CHAPTER V

SYNTHESIS OF SOME CYANO-FLAVONES

CHAPTER V

THEORETICAL

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

Aryl nitriles can be prepared by many methods. A survey of all the methods has been made by Mowry (1) in 1948.

Merz (2) 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 (3) 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 (4). 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 (5) 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. (6) 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 1913 (7).

Later, Diesbech et al. (8) 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 (9) converted α-bromonaphthalene with cuprous cyanide in pyridine solution to α-naphthonitrile in 93 % yield.

It was observed by von Braun (10) 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 Rosemund-von Braun synthesis has been studied in detail by Koelsch (11) 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 (12).

$$\mathrm{Ar{-}X} + \mathrm{Cu}^{++} \rightleftharpoons \left|\mathrm{Ar{-}X} \rightarrow \mathrm{Cu}^{++}\right| \xrightarrow{\mathrm{Cu}^{+}}$$

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

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

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

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

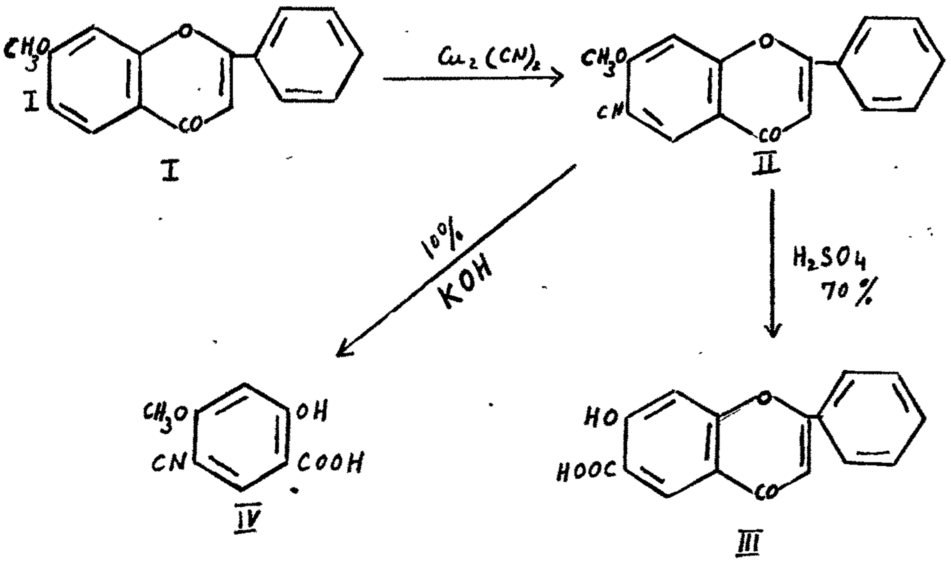
The above two techniques of aryl halide-copper cyanide reactions with or without a basic solvent have been discussed by Braun (13). For large scale runs as in commercial practice, the use of a solvent or an inert diluent is desirable to assist the dissipation of heat of reaction. This may be either a 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 flavones are known they have not been subjected to this reaction except by Shah and Sethna (14) who prepared 7-methoxy-8-cyanoflavone by Rosenmund-von Braun reaction on 7-methoxy-8-iodoflavone. These authors observed that addition of copper sulphate improved the yield. If cuprous cyanide, which was not very fresh, was used then no catalyst was required. A few cyano flavones have been synthesised by other methods. Da Re et al. (15) synthesised 4'-cyanoflavone by cyclisation of 2-hydroxy-4'-cyanobenzoyl-benzoyl methane. They also prepared 8-cyano-3-methylflavone from 2-hydroxy-3-cyanopropiophenone by treatment with sodium benzoate and benzoylchloride. In this laboratory Shah and Sethna (14) have prepared 6-cyano-7-methoxy-3-benzoylflavone by Kostanecki-Robinson benzoylation of 2-hydroxy-4-methoxy-5-cyanoacetophenone.

In the present work cyanoflavones have been obtained by Rosenmund-von Braun reaction on 7-methoxy-6-iodoflavone, 7,4'-dimethoxy-6-iodoflavone and 6-methoxy-5-iodoflavone described in chapter II. Their hydrolysis has also been studied.

