# THEORETICAL

## Section ( ii )

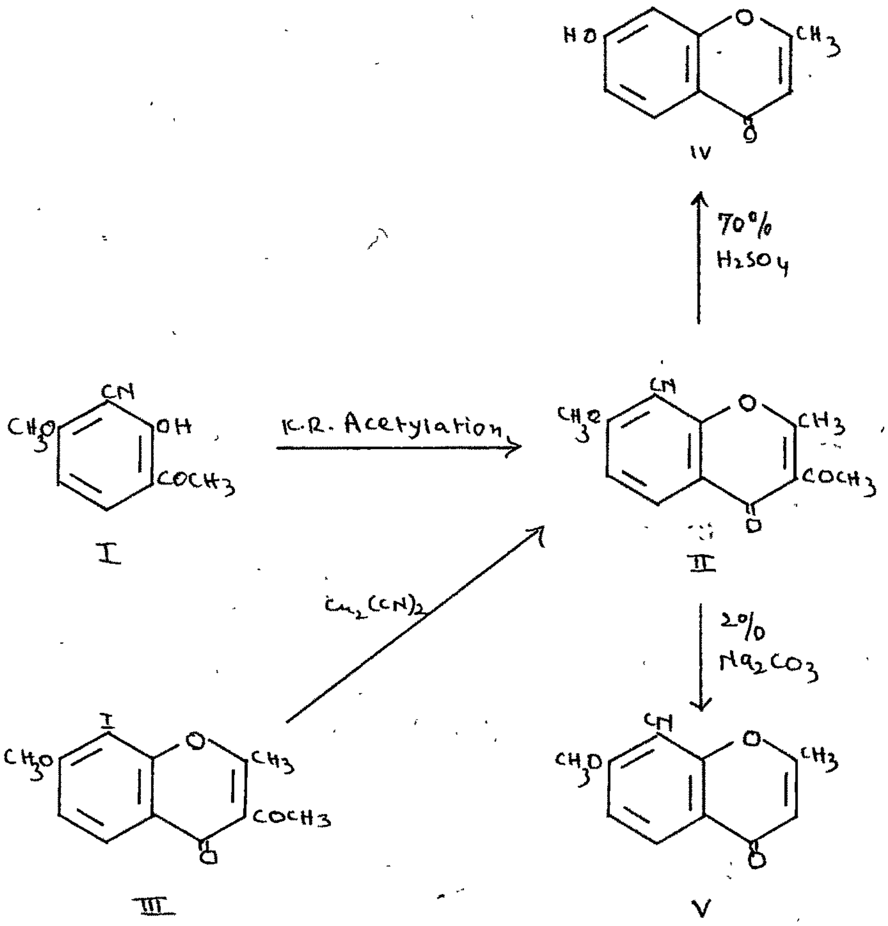
### Kostanecki-Robinson Acylation of some cyano derivatives of 2-hydroxy-4-methoxyacetophenone

As seen from the ~~introduction to~~ account of the Kostanecki-Robinson reaction ~~it is found th~~at the effect of the cyano substituent in o-hydroxyacetophenones on the course of the Kostanecki-Robinson reaction has not been studied so far. After the present work was completed it was found that recently Da Re et al. ( J. Med. Pharm. Chem., 1960, 2, 263 ; C.A., 1960, 54, 22613 ) have studied the action of benzoyl chloride and sodium benzoate on 2-hydroxy-3-cyanopropiophenone and obtained 8-cyano-3-methylflavone.

