SYNTHESIS OF NATURALLY OCCURRING CHROMONES AND QUINONES

A THESIS

SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

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PUNE 411 008, (INDIA)

MARCH 1992

CERTIFICATE

Certified that the work incorporated in the thesis entitled " **Synthesis of Naturally Occurring Chromones and Quinones**" by **RASHID A. KHAN** was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

March, 1992

(N.R.AYYANGAR)

Research Guide

DEDICATED
TO
MY
PARENTS

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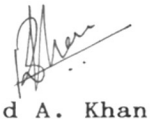


Rashid A. Khan.

GENERAL REMARKS

1. All the temperatures are in ^{o}C. All the melting points and boiling points are in ^{o}C and are uncorrected.

2. ^{1}H-NMR spectra were recorded either on Varian T-60 or FT-80 A or Bruker WH-90 or WH-300 FT spectrometer in $CDCl_3$ solution containing TMS as an internal standard with chemical shift (δ) expressed in ppm down field from TMS.
The following abbreviations are used : s = singlet, d = doublet, t=triplet, q=quartet, m=multiplet and br=broad.

3. Infra-red spectra (ν_{max} in cm^{-1}) were recorded as either thin film or nujol mull on Perkin-Elmer Infra-red-683 B spectrometer with sodium chloride optics.

4. Mass spectra were recorded on a CES-21-110B double focussing mass spectrometer operating at 70eV using direct inlet system.

5. All solvents and reagents were purified and dried by standard techniques. All evaporations were carried out under reduced pressure on Buchi rotary evaporator.

6. TLC was carried out on silica gel plates prepared by spreading the slurry (in CCl_4) and drying at room temperature.

7. Microanalyses were carried out in the microanalytical section of NCL.

8. The list of references pertaining to a chapter are given at the end of that chapter.

ABBREVIATIONS

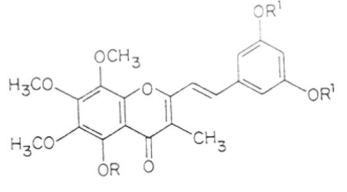
Ac	:	Acetyl
AIBN	:	2,2'-Azobisisobutyronitrile
Ar	:	Aryl
b.p.	:	Boiling point
n-Bu	:	n-Butyl
t-Bu	:	t-Butyl
CAN	:	Ceric ammonium nitrate
$CDCl_3$	:	Deuterated chloroform
CH_2Cl_2	:	Dichloromethane
DBU	:	1,8-Diazabicyclo[5,4,0]undec-7-ene
DDQ	:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	:	4-N,N-Dimethylaminopyridine
DMS	:	Dimethyl sulphate
DMSO	:	Dimethyl sulphoxide
DIBAL	:	Di-isobutylaluminium hydride
EDC	:	Ethylene dichloride
h	:	Hour/s
Et	:	Ethyl
g	:	Gram/s
IR	:	Infra red
LAH	:	Lithium aluminium hydride
LDA	:	Lithium diisopropyl amide
MCPBA	:	m-Chloroperbenzoic acid
Me	:	Methyl
min.	:	Minute/s
MOM	:	Methoxy methyl
m.p.	:	Melting point
MS	:	Mass spectrum
nm	:	Nanometer
NMR	:	Nuclear Magnetic Resonance
PCC	:	Pyridinium chlorochromate
PDC	:	Pyridinium dichromate
Ph	:	Phenyl
PTSA	:	p-Toluenesulfonic acid
TBTH	:	Tributyltin hydride
THF	:	Tetrahydrofuran
TFA	:	Trifluroacetic acid
TFAA	:	Trifluroacetic anhydride
UV	:	Ultra-violet.

ABSTRACT

The thesis entitled " Synthesis of Naturally Occurring Chromones and Quinones " is divided into six chapters.

CHAPTER I : Synthesis of Hormothamnione

Hormothamnione (1), the first naturally occurring styrylchromone isolated from the blue-green algae Hormothamnione enteromorphoides by Gerwick et al[1]. was found to be potent cytotoxic agent to P388 lymphocytic leukemia and HL-60 human promyelocytic cell lines.

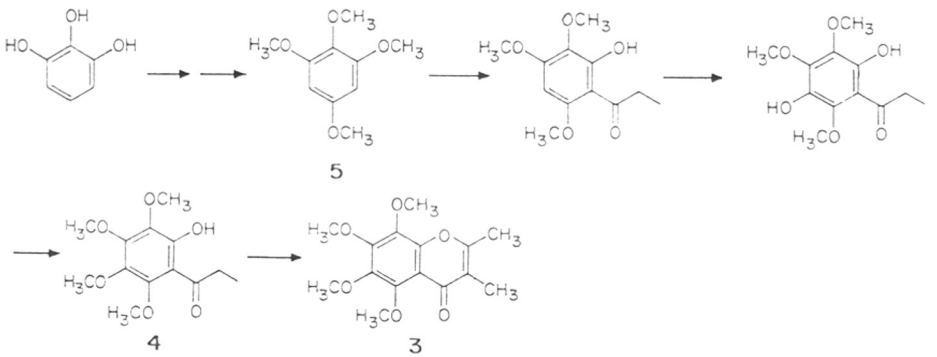


1: R = R¹ = H
2: R = CH₃ , R¹ = CH₂Ph

Total synthesis of 1 was achieved in two steps. Condensation of 2,3-dimethyl-5,6,7,8-tetramethoxychromone (3) with 3,5-bis (benzyloxy)benzaldehyde (NaOEt,EtOH) gave 2 which on debenzylation and selective demethylation of methoxy group at C-5 of the chromone nucleus with BCl_3 afforded 1. The key intermediate 2-hydroxy-3,4,5,6-tetramethoxypropiophenone (4) was prepared in three steps from easily accessible 1,2,3,5-tetramethoxybenzene (5) which was in turn prepared from pyrogallol. Thus 5 on Friedel-Crafts acylation with propionyl chloride (anhy. $AlCl_3$, Et_2O) followed by hydroxylation with potassium persulphate and partial methy-

lation gave 4. Application of Kostanecki-Robinson reaction on 4 (NaOAc,Ac_2O) afforded chromone 3 as summarised in SCHEME-1.1.

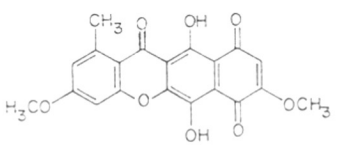
SCHEME-1.1



5 4 3

CHAPTER II : Total Synthesis of Bikaverin

Bikaverin (1), is a red pigment produced by several species of fungal genera Fusarium[2], Gibberalla and Mycogone. It possesses a number of interesting biological properties such as vacuolation inducing effect in fungi and in-vitro growth inhibiting activity towards the protozoan Leishmania brasiliensis and various tumor cells, the latter effected through uncoupling of the oxidative phosphorylation process.

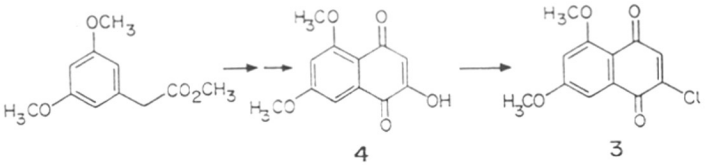


1

Although a number of syntheses of bikaverin are known, short, simple and regiospecific total synthesis of 1 was developed from methyl 2-hydroxy-4-methoxy-6-methylbenzoate (2)

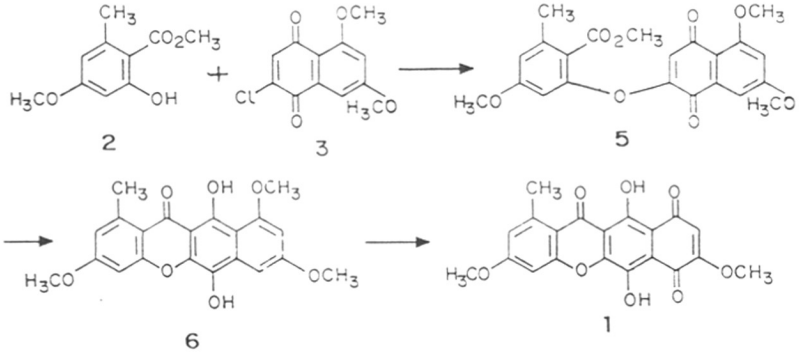
and 2-chloro-5,7-dimethoxy-1,4-naphthoquinone (3). Selective demethylation of methyl orsellinate dimethyl ether (anhyd.$AlCl_3$,CH_2Cl_2) gave 2, while 3 was prepared regiospecificaly from methyl 3,5-dimethoxyphenyl acetate as shown in SCHEME-2.1 .

SCHEME-2.1



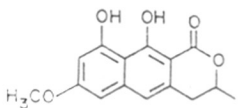
Phenoxynaphthoquinone 5 was obtained by coupling sodium salt of 2 (prepared with NaH) with chloronaphthoquinone 3 catalyzed by CuBr. Sodium dithionite reduction of 5 followed by cyclisation (conc. H_2SO_4) yielded xanthone derivative 6 [SCHEME-2.2]. Oxidation of 6 with trifluroperacetic acid in chloroform gave bikaverin (1).

SCHEME-2.2



CHAPTER III: Synthesis of Semivioxanthin

A number of antifungal naphtho[2,3-c]-pyran-1-(1H)-ones possessing a 7-methoxy and 9-and 10-phenolic hydroxy groups, eg.semivioxanthin (1), vioxanthin[3], SC-28762 and SC-30532 etc. have been isolated from natural sources. Biosynthetically they are considered to be produced from acetic acid *via* polyketides (ß-hydroxy oxoalkanoates). Semivioxanthin (1), was isolated under different culture conditions from *Penicillium citreo-viride*.



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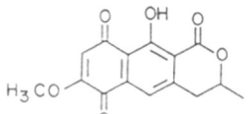
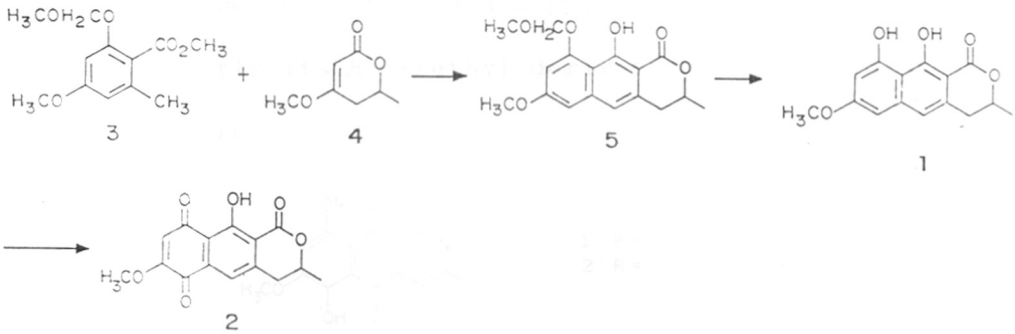


2

Although 1 was isolated in 1979, its first synthesis was reported by Yamaguchi *et al*.only in 1990 via polyketide approach in eleven steps. This prompted to develop a short and simple synthesis of 1 as outlined in SCHEME-3.1.

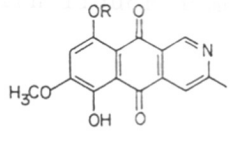
SCHEME-3.1



Methyl orsellinate dimethyl ether was selectively monodemethylated (CH_2Cl_2,anhy.$AlCl_3$) and the resulting -OH group was protected (NaH, $ClCH_2OCH_3$) as MOM ether to give 3 while the lactone 4, was prepared in two steps from triacetic lactone by hydrogenation (10% Pd-C,EtOAc,5 Kg/cm^2,) followed by methylation (DMS, K_2CO_3, acetone reflux). The anion of 3 was generated by treating it with 2 equiv. of LDA at -78°C and lactone 4 was slowly added at the same temperature,to give MOM protected semivioxanthin (5) which on deprotection (conc.HCl, THF) afforded 1 in good yield. Semivioxanthin (1) was then transformed to semixanthomegnin (2) by oxidation with potassium dichromate in acetic acid [SCHEME-3.1].

CHAPTER IV : Regiospecific Synthesis of Bostrycoidin

Bostrycoidin (1), the 2-azaanthraquinone was obtained from Fusarium bostrycoides[4] and F.solani D_2 purple, which showed in vitro activity against mycobacterium tuberculosis. Subsequently its 8-O-methyl derivative 2 was isolated from F. moiliforme.

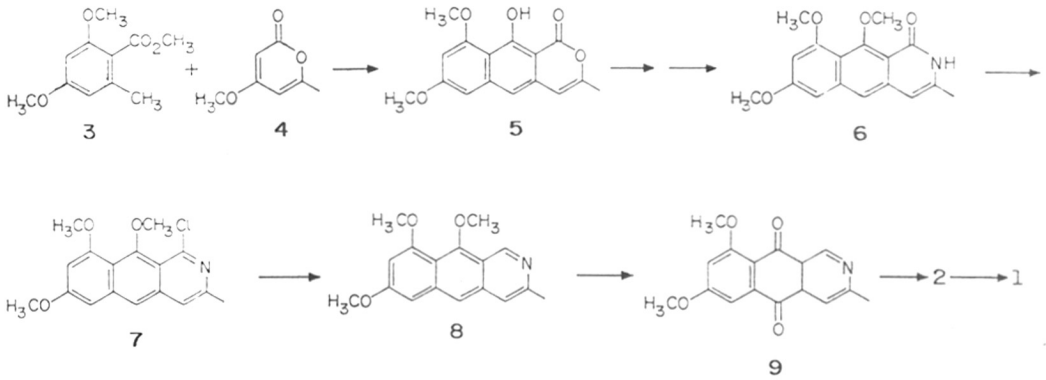


1 : R=H
2 : R=-CH_3

Synthetic approaches to 2-azaanthraquinones are limit-

ed. The existing methodologies for preparation of anthraquinones, such as Friedel-Crafts approaches are restricted because of lack of reactivity of pyridine ring towards electrophilic attack and inherent orientational ambiguities. Similar orientational problem which gives mixture of products also arises in free radical benzylation and benzoylation of pyridine ring. Therefore a simple, regiospecific and efficient synthetic sequence has been developed for bostrycoidin.

SCHEME-4.1



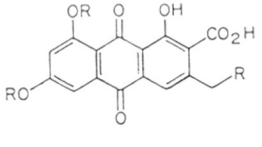
Reaction of the anion generated from methyl orsellinate dimethyl ether (3) (LDA,THF,-78°C) with triacetic lactone methyl ether (4) afforded naphthopyrone 5. The isoquinolone 6 was prepared from 5 by methylation followed by reaction with liquor ammonia. Conversion of isoquinolone 6 to chloroazaanthracene derivative was carried out with $POCl_3$. Reductive dehalogenation of 7 (TBTH,cat.AIBN) gave 8 which on oxidation with potassium dichromate in acetic acid

afforded azaanthraquinone 9. Since the photohydroxylation of 9 to 2 and its selective demethylation to 1 is known, this simple approach constitutes the formal total synthesis of bostrycoidin (1) as summarised in SCHEME-4.1.

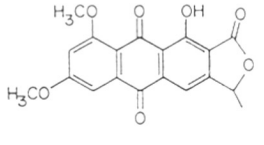
CHAPTER V: Synthesis of Austrocorticinic acid

Austrocorticinic acid (1), the first endocrocin type anthraquinone bearing a C_2 side chain, was isolated along with austrocorticin (2) from orange-red fruit bodies of an Australian toadstool belonging to genus Cortinaris[5].

The pigments 1 and 2 represents the first naturally occurring anthraquinones to be derived via a propionate triggered octaketides.



1: R = CH_3
1a: R = H



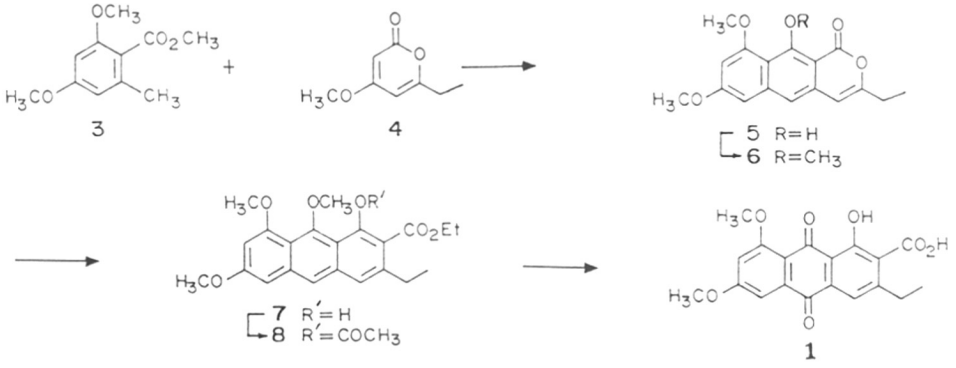
2

Naphthopyrone 5 obtained by condensation of methyl orsellinate dimethyl ether (3) and methyl triacetic lactone methyl ether (4) (LDA,THF,-78°C) was methylated to 6 (DMS,K_2CO_3,acetone).

Anthracene derivative 7 was obtained quantitatively by treating 6 with lithiated ethyl acetate at -78°C. The anthracene 7 was acetylated (Ac_2O, pyridine) to give 8. Oxida-

tion of 8 ($K_2Cr_2O_7$,acetic acid) followed by ester hydrolysis (KOH,MeOH) yielded autrocorticinic acid (1) as outlined in SCHEME-5.1.

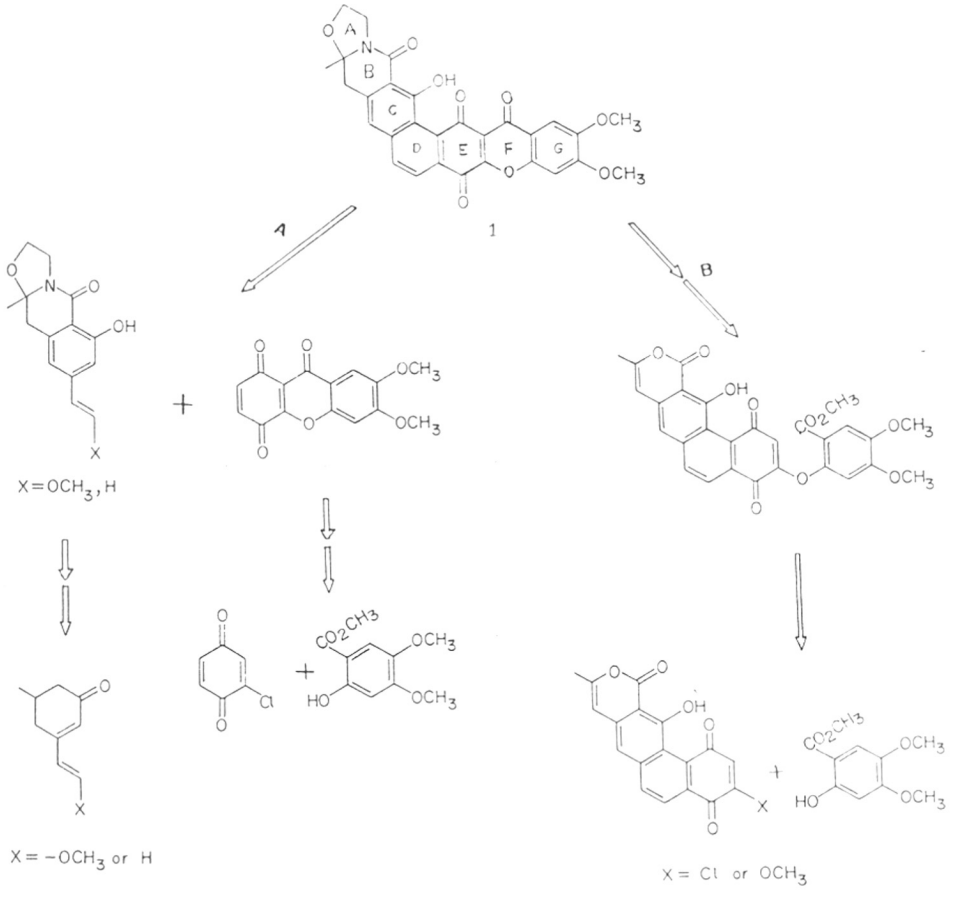
SCHEME-5.1



CHAPTER VI : Synthetic Approaches Towards Cervinomycin

Cervinomycins, novel antibiotics isolated by Omura et al. from Streptomyces cervinus sp. nov. consist of two components A_1 (1) and A_2 (2)(ring C hydroquinone) which are insoluble in most of the solvents. However the triacetyl derivative of 1 has high solubility and is being developed as a drug because of its low toxicity and antianaerobic activity against several bacteria. Cervinomycin's unique structure, a sensitive tetrahydro-oxasolo[3,2-b]benz[g]isoquinolone moiety fused angularly on xanthone unit, makes it synthetically challenging target.

RETROSYNTHETIC ANALYSIS



From retrosynthetic analysis it is readily revealed that cervinomycin could be synthesised by Diels-Alder approach (route A) or phenanthropyrone intermediate approach (route B).

DIELS-ALDER APPROACH (ROUTE A):

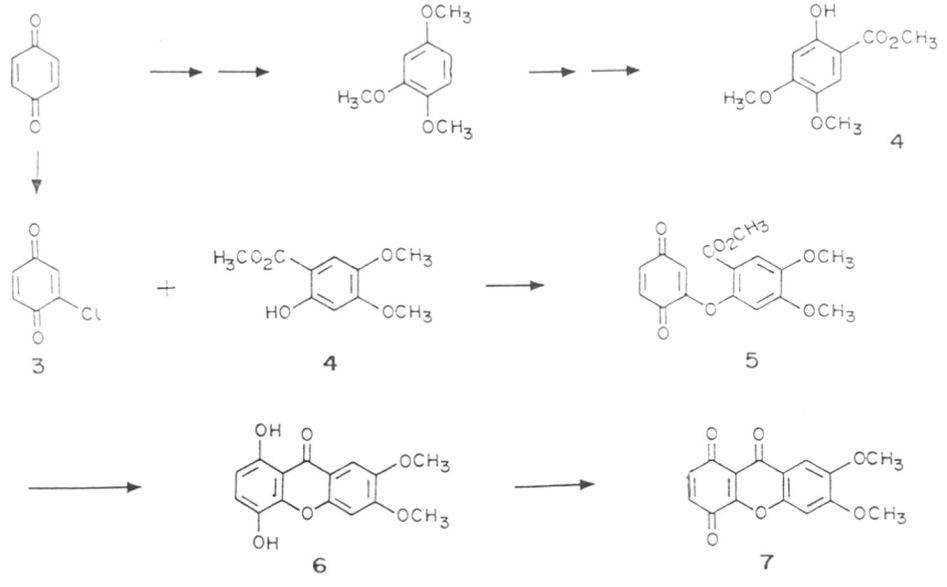
Diels-Alder reaction between the diene 10 and 6,7-dimethoxy xanthene-1,4,9-trione (7) can build up CDEFG ring system of cervinomycin which can be further elaborated to

cervinomycin.

Although a number of natural and unnatural xanthones are known, none of them is having a substitution pattern required for synthesis of cervinomycin. Therefore synthesis of the desired xanthone was developed starting from easily available 2-chloro-1,4-benzoquinone (3) and methyl 2-hydroxy-4,5-dimethoxybenzoate (4), which were prepared from 1,4-benzoquinone [SCHEME-6.1].

A mixture of O-hydroxy benzoate 4, chlorobenzoquinone 3 and anhyd. KF in anhyd. DMF was heated at 75°C to give phenoxybenzoquinone 5. Sodium dithionite reduction of 5 followed by cyclization (conc.H_2SO_4) yielded 1,4-dihydroxy-xanthone 6. Oxidation of 6 with silver(I) oxide gave

SCHEME-6.1

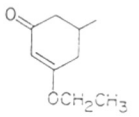


6,7-dimethoxyxanthene-1,4,9-trione (7) [SCHEME-6.1].

Preparation of dienes 10,11 and 12:

5-Methylcyclohexane-1,3-dione, required for preparation of dienes was obtained by Birch reduction (Na\liq.NH_3,EtOH) of orcinol dimethyl ether. Ethyl enol ether of 1,3-dione was prepared by refluxing it with benzene and ethanol in presence ofcatalytic P-TSA. Treatment of 8 with lithium acetylide-ethylene diamine complex gave ynone 9. Ynone 9 underwent MeOH addition reaction in presence of N-methyl morpholine to give diene 10. Grignard reaction of 8 with vinyl magnesium bromide yielded dienone 11, which was reduced to dienol 12 with diisobutyl aluminium hydride [FIGURE-I].

FIGURE-I



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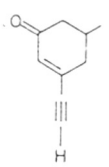

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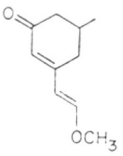

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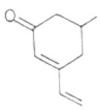

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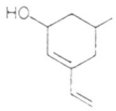


12

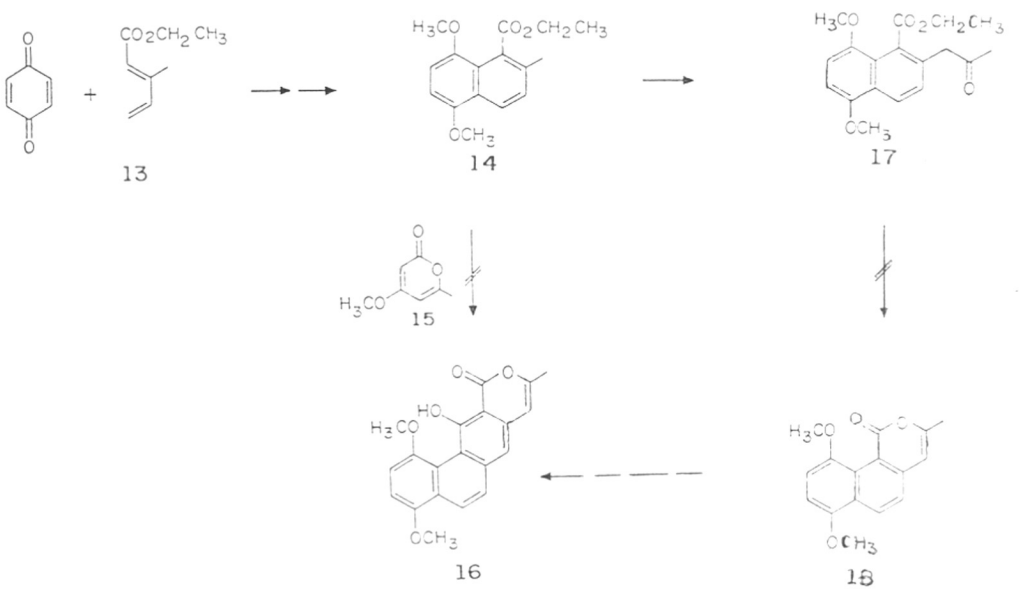
After successful preparation of quinone 7 and dienes 10,11 and 12,the Diels-Alder reaction of 7 or 5 with each diene (separately attempted under various conditions) failed to give desired cycloadduct. Therefore this approach was abandoned.

PHENANTHRENE INTERMEDIATE APPROACH (ROUTE B):

In this approach aim was to synthesise the intermediate phenanthropyrone 16 'or' naphthopyrone 18, which could be further elaborated to cervinomycin.

Diels-Alder adduct obtained by reaction between 1,4 benzoquinone and ethyl 3-methylpenta-2,4-dienoate (13) was methylated and aromatized to give naphthoate 14. Reaction of lithiated naphthoate 14 (LDA,THF,-78°C) with triacetic lactone methyl ether (15) failed to give required phenanthropyrone 16 while the same anion of 14 when treated with ethyl acetate at -78°C

SCHEME-6.2



gave keto-ester 17. However the cyclization of 17 under basic condition as well as basic hydrolysis and acidic

cyclization failed to give naphthopyrone 18, which could have been converted to phenanthropyrone 16 as outlined in SCHEME-6.2.

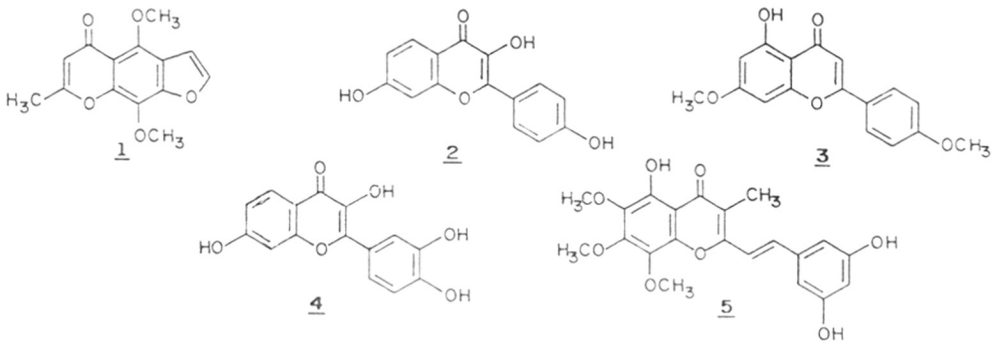
CHAPTER-I

SYNTHESIS OF HORMOTHAMNIONE

The chromones, flavones and related compounds which are widely distributed in nature have been found to play an important role in a number of biological processes.[1-3] In humans, naturally occurring chromones and flavones have shown biological effects as well. These compounds are typified by the furochromone khellin (1) (FIGURE-I), which has exhibited lipid-altering capabilities[4], or by 3,4',7-trihydroxyflavone (2), 5-hydroxy-4,7-dimethoxyflavone (3) and 3,3',4',7-tetrahydroxyflavone (4), which have been shown to possess antiinflammatory activity[5].

Hormothamnione (5), the first naturally occurring styrylchromone isolated by Gerwick et al.[6] from blue green algae Hormothamnion enteromorphides, was shown to be 2-(3',5'-dihydroxystyryl)-5-hydroxy-3-methyl-6,7,8-trimethoxy chromone. Its structure was determined on the basis of spectral properties and X-ray analysis of its triacetate derivative. Hormothamnione (5) has been shown to be a potent cytotoxin to several human leukemia cell lines in vitro[6]. While mechanism of its cytotoxic activity has not been fully understood, it appears to operate via selective inhibition of RNA synthesis[6]. Hormothamnione lacks the catechol moiety characteristic of other flavone materials that break nuclear material[7]. Furthermore, the 3-methyl substituent is rare in other naturally occurring chromones and flavones. Recently it was found that hormothamnione have no effect on the growth of HIV virus[8].

FIGURE-I



SYNTHESIS OF HORMOTHAMNIONE:

Under this sub-heading, the total synthesis of hormothamnione is covered. This includes two approaches reported in the literature[9,10]. The present work also describes total synthesis of hormothamnione.

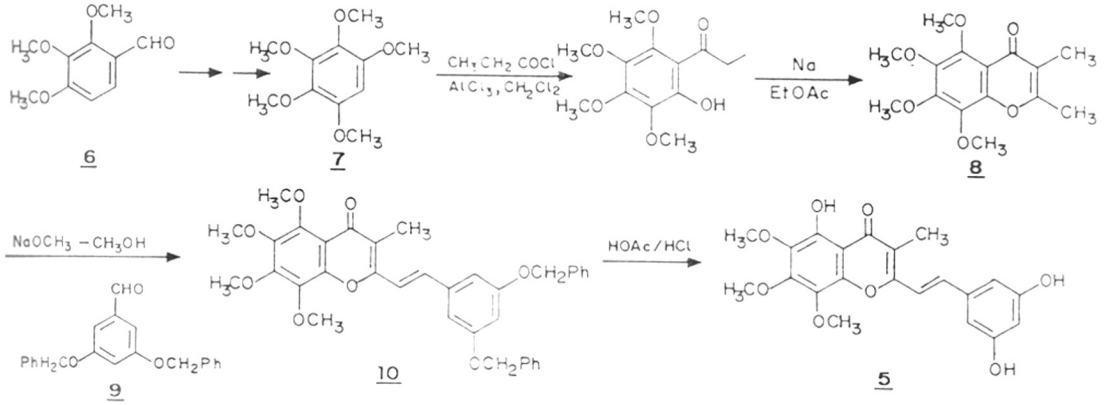
The first total synthesis of hormothamnione was reported by Alonso and Brossi[9] (SCHEME-1.1) wherein 2,3-dimethyl-5,6,7,8-tetramethoxychromone (8) was condensed with 3,5-bis(benzyloxy)benzaldehyde (9) using sodium methoxide in methanol at room temperature affording the styrylchromone 10. Debenzylation and selective demethylation of 10 was carried out by refluxing it with mixture of acetic acid and hydrochloride acid (10:2) to give hormothamnione (5) as a yellow solid.

The required chromone 8 was prepared from 1,2,3,4,5-pentamethoxybenzene (7) in two steps. The latter was prepared from 2,3,4-trimethoxybenzaldehyde (6) using known

literature procedure.

