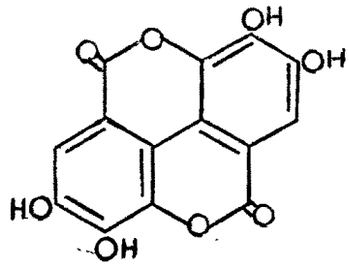
CHAPTER I

STUDIES IN THE SYNTHESES OF CYCLOHEXENOCOUMARINS

Studies in the syntheses of cyclohexenocoumarins

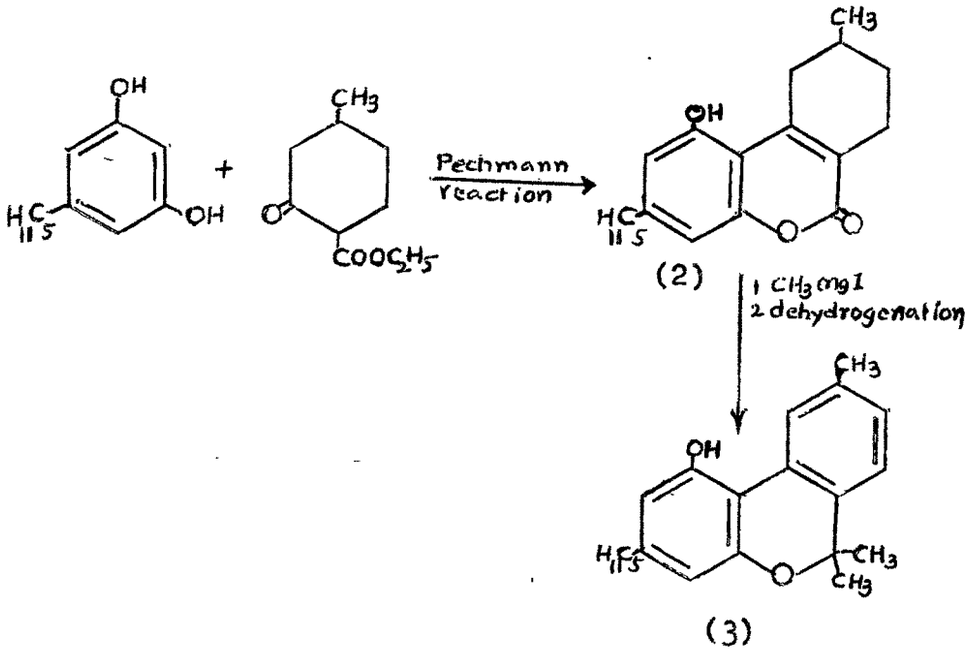
About ninety coumarins compose one of the most important groups of natural products[1-3]. All but six or so are derived from plants, especially Leguminosae, Orchidaceae, Rutaceae and Umbelliferae, the others coming from animals or micro-organisms. A few coumarins-coumarin itself, dihydrocoumarin[4], psoralene[5]-occur as glycosides of the corresponding o-hydroxycinnamic acids. Some 3,4-benzocoumarins are known of which ellagic acid (I), is one of the most common yellow pigments in the plant world.



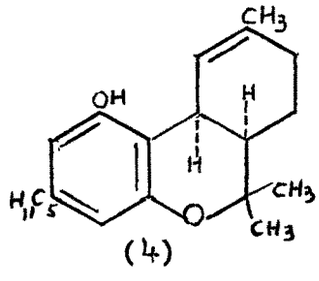
(1)

The crude resin obtained from the flowering tops of female plants of several Cannabiss sativa L. varieties has been known and used as a psychotomimetic agent for many years[6-8]. The structure of this material, known variously as marihuana, hashish, etc., had evaded elucidation for many years, and has been obtained synthetically by Todd *et al.*[9] and Adams *et al.*[10] Olivetol in a Pechmann condensation with β-oxo-ester affords the cyclohexenocoumarin (2), the orientation of which, unusual in the resorcinol series, is directed by the steric factor

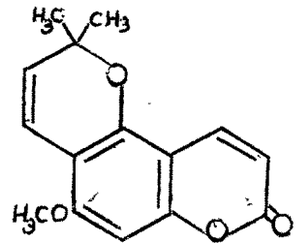
imposed by the amyl side chain. Interaction of (2) with methyl magnesium iodide followed by dehydrogenation, supplies Cannabinol (3).



Recently the components of marihuana have received renewed attention. In 1964, Gaoni and Mechoulam[11] on the basis of nmr studies, and Santavy[12], on the basis of infrared studies and molecular rotation differences, determined the complete structure of the major physiologically active constituent, 1 - Δ^9- tetrahydrocannabinol (4). Recently the total synthesis of dl - Δ^9- tetrahydrocannabinol and four of its isomers has been described by Fahrenholtz et al.[13]



Alloxanthoxyletin, an another cyclohexenocoumarin derivative from Xanthoxylum americanum Mill., has been allocated structure (5)[14], and Calophyllolide which can be extracted from the nuts of the Tahitian tree, Calophyllum inophyllum has the structure (6)[15].



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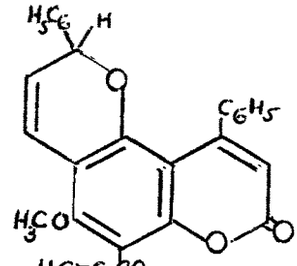
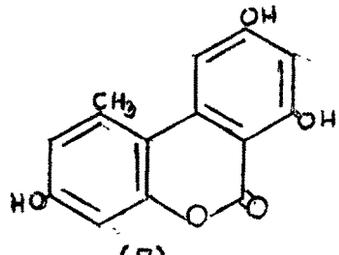


(6)

The fungus Alternaria tenuis produces the sole known fungal 3,4-benzocoumarin, alternariol (7), together with a methyl ether. A.tenuis is weakly parasitic on some plants, but is chiefly a saprophyte and a nuisance in the paper and flax industries, because it can destroy both pectin and cellulose, rotting fibres and discolouring wood pulp[16]. Lederer[17] has shown that the yellow colour of the secretion, Castoreum pigment from the scent glands of the



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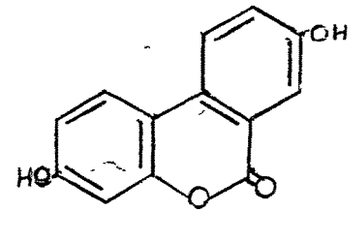


(8)

beaver, is due to the presence of two benzocoumarins out of which one is 2',7-dihydroxy-3,4-benzocoumarin (8).

Sen and Basu[18] studied the reaction between ethyl cyclohexanone-2-carboxylate and phenols and obtained benzo-α-pyrones. According to the theory of Jacobson and Ghosh[19], the γ-pyrones should be expected in this reaction. The structure of α-pyrones is based on the observation that keto nitriles of the type -COCCN when condensed with phenols give rise to the formation of imino compounds which yield α-pyrones on hydrolysis[20]. By hydrolysis of the condensation product prepared from 2-cyanocyclohexanone and resorcinol a compound identical with that prepared by condensation of resorcinol with ethyl cyclohexanone-2-carboxylate was obtained.

The present work has been carried out to synthesize different cyclohexenocoumarins in which cyclohexene ring is fused in 5,6-positions of the coumarin ring systems.

The work deals with the syntheses of the following cyclohexenocoumarins :

(a) 7-Methoxy-4-methyl-4'-ketocyclohexeno(5',6',5,6)coumarin

(b) 4-Methyl-4'-ketocyclohexeno(5',6',5,6)benzo(h)coumarin

(c) 4-Phenylcyclohexeno(h)coumarin.

(a) Synthesis of 7-methoxy-4-methyl-4'-ketocyclohexeno (5',6',5,6)coumarin (26) :

For the synthesis of compound (26), the starting material required was β-(2,4-dihydroxybenzoyl)propionic acid (9)