### Kostanecki-Robinson acetylation of 2-hydroxy-3-cyano-4-methoxyacetophenone

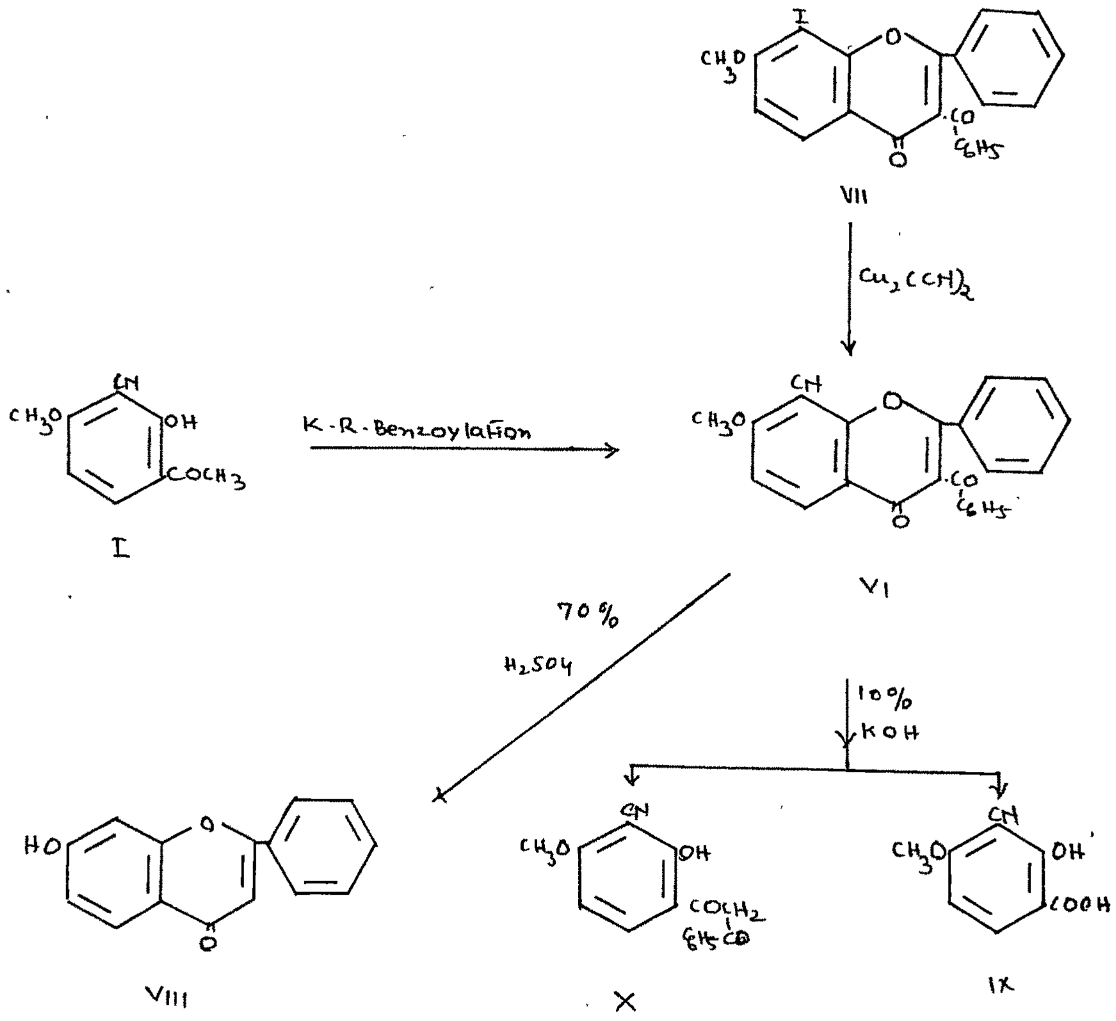
2-Hydroxy-3-cyano-4-methoxyacetophenone ( I ) on Kostanecki-Robinson acetylation with sodium acetate and acetic anhydride gave a product which did not undergo any change on keeping with cold concentrated sulphuric acid. Further, the same product was obtained on fusion of 7-methoxy-8-iodo-3-acetyl-2-methylchromone ( III ) with cuprous cyanide. Therefore the product obtained in the Kostanecki-Robinson acetylation must be 7-methoxy-8-cyano-3-acetyl-2-methylchromone ( II ). On heating with 70 % sulphuric acid it gave the known 7-hydroxy-2-methylchromone ( IV ), demethylation, de-acetylation and elimination of the cyano group having taken place. 7-Methoxy-8-cyano-3-acetyl-

2-methylchromone ( II ) could however be de-acetylated with aqueous alcoholic sodium carbonate solution to 7-methoxy-8-cyano-2-methylchromone ( V ) described in section( i ).



