CHAPTER VI

BECKMANN REARRANGEMENT OF THE OXIMES OF SOME C-ACYLFLAVONES

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T H E O R E T I C A L

Beckmann rearrangement of the oximes of some C-acylflavones

In its most general form the Beckmann rearrangement (1) consists in the transformation of a ketoxime into an acid amide. The rearrangement can be effected by a large number of reagents such as phosphorus pentachloride, phosphorus oxychloride, acetyl chloride, sulphuric acid and polyphosphoric acid.

Phosphorus pentachloride remains the most generally used and most valuable reagent. The rearrangement is carried out in ethereal solution and at a low temperature. Lechmann (2) used hydrochloric acid satisfactorily. Polyphosphoric acid has been found in recent years to be an excellent reagent for this rearrangement (3).

The Beckmann rearrangement was reviewed in 1958 in detail by Popp and Mcewen (4).

Simple ketoximes undergo rearrangement with polyphosphoric acid in almost quantitative yields. The reactions are satisfactory when applied to the oximes of diarylketones, aryl alkylketones and cyclic ketones. Under the proper conditions aldoximes also undergo the Beckmann rearrangement to yield either amides (5) or

nitriles (6).

$$RCH{=}NOH \longrightarrow RCONH_2 \text{ or/and } HCONHR \text{ or/and } RCN$$

It was Meisenheimer's work (7) which led to a better understanding of the Beckmann rearrangement and enhanced its usefulness from a preparative method to a tool for determining the configuration of the oximes.

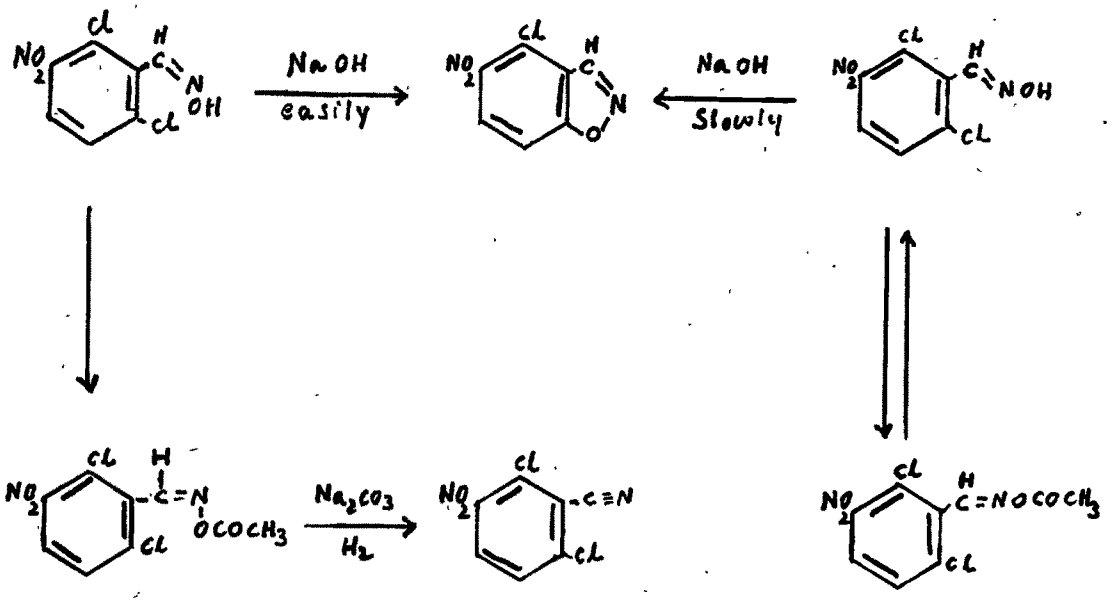
Configuration of isomeric ketoximes

With the discovery that unsymmetrical ketones furnished in many cases isomeric oximes, several theories were advanced to account for the isomerism of these compounds. The one which has received general acceptance is that of Hantzsch and Werner (8).