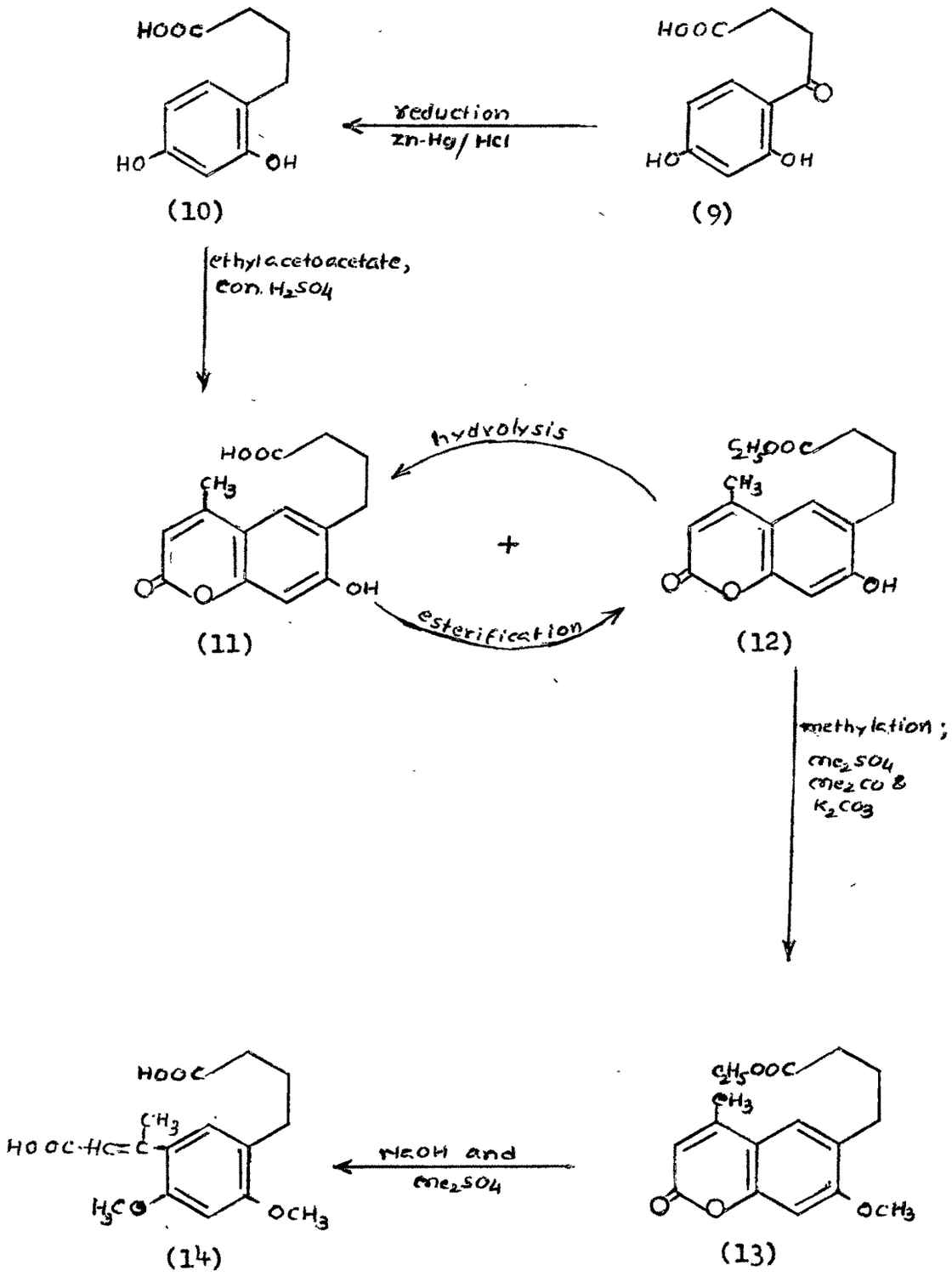
which was obtained by the Friedel-Craft's succinoylation of resorcinol according to Desai and Shroff[21]. The acid was reduced by Clemmensen's method using zinc amalgam and hydrochloric acid to γ-(2,4-dihydroxyphenyl)butyric acid (10), m.p. 111°. Julis et al.[22] have reported the reduced acid as a viscous oil. Desai and Figueredo[23] reported the compound having m.p. 105°.

7-Hydroxy-4-methylcoumarin-6-butyric acid (11) :

γ-(2,4-Dihydroxyphenyl)butyric acid (10) on Pechmann reaction with ethylacetoacetate and concentrated sulphuric acid gave the acid (11) as well as its ethyl ester (12). The mixture was separated by treating it with bicarbonate solution. The acid has been assigned the 7-hydroxy-4-methylcoumarin-6-butyric acid (11) structure on the basis of analytical results and also by the formation of 2,4-dimethoxy-5-carboxypropyl-β-methylcinnamic acid (14) from its methoxy-ethyl ester (13). The structure was also confirmed by the synthesis of 2-carboxy-6-methoxy-3-methyl-5-carboxypropylbenzofuran (17) from the acid (11). Both the compounds were synthesised as follows :

2,4-Dimethoxy-5-carboxypropyl-β-methylcinnamic acid (14):

Ethyl 7-hydroxy-4-methylcoumarin-6-butyrate(12) when refluxed with dimethylsulphate and anhydrous potassium carbonate in boiling acetone gave ethyl 7-methoxy-4-methyl-coumarin-6-butyrate (13) which on treatment with sodium hydroxide solution and excess of dimethylsulphate furnished

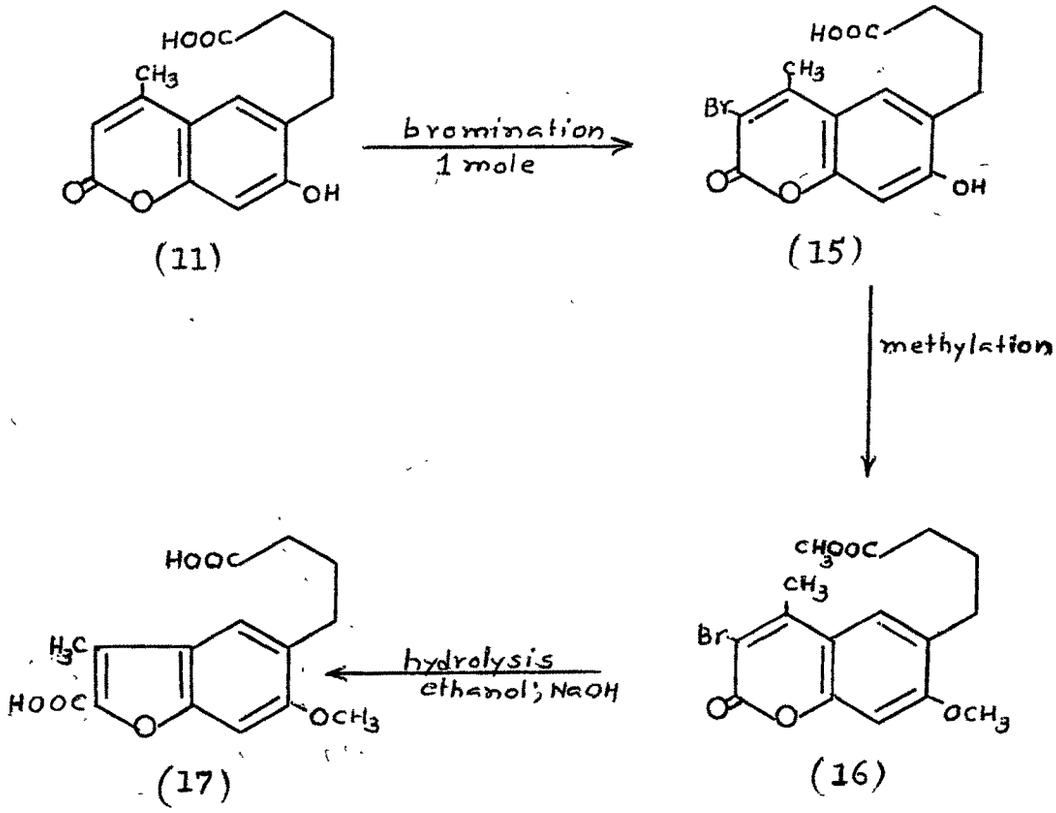

HOOC
HO
OH
(10)
reduction
Zn-Hg/ HCl
HOOC
HO
OH
(9)
ethylacetoacetate,
Con. H_2SO_4
HOOC
CH_3
OH
(11)
hydrolysis
+
esterification
C_2H_5OOC
CH_3
OH
(12)
methylation ;
me_2SO_4
me_2CO &
K_2CO_3
C_2H_5OOC
CH_3
OCH_3
(13)
NaOH and
me_2SO_4
HOOC
CH_3
$HOOC-HC=C$
H_3CO
OCH_3
(14)

2,4-dimethoxy-5-carboxypropyl-β-methylcinnamic acid (14). This is the criteria of the coumarin ring system where α-pyrone ring is hydrolysed partially to the corresponding cinnamic acid derivative and thus confirming the coumarin structure assigned to the product[24].

