CHAPTER III

Studies in the Synthesis of Coumarino-γ-pyrones

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T H E O R E T I C A L

Chromones and flavones, which are benzo-γ-pyrone derivatives, occur in a variety of plants either in combination with rhamnose and glucose or associated with tannins or in the uncombined state.

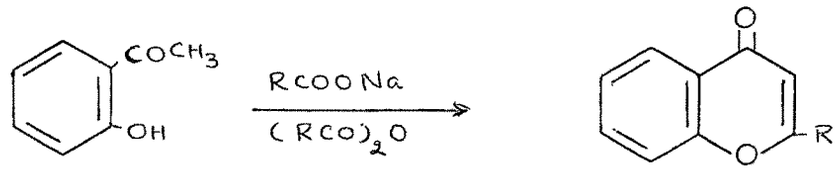
The structure of a large number of flavones have been elucidated and many of them have been synthesised. In recent years the interest in the study of these compounds has been enhanced as a result of the discovery of their interesting biochemical properties. Rutin (3-rhamnoglucoside of quercentin) shows vitamin p activity and is important in preventing capillary fragility[1]. Other flavones such as quercitrin, rhamnetin and 6,8-dihydrocyflavone are reported to reduce blood pressure[2] and to act as diuretics[3]. Further, calycopterin and its 4'-methyl ether, herbecetin, gossypetin etc. act as fish poisons[4,5]. The aminomethyl derivatives of chromones and flavones are reported to act as powerful central nervous system stimulants, especially on the brain stem and to have cardiokinetics and hypertensive action.[6]

Methods for the synthesis of chromones and flavones :

A number of methods are available for the synthesis of chromones and flavones and are briefly reviewed here.

Kostanecki and Rozycki[7] showed that a chromone derivative (2) was formed when resacetophenone(1) was

heated with sodium acetate and acetic anhydride.



(1) (2)

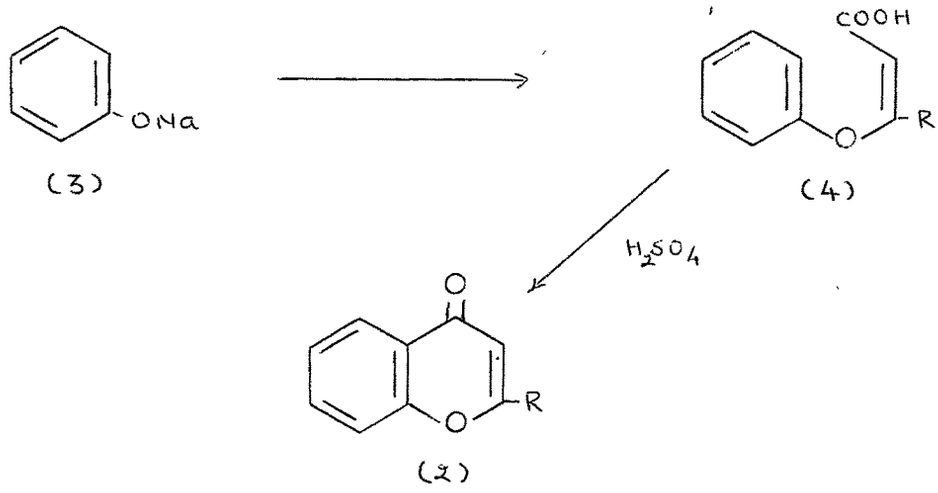
This method was further developed by Allan and Robinson[8] who found that when o-hydroxyacetophenones were heated with the sodium salt and the anhydride of an aromatic acid, a flavone derivative was obtained. This method now known as the Kostanecki-Robinson reaction has been extensively used for the synthesis of chromones and flavone derivatives.

It has been found that the Kostanecki-Robinson reaction does not give chromones in all cases. Coumarins or a mixture of coumarins and chromones may be formed in some cases. Bargellini[9] and Baker and Eastwood[10] have found that when a mixture of phenyl acetic anhydride and sodium phenyl acetate is used, Kostanecki-Robinson reaction leads to the formation of coumarins and not chromones.

The nature of this product formed depends on the nature of the o-hydroxyketone, the acid anhydride and the salt used.

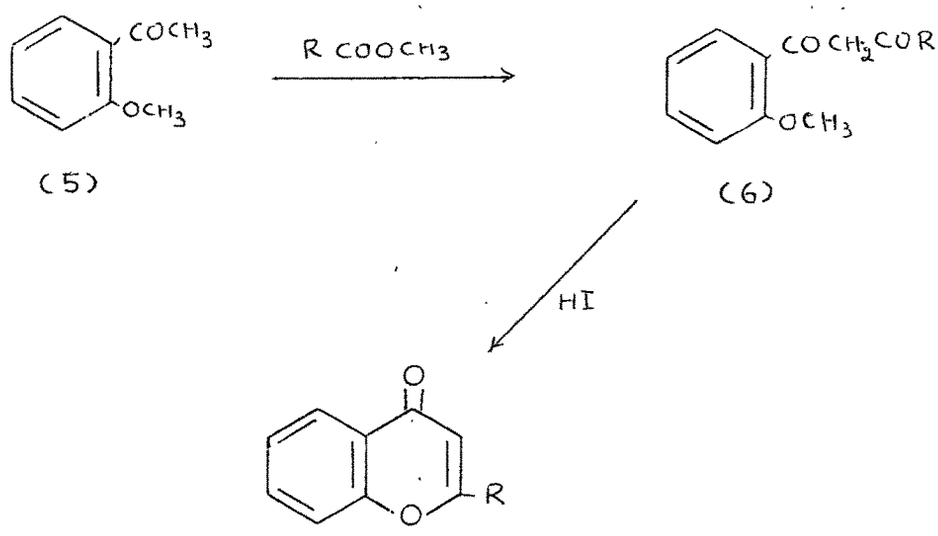
Considerable amount of work has been done on the effect of substituents like alkyl,[11,12,13] nitro,[14,15] carboxy and carbomethoxy[16,17,18] groups.

Ruhemann and coworkers[19] condensed sodium phenolets (3) with ethyl chlorofumarate, ethyl phenylpropiolate and ethyl β-chlorocrotonate. The intermediate acids (4) thus obtained were cyclised on treatment with con. sulphuric acid, phosphorous pentachloride or aluminium chloride to give chromones (2).



Kostanecki[20] found that when esters of aliphatic or aromatic acids were condensed with o-methoxyacetophenones (5), β-diketones (6) were formed which can be cyclised to chromones or flavones by heating with hydriodic acid. Alternately esters of o-methoxybenzoic acids can be condensed with ketones and the β-diketones formed cyclised with hydriodic acid to the corresponding chromones or flavones.

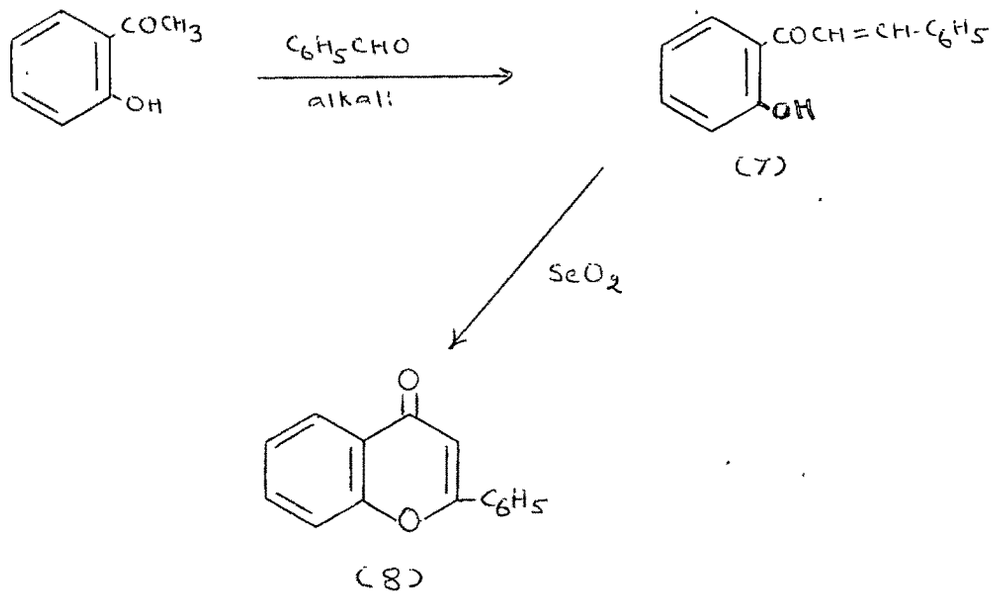
o-Hydroxyacetophenones on condensation with aromatic aldehydes in the presence of aqueous alkali or sodium ethylate yield chalkones (7). These can be converted directly into flavones (8) by heating with selenium dioxide[21]



(5) (6)