Recently in 1990, synthesis of hormothamnione was reported by McGarry et al.[10] (SCHEME-1.2) based on novel methodology for the synthesis of chromone derivatives. The key reaction involved in the synthesis of chromone 14 was the intramolecular acylation of 2,3,4,5-tetramethoxyphenol (11) with methylpropoilic acid (12) using Eaton's reagent (10% P_2O_5 in methanesulfonic acid). Therefore, the synthetic route to hormothamnione (5) was developed

SCHEME-1.1

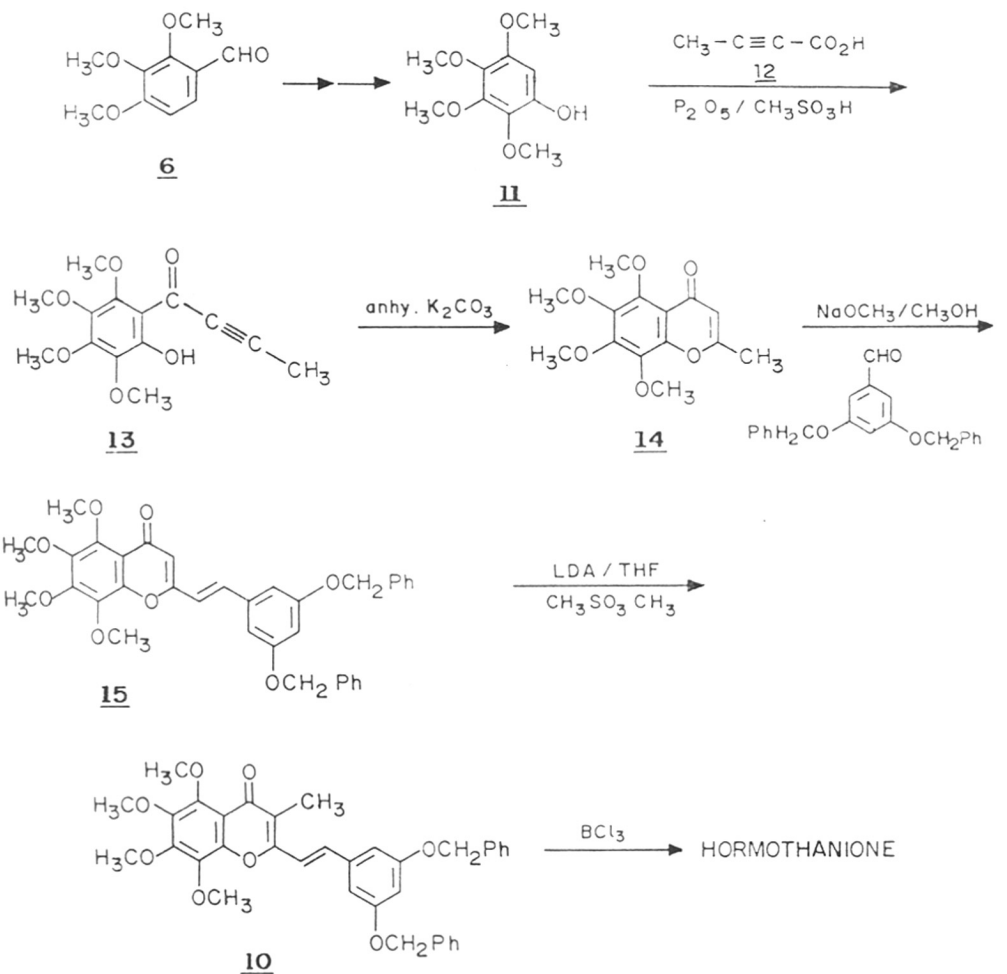


where both C-3 methyl substituent and styrylaryl group was introduced at the late state of the synthesis. The total synthesis of 5 was accomplished by the sequence of reactions as outlined in SCHEME-1.2. The synthesis of 5,6,7,8-tetramethoxy substituted styrylchromone (15) via cycloacylation procedure requires 2,3,4,5-tetramethoxyphenol (11). The phenol 11 was prepared in six steps with an overall yield

of 40% from 2,3,4-trimethoxybenzaldehyde (6).

In conclusion, this synthetic route to hormothamnione (5) gives an overall yield of 24% for the five steps of the reaction from the tetramethoxyphenol (11). The first synthesis of 5 has similar overall yield[10] from pentamethoxybenzene 6.

SCHEME-1.2



PRESENT WORK:

Blue green algae have recently received considerable attention by academic researchers,[12,13] the national cancer institute[14] and industry[15] as a new source of novel bioactive natural products. Hormothamnione (5) was isolated from Hormothamnion enteromorphoides and its novel styrylchromone structure solved by X-ray crystallography by Gerwick et al.[6] Metabolite 5 is a potent cytotoxin to several human cancerous cell lines and appear to operate via inhibition of RNA synthesis[6].

The styrylchromone structure of hormothamnione 5 is unprecedented in natural products although the carbon skeleton is known from synthetic studies[16]. Its attractive biological activity together with the limited resources[6] and tedious isolation method made its synthesis highly desirable. There was no synthesis of hormothamnione reported when the present work on the synthesis was undertaken in late 1987.

In the present work, synthesis of hormothamnione was effected by condensation of 2,3-dimethyl-5,6,7,8-tetramethoxychromone (8) with benzyl protected 3,5-dihydroxybenzaldehyde (9) followed by deprotection and selective demethylation of the methoxy group at C-5 of the chromone nucleus.

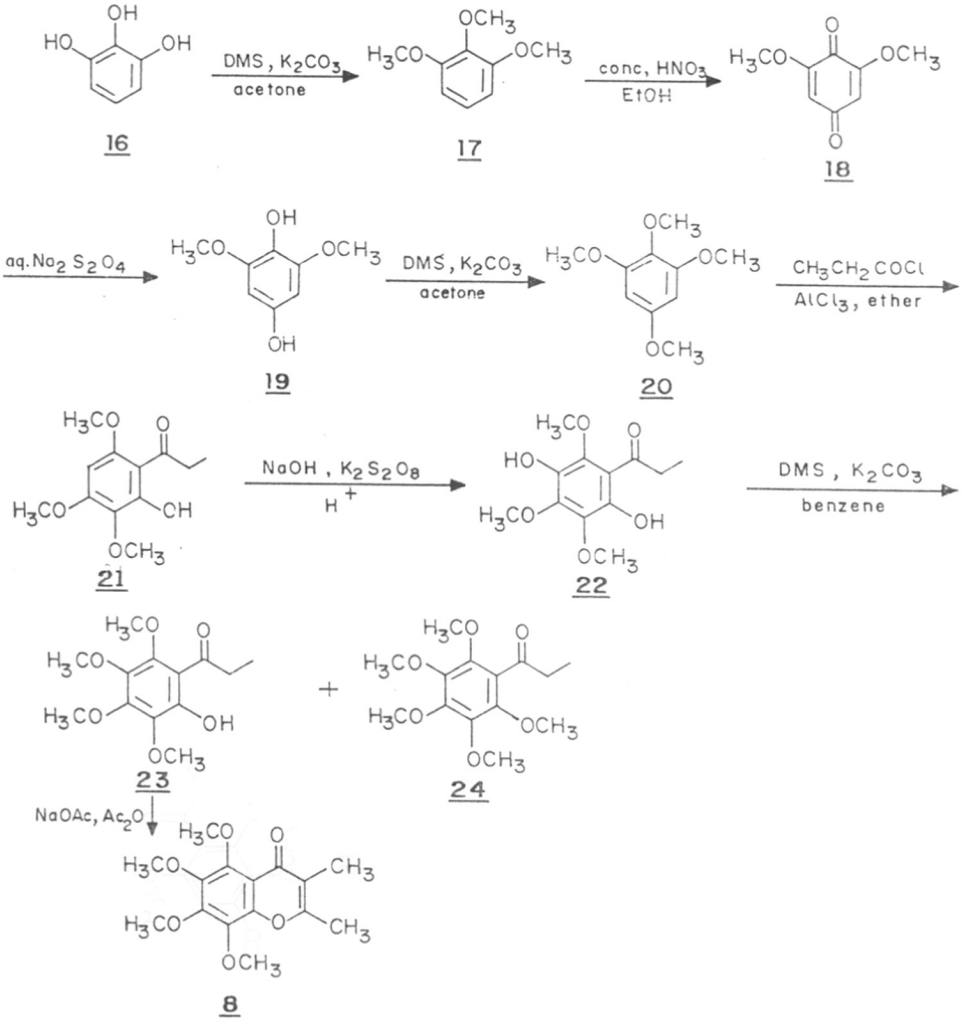
The fully functionalized chromone 8 required for the condensation reaction with benzaldehyde counterpart 9, was

obtained[17] from 1,2,3-trihydroxybenzene (16) (pyrogallol) as shown in SCHEME-1.3. Thus, methylation of 16 with dimethyl sulphate in the presence of potassium carbonate in acetone gave trimethyl ether 17, which was subjected to the oxidation reaction with concentrated nitric acid in ethanol to furnish the quinone 18. Reduction of the quinone 18 with sodium dithionite followed by methylation with dimethyl sulphate-potassium carbonate in acetone yielded 1,2,3,5-tetramethoxybenzene (20). Friedel-Crafts acylation of the compound 20 with propionyl chloride and anhydrous aluminium chloride in dry ethereal solution at room temperature yielded crystalline 2-hydroxy-3,4,6-trimethoxypropiophenone (21) (FIG.II) Oxidation[17] of the hydroxypropiophenone 21 with alkaline potassium persulphate gave 2,5-dihydroxy-3,4,6-trimethoxypropiophenone (22) in 46% yield. Partial methylation of 22 with dimethyl sulphate and potassium carbonate in benzene afforded 2-hydroxy-3,4,5,6-tetramethoxypropiophenone (23) (FIG.III) in 50% yield along with pentamethoxypropiophenone (24) (45%). The latter on treatment with anhydrous aluminium chloride in ether underwent selective dimethylation[18] reaction affording 23 quantitatively.

Having obtained the key intermediate, 2-hydroxy-3,4,5,6-tetramethoxypropiophenone (23), the next reaction (Kostanecki-Robinson reaction[19]) on it was carried out with acetic anhydride and sodium acetate at 180°C to give 2,3-dimethyl-5,6,7,8-tetramethoxychromone (8) in 35% yield (SCHEME-1.5). The IR spectrum of compound 8 showed carbonyl absorption

band at 1620 cm^{-1}. The ^1H-NMR spectrum (**FIG.IV**) revealed two singlets at δ 2.01 and 2.40 for two methyl protons and

SCHEME-1.3



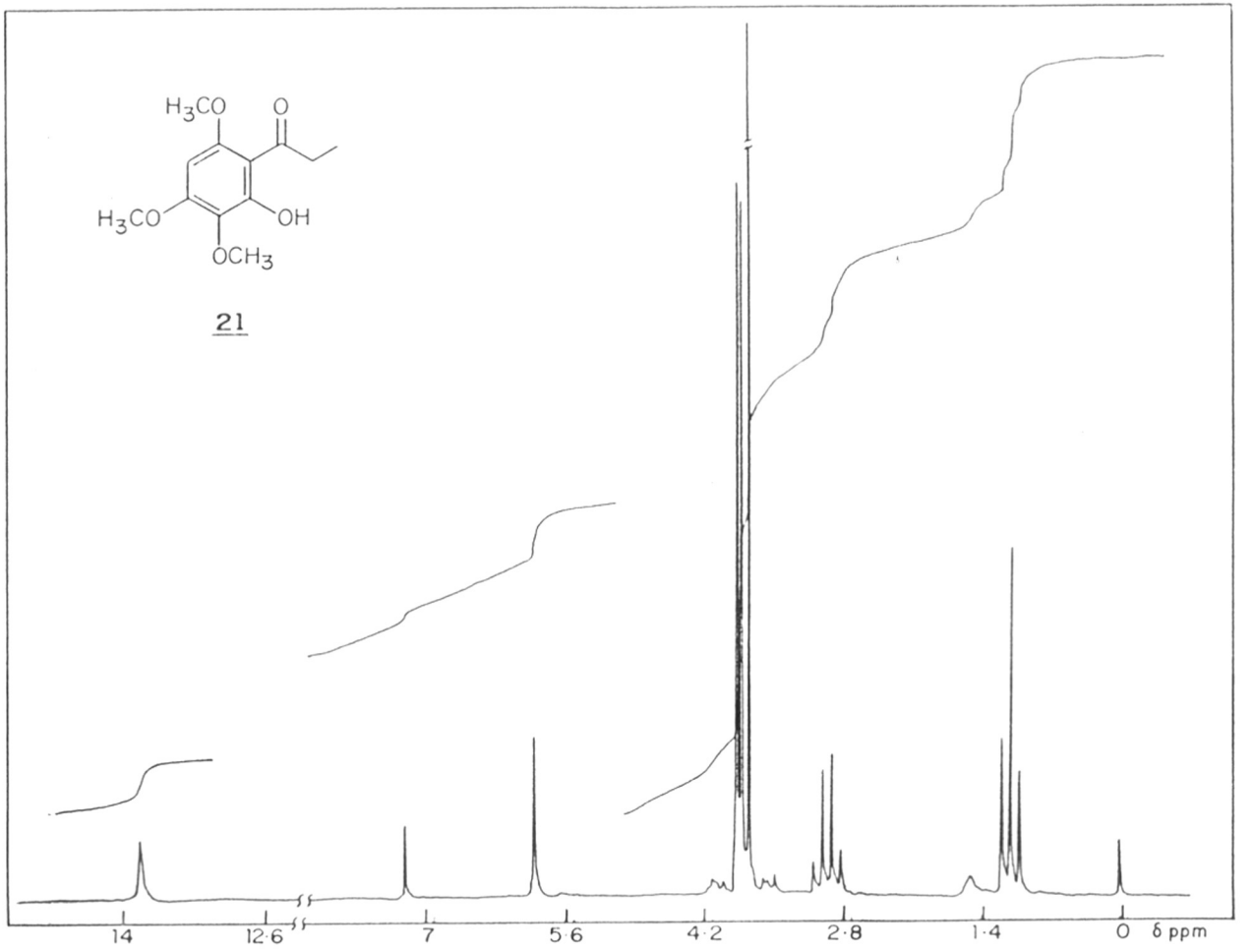


FIG. II : ^{1}H-NMR SPECTRUM OF THE COMPOUND (21) IN $CDCl_3$

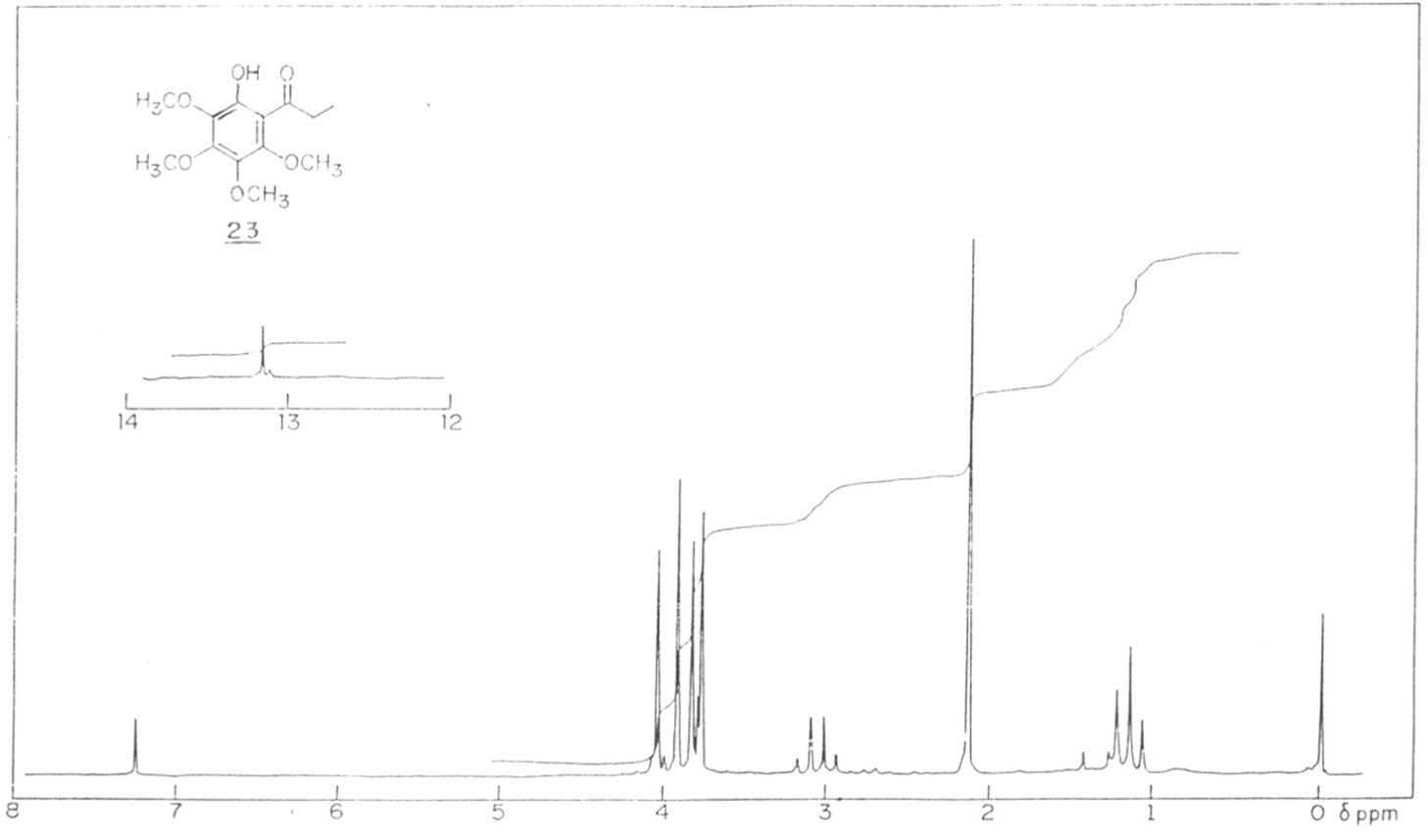
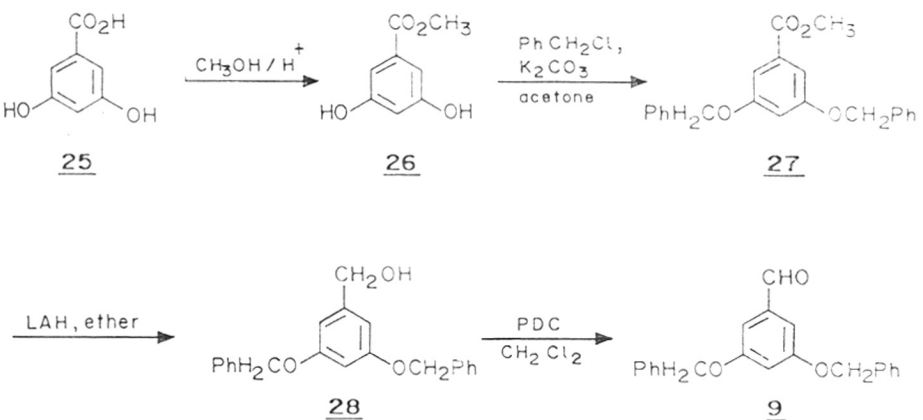


FIG. III: ^{1}H-NMR SPECTRUM OF THE COMPOUND (23) IN $CDCl_3$

disappearance of a peak at δ 13.15 for -OH chelated with carbonyl function providing necessary confirmation for the structure of 8.

After successful preparation of chromone 8, the aromatic aldehyde 9 required for the condensation was synthesised according to SCHEME-1.4 in four steps with 72% overall yield.

SCHEME 1.4



Thus, 3,5-dihydroxybenzoic acid (25) was esterified by refluxing it with anhydrous methanol in presence of catalytic sulphuric acid to furnish ester 26. Benzylation[20] of ester 26 with benzyl chloride-anhydrous potassium carbonate in refluxing acetone afforded dibenzyl ether 27, which was reduced[21] to an alcohol 28 by lithium aluminium hydride in diethyl ether. The alcohol 28 was oxidized with pyridinium dichromate[22] in dichloromethane to give 3,5-bis-(benzyloxy)benzaldehyde (9).

Condensation of the chromone 8 with aldehyde 9 by using

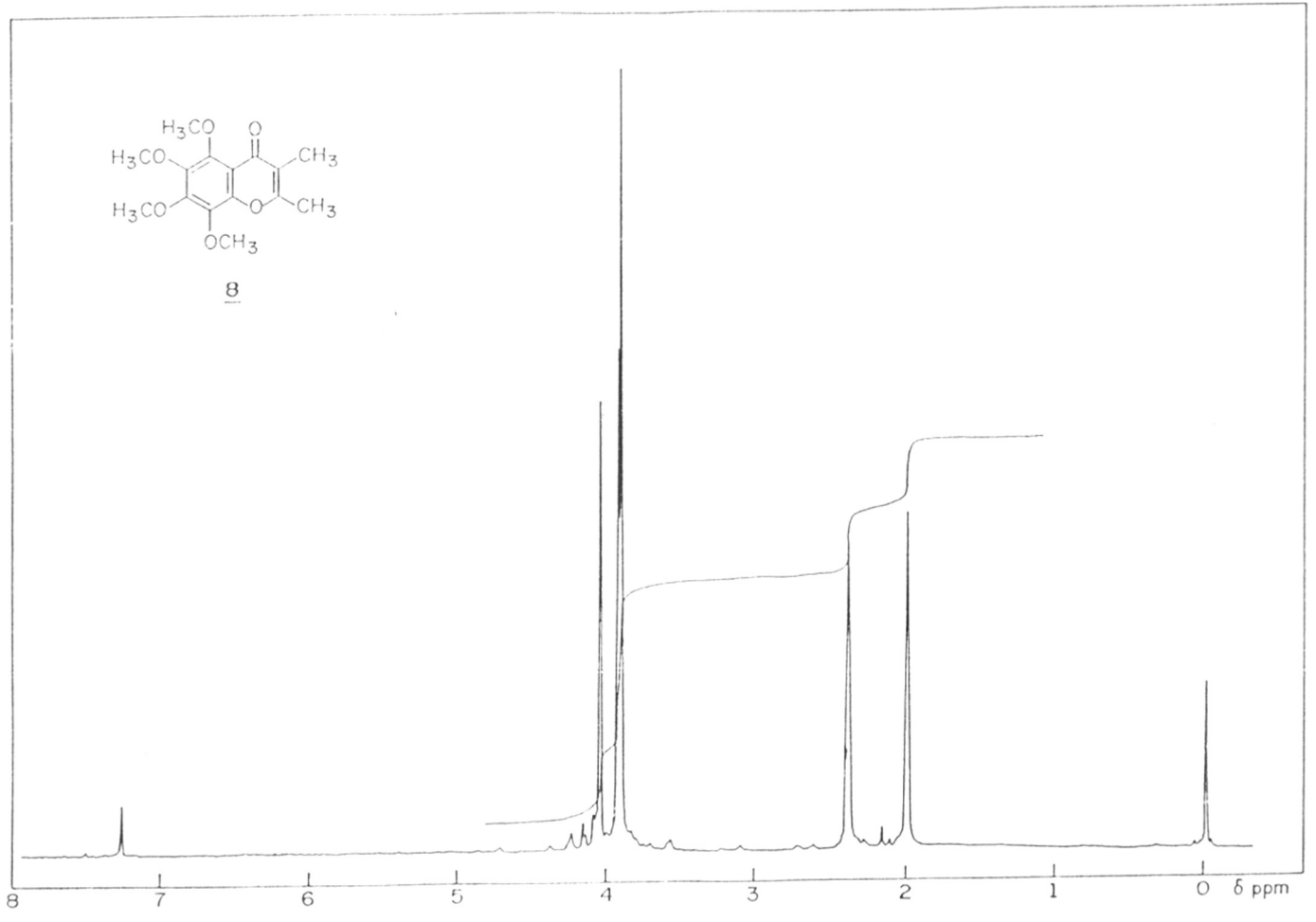
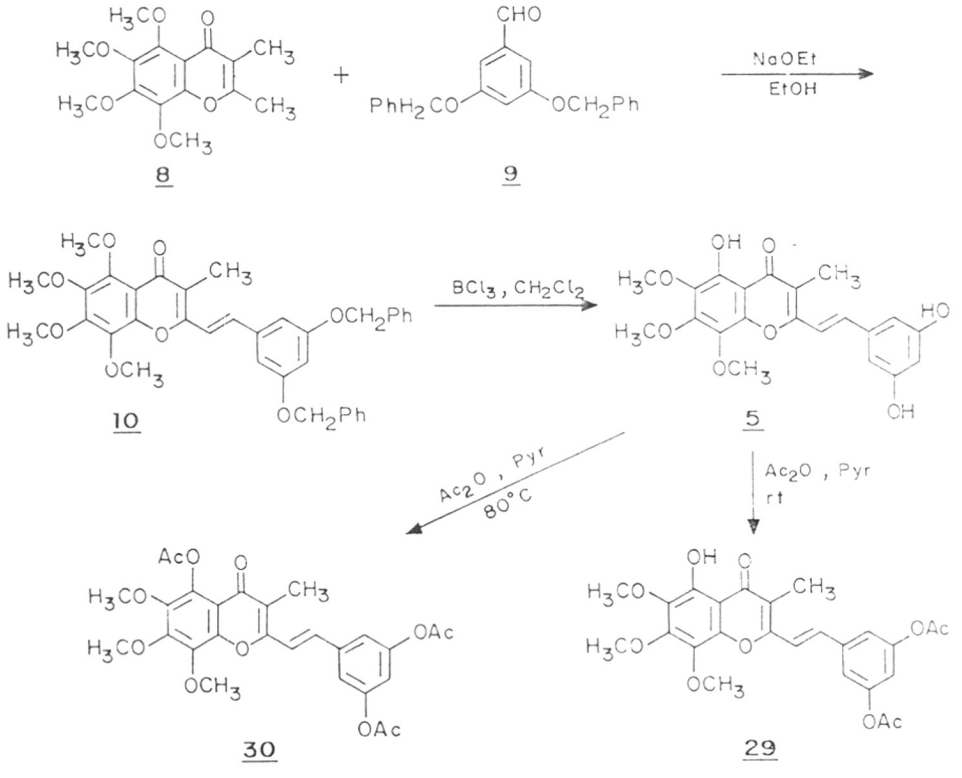


FIG. IV : ^{1}H-NMR SPECTRUM OF THE COMPOUND (8) IN $CDCl_3$

sodium ethoxide in ethanol afforded quantitative yield of 2-[2-[3,5-bis-(benzyloxy)phenyl]ethenyl]chromone (10)

SCHEME-1.5



8 + 9 → 10 → 5 → 30 and 29

(FIG.V). The styrylchromone 10 on treatment with boron trichloride[23] in dichloromethane at -15°C underwent selective demethylation of C-5 methoxy group at chromone nucleus as well as debenzylation to afford hormothamnione (5) (FIG.VI) in almost quantitative yield (SCHEME-1.5). It was found to be identical with natural hormothamnione[6] in all respects. With acetic anhydride and pyridine at room tem-

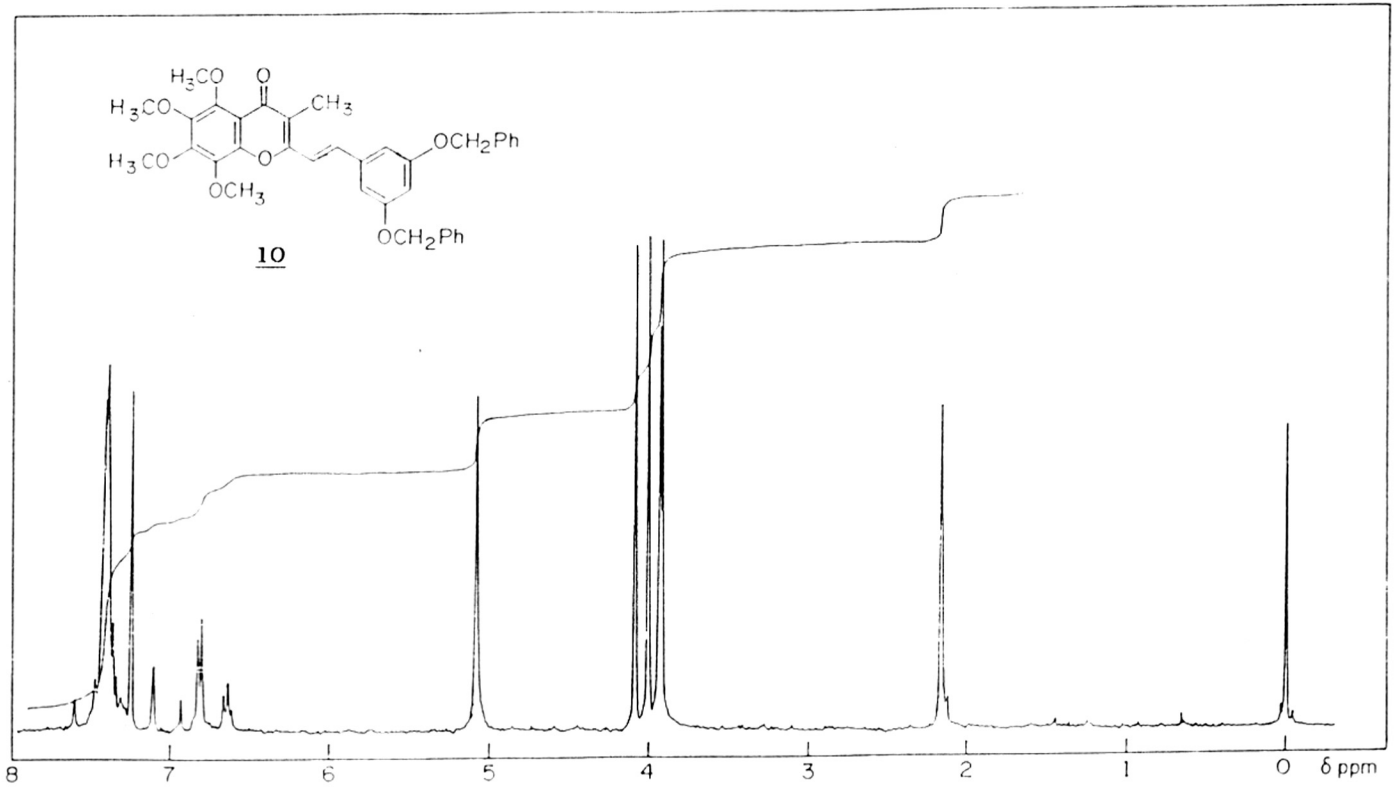


FIG. X : ^{1}H-NMR SPECTRUM OF THE COMPOUND (10) IN $CDCl_3$

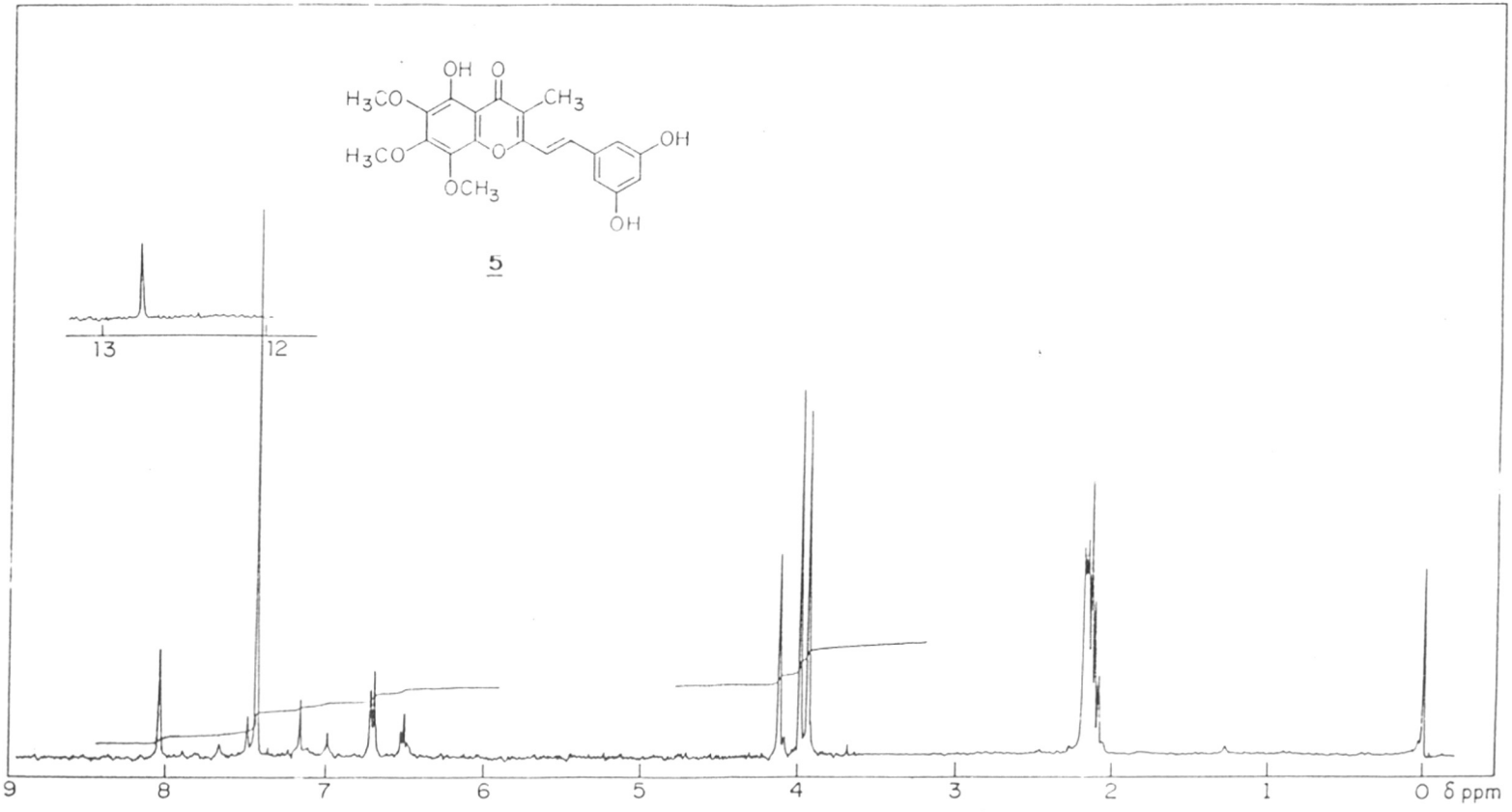


FIG. VI : ^{1}H-NMR SPECTRUM OF THE COMPOUND (5) IN ($CDCl_3$ + ACETONE D_6)

perature for 24 h, it gave the diacetate derivative 29; m.p. 180°C. The ^{1}H-NMR showed peak at δ 12.66 corresponding to chelated C-5 hydroxyl group, which exchanges with D_2O. Under similar conditions formation of triacetate 30 was reported[6]. The compound 5 was then heated with acetic anhydride-pyridine mixture at 80°C for 6 h to give triacetate 30 (85%) as colourless plates.