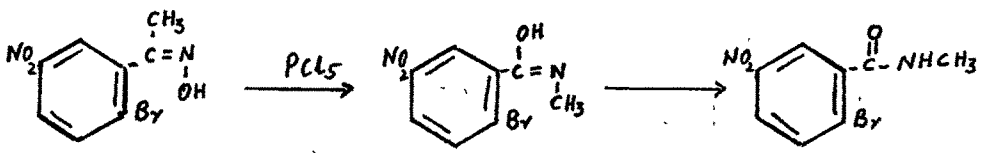
Hantzsch and Werner proposed a stereochemical explanation for the isomerism. They assumed that the three nitrogen valencies are non-planar and that a carbon-nitrogen double bond can give geometrical isomers inthe same way as a carbon-carbon double bond. Hantzsch proposed the terms syn and anti for the two forms.

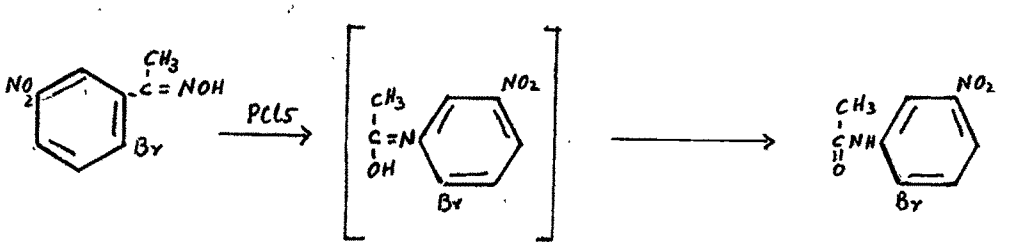
The currently accepted configurations of the isomeric forms were assigned by Meisenheimer et al.(7). If a reactive halogen atom is ortho to aldoximino group one form of the aldoxime undergoes ring formation easily in presence of alkali whereas the other form gives the same product much more slowly.

It seems likely therefore that the form undergoing ready cyclisation is the anti-aldoxime and that the syn-aldoxime first must rearrange to the anti-form before cyclisation takes place. Further, the form that undergoes easy ring closure gives an acetate which reacts with alkali to form a nitrile whereas the acetate of the other form regenerates the original oxime.



The syn and anti ketoximes yield different products on Beckmann rearrangement. This is illustrated in the case of the oxime of bromo-nitro acetophenone as shown below.





Thus the groups that exchange places in the rearrangement are those that are anti to each other.

$$C_6H_5-\underset{\underset{N-OH}{\|}}{C}-C_6H_4-CH_3 \xrightarrow[H_2O]{PCl_5} OH-\underset{\underset{N-C_6H_5}{\|}}{C}-C_6H_4-CH_3$$

anti-phenyl-tolyl ketoxime

$$O=\underset{\underset{NHC_6H_5}{|}}{C}-C_6H_4-CH_3 \xrightarrow{H_2O} CH_3-C_6H_4-COOH + C_6H_5NH_2$$

p-toluic acid Aniline

$$C_6H_5-\underset{\underset{OHN}{\|}}{C}-C_6H_4CH_3 \xrightarrow[H_2O]{PCl_5} C_6H_5-\underset{\underset{CH_3C_6H_4N}{\|}}{C}-OH$$

syn-phenyl-tolyl ketoxime

$$\begin{matrix} C_6H_5C{=}O \\ | \\ CH_3C_6H_4NH \end{matrix} \xrightarrow{H_2O} C_6H_5\text{-}COOH + CH_3C_6H_4NH_2$$

Aliphatic aldehydes and ketones do not give isomeric oximes, probably because one form is much more stable than the other.

A summary of the literature shows that there are very few examples of the study of Beckmann rearrangement of the oximes of C-acyl ~~or C-formyl~~ derivatives of oxygen heterocyclics. It was therefore thought of interest to study the reaction with the oximes of the C-acyl or C-formyl derivatives of flavones. Sugasawa (9) carried out the Beckmann rearrangement of the oxime of 5-hydroxy-6-acetylflavone with phosphorus oxychloride and obtained 5-hydroxy-6-aminoflavone. This appears to be the only instance in the literature of the Beckmann rearrangement of the oxime of a C-acylflavone.