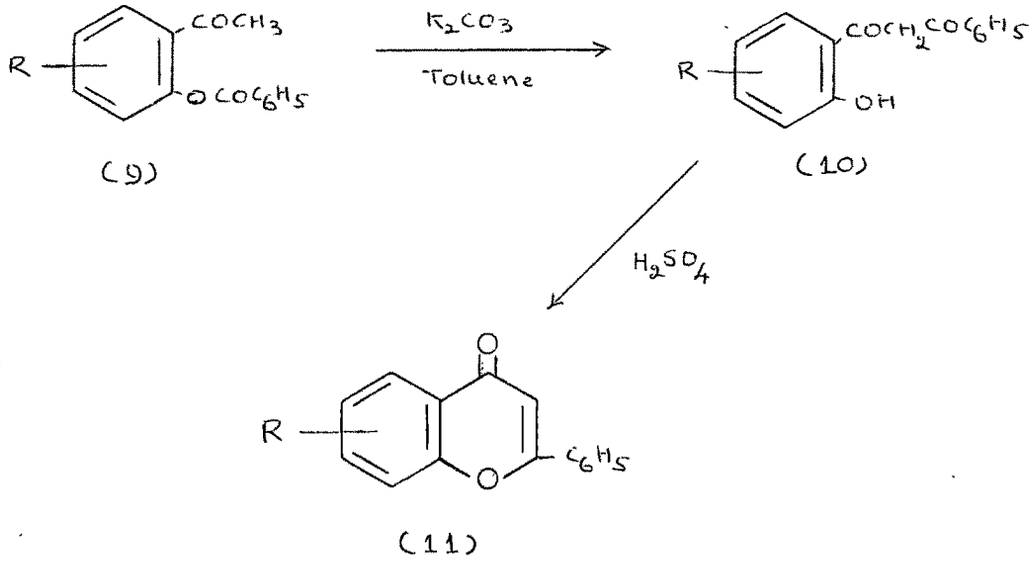
or cyclised first to flavenones by heating with a mineral acids and then subjected to phosphorøus pentachloride or selenium dioxide treatment[22,23].

The chalkones could be converted into the chalkone dibromides and then heated with alkali to get the flavones[24].



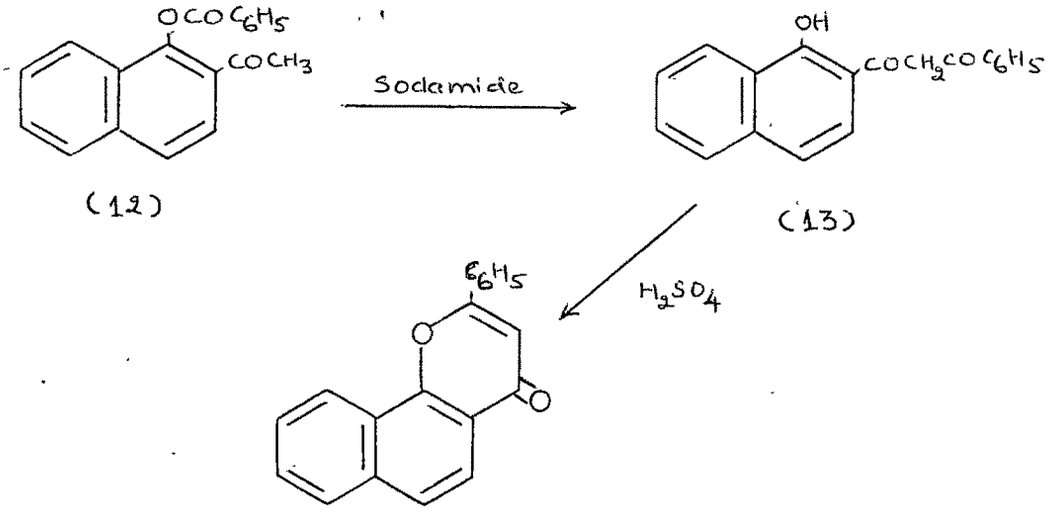
(7) (8)

Baker[25] observed that o-benzoyloxyaceto-arones or their derivatives (9) rearrange to o-hydroxydibenzoyl-methanes (10) when treated with anhydrous potassium carbonate in the presence of dry benzene or dry toluene which can be cyclised to the corresponding flavones (11) by treatment with suitable dehydrating agents such as sulphuric acid or boiling acetic acid and sodium acetate.



(9) (10) (11)

At about the same time Mahal and Venkataraman[26] observed that the action of sodamide on 2-acetyl-1-naphthyl-benzoate (12) in dry ether solution gave ω-benzoyl-2-acetyl-1-naphthol (13) which with sulphuric acid underwent cyclisation to yield corresponding flavone (14).



(12) (13) (14)

Many other reagents are also used to bring about this transformation like sodium metal[27] and sodium ethoxide[28].

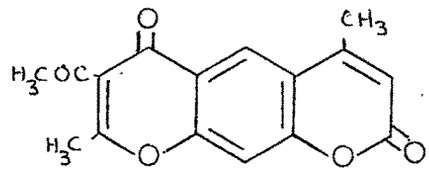
Mentzer and Pullon[29] found that if a phenol was heated with β-diketonic esters at a high temperature (about 250°) without any condensing agent, chromones were produced instead of coumarins.

Desai, Trivedi and Sethna[30] found that the reaction was more rapid and better products were obtained if diphenyl ether was used as a solvent and the reaction refluxed with a short condenser to remove the water formed.

By using some of these methods many workers have synthesised coumarino-γ-pyrones.

Desai and Hamid[31] carried out the Kostanecki-Robinson acetylation on 7-hydroxy-6-acetyl- and 7-hydroxy-8-acetyl-4-methylcoumarin and obtained 2,6-dimethyl-3-acetyl-4,8-dioxo-4H,8H-pyrano(3,2-g)benzopyran (4,2'-dimethyl-3'-acetylcoumarino-7,6-γ-pyrone) (15) and 2,8-dimethyl-3-

acetyl-4,6-dioxo-4H,6H-pyrano(2,3-h)benzopyran or (4,2'-dimethyl-3'-acetylcoumarino-7,8-γ-pyrone) (16).



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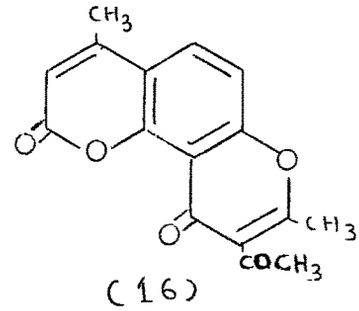
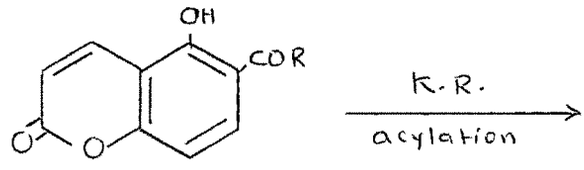


(16)

Shah and Shah[32] synthesised several coumarino-γ-pyrones (18) along with coumarino-α-pyrones when they subjected 5-hydroxy-6-acylcoumarins to Kostanecki-Robinson acylation.



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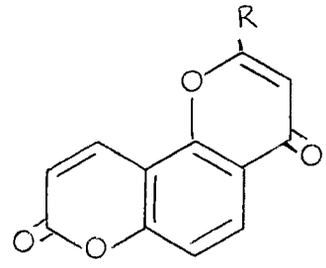
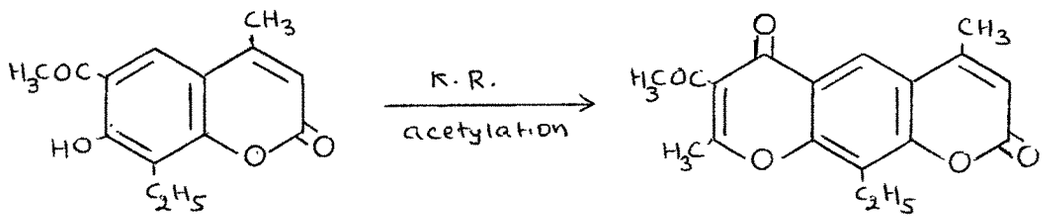


(18)

+

coumarino-α-pyrones.

Limaye and Ghate[33] obtained 2,6-dimethyl-10-ethyl-3-acetyl-4,8-dioxo-4H,8H-pyrano(3,2-g) benzopyran or (2',4-dimethyl-8-ethyl-3'-acetylcoumarino-γ-pyrone) (20) along with a coumarino-α-pyrone from 7-hydroxy-8-ethyl-6-acetyl-4-methylcoumarin (19) by Kostanecki-Robinson acetylation.