EXPERIMENTAL

1,2,3-Trimethoxybenzene (17):

A mixture of 1,2,3-trihydroxybenzene 16 (31.5 g, 0.25 mmol) dimethyl sulphate (138 g, 1 mol) and anhydrous potassium carbonate (126 g, 0.76 mol) in dry acetone (700 ml) was refluxed with occasional shaking for 12 h. The acetone was distilled off and cold water was introduced, whereby a solid separated was filtered, washed with water and dried to obtain 17 quantitatively as a white solid (41 g; 99%); m.p. 47°C, (Lit.[24], m.p. 47°C).

2,6-Dimethoxy-1,4-Benzoquinone (18):

The pyrogallol trimethyl ether 17 (26 g, 0.15 mmol), ethyl alcohol (125 ml) and conc. nitric acid (125 ml, d 1.2) were warmed to 35°C and allowed to stand until the vigorous reaction sets in and the temperature kept just below 50°C by external cooling with water till the main heat evolution ceases (15 min.) After 4 h with occasional shaking the quinone 18 collected, drained, washed with alcohol (125 ml), then water (200 ml) and dried to afford 16.5 g of 18 (63%); m.p. 251-252°C (yellow needles from acetic acid) (Lit.[17,24], m.p. 252°C).

2,6-Dimethoxyquinol (19):

To the mixture of quinone 18 (16.5 g, 0.098 mol) and sodium dithionite (33 g), boiling water (200 ml) was quickly added and the mixture vigorously shaken till a clear solu-

tion was obtained (less than 1 min.) and then cooled rapidly under the tap with shaking. After 30 min the product was collected by filtration, washed with ice cold water (100 ml) and dried on the steam-bath to yield 12.5 g of **19** (75%) as a white amorphous powder; m.p. 159°C (Lit.[24], m.p. 160°C).

1,2,3,5-Tetramethoxybenzene (20):

A mixture of quinol **19** (12.5 g, 0.0735 mol), anhydrous potassium carbonate (30.44 g, 0.22 mol) and dimethyl sulphate (27.75 g, 0.22 mol) in dry acetone (250 ml) was heated at reflux temperature for 10 h. The acetone distilled off, water (200 ml) was added to the residue and kept standing overnight to decompose any excess dimethyl sulphate. It was then cooled by adding crushed ice (100 g) and the solid separated was collected, washed with cold water and dried to give 13 g. of tetramethoxybenzene **20** (89%); m.p. 46-47°C (Lit.[17], m.p. 47°C and Lit.[25], b.p. 109-110°C/0.9 mm Hg).

2-Hydroxy-3,4,6-trimethoxypropiophenone (21):

Anhydrous aluminium chloride (10 g, 75 mmol) was dissolved in absolute ether (50 ml) with cooling, and then 1,2,3,5-tetramethoxybenzene **20** (9.9 g, 50 mmol) was added. To this stirred and cooled mixture propionyl chloride (5.1 g, 55 mmol) was added during 30 min. and stirred for 6 h. After standing overnight the mixture of water (70 ml) and conc. HCl (15 ml) was cautiously added and the mixture was heated on the water bath for 30 min., the ether being allowed to distill off. It was then cooled and extracted with

ethyl acetate (3 x 100 ml). The ethyl acetate layer was washed with water and concentrated to give a residue. To the residue 10% aqueous sodium hydroxide (100 ml) was added, shaken vigorously and filtered. Filtrate on acidification with dilute HCl gave sufficiently pure 21 as a colourless solid (10 g, 83%). It was crystallized from dilute alcohol to give colourless crystalline powder (9.2 g, 76%); m.p. 134°C.

IR (Nujol): $\tilde{\nu}$ max 1630 and 1600 cm^{-1}.

^{1}H-NMR : δ 1.26 (t, 3H), 3.08 (q, 2H), 3.85 (s, 3H), 3.92 (s, 3H), 3.99 (s, 3H), 6.02 (s, 1H) and 13.93 (s, 1H).

Ms (m/e): 240 (M^+).

Analysis cal. for $C_{12}H_{16}O_5$: C, 60.00; H, 6.66;

Found : C, 59.86; H, 6.86%.

2,5-Dihydroxy-3,4,6-trimethoxypropiophenone (22):

To the stirred solution of propiophenone 21 (10 g, 0.04 mol) in 16% aqueous NaOH (100 ml) was added a solution of potassium persulphate (16.9 g, in 340 ml H_2O, 0.063 mol) during 4 h at room temperature while cooling the reaction vessel in a trough of water. After standing for 48 h it was made distinctly acidic to congo-red paper with hydrochloric acid, extracted with benzene (100 ml), dried (Na_2SO_4) and the solvent distilled off leaving a residue of crude starting material 21 (2 g). To the aqueous solution were added concentrated hydrochloric acid (100 ml) and benzene (200 ml) and the mixture gently refluxed on water bath for 6 h,

partially cooled and the benzene layer separated. The aqueous solution was extracted with benzene (2 x 50 ml), the organic extracts were united, dried (Na_2SO_4) and concentrated. Pure compound 22 (3.9 g, 46%, m.p. 80°C) was obtained by chromatography on silica gel eluting with 5% ethyl acetate in pet. ether.

IR(Nujol): ν max 3485 and 1625 cm^{-1}.

^{1}H-NMR : δ 1.18 (t, 1H), 3.10 (q, 2H), 3.80 (s, 3H), 3.85 (s, 3H), 4.07 (s, 3H) and 12.82 (s, 1H).

MS(m/e): 256 (M^+).

Analysis cal. for $C_{12}H_{16}O_6$: C, 56.25; H, 6.25;

Found : C, 56.41; H, 6.39%.

2,Hydroxy,3,4,5,6-tetramethoxypropiophenone (23):

A mixture of 2,5-dihydroxy-3,4,6-trimethoxypropiophenone 22 (4 g, 15.6 mmol), dimethyl sulphate (2.95 g, 23.4 mmol) and anhydrous potassium carbonate (3.23 g, 23.4 mmol) in anhydrous benzene (30 ml) was refluxed with occasional shaking for 10 h. Water (50 ml) was added, the reaction mixture shaken, benzene layer separated and aqueous layer extracted with benzene (2 x 25 ml). The benzene extracts were combined, washed with saturated brine solution, dried (Na_2SO_4) and distilled leaving an oil which was chromatographed (silica gel, eluent: 2% ethyl acetate-pet. ether) to give 23 as a yellow oil (2.15 g, 50%) and pentamethoxypropiophenone 24 (1.9 g, 45%) also as an yellow oil.

A mixture of 24 (1.9 g) and anhydrous aluminium chloride (1.26 g, 9.5 mmol) in anhydrous ether (20 ml) was

stirred for 7.5 h at room temperature. The solvent ether was removed under reduced pressure to give greenish-yellow aluminium chloride complex which was decomposed by addition of water (25 ml) and conc. HCl (5 ml). The resulting solution was extracted with dichloromethane, washed with water, dried (Na_2SO_4) and evaporated to give almost quantitative yield of ortho-hydroxypropiophenone 23 (1.7 g) as a yellow oil.

IR (Neat): $\bar{\nu}$ max 1630 and 1600 cm^{-1}.

^{1}H-NMR : δ 1.13 (t, 3H), 3.04 (q, 2H), 3.77 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 4.04 (s, 3H) and 13.15 (s, 1H).

MS (m/e): 270 (M^+).

Analysis cal. for $C_{13}H_{18}O_6$: C, 61.22; H, 6.12;

Found : C, 61.40; H, 6.10%.

2,3-Dimethyl-5,6,7,8-tetramethoxychromone (8):

Compound 23 (2.0 g, 7.4 mmol) was mixed with freshly fused sodium acetate (2.4 g, 33 mmol) and acetic anhydride (20 ml) and refluxed gently with stirring vigorously in an oil bath for 8 h. The acetic anhydride distilled off under reduced pressure, water (20 ml) was added and stirred at room temperature for 30 min. It was then extracted with ethyl acetate (3 x 25 ml), combined extracts were dried (Na_2SO_4) and evaporated to leave a residue which after column chromatographic purification on silica gel with 10% ethyl acetate-pet. ether afforded chromone 8 as a colourless solid (0.769, 35%). Recrystallization from n-hexane gave

crystalline colourless solid; m.p. 98°C (Lit.[9], m.p. 95°C).

IR(Nujol): ν max 1625 cm^{-1}.

^{1}H-NMR : δ 2.01 (s, 3H), 2.40 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H) and 4.07 (s, 3H).

MS (m/e): 294 (M^+).

Analysis cal. for $C_{15}H_{18}O_6$: C, 61.22; H, 6.12;

Found : C, 61.13; H, 6.30%.

Methyl 3,5-dihydroxybenzoate (26):

A mixture of 3,5-dihydroxybenzoic acid **25** (10 g, 59.5 mmol), concentrated H_2SO_4 (0.5 ml) and anhydrous methanol (50 ml) was refluxed on water bath for 10 h. The methanol distilled off completely, water (100 ml) was added to the residue, solid separated was filtered, washed repeatedly with water and dried to give methyl 3,5-dihydroxy benzoate **26** (10.5 g, 97%); m.p. 162°C (Lit.[20], m.p. 163-165°C).

Methyl 3,5-bis(benzyloxy)benzoate (27):

A mixture of the ester **26** (10 g, 59 mmol), benzyl chloride (15 g, 119 mmol) and freshly dried potassium carbonate (24.6 g, 128 mmol) in dry acetone (200 ml) was refluxed for 18 h. The acetone was distilled off, water (200 ml) was added, whereby solid separated was collected, washed with water and dried to furnish methyl 3,5-dibenzyloxybenzoate **27** (19.2 g, 93%), as a crystalline colourless solid; m.p. 80°C (MeOH) (Lit.[20], m.p. 77.5-79.5°C).

3,5-Bis(benzyloxy)benzylalcohol (28):

A solution of benzoate **27** (19 g, 54.6 mmol) in anhydrous diethyl ether (30 ml) was added dropwise during 20 min. to an ice cold suspension of LAH (1.56 g, 41 mmol) in anhydrous ether (100 ml). After complete addition, it was stirred at room temperature for 4 h. The excess LAH was decomposed by dropwise addition of ethyl acetate to the reaction mixture. Water (2 ml) was introduced into the reaction mixture followed by saturated solution of sodium sulphate (5 ml) and stirred for 10 min. The solid separated was filtered and washed with ether (2 x 20 ml). The filtrate on concentration yielded 3,5-bis(benzyloxy)benzylalcohol **28** (16.24 g, 93%); m.p. 65°C (Lit.[21], m.p. 65-66°C).

3,5-bis(benzyloxy)benzaldehyde (9):

A mixture of 3,5-bis(benzyloxy)benzylalcohol **28** (16 g, 50 mmol) and pyridinium dichromate (28.12 g, 75 mmol) in anhydrous dichloromethane (75 ml) was stirred at room temperature for 6.5 h. Anhydrous ether (50 ml) was added and stirred for an additional 30 min. It was then filtered through celite pad and the filtrate was evaporated under reduced pressure to give crude aldehyde **9** (15 g, 94%). Recrystallization from aqueous ethanol afforded, shining colourless plates (14 g, 88%); m.p. 80°C (Lit[26], m.p. 80°C).

5,6,7,8-Tetramethoxy-2-[2-[3,5-bis(benzyloxy)phenyl]ethenyl] chromone (10):

A mixture of the chromone 8 (0.650 g, 2.2 mmol) and 3,5-bis(benzyloxy)benzaldehyde 9 (0.703 g, 2.2 mmol) and sodium ethoxide [prepared by dissolving sodium (0.1 g) in anhydrous ethanol (15 ml)] in anhydrous ethanol (50 ml) was refluxed with stirring for 5 h. The reaction mixture was allowed to cool to room temperature and stirred for 2h, whereby yellow solid separated was filtered, washed with water and dried to give styrylchromone 10 (1.25 g, 95%); m.p. 119°C (Lit.[9], 118°C).

IR (Nujol): ν max 1630 and 1580 cm^{-1}.

^{1}H-NMR : δ 2.18 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 4.02 (s, 3H), 4.10 (s, 3H), 5.11 (s, 4H), 6.64 (t, J = 2 Hz, 1H), 6.82 (d, J = 15.8 Hz, 1H), 7.05 (d, J = 15.8 Hz, 1H) and 7.36 - 7.48 (m, 11H).

MS (m/e): 594 (M^+).

Analysis calc. for $C_{36}H_{34}O_8$: C, 72.72; H, 5.72;

Found : C, 72.56; H, 5.91%.

Hormothamnione (5):

The styrylchromone 10 (0.5 g, 0.85 mmol) was dissolved in dichloromethane (15 ml) and cooled to -15°C. To this stirred solution under argon atmosphere was injected 1.0 M BCl_3 in CH_2Cl_2 (3 ml) dropwise and stirred for 1 h at -15°C. The reaction was quenched by addition of methanol (5 ml). The solvent was removed under reduced pressure, diluted with

water (50 ml) and extracted with chloroform. Evaporation of the chloroform extract after drying over Na_2SO_4 afforded hormothamnione 5 as a yellow powder. It was recrystallized from methanol (0.32 g, 96%); m.p. 270°C (Lit.[6], m.p. 270°C).

IR (Nujol): ν max 3400 and 1640 cm^{-1}.

UV (MeOH): λ max 294 and 353 nm.

^{1}H-NMR: ($CDCl_3$ + Acetone D_6): δ 2.17 (s, 3H), 3.94 (s, 3H), 4.00 (s, 3H), 4.11 (s, 3H), 6.51 (t, 1H), 6.75 (d, 2H), 7.07 (d, J = 16 Hz, 1H), 7.6 (d, J = 16 Hz, 1H), 8.04 (s, 2H, disappeared on D_2 treatment) and 12.7 (s, 1H, disappeared on D_2O treatment).

MS (m/e) : 400 (M^+).

Analysis cal. $C_{21}H_{20}O_8$: C, 62.98 ; H, 5.00;

Found : C, 62.92 ; H, 5.09%.

Hormothamnione Triacetate (30) :

A mixture of hormothamnione 5 (0.1 g, 0.25 mmol) acetic anhydride (0.1 g, 1 mmol) and pyridine (1 ml) was heated with stirring at 80°C in an oil bath for 6 h. It was then cooled to room temperature, cold water (10 ml) was added and stirred at room temperature for 1 h and extracted with dichloromethane (2 x 10 ml). The organic extract was washed with dilute hydrochloric acid followed by water, dried (Na_2SO_4) and evaporated to give hormothamnione triacetate 30 (0.129 g, 98%); m.p. 204°C (Lit. [6], m.p. 198-202°C).

IR ($CHCl_3$) : ν max 1780 and 1635 cm^{-1}.

^{1}H-NMR : δ 2.17 (s, 3H), 2.35 (s, 6H), 2.50 (s, 3H), 3.89 (s, 3H), 4.06 (s, 3H), 4.11 (s, 3H), 6.97 (t, 1H), 7.08 (d, J=16 Hz, 1H), 7.24 (d, 2H) and 7.58 (d, J = 16 Hz, 1H).

MS (m/e): 526 (M^+).

Hormothamnione diacetate (29):

Hormothamnione 5 (0.1 g, 0.25 mmol) was dissolved in pyridine (1 ml) and stirred with acetic anhydride (0.1 g, 1 mmol) at room temperature for 24 h. Water (10 ml) was added to the reaction mixture and stirred for 1 h. It was then extracted with dichloromethane (2 x 10 ml), the organic extract washed with dilute hydrochloric acid (25 ml) and water. Evaporation of the dichloromethane after drying (Na_2SO_4) afforded hormothamnione diacetate **29** as a colorless solid (0.110 g, 91%); m.p. 180°C.

IR ($CHCl_3$) : $\tilde{\nu}$ max 1780 and 1640 cm^{-1}.

^{1}-NMR : δ 2.18 (s, 3H), 2.33 (s, 6H), 3.93 (s, 3H), 3.95 (s, 3H), 4.11 (s, 3H), 6.97 (t, 1H), 7.08 (d, J = 16 Hz, 1H), 7.24 (d, 2H), 7.62 (d, J = 16 Hz, 1H) and 12.66 (s, 1H, exchanges with D_2O).

MS (m/e) : 484 (M^+).

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CHAPTER-II

SYNTHESIS OF BIKAVERIN

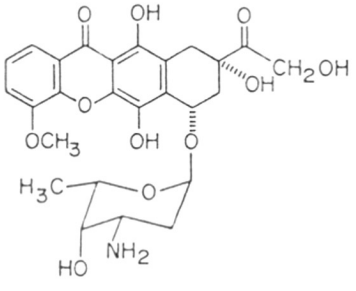
INTRODUCTION:

Xanthones, and especially hydroxyxanthones, have long been known to produce pharmacological and biological effects.[1] The 1,4-dihydroxydibenzo-τ-pyrone pattern is encountered in naturally occurring products[2] and constitutes a major part of the antitumour antibiotic bikaverin (2). As the structural feature, it and related ones also have been incorporated into synthetic xanthocyclins such as the xanthoadriyamycin (1)[3a] (FIGURE-I).

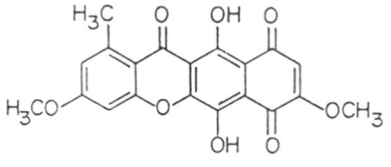
Bikaverin (2), a red pigment produced in several species of fungal genera Fusarium[4], Gibberella[5], and Mycogone[6]. The pigment possesses a number of interesting biological properties such as a vacuolation-inducing effect in fungi[4] and in vitro growth inhibiting activity towards the protozoan Leishmaia brasiliensis[7] and various tumour cell types,[8,9] the latter effected through uncoupling of the oxidative phosphorylation process.[10] Although partial assignment of the structure through chemical and spectral studies was possible,[4,5a] X-ray analysis was required to establish unambiguously the substitution pattern.[5b]

The notable attention accorded to bikaverin as a target of synthesis[11] because of its attractive biological properties, a cumbersome in vitro production, together with certain structural similarity with the tetracycline and anthracycline antibiotics.

FIGURE-I



XANTHOADRIAMYCIN (1)



BIKAVERIN (2)

Earlier Methods for the Synthesis of Bikaverin:

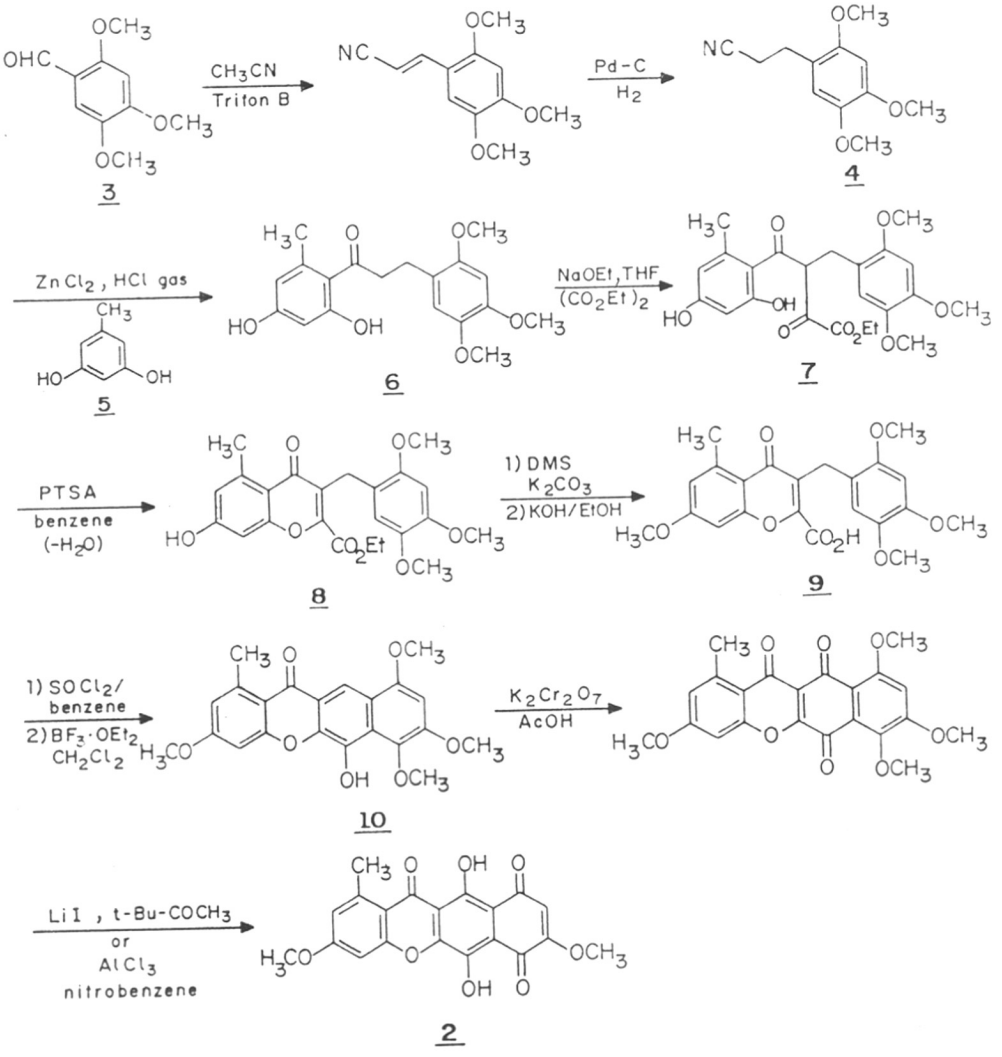
Under this sub-heading, the total synthesis of bikaverin (2) is covered. This includes four approaches reported in the literature.[11].

Barton's approach:

Shortly after the structure of bikaverin (2) was elucidated, an elegant regiospecific synthesis of 2 was reported by Barton et al.[11a] (SCHEME-2.1). They condensed 2,4,5-trimethoxybenzaldehyde (3) with acetonitrile in presence of Triton B and further carried out catalytic hydrogenation to give dihydrocinnamonitrile 4. Houben-Hosch reaction of nitrile 4 with orcinol 5 gave dihydrochalcone 6. Treatment of compound 6 with diethyl oxalate in presence of sodium ethoxide gave 7, which was azeotroped (PTSA-benzene) to give chromone 8. Methylation followed by alkaline hydrolysis of the chromone gave the corresponding acid 9. Cyclization of

the derived acid chloride with $BF_3.OEt_2$ in dichloromethane gave phenol 10. Oxidation of 10 with potassium dichromate in glacial acetic acid and demethylation ($AlCl_3$ in nitrobenzene, or LiI in methyl t-butyl ketone at reflux) gave bikaverin (2).

SCHEME-2.1



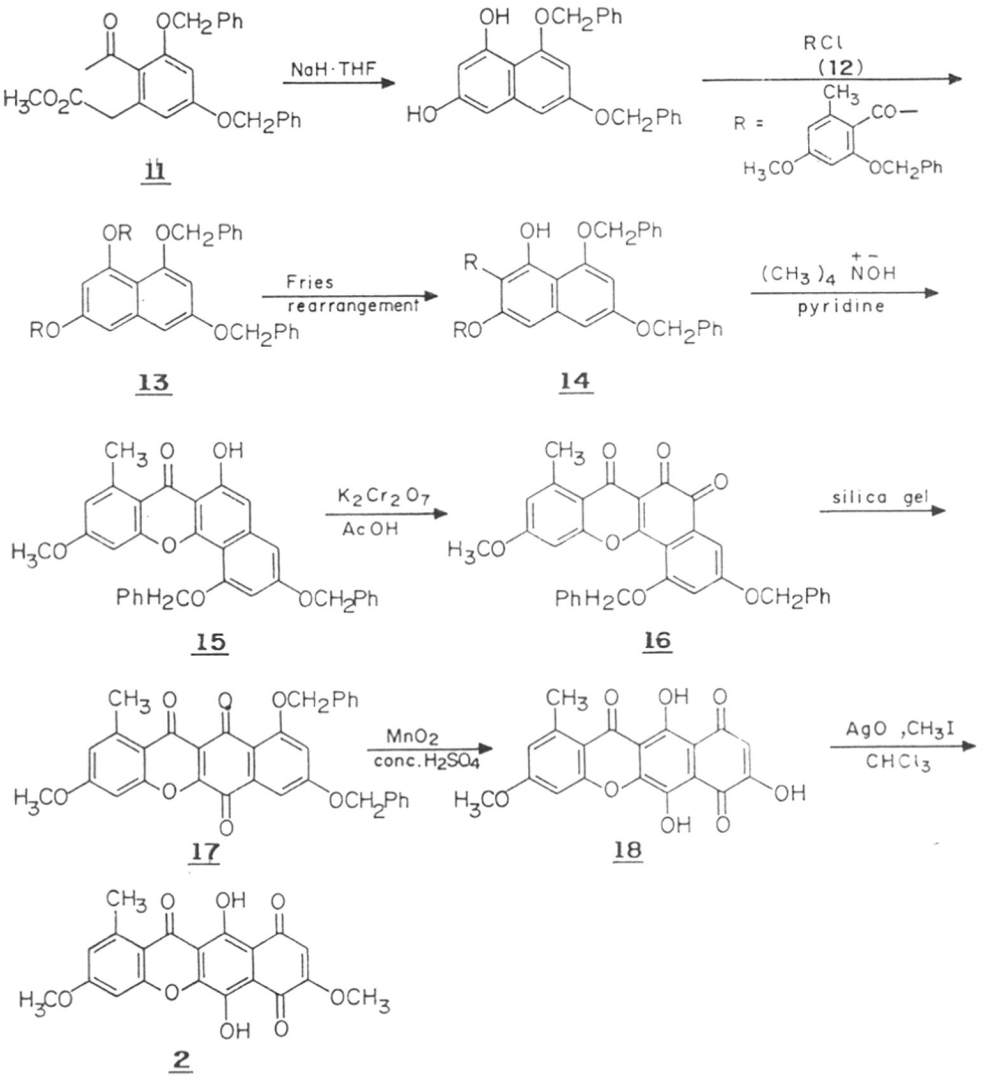
Kato's approach:

The second total synthesis of bikaverin (2) was reported by Kato et al.[11b] as outlined in SCHEME-2.2. Dieckmann condensation of methyl 2-acetyl-3,5-bis(benzyloxy)phenylacetate (11), prepared from 3,5-dihydroxybenzoic acid followed by treatment with benzyl protected everninic acid chloride (12) gave di-O-acylated naphthalene 13. Photoinduced Fries rearrangement of 13 afforded acylnaphthalene 14. Ring closure of 14 with tetramethylammonium hydroxide in pyridine gave angular benzoxanthene 15, which was oxidized with potassium dichromate to orthoquinone 16. By novel type rearrangement 16 was transformed into the linear benzoxanthene 17 by treatment with silica gel. Oxidation and debenzylation of 17 gave norbikaverin (18), which was selectively monomethylated to give bikaverin (2).

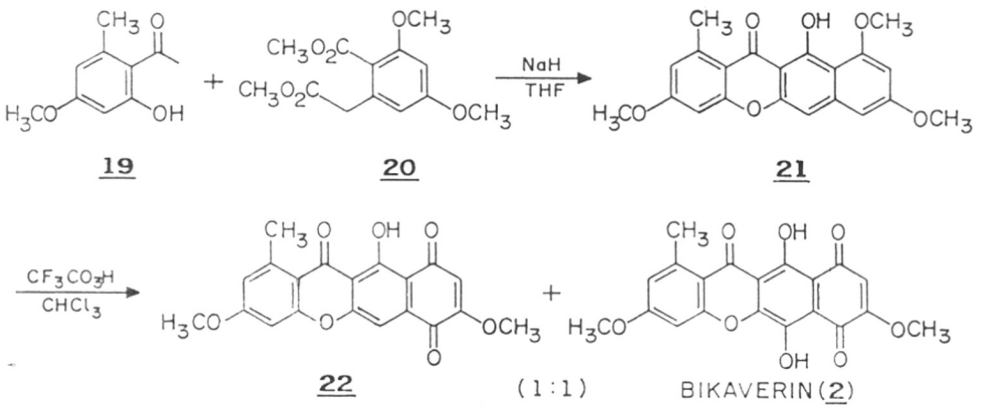
Kjaer's approach:

Kjaer et al.[11c] applied base catalyzed double acylation of 2-hydroxy-4-methoxy-6-methylacetophenone (19) with the carbonyl group of dimethyl 3,5-dimethoxyhomophthalate (20) to give hydroxy benzoxanthene 21 as a key step towards the total synthesis of bikaverin (2) (SCHEME-2.3). Oxidation of 21 with trifluoroperacetic acid under controlled conditions afforded bikaverin (2) and 6-deoxybikaverin (22) in 1:1 ratio.

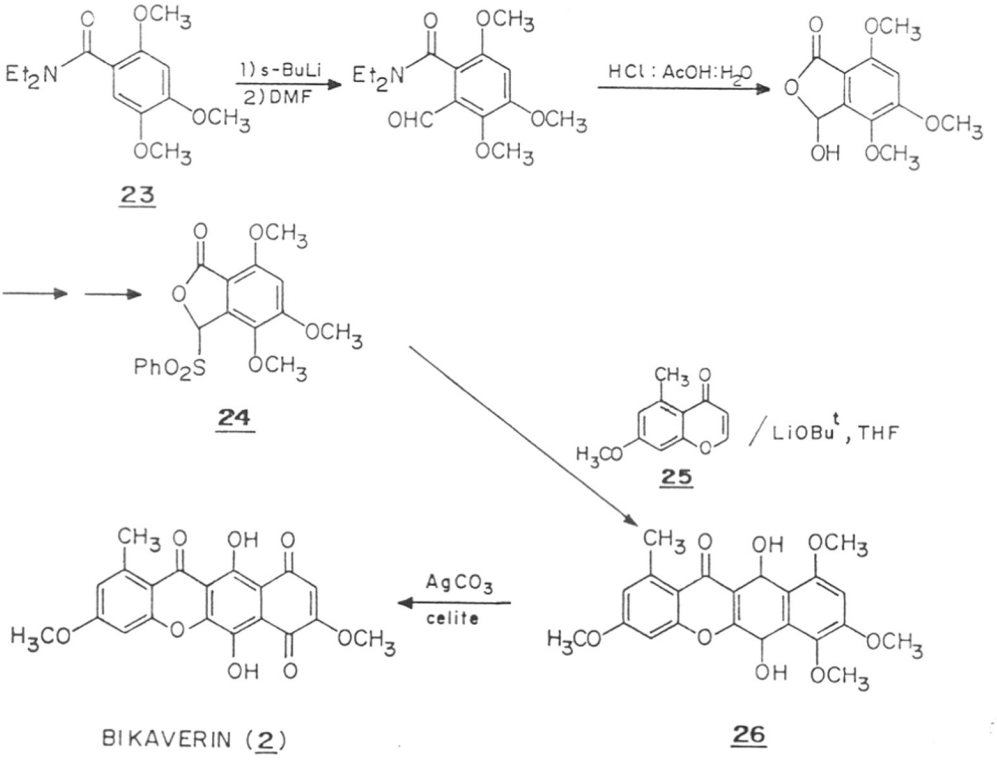
SCHEME-2.2


NaH·THF
RCl
(12)
R =
Fries
rearrangement
pyridine
$K_2Cr_2O_7$
AcOH
silica gel
MnO_2
conc.H_2SO_4
AgO ,CH_3I
$CHCl_3$
11
13
14
15
16
17
18
2

SCHEME-2.3



SCHEME-2.4



Hauser's approach:

A short and regiospecific synthesis of bikaverin (2) was accomplished recently (in 1988) by Hauser et al.[11d] (SCHEME-2.4). The key reaction involved was the condensation of (phenylsulfonyl)isobenzofuranone (24) with chromone 25 for the fabrication of the benz[b]xanthen-12-one (26) ring system of bikaverin. The sulfone 24, which serves as a synthon for the A and B rings, was prepared from the amide 23 in four steps. Oxidation followed by demethylation of dihydroxyxanthone 26 gave bikaverin (2).