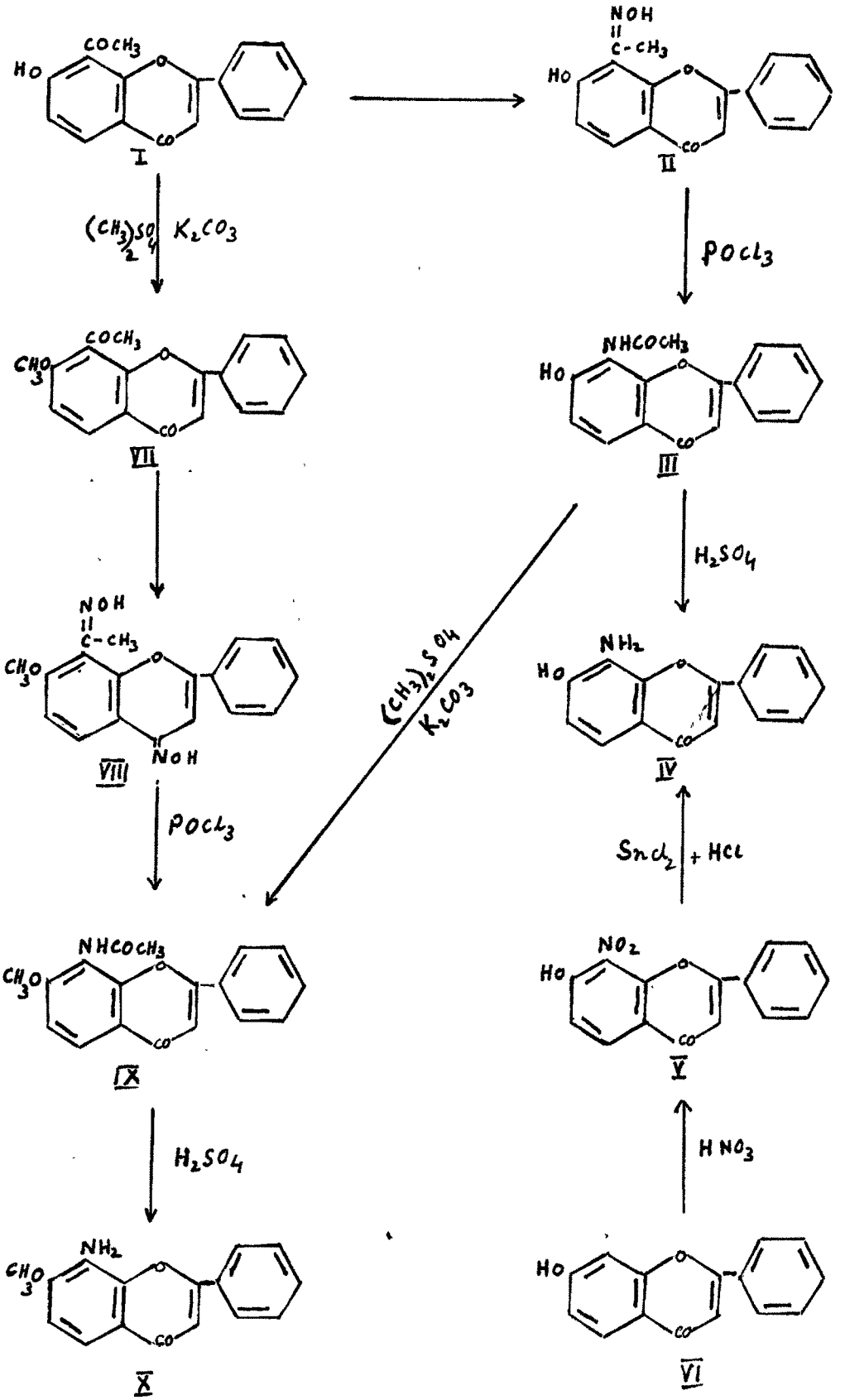
In the present work the Beckmann rearrangement of the oximes of (a) 7-hydroxy-8-acetylflavone and its methyl ether (b) 7-hydroxy-8-formylflavone and its methyl ether and (c) 7-hydroxy-8-benzoylflavone have been carried out. Attempts to prepare 6-hydroxy-5-acetylflavone did not succeed. 6-Hydroxyflavone did not undergo