2-Carboxy-6-methoxy-3-methyl-5-carboxypropyl-benzofuran (17) : Bromination of 7-Hydroxy-4-methylcoumarin-6-butyric acid (11)

3-Bromo-7-hydroxy-4-methylcoumarin-6-butyric acid (15) :

7-Hydroxy-4-methylcoumarin-6-butyric acid (11) was brominated with one mole of bromine in acetic acid when 3-bromocoumarin derivative (15) was obtained. The above compound was methylated with dimethyl sulphate in



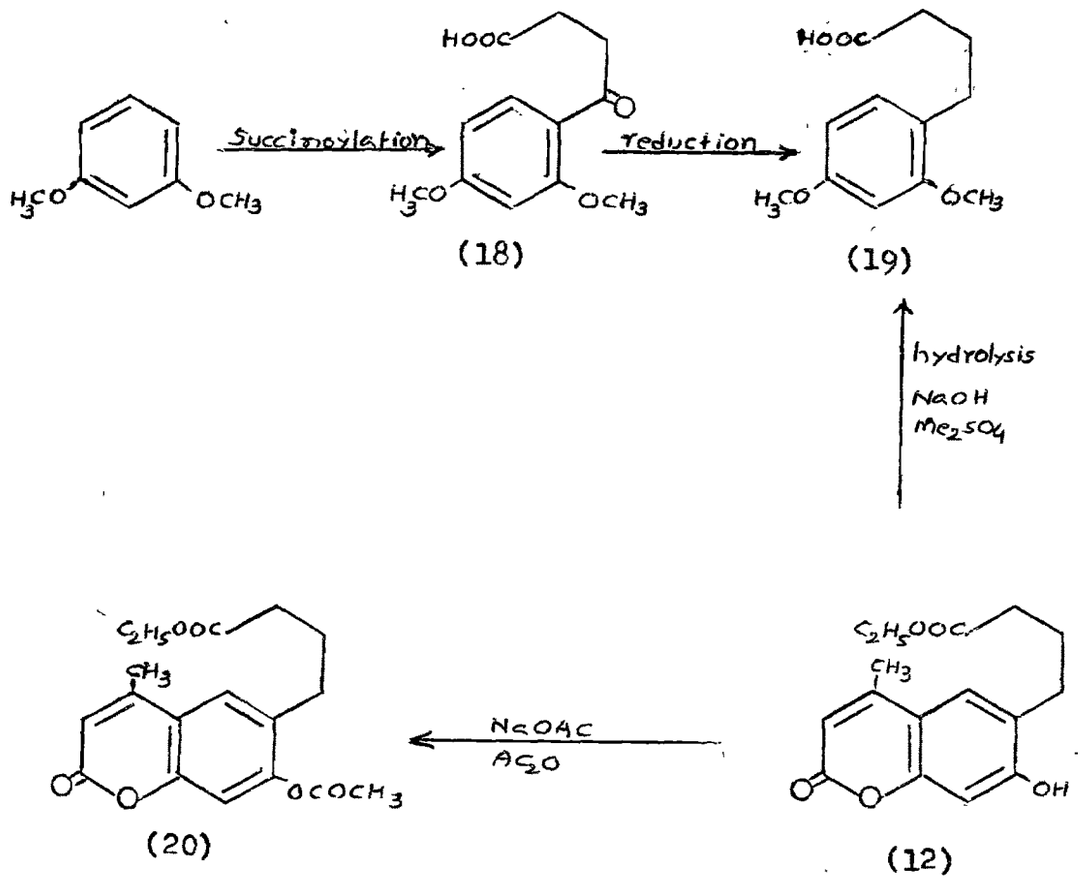
the presence of potassium carbonate and acetone to methyl-3-bromo-7-methoxy-4-methylcoumarin-6-butyrate (16) which on hydrolysis by refluxing it with alcoholic sodium hydroxide solution furnished 2-carboxy-6-methoxy-3-methyl-5-carboxypropylbenzofuran (17). This is also a standard reaction where 3-bromocoumarin is hydrolysed to the corresponding benzofuran derivative[25].

The bicarbonate insoluble product in the Pechmann condensation of γ-(2,4-dihydroxyphenyl)butyric acid was found to be an ethyl ester of the acid (11) and was assigned the structure ethyl-7-hydroxy-4-methylcoumarin-6-butyrate (12), as it gave the above acid (11) on hydrolysis with dilute sodium hydroxide solution. This ester was also prepared by refluxing the above acid (11) with ethanol and concentrated sulphuric acid.

γ-(2,4-Dimethoxyphenyl)butyric acid (19) :

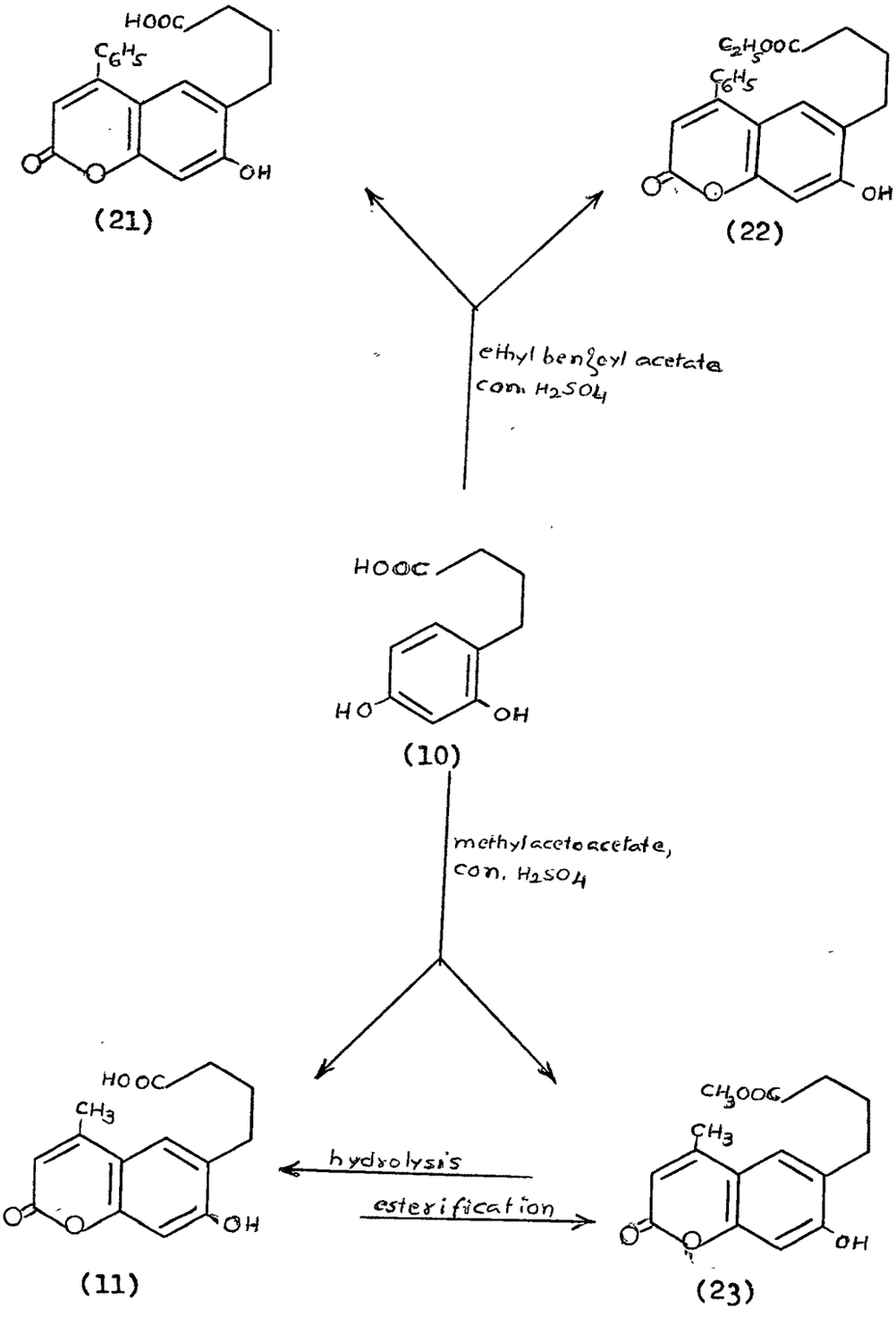
Ethyl-7-hydroxy-4-methylcoumarin-6-butyrate (12) when refluxed with sodium hydroxide and dimethyl sulphate gave γ-(2,4-dimethoxyphenyl)butyric acid. The structure of this acid was proved by its direct synthesis as follows :

Resorcinol on methylation with dimethyl sulphate gave dimethyl ether of resorcinol, which was then succinoylated to γ-(2,4-dimethoxybenzoyl)propionic acid (18) according to Rosenmund et al.[26] This on Clemmensens reduction gave the above γ-(2,4-dimethoxyphenyl)butyric acid (19). M.P. and mixed m.p. with the product described above was not depressed.



Ethyl-7-hydroxy-4-methylcoumarin-6-butyrate (12) when refluxed with acetic anhydride and sodium acetate afforded ethyl-7-acetoxy-4-methylcoumarin-6-butyrate (20).