Rosenmund-von Braun reaction on 7-methoxy-6-iodo-flavone

7-Methoxy-6-iodoflavone (I) on fusion with cuprous cyanide gave the corresponding 6-cyanoflavone (II). The same compound was prepared by Shah and Sethna (14) from 2-hydroxy-4-methoxy-5-cyanoacetophenone by Kostanecki Robinson benzoylation. On alkaline hydrolysis it gave 2-hydroxy-4-methoxy-5-cyanobenzoic acid (IV) as seen by direct comparison with an authentic specimen prepared according to Shah and Sethna (14). 7-Methoxy-6-cyanoflavone on hydrolysis with 70 % sulphuric acid gave an acid which gave red colouration with alcoholic ferric chloride indicating that simultaneous demethylation had also occured along with the hydrolysis of the cyano group. 7-Hydroxyflavone-6-carboxylic acid structure has been assigned to this product. Shah and Sethna (14) also obtained the same acid by hydrolysing 7-methoxy-6-cyano-3-benzoylflavone with 70 % sulphuric acid.

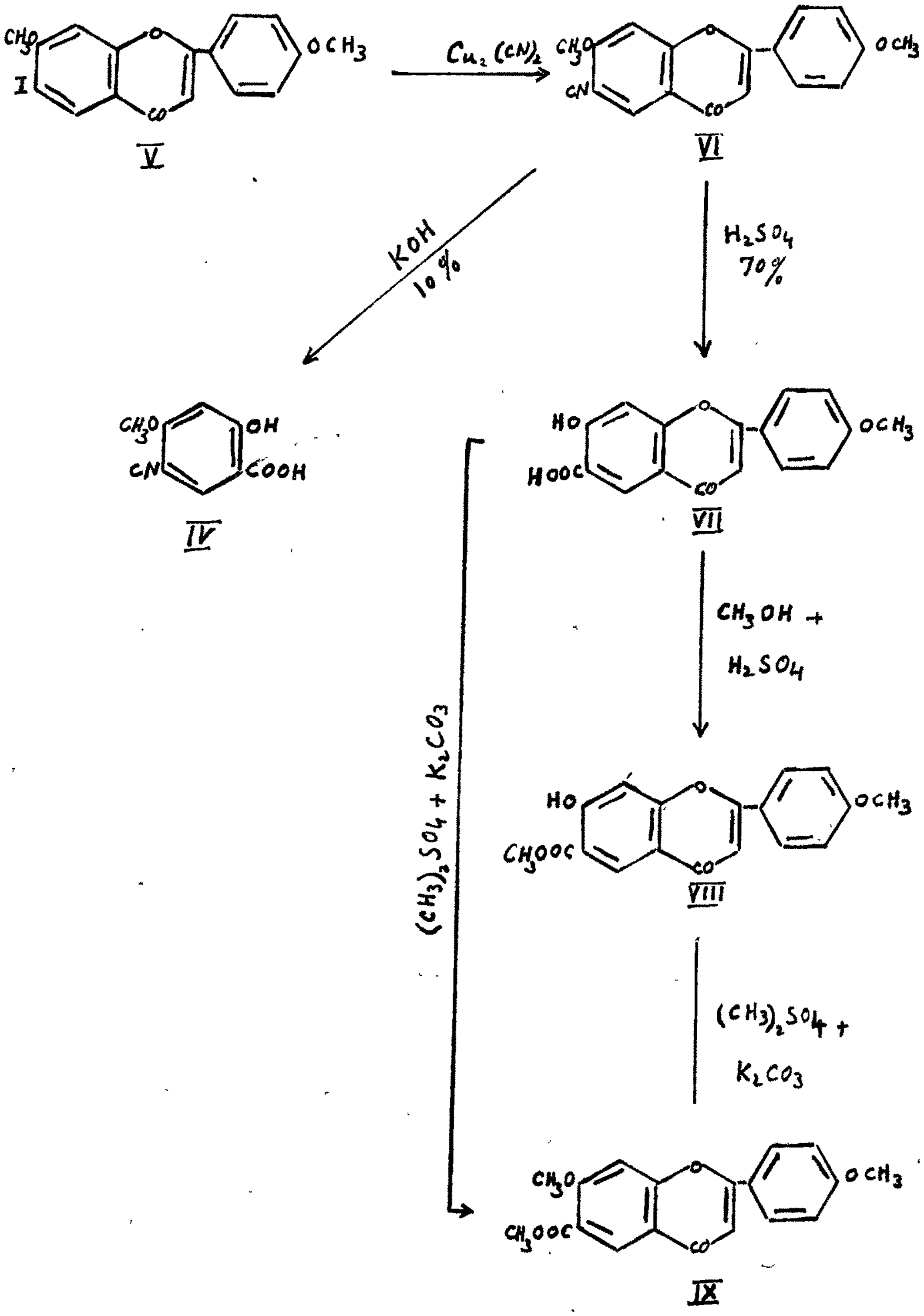


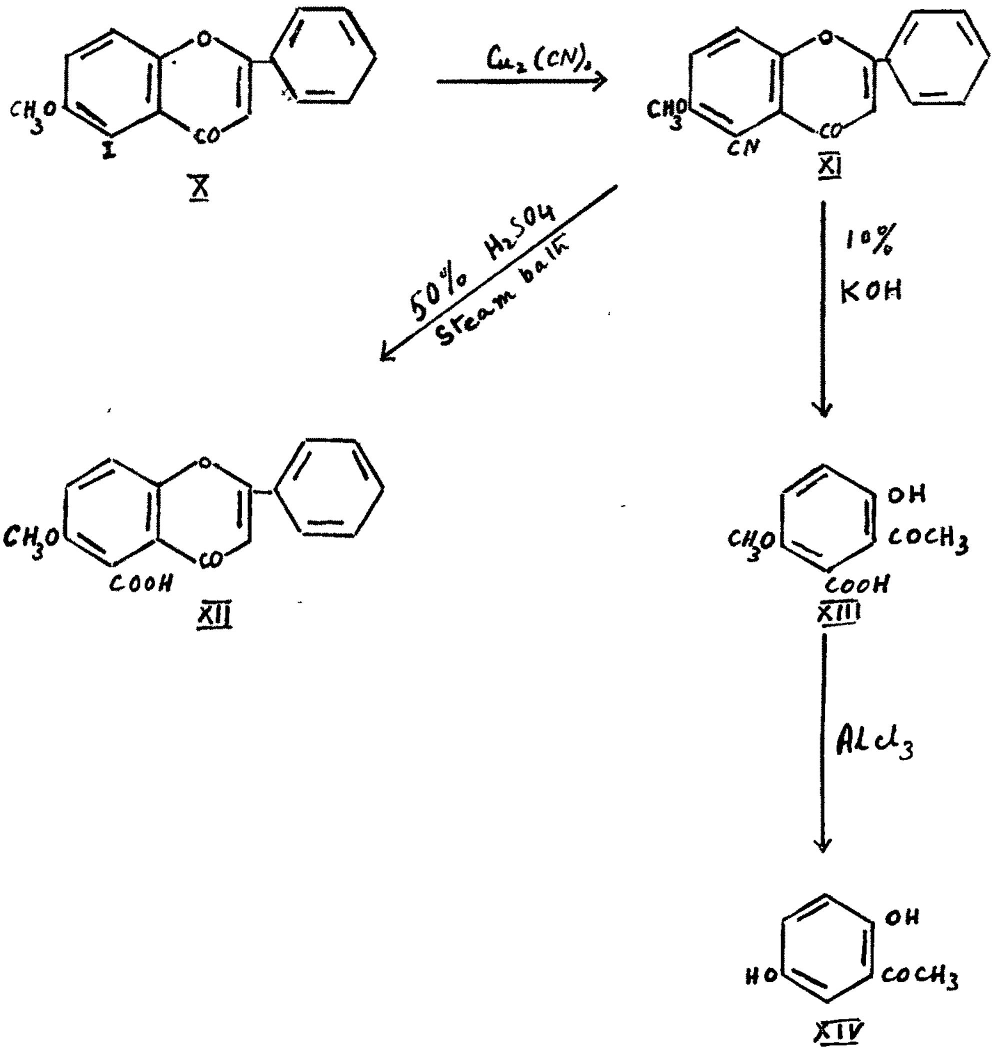
Rosemmund-von Braun reaction on 7,4'-dimethoxy-6-iodoflavone

7,4'-Dimethoxy-6-iodoflavone (V) on fusion with cuprous cyanide gave the corresponding 6-cyanoflavone (VI). On alkaline hydrolysis it gave 2-hydroxy-4-methoxy-5-cyano benzoic acid (IV) as seen by direct comparison with an authentic specimen prepared according to Shah and Sethna (14). 7,4'-Dimethoxy-6-cyanoflavone on hydrolysis with 70 % sulphuric acid gave an acid which gave a red colouration with alcoholic ferric chloride indicating that simultaneous demethylation of the 7-methoxy group had also occured along with the hydrolysis of the cyano group. The analysis indicated that only one methyl group had undergone demethylation. The methyl ester of the above acid was soluble in sodium hydroxide solution. This ester was further methylated and compared with the product obtained by simultaneous methylation and esterification of the 7-hydroxy-4'-methoxyflavone-6-carboxylic acid obtained above with dimethyl sulphate in acetone and potassium carbonate.