Friedel-Crafts reaction and 6-acetoxyflavone on Fries migration gave only 6-hydroxyflavone.

Beckmann rearrangement of the oximes of 7-hydroxy-8-acetylflavone and its methyl ether

The oxime of 7-hydroxy-8-acetylflavone (II) was mixed with phosphorus oxychloride with cooling and the reaction mixture then heated on a water bath at 70-80° for 2-3 minutes. The product obtained was found to be 7-hydroxy-8-acetamidoflavone (III). When refluxed with sulphuric acid (50 %) it gave 7-hydroxy-8-aminoflavone (IV) as seen by direct comparison with the product obtained on reduction of the known 7-hydroxy-8-nitroflavone (10) with stannous chloride and hydrochloric acid.

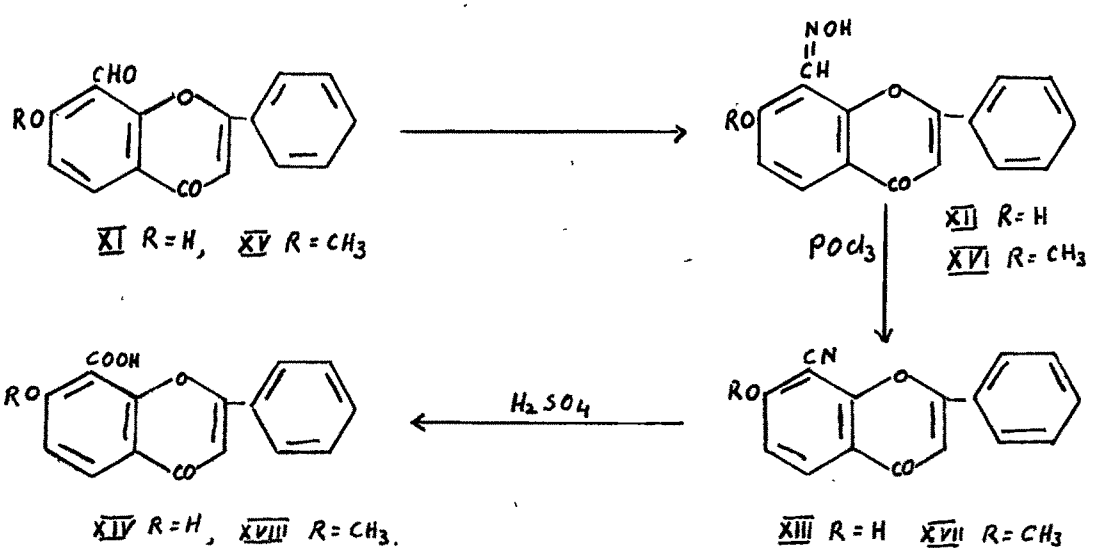
The oxime of 7-methoxy-8-acetylflavone (VIII) prepared as usual gave a compound which analysed for a di-oxime. The structure of this di-oxime has not been investigated. Probably the carbonyl group of the heterocyclic ring also reacts. On Beckmann rearrangement with phosphorus oxychloride by heating in a water bath at 70-80° for 10 minutes it gave 7-methoxy-8-acetamidoflavone (IX) as seen by direct comparison with the product obtained on methylation of 7-hydroxy-8-acetamidoflavone described above. When refluxed with sulphuric acid it gave 7-methoxy-8-aminoflavone (X).