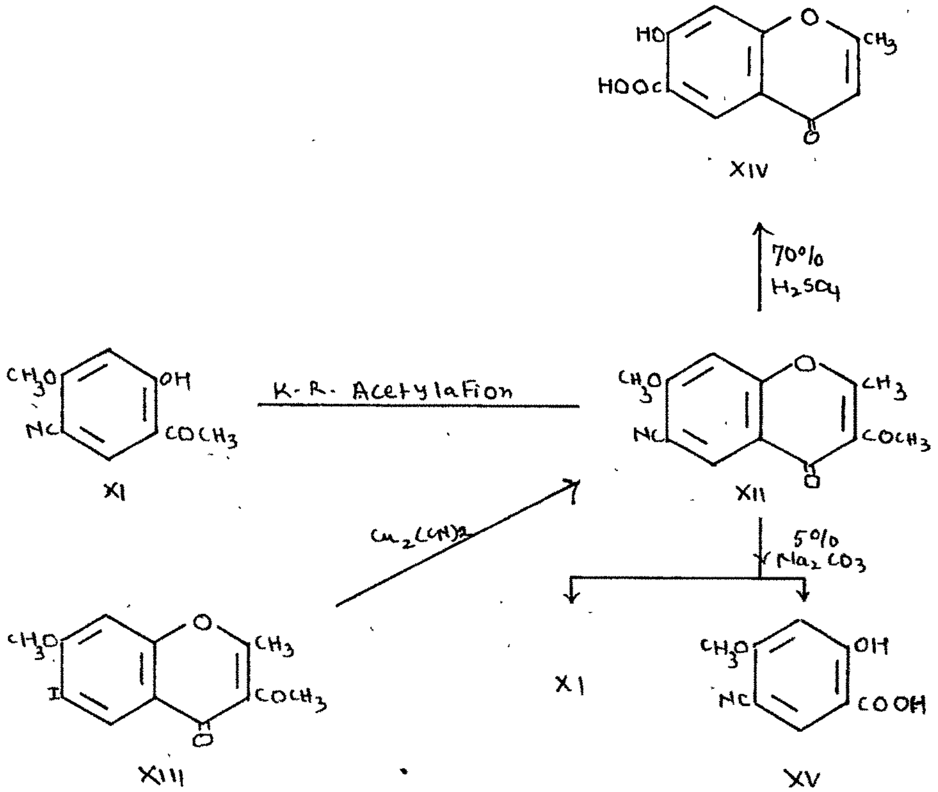
### Kostanecki-Robinson benzoylation of 2-hydroxy-3-cyano-4-methoxyacetophenone

2-Hydroxy-3-cyano-4-methyoxyacetophenone ( I ) on Kostanecki-Robinson benzoylation with sodium benzoate and benzoic anhydride gave a product which remained unchanged on treatment with cold concentrated sulphuric acid. It however agreed with the cyanoflavone obtained by the Rosenmund-von Braun reaction on 7-methoxy-8-iodo-3-benzoylflavone ( VII ). Therefore the benzoylation product must be 7-methoxy-8-cyano-3-benzoylflavone ( VI ). In the hydrolysis of the cyanoflavone with 70 % sulphuric acid demethylation, debenzoylation and elimination of the cyano group, probably through hydrolysis and decarboxylation, took place and 7-hydroxyflavone ( VIII ) was obtained. Attempted debenzoylation with alcoholic potassium hydroxide gave a mixture of 2-hydroxy-3-cyano-4-methoxybenzoic acid ( IX ) and the β-diketone : 2-hydroxy-3-cyano-4-methoxydibenzoylmethane ( X ). This β-diketone was synthesised from 2-benzoyloxy-3-cyano-4-methoxyacetophenone as mentioned in section ( i ).



