxy-3-iodo-4-methoxybenzoic acid

7,4'-Dimethoxy-8,3'-di-iodoflavone (1 g.) was refluxed with potassium hydroxide solution (10 % ; 30 ml.)

for 4 hours. The product obtained on acidification and working up as before gave 2-hydroxy-3-iodo-4-methoxyacetophenone and 2-hydroxy-3-iodo-4-methoxybenzoic acid as seen by direct comparison.

### 7,4'-Dihydroxy-8,3',5'-tri-iodoflavone

7,4'-Dihydroxyflavone (0.86 g.) was dissolved in aqueous ammonia (22 %) and a solution of iodine (2.58 g.) and potassium iodide (5.2 g.) was added to the ammoniacal solution of flavone with stirring. The stirring was continued for 2 hours. On working up as usual the ~~separated~~ product Separated, It was crystallised from acetic acid, m.p. 283° (decomp.).

Analysis : Found : I = 60.11 %.

$C_{15}H_7O_4I_3$ requires : I = 60.27 %.

The dimethyl ether ; prepared by refluxing the above iodoflavone (0.5 g.) in acetone on a steam bath for 8 hours with dimethyl sulphate (1 ml.) in the presence of anhydrous potassium carbonate (2 g.), was crystallised from toluene, m.p. 315°.

Analysis : Found : C = 30.66 ; H = 2.00 ; I = 58.15 %.

$C_{17}H_{11}O_4I_3$ requires : C = 30.91 ; H = 1.66 ; I = 57.71 %.

### Alkaline hydrolysis of 7,4'-dimethoxy-8,3',5'-tri-iodoflavone : 3,5-Di-iodo-4-methoxybenzoic acid and 2-hydroxy-3-iodo-4-methoxyacetophenone

7,4'-Dimethoxy-8,3',5'-tri-iodoflavone (1 g.) was refluxed with alcoholic potassium hydroxide (10 % ; 25 ml.)

till all the flavone dissolved. The product obtained on acidification, was treated with sodium bicarbonate and then sodium hydroxide. The latter on acidification gave 2-hydroxy-3-iodo-4-methoxyacetophenone as seen by direct comparison.

The sodium bicarbonate extract on acidification gave a product which crystallised from acetic acid, m.p. 255° (efferv.). Mixed m.p. with 3,5-di-iodo-4-methoxybenzoic acid prepared as described below was not depressed.

<u>Analysis</u> : Found : C = 23.55 ; H = 1.88 ; I = 62.68 %.

$C_8H_6O_3I_2$ requires : C = 23.76 ; H = 1.49 ; I = 62.87 %.

### Iodination of 4-hydroxybenzoic acid : 3,5-Di-iodo-4-hydroxybenzoic acid

4-Hydroxybenzoic acid (0.69 g.) was dissolved in warm ethyl alcohol and treated with iodine crystals (1 g.) with stirring followed by iodic acid (0.6 g.) in water. The reaction mixture was stirred for 2 hours. The separated product was crystallised from aqueous acetone in white needles, m.p. 262° (efferv.). Yield 0.5 g. Jones and Richardson (12) prepared the same compound by a different method and reported the same m.p.

The same di-iodo derivative could be obtained by iodinating 4-hydroxybenzoic acid (0.69 g.) with a solution of iodine (2.54 g.) and potassium iodide (5.2 g.) in water in presence of aqueous ammonia (22 %.)

Analysis : Found : I = 65.02 %.

$C_7H_4O_3I_2$ requires: I = 65.12 %.

### Methyl-3,5-di-iodo-4-methoxybenzoate :

3,5-Di-iodo-4-hydroxybenzoic acid ( 1 g.) in acetone was refluxed on a steam bath with dimethyl sulphate (2 ml.) and anhydrous potassium carbonate (4 g.) for 8 hours. The product obtained on removal of acetone was washed with a dilute solution of sodium hydroxide and crystallised from alcohol in white needles, m.p. 93°.

Analysis : Found : C = 26.01 ; H = 2.12 ; I = 60.87 %.
$C_9H_8O_3I_2$ requires : C = 25.83 ; H = 1.91 ; I = 60.75 %.

### 3,5-di-iodo-4-methoxybenzoic acid :

Methyl-3,5-di-iodo-4-methoxybenzoate (0.2 g.) was refluxed with alcoholic potassium hydroxide (20 % ; 25 ml.) on a steam bath for 2 hours. The product obtained on acidification was crystallised from acetic acid in white needles, m.p. 255° (efferv.).