PRESENT WORK:

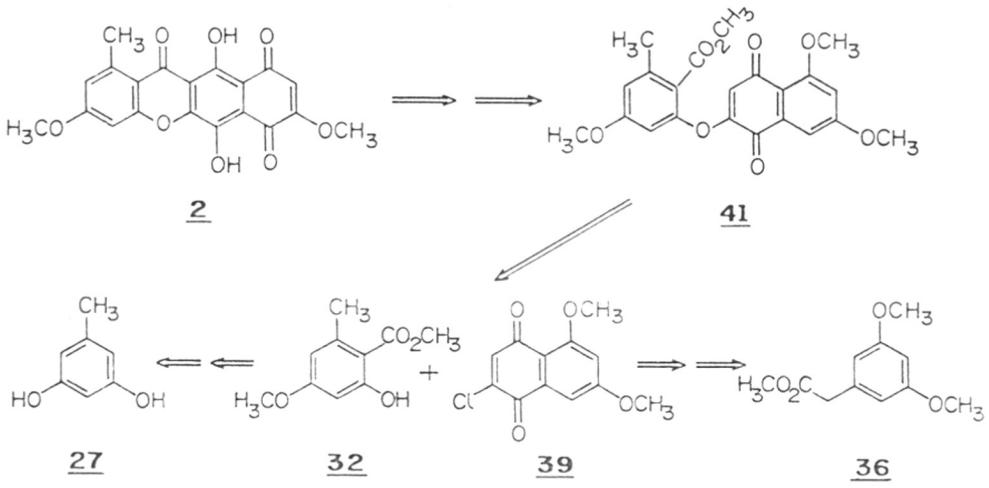
As is evident from what has been described so far, the first two independent syntheses of Barton et al.[11a] and Kato and his co-workers,[11b] proceed through a dozen individual steps or more while the other two approaches by Kjaer et al.[11c] and Hauser et al.[11d] involve fair to poor yields in few steps. It was therefore felt that a better and more efficient synthesis of bikaverin (2) can be achieved. With this view, the synthesis was undertaken and the same is reported in the present work.

A retrosynthetic analysis readily suggested the ortho-hydroxy ester 32 and the naphthoquinone 39 as the logical starting materials (SCHEME-2.5). The ortho-hydroxy ester 32 can be easily synthesised by selective demethylation of methyl orsellinate dimethyl ether 31, while the required chloronaphthoquinone 39 can be prepared from arylacetic ester 36. Thus one can envisage a C-O bond coupling via an addition/elimination mechanism between ortho-hydroxy ester 32 and chloronaphthoquinone 39 resulting in the intermediate phenoxyquinone 41. The latter could then be subjected to intramolecular acylation and oxidation with conventional reagents.

The required methyl 2-hydroxy-4-methoxy-6-methylbenzoate (32) was synthesised in five steps (SCHEME-2.6) from 3,5-dihydroxytoluene (27) with an overall yield of 55%. Thus 27 was methylated with dimethyl sulphate-potassium carbonate in acetone to give di-O-methyl ether 28, which on

SCHEME-2.5

Retrosynthetic Analysis

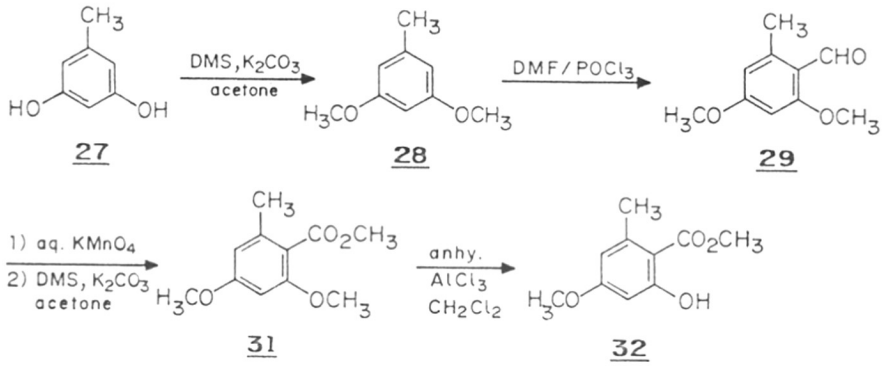


Vilsmeier-Haack reaction [15] furnished aldehyde 29. Ester 31 was prepared from the aldehyde 29 by oxidation with aqueous potassium permanganate solution to give acid 30 followed by esterification of the acid with dimethyl sulphate and potassium carbonate in acetone. Selective demethylation of ester 31 with anhydrous aluminium chloride in dichloromethane afforded methyl 2-hydroxy-4-methoxy-6-methylbenzoate (32). The spectral and physical properties of 32 were in full agreement with those reported[26] in the literature.

Having obtained the ortho-hydroxy ester 32, the next aim was to prepare chloronaphthoquinone 39. For the regiospecific synthesis of 39, the rightful choice was (3,5-dimethoxyphenyl)acetic acid (35). A detailed reaction sequence is depicted in SCHEME-2.7. The desired phenylacetic acid 35 was synthesised from 3',5'-dihydroxyacetophenone

(33). Thus, the methylation of 33 with dimethyl sulphate and potassium carbonate in refluxing acetone afforded

SCHEME-2.6



3',5'-dimethoxyacetophenone (34) quantitatively, which was subjected to Willgerodt reaction [16] with sulphur and morpholine followed by hydrolysis to give (3,5-dimethoxyphenyl) acetic acid (35) in 54% yield. The spectral analysis and physical properties were in full agreement with those reported in the literature [17]. Esterification of the acid 35 was carried out by treating it with dimethyl sulphate and potassium carbonate in refluxing acetone to give ester 36. Friedel-Crafts acylation[18] of the ester 36 with acetyl chloride in presence of anhydrous aluminium chloride in dichloromethane furnished keto-ester 37. Dieckmann condensation[19] of the keto-ester 37 with sodium methoxide in methanol followed by air oxidation [18] afforded hydroxynaphthoquinone 38 in 84% isolated yield. The spectral (FIG.II) and physical properties of compound 38 were consistent with

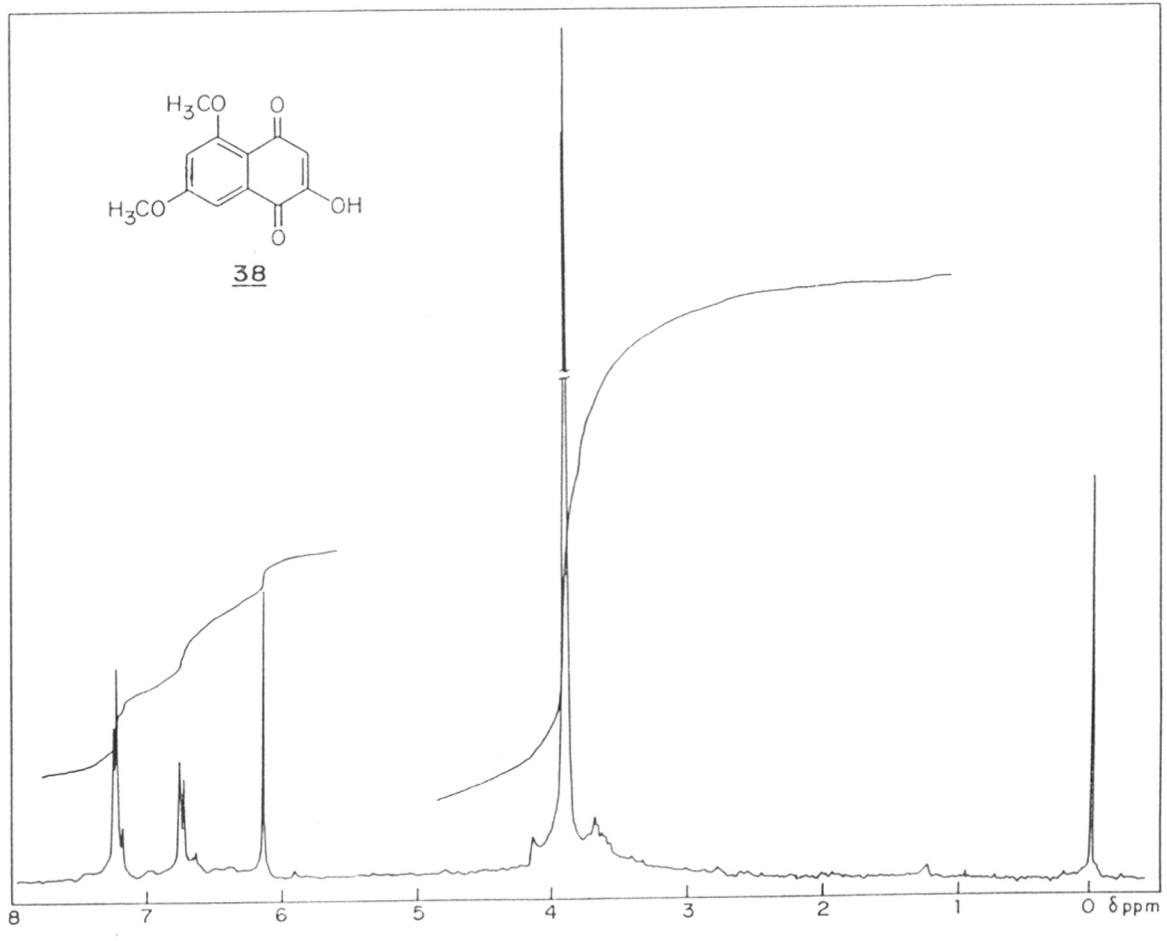
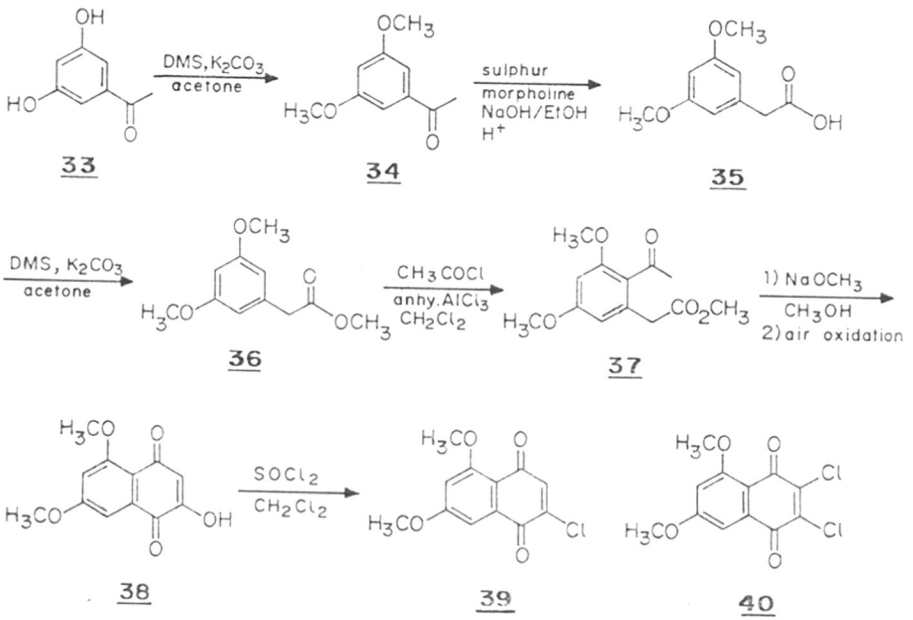


FIG. II : ^{1}H-NMR SPECTRUM OF THE COMPOUND (38) IN $CDCl_3$

those reported in literature [18].

Conversion of the hydroxynaphthoquinone 38 with an excess of thionylchloride to chloronaphthoquinone 39 by known [20] procedure yielded undesired 2,3-dichloro-5,7-dimethoxy-1,4-napthoquinone (40) in quantitative yield.

SCHEME-2.7



The ^{1}H-NMR spectrum of 40 revealed the absence of C-3 quinonic proton. However, 2-chloro-5,7-dimethoxy-1,4-naphthoquinone (39) was obtained quantitatively by refluxing a solution of the compound 38 in dichloromethane with two equivalents of thionyl chloride. No traces of dichloronaphthoquinone 40 were obtained. The structure of 39 was confirmed by spectral data. The ^{1}H-NMR spectrum (FIG.III)

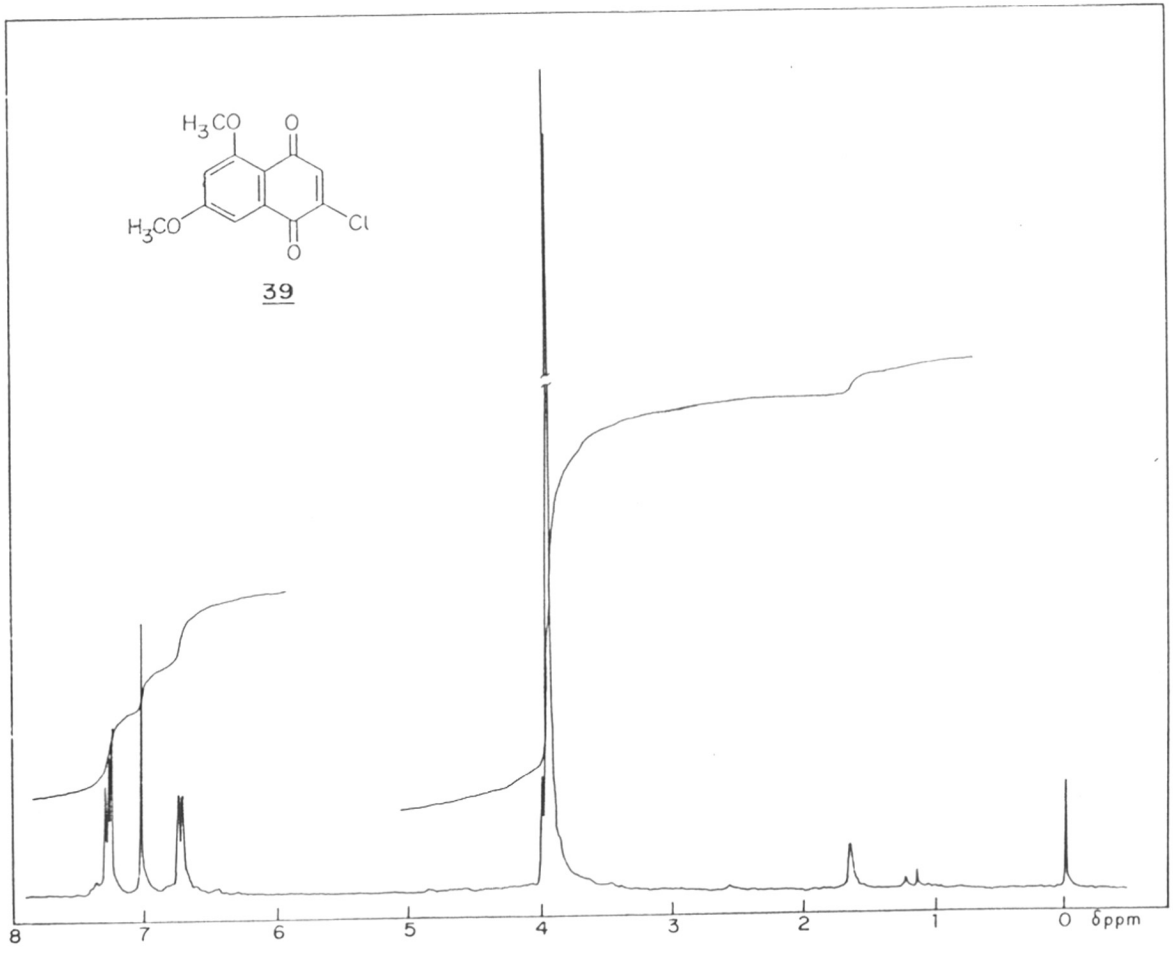
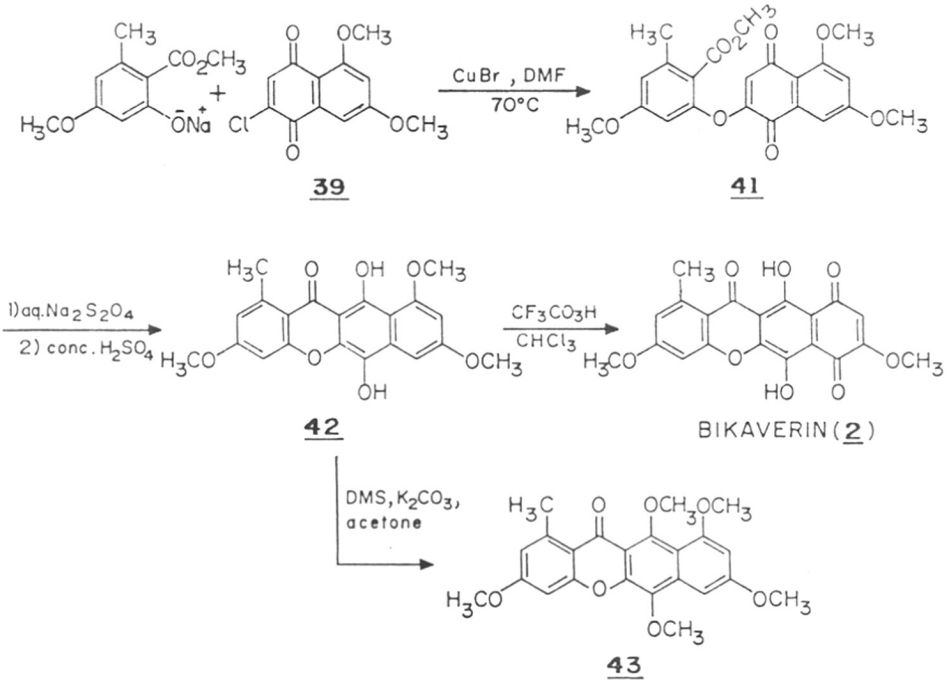


FIG. III : ^{1}H-NMR SPECTRUM OF THE COMPOUND (39) IN $CDCl_3$

showed a pair of meta-coupled doublets (δ 6.69 and 7.27; J = 2.5 Hz) and a singlet for C-3 quinonic proton at δ 7.03. Remainder of the spectrum showed two singlets for two methoxyl protons. The IR spectrum showed absorption bands at 1690, 1660 and 1600 cm^{-1}. Its structure was further confirmed by mass spectrum which showed molecular ion peak at m/e 252.

In accordance with the scheme the next aim was to find a suitable method for the preparation of 41. In order to achieve this coupling between O-hydroxy ester 32 and chloro-naphthoquinone 34 were attempted with potassium fluoride in

SCHEME-2.8



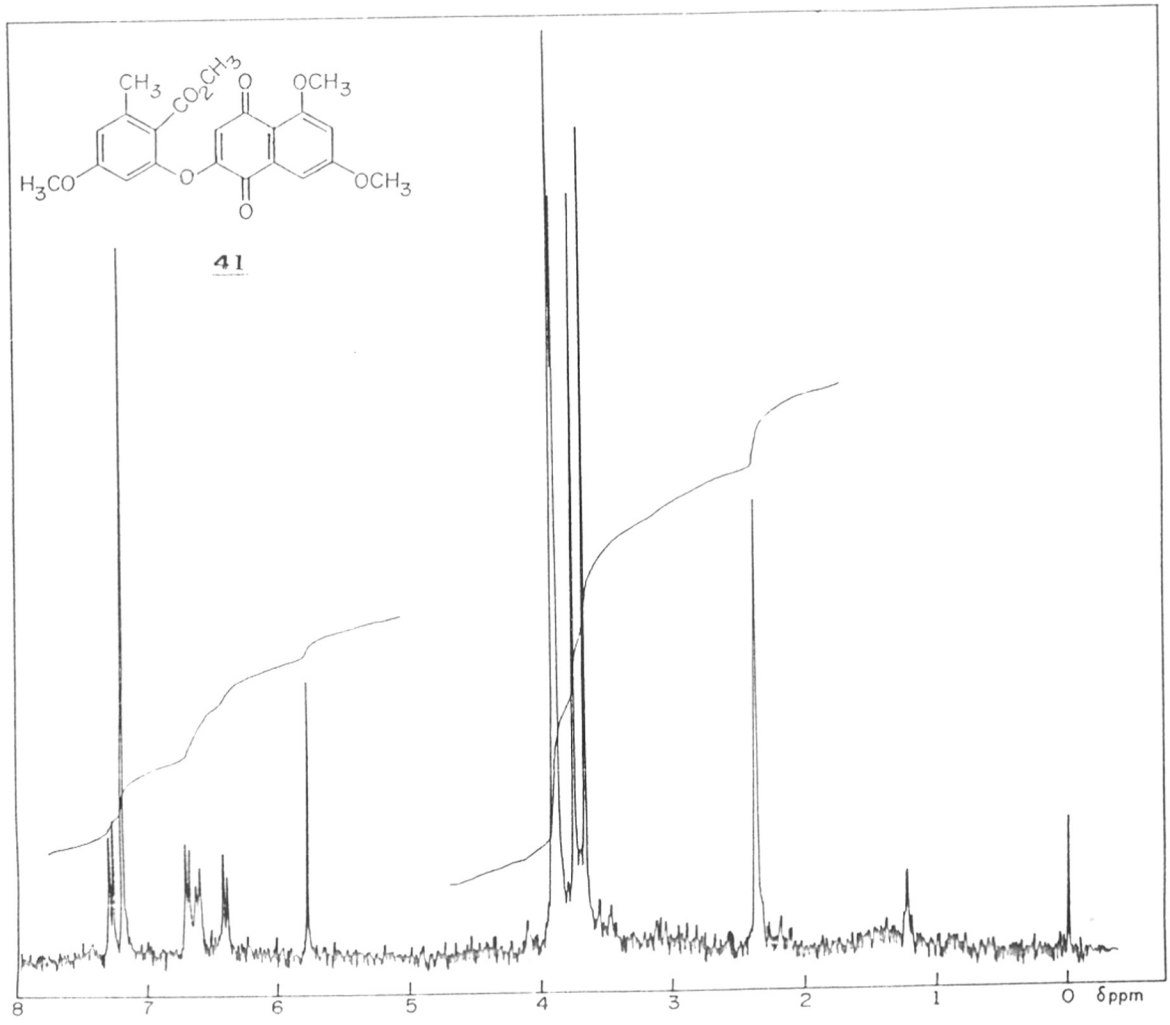


FIG. IV : ^{1}H-NMR SPECTRUM OF THE COMPOUND (41) IN $CDCl_3$

DMF[21] and under basic conditions[22] (sodium hydroxide, sodium ethoxide). Both of these methods resulted in poor yield of 41 mainly due to decomposition of the chloronaphthoquinone. Therefore a simple and mild coupling reaction between sodium salt of ester **32** and chloronaphthoquinone **39** catalyzed by cuprous bromide was developed. It gave an excellent yield of phenoxynaphthoquinone **41** (SCHEME-2.8).

Assigned structure for 41 was in good agreement with spectral data. The IR spectrum of 41 revealed absorption bands at 1740, 1695 and 1655 cm^{-1}. The ^{1}H-NMR spectrum (FIG.IV) showed aromatic methyl protons singlet at δ 2.34, quinonic proton at δ 5.78, three singlets integrating for four methoxyl protons, and four aromatic meta-coupled doublets. Mass spectrum of **41** showed molecular ion peak at m/e 412.

Reduction of phenoxynaphthoquinone **41** with sodium dithionite followed by intramolecular cycliacylation[21] with concentrated sulphuric acid afforded dihydroxyxanthone **42**. It was characterized by converting it to methyl ether derivative **43** (DMS, K_2CO_3-acetone). The IR spectrum of 42 showed absorption bands at 1654, 1618 and 1558 cm^{-1}. The ^{1}H-NMR (FIG.V) spectrum showed four singlets integrating for five methoxyl protons and a singlet at δ 2.81 for aromatic methyl protons. Mass spectrum of **43** showed molecular ion peak at m/e 410.

The dihydroxyxanthone **42** without any purification was subjected to oxidation with trifluoroperacetic acid [11c] in

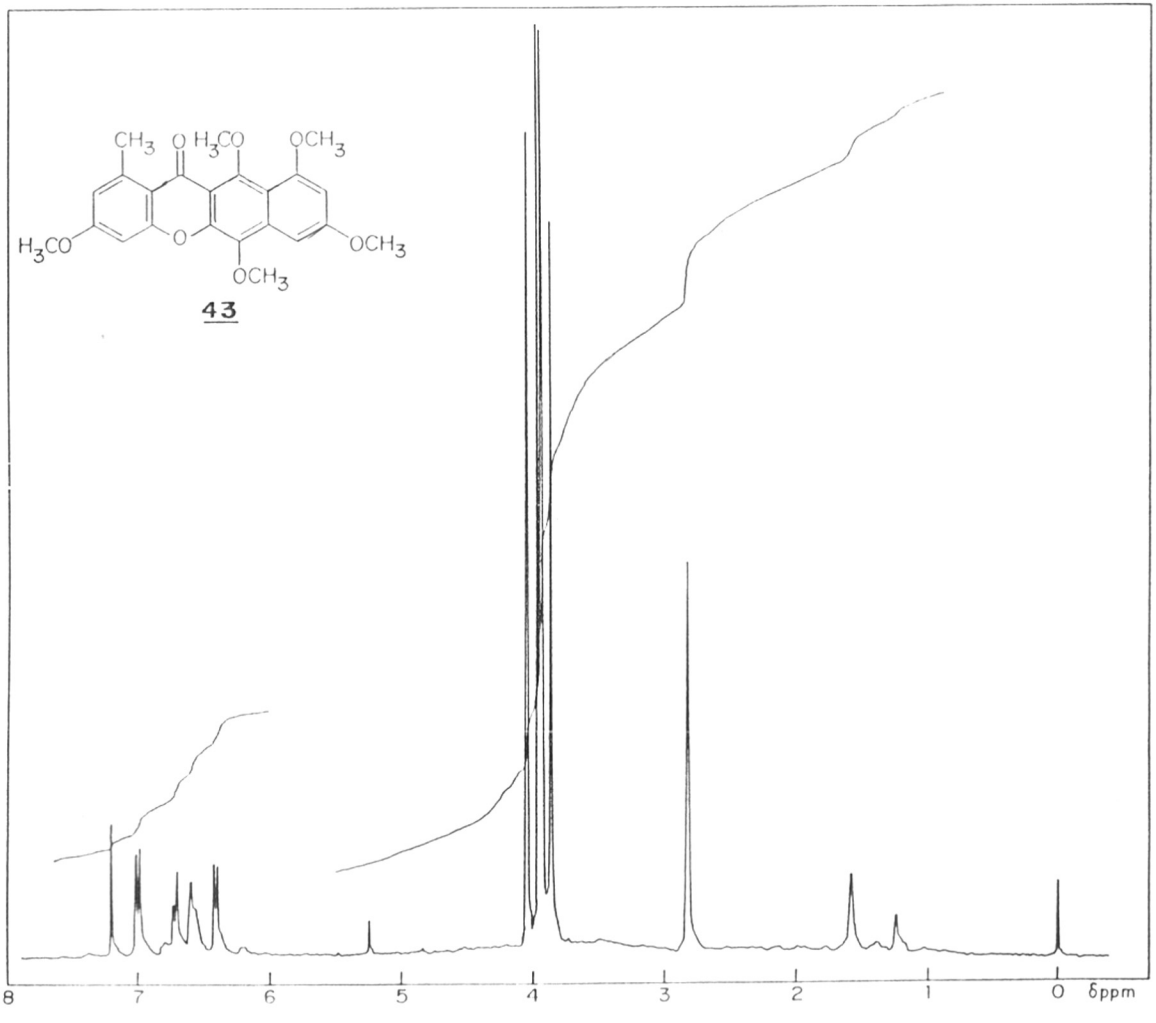


FIG. V : ^{1}H-NMR SPECTRUM OF THE COMPOUND (43) IN $CDCl_3$

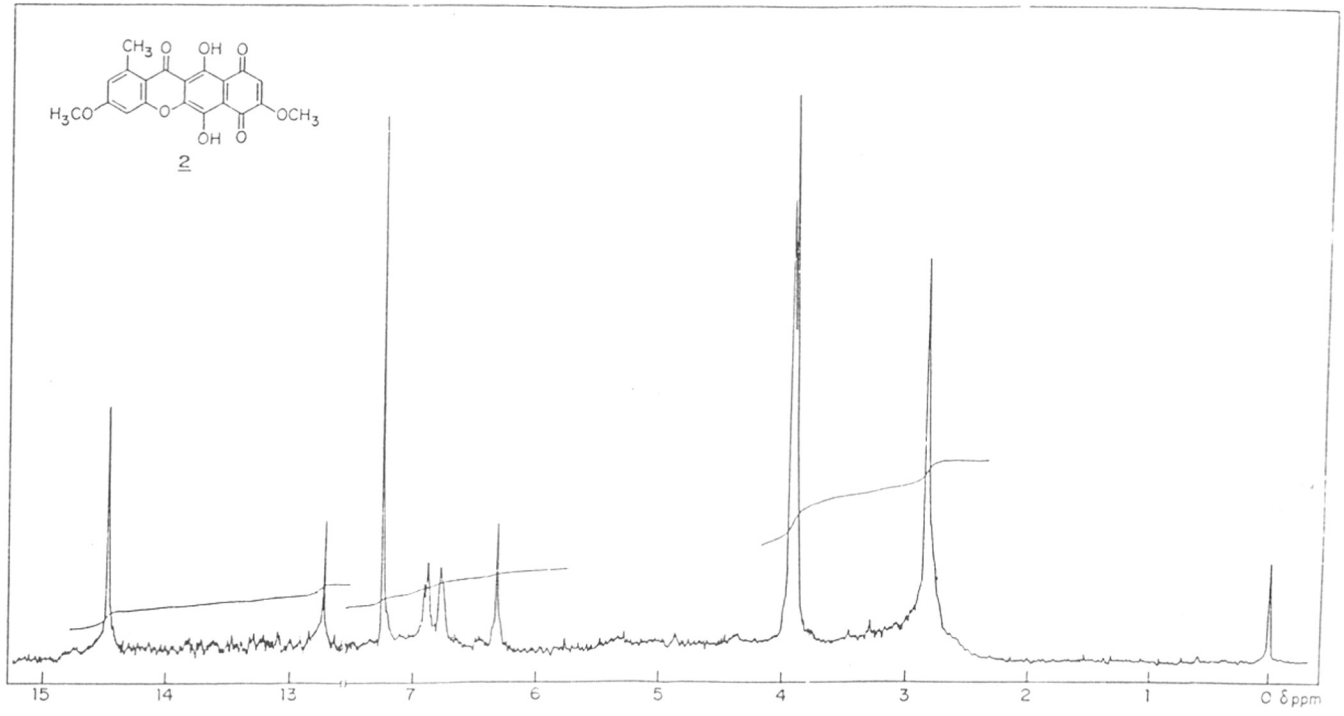


FIG XI: ^{1}H-NMR SPECTRUM OF THE COMPOUND (2) IN $CDCl_3$

chloroform at 0°C to afford bikarverin (2). The chromatographic purification (eluent: 5% methanol-chloroform) of the crude product yielded bikaverin (2) as a dark red solid. The synthetic material proved indistinguishable from authentic bikaverin (2) on critical comparison[5].

In conclusion this route to bikaverin 2 provides a useful way of preparing substantial quantities of material and should be readily adaptable for preparing analogues.