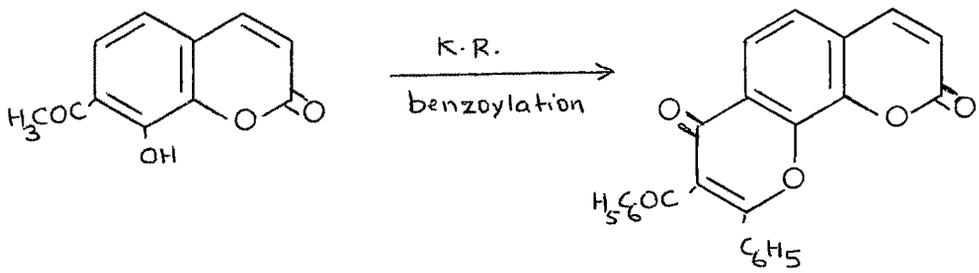


(20)

+

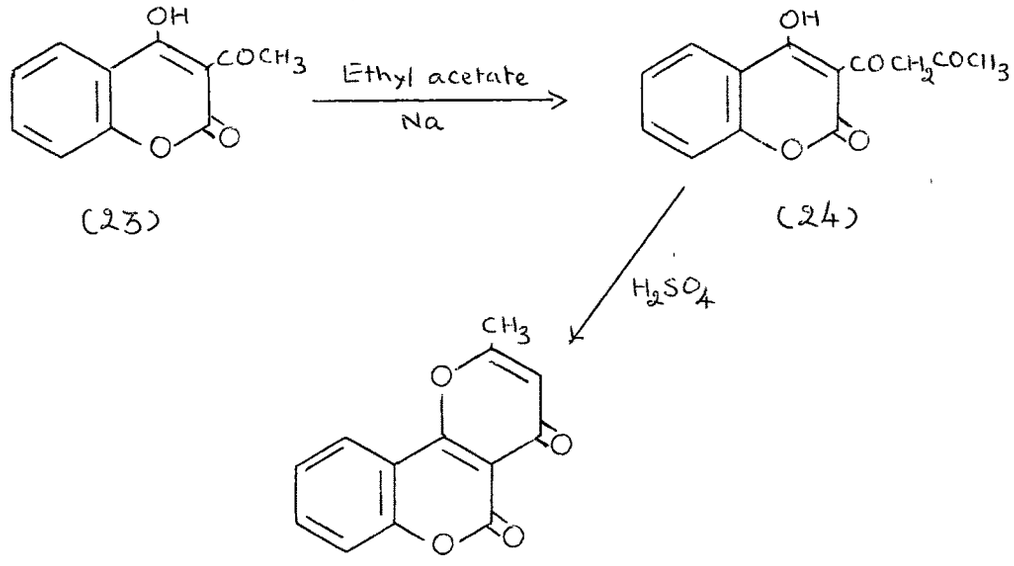
coumarino-α-pyrone

Mehta[34] carried out Kostanecki-Robinson benzoylation with benzoic anhydride and sodium benzoate on 8-hydroxy-7-acetylcoumarin (21) and obtained 2-phenyl-3-benzoyl-4,9-dioxo-4H,9H-pyrano(3,2-h)benzopyran or (2',3'-benzoyl-γ-pyrano(5',6',7,8)coumarin (22).

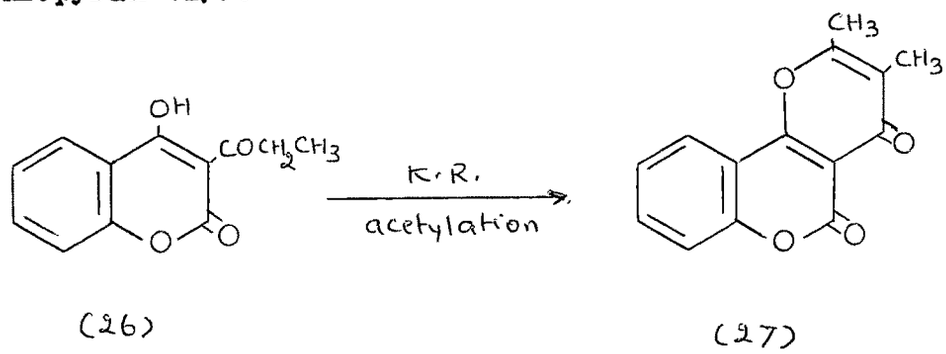


(21) (22)

Mustafa and coworkers[35] carried out Claisen condensation of 4-hydroxy-3-acetylcoumarin (23) with ethyl acetate in the presence of sodium to give an intermediate β-diketonic compound (24) which was cyclised by heating with sulphuric acid to 2-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (25).

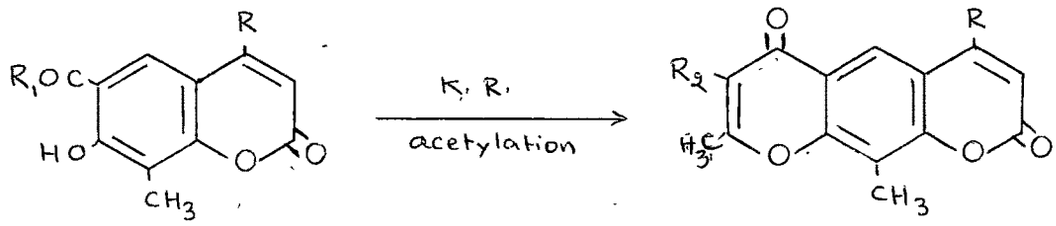


They also carried out Kostanecki-Robinson acetylation on 4-hydroxy-3-propionylcoumarin (26) and obtained 2,3-dimethyl-4,5-dioxo-4H,5H-pyrano(3,2-c) benzopyran (27).



Cook and McIntyre[36] carried out Kostanecki-Robinson acylation on 3-acyl-4-hydroxycoumarin derivatives and have obtained coumarino-α-pyrone and coumarino-γ-pyrano derivatives depending upon the acyl group, acid anhydride and sodium salt of the acid.

Recently Trivedi and coworkers[37] subjected 7-hydroxy-6-acetyl-4,8-dimethyl-, 7-hydroxy-6-acetyl-4-phenyl-8-methyl-, 7-hydroxy-6-propionyl-4,8-dimethyl- and 7-hydroxy-6-propionyl-4-phenyl-8-methylcoumarin (28) to Kostanecki-Robinson acetylation and obtained 7-acetyl-4,8,10-trimethyl-2,6-dioxo-2H,6H-pyrano(3,2-g)benzopyran, 7-acetyl-8,10-dimethyl-4-phenyl-2,6-dioxo-2H,6H-pyrano(3,2-g) benzopyran, 4,7,8,10-tetramethyl-2,6-dioxo-2H,6H-(3,2-g) benzopyran and 4-phenyl-7,8,10-trimethyl-2,6-dioxo-2H,6H-pyrano(3,2-g)benzopyran respectively (29). The structures of these coumarino-γ-pyrone derivatives were established on the basis of I.R.spectra.



(28) (29)

R = $-CH_3$, $-C_6H_5$

R_2= $-CH_3$, $-COCH_3$

R_1= $-CH_3$, $-C_2H_5$

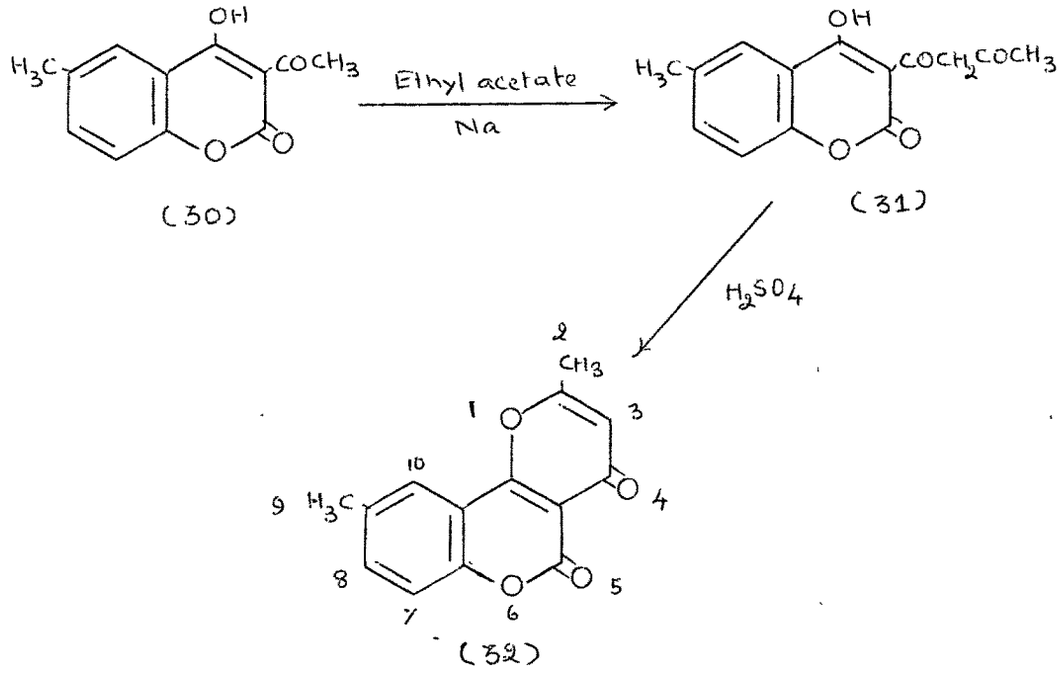
The present work deals with the synthesis of some coumarino-γ-pyrone derivatives.

Synthesis of 2,9-Dimethyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran :(32)

Claisen condensation of 3-acetyl-4-hydroxy-6-methyl-coumarin with ethyl acetate : 3-Acetoacetyl-4-hydroxy-6-methylcoumarin (31) :

4-Hydroxy-6-methylcoumarin was heated with glacial acetic acid in the presence of phosphorøus oxychloride to give 3-acetyl-4-hydroxy-6-methylcoumarin[38,39] (30).

