Part II

Section (i)

THEORETICAL

Rosenmund-von Braun reaction on some iodo-chromones and flavones : Synthesis of some cyano-chromones and flavones

Aryl nitriles can be prepared by many methods. A survey of all the methods has been made by Mowry (Chem. Revs., 1948, 42, 189) .

Merz (Z. Chem., 1868, 4, 33, 396) discovered the classical synthesis of benzonitrile by fusion of the alkali metal salts of benzene sulphonic acid with potassium cyanide. Further study of this reaction revealed that a good yield of β-naphthonitrile was obtained from sodium β-naphthalene sulphonate by treatment with excess of sodium cyanide. Witt (Ber., 1873, 6, 448) showed that the less toxic potassium ferrocyanide gave somewhat better results.

Generally, yields of purified aromatic nitriles vary from traces to 60-80 % depending upon the structure of the reacting compound. Dry reagents, intimate mixing and uniform heating of reaction mass to high temperatures appear desirable. The use of sand in the reaction mixture is recommended to increase the yield of the nitrile by moderating the exothermic reaction. The introduction of a small quantity of iron filings to aid distribution of heat also gives improved yields (Wahl et al. Bull. Soc. Chim., 1939, 5, 6, 533). Smooth reaction and increased yields are also obtained by heating the reagents in an inert diluent such as mineral oil.

A number of dicyano derivatives of benzene, biphenyl, naphthalene and higher condensed ring systems have been prepared from the corresponding disulphonates. Yields are usually low

(less than 20 %) and the dinitrile is contaminated with the mononitrile.

Merz and Weith (Ber., 1877, 10,746) obtained α-naphthonitrile from α-bromonaphthalene by heating with potassium ferrocyanide. They also synthesised benzonitrile from iodobenzene and silver cyanide, but the method has little preparative value.

Rosenmund et al. (Ber., 1919, 52, 1749)found that the replacement of aryl halogen atom by the cyano group can also be accomplished by the action of anhydrous cuprous cyanide. The use of cuprous cyanide dissolved in cyclic aromatic amines was introduced in the German Patent Literature in 1913 (No., 12390).

Later, Diesbach et al. (Helv. Chim. Acta.,1923, 6, 548) extended the cuprous cyanide reaction, and reported the conversion of a mixture of dibromoxylenes to the dinitriles. The technique generally used by many workers consists in taking the arylbromide and a slight excess of dry cuprous cyanide in sufficiently dry quinoline or pyridine to form homogeneous complex at reaction temperatures of 150-250°. Thus Newman (J. Amer. Chem. Soc., 1937, 59, 2473) converted α-bromonaphthalene with cuprous cyanide in pyridine solution to α-naphthonitrile in 93 % yield.

It was observed by von Braun (Ann., 1931, 488, 111) that bromo derivatives of high boiling aromatic hydrocarbons are smoothly converted into nitriles in a very high yield by treatment with a slight excess of cuprous cyanide at 260° without using any solvent or promoter. This method, now called the Rosenmund-von Braun synthesis has been studied in detail by Koelsch ~~and Whitney~~ (J. Amer. Chem. Soc., 1936, 58, 1328) who found that the reaction is autocatalytic and the addition of a small amount of nitrile from a previous run shortens the reaction time. Copper sulphate in small amounts has a marked catalytic effect whereas hydroquinone retards the reaction. They recommended the addition of 0.01 mole of copper sulphate per 0.1 mole of the iodo derivative and gradual addition of the halide to the mixture of cuprous cyanide and catalysts. This observation led to the hypothesis that only the divalent copper ion can react with aryl halide to form a stable complex. The following mechanism has been suggested by Koelsch and Whitney (J. Org. Chem., 1941, 6, 795).

$$\mathrm{Ar{-}X} + \mathrm{Cu}^{++} \rightleftharpoons \left[\mathrm{Ar}' - \mathrm{X} \longrightarrow \mathrm{Cu}\right]^{++} \xrightarrow{\mathrm{Cu}^{+}}$$

$$\mathrm{Cu}^{++} + \left[\mathrm{Ar} - \mathrm{X} \rightarrow \mathrm{Cu}\right]^{+}$$

$$\left[\mathrm{Ar} - \mathrm{X} \rightarrow \mathrm{Cu}\right]^{+} \longrightarrow \mathrm{CuX} + \mathrm{Ar}^{+}$$

$$\mathrm{Ar}^{+} + \mathrm{CN}^{-} \longrightarrow \mathrm{ArCN}$$

The gradual addition of the halide to the mixture of cuprous cyanide and catalysts promotes rapid conversion.

The above two techniques of aryl halide- copper cyanide reactions with or without a basic solvent have been discussed by Braun (German patent, 1942, 728943 and U.S. patent, 1940, 2195076). For large scale runs as in commercial practice, the use of a solvent or an inert diluent is desirable to assist the dissipation of heat of reaction. This may be either a solvent for the cuprous cyanide (pyridine, quinoline or phenyl acetonitrile) or a diluent such as nitrobenzene,dichlorobenzene or naphthalene. In general the use of solvents enable the reaction to be effected at low temperatures.

Though various halogenated chromones and flavones are known they have not been subjected to this reaction. A few cyano chromones and flavones have been synthesised by other methods. Schmutz et al. (Helv. Chim. Acta., 1952, 35, 1168 ; C.A., 1953, 47, 4879) obtained 2-cyanochromone from the oxime of chromone-2-aldehyde by heating with acetic anhydride. Da Re et al. (Farmaco, Pavia, Ed. Sci., 1956, 11, 678 ; Ann. Chim., 1958, 48, 762) synthesised 6- and 8-cyano-2,3-dimethylchromone from the corresponding nitro compounds by reduction,diazotisation and treatment with potassium cyanide. They also prepared 4'-cyanoflavone by cyclisation of 2'-hydroxy-4'-cyanodibenzoylmethane. 8-Cyano-3-methylflavone was prepared from 2-hydroxy-3-cyanopropiophenone by treatment with sodium benzoate and benzoylchloride. (Da Re et al., J. Med. Pharm. Chem., 1960, 2, 263)

No other work on the synthesis of cyanochromones and flavones appears to have been reported. Cyano chromones and flavones have now been obtained by the Rosenmund-von Braun reaction on some iodo chromones and flavones described in Part I.

Addition of copper sulphate or a little of cyano derivative from ~~the~~ a previous run as a catalyst,improved the yield (cf. Koelsch and Whitney,loc. cit.). If cuprous cyanide which was not very fresh was used then no catalyst was required.