EXPERIMENTAL

3,5-Dimethoxytoluene (28):

A mixture of 3,5-dihydroxytoluene 27 (6 g, 48 mmol), dimethyl sulphate (15.28 g, 121 mmol) and anhydrous potassium carbonate (16.7 g, 121 mmol) in dry acetone (100 ml) was heated under reflux for 16 h. The acetone was distilled out, water (100 ml) was introduced and kept standing overnight to decompose excess dimethyl sulphate. It was then extracted with ethyl acetate (2 x 100 ml), the combined organic extracts were dried (Na_2SO_4) and evaporated to leave an oil which on distillation under reduced pressure yielded 7.25 g (98.6%) of pure dimethyl ether 28; b.p. 92-95°C/4mm Hg (Lit.[23], b.p. 67.5-68.5°C/0.2 mm Hg).

2,4-Dimethoxy-6-methylbenzaldehyde (29):

A complex was prepared from $POCl_3$ (14.1 g, 92 mmol) and DMF (6.7 g, 92 mmol) at 0°C, to this complex was added 3,5-dimethoxytoluene 28 (7 g, 46 mmol) with cooling (°C). The mixture was allowed to warm to room temperature and stirring was continued for 5 h. The reaction mixture was cooled to 0°C, and decomposed with 20% aqueous sodium hydroxide solution (100 ml). Solid separated was filtered, washed with water and dried. Recrystallization from hot pet. ether (b.p. 60-80°C) yielded 8 g of the required aldehyde 29 as a colourless crystalline solid (96%); m.p. 182°C (Lit.[24], m.p. 182°C)

2,4-Dimethoxy-6-methylbenzoic acid (30) :

To a stirred solution of 2,4-dimethoxy-6-methylbenzaldehyde **29** (7 g 39 mmol) in acetone (50 ml), was added an aqueous solution of $KMnO_4$ (14 g in 200 ml of water) till the $KMnO_4$ colour persisted. The mixture was stirred for 2 h at room temperature. The brown precipitate of MnO_2 formed in the reaction was filtered off through celite pad and the residue was washed with water. Acidification of the aqueous layer with dilute hydrochloric acid gave colourless solid, which was filtered, washed with cold water and dried to afford acid **30** (5 g, 65%); m.p. 147°C, (Lit.[25], m.p. 147°C).

Methyl 2,4-dimethoxy-6-methylbenzoate (31) :

A mixture of acid **30** (3.92 g, 20 mmol), dimethyl sulphate (2.64 g, 21 mmol), and anhydrous potassium carbonate (2.9 g, 21 mmol) in dry acetone (35 ml) was refluxed on water bath for 6 h. The acetone was removed by distillation, cold water (50 ml) introduced, whereby solid separated. It was filtered, washed with cold water, and dried to give 4.1 g of ester **31** (98%); m.p. 44°C (Lit.[25], m.p. 43°C).

Methyl 2-hydroxy-4-methoxy-6-methylbenzoate (32) :

To the stirred solution of ester **31** (1.5 g, 7.15 mmol) in dry dichloromethane (25 ml) at 0°C was added powdered anhydrous $AlCl_3$ (1.43 g, 10.7 mmol). After 30 min. the mixture was allowed to warm to room temperature and stirred further 2.5 h. It was then poured slowly into cold dilute

HCl solution, warmed on water bath for 20 min. to decompose aluminium complex and remove dichloromethane. After cooling to room temperature, colourless crystalline solid separated was filtered, washed thoroughly with water and dried to obtain hydroxy ester **32** (1.26 g, 90%); m.p. 67°C (pet. ether) (Lit.[26], m.p. 67°C).

IR (Nujol): ν max 1665, 1630 and 1595 cm^{-1}.

^{1}H-NMR : δ 2.47 (s, 3H), 3.75 (s, 3H), 3.90 (s, 3H), 6.23 (d,J=2.5 Hz, 1H), 6.30 (d, J = 2.5 Hz, 1H) and 11.70(s, 1H).

MS (m/e): 196 (M^+).

3',5'-Dimethoxyacetophenone (34):

A mixture of 3',5'-dihydroxyacetophenone 33 (25 g, 0.164 mol), dimethyl sulphate (51.86 g, 0.411 mol) and anhydrous potassium carbonate (56.79 g, 0.411 mol) in dry acetone (750 ml) was heated at reflux for 10 h. The acetone was distilled off, water (250 ml) was added into the mixture and stirred for 4 h at room temperature. It was extracted with ethyl acetate (2 x 200 ml), washed with water, dried (Na_2SO_4) and the solvent was removed under reduced pressure to give 3',5'-dimethoxyacetophenone 34 as a colourless viscous oil; b.p. 138-145°C/4 mm of Hg (Lit.[27], b.p. 151-152°C/10 mm of Hg).

(3,5-Dimethoxyphenyl)acetic acid (35):

A mixture of 3',5'-dimethoxyacetophenone 34 (18 g, 0.1 mmol), sulphur powder (4.8 g, 0.150 mol) and morpholine

poured into cold water. The brown coloured thick semisolid obtained was washed thoroughly with water. To the crude morpholide so obtained was added 10% ethanolic sodium hydroxide (200 ml) and the mixture was heated at reflux temperature for 12 h. The excess ethanol was removed under reduced pressure, the residue was diluted with water (100 ml) and acidified with conc. hydrochloric acid. The precipitated solid was filtered, washed with cold water and dried to afford acid **35** (10.6 g, 54%); recrystallized from hot water, m.p. 100°C; (Lit.[17], 100-102°C).

Methyl 3,5-dimethoxyphenyl acetate (36):

A mixture of 3,5-dimethoxyphenylacetic acid 35 (5 g, 25.5 mmol), dimethyl sulphate (3.86 g, 30.6 mmol) and anhydrous potassium carbonate (3.28 g, 38.6 mmol) was heated at reflux in dry acetone (150 ml) for 6 h. The acetone was distilled off, water (100 ml) was added to it. The mixture was extracted with ethyl acetate (3 x 100 ml), the organic extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure to give residue. Distillation of the crude product under reduced pressure afforded methyl 3,5-dimethoxyphenyl acetate 36 (5.15 g, 96%) as a colourless oil; b.p. 145-150°C/10 mm of Hg (Lit.[18] 155-160°C/15 mm of Hg).

Methyl 2-acetyl-3,5-dimethoxyphenyl acetate (37):

To the externally cooled (5°C) solution of ester 36 (2.1 g, 1 mmol) and anhydrous $AlCl_3$ (2 g, 1.5 mmol) in dichloromethane (25 ml), was added freshly distilled acetyl

chloride (1.17 g, 1.5 mmol) dropwise over 10 min. and cooling trough was removed after 30 min. After stirring the reaction mixture for 4 h at room temperature, it was poured slowly into the cold dilute HCl solution and warmed on water bath for 30 min. The solid separated after cooling to the room temperature was collected by filtration, washed with water and dried to yield keto-ester 37 (2.4 g, 95%) as a crystalline solid; m.p. 64°C (Lit.[19], m.p. 64°C).

2-Hydroxy-5,7-dimethoxy-1,4-naphthoquinone (38):

A solution of keto ester 37 (0.350 g, 1.38 mmol) in methanol (10 ml) was added slowly to a refluxing solution of sodium methoxide (from 0.063 g of Na) in methanol (10 ml). The solution was heated under reflux for further 20 min. and cooled to room temperature. A stream of air was drawn through the solution during 4 h. Removal of the methanol left a bright red solid, which was treated with 1N sulfuric acid (100 ml). The dark yellow product obtained was filtered, washed with water and dried. Recrystallization from benzene gave 38 as dark yellow prisms (0.275 g, 84%); m.p. 218°C (Lit.[19], m.p. 218-219°C).

2-Chloro-5,7-dimethoxy-1,4-naphthoquinone (39):

A mixture of hydroxynaphthoquinone 38 (0.234 g, 1 mmol) and thionyl chloride (0.237 g, 2 mmol) in dichloromethane (25 ml) was refluxed with stirring under anhydrous conditions for 4 h. The excess $SOCl_2$ and dichloromethane was removed under reduced pressure. The residue was chromatographed [silica gel, eluent: 10% acetone in pet. ether]

to afford 2-chloro-5,7-dimethoxy-1,4-naphthoquinone 39 (0.245 g, 97%) as a yellow solid; m.p. 191°C.

IR ($CHCl_3$): $\tilde{\nu}$ max 1690, 1660 and 1600 cm^{-1}.

^{1}H-NMR : δ 3.90 (s,3H), 3.96(s,3H), 6.69(d, J=2.5 Hz, 1H), 7.03 (s, 1H) and 7.27 (d, J=2.5Hz, 1H).

MS (m/e) : 252 (M^+).

Analysis cal. for $C_{12}H_9ClO_4$: C, 57.14; H, 3.57;

found : C, 57.10; H,3.57%.

5,7-Dimethoxy-2-(3-methoxy-6-methoxycarbonyl-5-methylphenoxy)1,4-naphthoquinone (41) (KF method[21]) :

To the fine suspension of anhydrous KF (0.039 g, 1.5 mmol) in dry DMF (10 ml) containing the ortho-hydroxyester 32 (0.082 g, 0.5 mmol) was added a solution of Chloronaphthoquinone 39 (0.126 g, 0.5 mmol) in the same solvent (10 ml). The reaction mixture was kept at 75°C for 4 h, poured into water and extracted with dichloromethane. Purification of crude product was carried out by column chromatography (silica gel. eluent : 15% ethyl acetate-pet. ether) to afford 41 (0.085 g, 38%); m.p. 168°C.

IR ($CHCl_3$) : $\tilde{\nu}$ max. 1740, 1695, 1655 and 1610 cm^{-1}.

^{1}H-NMR : δ 2.34 (s, 3H), 3.65 (s, 3H), 3.87 (s, 3H), 3.90 (s, 6H), 5.78 (s, 1H), 6.40 (d, J=2.5 Hz, 1H), 6.62 (d, J=2.5 Hz, 1H), 6.68 (d, J=2.5 Hz,1H) and 7.28 (d, J=2.5 Hz, 1H).

MS (m/e) : 412 (M^+).

Analysis cal. for $C_{22}H_{20}O_8$: C, 64.07 ; H,4.85 ;

5,7-Dimethoxy-2-(3-methoxy-6-methoxycarbonyl-5-methylphenoxy)-1,4-naphthoquinone (41) : (CuBr method).

To the stirred suspension of sodium salt of **32** [prepared by treating ortho-hydroxy ester **32** (0.164 g, 1.0 mmol) with NaH (0.024 g, 1.0 mmol) in anhydrous DMF (10 ml)] in DMF (15 ml) under argon atmosphere was added chloronaphthoquinone **39** (0.252 g, 1 mmol) and cuprous bromide (20 mg) and mixture stirred at 75-80°C in an oil bath for 2.5 h. The reaction mixture was cooled to room temperature, water was added to the reaction mixture and extracted with dichloromethane (3 x 50 ml). The combined dichloromethane extracts were washed with dilute HCl followed by water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was subjected to chromatography [silica gel, eluent : 15% ethyl acetate-pet. ether] to afford compound **41** (0.350 g, 85%) as a yellow solid. Recrystallized from acetone-pet.ether as bright yellow needles; m.p. 168°C.

3,6,8,10,11-Pentamethoxy-1-methylbenzo[b]xanthen-12-one (43)

A solution of phenoxynaphthoquinone **41** (0.300 g 0.728 mmol) in CH_2Cl_2 (35 ml) was shaken with an aqueous solution (25 ml) of sodium dithionite (2 g) until the mixture became colourless.

The organic extracts after being dried (Na_2SO_4), were evaporated and the residue stirred with conc. H_2SO_4 (5 ml) for 5 min. at room temperature then at 60°C for 15-20 min. The reaction mixture after cooling was poured over mixture

of ice and water and a solid separated was filtered and dried to give **42** (0.200 g).

The solid **42** (0.050 g) was methylated by refluxing it in dry acetone (10 ml) with mixture of dimethyl sulphate (0.082 g, 0.65 mmol) and anhydrous potassium carbonate (0.089 g 0.65 mmol) for 10 h. The acetone was distilled out from the reaction mixture, water was added to the residue. It was extracted with dichloromethane (2x10 ml), dried (Na_2SO_4) and evaporated. The residue on chromatograpic purification [silica gel, eluent : chloroform] afforded compound 43 as a yellow crystalline solid (0.049 g, 93%) ; m.p. 192°C.

IR (Nujol) : ν max 1654, 1618 and 1558 cm^{-1}.

^{1}**H-NMR** : δ 2.81 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 4.03 (s, 3H), 6.40 (d, J=2.5Hz, 1H), 6.59 (d, J=2.5Hz, 1H), 6.72 (d, J=2Hz, 1H) and 7.00 (d, J=2.5Hz, 1H).

MS (m/e) : 410 (M^+).

Analysis cal. for $C_{23}H_{22}O_7$: C, 67.31 ; H, 5.36 ;

Found : C, 67.29 ; H, 5.32%.

7,12-Dihydro-6,7-dihydroxy-3,8-dimethoxy-1-methyl-10H-benzo[b]xanthen-7,10,12-trione (Bikaverin) (2) :

To the stirred suspension of 30% H_2O_2 (0.11 ml, 0.96 mmol) in chloroform (10 ml) was added trifluroacetic acid (0.11 g, 0.96 mmol) at 0°C and stirred for 15 min. at the same temperature. The crude **42** (0.100 g) was added to the above stirred solution at 0°C and stirring continued for 5

h. It was then poured into 5% aqueous sodium bicarbonate solution (100 ml) and extracted with chloroform (3 x 20 ml). The combined extracts were dried (Na_2SO_4) and evaporated to give black residue which was subjected to column chromatography over silica gel with 5% methanol-chloroform as a eluent to afford bikaverin 2 as a red crystalline solid (0.088 g, 68%); m.p. 320-323°C (Lit.[5], m.p. 321-323°C).

IR ($CHCl_3$) : $\tilde{\nu}$ max 1655, 1640 and 1610 cm^{-1}.

^{1}H-NMR : δ 2.84 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.30 (s, 1H), 6.77(d, J=2.5Hz, 1H), 6.90 (d, J=2.5Hz, 1H), 12.85 (s, 1H) and 14.50 (s, 1H).

MS (m/e) : 382 (M^+).

Analysis cal. for $C_{20}H_{14}O_8$: C, 62.80 ; H, 3.66 ;

found : C, 62.76 ; H, 3.66%.

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CHAPTER-III

SYNTHESIS OF SEMIVIOXANTHIN

INTRODUCTION:

Semivioxanthin (1), an antifungal natural product was isolated under different culture conditions from Penicillium cetreo-viride by Zeeck et al.[1] along with xanthomegnin 2, 3,4-dehydroxanthomegnin (3), viomellein (4) and vioxanthin (5) FIG.I). The structure of 1 was established as 3,4-dihydro-9,10-dihydroxy-7-methoxy-3-methyl-1-oxo-1H-naphtho-[2,3-c]pyran on the basis of spectral data and the fact that its oxidation with Fremy salt gives semixanthomegnin (6). A few of the other examples of antifungal natural products (FIG.3.1) having similar basic skeleton as semivioxanthin (1), are vioxanthin (5)[1] SC-28762(7)[2], SC-28763(8), SC-30532(9)[3], etc.

The major component xanthomegnin (2) was also isolated from Trichophyton strain[4,5,6], Microsporium cookii[7] and Aspergillus strain[8]. Viomellein (4) was produced essentially in a very small amount by P. cetreo-viride. Vioxanthin (5) was isolated for the first time from T. violaceum by Blank et al.[6] Biosynthesis of xanthomegnin (2), viomellein (4) and related compounds was studied by Simpson[9] from singly and doubly ^{13}C-labelled acetates and confirmed their polyketide origin. It also gives evidence for the assigned structure. Based on CD-spectral studies[10], semivioxanthin (1) was shown to have S configuration at C-3.

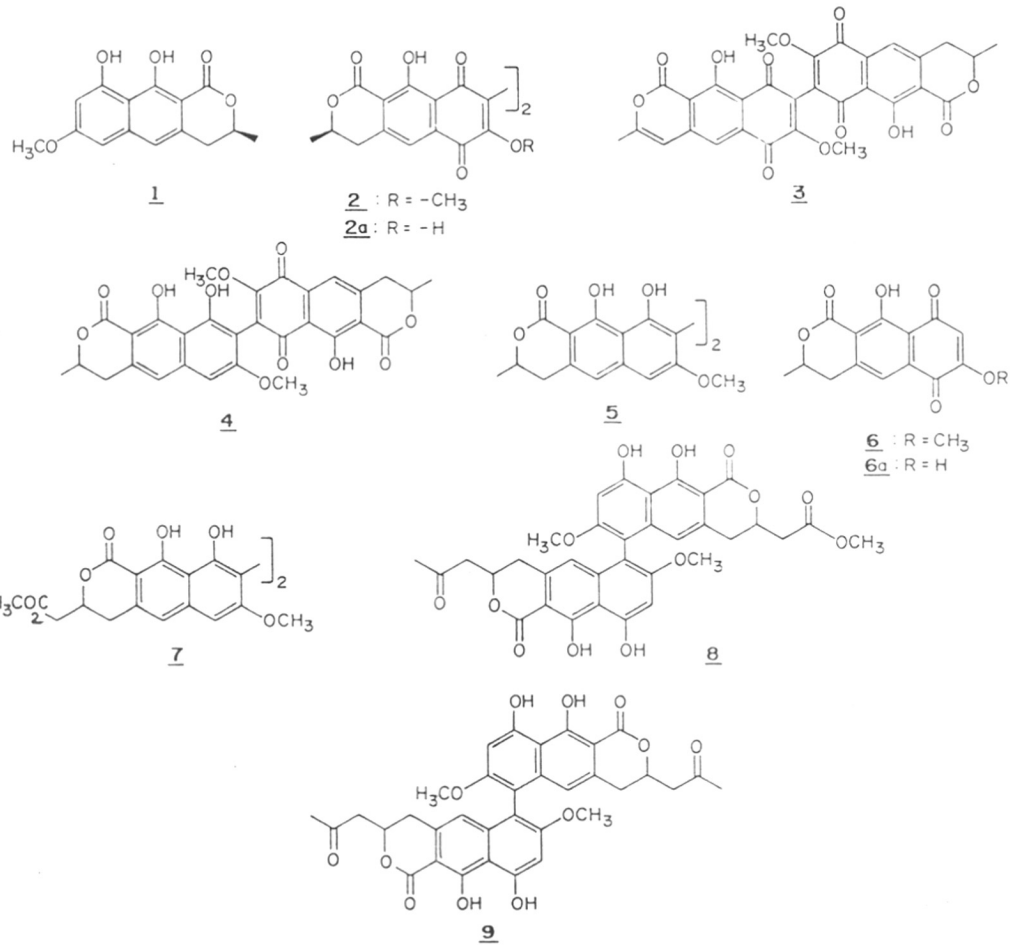
Xanthomegnin (2) was prepared by Zeeck et al.[1] by dimerisation of the hydroxyquinone **6a** with potassium persul-

phate in aqueous sodium hydroxide to compound 2a (FIGURE-I) followed by methylation with diazomethane in acetone.

Biological Activity:

Semivioxanthin (1), semixanthomegnin (6), viomellein (4), vioxanthin (5) and xanthomegnin (2) inhibit the growth of gram positive and gram negative bacteria.[1] The monomers 1 and 6 reduce the activity of E. coli and S. aureus to a considerable extent. Xanthomegnin (2) influences the oxidative phosphorylation in mitochondria of rat liver.[7]

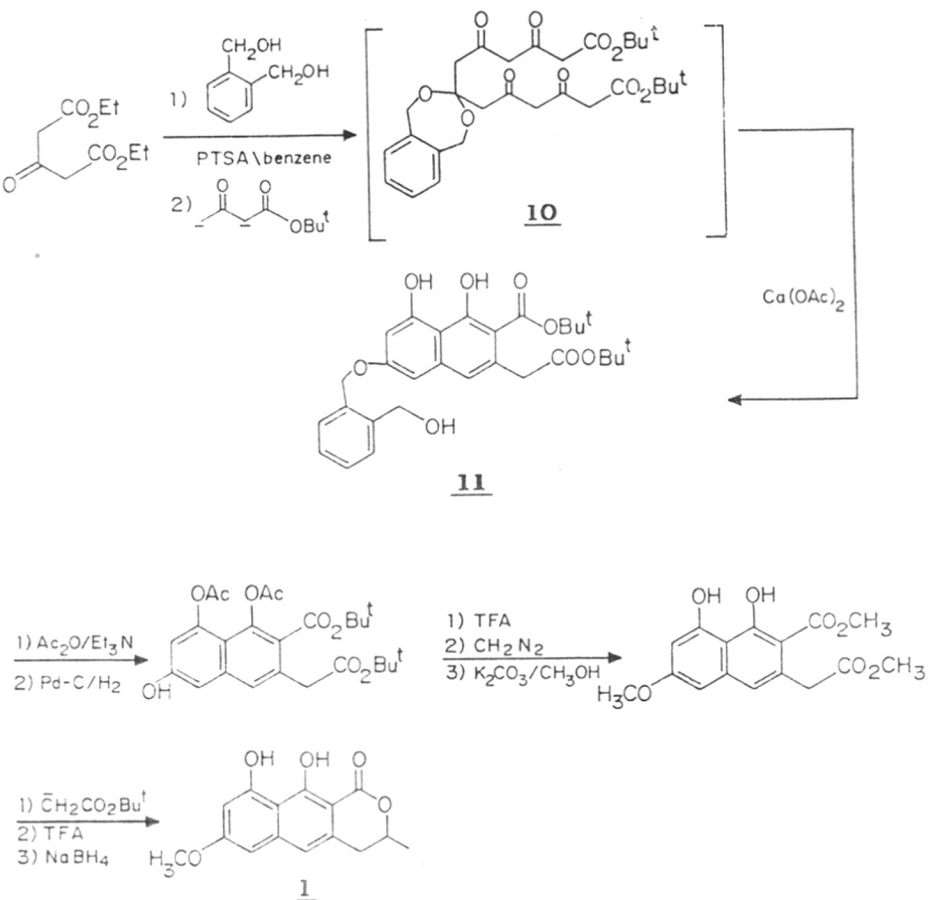
FIGURE-I



Some of the compounds were tested against arthropodes and were found to have no influence on longivity.[11] Xanthomegnin 2 and viomellein (4) are known to reduce the activity of the bean's beetle or bug (Eplilachna varivestis MULS)[11].

Although isolation and structure determination of semivioxanthin (1) was reported in 1979 there was no report of its synthesis until 1990 when Yamaguchi et al.[12] published its first synthesis via polyketide approach. The synthesis of 1 was characterized by the following features: (i) The polyketide intermediate 10 formed by Claisen condensation of the ß-oxoglutarate derivative and acetoacetate dianion (SCHEME-3.1) was converted into 7,9,10-trihydroxynaphthalene nucleus (11) by the $Ca(OAc)_2$ induced intramolecular condensation, (ii) The synthesis involves the use of a novel protecting group for a ketone (o-phenylenedimethanol), which allows selective methylation of 7-hydroxy group.

SCHEME-3.1


CO2Et
CO2Et
O
1)
CH2OH
CH2OH
PTSA\benzene
2)
OBut
CO2But
CO2But
10
Ca(OAc)2
OH
OH
O
OBut
COOBut
O
OH
11
1) Ac2O/Et3N
2) Pd-C/H2
OAc
OAc
CO2But
CO2But
OH
1) TFA
2) CH2N2
3) K2CO3/CH3OH
OH
OH
CO2CH3
CO2CH3
H3CO
1) CH2CO2But
2) TFA
3) NaBH4
OH
OH
O
O
H3CO
1

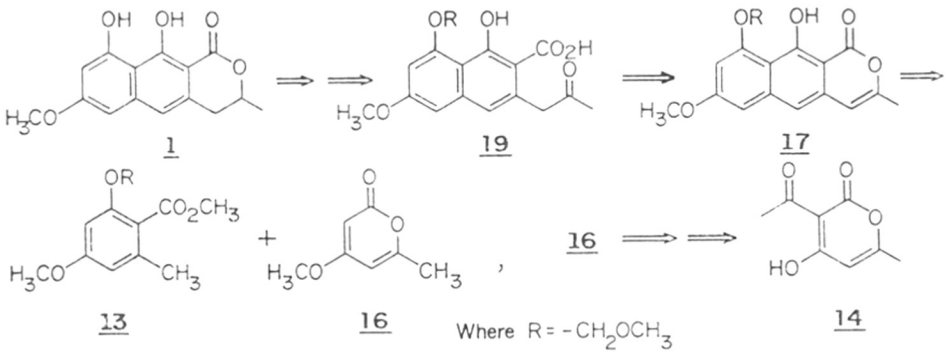
PRESENT WORK:

Although semivioxanthin (1) was isolated in 1979, its first eleven step synthesis was reported only recently in (1990) by Yamaguchi *et al*.[12] An examination of the structures of naphtho[2,3-c]pyran-1(1H)-ones eg. semivioxanthin (1), vioxanthin (5), SC-28762(7), SC-28763(8), SC-30532(9) etc. readily revealed that semivioxanthin (1) was the simplest member of the group. It was therefore considered appropriate to develop a short and efficient route to semivioxanthin (1) which can be applied for the total synthesis of other natural products having similar basic skeleton. Successful synthesis of semivioxanthin (1) and semixanthomegnin (6) are reported in this chapter.

Important structural features of the semivioxanthin (1) include a naphtho[2,3-c]pyran-1(1H)-one skeleton bearing a 7-methoxy group and 9 and 10 hydroxy groups. Biosynthetically, it is considered to be produced from acetic acid *via* polyketides. A retrosynthetic analysis readily suggested the orsellinate derivative 13 and the known [13, 14] triacetic lactone methyl ether (16) as the logical starting materials (SCHEME-3.2). The suitably protected orsellinate derivative 13 could be synthesised from methyl 2-hydroxy-4-methoxy-6-methylbenzoate (12). The latter has been synthesised and utilized in the total synthesis of bikaverin (CHAPTER-II). Thus one can envisage formation of two C-C bonds in a single step between 13 and 16, resulting in tricyclic intermediate

17. The latter could then be converted to keto-acid **19** by hydrolysis. Reduction of the keto acid **19** followed by cyclization and MOM deprotection would result in semivioxanthin (1). It could be then oxidized to semixanthomegnin 6 with conventional reagents.

SCHEME-3.2



The aromatic synthon **13** required for the coupling reaction with the pyrone **16** could be obtained from methyl 2-hydroxy-4-methoxy-6-methylbenzoate (12) whose synthesis has already been described in (CHAPTER-II). Thus, treatment of sodium salt of 12 with chloromethyl methyl ether (MOM) in benzene furnished 13 in good yield. The IR spectrum of 13 revealed band at 1740 cm^{-1} for ester carbonyl function. The ^1H-NMR (FIG.II) did not show any signal due the hydroxyl function (chelated to the ester carbonyl). Two singlets at δ 5.11 and δ 3.75 corresponding to methylene (-O-C$\underline{H}_2$-O) and methoxy protons of the MOM group were present. The mass spectrum showed expected molecular ion peak at m/e 240.

The pyrone counterpart **16** was prepared by known litera-

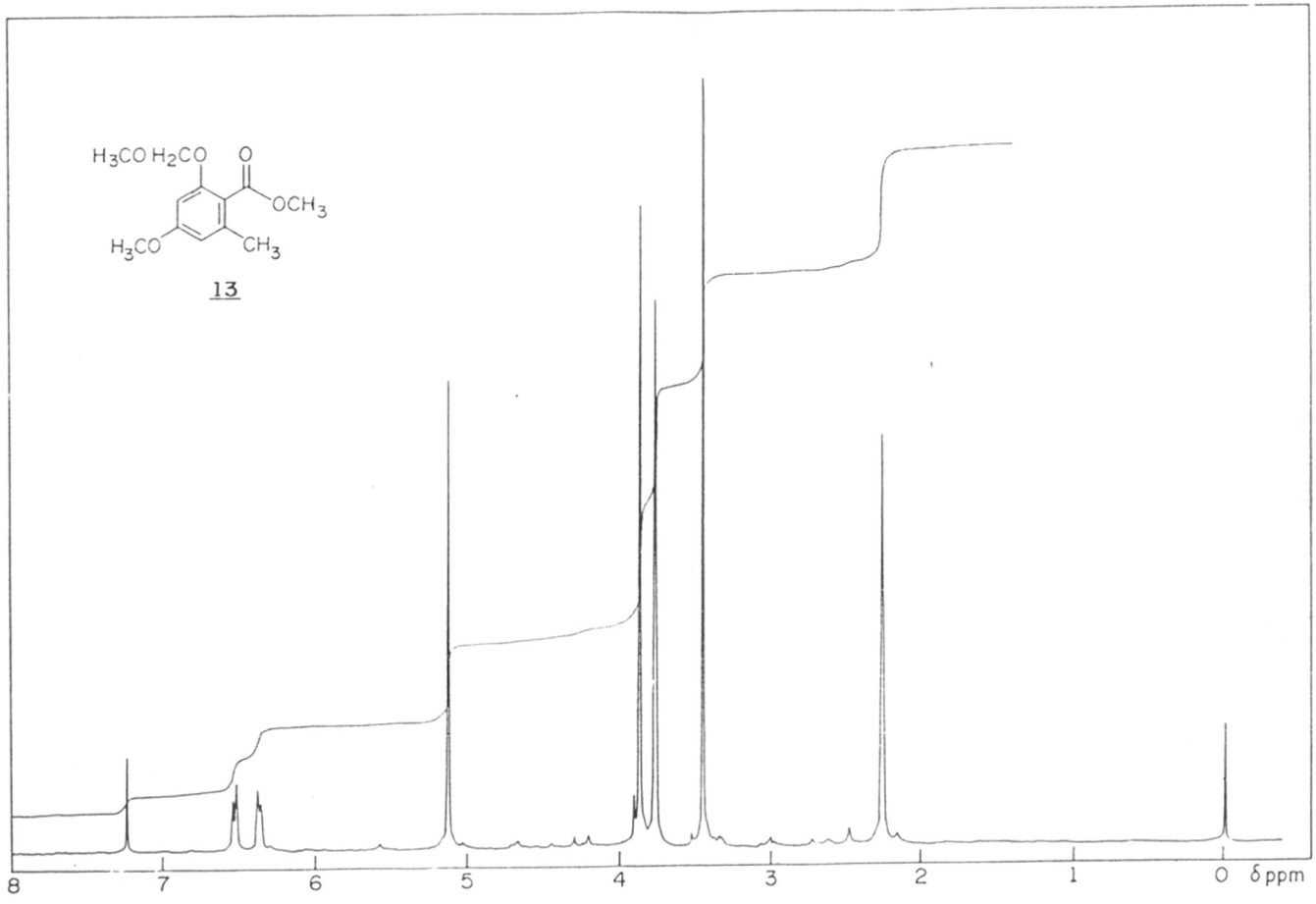
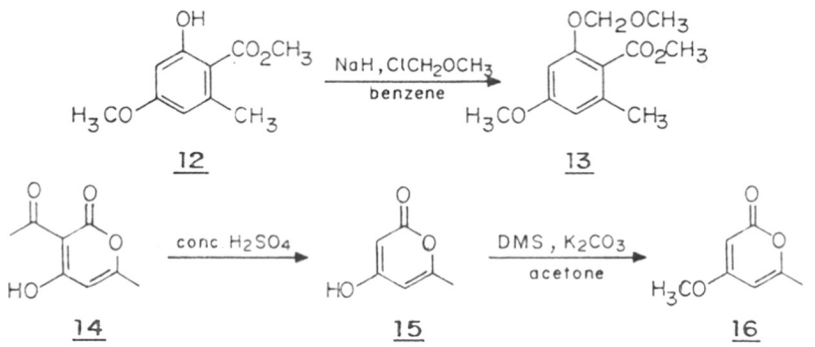


FIG II: ^{1}H-NMR SPECTRUM OF THE COMPOUND(13) IN $CDCl_3$

ture procedure[13,14] from commercially available dehydroacetic acid (14). Thus, the compound 14 was deacetylated[13]

SCHEME-3.3

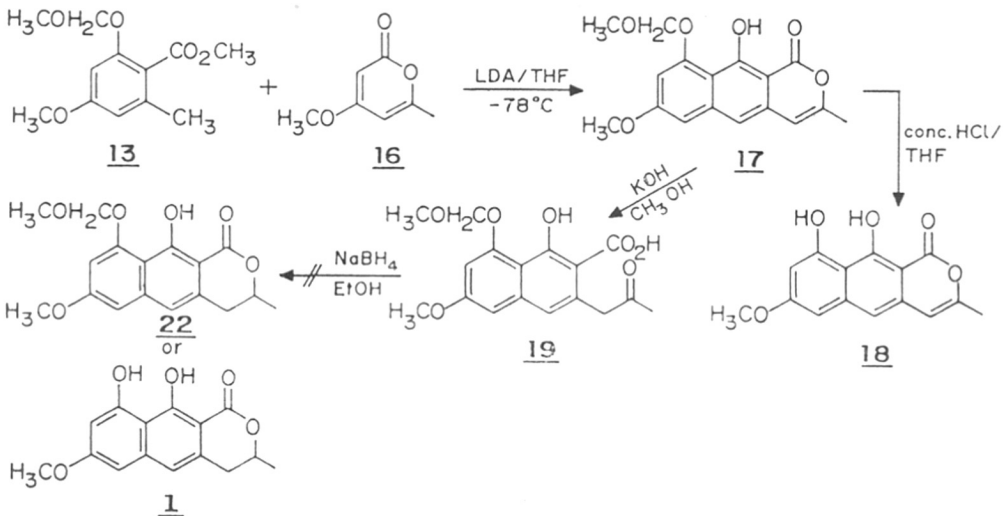


by heating it with concentrated sulphuric acid to give triacetic lactone (15). Methylation[14] of the compound 15 with dimethyl sulphate in presence of potassium carbonate in acetone furnished methyl ether (16). The physical and spectral properties of the triacetic lactone methyl ether (16) were in good agreement with those reported[13] in the literature.