## Kostanecki-Robinson acetylation of 2-hydroxy-4-methoxy-5-cyano-acetophenone

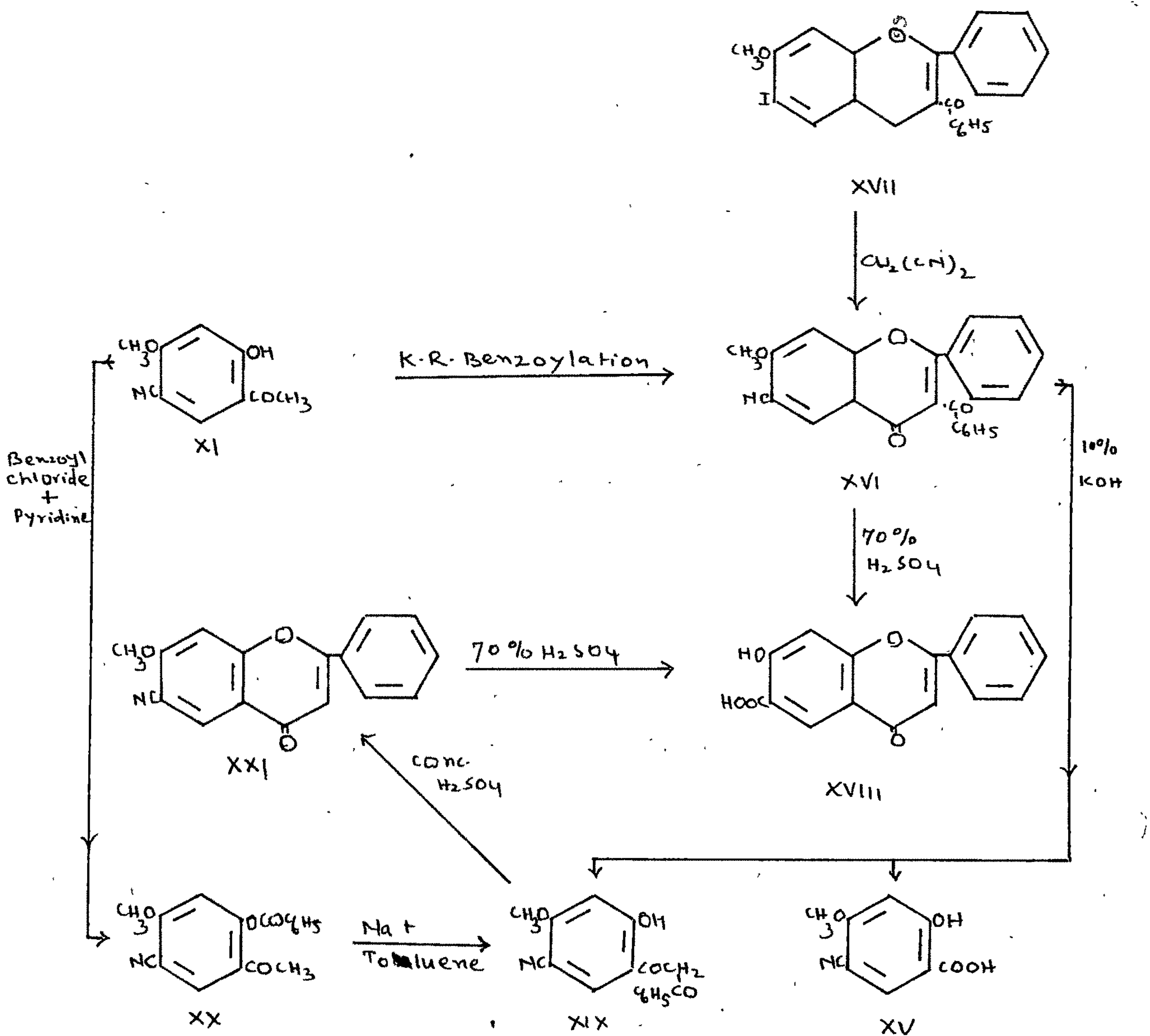
2-Hydroxy-4-methoxy-5-cyano-acetophenone ( XI ) on Kostanecki-Robinson acetylation gave a product which did not undergo any change on treatment with cold concentrated sulphuric acid. It agreed with the product obtained in the Rosenmund-von Braun reaction on 7-methoxy-6-iodo-3-acetyl-2-methylchromone ( XIII ) and was therefore assigned the 7-methoxy-6-cyano-3-acetyl-2-methylchromone ( XII ) structure. On treatment with 70 % sulphuric acid it gave 7-hydroxy-2-methylchromone-6-carboxylic acid ( XIV ), demethylation and de-acetylation having occurred along with the hydrolysis of the cyano group. Alkaline hydrolysis of the cyano-3-acetylchromone ( XII ) led to the formation of 2-hydroxy-



4-methoxy-5-cyano-acetophenone ( XI ) and 2-hydroxy-4-methoxy-5-cyano-benzoic acid ( XV ), describd in section ( i ), instead of the de-acetylated chromone.