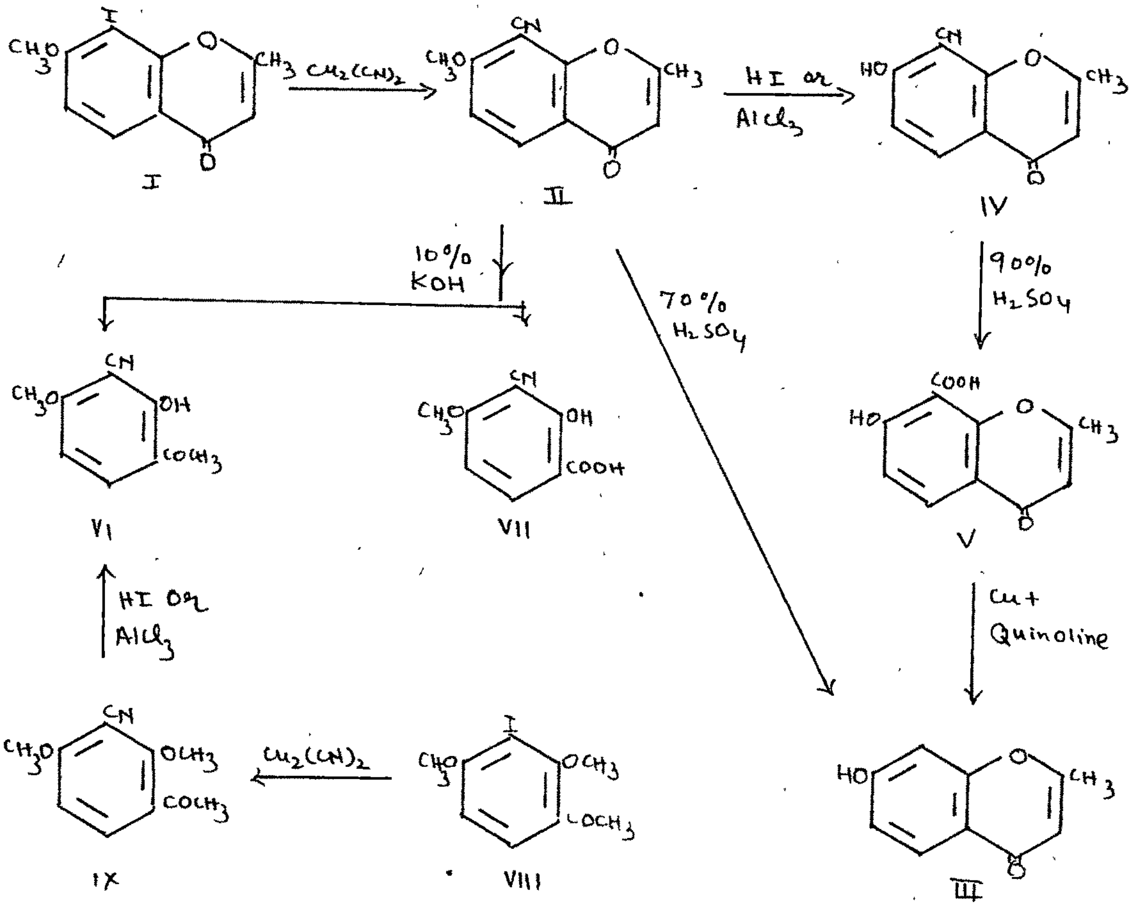
<u>Rosenmund-von Braun reaction on 7-methoxy-8-iodo-2-methylchromone</u>

7-Methoxy-8-iodo-2-methylchromone (I) on fusion with cuprous cyanide gave the corresponding 8-cyano derivative (II). With sulphuric acid of 70 % or higher strength this cyanochromone gave 7-hydroxy-2-methylchromone (III) the cyano group being eliminated probably through hydrolysis and decarboxylation. With 50 % sulphuric acid neither hydrolysis nor demethylation occurred. 7-Methoxy-8-cyano-2-methylchromone on demethylation either with aluminium chloride or with hydriodic acid gave 7-hydroxy-8-cyano-2-methylchromone (IV). This however on hydrolysis with 90 % sulphuric acid by volume gave a product which dissolved with effervescence in sodium hydrogen carbonate solution and gave a red colouration with alcoholic ferric chloride and so was assigned 7-hydroxy-2-methylchromone-8-carboxylic acid (V) structure. On decarboxylation with quinoline and copper powder it gave 7-hydroxy-2-methylchromone (III). 7-Methoxy-8-cyano-2-methylchromone (II) on alkaline hydrolysis gave a cyano ketone, identical with 2-hydroxy-3-cyano-4-methoxyacetophenone (VI) described below, and 2-hydroxy-3-cyano-4-methoxybenzoic acid (VII). Both the ketone and the acid gave red colouration with alcoholic ferric chloride. No chromone carboxylic acid was obtained.

2,4-Dimethoxy-3-iodo-acetophenone (VIII) on Rosenmund-von Braun reaction gave the corresponding 3-cyano derivative (IX). On demethylation with aluminium chloride in nitrobenzene or less well with hydriodic acid it gave a partially demethylated product which was soluble in aqueous sodium hydroxide solution and which gave a red colouration with alcoholic ferric chloride. It agreed with 2-hydroxy-3-cyano-4-methoxyacetophenone (VI) described above. Attempts to completely demethylate this compound (VI) did not succeed.

Attempts to hydrolyse 7-methoxy-8-cyano-2-methylchromone in absolute methanol with dry ~~hydrochloric acid gas~~ hydrogen chloride did not succeed. Only the cyano chromone was recovered unchanged.

Attempts to reduce 7-methoxy-8-cyano-2-methylchromone with sodium and alcohol or lithium aluminium hydride did not succeed. The cyanochromone remained unchanged.



Stephen reaction on 7-methoxy-8-cyano-2-methylchromone with anhydrous stannous chloride and hydrogen chloride using dry ether as solvent also failed. The original cyanochromone was recovered.

Rosenmund-von Braun reaction on 7-methoxy-6-iodo-2-methylchromone

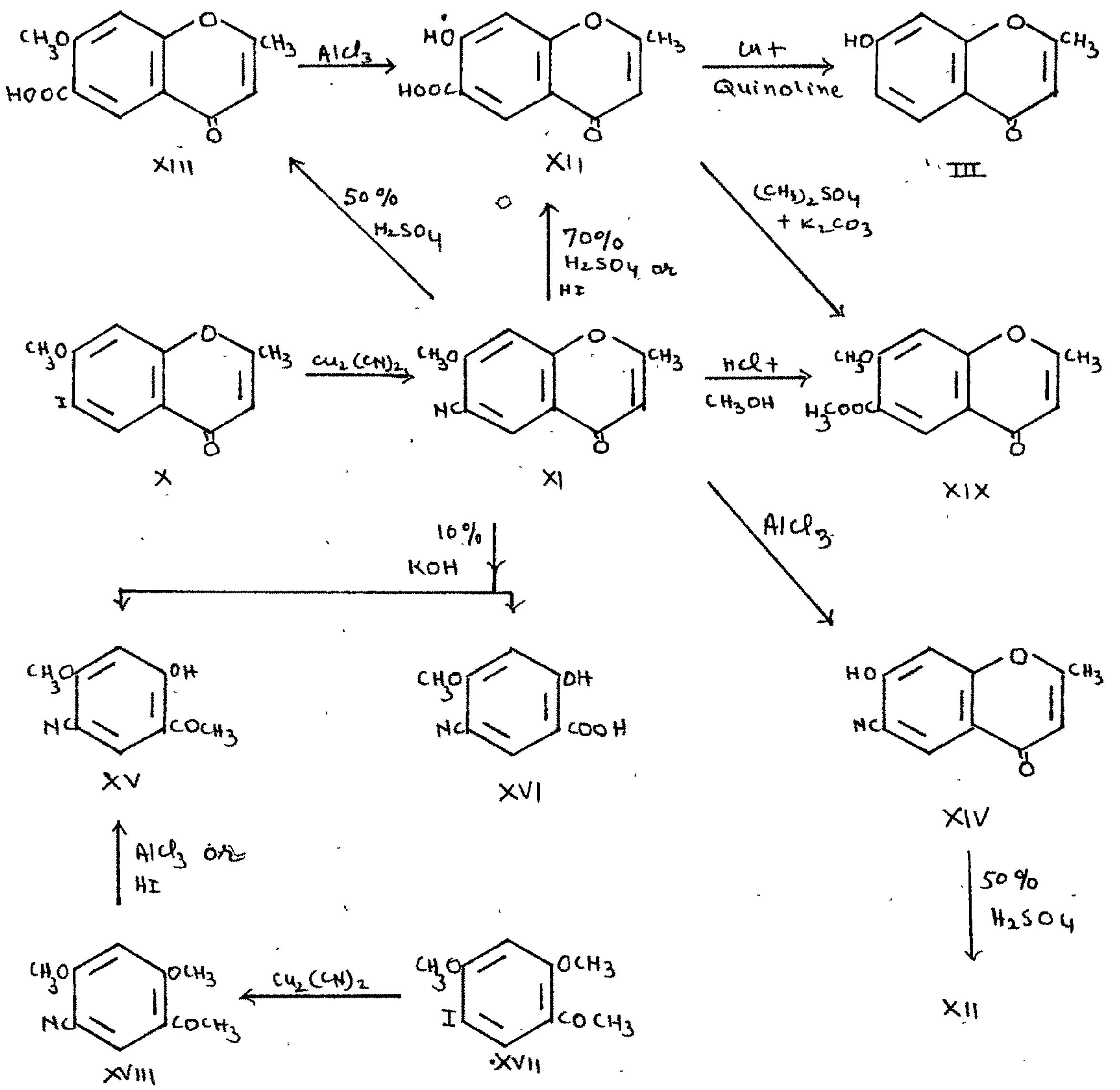
7-Methoxy-6-iodo-2-methylchromone (X) on Rosenmund-von Braun reaction gave the corresponding 6-cyano derivative (XI) which on hydrolysis with 70 % sulphuric acid gave a nitrogen free product. It gave a red colouration with alcoholic ferric chloride and formed a salt with sodium hydrogen carbonate solution. Therefore the hydrolysis product has been assigned 7-hydroxy-2-methylchromone-6-carboxylic acid (XII) structure. On decarboxylation, in quinoline solution in the presence of copper powder, the acid gave 7-hydroxy-2-methylchromone (III). As demethylation occurred with 70 % sulphuric acid hydrolysis with dilute sulphuric acid was also studied. 7-Methoxy-6-cyano-2-methylchromone (XI) on hydrolysis with 50 % sulphuric acid gave a nitrogen free product which was soluble in sodium hydrogen carbonate solution with effervescence but it did not give any coluration with ferric chloride. It was therefore assigned 7-methoxy-2-methylchromone-6-carboxylic acid (XIII) structure. On demethylation with aluminium chloride it gave 7-hydroxy-2-methylchromone-6-carboxylic acid (XII). 7-Methoxy-6-cyanochromone (XI) on heating with hydriodic acid gave 7-hydroxy-2-methylchromone-6-carboxylic acid (XII).