3-Acetyl-4-hydroxy-6-methylcoumarin (30) on condensation with ethyl acetate in the presence of pulverised sodium gave the product to which 3-acetoacetyl-4-hydroxy-6-methylcoumarin (31) structure was assigned.



(30) (31) (32)

Cyclisation of 3-acetoacetyl-4-hydroxy-6-methyl-coumarin : 2,9-Dimethyl-4,5-dioxo-4H,5H-pyrano(3,2-c) benzopyran (32) :

3-Acetoacetyl-4-hydroxy-6-methylcoumarin on cyclisation with 25 % sulphuric acid gave the product to which the structure 2,9-dimethyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran (32) was assigned. Principal absorption bands in I.R.region 1760 and 1672 cm^{-1}.

Synthesis of 2-Methyl-8-hydroxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (35) :

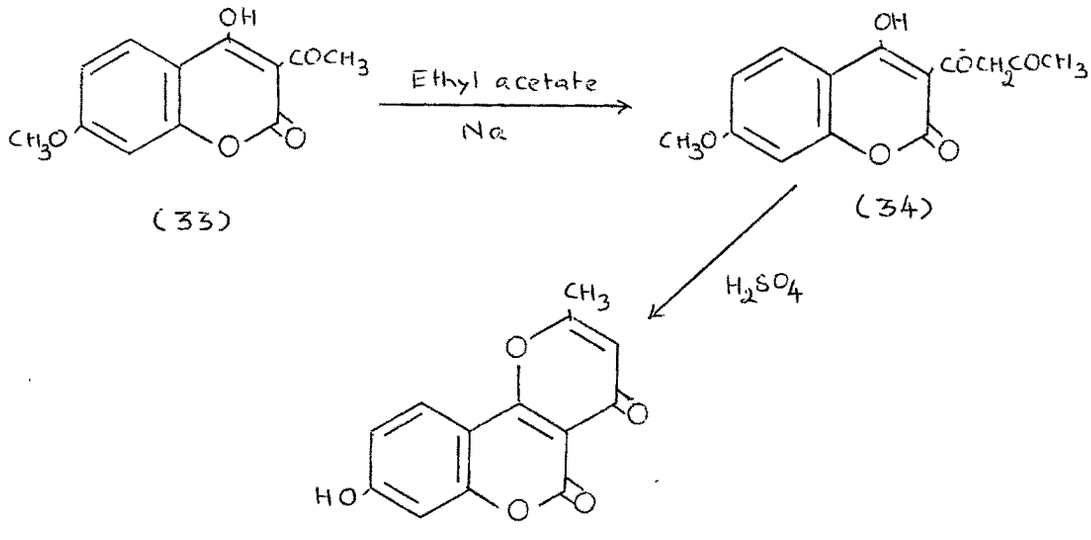
Claisen condensation of 3-acetyl-4-hydroxy-7-methoxy-coumarin with ethyl acetate : 3-Acetoacetyl-4-hydroxy-7-methoxycoumarin (34) :

3-Acetyl-4-hydroxy-7-methoxycoumarin[39] (33) was synthesised by condensing 4-hydroxy-7-methoxycoumarin with acetic acid in the presence of phosphorøus oxychloride. 3-Acetyl-4-hydroxy-7-methoxycoumarin (33) on Claisen condensation with ethyl acetate in the presence of sodium afforded 3-acetoacetyl-4-hydroxy-7-methoxycoumarin (34).

Cyclisation of 3-acetoacetyl-4-hydroxy-7-methoxy-coumarin : 2-Methyl-8-hydroxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (35) :

When 3-acetoacetyl-4-hydroxy-7-methoxycoumarin was heated with 25 % sulphuric acid, it cyclised but at the same time demethylation took place to give 2-methyl-8-hydroxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (35). Principal

absorption bands in I.R.region 1760 and 1672 cm^{-1}.



(33) (34) (35)

Synthesis of 2-Phenyl-9-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (37) :

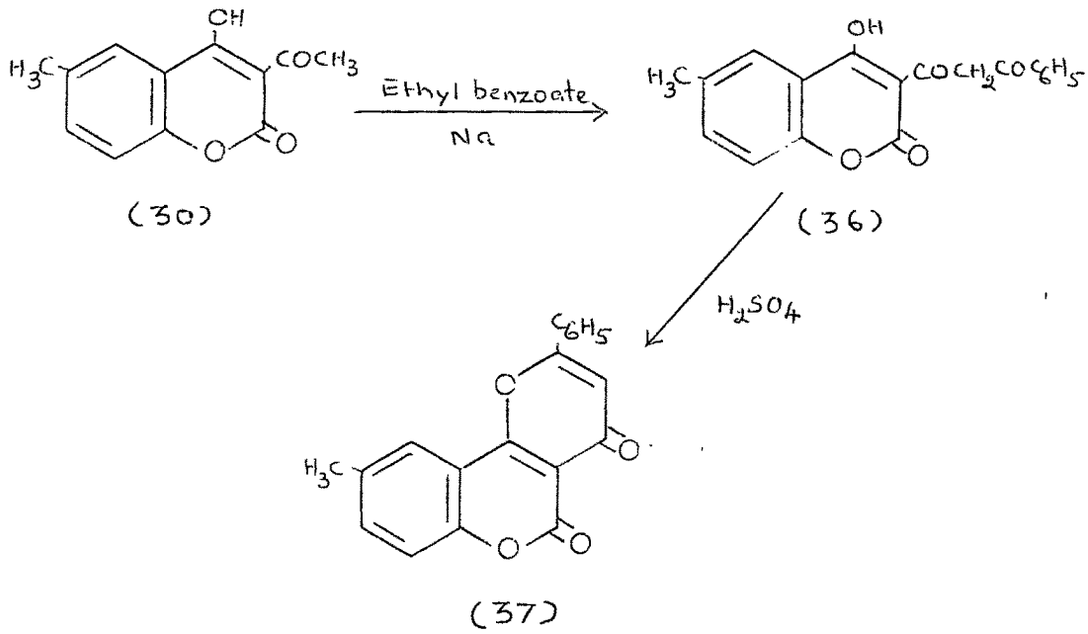
Claisen condensation of 3-acetyl-4-hydroxy-6-methylcoumarin with ethyl benzoate : 3-Benzoylacetyl-4-hydroxy-6-methylcoumarin (36) :

3-Acetyl-4-hydroxy-6-methylcoumarin (30) was condensed with ethyl benzoate in the presence of sodium to yield 3-benzoylacetyl-4-hydroxy-6-methylcoumarin (36).

Cyclisation of 3-benzoylacetyl-4-hydroxy-6-methylcoumarin : 2-Phenyl-9-methyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran (37) :

3-Benzoylacetyl-4-hydroxy-6-methylcoumarin (36) on cyclisation with alcoholic 50 % sulphuric acid gave the

product to which 2-phenyl-9-methyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran (37) structure was assigned.



Synthesis of 4,5-Dioxo-4H,5H-pyrano(3,2-c)benzopyran 2-carboxylic acid (39) :

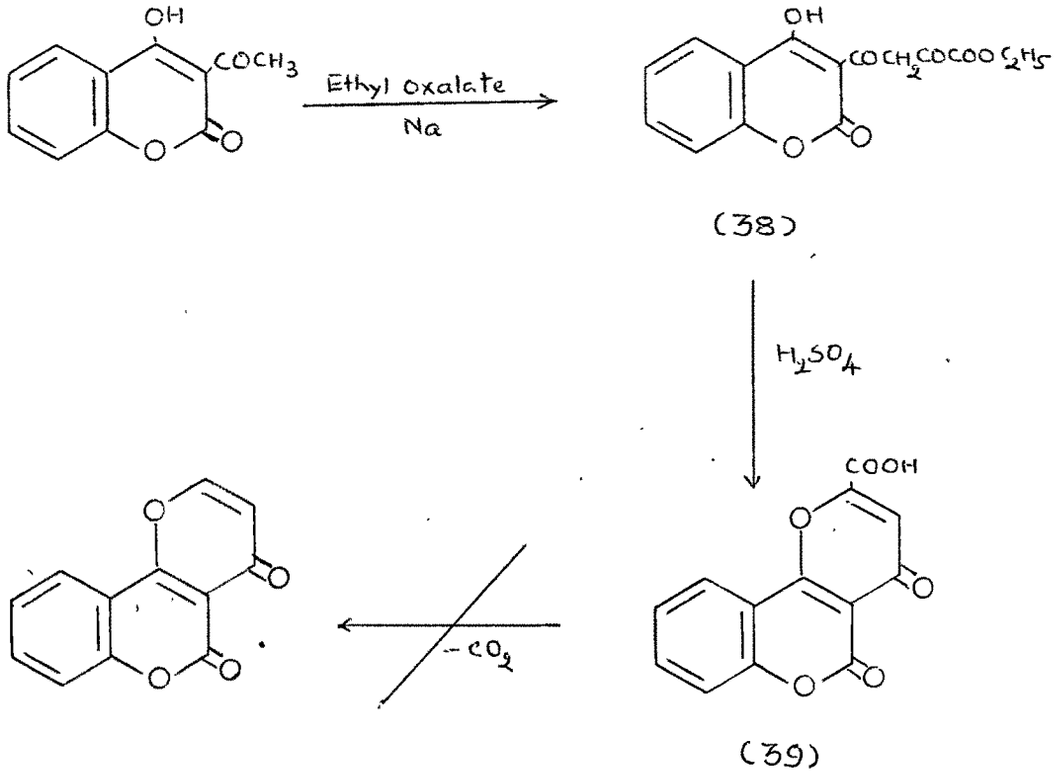
Claisen condensation of 3-acetyl-4-hydroxycoumarin with ethyl oxalate : 3-Oxalylacetyl-4-hydroxycoumarin (38):

3-Acetyl-4-hydroxycoumarin[38] on Claisen condensation with ethyl oxalate in the presence of sodium gave a product to which 3-oxalylacetyl-4-hydroxycoumarin (38) structure was assigned.