This is a unique case of esterification taking place during the Pechmann condensation. The Pechmann condensation of β-resorcylic acid with ethyl acetoacetate and sulphuric acid as condensing agent gave the decarboxylated product rather than the esterfied one[27]. In order to study this esterification process further,


HOOC
C6H5
OH
(21)
C2H5OOC
C6H5
OH
(22)
ethyl benzoyl acetate
con. H2SO4
HOOC
HO
OH
(10)
methylacetoacetate,
con. H2SO4
HOOC
CH3
OH
(11)
hydrolysis
esterification
CH3OOC
CH3
OH
(23)

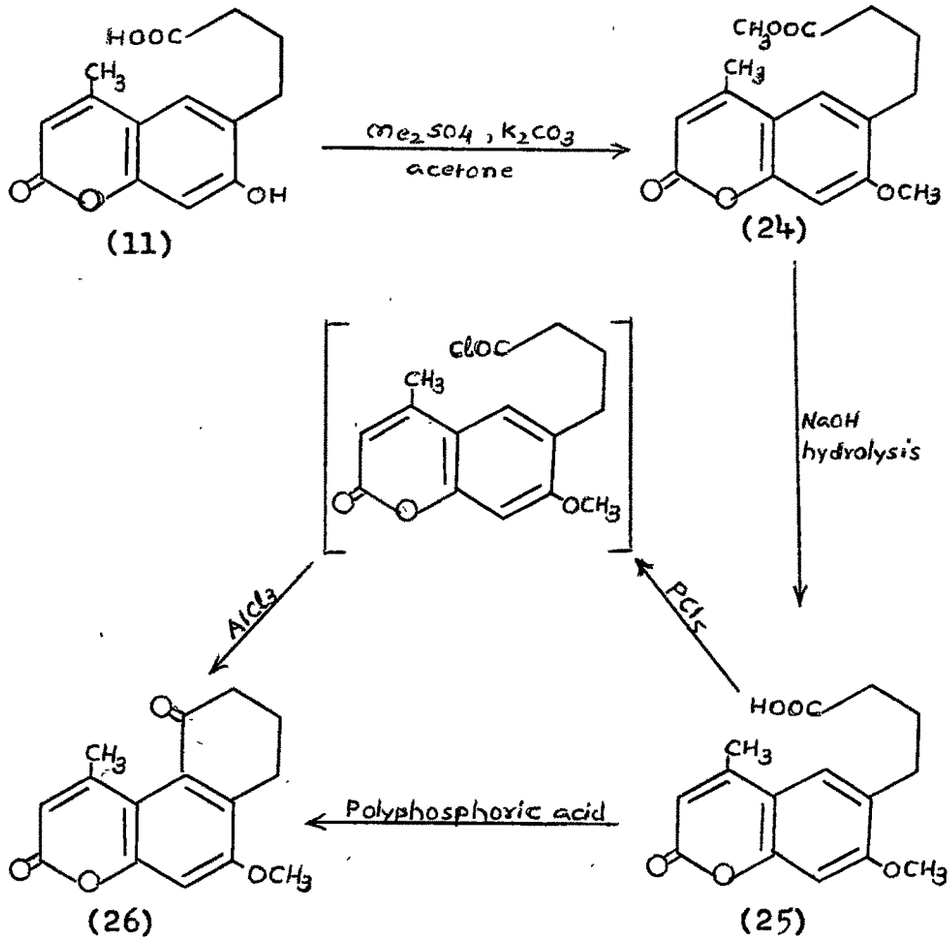
the γ-(2,4-dihydroxyphenyl)butyric acid (10) was condensed with ethyl benzoylacetate in the presence of concentrated sulphuric acid when it gave 7-hydroxy-4-phenylcoumarin-6-butyric acid (21) and its ethyl ester(22). Similar condensation of (10) with methyl acetoacetate and concentrated sulphuric acid afforded 7-hydroxy-4-methylcoumarin-6-butyric acid (11) and its methyl ester (23). The structure of the methyl ester was assigned as methyl 7-hydroxy-4-methylcoumarin-6-butyrate and was proved by its hydrolysis to the above acid (11) and also by esterification of the acid (11) with methanol and concentrated sulphuric acid to the ester (23).

7-Methoxy-4-methylcoumarin-6-butyric acid (25) :

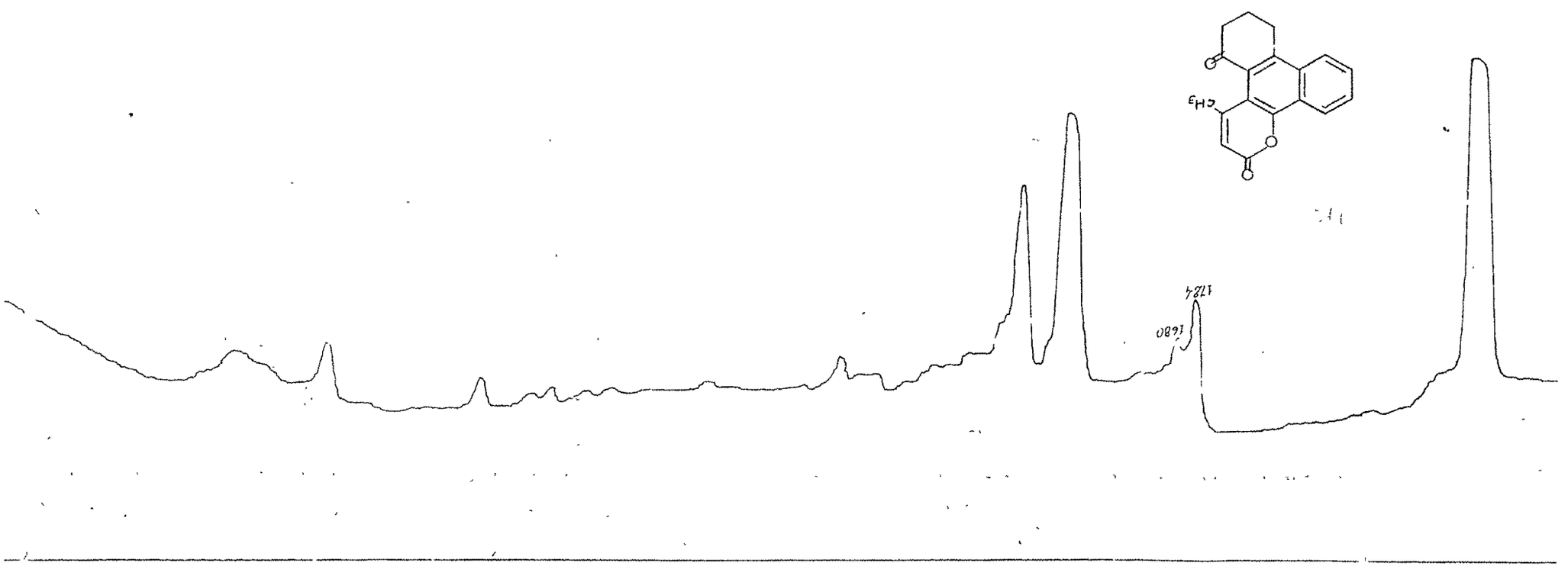
7-Hydroxy-4-methylcoumarin-6-butyric acid (11) was methylated with dimethylsulphate in the presence of anhydrous potassium carbonate in boiling acetone to methyl 7-methoxy-4-methylcoumarin-6-butyrate (24), which was then hydrolysed with sodium hydroxide solution to 7-methoxy-4-methylcoumarin-6-butyric acid.

7-Methoxy-4-methyl-4'-ketocyclohexeno(5',6',5,6)-coumarin (26) :

The above 7-methoxy-4-methylcoumarin-6-butyric acid (25) was cyclised with phosphorus pentachloride, dry benzene and anhydrous aluminium chloride to 7-methoxy-4-methyl-4'-ketocyclohexeno(5',6',5,6)coumarin (26) according to Johnson's inverse process of cyclisation.[28]



This cyclised compound was also prepared by heating the mixture of 7-methoxy-4-methylcoumarin-6-butyric acid and polyphosphoric acid. Melting point and mixed m.p. was 160°. The structure has been further confirmed by taking the I.R.Spectra of this compound. It showed two bands in the carbonyl region, viz. 1724 cm^{-1} (lactonyl >C=O group) and 1670 cm^{-1} (aromatic ketone).


1784
1680

Decarboxylation of 7-hydroxy-4-methylcoumarin-6-butyric acid (11) :