However, demethylation with aluminium chloride in a dry state gave the demethylated cyano derivative; 7-hydroxy-6-cyano-2-methylchromone (XIV) which ~~was~~ hydrolysed with sulphuric acid to the chromone carboxylic acid (XII) described above. Hydrolysis of the cyano compound (XI) with alkali gave a mixture of 2-hydroxy-4-methoxy-5-cyano-acetophenone (XV) identical with the product described below and 2-hydroxy-4-methoxy-5-cyanobenzoic acid (XVI). Both the ketone and the acid showed red colouration with alcoholic ferric chloride.

2,4-Dimethoxy-5-iodo-acetophenone (XVII) on Rosenmund-von Braun reaction gave the corresponding 5-cyano derivative (XVIII). On demethylation with aluminium chloride in nitrobenzene or less well with hydriodic acid it gave a partially demethylated product which was soluble in aqueous alkali and gave a red colouration with alcoholic ferric chloride. It was identical with 2-hydroxy-4-methoxy-5-cyano-acetophenone (XV) described before. Attempts to demethylate this compound (XV) completely did not succeed.

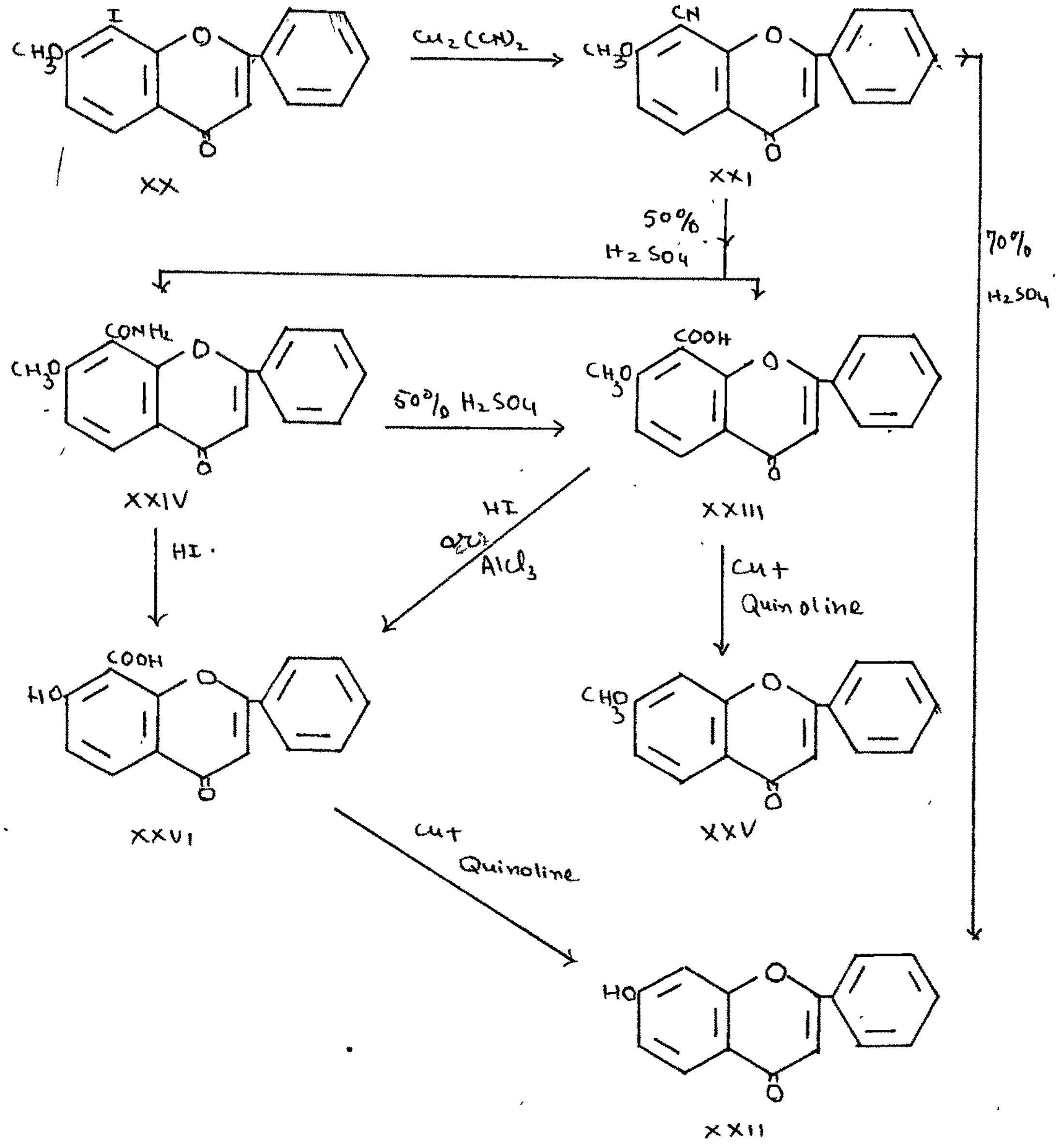
When 7-methoxy-6-cyano-2-methylchromone (XI) was dissolved in methanol and the solution saturated with dry hydrochloric acid gas, it gave methyl 7-methoxy-2-methylchromone-6-carboxylate (XIX) identical with the methyl ether of the methyl ester of 7-hydroxy-2-methylchromone-6-carboxylic acid described before.

Attempts to reduce 7-methoxy-6-cyano-2-methylchromone (XI) with sodium and alcohol or lithium aluminium hydride or stannous chloride in ether did not succeed. Only the original cyanochromone was recovered.