Cyclisation of 3-oxalylacetyl-4-hydroxycoumarin : 4,5-Dioxo-4H,5H-pyrano(3,2-c)benzopyran-2-carboxylic acid (39) :

3-Oxalylacetyl-4-hydroxycoumarin (38) on cyclisation with 50 % sulphuric acid gave the product which

was soluble in sodium bicarbonate solution. On the basis of analytical data 4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran-2-carboxylic acid (39) structure was assigned to it.



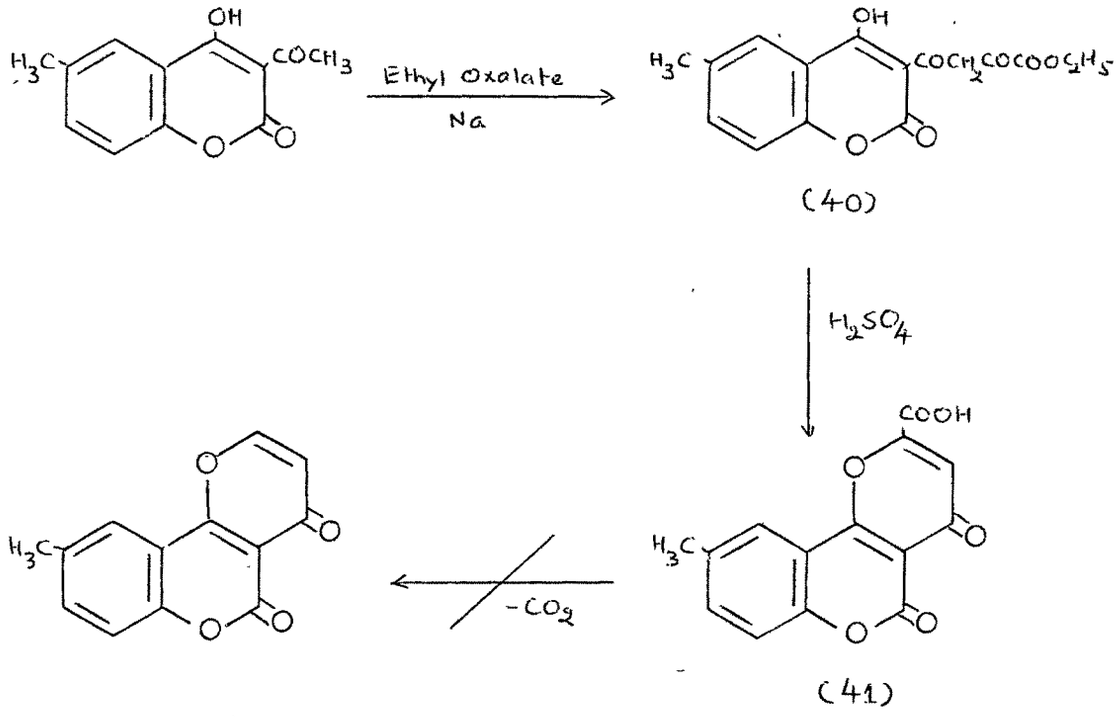
Attempted decarboxylation of 4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran-2-carboxylic acid :

When 4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran-2-carboxylic acid (39) was heated with copper and quinoline or heated above its melting point it gave an unworkable product.

Synthesis of 9-Methyl-4,5-dioxo-4H,5H-pyrano(3,2-c) benzopyran-2-carboxylic acid (41) :

Claisen condensation of 3-acetyl-4-hydroxy-6-methyl-coumarin with ethyl oxalate : 3-Oxalylacetyl-4-hydroxy-6-methylcoumarin (40) :

3-Acetyl-4-hydroxy-6-methylcoumarin (30) when condensed with ethyl oxalate in the presence of sodium it gave a β-dicarbonyl compound to which 3-oxalylacetyl-4-hydroxy-6-methylcoumarin (40) structure was assigned.



Cyclisation of 3-oxalylacetyl-4-hydroxy-6-methylcoumarin : 9-Methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran-2-carboxylic acid (41) :

3-Oxalylacetyl-4-hydroxy-6-methylcoumarin (40) on cyclisation with 50 % sulphuric acid gave a product which

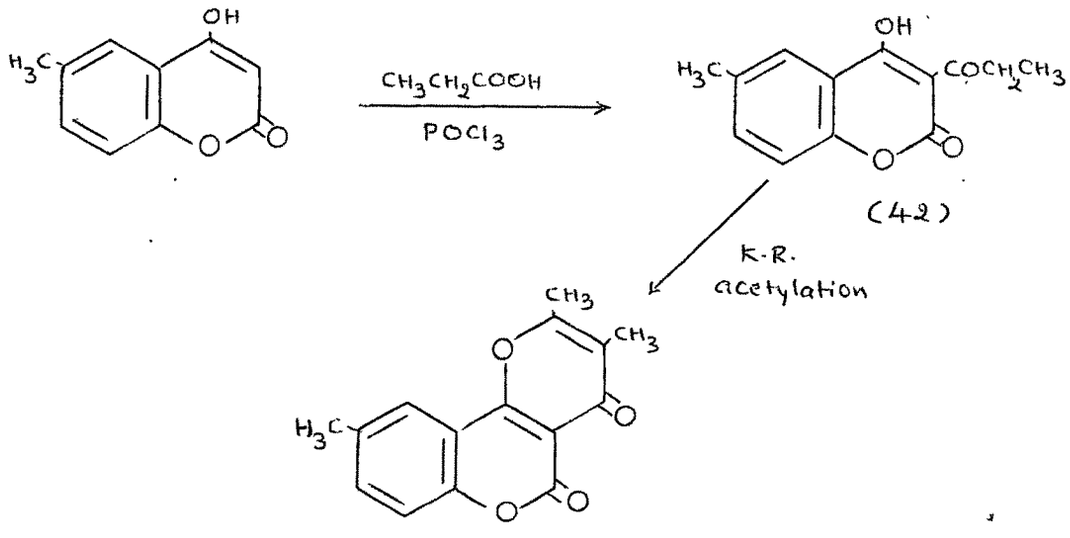
was soluble in sodium bicarbonate solution. On the basis of analytical data 9-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c) benzopyran-2-carboxylic acid (41) structure was assigned.

When 9-methyl-4,5-dioxo-4H,5H-pyrano (3,2-c) benzopyran-2-carboxylic acid (41) was heated with copper and quinoline or heated above its melting point it gave an unworkable product.

Kostanecki-Robinson Acetylation of 3-propionyl-4-hydroxy-6-methylcoumarin : 2,3,9-Trimethyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (43) :

3-Propionyl-4-hydroxy-6-methylcoumarin[38] (42) was prepared by heating 4-hydroxy-6-methylcoumarin with propionic acid in the presence of phosphorous oxychloride.

3-Propionyl-4-hydroxy-6-methylcoumarin (42) was heated with acetic anhydride and sodium acetate to give the product to which 2,3,9-trimethyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (43) structure was given.

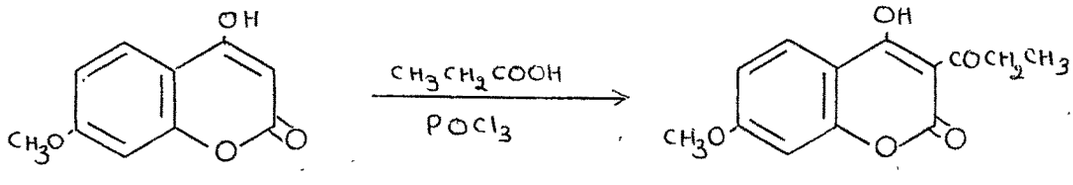


Friedel-Crafts propionylation of 4-hydroxy-7-methoxycoumarin : 3-Propionyl-4-hydroxy-7-methoxycoumarin (44) :

4-Hydroxy-7-methoxycoumarin when heated with propionic acid in the presence of phosphorous oxychloride it afforded 3-propionyl-4-hydroxy-7-methoxycoumarin (44). It gave red colouration with alcoholic ferric chloride solution.

Kostanecki-Robinson Acetylation of 3-propionyl-4-hydroxy-7-methoxycoumarin : 2,3-Dimethyl-8-methoxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (45) :

When 3-propionyl-4-hydroxy-7-methoxycoumarin was heated with sodium acetate and acetic anhydride it gave a product to which 2,3-dimethyl-8-methoxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran (45) structure was assigned.