Rosemmund-von Braun reaction on 6-methoxy-5-iodoflavone

6-Methoxy-5-iodoflavone (X) on fusion with cuprous cyanide gave the corresponding 5-cyanoflavone (XI). This on refluxing with 70 % or 50 % sulphuric acid for 3 hrs. gave the known 6-hydroxyflavone. 6-Methoxy-5-cyanoflavone on heating with 50 % sulphuric acid on a


CH3O
I
OCH3
V
Cu2 (CN)2
CH3O
CN
OCH3
VI
KOH 10%
H2SO4 70%
CH3O
OH
CN
COOH
IV
HO
HOOC
OCH3
VII
CH3OH + H2SO4
HO
CH3OOC
OCH3
VIII
(CH3)2SO4 + K2CO3
(CH3)2SO4 + K2CO3
CH3O
CH3OOC
OCH3
IX

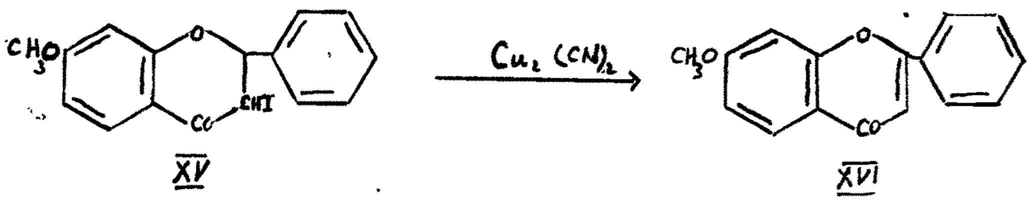

CH3O
I
O
CO
X
Cu2(CN)2
CH3O
CN
O
CO
XI
50% H2SO4
Steam bath
10% KOH
CH3O
COOH
O
CO
XII
OH
COCH3
CH3O
COOH
XIII
AlCl3
OH
HO
COCH3
XIV

steam bath for 5 hrs. gave an acid. The acid did not give any colouration with alcoholic ferric chloride solution indicating that no demethylation had occured and so was assigned 6-methoxyflavone-5-carboxylic acid (XII) structure.

6-Methoxy-5-cyanoflavone (XI) on alkaline hydrolysis gave an acid, m.p. 174° which did not contain nitrogen and gave a deep brown colouration with alcoholic ferric chloride. It also gave a 2,4-dinitrophenyl hydrazone derivative. These observations indicate that it was a keto acid and the cyano group was hydrolysed to a carboxylic acid group. On heating with anhydrous aluminium chloride demethylation and decarboxylation took place and quinacetophenone (XIV) was obtained as seen by direct comparison. The keto acid must, therefore, be 2-acetyl-3-hydroxy-6-methoxybenzoic acid (XIII).

Attempted Rosenmund-von Braun reaction on 7-methoxy-3-iodoflavanone

7-Methoxy-3-iodoflavanone (XV) on fusion with cuprous cyanide gave a product which was found on direct comparison to be 7-methoxyflavone (XVI).



XV

XVI

EXPERIMENTAL

Rosenmund-von Braun reaction on 7-methoxy-6-iodoflavone : 7-Methoxy-6-cyanoflavone

7-Methoxy-6-iodoflavone (3.78 g.) was intimately mixed with cuprous cyanide (1.78 g.) and copper sulphate (0.25 g.). The reaction mixture was heated at 220-225° for 10 minutes and then extracted repeatedly with hot acetone. The product which separated from the acetone extracts on concentration, crystallised from ethyl alcohol in needles, m.p. 227°. Shah and Sethna (14) also reported the same m.p.

<u>Analysis</u> : Found : C=73.79 ; H=4.02 ; N=4.92 %.

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

Hydrolysis of 7-methoxy-6-cyanoflavone with 70 % sulphuric acid : 7-Hydroxyflavone-6-carboxylic acid

7-Methoxy-6-cyanoflavone (0.7 g.) was heated with sulphuric acid (70 % ; 25 ml.) under gentle reflux for 3 hrs. The reaction mixture was then added to crushed ice and the separated product treated with sodium bicarbonate solution. On acidification of sodium bicarbonate extract, a product was obtained which crystallised from ethanol in colourless needles, m.p. 311°. Shah and Sethna (14) also reported the same m.p.