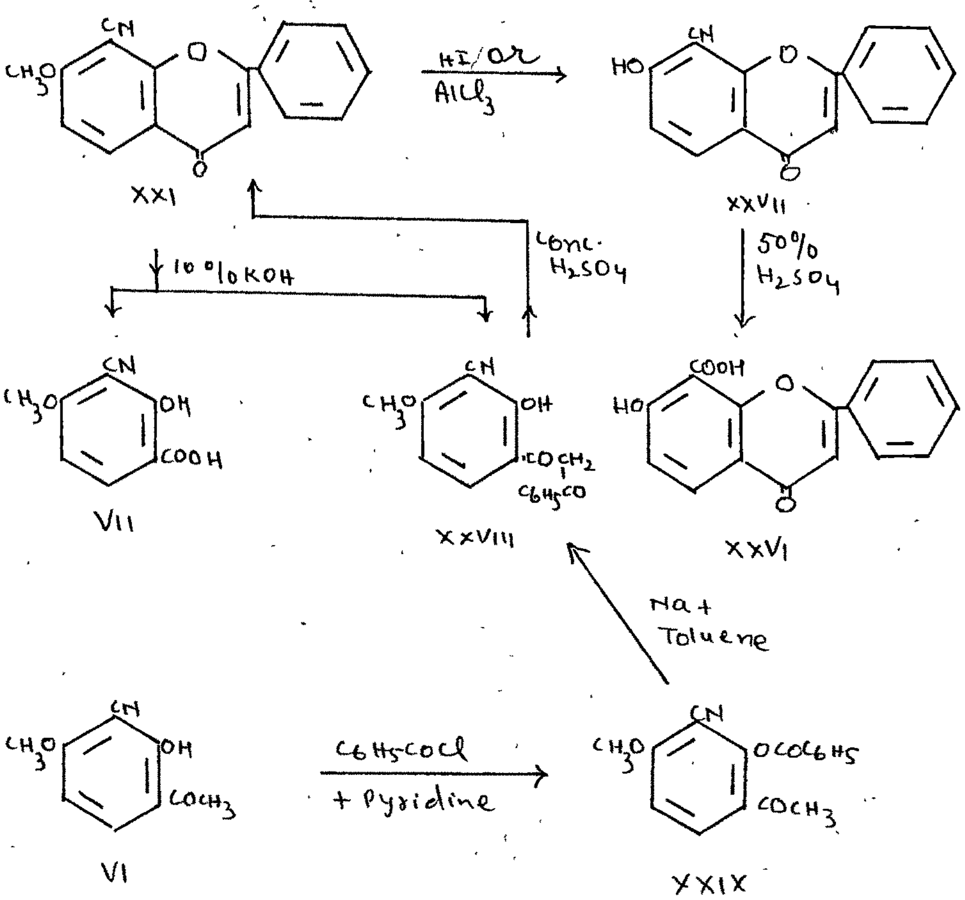
Rosenmund-von Braun reaction on 7-methoxy-8-iodoflavone

7-Methoxy-8-iodoflavone (XX) on fusion with cuprous cyanide gave the corresponding cyanoflavone (XXI). This on hydrolysis with 70 % sulphuric acid gave the known 7-hydroxyflavone (XXII). 7-Methoxy-8-cyanoflavone (XXI) on hydrolysis with 50 % sulphuric acid however gave a mixture of an acid and a carbamoylflavone which were separated by treatment with sodium hydrogen carbonate solution. The carbamoylflavone on further hydrolysis with 50 % sulphuric acid gave the same acid. The acid did not give any colouration with alcoholic ferric chloride, indicating that no demethylation had occurred and so was assigned 7-methoxyflavone-8-carboxylic acid (XXIII) structure and the carbamoylflavone was 7-methoxy-8-carbamoylflavone (XXIV). On decarboxylation the acid gave 7-methoxyflavone (XXV). The methoxy acid could be demethylated with aluminium chloride or with hydriodic acid to 7-hydroxyflavone-8-carboxylic acid (XXVI). On decarboxylation with quinoline



and copper powder it gave the known 7-hydroxyflavone (XXII). Attempts to reduce 7-methoxy-8-cyanoflavone with lithium aluminium hydride or sodium and alcohol or stannous chloride did not succeed. Only the original cyanoflavone was recovered unchanged.

7-Methoxy-8-cyanoflavone (XXI) on demethylation with either aluminium chloride or hydriodic acid gave 7-hydroxy-8-cyanoflavone (XXVII) which on hydrolysis with 50 % sulphuric acid gave 7-hydroxyflavone-8-carboxylic acid (XXVI) in good yield. Alkaline hydrolysis of 7-methoxy-8-cyanoflavone (XXI) gave a cyanobenzoic acid identical with 2-hydroxy-3-cyano-4-methoxybenzoic acid (VII) described

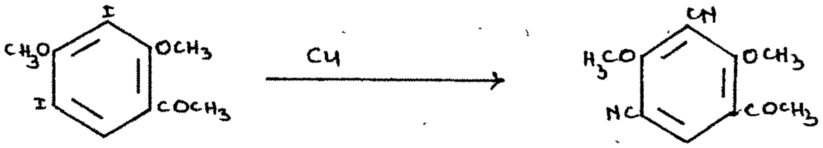


before and another product containing nitrogen which gave a red colouration with alcoholic ferric chloride and was soluble in sodium hydroxide solution indicating that it might be a β-diketone. This was found to be 2-hydroxy-3-cyano-4-methoxy-dibenzoylmethane (XXVIII) by comparison with an authentic specimen synthesised as follows :

2-Hydroxy-3-cyano-4-methoxyacetophenone (VI) on treatment with benzoylchloride and pyridine gave 2-benzoyloxy-3-cyano-4-methoxyacetophenone (XXIX) which on Baker-Venkataraman transformation with sodium gave 2-hydroxy-3-cyano-4-methoxy-dibenzoyl methane (XXVIII) identical with theproduct described above. It cyclised with concentrated sulphuric acid to give 7-methoxy-8-cyanoflavone (XXI).

Rosenmund-von Braun reaction on 2,4-dimethoxy-3,5-di-iodo-acetophenone

2,4-Dimethoxy-3,5-di-iodo-acetophenone (XXX) on heating with cuprous cyanide with or without copper sulphate did not give any pure product. When the reaction was repeated by using nitrobenzene as a solvent it gave the dicyano derivative (XXXI) in very poor yield. Attempts to improve the yield by using pyridine gave a polymeric product~~s~~ m.p. 232° which

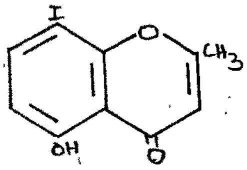


XXX XXXI

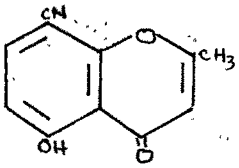
has not been investigated.

Rosenmund-von Braun reaction on 5-hydroxy-8-iodo-2-methylchromone

5-Methoxy-8-iodo-2-methylchromone on heating with cuprous cyanide did not give any cyano derivative, only the the original iodochromone was recovered. When 5-hydroxy-8-iodo-2-methylchromone (XXXII) was heated with cuprous cyanide and traces of copper sulphate the cyano derivative (XXXIII) was obtained but in a very poor yield (XXXIII).



XXXII



XXXIII

EXPERIMENTAL

Rosenmund-von Braun reaction on 7-methoxy-8-iodo-2-methylchromone : 7-Methoxy-8-cyano-2-methylchromone

7-Methoxy-8-iodo-2-methylchromone (3.16 g. ; 0.01 mole)was thoroughly mixed with anhydrous cuprous cyanide (1.78 g. ; 0.02 mole) and a trace of copper sulphate as a catalyst. Sand was also added(as a diluent) to the reaction mixture. It was then heated in an oil bath at 235-240° in a fume chamber. The reaction mixture melted . It was stirred with a glass rod to make it homogeneous. The reaction commenced in about five minutes and the pungent vapours started issuing out. The reaction mixture soon solidified. The sublimed product settled in the form of shining needles on the cooler sides of the tube and heating was continued for further five minutes. After cooling the reaction mixture was powdered and extracted repeatedly with ethyl alcohol, by refluxing on a wire gauze. The alcoholic filtrate after concentration and cooling gave yellow shining product which crystallised from acetic acid (charcoal) in yellowish plates, m.p. 262°. Yield 1.36 g.