### Iodination of 7-hydroxy-4'-methoxyflavone : 7-Hydroxy-8-iodo-4'-methoxyflavone :

7-Hydroxy-4'-methoxyflavone (1.34 g.) was dissolved in warm ethyl alcohol and iodine crystals (0.5 g.) were added with stirring. Iodic acid (0.3 g.) dissolved in minimum quantity of water was then added to the reaction mixture at room temperature and the stirring continued for 2 hours. The separated product was crystallised from acetic acid as brownish needles, m.p. 264° (decomp.). Jurd (6) reports m.p. 274°. Yield 0.8 g.

The same 8-iodo derivative was also obtained

When 7-hydroxy-4'-methoxyflavone (0.67 g.) was dissolved in aqueous ammonia (22 %) and a solution of iodine (0.63 g.) and potassium iodide (1.3 g.) was added drop wise during half an hour with stirring. Finally it was acidified with cold dilute sulphuric acid. The separated product was washed and crystallised from acetic acid. Yield 0.6 g.

Analysis : Found : I = 32.32 %.
$C_{16}H_{11}O_4I$ requires: I = 32.24 %.

Iodination with twice the above mentioned amounts of iodine (1 g.) and iodic acid (0.6 g.) gave only the above 8-iodo derivative in better yield. Yield 1.2 g.

The methyl ether : The above iodoflavone (0.5 g.) dissolved in acetone (200 ml.) was refluxed on a steam bath with dimethyl sulphate (0.5 ml.) and anhydrous potassium carbonate (1 g.) for 12 hours. The product obtained on removal of acetone was washed with dilute sodium hydroxide solution and the residue after washing with water crystallised from ethyl alcohol in colourless needles, m.p. 264-65°. The mixed m.p. with 7,4'-dimethoxy-8-iodoflavone prepared earlier was not depressed.

The same methyl ether was obtained by the action of dimethyl sulphate (1 ml.) on 7-hydroxy-8-iodo-4'-methoxyflavone (0.5 g.) in presence of sodium hydroxide solution (10 % ; 40 ml.). The reaction mixture was kept at room temperature for 2 hours with occasional shaking. The separated product was washed with water and crystallised as above.

### 7-Hydroxy-6,8-di-iodo-4'-methoxyflavone

7-Hydroxy-4'-methoxyflavone (1.34 g.) was dissolved in ethyl alcohol and treated with iodine crystals (1.5 g.) and iodic acid (0.9 g.) in water, in hot, and with vigorous stirring for 2 hours. The separated product was washed and crystallised from acetic acid, m.p. 283° (decomp.). Yield 1.5 g.

Analysis : Found : I = 48.66 %.
$C_{16}H_{10}O_4I_2$ : requires: I = 48.82 %.

The product was stable in boiling acetic acid.

With excess of iodinating agents the same di-iodo derivative was obtained in better yield.

The methyl ether : It was prepared by refluxing the above iodoflavone (1 g.) in acetone, on a steam bath, with dimethyl sulphate (1 ml.) in the presence of anhydrous potassium carbonate (2 g.) for 8 hours. It was crystallised from acetic acid in white needles, m.p. 246-47°.

Analysis : Found : C = 38.55 ; H = 2.29 ; I = 47.22 %.
$C_{17}H_{12}O_4I_2$ : requires : C = 38.20 ; H = 2.25 ; I = 47.56 %.

### Alkaline hydrolysis of 7,4'-dimethoxy-6,8-di-iodoflavone: 2-Hydroxy-3,5-di-iodo-4-methoxybenzoic acid

7,4'-Dimethoxy-6,8-di-iodoflavone (1 g.) was heated with alcoholic potassium hydroxide solution (10 % ; 30 ml.) for 4 hours. The product obtained on acidification was extracted with sodium bicarbonate . The extract on acidification gave an iodo acid which was crystallised from alcohol in white needles, m.p. 217° (efferv.). Its alcoholic solution gave a deep red colouration with alcoholic ferric chloride. Mixed m.p. with 2-hydroxy-3,5-di-iodo-4-methoxybenzoic acid, prepared according to Shah and Sethna (1), was not depressed.