<u>Analysis</u> : Found : C=67.88 ; H=3.67 %.

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

Alkaline hydrolysis of 7-methoxy-6-cyanoflavone : 2-Hydroxy-4-methoxy-5-cyanobenzoic acid

7-Methoxy-6-cyanoflavone (0.5 g.) was heated with alcoholic potassium hydroxide solution (10 % ; 20 ml.) on a steam bath for 2 hrs. The product obtained after acidification on extraction with sodium bicarbonate solution gave 2-hydroxy-4-methoxy-5-cyanobenzoic acid. The m.p. and mixed m.p. with 2-hydroxy-4-methoxy-5-cyano benzoic acid prepared according to Shah and Sethna (14) was 232-233°.

Rosenmund-von Braun reaction on 7,4'-dimethoxy-6-iodoflavone : 7,4'-Dimethoxy-6-cyanoflavone

7,4'-Dimethoxy-6-iodoflavone (4.08 g.) was intimately mixed with cuprous cyanide (1.78 g.) and copper sulphate (0.25 g.). The reaction mixture was heated at 220-225° for 10 minutes and then extracted repeatedly with hot acetone. The product which separated from acetone extract on concentration , crystallised from acetic acid in white needles, m.p. 244°.

Analysis : Found : C=70.65 ; H=4.05 ; N=4.65 %.
$C_{18}H_{13}O_4N$ requires : C=70.35 ; H=4.26 ; N=4.56 %.

Hydrolysis of 7,4'-dimethoxy-6-cyanoflavone with 70 % sulphuric acid : 7-Hydroxy-4'-methoxyflavone-6-carboxylic acid

7,4'-Dimethoxy-6-cyanoflavone (0.7 g.) was heated with sulphuric acid (70 % ; 25 ml.) under gentle reflux for 3 hrs. The reaction mixture was then added to crushed ice and the separated product treated with sodium bicarbonate solution. On acidification of sodium bicarbonate extract a product was obtained which crystallised from ethanol in colourless needles, m.p. 319-320° (decomp. efferv.). Its alcoholic solution gave red colouration with alcoholic ferric chloride.

Analysis : Found : C=65.89 ; H=4.37 %.
$C_{17}H_{12}O_6$ requires : C=65.39 ; H=3.84 %.

Methyl-7-hydroxy-4'-methoxyflavone-6-carboxylate

7-Hydroxy-4'-methoxyflavone-6-carboxylic acid (0.2 g.) was treated with methyl alcohol (5 ml.) and concentrated sulphuric acid (2 drops). The reaction mixture was heated on a steam bath for 2 hrs. The reaction mixture was then poured into ice cold water when a product separated. It crystallised from alcohol in white needles, m.p. 190°. It did not give any colouration with alcoholic ferric chloride solution and did not dissolve in sodium bicarbonate solution. It was however soluble in sodium hydroxide solution.

Analysis : Found : C=67.41 ; H=4.64 %.
$C_{18}H_{14}O_6$ requires : C=67.51 ; H=4.37 %.

Methyl-7,4'-dimethoxyflavone-6-carboxylate

The above ester (0.5 g.) was refluxed in dry acetone and dimethyl sulphate (1.0 ml.) on a steam bath for 8 hrs. in the presence of anhydrous potassium carbonate (2 g.). The product obtained on removal of acetone was crystallised from alcohol in white needles, m.p. 208°.

The same product was also obtained on simultaneous methylation and esterification of the 7-hydroxy-4'-methoxyflavone-6-carboxylic acid with dimethyl sulphate in the presence of potassium carbonate in acetone solution.

Analysis : Found : C=63.65 ; H=4.85 %.
$C_{19}H_{16}O_6$ requires : C=64.11 ; H=4.70 %.

Alkaline hydrolysis of 7,4'-dimethoxy-6-cyanoflavone : 2-Hydroxy-4-methoxy-5-cyanobenzoic acid

7,4'-Dimethoxy-6-cyanoflavone (0.5 g.) was heated with alcoholic potassium hydroxide solution (10 % ; 20 ml.) on a steam bath for 2 hrs. The product obtained on acidification, on extraction with sodium bicarbonate solution gave 2-hydroxy-4-methoxy-5-cyanobenzoic acid. The m.p. and mixed m.p. with 2-hydroxy-4-methoxy-5-cyanobenzoic acid, prepared according to Shah and Sethna (14), was 231°.