HO
COCH3
O
CO
I
NOH
C-CH3
II
(CH3)2SO4
K2CO3
POCl3
CH3O
VII
NHCOCH3
III
H2SO4
NOH
VIII
NH2
IV
(CH3)2SO4
K2CO3
SnCl2 + HCl
NO2
V
HNO3
IX
NHCOCH3
H2SO4
X
NH2
VI

Beckmann rearrangement of the oximes of 7-hydroxy-8-formylflavone and its methyl ether

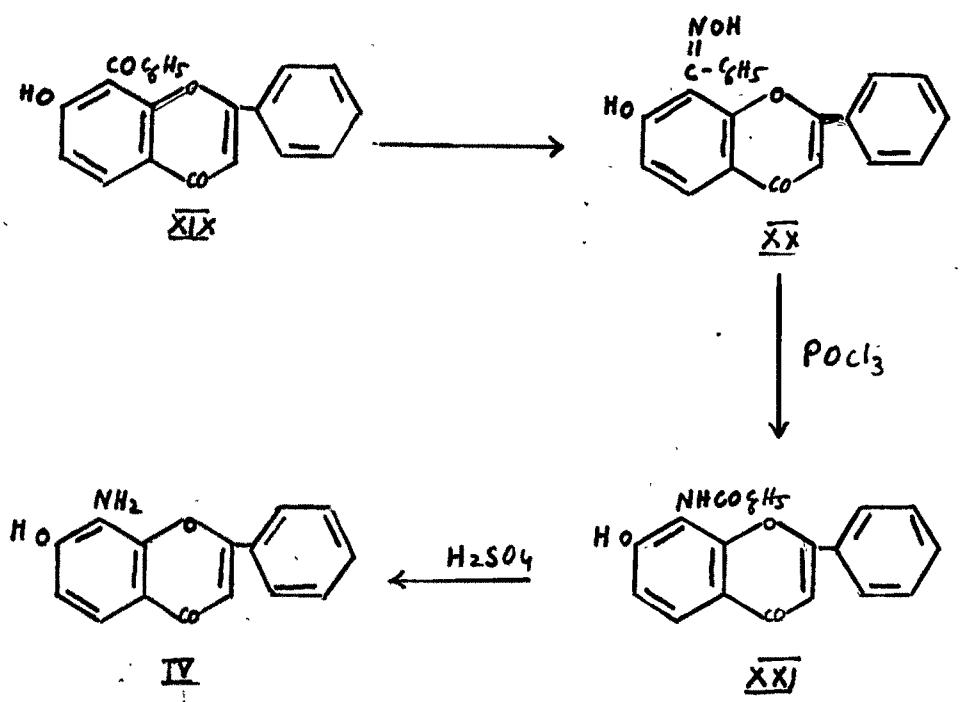
The oxime of 7-hydroxy-8-formylflavone, prepared as usual, when heated on a steam bath with phosphorus oxychloride for 10 minutes gave a product which was found to be 7-hydroxy-8-cyanoflavone (XIII). When refluxed with sulphuric acid it gave the known 7-hydroxyflavone-8-carboxylic acid (11) as seen by direct comparison with an authentic specimen.

The oxime of 7-methoxy-8-formylflavone (XVI) when heated on a steam bath for 10 minutes with phosphorus oxychloride gave 7-methoxy-8-cyanoflavone (XVII) which when refluxed with sulphuric acid (50 %) for 3 hours gave the known 7-methoxyflavone-8-carboxylic acid (11) as seen by direct comparison with an authentic specimen.



Beckmann rearrangement of the oxime of 7-hydroxy-8-benzoylflavone

The oxime of 7-hydroxy-8-benzoylflavone (XX) prepared as usual when heated on a steam bath for 10 minutes with phosphorus oxychloride gave 7-hydroxy-8-benzamidoflavone (XXI) which when refluxed with sulphuric acid (50 %) gave 7-hydroxy-8-aminoflavone (IV) described before.