Iodination of 5,7-dihydroxyflavone : 5,7-dihydroxy-6,8-di-iodoflavone

5,7-Dihydroxyflavone (1.27 g.) was dissolved in warm ethyl alcohol and iodine crystals (0.5 g.) and iodic acid (0.3 g.) in water were added with stirring, ~~and~~ The reaction mixture was stirred further for 2 hours. The separated product was crystallised from dioxane in yellow needles, m.p. 284° (decomp.). Yield 0.9 g. Its alcoholic solution gave bluish colour with alcoholic ferric chloride.

No mono-iodo derivative could be isolated.

Analysis : Found : I = 50.02 %.

$C_{15}H_8O_4I_2$ requires : I = 50.19 %.

The same di-iodoflavone was obtained in better yield by iodination of 5,7-dihydroxyflavone (1.27 g.) with iodine (1 g.) and iodic acid (0.6 g.) under vigorous stirring. Yield 1.5 g.

The same 6,8-di-iodoflavone was obtained by iodination of 5,7-dihydroxyflavone with iodine solution in presence of aqueous ammonia as usual.

The product was stable in boiling acetic acid.

The dimethyl ether : The dimethyl ether was obtained as before by refluxing the di-iodoflavone (0.2 g.) in acetone (200 ml.) on a steam bath with dimethyl sulphate (1 ml.) in the presence of anhydrous potassium carbonate (2 g.) for 48 hours. The product obtained on removal of acetone was washed with dilute sodium hydroxide solution and crystallised from ethyl alcohol in white needles, m.p. 209°.

Analysis : Found : C = 38.22 ; H = 1.91 ; I = 48.14 %.

$C_{17}H_{12}O_4I_2$ requires : C = 38.20 ; H = 2.25 ; I = 47.56 %.

Attempted alkaline hydrolysis of 5,7-dimethoxy-6,8-di-iodoflavone

5,7-Dimethoxy-6,8-di-iodoflavone (0.5 g.)was refluxed with alcoholic potassium hydroxide (10 % ; 15 ml.) for 4 hours. On working up, unreacted 5,7-dimethoxy-6,8-di-iodoflavone was obtained back.

Iodination of 6-hydroxyflavone : 6-Hydroxy-5-iodoflavone

6-Hydroxyflavone (1.19 g.) was dissolved in warm ethyl alcohol and iodine crystals (0.5 g.) were added. To this stirred solution iodic acid (0.3 g.) in water was added and the reaction mixture stirred for further 2 hours. The separated product was crystallised from ethyl acetate in brownish plates, m.p. 208-09° (decomp.). Yield 0.9 g.

No di-iodo derivative could be obtained even with a large excess of iodine and iodic acid.

The same mono-iodo derivative could be obtained with iodine and ammonia in the usual manner as described earlier.

Analysis : Found : I = 34.97 %.

$C_{15}H_9O_3I$ requires : I = 34.89 %.

The methyl ether : The methyl ether was obtained as before by refluxing on a steam bath the above iodoflavone (1.7 g.) in acetone with dimethyl sulphate (1.7 ml.) in the presence of anhydrous potassium carbonate (3.4 g.) for 8 hours. The product obtained on removal of acetone was crystallised from ethyl alcohol in yellow needles, m.p. 204°.

Analysis : Found : C = 50.66 ; H = 2.70 ; I = 33.50 %.

$C_{16}H_{11}O_3I$ requires : C = 50.79 ; H = 2.91 ; I = 33.59 %.

Attempted preparation of 6-hydroxy-5-iodoflavone from 6-hydroxy-5-aminoflavone

6-Hydroxy-5-aminoflavone (13) (0.2 g.) was added to dilute hydrochloric acid (10 % ; 10 ml.) and cooled to 0°. The solution of sodium nitrite (1 g.) was added to the above reaction mixture at 0°, drop by drop during half an hour. and The reaction mixture on pouring into potassium iodide solution or on treating with cuprous iodide gave a product which did not contain iodine.

## Attempted iodination of 7,8-dihydroxyflavone and 6-methoxyflavone

### (a) With iodine and iodic acid

The flavone derivative was dissolved in warm ethyl alcohol and treated with iodine crystals and iodic acid in minimum quantity of water. The reaction mixture after stirring for 2 hours was poured into sodium hydrogen sulphite solution. The isolated product was the starting material in every case.

### (b) Iodine and ammonia

The flavone derivative was subjected to the action of iodine solution in the presence of aqueous ammonia in the usual manner. In all cases the unreacted product was isolated.