### Kostanecki-Robinson benzoylation of 2-hydroxy-4-methoxy-5-cyano-acetophenone

2-Hydroxy-4-methoxy-5-cyano-acetophenone ( XI ) on Kostanecki-Robinson benzoylation with sodium benzoate and benzoic anhydride gave a product which was identical with the product obtained in the Rosenmund-von Braun reaction on 7-methoxy-6-iodo-3-benzoylflavone ( XVII ) and was therefore assigned 7-methoxy-6-cyano-3-benzoylflavone ( XVI ) structure. On treatment with 70 % sulphuric acid it gave a product which did not contain any nitrogen and formed an insoluble sodium salt with sodium hydrogen carbonate solution and gave a red colouration with alcoholic ferric chloride. It has been assigned 7-hydroxyflavone-6-carboxylic acid ( XVIII ) structure. On decarboxylation it gave the known 7-hydroxyflavone ( VIII ). Further, ~~its~~ the attempted debenzoylation of (XVII) with alkali gave a mixture of 2-hydroxy-4-methoxy-5-cyanobenzoic acid ( XV ) described in secion ( i ), and a product containing nitrogen which was soluble in alkali and which gave a red colouration with alcoholic ferric chloride. It was different from 2-hydroxy-4-methoxy-5-cyano-acetophenone ( XI ) and was therefore presumed to be the $\beta$-diketone; 2-hydroxy-4-methoxy-5-cyano-dibenzoylmethane ( XIX ). The structure was confirmed by its direct synthesis as follows:



2-Hydroxy-4-methoxy-5-cyano-acetophenone ( XI ) on benzoylation wih benzoyl chloride andpyridine gave 2-benzoyloxy-4-methoxy-5-cyano-acetophenone ( XX ) which on Baker-Venkataraman transformation with sodium in toluene gave the same β-diketone ( XIX ) described above. On cyclisation with sulphuric acid it gave a product insoluble in alkali.

It must therefore be 7-methoxy-6-cyanoflavone ( XXI ). On hydrolysis with 70 % sulphuric acid it gave 7-hydroxyflavone-6-carboxylic acid ( XVIII ) described before, simultaneous demethylation having occurred along with the hydrolysis of the cyano group.

## SECTION (ii)

## EXPERIMENTAL

Kostanecki-Robinson acetylation of 2-hydroxy-3-cyano-4-methoxyacetophenone : 7-Methoxy-8-cyano-3-acetyl-2-methylchromone

2-Hydroxy-3-cyano-4-methoxyacetophenone ( 2 g. ) was heated with freshly fused and powdered sodium acetate ( 5 g. ) and acetic anhydride ( 25 ml. ) in an oil bath at 170-180° for 8 hours. The reaction mixture was added to cold water and kept over-night in a refrigerator. The solid obtained crystallised in yellowish needles from acetic acid ( charcoal ), m.p. 230°. Yield 1 g.

Analysis :

9.70 mg. of the substance gave 23.20 mg. of carbon dioxide and 3.48 mg. of water.

9.44 mg. of the same substance gave 0.505 ml. of nitrogen at 31° and 755 mm.

Found : C = 65.27 % ; H = 4.01 % ; N = 5.83 %.

$C_{14}H_{11}O_4N$ requires : C = 65.37 % ; H = 4.28 % ; N = 5.44 %.

The same cyano-chromone was obtained by heating an intimate mixture of 7-methoxy-8-iodo-3-acetyl-2-methylchromone ( 1.8 g. ; 0.005 mole ) with cuprous cyanide ( 0.89 g. ; 0.01 mole ) at 220-225° for ten minutes and extracting the reaction mixture with acetone. Yield 0.4 g.

Hydrolysis of 7-methoxy-8-cyano-3-acetyl-2-methylchromone with sulphuric acid

The above chromone ( 1 g. ) was gently refluxed with sulphuric acid ( 70 % ; 20 ml. ) for 3 hours. The product obtained on pouring the cooled reaction mixture over crushed ice and keeping over-night, crystallised in thick white plates. M.P. and mixed m.p. with 7-hydroxy-2-methylchromone was 249°.

Alkaline hydrolysis of 7-methoxy-8-cyano-3-acetyl-2-methylchromone : 7-Methoxy-8-cyano-2-methylchromone

7-Methoxy-8-cyano-3-acetyl-2-methylchromone ( 2 g. ) was heated with aqueous alcoholic sodium carbonate solution ( 2 % ; 60 ml. ) for fifteen minutes on a steam bath. The product obtained on acidification was treated first with sodium hydrogen carbonate solution and then with sodium hydroxide. The residue crystallised in shining yellowish plates from ethyl alcohol. M.P. and mixed m.p. with 7-methoxy-8-cyano-2-methylchromone described in section (i) was 262°.