EXPERIMENTAL

Oxime of 7-hydroxy-8-acetylflavone

7-Hydroxy-8-acetylflavone (0.2 g.) dissolved in minimum quantity of alcohol was mixed with a solution of hydroxylamine hydrochloride (0.5 g.) in water (3 ml.) and sodium hydroxide (10 % ; 2 ml.). The reaction mixture was refluxed for 2 hrs. The product obtained on acidification and dilution was crystallised from alcohol in yellow shining needles, m.p. 237°. Yield 0.1 g.

Analysis : Found : C=68.72 ; H=4.36 ; N=4.50 %.
$C_{17}H_{13}O_4N$ requires : C=69.14 ; H=4.44 ; N=4.74 %.

Beckmann rearrangement of the oxime of 7-hydroxy 8-acetylflavone : 7-Hydroxy-8-acetamidoflavone

The above oxime (1.0 g.) was added to a well cooled phosphorus oxychloride (10 ml.) and the reaction mixture was heated at 70-80° for 3-5 minutes, when the reaction mixture became dark brown in colour. The reaction mixture was poured into ice and stirred for half an hour. The solid which separated out was crystallised from acetic acid. M.P. 250°. Yield 0.3 g.

Analysis : Found : C=69.62 ; H=4.72 ; N=4.95 %.
$C_{17}H_{13}O_4N$ requires : C=69.14 ; H=4.44 ; N=4.74 %.

7-Hydroxy-8-aminoflavone

7-Hydroxy-8-acetamidoflavone (0.5 g.) was refluxed with sulphuric acid (50 % ; 25 ml.) for 3 hrs. The reaction mixture was then diluted with ice cold water and filtered. The filtrate was treated with ammonium chloride (2.0 g.) and neutralised with dilute ammonium hydroxide solution. The product obtained was crystallised from nitrobenzene, m.p. 246°. Mixed m.p. with 7-hydroxy-8-aminoflavone obtained as described below was not depressed.

Analysis : Found : C=71.20 ; H=4.21 ; N=5.26 %.
$C_{15}H_{11}O_3N$ requires : C=71.14 ; H=4.34 ; N=5.53 %.

7-Hydroxy-8-nitroflavone, previously prepared by Shah et al.(10), was prepared in the present work by an improved method given below which gave a purer product.

7-Hydroxyflavone (1.0 g.) was added to concentrated nitric acid (20 ml.) and heated on a steam bath till the fumes of nitrogen peroxide ceased and the product separated. The reaction mixture was diluted with cold water and filtered. The product obtained was crystallised from acetic acid.

7-Hydroxy-8-nitroflavone (1.0 g.) was dissolved in glacial acetic acid (20 ml.) and a solution of stannous chloride (2.0 g.) in glacial acetic acid was added. The

reaction mixture was heated on a steam bath for an hour. The reaction mixture was then saturated with hydrochloric acid by passing dry hydrogen chloride gas through the mixture for an hour, when amine hydrochloride separated. It was filtered and again redissolved in water and the solution treated with sodium bicarbonate solution when the free base separated. It was crystallised from nitrobenzene, m.p. 246°.

Di-oxime of 7-methoxy-8-acetylflavone

7-Methoxy-8-acetylflavone (0.4 g.) was dissolved in alcohol and treated with a solution of hydroxylamine hydrochloride (1.0 g.) in water (6 ml.) and sodium hydroxide (10 % ; 4 ml.). The reaction mixture was refluxed for 2 hrs. The product obtained on dilution was crystallised from alcohol in white buds, m.p. 218°. Yield 0.3 g.

The same dioxime was obtained when 7-methoxy-8-acetylflavone was refluxed with hydroxylamine hydrochloride and fused sodium acetate in alcohol. No monoxime could be obtained.

Analysis : Found : C=66.51 ; H=4.53 ; N=9.16 %.
$C_{18}H_{16}O_4N_2$ requires: C=66.66 ; H=4.93 ; N=8.64 %.