### (c) Iodine monochloride

6-Methoxyflavone was treated with iodine monochloride in acetic acid and kept at 60° in an oven, overnight. On working up with the reaction mixture 6-methoxyflavone was recovered unchanged.

Iodination in each case with excess of the above reagents and keeping the reaction mixture for different periods failed to yield any iodo derivative.

## Iodination of simple flavanone : 3-Iodoflavanone

Simple flavanone (1 g.) was dissolved in glacial acetic acid (5 ml.) and iodine monochloride (4 g., excess) was added. The reaction mixture was shaken and kept at 60° overnight. Next day it was treated with cold sodium hydrogen sulphite solution and the pasty product on repeated crystallisation from ethyl alcohol gave white needles, m.p. 123° (decomp.)

Analysis : Found : I = 36.72 %.
$C_{15}H_{11}O_2I$ requires : I = 36.29 %.

## Simple flavone

3-Iodoflavanone (0.5 g.) was treated with glacial acetic acid (5 ml.) and potassium hydroxide (0.5 g.) and the reaction mixture was refluxed for 1 hour. The product obtained on dilution was washed with dilute solution of sodium bisulphite and then with water and the residue was crystallised from ethyl alcohol. M.p. and mixed m.p. with simple flavone was 97°.

## Iodination of 7-hydroxyflavanone : 7-Hydroxy-3-iodoflavanone

7-Hydroxyflavanone (1.2 g.) was dissolved in warm ethyl alcohol (20 ml.) and iodine crystals (0.5 g.) were added with stirring. Iodic acid (0.3 g.) dissolved in minimum quantity of water was added to the reaction mixture at room temperature, and the stirring continued for 2 hours. The separated product was crystallised from benzene in buff coloured buds, m.p. 192° (decomp.). Yield 0.6 g.

The same mono-iodo derivative was also isolated when 7-hydroxyflavanone (0.6 g.) was dissolved in aqueous ammonia (22 %) and solution of iodine (0.6 g.) and potassium iodide (1.2 g.) was added dropwise to the stirred solution of the flavanone at room temperature during half an hour. It was then acidified with cold dilute sulphuric acid. The separated product was washed with water and crystallised from benzene as before.

<u>Analysis</u> : Found : I = 35.22 %.

$C_{15}H_{11}O_3I$ requires : I = 34.70 %.

### 7-Hydroxyflavone

7-Hydroxy-3-iodoflavanone (1 g.) was dissolved in glacial acetic acid (10 ml.) and potassium hydroxide (1 g.) was added to the well cooled reaction mixture and then refluxed for 2 hours. The separated product was washed with sodium bisulphite solution and then with water and finally crystallised from acetic acid. The melting point and mixed m.p. with 7-hydroxyflavone was 235°.

### 3,6-Di-iodo-7-hydroxyflavanone

7-Hydroxyflavanone (1.2 g.) was dissolved in warm ethyl alcohol (20 ml) and iodine crystals (1 g.) were added with stirring. Iodic acid (0.6 g.) dissolved in minimum quantity of water was then added to the reaction mixture and the stirring continued for 2 hours. The separated product was crystallised from benzene in violet needles, m.p. 187° (decomp.). Yield 1 g.

The same 3,6-di-iodoflavanone could also be obtained on iodination of 7-hydroxyflavanone (0.6 g.) with a solution of iodine (1.27 g.) and potassium iodide (2.5 g.) in presence of aqueous ammonia (22 %) or when 3-iodo-7-hydroxyflavanone (1.83 g.) was dissolved in warm ethyl alcohol and iodine crystals (0.5 g.) added followed by iodic acid (0.3 g.) in water as in the previous case. The product separating on stirring was crystallised from benzene. The mixed m.p. with 3,6-di-iodo-7-hydroxyflavanone was not depressed.

<u>Analysis</u> : Found : I = 51.59 %.

$C_{15}H_{10}O_3I_2$ requires : I = 51.62 %.

<u>7-Hydroxy-6-iodoflavone</u>

3,6-Di-iodo-7-hydroxyflavanone (1 g.) was dissolved in glacial acetic acid (10 ml.) and potassium hydroxide (1 g.) added to the well cooled solution of di-iodoflavanone and then the reaction mixture was refluxed for 2 hours. The separated product was washed with sodium bisulphite solution and then with water and finally crystallised from acetic acid in buff coloured needles, m.p. 294° (decomp.). Yield 0.7 g.