On acidification, the bicarbonate extract, gave 2-hydroxy-3-cyano-4-methoxybenzoic acid and the sodium hydroxide extract yielded 2-hydroxy-3-cyano-4-methoxyacetophenone as seen by direct comparison.

Kostanecki-Robinson benzoylation of 2-hydroxy-3-cyano-4-methoxyacetophenone : 7-Methoxy-8-cyano-3-benzoylflavone

2-Hydroxy-3-cyano-4-methoxyacetophenone ( 2 g. ) was intimately mixed with freshly fused and powdered sodium benzoate ( 4 g. ) and benzoic anhydride ( 20 g. ) and heated

at 170-180° in an oil bath for 8 hours. The cooled reaction mixture was repeatedly extracted with hot water and sodium hydrogen carbonate solution and the residue crystallised from acetic acid ( charcoal ) in tiny needles, m.p. 258°.
Yield 1.90 g.

<u>Analysis</u> :

10.22 mg. of the substance gave 28.48 mg. of carbon dioxide and 3.52 mg. of water.

7.00 mg. of the same substance gave 0.228 ml. of nitrogen at 30° and 761 mm.

Found : C = 76.03 % ; H = 3.85 % ; N = 3.59 %.
$C_{24}H_{15}O_4N$ requires : C = 75.59 % ; H = 3.94 % ; N = 3.67 %.

The same cyano-flavone was obtained by heating an intimate mixture of 7-methoxy-8-iodo-3-benzoylflavone ( 2.40 g. ; 0.005 mole ) and cuprous cyanide ( 0.89 g. ; 0.01 mole ) at 250° in an oil bath for ten minutes. and extracting the reaction mixture with acetone. Yield 0.8 g.

### Hydrolysis of 7-methoxy-8-cyano-3-benzoylflavone with sulphuric acid

7-Methoxy-8-cyano-3-benzoylflavone ( 1 g. ) was heated under gentle reflux with sulphuric acid ( 70 % ; 15 ml. ) for 3 hours. The product obtained crystallised from ethyl alcohol in long colourless needles. M.P. and mixed m.p. with 7-hydroxyflavone was 240°.

### Alkaline hydrolysis of 7-methoxy-8-cyano-3-benzoylflavone : 2-Hydroxy-3-cyano-4-methoxybenzoic acid and 2-hydroxy-3-cyano-4-methoxy-dibenzoylmethane

7-Methoxy-8-cyano-3-benzoylflavone ( 1 g. ) was heated with alcoholic potassium hydroxide solution ( 10 % ; 20 ml. ) on a steam bath for 2 hours. The product obtained on acidification was treated with sodium hydrogen carbonate solution. The sodium hydrogen carbonate solution on acidification gave 2-hydroxy-3-cyano-4-methoxybenzoic acid and the residue on crystallisation from ethyl alcohol gave 2-hydroxy-3-cyano-4-methoxy-dibenzoyl methane both of which have been described before.

### Kostanecki-Robinson acetylation of 2-hydroxy-4-methoxy-5-cyano-acetophenone : 7- Methoxy-6-cyano-3-acetyl-2-methylchromone

2-Hydroxy-4-methoxy-5-cyano-acetophenone ( 2 g. ) was heated with fused sodium acetate ( 5 g. ) and acetic anhydride ( 18 ml. ) in an oil bath at 180° for 8 hours. The product obtained on dilution with excess of water crystallised from acetic acid ( charcoal ) in yellowish needles, m.p. 220°. Yield 0.95 g.

Analysis :

9.58 mg. of the substance gave 23.08 mg. of carbon dioxide and 3.74 mg. of water.

8.92 mg. of the same substance gave 0.426 ml. of nitrogen at 34° and 753 mm.

Found : C= 65.73 % ; H = 4.37 % ; N = 5.26 %.

$C_{14}H_{11}O_4N$ requires : C = 65.37 % ; H = 4.28 % ; N = 5.44 %.