Analysis :

9.80 mg. of the substance gave 24.06 mg. of carbon dioxide and 3.74 mg. of water.

10.62 mg. of the same substance gave 0.644 ml. of nitrogen at 29° and 757 mm.

Found : C = 67.00 % ; H = 4.27 % ; N = 6.83 %.

$C_{12}H_9O_3N$ requires : C = 66.99 % ; H = 4.19 % ; N = 6.51 %.

When cuprous cyanide of some standing was used in the above reaction no catalyst was necessary. Fresh cuprous cyanide gave poor yields.

Hydrolysis of 7-methoxy-8-cyano-2-methylchromone

(i) With 70 % sulphuric acid

7-Methoxy-8-cyano-2-methylchromone (0.5 g.) was heated with sulphuric acid (70 % ; 15 ml.) under gentle reflux for 3 hours with occasional stirring. The deep red coloured reaction mixture, after cooling, was added to crushed ice and the brown turbid solution was filtered. The filtrate on keeping over-night in the refrigerator gave needles which crystallised from dilute alcohol in thick white plates, m.p. and mixed m.p. with 7-hydroxy-2-methylchromone was 249°. The cyano group must have been hydrolysed and the acid formed must have got decarboxylated. Demethylation also took place.

70 % sulphuric acid was prepared by mixing sulphuric acid (39 ml.) in acetic acid (20 ml.) and water (10 ml.).

(ii) With 50 % sulphuric acid

When the hydrolysis was repeated with sulphuric acid (50 % ; 20 ml.) unchanged 7-methoxy-8-cyano-2-methylchromone was recovered. No other product was obtained.

50 % sulphuric acid was prepared by mixing concentrated sulphuric acid (28 ml.) in acetic acid (20 ml.) and water (30 ml.).

Attempts to hydrolyse the cyano compound by refluxing its methyl alcoholic solution after saturation with hydrogen chloride for 3 hours also did not succeed. The original chromone was recovered unchanged.

Demethylation : 7-Hydroxy-8-cyano-2-methylchromone

(i) With hydriodic acid

7-Methoxy-8-cyano-2-methylchromone (0.6 g.) dissolved in acetic anhydride (15 ml.) was heated with hydriodic acid (5 ml.) in an oil bath at 125-130° for 3 hours and then added to sodium hydrogen sulphite solution. The product obtained was purified through sodium hydroxide solution. It crystallised from acetic acid in yellow shining cubes, m.p. 368° (decomp.). It was sparingly soluble in ethyl alcohol. Higher reaction temperatures during demethylation gave deeply coloured unworkable product. Its alcoholic solution did not give any colouration with alcoholic ferric chloride. It dissolved in sodium hydrogen carbonate solution with effervescence.

(ii) With aluminium chloride

7-Methoxy-8-cyano-2-methylchromone (0.5 g.) was dissolved in nitrobenzene (10 ml.) and heated with aluminium chloride (0.8 g.) at 125-130° for 3 hours. The product obtained on removal of nitrobenzene was 7-hydroxy-8-cyano-2-methylchromone in good yield.

Analysis :

9.08 mg. of the substance gave 21.70 mg. of carbon dioxide and 2.82 mg. of water.

9.78 mg. of the same substance gave 0.634 ml. of nitrogen at 31° and 757 mm.

Found : C = 65.22 % ; H = 3.47 % ; N = 7.25 %.

$C_{11}H_7O_3N$ requires : C = 65.67 % ; H = 3.51 % ; N = 6.96 %.

Hydrolysis of 7-hydroxy-8-cyano-2-methylchromone with sulphuric acid : 7-Hydroxy-2-methylchromone-8-carboxylic acid

7-Hydroxy-8-cyano-2-methylchromone (1 g.) was dissolved in sulphuric acid (90 % by volume ; 20 ml.) and heated on a steam bath for 3 hours. The red coloured reaction mixture was poured over crushed ice. Thick yellow needles separated on keeping it over-night in a refrigerator. Recrystallised from dilute alcohol (charcoal) in thick yellowish needles, m.p. 259° (efferv.). Yield 0.36 g. Its alcoholic solution gave a deep red colouration with alcoholic ferric chloride.

Analysis :

10.62 mg. of the substance gave 23.26 mg. of carbon dioxide and 3.82 mg. of water.

Found : C = 59.77 % ; H = 4.02 %.

$C_{11}H_8O_5$ requires : C = 60.00 % ; H = 3.66 %.

Decarboxylation The above acid (0.5 g.) was powdered and heated in an oil bath at 260° till the effervescence ceased. The reaction mixture was treated with sodium hydrogen carbonate solution and the residue after purification through sodium hydroxide solution crystallised from dilute ethyl alcohol in colourless thick plates. M.P.

and mixed m.p. with 7-hydroxy-2-methylchromone was 249°.

Alkaline hydrolysis of 7-methoxy-8-cyano-2-methylchromone : 2-Hydroxy-3-cyano-4-methoxyacetophenone and 2-hydroxy-3-cyano-4-methoxybenzoic acid

7-Methoxy-8-cyano-2-methylchromone (1 g.) was heated with alcoholic potassium hydroxide solution (10 % ; 20 ml.) on a steam bath for 3 hours. The product obtained on acidification was first extracted with sodium hydrogen carbonate solution and then with sodium hydroxide solution The sodium hydrogen carbonate extract on acidification gave 2-hydroxy-3-cyano-4-methoxybenzoic acid. It crystallised in yellowish needles, m.p. 234-235° (efferv.). Its alcoholic solution gave a deep red colouration with alcoholic ferric chloride.

Analysis :

9.82 mg. of the substance gave 20.12 mg. of carbon dioxide and 3.00 mg. of water.

10.62 mg. of the same substance gave 0.743 ml. of nitrogen at 32° and 759 mm.

Found : C = 55.91 % ; H = 3.42 % ; N = 7.82 %.
$C_9H_7O_4N$ requires : C = 55.95 % ; H = 3.63 % ; N = 7.25 %.

The sodium hydroxide extract on acidification gave a ketone which crystallised in yellowish needles from dilute alcohol. M.P. and mixed m.p. with 2-hydroxy-3-cyano-4-methoxyacetophenone prepared as described below was 169°.

Rosenmund-von Braun reaction on 2,4-dimethoxy-3-iodo-acetophenone : 2,4-Dimethoxy-3-cyano-acetophenone

2,4-Dimethoxy-3-iodo-acetophenone (9.2 g. ; 0.03 mole) (prepared as in part I) and cuprous cyanide (5.34 g. ; 0.06 mole) were intimately mixed with sand (a diluent) and heated at 165-170° for 10 minutes. The powdered material was then repeatedly extracted with acetone. The product obtained on removal of acetone crystallised in colourless needles from dilute alcohol, m.p. 131°. Yield 3.54 g.

Analysis :

10.44 mg. of the substance gave 24.86 mg. of carbon dioxide and 4.88 mg. of water.

8.94 mg. of the same substance gave 0.534 ml. of nitrogen at 33° and 756 mm.

Found : C = 65.00 % ; H = 5.23 % ; N = 6.62 %.
$C_{11}H_{11}O_3N$ requires : C = 64.39 % ; H = 5.36 % ; N = 6.83 %.

Demethylation : 2-Hydroxy-3-cyano-4-methoxy-acetophenone

(i) With hydriodic acid: 2,4-Dimethoxy-3-cyanoacetophenone (2 g.) in acetic anhydride (20 ml.) was heated with hydriodic acid (10 ml.) at 125-130° for 3 hours in an oil bath. The product obtained on working up the reaction mixture as usual crystallised from ethyl alcohol in yellowish needles, m.p. 169°. Yield 0.9 g. It gave a deep red colouration with alcoholic ferric chloride.