Rosenmund-von Braun reaction on 6-methoxy-5-iodoflavone : 6-Methoxy-5-cyanoflavone

6-Methoxy-5-iodoflavone (3.78 g.) was intimately mixed with cuprous cyanide (1.78 g.) and copper sulphate (0.25 g.). The reaction mixture was heated at 260-65°

for 10 minutes, cooled and then extracted repeatedly with hot acetone. The product, which separated from acetone extract on concentration, crystallised from acetic acid in white needles, m.p. 251°.

Analysis : Found : C=73.50 ; H=4.00 ; N=5.18 %.
$C_{17}H_{11}O_3N$ requires : C=73.64 ; H=4.00 ; N=5.05 %.

Hydrolysis of 6-methoxy-5-cyanoflavone with 50 % sulphuric acid : (1) 6-Hydroxyflavone

6-Methoxy-5-cyanoflavone (0.7 g.) was heated with sulphuric acid (50 % ; 25 ml.) under gentle reflux for 3 hrs. The reaction mixture was then added to crushed ice and the separated product treated successively with sodium bicarbonate and sodium hydroxide solution. No product was obtained from the former but the sodium hydroxide extract on acidification gave a product which crystallised from ethyl alcohol. M.p. and mixed m.p. with 6-hydroxyflavone was 232°.

(ii) 6-Methoxyflavone-5-carboxylic acid

When the hydrolysis was repeated by heating the reaction mixture on a steam bath for 5 hrs. the sodium bicarbonate extract gave an acid which crystallised from alcohol, m.p. 244° (decomp. efferv.). It dis not give any colouration with alcoholic ferric chloride solution.

Analysis : Found : C=68.87 ; H=3.88 %.
$C_{17}H_{12}O_5$ requires : C=68.92 ; H=4.05 %.

Alkaline hydrolysis of 6-methoxy-5-cyanoflavone : 2-Acetyl-3-hydroxy-6-methoxybenzoic acid

6-Methoxy-5-cyanoflavone (0.5 g.) was heated with alcoholic potassium hydroxide (10 % ; 20 ml.) on a steam bath for 3 hrs. The product obtained on acidification was extracted with sodium bicarbonate solution. The sodium bicarbonate extract on acidification gave a product which crystallised from alcohol in needles, m.p. 174°. Its alcoholic solution gave a deep brown colouration with alcoholic ferric chloride solution.

Analysis : Found : C=57.01 ; H=4.88 %.
$C_{10}H_{10}O_5$ requires : C=57.14 ; H=4.76 %.

The 2,4-dinitrophenyl hydrazone

Solution of 2,4-dinitrophenyl hydrazine (0.3 g.) in ethyl alcohol (5 ml.) containing few drops of concentrated hydrochloric acid was added to a solution of the above keto acid (0.3 g.) in alcohol. The reaction mixture was refluxed on a steam bath for an hour when an orange coloured product separated out. It was filtered and crystallised from nitro-benzene in tiny needles, m.p. 265°(decomp.)

Analysis : Found : N=14.22 %.
$C_{16}H_{14}O_8N_4$ requires : N=14.35 %.

De-carboxylation and demethylation of 2-acetyl-3-hydroxy-6-methoxy-benzoic acid : 2,5-Dihydroxyacetophenone

An intimate mixture of dry 2-acetyl-3-hydroxy-6-

-methoxy-benzoic acid (1 g.) and finely powdered anhydrous aluminium chloride was heated in an oil bath at 145-150° for 3 hrs. After cooling, ice cold dilute hydrochloric acid was added and the product obtained crystallised from water, m.p. and mixed m.p. with quin-acetophenone was 202°.

Attempted Rosenmund-von Braun reaction on 7-methoxy 3-iodoflavanone : 7-Methoxyflavone

7-Methoxy-3-iodoflavanone (3.80 g.) was intimately mixed with cuprous cyanide (1.78 g.) and copper sulphate (0.25 g.) was added. The reaction mixture was heated at 125-130° for 10 minutes. The reaction mixture was extracted repeatedly with hot acetone. The product which separated from acetone extract on concentration did not contain any nitrogen. It crystallised from ethyl alcohol in white needles. M.p. and mixed m.p. with 7-methoxyflavone was 110°.

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