Beckmann rearrangement of the di-oxime of 7-methoxy-8-acetylflavone : 7-Methoxy-8-acetamidoflavone

The above dioxime (1.0 g.) was introduced into well cooled phosphorus oxychloride (10 ml.) and the reaction mixture heated on a water bath at 70-80° till the reaction mixture became dark brown in colour (10 minutes.). It was then poured on crushed ice. The separated solid was crystallised from acetic acid, m.p. 285°.

Analysis : Found : C=69.77 ; H=4.64 ; N=4.65 %.

$C_{18}H_{15}O_4N$ requires : C=69.90 ; H=4.85 ; N=4.53 %.

Mixed m.p. with 7-methoxy-8-acetamidoflavone obtained as described below was not depressed.

7-Hydroxy-8-acetamidoflavone (0.5 g.) in acetone was refluxed on a steam bath with dimethyl sulphate (1 ml.) in the presence of anhydrous potassium carbonate (2.0 g.) for 8 hrs. The product obtained on removal of acetone was washed with dilute sodium hydroxide solution and crystallised from acetic acid as above.

7-Methoxy-8-aminoflavone

7-Methoxy-8-acetamidoflavone (0.5 g.) was refluxed with sulphuric acid (50 % ; 25 ml.) for 3 hrs. The reaction mixture was diluted with ice cold water and then neutralised with sodium hydroxide solution. The product which separated was crystallised from alcohol in yellow needles, m.p. 196°.

Analysis : Found : C=72.21 ; H=5.03 ; N=4.92 %.
$C_{16}H_{13}O_3N$ requires : C=71.90 ; H=4.90 ; N=5.24 %.

Oxime of 7-hydroxy-8-formylflavone

A mixture of hydroxylamine hydrochloride (0.5 g.) in water (3 ml.), sodium hydroxide (10 % ; 2 ml.) and 7-hydroxy-8-formylflavone (0.2 g.) in alcohol was refluxed for 2 hrs. The solid separated on cooling after acidification was crystallised from alcohol, m.p. 273-4°. Yield 0.1 g.

Analysis : Found : C=67.97 ; H=4.11 ; N=5.15 %.
$C_{16}H_{11}O_4N$ requires : C=68.33 ; H=3.91 ; N=4.98 %.

Beckmann rearrangement of the oxime of 7-hydroxy 8-formylflavone : 7-Hydroxy-8-cyanoflavone

The above oxime (1.0 g.) was added to well cooled phosphorus oxychloride (10 ml.) and the reaction mixture heated on a steam bath for 10 minutes and then poured on crushed ice. The separated solid crystallised from acetic acid, m.p. 315°. Shah and Sethna (11) prepared the same cyanoflavone from 7-methoxy-8-iodo-flavone by Rosenmund Von Braun reaction and subsequent demethylation and reported the same m.p.

Analysis : Found : C=72.86 ; H=3.65 ; N=4.95 %.
$C_{16}H_9O_3N$ 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 (0.6 g.) was gently refluxed with sulphuric acid (50 % ; 20 ml.) for 3 hrs. The product obtained on pouring the reaction mixture in ice cold water after purification through sodium bicarbonate solution crystallised in colourless needles from ethyl alcohol. M.p. and mixed m.p. with 7-hydroxyflavone-8-carboxylic acid (11) was 242° (efferv). Yield 0.3 g.

Oxime of 7-methoxy-8-formylflavone

A mixture of 7-methoxy-8-formylflavone (0.2 g.) in alcohol, hydroxylamine hydrochloride (0.5 g.) and sodium hydroxide (10 % ; 2 ml.) was refluxed for 2 hrs. The solid which separated on cooling was crystallised from alcohol in white needles, m.p. 237°.

Analysis : Found : C=69.23 ; H=4.23 ; N=4.42 %.
$C_{17}H_{13}O_4N$ requires : C=69.14 ; H=4.44 ; N=4.74 %.