The same cyano compound was obtained when 7-methoxy-6-iodo-3-acetyl-2-methylchromone ( 1.8 g. ; 0.005 mole ) was heated with cuprous cyanide ( 0.89 g. ; 0.01 mole ) at 225° for fifteen minutes in an oil bath and the powdered reaction mixture repeatedly extracted with ethyl alcohol. Yield 0.3 g.

Hydrolysis of 7-methoxy-6-cyano-3-acetyl-2-methylchromone with sulphuric acid : 7-Hydroxy-2-methylchromone-6-carboxylic acid

7-Methoxy-6-cyano-3-acetyl-2-methylchromone ( 1 g. ) was gently refluxed with sulphuric acid ( 70 % ; 20 ml. ) for 3 hours. The product which separated on pouring the reaction mixture over crushed ice was purified through dilute sodium hydrogen carbonate solution. The product obtained on acidification crystallised in colourless needles from acetic acid. M.P. and mixed m.p. with 7-hydroxy-2-methylchromone-6-carboxylic acid described earlier was 302° ( decomp. )

Alkaline hydrolysis of 7-methoxy-6-cyano-3-acetyl-2-methylchromone : 2-Hydroxy-4-methoxy-5-cyanobenzoic acid and 2-hydroxy-4-methoxy-5-cyano-acetophenone

7-Methoxy-6-cyano-3-acetyl-2-methylchromone ( 1 g. ) was refluxed with aqueous alcoholic sodium carbonate solution ( 5 % ; 20 ml. ) on a steam bath for 2 hours. The product obtained on acidification was treated first with sodium hydrogen carbonate solution and then with sodium hydroxide solution. The bicarbonate extract on acidification gave 2-hydroxy-4-methoxy-5-cyano-benzoic acid and the sodium hydroxide extracts yielded

2-hydroxy-4-methoxy-5-cyano-acetophenone described in section (i).

### Kostanecki-Robinson benzoylation of 2-hydroxy-4-methoxy-5-cyano-acetophenone : 7-Methoxy-6-cyano-3-benzoylflavone

2-Hydroxy-4-methoxy-5-cyano-acetophenone ( 2 g. ) was mixed intimately with fused sodium benzoate ( 5 g. ) and benzoic anhydride ( 18 g. ) and heated in an oil bath at 170-180° for 8 hours. The reaction mixture was then repeatedly extracted with hot water and sodium hydrogen carbonate solution. The residue crystallised from acetic acid ( charcoal ) in tiny needles, m.p. 281°. Yield 2.2 g.

Analysis :

9.84 mg. of the substance gave 27.06 mg. of carbon dioxide and 3.78 mg. of water.

9.90 mg. of the same substance gave 0.342 ml. of nitrogen at 33° and 754 mm.

Found : C = 75.02 % ; H = 4.30 % ; N = 3.82 %.

$C_{24}H_{15}O_4N$ requires : C = 75.59 % ; H = 3.94 % ; N = 3.67 %.

The same cyano flavone was obtained by heating an intimate mixture of 7-methoxy-6-iodo-3-benzoylflavone ( 1.2 g. ; 0.0025 mole ) and cuprous cyanide ( 0.6~~5~~7 g. ; 0.0075 mole ) at 285° for ten minutes. Yield 0.24 g.

### Hydrolysis of 7-methoxy-6-cyano-3-benzoylflavone with sulphuric acid : 7-Hydroxyflavone-6-carboxylic acid

7-Methoxy-6-cyano-3-benzoylflavone ( 1 g. ) was gently refluxed with sulphuric acid ( 70 % ; 15 ml. ) for 3 hours. The product obtained on pouring the reaction mixture over crushed ice was purified through dilute sodium hydrogen carbonate solution and crystallised in colourless needles from acetic acid, m.p. 311° ( decomp. ) Its alcoholic solution gave a red colouration with alcoholic ferric chloride.

Analysis :

10.14 mg. of the substance gave 25.18 mg. of carbon dioxide and 3.24 mg. of water.

Found : C = 67.77 % ; H = 3.57 %.

$C_{16}H_{10}O_5$ requires : C = 68.08 % ; H = 3.57 %.

Decarboxylation :

The above hydroxy acid ( 0.5 g. ) was refluxed in quinoline ( 15 ml. ) solution in presence of a pinch of copper powder for 20 minutes. The product obtained on pouring the reaction mixture in dilute hydrochloric acid crystallised in long colourless needles, M.P. and mixed m.p. with 7-hydroxyflavone was 240°.