<u>Analysis</u> : Found : C = 49.22 ; H = 2.14 ; I = 34.51 %.

$C_{15}H_9O_3I$ requires : C = 49.45 ; H = 2.47 ; I = 34.89 %.

<u>The methyl ether</u> : The mono-iodoflavone (0.5 g.) dissolved in acetone (200 ml.) was refluxed on a steam bath

with dimethyl sulphate (0.5 ml.) and anhydrous potassium carbonate (1 g.) for 8 hours. The product obtained on removal of acetone was washed with dilute sodium hydroxide solution and the residue washed with water and crystallised from acetic acid in brownish needles, m.p. 172-73°.
Yield 0.4 g.

Analysis : Found : C = 50.66 ; H = 3.26 ; I = 33.60 %.
$C_{16}H_{11}O_3I$ requires : C = 50.79 ; H = 2.91 ; I = 33.60 %.

### Alkaline hydrolysis of 6-iodo-7-methoxyflavone : 2-Hydroxy-4-methoxy-5-iodobenzoic acid and 2-hydroxy-4-methoxy-5-iodoacetophenone

6-Iodo-7-methoxyflavone (0.8 g.) was refluxed with alcoholic potassium hydroxide (10 % ; 30 ml.) for 4 hours. The product obtained on acidification was first treated with sodium bicarbonate solution and the residue treated with sodium hydroxide solution. The sodium bicarbonate extract on acidification gave an iodo acid which crystallised from acetic acid in yellow needles. Its alcoholic solution gave a red colouration with alcoholic ferric chloride. M.p. and mixed m.p. with 2-hydroxy-4-methoxy-5-iodobenzoic acid prepardd according to Shah and Sethna (1) was 245° (efferv). The sodium hydroxide extract on acidification gave an iodo ketone which crystallised from ethyl alcohol in white needles. Its alcoholic solution gave a red colouration with alcoholic ferric chloride. M.p. and mixed m.p. with 2-hydroxy-4-methoxy-5-iodoacetophenone, prepared according to Shah and

Sethna (1), was 161°.

Iodination of 7-hydroxy-4'-methoxyflavanone : 3,6-Di-iodo-7-hydroxy-4'-methoxyflavanone

7-Hydroxy-4'-methoxyflavanone (1.35 g.) was dissolved in warm ethyl alcohol and treated with iodine crystals (0.5 g.) and iodic acid (0.3 g.) in water with stirring. The reaction mixture was stirred for 2 hours and the product which separated, was crystallised from benzene, m.p. 201° (decomp.). Yield 0.8 g.

No mono-iodo derivative was obtained.

The same di-iodo derivative was obtained in better yield by iodinating 7-hydroxy-4'-methoxyflavanone (1.35 g.) with iodine crystals (1 g.) and iodic acid (0.6 g.) in water as described above. Yield 1.7 g.

The same 3,6-di-iodoflavanone was also obtained by iodinating 7-hydroxy-4'-methoxyflavanone with iodine in presence of aqueous ammonia in the usual manner.

Analysis : Found : I = 48.41 %.
$C_{16}H_{12}O_4I_2$ requires : I = 48.60 %.

The methyl ether was obtained by refluxing on a steam bath, the above di-iodoflavanone (0.5 g.) in dry benzene with dimethyl sulphate (0.5 ml.) in the presence of anhydrous potassium carbonate (1 g.) for 8 hours. It was crystallised from ethyl alcohol in white thick needles, m.p. 125°.

Analysis : Found : C = 38.22 ; H = 2.48 ; I = 47.42 %.
$C_{17}H_{14}O_4I_2$ requires : C = 38.06 ; H = 2.61 ; I = 47.39 %.

### 6-Iodo-7-hydroxy-4'-methoxyflavone

3,6-Di-iodo-7-hydroxy-4'-methoxyflavanone (1 g.) was treated with glacial acetic acid (20 ml.) and potassium hydroxide (1 g.). The reaction mixture was then refluxed for one and a half hours and diluted with water containing a little sodium bisulphite. The product, which separated, was washed and crystallised from acetic acid in brownish needles, m.p. 280-83$^{\circ}$ (decomp.).

Analysis : Found : C = 48.66 ; H = 2.55 ; I = 32.00 %.