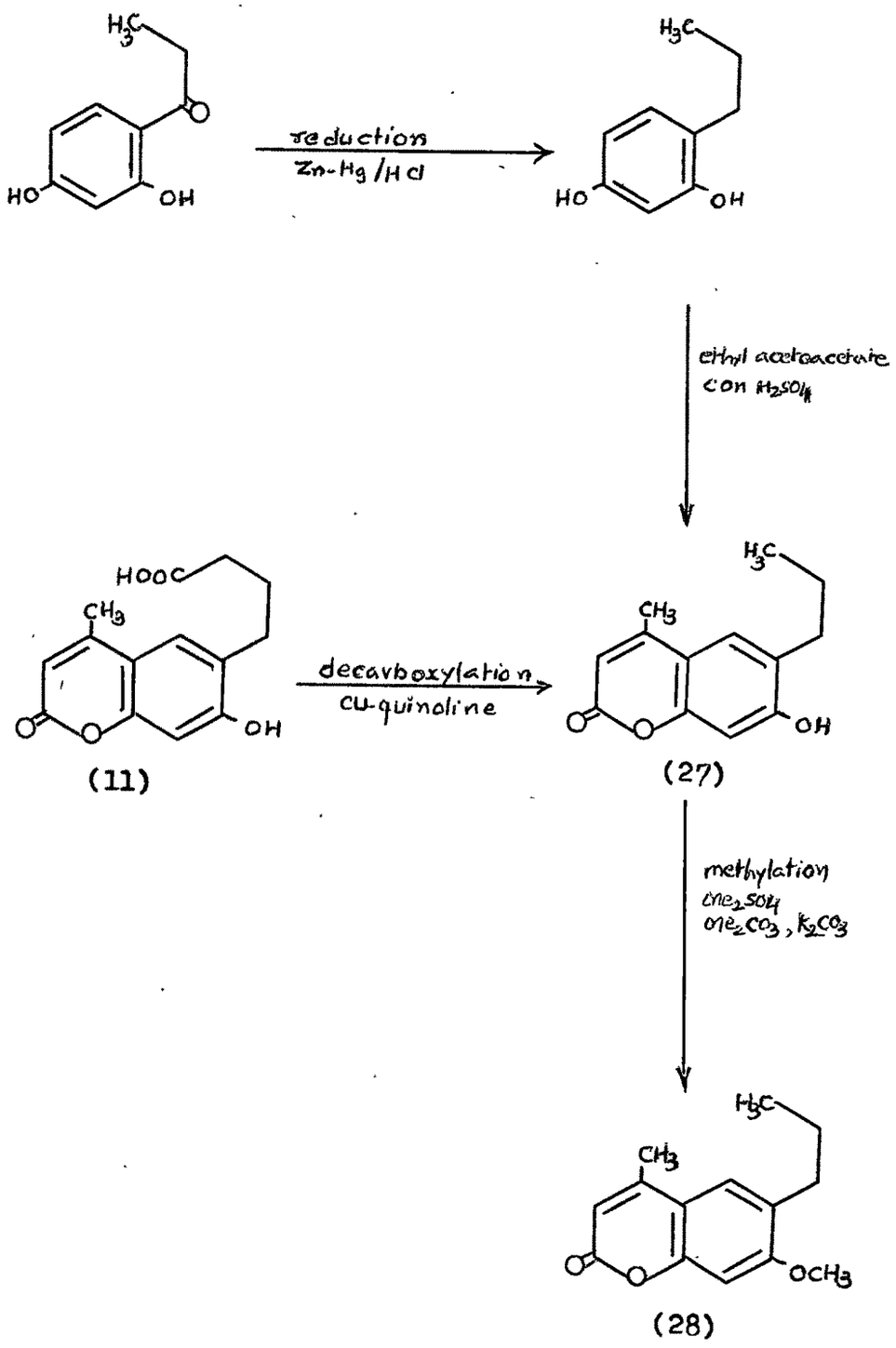
7-Hydroxy-4-methyl-6-propylcoumarin (27) :

7-Hydroxy-4-methylcoumarin-6-butyric acid on decarboxylation with copper powder and quinoline gave the bicarbonate insoluble compound, which was assigned the structure 7-hydroxy-4-methyl-6-propylcoumarin (27).

The structure of (27) was proved by the direct synthesis of 7-hydroxy-4-methyl-6-propylcoumarin as follows :

Respropiophenone was reduced by Clemmensen's[29] reduction with zinc amalgam and hydrochloric acid to give 4-propyl resorcinol according to Johnson and Hodge[29]. This on Pechmann condensation with ethyl acetoacetate and concentrated sulphuric acid, furnished 7-hydroxy-4-methyl-6-propylcoumarin (27). Mixed m.p. of the compounds prepared by these two routes was not depressed.

7-Hydroxy-4-methyl-6-propylcoumarin was methylated by refluxing it with dimethylsulphate, anhydrous potassium carbonate and acetone when 7-methoxy-6-propyl-4-methylcoumarin (28) was obtained.


reduction
Zn-Hg / HCl
ethyl acetoacetate
con H_2SO_4
decarboxylation
cu-quinoline
methylation
$(Me)_2SO_4$
$(Me)_2CO_3$, K_2CO_3

(11)

(27)

(28)

(b) Synthesis of 4-methyl-4'-ketocyclohexeno(5',6',5,6) benzo(h) coumarin (35) :

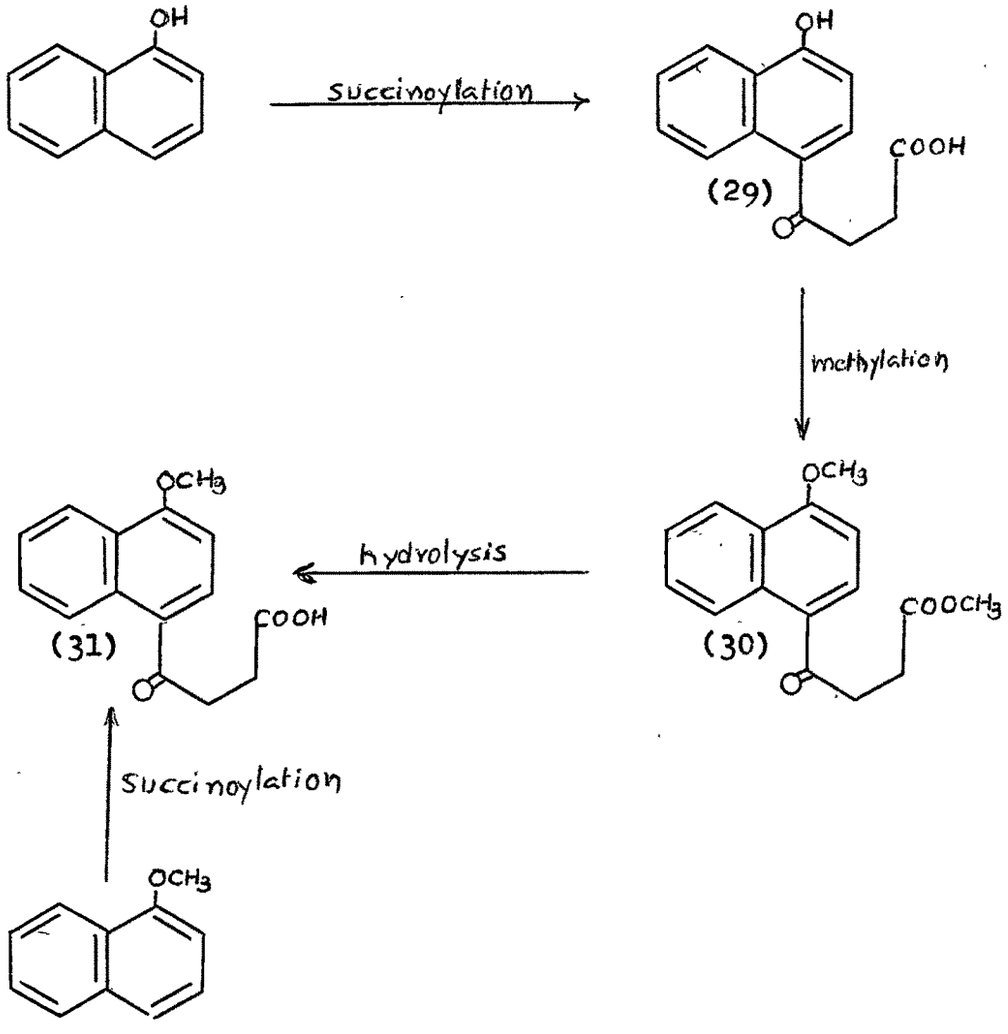
α-and β-Naphthacoumarins, their methyl derivatives as well as their reduced products are potent anthelmintic agents[30]. It was therefore thought of interest to synthesise coumarin derivatives in which the cyclohexene ring is build up in the 5,6 position of α-naphthacoumarin.

β-1-(4-Hydroxynaphthoyl)propionic acid (29) :

Desai et al.[31] attempted the condensation of resacetophenone, methyl-β-resorcylate, phloroglucinol and α-naphthol with succinic anhydride in the presence of either anhydrous aluminium chloride or zinc chloride and in nitrobenzene and acetylene tetrachloride as solvents. They however did not succeed. Now α-naphthol could be succinoylated in a similar manner to resorcinol with succinic anhydride in the presence of anhydrous aluminium chloride and nitrobenzene. The product obtained was assigned the structure β-1-(4-hydroxynaphthoyl) propionic acid.

The structure of (29) was proved by first converting it to methyl-β-1-(4-methoxynaphthoyl) propionate (30) by dimethyl sulphate and then hydrolysing the ester to the known β-1-(4-methoxynaphthoyl) propionic acid (31). This acid was synthesised by the succinoylation of methyl ether of α-naphthol in the presence of anhydrous aluminium chloride according to Ruzicka and Waldmann[32].

Mixed m.p. with the known β-1-(4-methoxynaphthoyl) propionic acid was not depressed.



<u>γ-1-(4-Hydroxynaphthyl)butyric acid (32)</u> :

β-1-(4-Hydroxynaphthoyl) propionic acid on Clemmensen reduction with zinc amalgam and hydrochloric acid gave the product to which γ-1-(4-hydroxynaphthyl) butyric acid structure was assigned.