Having obtained the two key starting materials, viz. methyl 4-methoxy-2-methoxymethoxy-6-methylbenzoate (13) and 4-methoxy-6-methyl-2-pyrone (16), the next coupling reaction was carried out. The anion of 13 was generated with LDA[15] in dry THF at -78°C and to it pyrone 16 was added to afford the tricyclic coupled product, 10-hydroxy-7-methoxy-9-methoxymethoxy-3-methyl-1H-naphtho[2,3-c]pyran-1-one (17) after work-up. The spectral data of 17 was consistent with the structure assigned. The IR spectrum showed absorption bands at 1680 and 1625 cm^{-1}. The ^1H-NMR spectrum revealed a broad singlet at δ 6.65 integrating for two

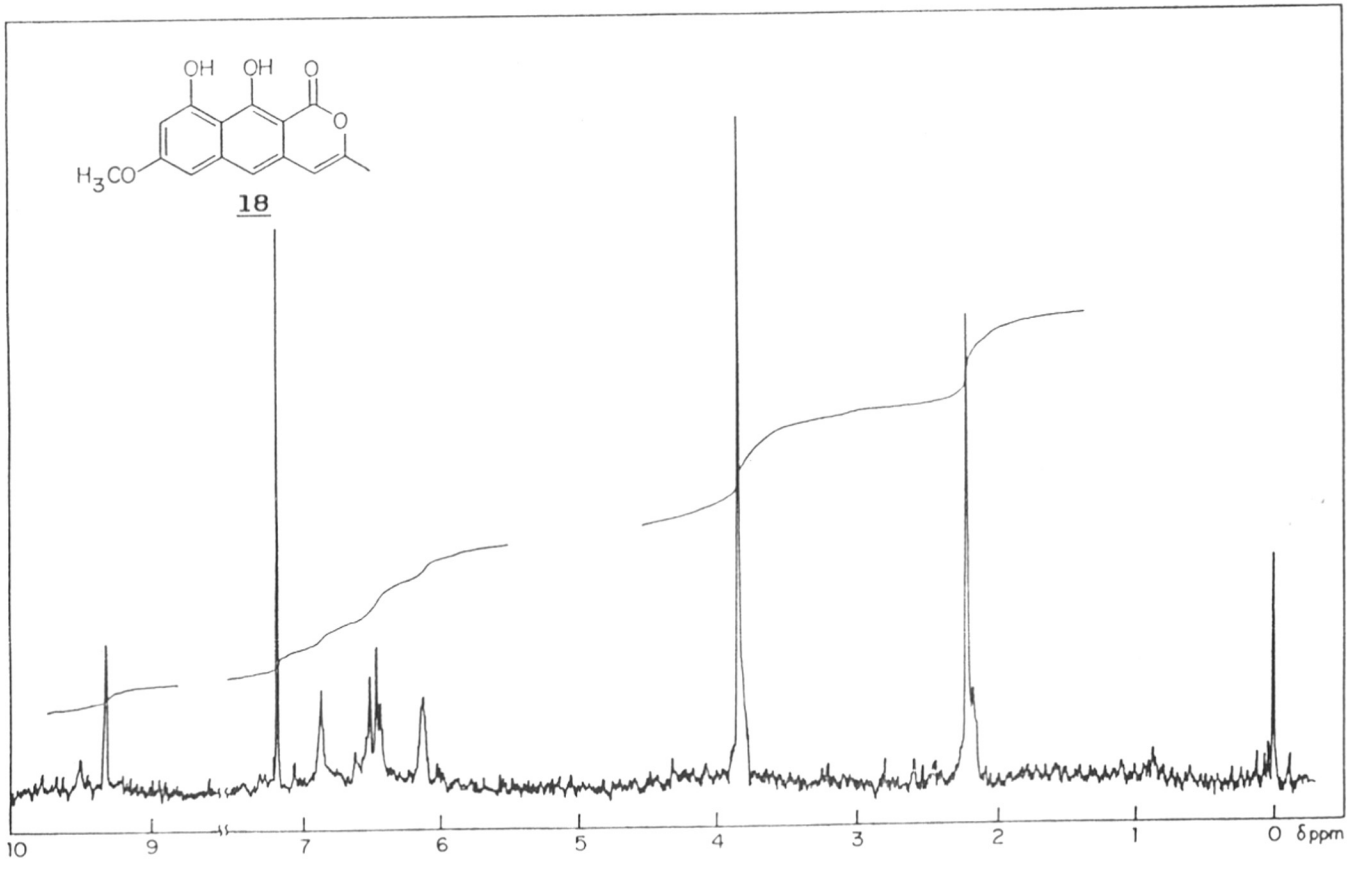
aromatic protons and singlet at δ 6.87 for one aromatic

SCHEME-3.4



proton. Remainder of the spectrum showed a methyl protons singlet (δ 2.21), two methoxyl protons singlet (δ 3.56 and 3.87), a methylene singlet (δ 5.31), a olefinic proton singlet (δ 6.15) and chelated hydroxyl proton singlet (δ 12.80). Assigned structure for 17 was further supported by mass spectrum [m/e:316 (M^+)].

Deprotection of the C-9 hydroxyl function of 17 (removal of MOM protection) with few drops of concentrated hydrochloric acid in THF at room temperature afforded toralactone (18). It was isolated from the seeds of Cassia (purgative crude drug) and characterized as naphtho-α-pyrone by Takahashi and Takido[16]. Its ^{1}H-NMR spectrum (FIG. III) showed presence of two singlets due to two chelated hydroxyl protons at δ 9.34 and 13.2 and a pair of meta-coupled doublets (δ 6.4 and 6.53, J = 2 Hz) alongwith other required peaks. The IR spectrum revealed absorption bands at 1682 and 1621



18

cm^{-1}. The mass spectrum showed molecular ion peak at m/e 276.

According to (SCHEME 3.4), the conversion of naphthopyrone 17 to semivioxanthin (1) can be effected by hydrolysis of 17 to keto-acid followed by reduction with sodium borohydride and acidification[17]. Thus, the compound 17 was treated with refluxing methanolic potassium hydroxide solution to give keto-acid 19. The structure of 19 was confirmed by its spectral data (FIG.IV). To obtain 22, the keto-acid was subjected to reduction with sodium borohydride in ethanol. Although the TLC picture of the reaction mixture showed disappearance of the starting keto-acid 19, the product obtained did not give satisfactory spectral data for the desired 3,4-dihydronaphthopyrone (22). As all the efforts to obtain compound 22 failed this approach was abandoned.

As the conversion of naphthopyrone 17 to 3,4-dihydronaphthopyrone (22) posed problems, it was decided to have 4-methoxy-6-methyl-5,6-dihydro-2-pyrone (2) as a starting material in place of pyrone 16, which could give directly 3,4-dihydronaphthopyrone 22 in one step. With this in view, an alternate scheme for 1 was employed (SCHEME-3.5). Thus triacetic lactone (15) was hydrogenated[18] under pressure (Pd-C/H_2, 5 kg/cm^2) in ethyl acetate at room temperature to give dihydropyrone (20). Its physical and spectral properties were in good agreement with those reported[18] in the literature. Methylation[19] of compound 21 with dimethyl

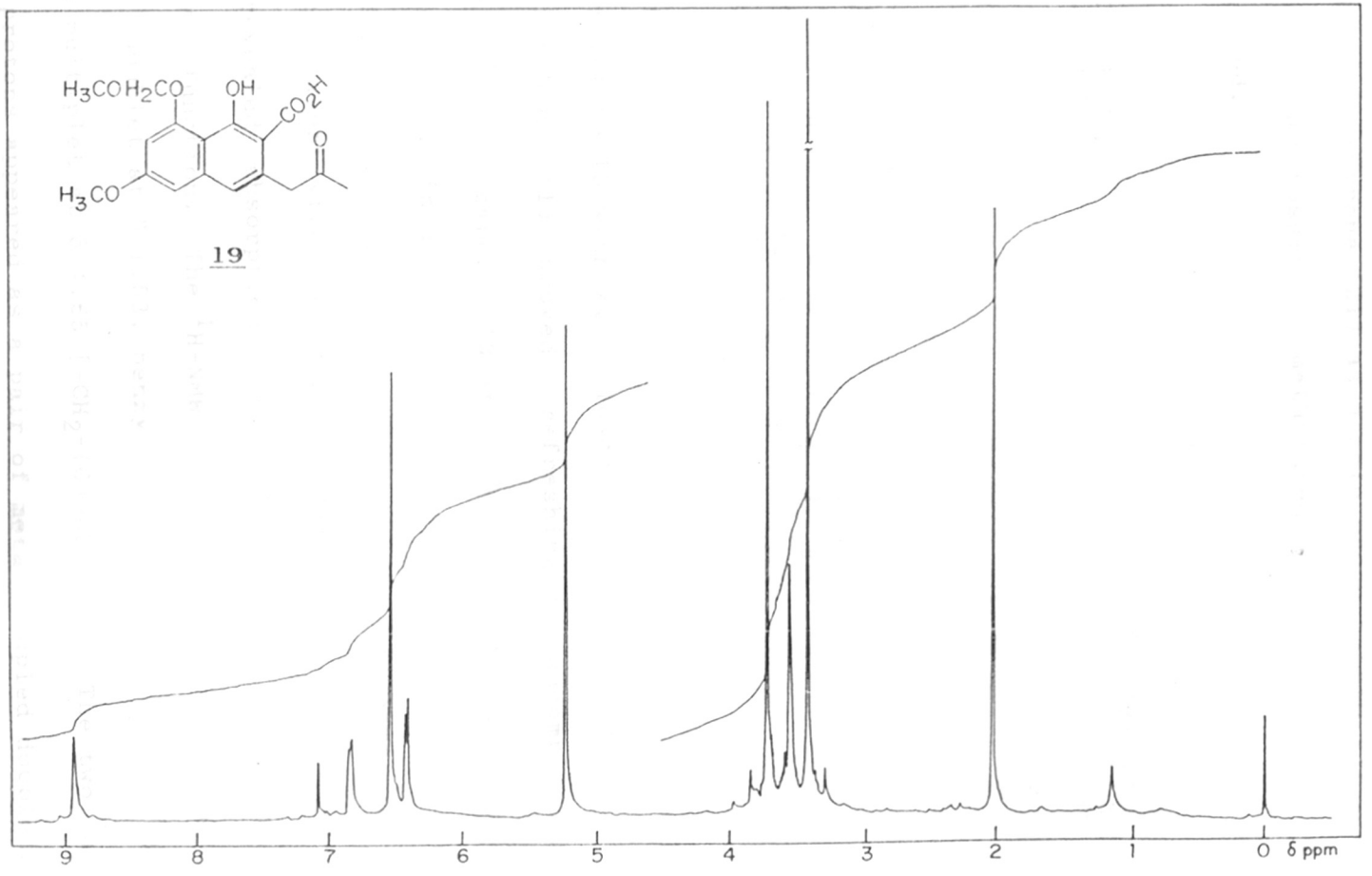
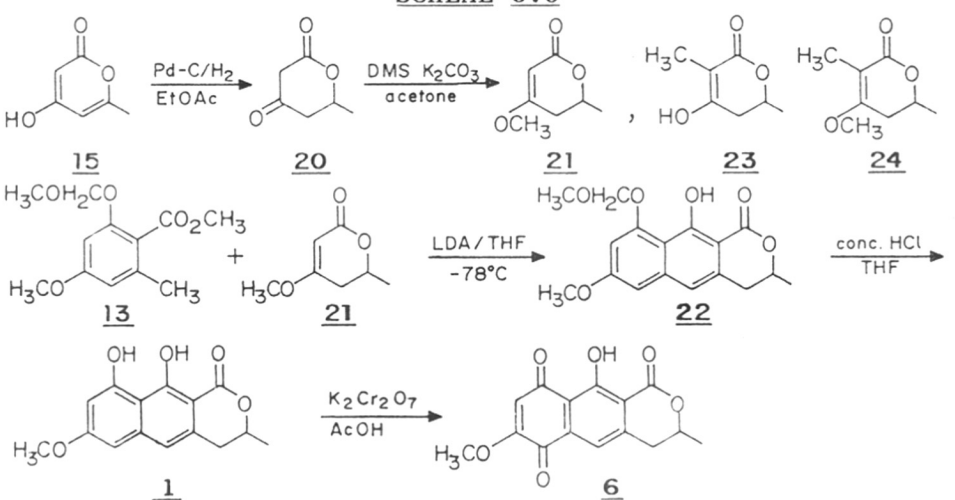


FIG. IV : ^{1}H-NMR SPECTRUM OF THE COMPOUND (19) IN $CDCl_3$

sulphate and potassium carbonate afforded 4-methoxy-6-methyl-5,6-dihydro-2-pyrone (21) as a sole product (FIG.V). No traces of other possible C-methylated products 23 and 24 were obtained.

SCHEME 3.5



With key synthon 21 in hand, condensation of orsellinate derivative 13 with 21 followed by deprotection to give semivioxanthin (1) proved refreshingly uncomplicated. Lithiation[15] of compound 13 at -78°C with LDA followed by treatment with dihydropyrone 21 led to MOM protected semivioxanthin (22). The spectral properties of compound 22 were consistent with the assigned structure. The IR spectrum revealed absorption band at 1654 cm^{-1} for lactone carbonyl function. The ^{1}H-NMR (FIG.VI) spectrum showed a methyl doublet at δ 1.53, benzylic -C$\underline{H}_2$ doublet at δ 2.92 and a multiplet at δ 4.65 [-CH_2-(O)-C$\underline{H}$-CH_3]. The two aromatic protons appeared as a pair of <u>meta</u>- coupled doublets (δ 6.59 and 6.68; J= 2.5 Hz) and third C-5 aromatic proton appeared as a singlet at δ 6.81. The chelated hydroxyl

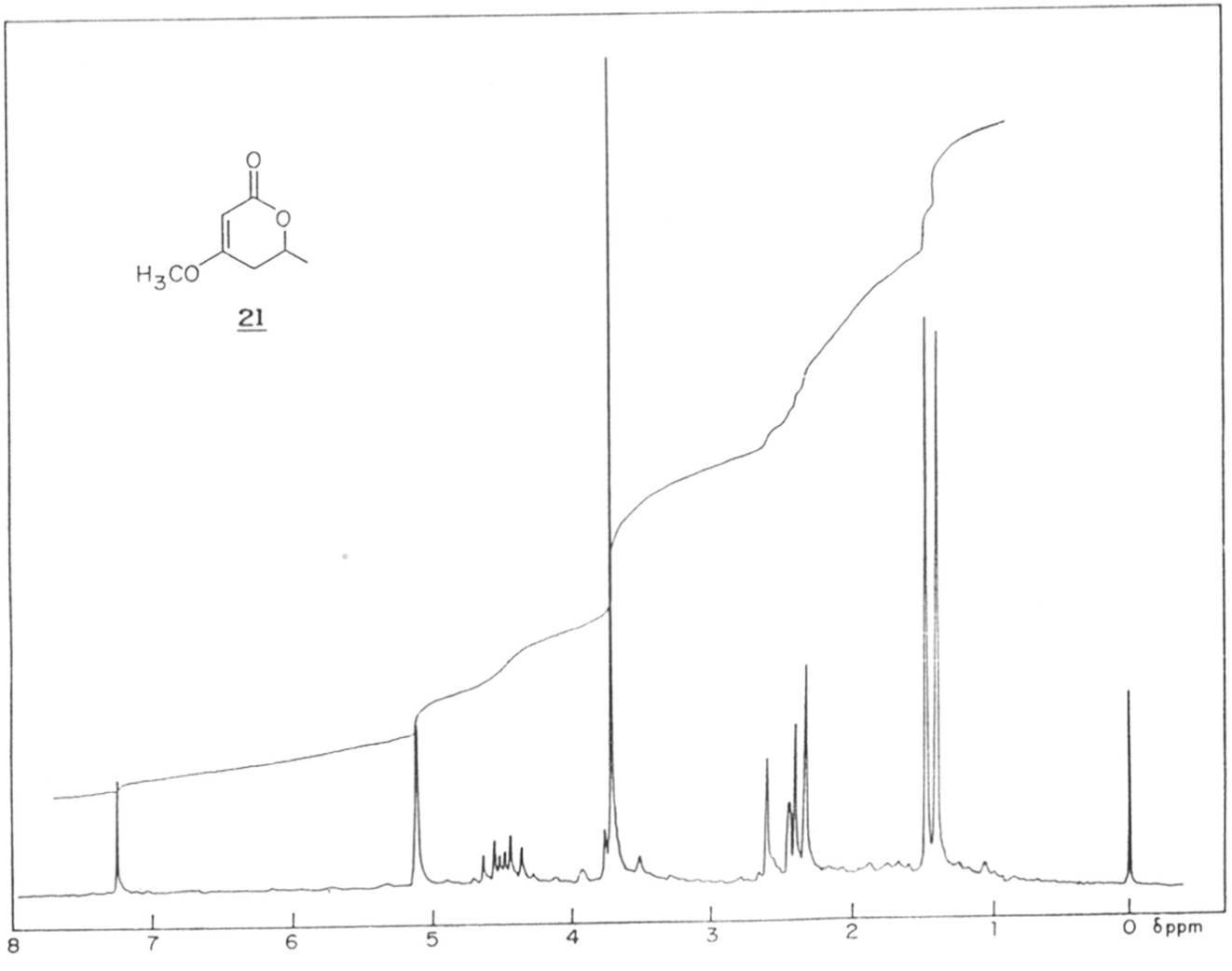


FIG. V : ^{1}H-NMR SPECTRUM OF THE COMPOUND (21) IN $CDCl_3$

proton was oserved at δ 9.03. The mass spectrum of 22 showed molecular ion peak at m/e 318.

Having thus obtained the required skeleton of semivioxanthin (1), the next reaction i.e. C-9 hydroxyl MOM deprotection of compound 22 was attempted with several well known reagents employed in literature. Among the known methods that were employed were 6M HCl in aqueous THF at 50°C[19], conc. HCl in methanol at 60°C[20], tritylfluoroborate in CH_2Cl_2[21], aqueous TFA in THF[22], anhydrous HCl (gas) in acetonitrile at 0°C[23], etc. Satisfactory yields of the required semivioxanthin (1) could however not be obtained from any of these methods. Deprotection of MOM ether with concentrated hydrochloric acid in THF at room temperature proved to be the best for the preparation of semivioxanthin (1). Semivioxanthin (1) was obtained as a crystalline solid after purification by column chromatography.

The semivioxanthin (1) was confirmed from its IR, UV, ^{1}H-NMR and mass spectral data. The IR spectrum showed typical band for the lactone carbonyl function at 1642 cm^{-1}. The ^{1}H-NMR spectrum (FIG.VII) was fully compatible with the structure 1. A methyl doublet at δ 1.53, two multiplets at δ 2.94 (Ar-C<u>H</u>$_2$) and at δ 4.72 [H_2C-(O)-<u>CH</u>-CH_3], a methoxyl protons singlet at δ 3.84, an aromatic proton singlet at δ 6.84 and the two <u>meta</u> coupled doublets for two aromatic protons (δ 6.47 and 6.50, J = 2 Hz) were observed. Remainder of the ^{1}H-NMR spectrum consisted of two singlets at δ 9.37 and δ 13.57 corresponding to chelated 9- and 10-hydroxyl protons respectively. The mass spectrum

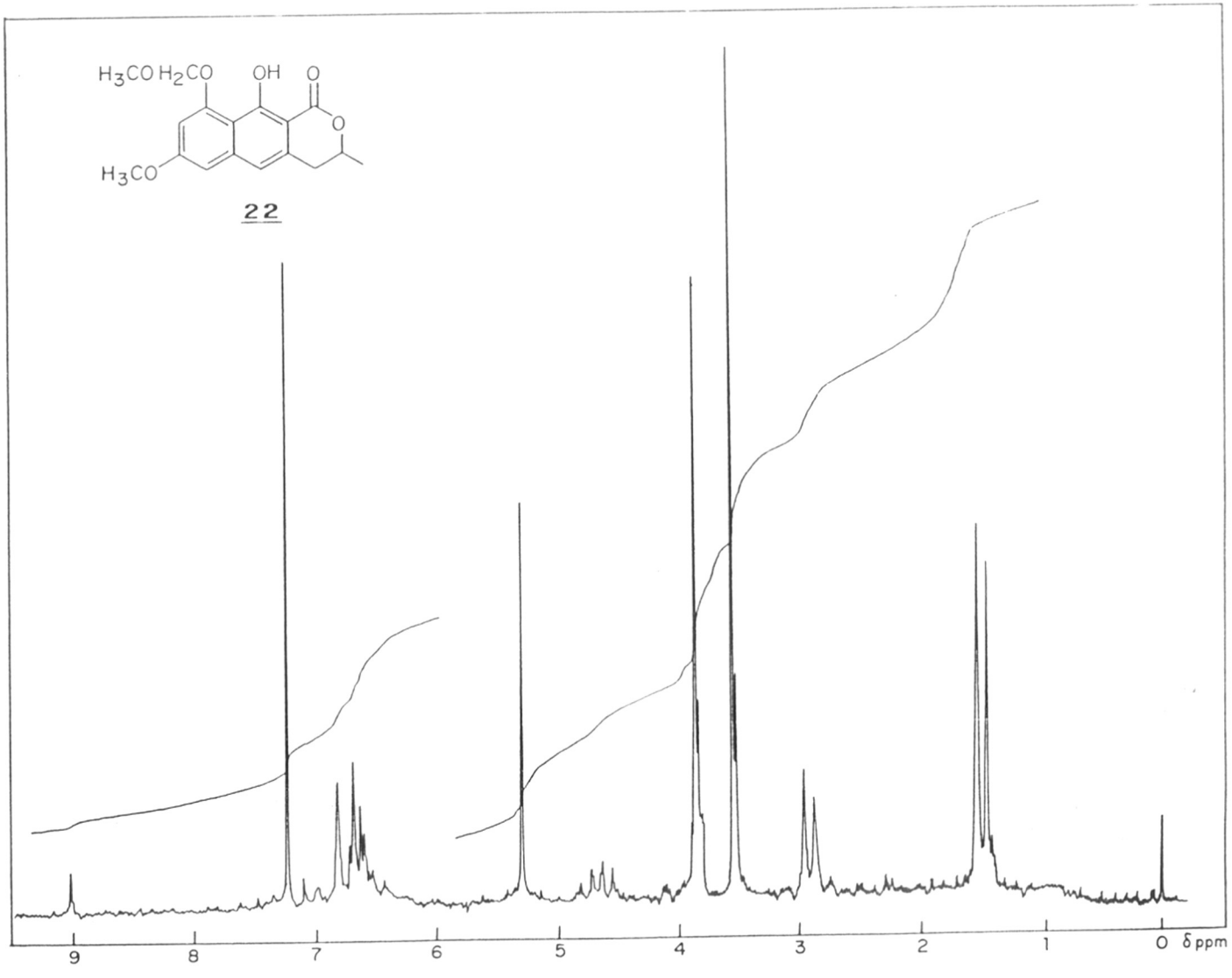


FIG. VI : ^{1}H-NMR SPECTRUM OF THE COMPOUND (22) IN $CDCl_3$

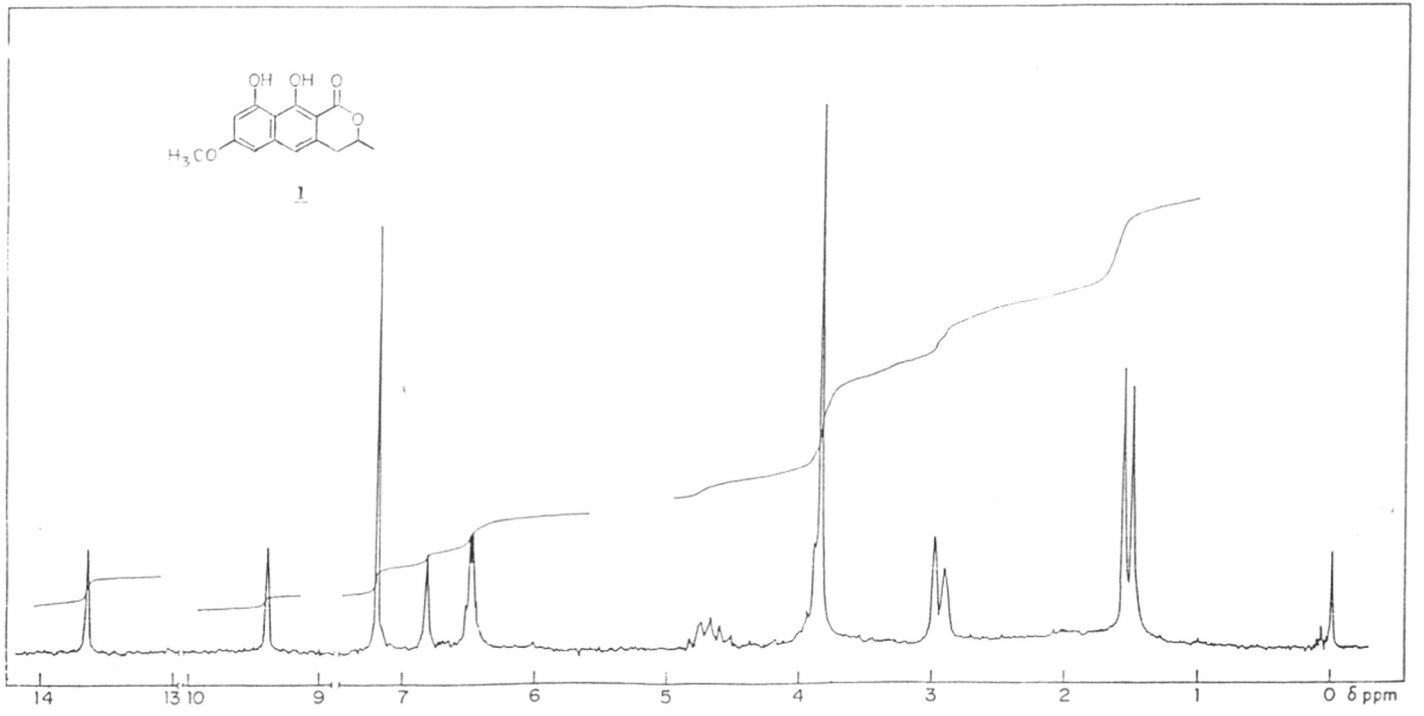
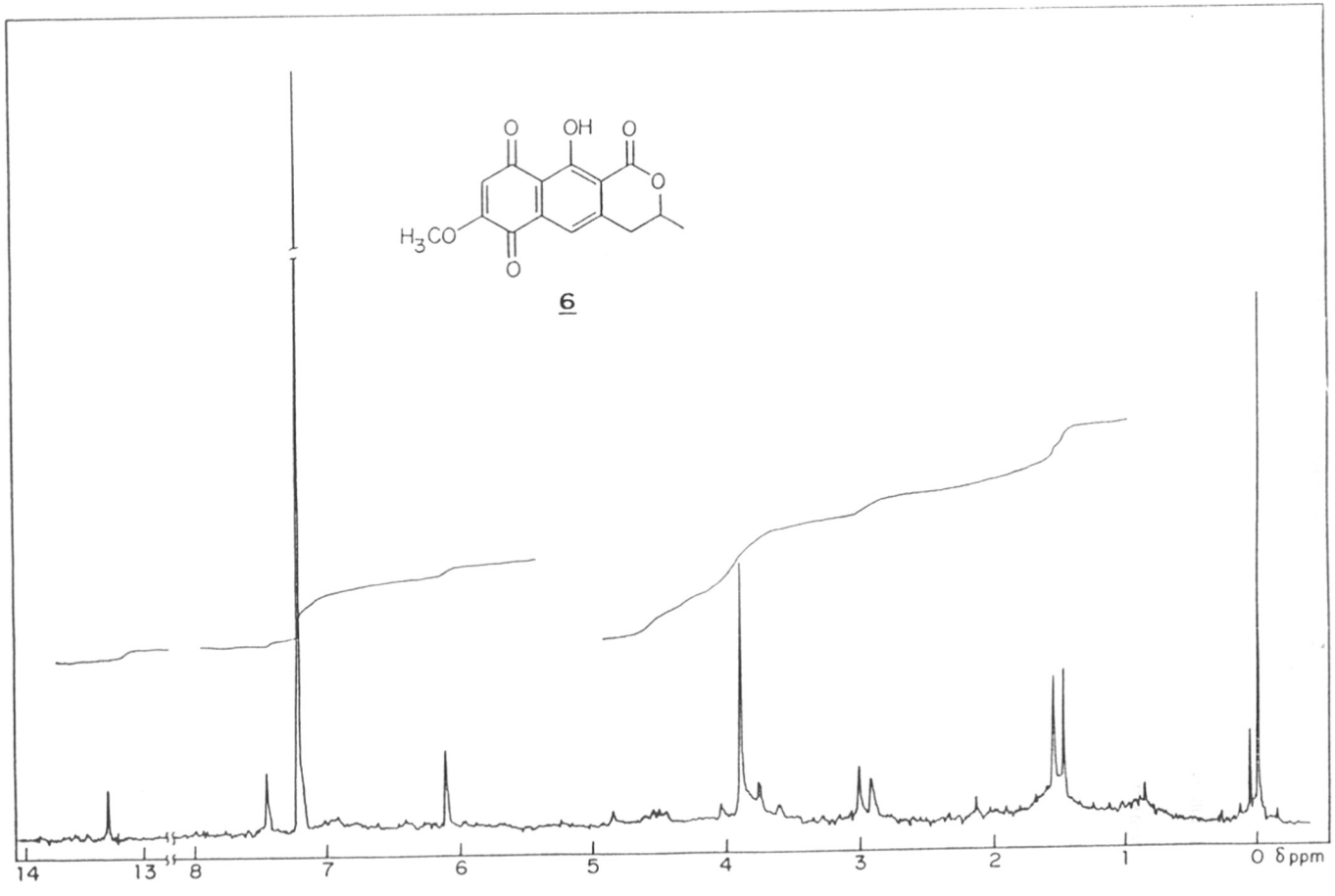


FIG. XII : ^{1}H-NMR SPECTRUM OF THE COMPOUND (1) IN $CDCl_3$



6

FIG. VIII : ^{1}H-NMR SPECTRUM OF THE COMPOUND (6) IN $CDCl_3$

of 1 showed molecular ion peak at m/e 274. Further, the IR and ^{1}H-NMR spectra of the synthetic semivioxanthin (1) were found to be identical with the spectra supplied by Prof. Yamaguchi.[12]

Conversion of semivioxanthin (1) to semixanthomegnin (6) has been reported by Zeeck et al[1] using Fremy salt (75% yield). In the present work this conversion was effected smoothly in comparable [1] yield (77%) by oxidation of 1 with potassium dichromate in acetic acid at room temperature. The structure of semixanthomegnin (6) was confirmed by comparing spectroscopic and physical properties with those previously reported[1]. The IR spectrum indicated absorption bands at 1730, 1690, 1672, 1620 and 1600 cm^{-1}. In the ^{1}H-NMR (FIG.VIII), a singlet at δ 6.15 for C-8 quinonic proton, a singlet at δ 7.49 for aromatic proton and a singlet at δ 13.20 for chelated hydroxyl proton were observed. Further confirmation was also obtained from the mass spectral data, which revealed a molecular ion peak at m/e 288.

In summary, the important features of the synthesis of semivioxanthin 1 discussed in the present work are as follow

1. The synthesis starts from easily accessible starting materials.
2. It represent simple and efficient synthesis of semivioxanthin (1) and therefore semixanthomegnin (6).
3. All the reactions were very smooth and high yielding.

4. This route to semivioxanthin (1) provides a useful way of preparing substantial quantities of material and can be readily adaptable for preparing analogues.