Analysis :

9.84 mg. of the substance gave 22.72 mg. of carbon dioxide and 4.50 mg. of water.

9.12 mg. of the same substance gave 0.594 ml. of nitrogen at 33° and 757 mm.

Found : C = 63.01 % ; H = 5.12 % ; N = 7.24 %.

$C_{10}H_9O_3N$ requires : C = 62.82 % ; H = 4.71 % ; N = 7.33 %.

(ii) With aluminium chloride : Demethylation of the dimethoxy ketone (2 g.) with anhydrous aluminium chloride (3 g.) with or without nitrobenzene as solvent by heating on a steam bath for 3 hours gave only 2-hydroxy-3-cyano-4-methoxyacetophenone. Yield 1.25 g.

Further demethylation of 2-hydroxy-3-cyano-4-methoxyacetophenone did not succeed.

Attempted reduction of the cyano group in 7-methoxy-8-cyano-2-methylchromone

(i) With sodium metal and alcohol : 7-Methoxy-8-cyano-2-methylchromone (0.5 g.) was dissolved in absolute ethyl alcohol (80 ml.) and sodium metal (0.2 g.) added slowly. The reaction mixture was then heated on a steam bath for 15 minutes when it became red in colour. It was concentrated and acidified after dilution with water when the original cyanochromone was obtained.

(ii) With lithium aluminium hydride : The cyano chromone (0.2 g.) was suspended in dry ether (150 ml.) and lithium aluminium hydride (0.01 g.) in ether was added slowly with stirring to the reaction mixture. After 2 hours it was decomposed by adding a little water. The original chromone was obtained back.

Reduction was also tried by taking the substance in the thimble of a soxhlet and lithium aluminium hydride and dry isopropyl ether in the flask and heating the flask on a steam bath, but it did not succeed.

Attempted Stephen's reduction

Dry hydrogen chloride was passed through a suspension of anhydrous stannous chloride (0.9 g.) in anhydrous ether (100 ml.) kept below 5° for about 4 hours. To this 7-methoxy-8-cyano-2-methylchromone (0.3 g.) was added and hydrogen chloride passed for further 5 hours maintaining the temperature below 5°. The reaction mixture was then left over-night. Next day after removal of ether the residue was heated with water on a steam bath for 2 hours. The product obtained was found to be the unchanged cyanochromone.

Anhydrous stannous chloride was prepared according to Stephen (J. Chem. Soc., 1930, 2786) by gradually adding with agitation stannous chloride dihydrate (2.3 g.) to acetic anhydride (2.3 ml.). Dehydration was instantaneous.

Rosenmund-von Braun reaction on 7-methoxy-6-iodo-2-methylchromone : 7-Methoxy-6-cyano-2-methylchromone

7-Methoxy-6-iodo-2-methylchromone (3.16 g. ; 0.01 mole) was mixed with cuprous cyanide (1.78 g. ; 0.02 mole) and a trace of copper sulphate (or the cyano derivative from the previous run in subsequent preparations) was added. The reaction mixture was heated in an oil bath at 245-250° for 10 minutes. The powdered reaction mixture was then extracted with hot acetone repeatedly. The product obtained on removal of acetone crystallised from ethyl alcohol in yellow needles, m.p. 249° (decomp.). Yield 1.26 g.

Analysis :

10.32 mg. of the substance gave 25.52 mg. of carbon dioxide and 3.78 mg. of water.

8.64 mg. of the same substance gave 0.495 ml. of nitrogen at 34° and 754 mm.

Found : C = 67.46 % ; H = 4.10 % ; N = 6.32 %.

$C_{12}H_9O_3N$ requires : C = 66.99 % ; H = 4.19 % ; N = 6.51 %.

Hydrolysis of 7-methoxy-6-cyano-2-methylchromone

(i) With 70 % sulphuric acid : 7-Hydroxy-2-methylchromone-6-carboxylic acid

The above cyanochromone (0.5 g.) was heated with sulphuric acid (70 % ; 30 ml.) under gentle reflux for 3 hours. The reaction mixture was then added to crushed ice and the separated product was purified through dilute sodium hydrogen carbonate solution. It crystallised from acetic acid in colourless needles, m.p. 302° (decomp.). Yield 0.23 g. Its alcoholic solution gave a red colouration with alcoholic ferric chloride, indicating that demethylation had also occured during the hydrolysis of the cyano group.

Analysis :

10.68 mg. of the substance gave 23.70 mg. of carbon dioxide and 3.86 mg. of water.

Found : $C = 60.52$ % ; $H = 4.04$ %.

$C_{11}H_8O_5$ requires : $C = 60.00$ % ; $H = 3.66$ %.

Methyl 7-methoxy-2-methylchromone-6-carboxylate

The above chromone carboxylic acid (0.5 g.) was simultaneously methylated and esterified by refluxing its acetone solution with dimethyl sulphate (1 ml.) in presence of anhydrous ptassium carbonate (2 g.) on a steam bath for 4 hours. The product obtained crystallised in colourless needles from hot water, m.p. 165-166°.

Analysis :

10.32 mg. of the substance gave 23.90 mg. of carbon dioxide and 4.50 mg. of water.

Found : $C = 63.20$ % ; $H = 4.88$ %.

$C_{13}H_{12}O_5$ requires : $C = 62.90$ % ; $H = 4.84$ %.

(ii) With 50 % sulphuric acid : 7-Methoxy-2-methylchromone-6-carboxylic acid

When the hydrolysis of the above cyanochromone (0.5 g.) was carried out with dilute sulphuric acid (50 % ; 20 ml.) under the same conditions as above a different product was obtained which crystallised from dilute alcohol in colourless needles, m.p. 245°. Yield 0.25 g. It did not give any colouration with alcoholic ferric chloride, indicating that the demethylation had not taken place.

Analysis :

10.76 mg. of the substance gave 24.18 mg. of carbon dioxide and 4.26 mg. of water.

Found : C = 61.31 % ; H = 4.43 %.

$C_{12}H_{10}O_5$ requires : C = 61.54 % ; H = 4.30 %.

(iii) With hydrochloric acid : Methyl-7-methoxy-2-methylchromone-6-carboxylate

The cyanochromone (0.5 g.) was dissolved in absolute methyl alcohol (50 ml.) and hydrogen chloride gas was passed at room temperature for about 3 hours. The reaction mixture was left over-night. Next day the excess of alcohol was removed after refluxing for 3 hours and the mixture added to cold water. The separated product crystallised from water in colourless needles, yield 0.2 g. It was identical with methyl-7-methoxy-2-methylchromone-6-carboxylate described before.

Action of hot hydriodic acid on 7-methoxy-6-cyano-2-methylchromone

7-Methoxy-6-cyano-2-methylchromone (0.5 g.) was dissolved in acetic anhydride (15 ml.) and hydriodic acid (5 ml.) was added. The reaction mixture was heated in an oil bath at 125-130° for 3 hours. The product obtained on working up the reaction mixture was purified through sodium hydroxide solution. It crystallised from acetic acid in colourless needles, yield 0.25 g. M.P. and mixed m.p. with 7-hydroxy-2-methylchromone-6-carboxylic acid described above was 302° (decomp.).

Demethylation : 7-Hydroxy-6-cyano-2-methylchromone

7-Methoxy-6-cyano-2-methylchromone (0.5 g.) was mixed with anhydrous aluminium chloride (0.8 g.) and heated in an oil bath at 120° for 3 hours. The product obtained on working up the reaction mixture as usual was purified through sodium hydroxide solution and crystallised from acetic acid in thick yellowish needles, m.p. 340° (decomp.). It dissolved in sodium hydrogen carbonate solution with effervescence. It did not give any colouration with alcoholic ferric chloride.