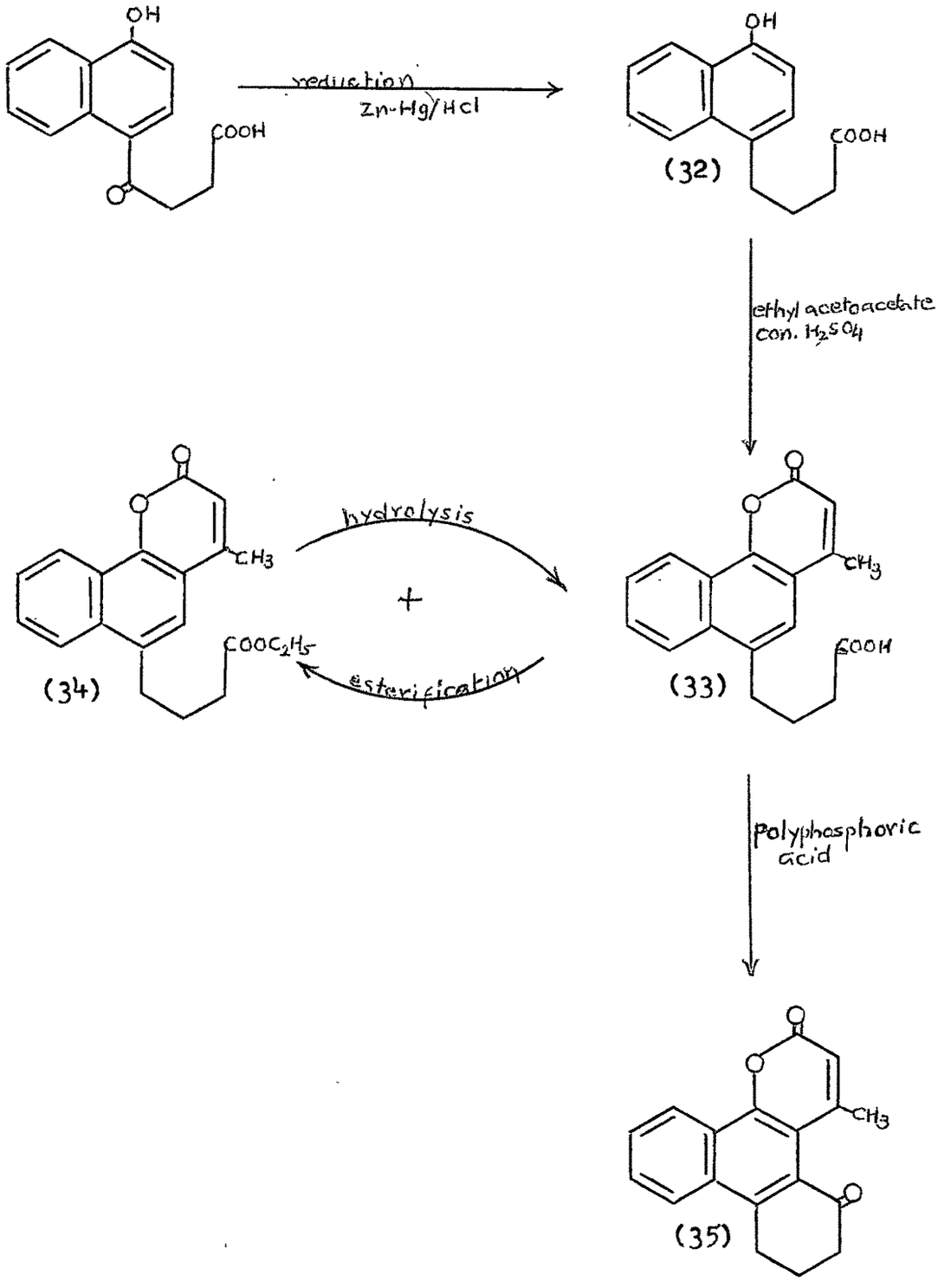
4-Methyl-7,8-benzocoumarin-6-butyric acid (33) and its ethyl ester (34) :

The above γ-1-(4-hydroxynaphthyl) butyric acid on Pechmann condensation with ethyl acetoacetate and concentrated sulphuric acid furnished a mixture of 4-methyl-7,8-benzocoumarin-6-butyric acid (33) and ethyl 4-methyl-7,8-benzocoumarin-6-butyrate (34). The mixture was separated by treating it with bicarbonate solution. The structure of (34) was proved by the esterification of (33) with ethanol and concentrated sulphuric acid and also by its hydrolysis to (33).

4-Methyl-4'-ketocyclohexeno(5',6',5,6)benzo(h) coumarin (35) :

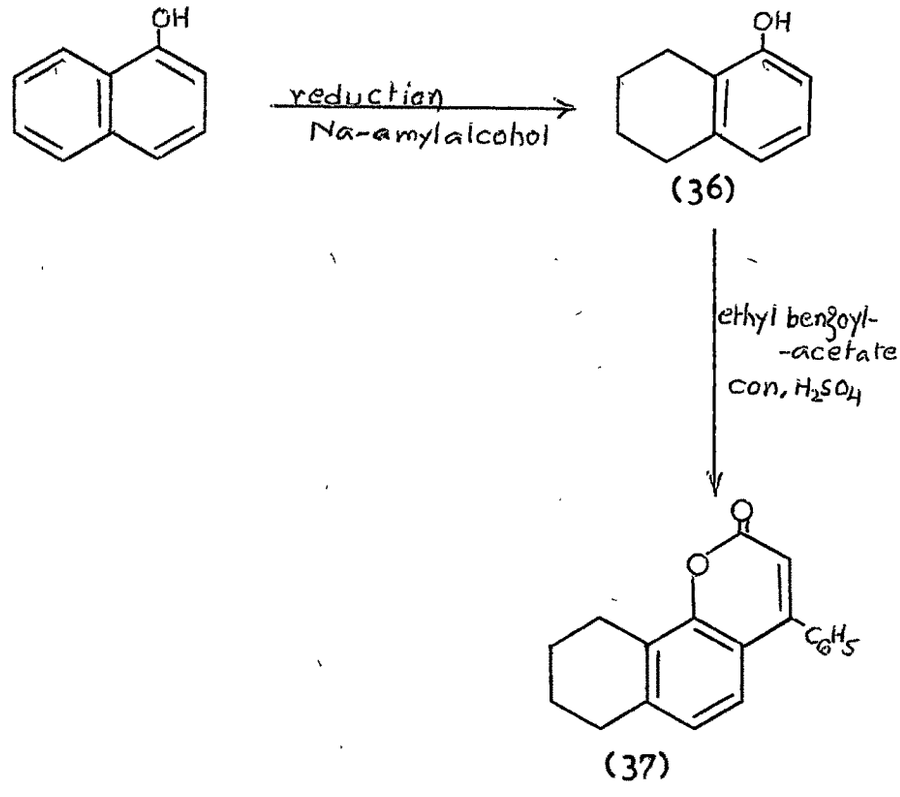
4-Methyl-7,8-benzocoumarin-6-butyric acid on heating with polyphosphoric acid gave the product which was found to be insoluble in bicarbonate and was assigned the structure 4-methyl-4'-keto-cyclohexeno(5',6',5,6)benzo(h)coumarin. The structure was further confirmed by taking its I.R.spectra. It showed two bands in the carbonyl region, viz. 1724 cm^{-1} (lactonyl >C=O group) and 1680 cm^{-1} (aromatic ketone).

1724
1670
OCH3
H


OH
COOH
reduction
Zn-Hg/HCl
(32)
ethyl acetoacetate
con. H_2SO_4
CH_3
$COOC_2H_5$
hydrolysis
+
esterification
(34)
(33)
polyphosphoric acid
(35)

(c) Synthesis of 4-phenylcyclohexeno(h)coumarin (37) :

ar-Tetrahydro-α-naphthol (36) was prepared according to Eug. Bamberger [33]. The Pechmann condensation of ar-tetrahydro-α-naphthol with ethyl benzoylacetate and concentrated sulphuric acid, similar to ethyl acetoacetate[30] gave the alkali insoluble product to which 4-phenylcyclohexeno(h) coumarin (37) structure has been assigned.



EXPERIMENTAL

Syntheses of cyclohexenocoumarins

(a) **Synthesis of 7-methoxy-4-methyl-4'-keto-cyclohexeno(5',6',5,6)coumarin :**

γ-(2,4-Dihydroxyphenyl) butyric acid was prepared as follows according to Desai and Figueredo[23].

γ-(2,4-Dihydroxyphenyl) butyric acid :

β-(2,4-Dihydroxybenzoyl) propionic acid was prepared by succinoylation of resorcinol according to Desai and Shroff[21]. The acid (10 g.) was heated with zinc amalgam (30 g.) and concentrated hydrochloric acid (75 ml.) for 15 hours. The mixture was cooled and the product was extracted with ether. On evaporation of the solvent the product was obtained in pasty form which on crystallisation from benzene gave the colourless crystals, m.p. 111°. Yield 6.0 g. Julis et al. have reported the reduced acid as a viscous oil but Desai and Figueredo have reported m.p. 105°.

7-Hydroxy-4-methylcoumarin-6-butyric acid :

γ-(2,4-Dihydroxyphenyl) butyric acid (1.96 g. ; 0.01 M) was mixed with ethyl acetoacetate (1.3 g. ; 0.01 M) and to the cooled solution concentrated sulphuric acid (80 % ; 8 ml.) was slowly added. After keeping the mixture overnight, at the room temperature,

the solution was added to the ice-water. The product was taken in bicarbonate solution and filtered. The filtrate on acidification with hydrochloric acid gave the above acid, crystallised from glacial acetic acid in shining needles, m.p. 230°. Yield 1.7 g.