Alkaline hydrolysis of 7-methoxy-6-cyano-3-benzoylflavone : 2-Hydroxy-4-methoxy-5-cyano-benzoic acid and 2-hydroxy-4-methoxy-5-cyano-dibenzoylmethane

7-Methoxy-6-cyano-3-benzoylflavone ( 1 g. ) was refluxed on a steam bath with alcoholic potassium hydroxide solution for 2 hours. The product obtained on acidification was extracted with sodium hydrogen carbonate solution. On acidification it yielded 2-hydroxy-4-methoxy-5-cyanobenzoic acid described earlier.

The residue from above crystallised from alcohol in yellow needles, m.p. 204°. It gave a red colouration with alcoholic ferric chloride. It was identical with 2-hydroxy-4-methoxy-5-cyano-dibenzoylmethane synthesised by the Baker-Venkataraman transormation of 2-benzoyloxy-4-methoxy-5-cyano-acetophenone as described below.

### 2-Benzoyloxy-4-methoxy-5-cyano-acetophenone

2-Hydroxy-4-methoxy-5-cyano-acetophenone ( 1 g. ) was mixed with benzoyl chloride ( 1 ml. ) and pyridine ( 0.1 ml. ) and heated on a steam bath for 4 hours. The product obtained on pouring the reaction mixture in dilute hydrochloric acid was washed with aqueous sodium hydrogen carbonate solution. It crystallised from ethyl alcohol in yellowish needles, m.p. 195-196°.

Analysis :

9.24 mg. of the substance gave 23.54 mg. of carbon dioxide and 3.62 mg. of water.

7.07 mg. of the same substance gave 0.327 ml. of nitrogen at 32° and 756 mm.

Found : C = 69.52 % ; H = 4.38 % ; N = 5.15 %.

$C_{17}H_{13}O_4N$ requires : C = 69.15 % ; H = 4.40 % ; N = 4.75 %.

### 2-Hydroxy-4-methoxy-5-cyano-dibenzoylmethane

2-Benzoyloxy-4-methoxy-5-cyano-acetophenone ( 1 g. ) was added to pulverised sodium metal ( 0.2 g. ) in toluene ( 30 ml. ) and refluxed for 4 hours. The separated sodium salt was collected and acidified with cold dilute acetic acid. The product obtained crystallised in yellow needles, m.p. 204°.

Analysis :

9.280 mg. of the substance gave 23.48 mg. of carbon dioxide and 3.72 mg. of water.

6.712 mg. of the same substance gave 0.258 ml. of nitrogen at 32° and 755 mm.

Found : C = 69.06 % ; H = 4.48 % ; N = 4.27 %.

$C_{17}H_{13}O_4N$ requires : C = 69.15 % ; H = 4.40 % ; N = 4.74 %.

### 7-Methoxy-6-cyano-flavone

The above β-diketone ( 0.5 g. ) was dissolved in concentrated sulphuric acid ( 10 ml. ) and kept at room temperature for 4 hours. The product obtained on pouring the reaction mixture over crushed ice was washed with dilute sodium hydroxide solution and the residue crystallised from ethyl alcohol in colourless needles, m.p. 226-227°.

Analysis :

9.48 mg. of the substance gave 25.40 mg. of carbon dioxide and 3.68 mg. of water.

6.26 mg. of the same substance gave 0.288 ml. of nitrogen at 33° and 756 mm.

Found : C = 73.12 % ; H = 4.34 % ; N = 5.11 %.

$C_{17}H_{11}O_3N$ requires : C = 73.64 % ; H = 4.19 % ; N = 5.05 %.

### Hydrolysis of 7-methoxy-6-cyanoflavone with sulphuric acid : 7-Hydroxyflavone-6-carboxylic acid

7-Methoxy-6-cyanoflavone ( 0.5 g. ) was dissolved in sulphuric acid ( 70 % ; 10 ml. ) and heated under gentle reflux for 3 hours. The product obtained after dilution with water was purified through dilute sodium hydrogen carbonate solution. It crystallised in colourless needles from ethyl alcohol. M.P. and mixed m.p. with 7-hydroxyflavone-6-carboxylic acid described earlier was 311° ( decomp. ).