Beckmann rearrangement of the oxime of 7-methoxy-8-formylflavone : 7-Methoxy-8-cyanoflavone

Oxime of 7-methoxy-8-formylflavone (1.0 g.) was added to well cooled phosphorus oxychloride (10 ml.) and the reaction mixture heated on a steam bath for 10 minutes and then poured on ice. The solid which

separated on stirring the reaction mixture was crystallised from acetic acid in needles, m.p. 235°. Shah and Sethna (11) prepared the same cyanoflavone from 7-methoxy-8-iodoflavone by Rosenmund-von Braun reaction and reported the same m.p.

Analysis : Found : C=73.53 ; H=3.41 ; N=4.64 %.
$C_{17}H_{11}O_3N$ requires : C=73.64 ; H=4.00 ; N=5.05 %.

Hydrolysis of 7-methoxy-8-cyanoflavone : 7-Methoxyflavone-8-carboxylic acid

7-Methoxy-8-cyanoflavone (1.4 g.) was gently refluxed with sulphuric acid (50 % ; 20 ml.) for 3 hrs. and the reaction mixture worked up as usual . The sodium bi-carbonate extract gave an acid which crystallised from dilute ethyl alcohol in colourless needles. The m.p. and mixed m.p. with 7-methoxyflavone-8-carboxylic acid (11) was 216°. (efferv.)

Oxime of 7-hydroxy-8-benzoylflavone

7-Hydroxy-8-benzoylflavone (0.2 g.) dissolved in minimum quantity of alcohol was refluxed with an aqueous solution of hydroxylamine hydrochloride (0.5 g.) in the presence of sodium hydroxide (10 % ; 2 ml.) for 8 hrs. The product obtained crystallised from alcohol in colourless needles, m.p. 262-3°. Yield 0.1 g.

Analysis : Found : C=73.79 ; H=4.06 ; N=3.77 %.
$C_{22}H_{15}O_4N$ requires : C=73.97 ; H=4.23 ; N=3.92 %.

Beckmann rearrangement of the oxime of 7-hydroxy-8-benzoylflavone : 7-Hydroxy-8-benzamidoflavone

Oxime of 7-hydroxy-8-benzoylflavone (1.0 g.) was introduced into well cooled phosphorus oxychloride (10 ml.) and the reaction mixture heated on a steam bath till it became brown in colour (10 minutes). It was then poured on crushed ice and the solid which separated was crystallised from acetone, m.p. 267°.

Analysis : Found : C=73.79 ; H=3.97 ; N=3.88 %.
$C_{22}H_{15}O_4N$ requires : C=73.94 ; H=4.23 ; N=3.92 %.

7-Hydroxy-8-aminoflavone

7-Hydroxy-8-benzamidoflavone (0.5 g.) was treated with sulphuric acid (50 % ; 25 ml.) and the reaction mixture refluxed for 3 hrs. The solid obtained on working up as usual was crystallised from nitrobenzene. M.p. and the mixed m.p. with 7-hydroxy-8-aminoflavone described before was 246°.

REFERENCES

1. Beckmann., Ber., 19, 988 (1886).
2. Lachmann., J.Am.Chem.Soc., 46, 1477 (1924).
3. Horning, Stromberg and Lloyd., J.Am.Chem.Soc., 74, 5153 (1952).
4. Popp. and Mcewen., Chem.Revs., 58, 370 (1958).
5. Horning and Stromberg., J.Am.Chem.Soc., 74, 2680 (1952).
6. Yamaguchi., Bull.Chem.Soc., Japan. 1, 35 (1926) ; C.A., 21, 75 (1927).
7. Meisenheimer, Beisswenger, Kauffmann, Kunner and Link., Ann. 468, 202 (1929).
8. Hantzsch and Werner., Ber., 23, 11 (1890).
9. Sugasawa., J.Pharm.Soc., Japan. 56, 105 (1936); C.A., 32, 5833 (1938).
10. Mehta, Jadhav and Shah., Proc.Indian Accad.Sci., 29A, 314 (1949) ; C.A., 43, 9067 (1949).
11. Shah and Sethna., J.Chem.Soc., 2663 (1961).