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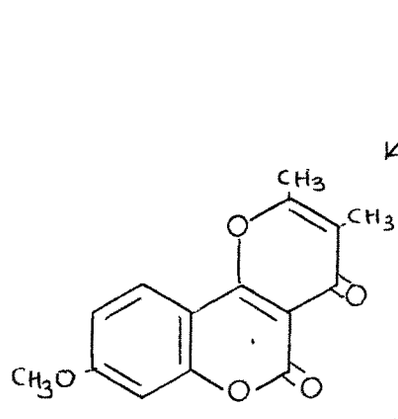
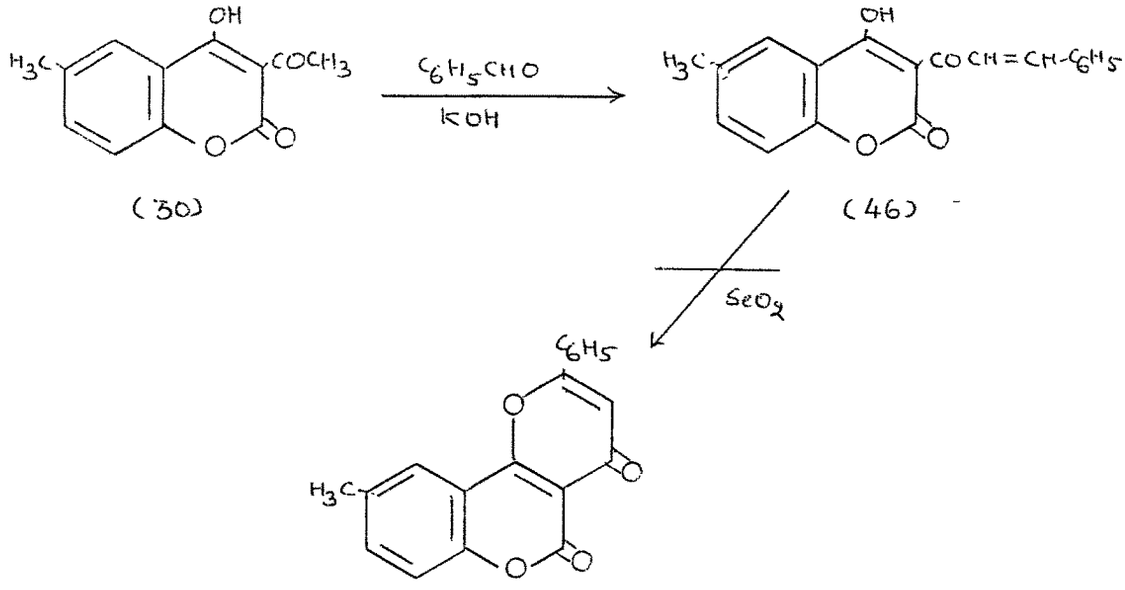


(45)

Chalkone synthesis : 3-Cinnamoyl-4-hydroxy-6-methyl-coumarin (46) :

3-Acetyl-4-hydroxy-6-methylcoumarin (30) was condensed with benzaldehyde in the presence of alcoholic potassium hydroxide to give a product to which 3-cinnamoyl-4-hydroxy-6-methylcoumarin (46) structure was assigned.

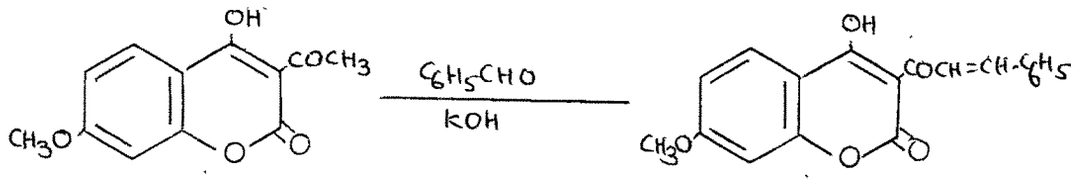


Attempted cyclisation of 3-cinnamoyl-4-hydroxy-6-methylcoumarin to 2-phenyl-9-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran :

When 3-cinnamoyl-4-hydroxy-6-methylcoumarin (46) was refluxed with selenium dioxide in isoamyl alcohol for 40 hr. only original chalkone was recovered.

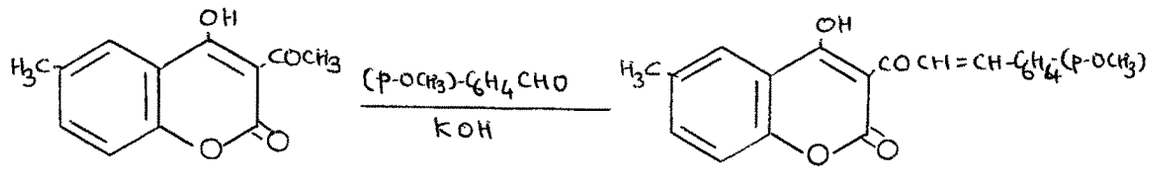
Chalkone synthesis : 3-Cinnamoyl-4-hydroxy-7-methoxy-coumarin (47) :

3-Acetyl-4-hydroxy-7-methoxycoumarin (33) was condensed with benzaldehyde in the presence of alcoholic potassium hydroxide to yield 3-cinnamoyl-4-hydroxy-7-methoxycoumarin (47).



Synthesis of 3-(p-Methoxy)-cinnamoyl-4-hydroxy-6-methylcoumarin (48) :

3-Acetyl-4-hydroxy-6-methylcoumarin (30) was condensed with anisaldehyde in the presence of alcoholic potassium hydroxide and the product was assigned 3-(p-methoxy)-cinnamoyl-4-hydroxy-6-methylcoumarin (48) structure.

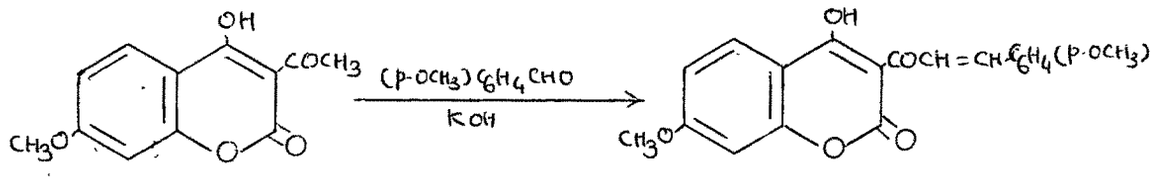


(30) (48)

Synthesis of 3-(p-Methoxy)cinnamoyl-4-hydroxy-7-methoxycoumarin (49) :

3-Acetyl-4-hydroxy-7-methoxycoumarin (33) was

condensed with anisaldehyde in the presence of alcoholic potassium hydroxide to yield a chalkone, 3-(p-methoxy)-cinnamoyl-4-hydroxy-7-methoxycoumarin (49).



(33) (49)

Attempted cyclisation of chalkones to the corresponding coumarino-γ-pyrones :

When above described 3-cinnamoyl-4-hydroxy-coumarin derivatives were heated with selenium dioxide in isoamyl alcohol for a very long time only original chalkone derivatives were recovered.

Attempted Baker-Venkataraman transformation on 3-acetyl-4-hydroxy-6-methylcoumarin to synthesise 2-phenyl-9-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c) benzopyran :

When 3-acetyl-4-hydroxy-6-methylcoumarin was refluxed with benzoyl chloride and potassium carbonate in dry acetone for 40 hr. it did not meet with success and only original coumarin was recovered.

Attempted Claisen condensation of 3-acetyl-4-hydroxy-coumarin with ethyl formate to synthesise 4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran :

When 3-acetyl-4-hydroxycoumarin was heated with ethyl formate in the presence of sodium it did not give the corresponding 4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran, but only the original compound was recovered.

EXPERIMENTAL

Synthesis of 2,9-Dimethyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran :

Claisen condensation of 3-acetyl-4-hydroxy-6-methyl-coumarin with ethyl acetate : 3-Acetoacetyl-4-hydroxy-6-methylcoumarin :

A solution of 3-acetyl-4-hydroxy-6-methyl-coumarin (1 g.) in freshly distilled ethyl acetate (25 ml.) was added to pulverised sodium (1 g.). The reaction mixture was heated on a water bath for 6 hr. After the completion of reaction a few ml. of ethanol were added to decompose unreacted sodium. It was then added to ice and water and ether extracted. The aqueous layer was acidified and the separated product was filtered,dried and crystallised from dil.acetic acid,m.p.153°. Yield 0.7 g.

Analysis : Found : C,64.49 ; H,4.72 %.

$C_{14}H_{12}O_5$ requires : C,64.61 ; H,4.65 %.

Cyclisation of 3-aceetoacetyl-4-hydroxy-6-methyl-coumarin : 2,9-Dimethyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran :

3-Acetoacetyl-4-hydroxy-6-methylcoumarin (0.5 g.) was heated with sulphuric acid (50 ml. ; 25 %) on a sand bath for 1 hr. The reaction mixture was allowed to cool and neutralised with sodium carbonate. The separated product was filtered,dried and crystallised from dil.

acetic acid, m.p. 248°. Yield 0.2 g. Principal absorption bands in I.R. region 1760 and 1672 cm^{-1}.

Analysis : Found : C, 69.69 ; H, 3.76 %.