Analysis :

10.22 mg. of the substance gave 24.68 mg. of carbon dioxide and 3.38 mg. of water.

6.32 mg. of the same substance gave 0.407 ml. of nitrogen at 31° and 756 mm.

	Found	: C = 65.89 % ; H = 3.70 % ; N = 7.19 %.
$C_{11}H_7O_3N$	requires	: C = 65.67 % ; H = 3.51 % ; N = 6.96 %.

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

7-Methoxy-6-cyano-2-methylchromone (1 g.) was heated with alcoholic potassium hydroxide solution (10 % ; 25 ml.) on a steam bath for 3 hours. The product obtained on acidification was treated successively with sodium hydrogen carbonate and sodium hydroxide solution. The product obtained on acidification of the sodium hydrogen carbonate extract crystallised from dilute alcohol in yellowish needles, m.p. 232-233° (efferv.). Its alcoholic solution gave a red colouration with alcoholic ferric chloride.

Analysis :

10.92 mg. of the substance gave 22.40 mg. of carbon dioxide and 3.58 mg. of water.

11.64 mg. of the same substance gave 0.773 ml. of nitrogen at 30° and 760 mm.

	Found	: C = 55.98 % ; H = 3.66 % ; N = 7.48 %.
$C_9H_7O_4N$	requires	: C = 55.95 % ; H = 3.63 % ; N = 7.25 %.

The product obtained from the sodium hydroxide extract on acidification crystallised from ethyl alcohol in yellowish needles. M.P. and mixed m.p. with 2-hydroxy-4-methoxy-5-cyano-acetophenone prepared as described below was ~~[illegible]~~ 180°. Its alcoholic solution gave a red colouration with alcoholic ferric chloride.

Rosenmund-von Braun reaction on 2,4-dimethoxy-5-iodo-acetophenone : 2,4-Dimethoxy-5-cyano-acetophenone

2,4-Dimethoxy-5-iodo-acetophenone (4.6 g. ; 0.015 mole) was intimately mixed with cuprous cyanide (2.67 g.; 0.03 mole), sand (a diluent) and a little copper sulphate and heated in an oil bath at 185-190° for ten minutes. The powdered reaction mixture was extracted repeatedly with hot ethyl alcohol. The extract was then concentrated and the separated product recrystallised from ethyl alcohol in colourless needles, m.p. 192°. Yield 2.1 g.

Analysis :

10.18 mg. of the substance gave 24.08 mg. of carbon dioxide and 5.34 mg. of water.

6.12 mg. of the same substance gave 0.361 ml. of nitrogen at 29° and 761 mm.

Found : C = 64.49 % ; H = 5.86 % ; N = 6.68 %.

$C_{11}H_{11}O_3N$ requires : C = 64.39 % ; H = 5.36 % ; N = 6.83 %.

Demethylation : 2-Hydroxy-4-methoxy-5-cyano-acetophenone

2,4-Dimethoxy-5-cyano-acetophenone (2 g.) in acetic anhydride (15 ml.) was heated with hydriodic acid (8 ml.) in an oil bath at 125-130° for 3 hours. The product obtained on working up the reaction mixture as usual was purified through sodium hydroxide solution and crystallised from ethyl alcohol in yellowish needles, m.p. 180°. Its alcoholic solution gave a deep colouration with ferric chloride.

Analysis :

10.44 mg. of the substance gave 23.84 mg. of carbon dioxide and 4.44 mg. of water.

10.38 mg. of the same substance gave 0.703 ml. of nitrogen at 34° and 755 mm.

Found : C = 62.31 % ; H = 4.76 % ; N = 7.48 %.

$C_{10}H_9O_3N$ requires : C = 62.82 % ; H = 4.71 % ; N = 7.33 %.

Demethylation of the dimethoxy ketone (0.5 g.) with aluminium chloride (0.8 g.) by heating at 110-115° for 3 hours also gave only the above partially demethylated product.

Attempted reduction of 7-methoxy-6-cyano-2-methylchromone

Attempts to reduce the above cyanochromone with (i) sodium in alcohol (ii) lithium aluminium hydride and

(iii) stannous chloride (Stephen reaction) as in the case of the 8-cyano-isomer did not succeed. The original chromone was obtained back.

Rosenmund-von Braun reaction on 7-methoxy-8-iodoflavone : 7-Methoxy-8-cyanoflavone

7-Methoxy-8-iodoflavone (3.78 g. ; 0.01 mole) was intimately mixed with cuprous cyanide (1.78 g. ; 0.02 mole) and a trace of copper sulphate was added. The reaction mixture was heated at 220-225° for 10 minutes. The reaction mixture was extracted repeatedly with hot acetone. The product which separated from the acetone extract on concentration, crystallised from ethyl alcohol in needles, m.p. 235°. Yield 1.51 g.

Analysis :

10.36 mg. of the substance gave 27.92 mg. of carbon dioxide and 3.16 mg. of water.

8.84 mg. of the same substance gave 0.421 ml. of nitrogen at 33° and 750 mm.

Found : C = 73.53 % ; H = 3.41 % ; N = 5.28 %.
$C_{17}H_{11}O_3N$ requires : C = 73.64 % ; H = 4.00 % ; N = 5.05 %.

Hydrolysis of 7-methoxy-8-cyanoflavone

(i) **With 70 % sulphuric acid**

7-Methoxy-8-cyanoflavone (0.7 g.) was heated with sulphuric acid (70 % ; 20 ml.) under gentle reflux for 3 hours. The brown coloured reaction mixture was then added to crushed ice and the separated product treated successively with sodium hydrogen carbonate and sodium hydroxide solution.

No product was obtained from the former but the sodium hydroxide extract on acidification gave a product which crystallised in colourless long needles from ethyl alcohol. M.P. and mixed m.p. with 7-hydroxyflavone was 240°.

(ii) <u>With 50 % sulphuric acid : 7-Methoxy-8-carbamoyl flavone and 7-methoxyflavone-8-carboxylic acid</u>

When the hydrolysis was repeated with 7-methoxy-8-cyanoflavone (1.4 g.) and sulphuric acid (50 % ; 25 ml.) and the reaction mixture worked up as above, the sodium hydrogen carbonate extract gave an acid which crystallised from dilute ethyl alcohol in colourless needles, m.p. 216° (efferv.). Yield 0.27 g. It did not give any colouration with alcoholic ferric chloride.

<u>Analysis</u> :

10.02 mg. of the substance gave 25.22 mg. of carbon dioxide and 4.12 mg. of water.

Found : C = 68.66 % ; H = 4.60 %.

$C_{17}H_{12}O_5$ requires : C = 68.91 % ; H = 4.08 %.

The residue left after extraction with sodium hydrogen carbonate was 7-methoxy-8-carbamoyl flavone which crystallised from alcohol (charcoal) in thick colourless needles, m.p. 296°. Yield 0.55 g.

<u>Analysis</u> :

9.88 mg. of the substance gave 25.00 mg. of carbon dioxide and 4.02 mg. of water.

6.082 mg. of the same substance gave 0.268 ml. of nitrogen at 32° and 757 mm.

Found : C = 69.05 % ; H = 4.55 % ; N = 4.91 %.
$C_{17}H_{13}O_4N$ requires : C = 69.14 % ; H = 4.49 % ; N = 4.74 %.

7-Methoxy-8-carbamoylflavone (0.5 g.) on further hydrolysis with sulphuric acid (50 % ; 20 ml.) gave 7-methoxyflavone-8-carboxylic acid, described above.

Decarboxylation

7-Methoxyflavone-8-carboxylic acid (0.5 g.) dissolved in quinoline (10 ml.) was heated at 180° in presence of a pinch of copper powder for about 15 minutes. The product obtained on working up as usual crystallised in colourless needles from petroleum ether (b.p. 60-80°). M.P. and mixed m.p. with 7-methoxyflavone (Robinson and Venkataraman, J. Chem. Soc., 1926, 2346) was 113°.