$C_{16}H_{11}O_4I$ requires : C = 48.73 ; H = 2.79 ; I = 32.24 %.

The methyl ether : The above iodoflavone (1 g.) was dissolved in acetone and refluxed on a steam bath with dimethyl sulphate (1 ml.) and potassium carbonate (2 g.) for 8 hours. The separated product on removal of acetone was crystallised from ethyl alcohol in white needles, m.p. 208-10$^{\circ}$.

Analysis : Found : C = 49.72 ; H = 3.02 ; I = 30.89 %.

$C_{17}H_{13}O_4I$ requires : C = 49.99 ; H = 3.18 ; I = 31.13 %.

### Alkaline hydrolysis of 6-iodo-7,4'-dimethoxyflavone : 2-Hydroxy-4-methoxy-5-iodobenzoic acid and 2-hydroxy-4-methoxy-5-iodoacetophenone

6-Iodo-7,4'-dimethoxyflavone (0.8 g.) was refluxed with alcoholic potassium hydroxide (10 % ; 30 ml.) for 4 hours. On working up the reaction mixture in the usual way the sodium bicarbonate extract on acidification gave 2-hydroxy-4-methoxy-5-iodobenzoic acid as seen by direct comparison and the sodium hydroxide extract on acidification gave 2-hydroxy-4-methoxy-5-iodoacetophenone as seen by direct comparison.

Iodination of 4'-hydroxyflavanone : 3',5'-Di-iodo-4'-hydroxyflavanone

4'-Hydroxyflavanone (1.2 g.) was dissolved in warm ethyl alcohol and iodinated with iodine (0.5 g.) and iodic acid (0.3 g.) in water as described in earlier cases. The product, which separated, was crystallised from benzene in white needles, m.p. 178-79° (decomp.). Yield 0.5 g.

The same 3',5'-di-iodo-4'-hydroxyflavanone was obtained in better yield by iodinating 4'-hydroxyflavanone (1.2 g.) with iodine (1 g.) and iodic acid (0.6 g.) in water. Yield 0.9 g.

Analysis : Found : I = 51.51 %.
$C_{15}H_{10}O_3I_2$ requires : I = 51.62 %.

No tri-iodo derivative could be obtained even with large excess of iodinating agents.

The methyl ether : The above iodoflavanone (1 g.) was dissolved in dry benzene and refluxed on a steam bath with dimethyl sulphate (1 ml.) and potassium carbonate (2 g.) for 8 hours. The product obtained on removal of benzene was washed with dilute sodium hydroxide solution and then with water and crystallised from ethyl alcohol in white needles, m.p. 147°. Yield 0.7 g.

Analysis : Found : C = 37.88 ; H = 2.11 ; I = 49.88 %.
$C_{16}H_{12}O_3I_2$ requires : C = 37.94 ; H = 2.37 ; I = 50.19 %.

### Alkaline hydrolysis of 3',5'-di-iodo-4'-methoxyflavanone : 3,5-di-iodo-4-methoxybenzoic acid

3',5'-Di-iodo-4'-methoxyflavanone (0.7 g.) was refluxed with alcoholic potassium hydroxide (10 % ; 20 ml.) for 4 hours. The reaction mixture was acidified and extracted with ether. The ether extract was treated with sodium bicarbonate which on acidification gave a product which crystallised from ethyl alcohol, m.p. 255$^{\circ}$ (efferv.). The mixed m.p. with 3,5-di-iodo-4-methoxybenzoic acid described earlier was not depressed.

### Attempted iodination of 6-hydroxyflavanone

(a) With iodine and iodic acid

6-Hydroxyflavanone (1.2 g.) was dissolved in warm ethyl alcohol and treated with iodine crystals (0.5 g.) and iodic acid (0.3 g.) in water. On working up as usual the unreacted 6-hydroxyflavanone was obtained.

(b) With iodine and ammonia

6-Hydroxyflavanone (0.6 g.) was treated with a solution of iodine (0.6 g.) and potassium iodide (1.2 g.) in the presence of aqueous ammonia (22 %.). On working up as usual the unchanged product was obtained.

(c) With iodine monochloride

6-Hydroxyflavanone (1 g.) was dissolved in glacial acetic acid and iodine monochloride ( 2 g.excess) added. On working up ~~with~~ the reaction mixture, a chlorinated product was isolated.

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