$C_{14}H_{10}O_4$ requires : C, 69.42 ; H, 4.16 %.

Synthesis of 2-Methyl-8-hydroxy-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran :

Claisen condensation of 3-acetyl-4-hydroxy-7-methoxy-coumarin with ethyl acetate : 3-Acetoacetyl-4-hydroxy-7-methoxycoumarin :

A solution of 3-acetyl-4-hydroxy-7-methoxy-coumarin (1 g.) in ethyl acetate (25 ml.) was added to pulverised sodium (1 g.) and the reaction mixture was refluxed on a water bath for 6 hr. The reaction mixture was decomposed with ice and water and ether extracted. The aqueous layer was acidified and the separated product was filtered, dried and crystallised from dil. acetic acid, m.p. 153°. Yield 0.8 g.

Analysis : Found : C, 60.95 ; H, 4.23 %.

$C_{14}H_{12}O_6$ requires : C, 60.87 ; H, 4.38 %.

Cyclisation of 3-acetoacetyl-4-hydroxy-7-methoxy-coumarin : 2-Methyl-8-hydroxy-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran :

3-Acetoacetyl-4-hydroxy-7-methoxycoumarin (0.7 g.) was refluxed in sulphuric acid (75 ml. ; 25 %) on a sand bath for 1 hr. The reaction mixture was allowed to cool and neutralised with sodium carbonate. The separated

product wasfiltered and purified by the treatment with dilute sodium hydroxide solution. On acidification the product was separated,which was filtered,dried and crystallised from dil.acetic acid, m.p. 221°. Yield 0.3 g. Principal absorption bands in I.R.region 1760 and 1672 cm^{-1}.

Analysis : Found : C,63.44 ; H,3.80 %.

$C_{13}H_8O_5$ requires : C,63.94 ; H,3.30 %.

Synthesis of 2-Phenyl-9-methyl-4,5-dioxo-4H,5H-pyrano-(3,2-c)benzopyran :

Claisen condensation of 3-acetyl-4-hydroxy-6-methylcoumarin with ethyl benzoate : 3-Benzoylacetyl-4-hydroxy-6-methylcoumarin :

A mixture of 3-acetyl-4-hydroxy-6-methylcoumarin (1 g.),ethyl benzoate (25 ml.) and pulverised sodium(1 g.) was heated in an oil bath at 180° for 5 hr. After the completion of reaction little alcohol was added to decompose unreacted sodium and then added to water. It was ether extracted and aqueous layer was acidified. The separated product was filtered,dried and crystallised from dil.acetic acid, m.p.168°. Yield 0.4 g.

Analysis : Found : C,70.72 ; H,4.47 %.

$C_{19}H_{14}O_5$ requires : C,70.80 ; H,4.38 %.

Cyclisation of 3-benzoylacetyl-4-hydroxy-6-methylcoumarin : 2-Phenyl-9-methyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran :

3-Benzoylacetyl-4-hydroxy-6-methylcoumarin(0.4 g.)

was heated with alcoholic sulphuric acid (50 ml. ; 50 %.) on a sand bath for 2 hr. The reaction mixture was diluted with water and the separated product was filtered,washed with sodium bicarbonate solution,dried and crystallised from dil.acetic acid, m.p. 275°. Yield 0.2 g.

Analysis : Found : C,74.69 ; H,4.05 %.
$C_{19}H_{12}O_4$ requires : C,74.99 ; H,3.97 %.

Synthesis of 4,5-Dihydro-4H,5H-pyrano(3,2-c) benzopyran-2-carboxylic acid :

Claisen condensation of 3-acetyl-4-hydroxycoumarin with ethyl oxalate : 3-Oxalylacetyl-4-hydroxycoumarin :

A mixture of 3-acetyl-4-hydroxycoumarin (1 g.) , ethyl oxalate (12 ml.) and pulverised sodium (1 g.) was heated on a steam bath for 6 hr. After the completion of reaction little alcohol was added to decompose unreacted sodium and then added to ice and water. It was then ether extracted and aqueous layer was acidified. The separated product was filtered,dried and crystallised from acetic acid, m.p. 168°. Yield 0.6 g.

Analysis : Found : C,59.14 ; H,3.85 %.
$C_{15}H_{12}O_7$ requires : C,59.21 ; H,3.98 %.

Cyclisation of 3-oxalylacetyl-4-hydroxycoumarin : 4,5-Dioxo-4H,5H-pyrano(3,2-c)benzopyran-2-carboxylic acid :

3-Oxalylacetyl-4-hydroxycoumarin (0.5 g.) was heated with sulphuric acid (25 ml. ; 50 %) on a sand bath for 2 hr. The reaction mixture was diluted with water and the separated product was filtered,treated with sodium bicarbonate solution,dried and crystallised from acetic acid, m.p. 270°. Yield 0.2 g.

Analysis : Found : C,60.22 ; H,2.05 %.

$C_{13}H_6O_6$ requires : C,60.47 ; H,2.34 %.

Attempted decarboxylation of 4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran-2-carboxylic acid :

4,5-Dioxo-4H,5H-pyrano(3,2-c)benzopyran (0.5 g.) was dissolved in freshly distilled quinoline (4 ml.) and was refluxed with copper bronze (0.1 g.). The reaction mixture was decomposed with ice and hydrochloric acid and then ether extracted. On evaporation of ether an unworkable product was obtained. Attempt to decarboxylate the acid by heating above its melting point also met with failure.

Synthesis of 9-Methyl-4,5-dioxo-4H,5H-pyrano(3,2-c) benzopyran-2-carboxylic acid :

Claisen condensation of 3-acetyl-4-hydroxy-6-methyl-coumarin with ethyl oxalate : 3-Oxalylacetyl-4-hydroxy-6-methylcoumarin :

A mixture of 3-acetyl-4-hydroxy-6-methylcoumarin

(1 g.),ethyl oxalate (12 ml.) and pulverised sodium (1 g.) was heated on a steam bath for 6 hr. The reaction mixture was poured into ice and water and extracted with ether. The aqueous layer was acidified and the separated product was filtered,dried and crystallised from acetic acid,m.p.169°. Yield 0.7 g.

Analysis : Found : C,60.14 ; H,4.04 %.

$C_{16}H_{14}O_7$ requires : C,60.38 ; H,4.43 %.

Cyclisation of 3-oxalylacetyl-4-hydroxy-6-methylcoumarin : 9-Methyl-4,5-dioxo-4H,5H-pyrano(3,2-c) benzopyran-2-carboxylic acid :

3-Oxalylacetyl-4-hydroxy-6-methylcoumarin (0.5 g.) was refluxed with sulphuric acid (25 ml. ; 50 %) on a sand bath for 2 hr. The reaction mixture was poured into ice and water and the separated product was filtered,treated with sodium bicarbonate solution and crystallised from acetic acid,m.p.262°. Yield 0.2 g.

Analyais : Found : C,61.52 ; H,2.88 %.

$C_{14}H_8O_6$ requires : C,61.77 ; H,2.96 %.

Attempted decarboxylation of 9-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran-2-carboxylic acid :

9-Methyl-4,5-dioxo-4H,5H-pyrano(3,2-c)benzopyran-2-carboxylic acid (0.5 g.) was dissolved in freshly distilled quinoline (4 ml.) and was heated with copper bronze(0.1 g.) on a sand bath for 1 hr. On working up the reaction

mixture as usual an unworkable product was obtained.

K.R.Acetylation of 3-propionyl-4-hydroxy-6-methyl-coumarin : 2,3,9-Trimethyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran :

A mixture of 3-propionyl-4-hydroxy-6-methyl-coumarin (1 g.), freshly fused sodium acetate (3 g.) and acetic anhydride (20 ml.) was heated in an oil bath at 140-60° for 6 hr. The reaction mixture was cooled and poured into ice and water. The separated product was filtered,washed with sodium bicarbonate solution,dried and crystallised from dil.acetic acid, m.p.247°. Yield 0.3 g.

Analysis : Found : C,70.00 ; H,4.30 %.

$C_{15}H_{12}O_4$ requires : C,70.30 ; H,4.72 %.

Friedel-Crafts propionylation of 4-hydroxy-7-methoxy-coumarin : 3-Propionyl-4-hydroxy-7-methoxycoumarin :

A mixture of 4-hydroxy-7-methoxycoumarin (3 g.), propionic acid (15 ml.) and phosphorous oxychloride (6 ml.) was refluxed on a wire gauze for 45 minutes. The reaction mixture was decomposed with ice and water. The separated product was filtered,dried and crystallised from acetic acid,m.p.168°. Yield 1.5 g.

Analysis : Found : C,62.91 ; H,4.67 %.

$C_{13}H_{12}O_5$ requires : C,62.90 ; H,4.87 %.

K.R.Acetylation of 3-propionyl-4-hydroxy-7-methoxy-coumarin : 2,3-Dimethyl-8-methoxy-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran :

A mixture of 3-propionyl-4-hydroxy-7-methoxy-coumarin (1 g.),freshly fused sodium acetate (3 g.) and acetic anhydride (20 ml.) was heated in an oil bath at 140-60° for 6 hr. The reaction mixture was decomposed with ice and water and the separated product was filtered, dried and crystallised from dil.acetic acid,m.p.228°. Yield 0.4 g.