EXPERIMENTAL

Methyl 4-methoxy-2-methoxymethoxy-6-methylbenzoate (13):

To the stirred suspension of sodium hydride (0.086 g, 3.6 mmol) [50% sodium hydride (0.172 g) emulsion in paraffin was washed with dry benzene (5 ml) under argon atmosphere] in dry benzene (25 ml) was injected a solution of ortho-hydroxy ester 12 (0.700 g, 3.6 mmol) in dry benzene (5 ml). It was stirred at room temperature for 30 min and then cooled to 0°C. To the resulting sodium phenoxide suspension, chloromethyl methyl ether (0.43 g, 5.4 mmol) was added with vigorous stirring. It was stirred at 5 to 10°C for 1 h and then at room temperature for 4 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (eluent: 5% acetone-pet. ether) to afford compound 13 as a colourless viscous oil, (0.685 g, 80%).

IR (Neat): ν max 1740 and 1620 cm^{-1}.

^{1}H-NMR : δ 2.26 (s, 3H), 3.44 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 5.11 (s, 2H), 6.35 (d, J = 2.5 Hz, 1H) and 6.57 (d, J = 2.5 Hz, 1H).

MS (m/e): 240 (M^+).

Analysis cal. for $C_{12}H_{16}O_5$: C, 60.00; H, 6.67;

Found : C, 59.90; H, 6.66%.

6-Methyl-2H-pyran-2,4-(3H)-dione (15):

To the stirred solution of 90% sulphuric acid (75 g) was added dehydroacetic acid 14 (25 g, 0.149 mmol) and the

mixture was heated. When temperature of the reaction mixture reached to 130°C it was cooled rapidly and poured into cold water (100 ml). A colourless solid separated was filtered, washed with cold water and dried to obtain compound **15** (15 g, 80%); m.p. 188-190°C (from hot water) (Lit.[13], m.p. 188-189°C).

4-Methoxy-6-methyl-2-pyrone (16):

A mixture of triacetic lactone 15 (12.6 g, 0.1 mmol) dimethyl sulphate (18.9 g, 0.15 mmol) and anhydrous potassium carbonate (20.7 g, 0.15 mmol) in dry acetone (200 ml) was heated to reflux for 11 h. The reaction mixture was filtered, washed with acetone, filtrate and washings were united and the acetone was distilled off to leave an oil. It was then chromatographed [silica gel, eluent: 10% acetone-pet. ether] to obtain 4-methoxy-6-methyl-2-pyrone **16** (11 g, 78%); m.p. 88°C (Lit.[14]; m.p. 87-88°C).

10-Hydroxy-7-methoxy-9-methoxymethoxy-3-methyl-1H-naphtho [2,3-c] pyran-1-one (Toralactone MOM ether) (17):

To the stirred solution of LDA [prepared from 1.6 M solution of n-BuLi in hexane (2.5 ml) and diisopropyl amine (0.56 ml) at 0°C under argon atmosphere] in THF (15 ml) at -78°C was injected a solution of methyl orsellinate derivative 13 (0.480 g, 2 mmol) in THF (3 ml) and stirred for 15 min. To the resultant orange-red solution was added solution of 4-methoxy-6-methyl-2-pyrone **16** (0.280 g, 2 mmol)

in THF (5 ml) and stirred further for 30 min at -78°C. It was then warmed to room temperature by removing dry ice-acetone bath and stirred for 20 min. at room temperature. The reaction mixture was poured slowly into the ice cold dil. hydrochloric acid (50 ml) and extracted with dichloromethane. The organic extracts were washed with saturated brine solution, dried (Na_2SO_4) and concentrated. It was chromatographed (silica gel; eluent: 20% acetone-pet. ether) to afford naphthopyrone 17 (0.400 g, 63%); m.p. 175°C.

IR ($CHCl_3$): ν max 1680, 1625 and 1585 cm^{-1}.

^{1}H-NMR : δ 2.22 (s, 3H), 3.56 (s, 3H), 3.87 (s, 3H), 5.31 (s, 2H), 6.15 (s, 1H), 6.65 (br s, 2H), 6.87 (s, 1H) and 12.80 (s, 1H).

MS (m/e): 316 (M^+).

Analysis cal. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.06;

Found : C, 64.58; H, 5.08%.

9,10-Dihydroxy-7-methoxy-3-methyl-1H-naphtho[2,3-c]pyran-1-one (Toralactone) (18):

To the stirred solution of naphthopyrone 17 (0.100 g, 0.316 mmol) in THF (6 ml) was added 4-5 drops of concentrated hydrochloric acid and stirred at room temperature for 5 h. To the reaction mixture an aqueous solution of 5% sodium bicarbonate (15 ml) was added and extracted with dichloromethane (2 x 15 ml). The dichloromethane extract was washed with water followed by saturated brine solution, dried over sodium sulphate and concentrated. It was purified by

passing through short column of silica gel (eluent: 5% methanol-chloroform) to yield toralactone 18 (0.081 g, 94%) as a crystalline solid; m.p. 228-229°C.

IR ($CHCl_3$): ν max 1682 and 1621 cm^{-1}.

^{1}H-NMR : δ 2.22 (s, 3H), 3.84 (s, 3H), 6.12 (s, 1H), 6.40 (d, J = 2Hz, 1H), 6.53 (d, J = 2 Hz, 1H), 6.84 (s, 1H), 9.34 (s, 1H) and 13.20 (s, 1H).

MS (m/e): 276 (M^+).

Analysis cal. for $C_{15}H_{12}O_5$: C, 65.22; H, 4.35;

Found : C, 65.31; H, 4.36%.

1-Hydroxy-6-methoxy-8-methoxymethoxy-3(2'-oxopropyl)-2-naphthoic acid (19):

The naphthopyrone 17 (0.200 g, 0.633 mmol) was heated under reflux with an aqueous potassium hydroxide solution [0.354 g in water (0.5 ml)] and methanol (15 ml) for 5 h. The resulting solution was cooled, acidified with concentrated hydrochloric acid and extracted with dichloromethane. The organic extract was shaken with 5% aqueous sodium bicarbonate solution. The aqueous bicarbonate solution was acidified (concentrated hydrochloric acid) and extracted with dichloromethane. The dichloromethane extract was washed with water, dried (Na_2SO_4) and evaporated to give keto-acid 19 (0.150g, 71%) as a semisolid.

IR (Nujol): ν max 1660 and 1600 cm^{-1}.

^{1}H-NMR : δ 2.03 (s, 3H), 3.43 (s, 3H), 3.56 (s, 2H), 3.72 (s, 3H), 5.22 (s, 2H), 6.41 (d, J = 2 Hz, 1H), 6.53 (s, 1H), 6.84 (d, J = 2 Hz, 1H) and 8.94 (s, 1H).

MS (m/e): 334 (M^+).

4-Hydroxy-6-methyl-5,6-dihydro-2-pyrone (20):

In an autoclave the triacetic lactone 15 (10 g, 79.3 mmol) was hydrogenated in ethyl acetate (50 ml) using 10% Pd on charcoal (0.100 g) under pressure (5 kg/cm^2) for 24 h at room temperature. The catalyst was removed by filtration. The ethyl acetate was distilled off under reduced pressure to give a crude product (7.5 g). It was recrystallized from ethanol to afford 6.6 g of pure compound 20 (65%); m.p. 123°C (Lit.[18]; m.p. 123°C).

IR ($CHCl_3$): $\tilde{\nu}$ max 3500-3200, 1690 and 1600 cm^{-1}.

^{1}H-NMR: δ 1.53 (d, J = 6 Hz, 3H), 2.50 (d, J = 18 Hz, 2H), 3.50 (d, J = 18 Hz, 2H) and 4.80 (m, 1H).

MS (m/e): 128 (M^+).

4-Methoxy-6-methyl-5,6-dihydro-2-pyrone (21):

A mixture of pyrone 20 (1.28 g, 10 mmol), dimethyl sulphate (1.51 g, 12 mmol) and anhydrous potassium carbonate (2.1 g, 15 mmol) in dry acetone (50 ml) was heated to reflux for 8 h. The acetone was distilled off from the reaction mixture, water (50 ml) was added to the residue and extracted with dichloromethane (3 x 25 ml). The organic extracts were combined, dried (Na_2SO_4) and evaporated to leave a viscous oil. Chromatographic purification of the crude

product on silica gel using 5% acetone-pet. ether as eluent afforded 1.35 g of methoxypyrone **21** (95%); m.p. 56°C.

IR (Nujol): ν max 1735 and 1620 cm^{-1}.

^{1}H-NMR : δ 1.39 (d, J = 6.8 Hz, 3H), 2.93 (m, 2H), 3.69 (s, 3H), 4.48 (m, 1H) and 5.10 (s, 1H).MS (m/e): 142 (M^+).

Analysis cal. for $C_7H_{10}O_3$: C, 59.15; H, 7.04;

Found : C, 59.20; H, 7.00%.

3,4-Dihydro-10-hydroxy-7-methoxy-9-methoxymethoxy-3-methyl-1-oxo-1H-naphtho[2,3-c]pyran (22):

Into the flask containing LDA [prepared from a hexane solution of 1.6 M BuLi (2 ml) and diisopropyl amine (0.44 ml, 3.15 mmol) at 0°C under argon atmosphere] in THF (10 ml), a solution of compound **13** (0.378 g, 1.57 mmol) in THF (2 ml) was injected through syringe at -78°C. After 15 min. the resultant orange-red anionic solution was treated with dihydropyrone **21** (0.223 g, 1.57 mmol) in THF (2 ml) and the reaction mixture was stirred further for 30 min. at -78°C. It was then allowed to warm to room temperature and stirred for 20 min. The reaction mixture was poured into an ice cold dilute hydrochloric acid solution and extracted with dichloromethane. The organic extract was washed with saturated brine solution, dried (Na_2SO_4) and evaporated to give brown thick oily residue. It was chromatographed (silica gel, eluent: 15% acetone-pet. ether) to yield compound **22** (0.340 g, 68%) as a pale yellow crystalline solid; m.p. 138°C.

IR ($CHCl_3$): ν max 1654 and 1633 cm^{-1}.

^{1}H-NMR: δ 1.53 (d, J = 6.4 Hz, 3H), 2.92 (d, J = 6.8 Hz, 2H), 3.53 (s, 3H), 3.86 (s, 3H), 4.65 (m, 1H), 5.31 (s, 2H), 6.59 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 2.5 Hz, 1H), 6.81 (s, 1H) and 9.03 (s, 1H).

MS (m/e): 318 (M^+).

Analysis cal. for $C_{17}H_{18}O_6$: C, 64.15; H, 5.66;

Found : C, 64.09; J, 5.62%.

3,4-Dihydro-9,10-dihydroxy-7-methoxy-3-methyl-1-oxo-1H-naphtho [2,3-c]pyran (Semivioxanthin) (1):

To the stirred solution of naphthopyrone 22 (0.100 g, 0.365 mmol) in THF (5 ml) was added 4-5 drops of concentrated hydrochloric acid and stirred at room temperature for 4 h. To the reaction mixture an aqueous 5% sodium bicarbonate solution (10 ml) was added and the resulting solution was extracted with dichloromethane (2 x 15 ml). The dichloromethane extract was washed with water, saturated brine solution, dried over sodium sulphate and evaporated. Purification of the crude product by passing through short column of silica gel (eluent: 5% methanol-chloroform) afforded 0.071 g of semivioxanthin 1 in 82% yield as a crystalline solid; m.p. 185°C (Lit.[1], m.p. 185°C).

IR ($CHCl_3$): ν max 1642 and 1585 cm^{-1}.

UV (MeOH): λ max (ϵ) 371.8 (10,000), 308 (3,600), and 261.2 (48,200) nm.

^{1}H-NMR : δ 1.53 (d, J = 6.5 Hz, 3H), 2.94 (m, 2H), 3.84 (s, 3H), 4.72 (m, 1H), 6.47 (d, J = 2Hz, 1H), 6.50 (d, J=2

Hz, 1H), 6.84 (s, 1H), 9.37 (s, 1H) and 13.57 (s, 1H).

MS (m/e): 274 (M^+).

Analysis cal. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.11;

Found : C,65.60; H,5.10%.

3,4,5,9-Tetrahydro-10-hydroxy-7-methoxy-3-methyl-1,6,9-trioxo-1H-naphtho[2,3-c]pyran (Semixanthomegnin) (6):

To the stirred solution of semivioxanthin 1 (0.050 g, 0.175 mmol) in glacial acetic acid (5 ml) was added solid potassium dichromate (0.322 g, 1.09 mmol). After stirring for 8 h at room temperature a mixture of chloroform (10 ml) and water (20 ml) was added. The chloroform layer was separated and the aqueous part was extracted with chloroform (2 x 10 ml). The chloroform extracts were united, washed successively with water, 5% aqueous sodium bicarbonate solution, saturated brine solution, dried (Na_2SO_4) and concentrated. Purification of the product by column chromatography on silica gel (eluent: chloroform) afforded semixanthomegnin **6** as a orange-red solid (0.041 g, 77%). Recrystallization from chloroform-acetone gave orange-red needles; m.p. 225-226°C, [Lit.[1]; m.p. 226°C).

IR ($CHCL_3$): ν max 1730, 1690, 1672, 1620 and 1600 cm^{-1}.

UV (CH_3OH): λmax (ϵ): 410 (4,800), 286 (8,600) and 226 (29,500) nm.

^{1}H-NMR:δ 1.52(d, J = 6.5 Hz, 3H), 2.99(m, 2H), 3.90 (s, 3H), 4.66 (m, 1H), 6.15 (s, 1H), 7.49 (s, 1H) and 13.20 (s, 1H).

MS (m/e): 288 (M^+).

Analysis cal. for $C_{15}H_{12}O_6$: C, 62.50; H, 4.16;

Found : C, 62.41; H, 4.16%.

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CHAPTER-IV

REGIOSPECIFIC SYNTHESIS OF BOSTRYCOIDIN

INTRODUCTION:

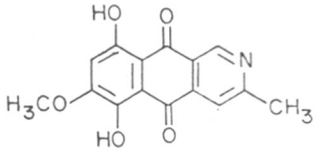
The quinone moiety is found commonly in nature. Quinones, including heterocyclic analogues, are involved in numerous biochemical processes because of their facile reduction-oxidation. They play an important role in electron transport processes and oxidative phosphorylation processes. Furthermore their biological activity includes enzyme inhibition and some have chemotherapeutic values as antitumor, antibacterial, antifungal and anticancer agent. Heterocyclic quinones were hypothesized to function as bioreductive alkylating agents in that after they undergo a reduction *in vitro* they become potent alkylating agents.[2]

Although anthraquinones represent a large class of natural products,[1] their aza analogues are rarely found in nature. The mould metabolite bostrycoidin **1** was first isolated by Hamilton *et al.* from *Fusarium bostrycoides*[3]. Later on the same pigment was isolated by Arsenault from *F. Solani* D_2 purple[4] while its 8-O-methyl derivative **2** was isolated by Steyn *et al.* as the major pigment of the toxinogenic strain of *F. moniliforme*[5]. Bostrycoidin was shown to possess an antibiotic activity against the tubercle bacillus *in vitro*[3]. Its structure was elucidated by Arsenault as 6,9-dihydroxy-7-methoxy-3-methylbenz[g]isoquinolin-5,10-dione on the basis of its ultraviolet, visible, infrared and proton magnetic resonance spectra and biogenetic considerations.

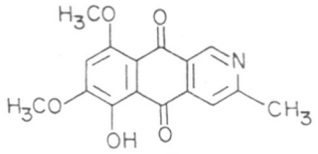
The first total syntheses of bostrycoidin and its 8-*O*-methyl derivative were achieved by Cameron *et al.*[6]

in 1980 using two key reactions for the construction of 2-azaanthraquinone skeleton.

FIGURE-I



1

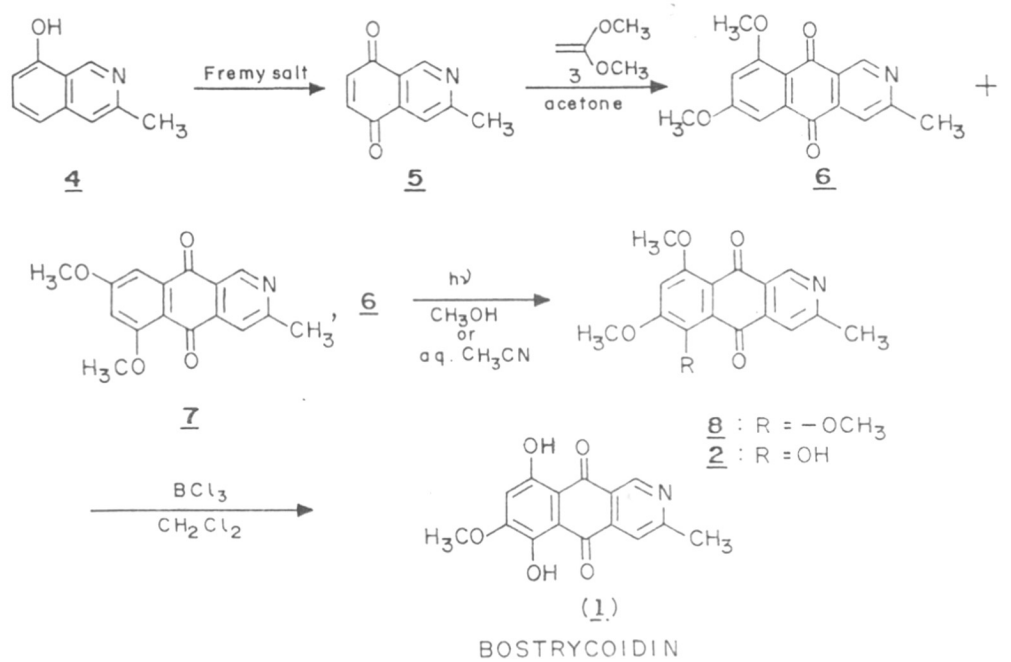


2

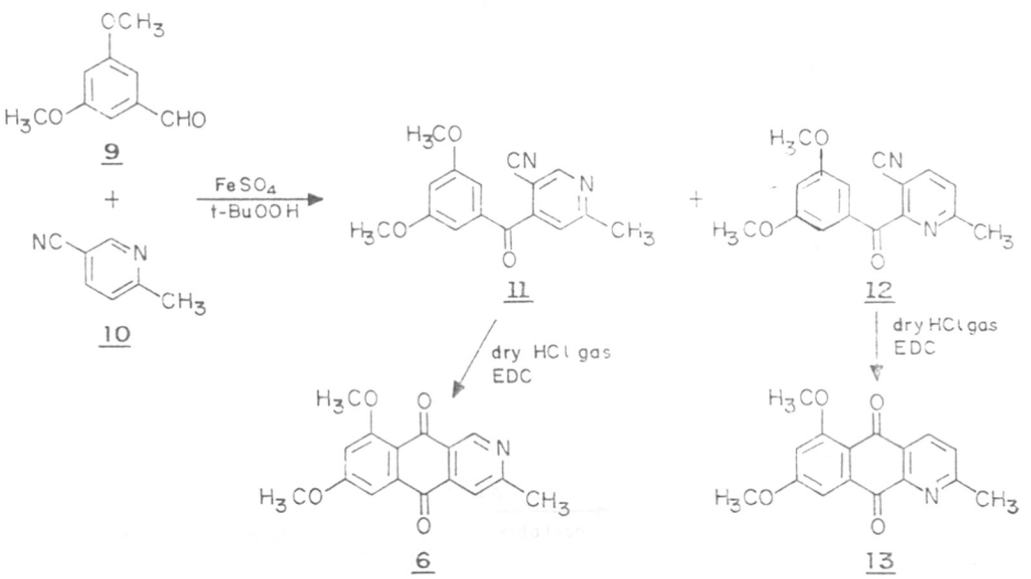
Syntheses of bostrycoidin 1 and 8-O-methyl bostrycoidin 2 were planned from the 2-azanaphthoquinone and 1,1-dimethoxyethene 3 as shown in scheme 4.1. Thus, the required azanaphthoquinone 5 was readily obtained from 3-methylisoquinoline-8-ol 4 by oxidation with Fremy salt. Annelation of 3-methylisoquinoline-5,8-dione 5 with 3 in acetone gave a 1:7 mixture of quinones 6 and 7 in 70% yield. Syntheses of natural products 1 and 2 required introduction of an oxygen function at C-6 of the azaanthraquinone 6. Therefore, methanolic solution of quinone 6 was exposed to bright sunlight to give the required bostrycoidin dimethyl ether (8). Irradiation of an aqueous acetonitrile solution of 6 to ultraviolet light gave 8-O-methylbostrycoidin (2) in 74% yield. Treatment of 8 or 2 with borontrichloride at room temperature yielded bostrycoidin (1).

A confirmatory approach to bostrycoidin (1) was applied by Cameron et al.[6,7] using radical benzoylation of 6-methylpyridine-3-carbonitrile (10) with the radical derived from 3,5-dimethoxybenzaldehyde (9) to give a mixture

SCHEME-4.1

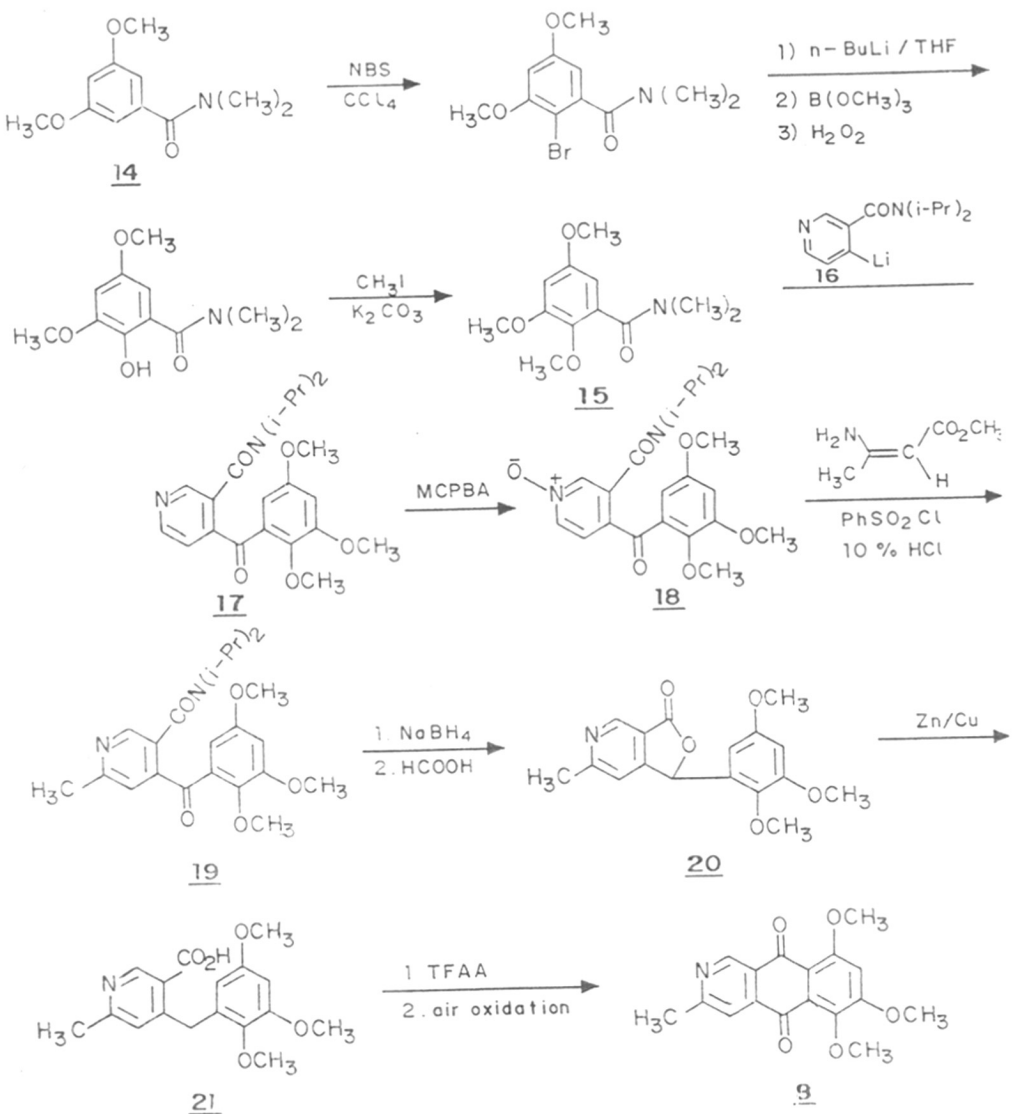


SCHEME-4.2



of desired 4 benzoylated pyridine 11 (13%) and undesired 2-benzoylated pyridine 12 (35%). Houben-Hoesch reaction of 11 with dry hydrogen chloride gas in 1,2-dichloroethane afforded the compound 6 in 35% yield. Similar ring closure of 12 gave 1-azaanthraquinone 13 as depicted in SCHEME-4.2.

SCHEME 4.3



Watanabe *et al.*[8] applied hetero-atom directed lithiation strategy for the regiospecific formal total synthesis of bostrycoidin (1) (SCHEME-4.3). The key reaction in this approach involves condensation of lithiated nicotinamide 16 with *N,N*-dimethyl-2,3,5-trimethoxybenzamide (15). The methyl group at 3-position of bostrycoidin (1) was introduced after the condensation of 15 and 16 was accomplished. The *N,N*-dimethyl-2,3,5-trimethoxybenzamide (15), the C-ring of bostrycoidin, was synthesised from *N,N*-dimethyl-3,5-dimethoxybenzamide (14) with an overall yield of 60% as outlined in SCHEME-4.3.

PRESENT WORK:

The antibiotic bostrycoidin (1) and its 8-O-methyl derivative are (2) the two naturally occurring 2-azaanthraquinones. The chemistry[3] and antibiotic properties[9] of bostrycoidin were investigated by Cajori, Hamilton and co-workers who isolated this pigment from Fusarium bostrycoides. They suggested molecular formula $C_{18}H_{14}O_7$ and concluded that bostrycoidin was a substituted naphthazarin with one methoxy and one methyl group.

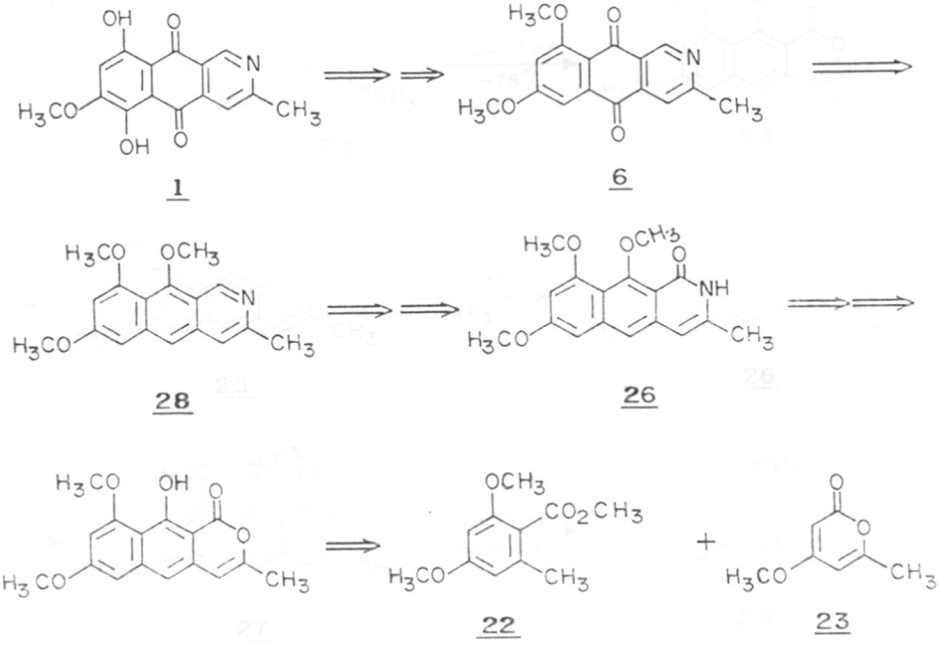
The first two syntheses[6] of bostrycoidin mentioned earlier utilize two different key reactions for the construction of azaanthraquinone skeleton, i.e. reaction of 1,1-dimethoxyethene with azanaphthoquinone and radical benzoylation with 3,5-dimethoxy benzaldehyde (9) of a pyridine ring containing a cyano and methyl groups in 3 and 6 positions. However, each of these reactions suffers from the disadvantages of poor regioselectivity and low yields, while the regioselective third synthesis[8] based on directed lithiation strategy starting from nicotinamide (16) and trimethoxyamide 15. This results in fair to poor yields in a few steps. Therefore, a more efficient and regioselective synthesis of bostrycoidin was developed and the same is reported in the present work.

An examination of the structure of bostrycoidin (retrosynthetic analysis) readily revealed that 2 can be synsthesised from easily available naphthopyrone[10a,b] 25 as a key

intermediate (SCHEME-4.4).

Isocoumarins are known[11] to undergo transformation to isoquinolines *via* chloroisoquinoline. This allows C-ring construction of brostrycoidin from pyrone ring of naphthopyrone **25** *via* benzo[g] isoquinolone **26**. This approach was selected as the method of choice based on which the present synthesis was completed successfully.

SCHEME-4.4

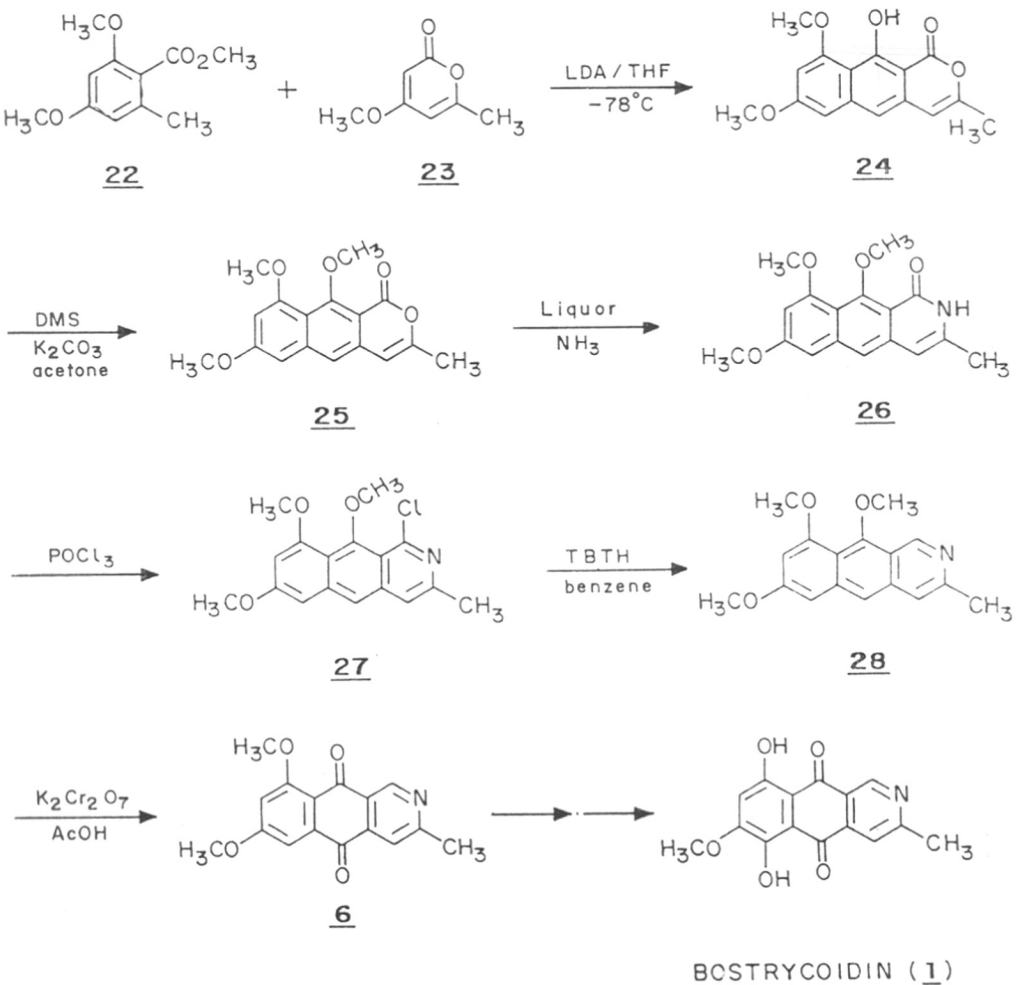


The required naphthopyrone trimethyl ether (25) was prepared in quantitative yield by methylation of hydroxynaphthopyrone 24, with dimethyl sulphate-potassium carbonate in refluxing acetone. The hydroxynaphthopyrone 24 was synthesised by known[10] literature procedure from methyl

orsellinate dimethyl ether (22) and 4-methoxy-6-methyl-2-pyrone (23).