Analysis : Found : C,64.25 ; H,5.47 %.
$C_{14}H_{14}O_5$ requires : C,64.11 ; H,5.38 %.

Ethyl 7-hydroxy-4-methylcoumarin-6-butyrate :

The bicarbonate insoluble product in the above reaction was dried, washed with water and crystallised from dilute ethanol in colourless shining plates, m.p. 153°. Yield 0.1 g.

Analysis : Found : C,66.43 ; H,6.12 %.
$C_{16}H_{18}O_5$ requires : C,66.19 ; H,6.25 %.

This ester was prepared by refluxing the above acid (1.0 g.) with ethanol (4 to 5 ml.) and concentrated sulphuric acid (0.5 ml.) for 3 to 4 hours. On cooling the mixture, the separated crystals were filtered, washed with bicarbonate solution and crystallised from ethanol. M.p. and mixed m.p. with the above product was 153°.

The above ethyl ester (0.5 g.) was hydrolysed with sodium hydroxide solution (6 % ; 15 ml.) by keeping it overnight at the room temperature. Next day it was filtered and acidified. The compound was crystallised

from glacial acetic acid in shining needles, m.p. 230°. Mixed m.p. with the acid prepared as above was not depressed.

Ethyl-7-methoxy-4-methylcoumarin-6-butyrate :

Ethyl-7-hydroxy-4-methylcoumarin-6-butyrate (2.9 g. ; 0.01 M), dimethyl-sulphate (2.5 g. ; 0.02 M) and anhydrous potassium carbonate (5.5 g. ; 0.04 M) were refluxed in boiling acetone for 8 hours. On evaporation of the acetone, the product was washed with dilute alkali and was crystallised from dilute ethanol in shining needles, m.p. 116°. Yield 2.5 g.

Analysis : Found : C,67.45 ; H,6.45 %.
$C_{17}H_{20}O_5$ requires : C,67.10 ; H,6.50 %.

2,4-Dimethoxy-5-carboxypropyl-β-methylcinnamic acid :

Ethyl-7-methoxy-4-methylcoumarin-6-butyrate (0.5 g.) was heated with sodium hydroxide solution (5% ; 15 ml.) for 15 minutes. Dimethyl-sulphate (2 ml.) was then added with constant shaking. More sodium hydroxide and dimethyl-sulphate were added and the mixture was heated for a few minutes. The alkaline solution was left overnight. It was filtered and the filtrate on acidification gave 2,4-dimethoxy-5-carboxy-propyl-β-methylcinnamic acid which was crystallised from ethanol in colourless crystals, m.p. 195°. Yield 0.1 g.

Analysis :Found : C,61.84 ; H,6.42 %.
$C_{16}H_{20}O_6$ requires : C,62.33 ; H,6.49 %.

3-Bromo-7-hydroxy-4-methylcoumarin-6-butyric acid :

7-Hydroxy-4-methylcoumarin-6-butyric acid (2.62 g. ; 0.01 M) was dissolved in minimum acetic acid (60 ml.) by warming and bromine in acetic acid (10 % ; 16 ml. ; 0.01 M) was added dropwise. The reaction mixture was kept at the room temperature for 30 minutes, after the addition was complete. The solid which separated out was crystallised from alcohol in shining needles, m.p. 224°. Yield 2.1 g.

Analysis : Found : Br, 23.21 %.
$C_{14}H_{13}O_5Br$ requires : Br, 23.46 %.

Methyl-3-bromo-7-methoxy-4-methylcoumarin-6-butyrate :

3-Bromo-7-hydroxy-4-methylcoumarin-6-butyric acid (3.41 g. ; 0.01 M) was refluxed with dimethyl sulphate (2.52 g. ; 0.02 M), anhydrous potassium carbonate (4.8 g. ; 0.04 M) and dry acetone for 4 hours on a water bath. The acetone was evaporated and the compound was washed with dilute alkali. It was dried and crystallised from alcohol in colourless shining needles, m.p. 99°. Yield 2.4 g.

Analysis : Found : C, 51.93 ; H, 4.54 ; Br, 22.01 %.
$C_{16}H_{17}O_5Br$ requires : C, 52.04 ; H, 4.61 ; Br, 21.68 %.

2-Carboxy-6-methoxy-3-methyl-5-carboxypropyl-benzofuran :

The above bromocoumarin (1 g.) was refluxed with ethanolic sodium hydroxide solution (6 % ; 15 ml.)

for 3 hours on a low flame. The mixture was cooled and filtered. The filtrate on acidification gave the compound which was crystallised from alcohol in colourless crystals melting at 228° (dec.). Yield 0.3 g.

Analysis : Found : C,61.54 ; H,5.62 %.
$C_{15}H_{16}O_6$ requires : C,61.64 ; H,5.52 %.

γ-(2,4-Dimethoxyphenyl) butyric acid :

Ethyl 7-hydroxy-4-methylcoumarin-6-butyrate (0.7 g.) was refluxed with sodium hydroxide solution (4 % ; 15 ml.) for 15 minutes on a low flame. Dimethyl sulphate (2 ml.) was then added with continuous shaking. Sodium hydroxide (4 % ; 15 ml.) and dimethyl sulphate (2 ml.) were again added. The mixture was then heated on the water bath for 2 minutes and was left overnight, keeping it an alkaline. Next day the solution was filtered and acidified. The compound was dried in vacuum and crystallised from petroleum ether in colourless crystals, m.p. 47°. Yield 0.4 g.

Analysis Found : C,63.86 ; H,6.64 %.
$C_{12}H_{16}O_4$ requires : C,64.28 ; H,7.14 %.

Ethyl 7-acetoxy-4-methylcoumarin-6-butyrate :

The mixture of ethyl 7-hydroxy-4-methylcoumarin-6-butyrate (2.9 g. ; 0.01 M), acetic anhydride (5.1 ml. ; 0.05 M) and freshly fused sodium acetate (2.0 g.) was refluxed for 1 hour. The product obtained on working up as usual was crystallised from acetic acid in shining

needles, m.p. 124°. Yield 2.5 g.

Analysis : Found : C,64.48 ; H,5.77 %.
$C_{18}H_{20}O_6$ requires : C,65.00 ; H,6.00 %.

7-Hydroxy-4-phenylcoumarin-6-butyric acid and its ethyl ester :

γ-(2,4-Dihydroxyphenyl) butyric acid (1.96 g. ; 0.01 M) was mixed with ethyl benzoylacetate (1.92 g. ; 0.01 M). Concentrated sulphuric acid (80 % ; 8 ml.) was then slowly added to the above cold mixture and left overnight. Next day the mixture was added to the ice water and treated with bicarbonate solution. The filtrate on acidification gave 7-hydroxy-4-phenylcoumarin-6-butyric acid which was crystallised from ethanol in rosy plates, m.p. 235°. Yield 1.5 g.

Analysis : Found : C,70.39 ; H,4.72 %.
$C_{19}H_{16}O_5$ requires : C,70.36 ; H,4.98 %.

Ethyl 7-hydroxy-4-phenylcoumarin-6-butyrate :

In the above Pechmann condensation, the bicarbonate insoluble product was washed with water, dried and crystallised from ethanol in shining plates, m.p. 156°. Yield 0.04 g.

Analysis : Found : C,72.20 ; H,5.63 %.
$C_{21}H_{20}O_5$ requires : C,71.90 ; H,5.69 %.

7-Hydroxy-4-methylcoumarin-6-butyric acid and its methyl ester :

γ-(2,4-Dihydroxyphenyl) butyric acid (1.96 g. ; 0.01 M) was mixed with methyl acetoacetate (1.1 g. ; 0.01 M) and concentrated sulphuric acid (80 % ; 8 ml.) was added dropwise keeping the reaction mixture in cold condition. It was left overnight and worked up as above . 7-Hydroxy-4-methylcoumarin-6-butyric acid was crystallised from ethyl alcohol in colourless crystals, m.p. 230°. Yield 1.5 g.

Methyl 7-hydroxy-4-methylcoumarin-6-butyrate :

In the Pechmann condensation of γ-(2,4-dihydroxyphenyl) butyric acid with methyl acetoacetate, the bicarbonate insoluble product was washed with water and crystallised from ethanol in shining plates, m.p. 154°.

Analysis : Found : C, 65.57 ; H, 5.90 %.
$C_{15}H_{16}O_5$ requires : C, 65.21 ; H, 5.84 %.

Methyl 7-methoxy-4-methylcoumarin-6-butyrate :

7-Hydroxy-4-methylcoumarin-6-butyric acid (2.62 g. ; 0.01 M) was mixed with dry acetone (60 ml.), anhydrous potassium carbonate (5.5 g. ; 0.04 M), dimethyl sulphate (2.5 g. ; 0.02 M) and refluxed on a water bath for 6 to 7 hours. The residue on evaporation of the acetone was washed with dilute sodium hydroxide solution and crystallised from alcohol in colourless plates, m.p. 118°.

Yield 1.8 g.

Analysis : Found : C,66.45 ; H,6.21 %.

$C_{16}H_{18}O_5$ requires : C,66.19 ; H,6.25 %.