Demethylation : 7-Hydroxy-8-cyanoflavone

7-Methoxy-8-cyanoflavone (0.5 g.) was heated with acetic anhydride (15 ml.) and hydriodic acid (5 ml.) at 125-130° for 3 hours. The product obtained on working up the reaction mixture was purified through sodium hydroxide solution. It crystallised from ethyl alcohol in buff coloured needles, m.p. 315° (decomp.). It dissolved in sodium hydrogen carbonate solution with effervescence and showed intense violet fluorescence with sulphuric acid.

Analysis :

10.24 mg. of the substance gave 27.34 mg. of carbon dioxide and 3.56 mg. of water.

10.78 mg. of the same substance gave 0.510 ml. of nitrogen at 34° and 755 mm.

Found : $C = 72.86\ \%$; $H = 3.88\ \%$; $N = 5.23\ \%$.
$C_{16}H_9O_3N$ requires : $C = 73.00\ \%$; $H = 3.45\ \%$; $N = 5.32\ \%$.

Hydrolysis of 7-hydroxy-8-cyanoflavone with sulphuric acid : 7-Hydroxyflavone-8-carboxylic acid

7-Hydroxy-8-cyanoflavone (0.65 g.) was gently refluxed with sulphuric acid (50 % ; 20 ml.) for 3 hours. The product obtained on pouring the reaction mixture on ice and purification through sodium hydrogen carbonate solution crystallised in colourless needles from ethyl alcohol, m.p. 242°(efferv.). Yield 0.3 g. Its alcoholic solution gave a deep red colouration with alcoholic ferric chloride.

Analysis :

10.30 mg. of the substance gave 25.62 mg. of carbon dioxide and 3.38 mg. of water.

Found : $C = 67.88\ \%$; $H = 3.67\ \%$.
$C_{16}H_{10}O_5$ requires : $C = 68.08\ \%$; $H = 3.57\ \%$.

The same hydroxy acid was obtained when 7-methoxy-8-carbamoylflavone (0.5 g.) was heated with acetic anhydride (10 ml.) and hydriodic acid (5 ml.) at 125-130° for 3 hours and when 7-methoxyflavone-8-carboxylic acid (0.3 g.) was demethylated by heating with acetic anhydride (5 ml.) and hydriodic acid (5 ml.) under similar conditions.

Decarboxylation

7-Hydroxyflavone-8-carboxylic acid (0.5 g.) was dissolved in quinoline (15 ml.) and heated at 210° for 20 minutes in presence of a pinch of copper powder till the effervescence ceased. The product obtained on addition to cold dilute hydrochloric acid crystallised in colourless long needles. M.P. and mixed m.p. with 7-hydroxyflavone was 240°.

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

7-Methoxy-8-cyanoflavone (0.5 g.) was heated with alcoholic potassium hydroxide solution (10 % ; 20 ml.) on a steam bath for 2 hours. The product, obtained after acidification, on extraction with sodium hydrogen carbonate solution gave 2-hydroxy-3-cyano-4-methoxybenzoic acid described before. The residue on sodium hydroxide treatment gave a product which gave a red colouration with alcoholic ferric chloride. It was found to be identical on direct comparison with 2-hydroxy-3-cyano-4-methoxydibenzoylmethane synthesised from 2-benzoyloxy-3-cyano-4-methoxyacetophenone as shown below.

2-Benzoyloxy-3-cyano-4-methoxyacetophenone

2-Hydroxy-3-cyano-4-methoxyacetophenone (1 g.) was mixed with benzoyl chloride (1 ml.) and pyridine (0.1 ml.) and heated on a steam bath for 3 hours. It was then added to cold dilute hydrochloric acid and left over-night. The product was washed with sodium hydrogen carbonate solution and the residue crystallised from ethyl alcohol in buff coloured needles, m.p. 182°.

Analysis :

8.46 mg. of the substance gave 21.52 mg. of carbon dioxide and 3.18 mg. of water.

6.582 mg. of the same substance gave 0.263 ml. of nitrogen at 34° and 756 mm.

Found : C = 69.42 % ; H = 4.21 % ; N = 4.42 %.

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

2-Hydroxy-3-cyano-4-methoxy-dibenzoylmethane

2-Benzoyloxy-3-cyano-4-methoxyacetophenone (2 g.) was refluxed with pulverised sodium metal (0.3 g.) in benzene (30 ml.) for 4 hours. The precipitated sodium salt was collected and acidified with cold dilute acetic acid. The product crystallised in yellow needles from ethyl alcohol, m.p. 230°.

Analysis :

9.98 mg. of the substance gave 25.36 mg. of carbon dioxide and 4.02 mg. of water.

6.182 mg. of the same substance gave 0.267 ml. of nitrogen at 34° and 756 mm.

Found : C = 69.35 % ; H = 4.51 % ; N = 4.77 %.

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

The above β-diketone (0.5 g.) was dissolved in concentrated sulphuric acid (10 ml.) and kept for 4 hours, at room temperature. The reaction mixture on working up as usual yielded 7-methoxy-8-cyanoflavone.

Attempted reduction of 7-methoxy-8-cyanoflavone

Attempts to reduce the above cyanoflavone with (i) sodium and alcohol (ii) lithium aluminium hydride and (iii) anhydrous stannous chloride under the conditions described before did not succeed. Only the original cyano flavone was obtained.

Rosenmund-von Braun reaction on 2,4-dimethoxy-3,5-di-iodo-acetophenone : 2,4-Dimethoxy-3,5-dicyano-acetophenone

2,4-Dimethoxy-3,5-di-iodo-acetophenone (12.96 g. ; 0.03 mole) was dissolved in dry nitrobenzene (40 ml.) and refluxed with cuprous cyanide (8 g. ; 0.09 mole) and copper sulphate (0.75 g. ; 0.003 mole) for 2 hr. The reaction mixture was then steam distilled to remove the nitrobenzene and the brown pasty ~~mass~~ residue was left in ~~the~~ a desiccator for 3 days when it solidified. It was then extracted with petroleum ether (b.p. 60-80°) and the solid obtained on removal of petroleum ether crystallised from dilute alcohol in colourless needles, m.p. 100°. Yield 0.15 g.

Attempts to improve the yield did not succeed.

Analysis :

4.070 mg. of the substance gave 9.318 mg. of carbon dioxide and 1.568 mg. of water.

6.74 mg. of the same substance gave 0.703 ml. of nitrogen at 29° and 761 mm.

Found : C = 62.48 % ; H = 4.31 % ; N = 11.80 %.

$C_{12}H_{10}O_3N_2$ requires : C = 62.60 % ; H = 4.34 % ; N = 12.17 %.

Rosenmund-von Braun reaction on 5-hydroxy-8-iodo-2-methylchromone : 5-Hydroxy-8-cyano-2-methylchromone

5-Hydroxy-8-iodo-2-methylchromone (1.5 g. ; 0.005 mole) was intimately mixed with cuprous cyanide (1.34 g. ; 0.015 mole) and copper sulphate (0.~~02~~12 g.). ~~as a catalyst~~. The reaction mixture was then heated at 195-200° for half an hour with occasional stirring. The brown reaction product was powdered and extracted repeatedly with hot acetone. The product obtained on repeated crystallisations from dilute ethyl alcohol gave reddish brown needles, m.p. 192°. It gave a red colouration with alcoholic ferric chloride.

Analysis :

4.226 mg. of the substance gave 10.128 mg. of carbon dioxide and 1.182 mg. of water.

5.746 mg. of the same substance gave 0.362 ml. of nitrogen at 40° and 753 mm.

Found : C = 65.40 % ; H = 3.13 % ; N = 6.80 %.

$C_{11}H_7O_3N$ requires : C = 65.67 % ; H = 3.51 % ; N = 6.96 %.