Analysis : Found : C,66.05 ; H,4.47 %.

$C_{15}H_{12}O_5$ requires : C,66.17 ; H,4.44 %.

Chalkone synthesis : 3-Cinnamoyl-4-hydroxy-6-methyl-coumarin :

4-Hydroxy-3-acetyl-6-methylcoumarin (1 g.) was dissolved in ethanol (20 ml.) and to the solution benzaldehyde (1 ml.) and potassium hydroxide solution (10 ml. ; 50 %) were added. The mixture was shaken and kept for 3 days at room temperature. It was diluted with water and extracted with ether. The aqueous layer was acidified and the separated product was filtered,dried and crystallised from acetic acid,m.p.207°.Yield 0.8 g.

Analysis : Found : C,74.44 ; H,4.62 %.

$C_{19}H_{14}O_4$ requires : C,74.45 ; H,4.60 %.

Attempted cyclisation of 3-cinnamoyl-4-hydroxy-6-methylcoumarin to 2-phenyl-9-methyl-4,5-dioxo-4H,5H-pyrano (3,2-c)benzopyran :

3-Cinnamoyl-4-hydroxy-6-methylcoumarin (0.7 g.) was refluxed with selenium dioxide (1 g.) in isoamyl alcohol (10 ml.) on a wire gaize for 40 hr. Isoamyl alcohol was then steam distilled and the separated product was found to be the original coumarin .

3-Cinnamoyl-4-hydroxy-7-methoxycoumarin :

To a solution of 4-hydroxy-3-acetyl-7-methoxycoumarin (1 g.) in ethanol (25 ml.), benzaldehyde (1 ml.) and potassium hydroxide solution (10 ml. ; 50 %) were added and the reaction mixture was kept for 3 days at room temperature. On working up the reaction mixture as usual the product was obtained which crystallised from acetic acid, m.p.236°. Yield 0.8 g.

Analysis : Found : C,70.33 ; H,4.11 %.

$C_{19}H_{14}O_5$ requires : C,70.80 ; H,4.38 %.

3-(p-Methoxy)cinnamoyl-4-hydroxy-6-methylcoumarin :

To a solution of 4-hydroxy-3-acetyl-6-methylcoumarin (1 g.) in ethanol (20 ml.), anisaldehyde (1 ml.) and potassium hydroxide solution (10 ml. ; 50 %)were added gradually with stirring and kept for 3 days at room temperature. The reaction mixture was worked up as usual and the product crystallised from acetic acid, m.p.218°. Yield 0.6 g.

Analysis : Found : C,71.89 ; H,5.15 %.

$C_{20}H_{16}O_5$ requires : C,71.42 ; H,4.80 %.

3-(p-Methoxy)cinnamoyl-4-hydroxy-7-methoxycoumarin :

To a solution of 4-hydroxy-3-acetyl-7-methoxy-coumarin (1 g.) in ethanol (20 ml.),anisaldehyde (1 ml.) and potassium hydroxide solution (10 ml. ; 50 %) were added with stirring and was kept for 3 days at room temperature. The reaction mixture was worked up as usual and the product crystallised from acetic acid,m.p.213°. Yield 0.6 g.

Analysis : Found : C,67.70 ; H,4.70 %.

$C_{20}H_{16}O_6$ requires : C,68.18 ; H,4.58 %.

Attempted cyclisation of 3-cinnamoyl-4-hydroxy-7-methoxycoumarin, 3-(p-methoxy)-cinnamoyl-4-hydroxy-6-methylcoumarin and 3-(p-methoxy)-cinnamoyl-4-hydroxy-7-methoxycoumarin to corresponding coumarino-y-pyrone derivatives :

A mixture of 3-cinnamoyl-4-hydroxycoumarin derivative (0.5 g.),isoamyl alcohol (5 ml.) and selenium dioxide (0.5 g.) was heated on a wire gauze for 40 hr. The reaction mixture was filtered hot and isoamyl alcohol was steam distilled. The separated product was found to be unchanged 3-cinnamoyl-4-hydroxycoumarin derivative.

Attempted Baker-Venkataraman transformation on 3-acetyl-4-hydroxy-6-methylcoumarin to synthesise 2-phenyl-9-methyl-4,5-dioxo-4H,5H-pyrano(3,2-c) benzopyran :

A mixture of 4-hydroxy-3-acetyl-6-methylcoumarin (1 g.),anhydrous potassium carbonate (3 g.) and benzoyl chloride (1.5 ml.) in dry acetone (30 ml.) was refluxed on a steam bath for 40 hr. On evaporation of acetone and working up as usual original coumarin was isolated.

Attempted Claisen condensation of 3-acetyl-4-hydroxy-coumarin with ethyl formate :

A mixture of 3-acetyl-4-hydroxycoumarin (1 g.), ethyl formate (20 ml.) and pulverised sodium (1 g.) was refluxed on a water bath for 10 hr. The reaction mixture was filtered and the separated product on evaporation of acetone was found to be the original coumarin.

REFERENCES

1. J.F.Couch and C.F.Krewson, U.S.Dept. Agr., Eastern Regional Research Lab., AIC 52, 4 (1944); C.A., 39, 4326 (1945).
2. R.H.Higby., J.Am.Pharm.Assoc., 32, 74 (1943).
3. H.Nakamura, T.Ota and G.Fukuchi., J.Pharm.Soc., Japan, 56, 68 (1936) ; C.A., 32, 5833 (1938).
4. V.V.S.Murti, N.V.S.Rao and T.R.Seshadri., Proc.Indian Acad.Sci., 25A, 22 (1947).
5. N.Viswanadham and T.R.Seshadri., Proc.Indian Acad. Sci., 25A, 337 (1947).
6. P.Da Re et al., Farmaco(Pavia) Ed.Sci., 13, 561 (1958); C.A., 54, 517 (1960).
7. Kostanecki and A.Rozycki., Ber., 34, 702 (1901).
8. J.Allan and R.Robinson., J.Chem.Soc., 2192 (1924).
9. G.Bargellini., Atti.R.Accad.Lincei., 2, 178,261 (1925).; C.A., 20, 594 (1926).
10. W.Baker and F.M.Eastwood., J.Chem.Soc., 2897 (1929).
11. G.Wittig., Ber., 57B, 88 (1924).
12. D.Chakravarti and P.N.Bagchi., J.Indian Chem.Soc., 13, 689 (1936).
13. D.Chakravarti and B.Majumdar., J.Indian Chem.Soc., 16, 151 (1939).
14. W.Baker., J.Chem.Soc., 261 (1930).
15. R.M.Naik and V.M.Thakor., Proc.Indian Acad.Sci., 37A, 774 (1953).

16. B.M.Desai and R.D.Desai., J.Sci.Ind.Res. India., 13B, 249 (1954).

17. G.G.Joshi and N.M.Shah., J.Indian Chem.Soc.,31, 223(1954).

18. R.D.Desai and coworkers., J.Indian Chem.Soc., 37, 491 (1960).

19. S.Ruhemann and coworkers., J.Chem.Soc., 77, 1185 (1900); Ber., 46, 2188 (1913) ; 53, 285 (1920).

20. Kostanecki., Ber., 33, 330,471 (1900).

21. H.S.Mahal, H.S.Rai and K.Venkataraman., J.Chem.Soc., 866 (1935).

22. Kostanecki and Szabranski., Ber., 37, 2634 (1904).

23. A.Lowenbein., Ber., 57, 1515 (1925).

24. T.S.Wheeler et al., J.Chem.Soc., 1798 (1937).

25. W.Baker., J.Chem.Soc., 1386 (1933).

26. H.S.Mahal and K.Venkataraman., Current Sci., 2, 214 (1933) ; J.Chem.Soc., 1767 (1934).

27. V.V.Virkar and T.S.Wheeler., J.Chem.Soc., 1679 (1939).

28. V.V.Ullal, R.C.Shah and T.S.Wheeler., J.Chem.Soc., 1499 (1940) ; J.Univ.Bombay., X(3), 118 (1941).

29. C.Mentzer and D.Pillon., Bull.Soc.Chim.France., 538 (1953) ; C.A., 48, 8779 (1954).

30. K.B.Desai, K.N.Trivedi and S.Sethna., J.M.S.Univ. of Baroda., IV,No.2 (1955).

31. R.D.Desai and S.A.Hamid., Proc.Indian Acad.Sci., 6A, 185 (1937).

32. N.M.Shah and R.C.Shah., J.Chem.Soc., 228, 1424 (1938).

33. D.B.Limaye and I.Ghate., Rasayanam., 1, 169 (1939).

34. R.H.Mehta., Indian J.Chem., 3(4), 186 (1965).

35. A.Mustafa and coworkers., Tetrahedron., 19, 1831 (1963).

36. D.Cook and J.S.McIntyre., J.Org.Chem., 33, 1746 (1968).

37. (Miss) N.H.Pardanani, M.G.Parekh and K.N.Trivedi., J.Indian Chem.Soc., 47, 36 (1970).

38. J.Klosa., Arch.Pharm., 289, 104,156 (1956).

39. G.G.Badcock, F.M.Dean and A.Robertson., J.Chem.Soc., 908 (1950).