7-Methoxy-4-methylcoumarin-6-butyric acid :

Methyl-7-methoxy-4-methylcoumarin-6-butyrate (1 g.) was hydrolysed with sodium hydroxide solution (6 % ; 25 ml.) by keeping the reaction mixture overnight at the room temperature. Next day it was filtered, acidified and crystallised from dilute ethanol in shining needles, m.p. 176°. Yield 0.5 g.

Analysis : Found : C,65.48 ; H,5.85 %.

$C_{15}H_{16}O_5$ requires : C,65.21 ; H,5.84 %.

7-Methoxy-4-methyl-4-ketocyclohexeno(5',6',5,6)coumarin :

7-Methoxy-4-methylcoumarin-6-butyric acid (3 g.) was mixed with phosphorus pentachloride (4 g.) and dry benzene (20 ml.). The mixture was refluxed on a water bath for 6 to 7 hours. Benzene, phosphorus pentachloride and volatile matter were removed under vacuum at 60° to 70°. Benzene (15 to 20 ml.) was added and the process repeated. The acid chloride was dissolved in benzene and slowly added to the mixture of anhydrous aluminium chloride(3 g.) and dry benzene (40 ml.), keeping the reaction mixture in ice bath. It was stirred for 2 to 3 hours and ether (50 ml.) was added with stirring. The organic layer was washed with hydrochloric acid, sodium bicarbonate solution and then with potassium hydroxide solution. The evaporation

of the ether gave 7-methoxy-4-methyl-4'-ketocyclohexeno-(5',6',5,6) coumarin which was crystallised from benzene - petroleum ether, m.p. 160°. IR spectra showed two bands in the carbonyl region, viz. 1724 cm^{-1} (lactonyl >C=O group) and 1670 cm^{-1} (aromatic ketone).

Analysis Found : C,69.56 ; H,5.21 %.
$C_{15}H_{14}O_4$ requires : C,69.76 ; H,5.42 %.

The same compound described above was also synthesised by the cyclisation of the acid (1 g.) with polyphosphoric acid (10 g.) at 170° for 30 minutes. The mixture was added to ice-water, filtered and washed with sodium hydroxide solution. The compound was crystallised from benzene-petroleum ether, m.p. 160°. Mixed m.p. of this with the above sample was not depressed. In both the methods the yield was poor.

7-Hydroxy-4-methyl-6-propylcoumarin :

A mixture of 7-hydroxy-4-methylcoumarin-6-butyric acid (1 g.), copper powder (0.5 g.) and quinoline (10 ml.) was refluxed on a sand bath for 1 to 2 hours till the effervecence ceased. The mixture was filtered hot and decomposed with ice cold hydrochloric acid (1:1). The separated product was filtered, dried and crystallised from alcohol in colourless crystals, m.p. 173-6°.

The same compound described above was obtained by Pechmann reaction on 4-propylresorcinol as follows :

Respropiophenone was reduced by Clemmensens method with zinc amalgam and hydrochloric acid to

4-propylresorcinol according to Johnson and Hodge.[29] 4-Propylresorcinol (4 g.) was mixed with ethyl acetoacetate (4 g.) and concentrated sulphuric acid (80 % ; 16 ml.) was slowly added to the above cooled reaction mixture. It was left overnight and the product obtained on working up as usual crystallised from acetic acid in colourless crystals, m.p. 173°. Mixed m.p. with the above compound was not depressed.

Analysis : Found : C,71.60 ; H,6.29 %.
$C_{13}H_{14}O_3$ requires : C,71.54 ; H,6.47 %.

7-Methoxy-6-propyl-4-methylcoumarin :

A mixture of 7-hydroxy-4-methyl-6-propylcoumarin (2.18 g. ; 0.01 M),dimethyl sulphate (1.26 g. ; 0.01 M), anhydrous potassium carbonate (2.4 g. ; 0.02 M) was refluxed in boiling acetone for 4 to 5 hours. Acetone was evaporated and the compound was washed with alkali and crystallised from alcohol in shining needles, m.p. 171°. Yield 0.7 g.

Analysis : Found : C,71.90 ; H,7.00 %.
$C_{14}H_{16}O_3$ requires : C,72.39 ; H,6.94 %.

(b) Synthesis of 4-methyl-4'-ketocyclohexeno(5',6',5,6) benzo(h)coumarin :

Succinoylation of α-naphthol :

β-1-(4-Hydroxynaphthoyl) propionic acid :

α-Naphthol (14.4 g. ; 0.01 M) and succinic anhydride (12 g. ; 0.12 M) were mixed together with dry

nitrobenzene (20 ml.). Anhydrous aluminium chloride (26.8 g. ; 0.2 M) dissolved in nitrobenzene was added slowly with stirring to the above cold mixture and was left for 15 hours at room temperature under dry condition. The mixture was then decomposed by ice cold hydrochloric acid (1:1) and steam distilled to remove the nitrobenzene. The paste obtained, was taken in bicarbonate solution, filtered and acidified. The yellow compound was crystallised from hot water in shining crystals, m.p. 230°. Yield 5.5 g. It developed green colouration with alcoholic ferric chloride solution.

Analysis : Found : C,68.73 ; H,4.94 %.
$C_{14}H_{12}O_4$ requires : C,68.84 ; H,4.95 %.

Clemmensens reduction of β-1-(4-Hydroxynaphthoyl) Propionic acid :

γ-1-(4-Hydroxynaphthyl) butyric acid :

β-1-(4-Hydroxynaphthoyl) propionic acid (10 g.) was mixed with dioxan (10 ml.), water (15 ml.) and concentrated hydrochloric acid (50 ml.). The mixture was boiled and zinc amalgam (20 g.) was added at some intervals and the refluxing was continued for 15 hours. After every 5 hours interval concentrated hydrochloric acid (5 ml.) was added. The solution was cooled, ether extracted and the paste obtained after evaporation of the ether was crystallised from hot water in shining crystals, m.p. 144°. Yield 3.4 g. It gave violet

colouration with alcoholic ferric chloride solution.

Analysis : Found : C,72.71 ; H,6.17 %.

$C_{14}H_{14}O_3$ requires : C,73.02 ; H,6.13 %.

4-Methyl-7,8-benzocoumarin-6-butyric acid :

γ-1-(4-Hydroxynaphthyl) butyric acid (2.30 g. ; 0.01 M) was mixed with ethyl acetoacetate (1.3 g. ; 0.01 M) and to the cooled solution concentrated sulphuric acid (80 % ; 15 ml.) was slowly added. Next day the mixture was decomposed with ice-water and treated with bicarbonate solution and filtered. The filtrate on acidification gave the above product which crystallised from acetic acid in colourless crystals, m.p. 207°. Yield 0.5 g.

Analysis : Found : C,72.91 ; H,5.66 %.

$C_{18}H_{16}O_4$ requires : C,72.90 ; H,5.44 %.

Ethyl 4-Methyl-7,8-benzocoumarin-6-butyrate :

In the above Pechmann reaction, the bicarbonate insoluble product was washed with water, dried and crystallised from acetic acid in colourless needles, m.p. 130°. Yield 0.1 g. The same ester was also synthesised by refluxing the mixture of the acid (2.0 g.), ethanol (5 ml.) and concentrated sulphuric acid (0.5 ml.) on a low flame for 2-3 hours. The mixture was cooled and the product separated was crystallised from acetic acid. M.p and mixed m.p. was 130°.

Analysis : Found : C,73.98 ; H,5.98 %.

$C_{20}H_{20}O_4$ requires : C,74.05 ; H,6.22 %.

4-Methyl-4'-ketocyclohexeno(5',6',5,6)benzo(h) coumarin :

4-Methyl-7,8-benzocoumarin-6-butyric acid (0.5 g.) was cyclised by heating it with polyphosphoric acid (5 g.) at 160° for 30 minutes. The mixture was decomposed in ice water, filtered and washed with bicarbonate solution. The compound was crystallised from glacial acetic acid in yellow shining needles. M.p. 220°. Yield 0.1 g. IR spectra showed two bands in the carbonyl region, viz. 1724 cm^{-1} (lactonyl >C=O group) and 1680 cm^{-1} (aromatic ketone).

Analysis : Found : C,77.72 ; H,5.08 %.

$C_{18}H_{14}O_3$ requires : C,77.69 ; H,5.03 %.

(c) Synthesis of 4-phenylcyclohexeno(h)coumarin :

Reduction of α-naphthol with sodium and amyl alcohol :

Ar-tetrahydro-1-naphthol :

It was prepared by reducing α-naphthol with sodium and amyl alcohol according to Eug. Bamberger and F. Brodt.[33] The reduced product (1.48 g. ; 0.01 M) was mixed with ethyl benzoylacetate (1.3 g. ; 0.01 M) and to the cooled mixture concentrated sulphuric acid (80 % ; 6 ml.) was added slowly with shaking. It was then left overnight at the room temperature and decomposed in ice water. The crude product was washed with dilute sodium hydroxide solution and crystallised from alcohol in greenish shining crystals. M.p. 151°.

Analysis : Found : C,82.30 ; H,5.89 %.

$C_{19}H_{16}O_2$ requires : C,82.56 ; H,5.83 %.

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