The methyl orsellinate dimethyl ether 22, whose preparation has already been described in CHAPTER-II was lithiated at -78°C in THF and to it the pyrone 23[20] (for its synthesis see CHAPTER-III) was added to yield the desired naphthopyrone 24 (FIG. II) (SCHEME-4.5).

SCHEME-4.5



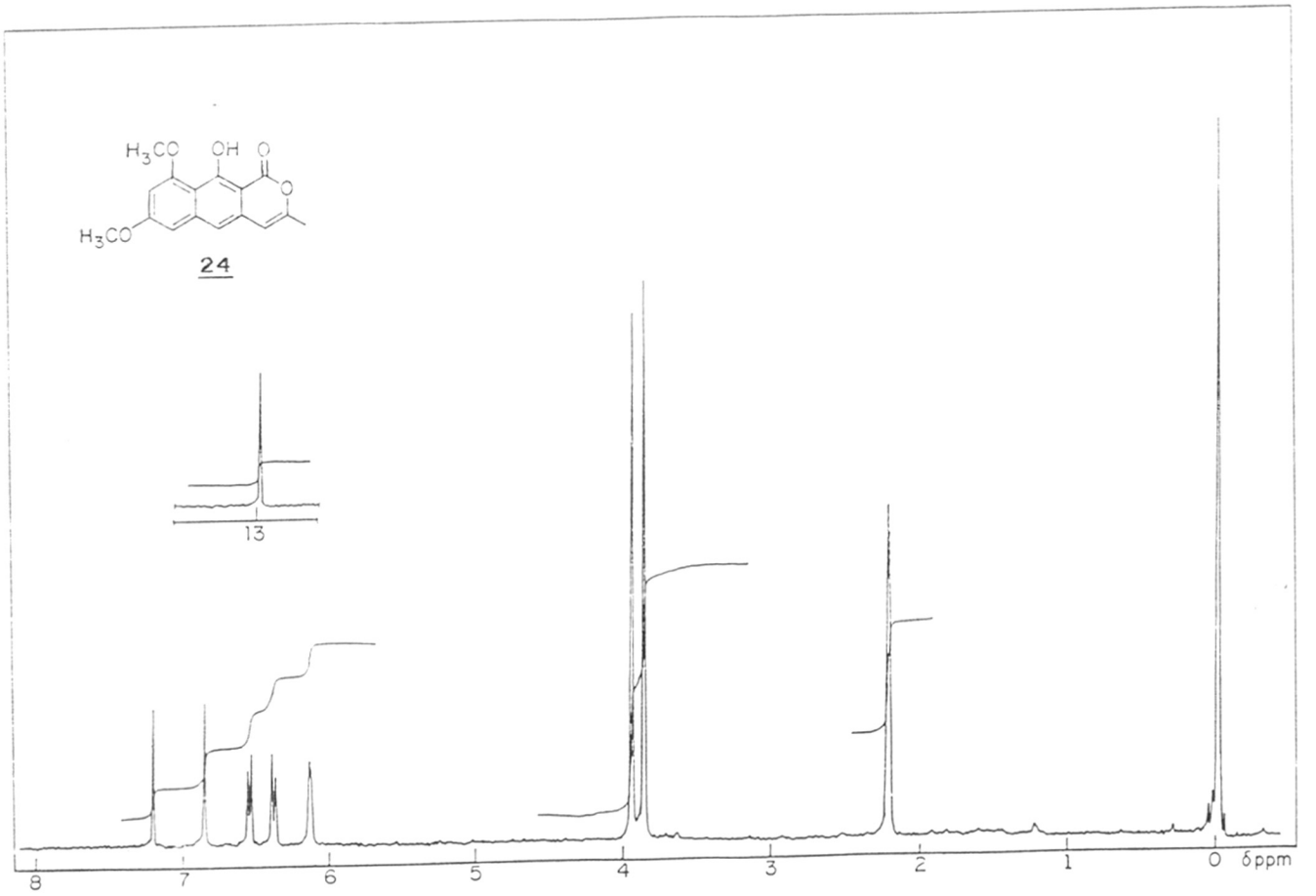


FIG. II : ^{1}H-NMR SPECTRUM OF THE COMPOUND (24) IN $CDCl_3$

Conversion of 7,9,10-trimethoxy-3-methylnaphtho[2,3-c]-pyran-2-one (25) to the 7,9,10-trimethoxy-3-methylbenz[g]-isoquinolone (26) was effected quantitatively by treating it with aqueous ammonia[15] at room temperature. Its structure was confirmed from the IR and ^{1}H-NMR spectral data. The IR spectrum showed typical bands for the amide carbonyl and weak band for -NH function at 1660 and 3150 cm^{-1} respectively. The ^{1}H-NMR spectrum was (FIG. III) fully compatible with the structure 26. A -NH singlet at δ 9.00 was observed.

The benz[g]isoquinolone 26 was converted to chloroazaanthracene 27 by treating it with $POCl_3$[12]. The product 27 was isolated in 88% yield by chromatography through short column of silica gel. Its structure was confirmed as 1-chloro-7,9,10-trimethoxy-3-methyl-2-azaanthracene (27) on the basis of spectral evidence. The IR spectrum indicated a disappearance of carbonyl absorption. In the ^{1}H-NMR, (FIG. IV); the -NH singlet at δ 9.00 disappeared while singlet at δ 6.13 due to C-4 proton was shifted to downfield at δ 7.72. Further confirmation was also obtained from the mass spectral data, which revealed molecular ion peak at m/e 317 as a base peak.

Chloroisoquinolines are known to undergo transformation to isoquinolines by hydrogenation over Pd/c[11] in acetic acid-sodium acetate or Raney nickel[12] in 5% alkaline ethanol. Thus reductive dehalogenation of chloroazaanthracene 27 under both of these conditions[11,12] was attempted.

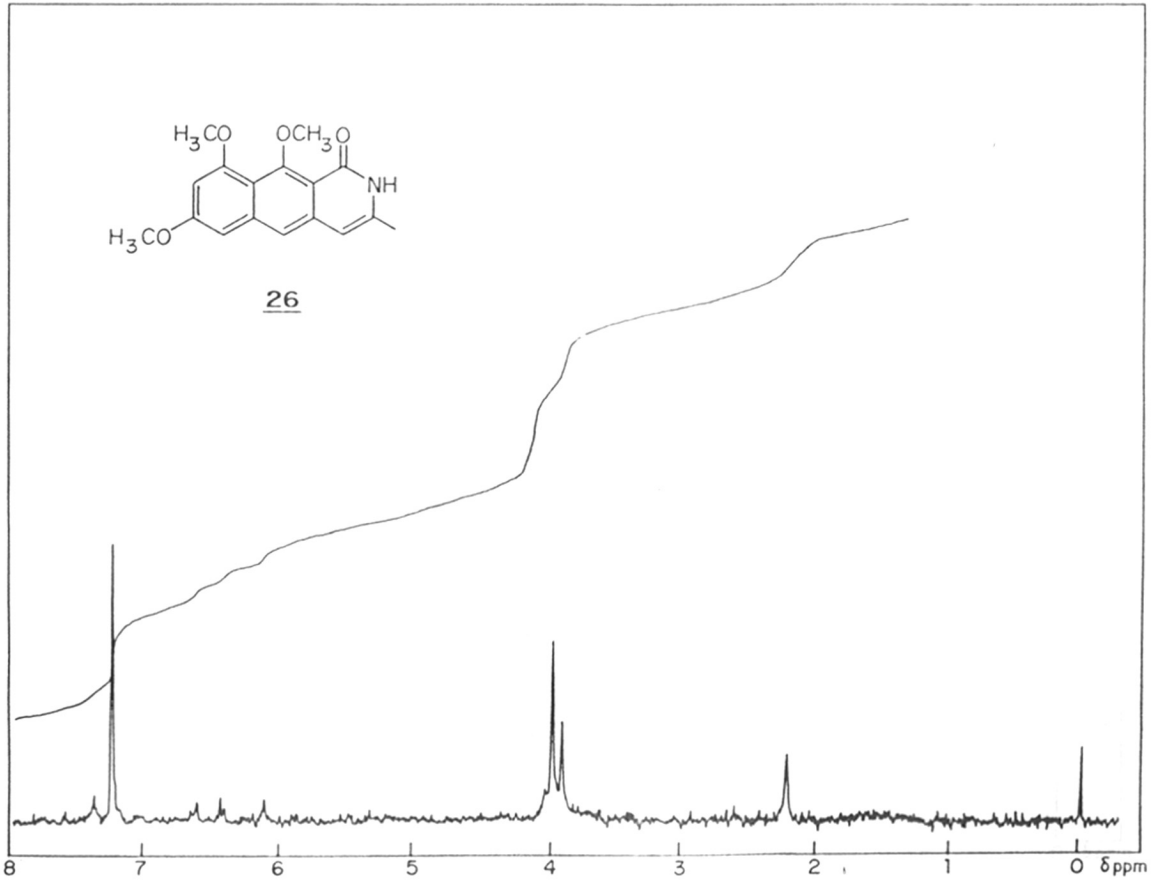


FIG. III : ^{1}H-NMR SPECTRUM OF THE COMPOUND (26) IN $CDCl_3$

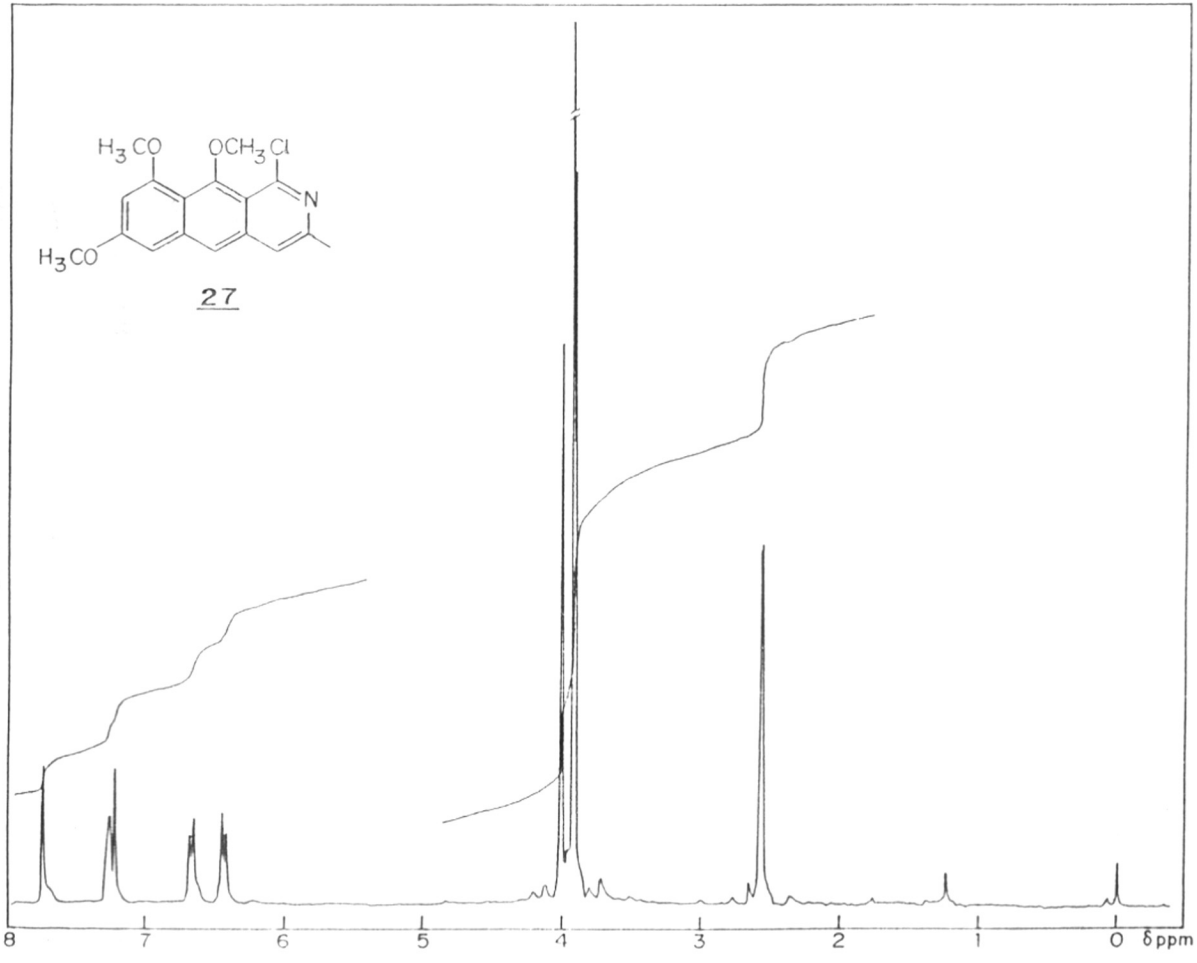


FIG. IV: ^{1}H-NMR SPECTRUM OF THE COMPOUND(27) IN $CDCl_3$

Satisfactory yields of the required 2-azaanthracene 28, however could not be obtained from any of these methods.

A detailed literature survey for the dehalogenation of aromatic and heterocyclic halides revealed a number of methods and reagents[13] viz. catalytic hydrogenolysis[11,12], Lithium aluminium hydride[14], magnesium and an methanol[15], metal halogen exchange[16], tributyltin hydride-AIBN etc.[17] The method using tributyltin hydride proved to be the best for the dehalogenation of chloroazaanthracene 27. Thus, the mixture of 27, tributyltin hydride and AIBN[18] in dry benzene was refluxed for 12 h. Dehalogenated azaanthracene 28 was obtained quantitatively after passing through short column of silica gel to remove tin impurities. All the spectral data for 28 were in conformity with the structure. Appearance of an additional peak at δ 9.59 in the ^{1}H-NMR spectrum (FIG. V) was indicative of introduction of H atom in place of Cl atom. Further confirmation was also obtained from its mass spectrum (M^+, 283).

The next reaction in this scheme involved oxidation of the 2-azaanthracene 28 to 2-azaanthraquinone 6. For this purpose, compound 28 was treated with potassium dichromate[19] in acetic acid (SCHEME-4.5) to give corresponding quinone 6. The ^{1}H-NMR spectral data of 6 was in full agreement with the structure (FIG.VI). As photochemical hydroxylation and demethylation has already been carried out by Cameron et al.[6] the present work in effect constitutes a total synthesis of bostrycoidin (1).

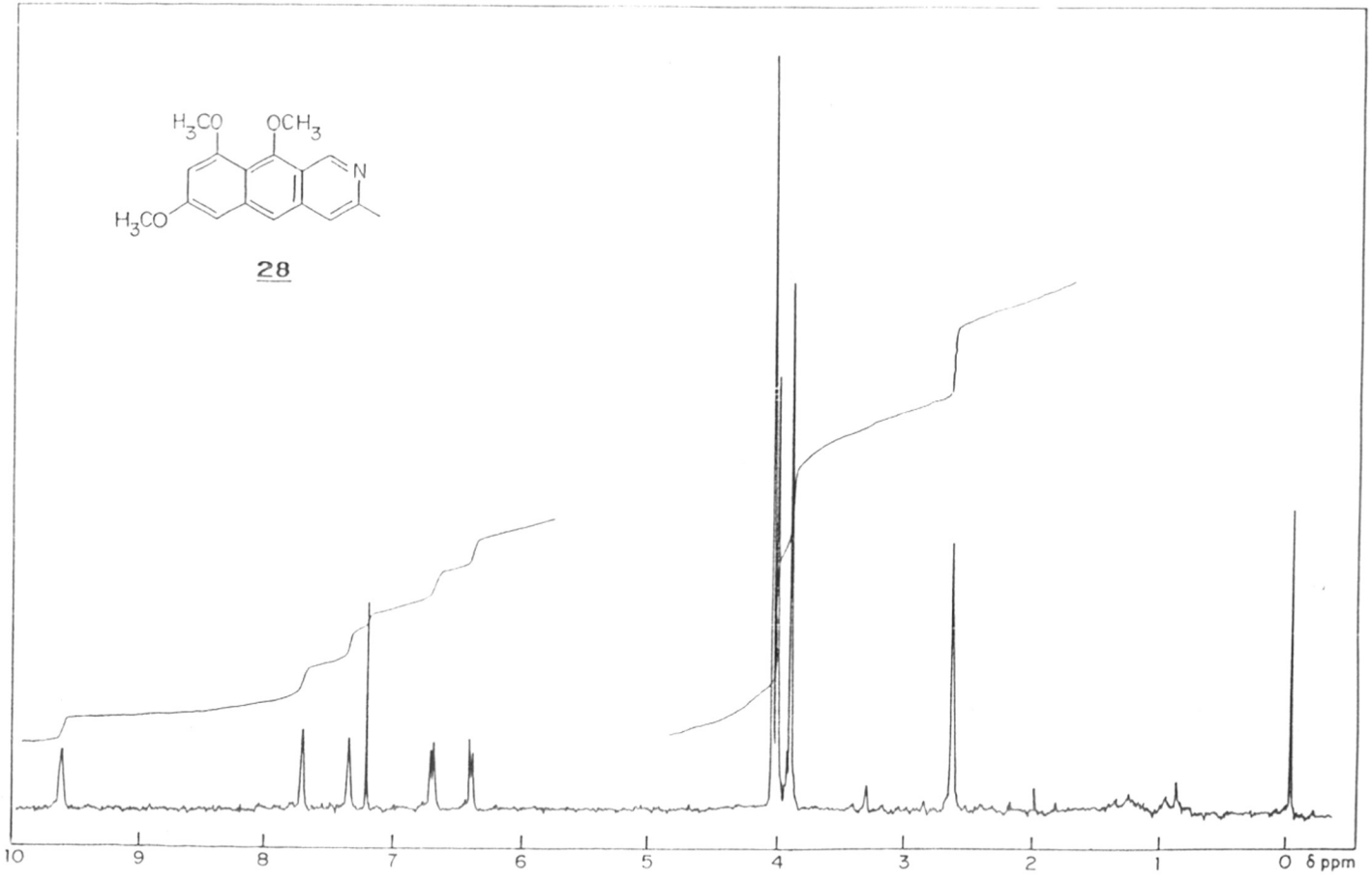


FIG. V : ^{1}H-NMR SPECTRUM OF THE COMPOUND (28) IN $CDCl_3$

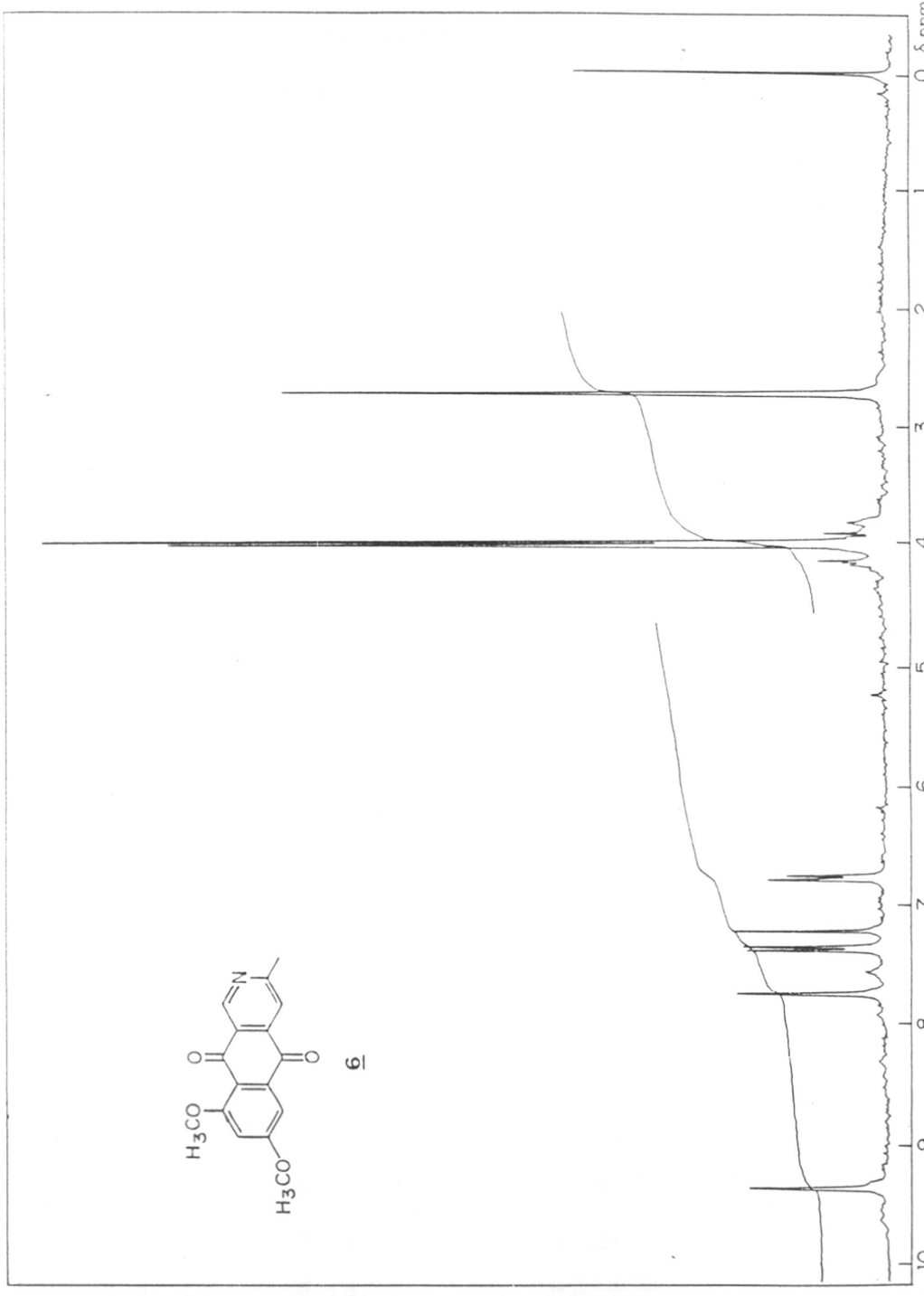


FIG. XI : ^{1}H-NMR SPECTRUM OF THE COMPOUND (6) IN $CDCl_3$

In conclusion simple, efficient and regiospecific synthesis of bostrycoidin was achieved from easily available starting materials.

EXPERIMENTAL

10-Hydroxy-7,9-dimethoxy-3-methyl-1H-naphtho[2,3-c]-pyran-1-one (24):

Under inert atmosphere of argon, a solution of 1.6M n-BuLi in hexane (6.25 ml) was injected to a stirred solution of diisopropyl amine (1.4 ml, 10 mmol) in THF (10 ml) at 0°C and the mixture was stirred for 30 min. after which it was cooled to -78°C using dry ice acetone bath. A solution of methyl 2,4-dimethoxy-6-methylbenzoate 22 (1.05 g, 5 mmol) in dry THF (5 ml) was injected dropwise to the stirred LDA solution at -78°C. After being stirred for 15 min. a solution of 4-methoxy-6-methyl-2-pyrone 23 (0.700 g, 5 mmol) in THF was injected dropwise to the resulting orange-red solution and stirred for 30 min. at -78°C. The reaction mixture was allowed to warm to room temperature and when it was stirred for 15 min. The reaction mixture was then poured slowly into ice cold dilute hydrochloric acid and extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and evaporated to dryness. Chromatographic purification [eluent: 15% acetone-pet. ether (60-80°C)] on silica gel afforded naphthopyrone 24 (0.715 g, 52%) as a yellow solid; m.p. 208-209°C (MeOH) [Lit.[10], m.p. 209°C].

IR ($CHCl_3$): ν max 1680, 1625 and 1580 cm^{-1}.

^{1}H-NMR : δ 2.27 (s, 3H), 3.94 (s, 3H), 4.02 (s, 3H), 6.20 (br s, 1H), 6.45 (d, J = 2 Hz, 1H), 6.61 (d, J = 2 Hz, 1H),

6.91 (s, 1H) and 12.9 (s, 1H).

MS (m/e): 286 (M^+).

7,9,10-Trimethoxy-3-methyl-1H-naphtho[2,3-c]pyran-1-one (25):

A mixture of naphthopyrone **24** (0.550 g, 2 mmol), dimethyl sulphate (0.379 g, 3 mmol) and anhydrous potassium carbonate (0.415 g, 3 mmol) in dry acetone (30 ml) was refluxed for 15 h. The acetone was distilled off from the reaction mixture, water (50 ml) was added to the residue and kept standing overnight to decompose excess dimethyl sulphate. The suspended colourless solid was collected by filtration, washed with water and air dried to give 25 (0.570 g, 98%); m.p. 182-183°C (MeOH), [Lit.[10], 181-184°C].

IR ($CHCl_3$): $\tilde{\nu}$ max 1725, 1675 and 1620 cm^{-1}.

^{1}H-NMR : δ 2.22 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.12 (br s, 1H), 6.46 (d, J = 2 Hz, 1H), 6.03 (d, J = 2 Hz, 1H) and 7.22 (s, 1H).

MS (m/e): 300 (M^+).

7,9,10-Trimethoxy-3-methylbenz[g]isoquinolone (26):

A mixture of compound **25** (0.500 g, 1.7 mmol) and liquor ammonia (30 ml, sp. gr. 0.91, about 25% NH_3) stirred vigorously at room temperature for 15 h. The reaction mixture was then made acidic with dilute hydrochloric acid to give brown yellow solid. It was filtered at suction, washed thoroughly with water and dried to give **26** quantitatively

(0.490 g); m.p. 278°C (dec.) (from $CHCl_3$).

IR ($CHCl_3$): $\tilde{\nu}$ max 1660, 1630, 1610 and 1570 cm^{-1}.

UV (MeOH): λ max (ϵ) 386 (6727), 360 (7580), 300 (75074), 288 (43355), 278 (30348) and 255 (44102) nm.

^{1}H-NMR : δ 2.22 (s, 3H), 3.91 (s, 3H), 3.97 (s, 6H), 6.13 (s, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 7.37 (s, 1H) and 9.00 (br.s, 1H).

MS (m/e): 299 (M^+).

Analysis cal. for $C_{17}H_{17}O_4$: C, 68.23; H, 5.68;

Found : C, 68.19; H, 5.67%.

1-Chloro-6,8,9-trimethoxy-3-methyl-2-azaanthracene (27):

A mixture of compound 26 (0.300 g, 1 mmol) and phosphorous oxychloride (2 ml) was stirred for 1h at 60°C in an oil bath. The reaction mixture was cooled to room temperature and stirred for 10 h. It was then poured on the crushed ice (25 g) and made basic with 10% aqueous sodium hydroxide. It was extracted with dichloromethane (3 x 20 ml), the organic extracts were combined, washed with water, dried over sodium sulphate and concentrated. The crude product was purified by passing through a short column of silica gel [eluent:5% ethyl acetate-pet.ether (b.p. 60-80°C)] to yield compound 27 as a yellow solid, (0.280 g, 88%); m.p. 128°C (n-hexane).

IR (Nujol): $\tilde{\nu}$ max 1668, 1614 and 1562 cm^{-1}.

UV (MeOH): λ max (ϵ) 410 (4475), 370 (3636), 345 (2517), 274 (64891) and 230 (30096) nm.

^{1}H-NMR : δ 2.56 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 4.00 (s, 3H), 6.40 (d, J = 2.5 Hz, 1H), 6.66 (d, J = 2.5 Hz, 1H),

7.25 (s, 1H) and 7.72 (s, 1H).

MS (m/e): 317 (M^+).

Analysis cal. for $C_{17}H_{16}ClNO_3$: C, 64.35; H, 5.04;

Found : C, 64.40; H, 5.00%.

6,8,9-Trimethoxy-3-methyl-2-azaanthracene (28):

Under an inert atmosphere of argon chloroazaanthracene 27 (0.250 g, 0.79 mmol) in dry benzene (10 ml) was refluxed with tributyltin hydride (0.918 g, 3.15 mmol) and AIBN (0.025 g, 1.57 mmol) for 12 h in an oil bath. Benzene was distilled out from reaction mixture and the residue was chromatographed on silica gel to eliminate tin impurities providing pure 28 (0.213 g, 95%) as a bright yellow solid; [eluent: 5% ethyl acetate-pet. ether]; m.p. 115°C.

IR (Nujol): ν max 1620 and 1566 cm^{-1}.

UV (MeOH): λ max (ε) 410 (4125), 365 (3438), 345 (2380), 270 (66914) and 230 (29093) nm.

^{1}H-NMR : δ 2.62 (s, 3H), 3.91 (s, 3H), 4.00 (s, 3H), 4.04 (s, 3H), 6.37 (d, J = 2.5 Hz, 1H), 6.68 (d, J = 2.5 Hz, 1H), 7.31 (s, 1H), 7.68 (s, 1H) and 9.59 (s, 1H).

MS (m/e): 283 (M^+).

Analysis cal. for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.07;

Found : C, 72.19; H, 5.96%.

7,9-Dimethoxy-3-methylbenz[g]isoquinolin-5,10-dione (6):

A solution of 2-azaanthracene 28 (0.141 g, 0.5 mmol) in glacial acetic acid (4 ml) was treated with potassium di-

chromate (0.735 g, 2.5 mmol) with stirring at room temperature for 6 h. Water (50 ml) and chloroform (20 ml) were added to the reaction mixture. The chloroform layer was separated and the aqueous layer was extracted with chloroform (2 x 20 ml). The chloroform extracts were combined, washed successively with water (50 ml), 5% aqueous sodium bicarbonate and saturated brine solution, dried over sodium sulphate and concentrated to give residue (0.140 g). It was chromatographed [silica gel, eluent: chloroform] to afford 2-azaanthraquinone 6 (0.130 g, 92%) as a yellow solid. It was recrystallized from MeOH as yellow micro needles; m.p. 214°C (Lit.[6], m.p. 214-215°C).

IR ($CHCl_3$): $\bar{\nu}$ max 1677, 1658 and 1596 cm^{-1}.

UV (EtOH): λ max (ϵ) 400 (4580), 321 (6098), 282 (12620) and 238 (28590) nm.

^{1}H-NMR : δ 2.74 (s, 3H), 3.99 (s, 3H), 4.02 (s, 3H), 6.84 (d, J = 2.5 Hz, 1H), 7.45 (d, J = 2.5 Hz, 1H), 7.82 (s, 1H) and 9.42 (s, 1H).

MS (m/e): 283 (M^+).

Analysis cal. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.59;

Found : C, 67.88; H, 4.60%.

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CHAPTER-V

SYNTHESIS OF AUSTROCORTICINIC ACID

INTRODUCTION:

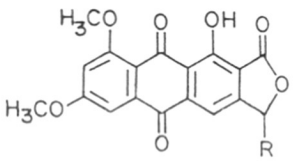
Anthraquinone form a large and important group of naturally occurring colouring matters distinguished by their wide distribution and structural diversity[1]. Majority of anthraquinone pigments isolated from plant and particularly from fungal species have their origins from acetate (as a acetyl CoA) as the primer in the polyketide pathway of their biogenesis[2].

The anthraquinones austrocorticin (1), noraustrocorticin (1a), austrocorticinic acid (2), 4-hydroxyaustrocorticinic acid (2a), austrocorticone (3a) and 4-hydroxyaustrocorticone (3b) (FIGURE-I) have been isolated by Gill and Gimenez[3] from the orange fruit bodies of an Australian toadstool belonging to the genus Dermocybe. Five of the six pigments bear a unique C_2 side chain at C-3 in the anthraquinone nucleus, the biogenetic origin of which has been studied[3] by feeding sodium [3-^{13}C] propionate to young toadstool. High specific incorporation of isotope into the C-3' methyl group of pigments 1, 2, 2a, 3a and 3b indicates that a propionates 'starter' effect is operating. The sixth pigment 1a utilizes acetate (as acetyl CoA) as the primer in its biosynthesis[3].

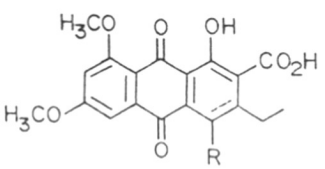
The pigments 1 and 2 are the first examples of a whole family of ethyl homologues of anthraquinones of the endocrocin (3) and emodin (FIGURE-I) types.[3] Although several syntheses of endocrocin (3) are known the syntheses of austrocorticinic acid (2) and austrocorticin (1) have not been reported. In the present work the synthesis of austrocorti-

cinic acid (2) and attempted synthesis of austrocorticin (1) are described.

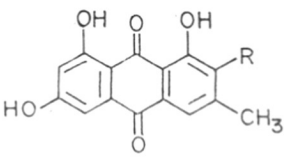
FIGURE-I



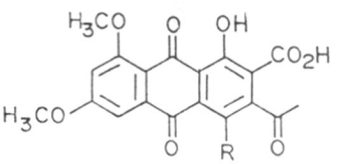
1 : R = CH_3
1a : R = H



2 : R = H
2a : R = −OH



3 : R = $-CO_2H$
Emodin R = H



3a : R = H
3b : R = −OH

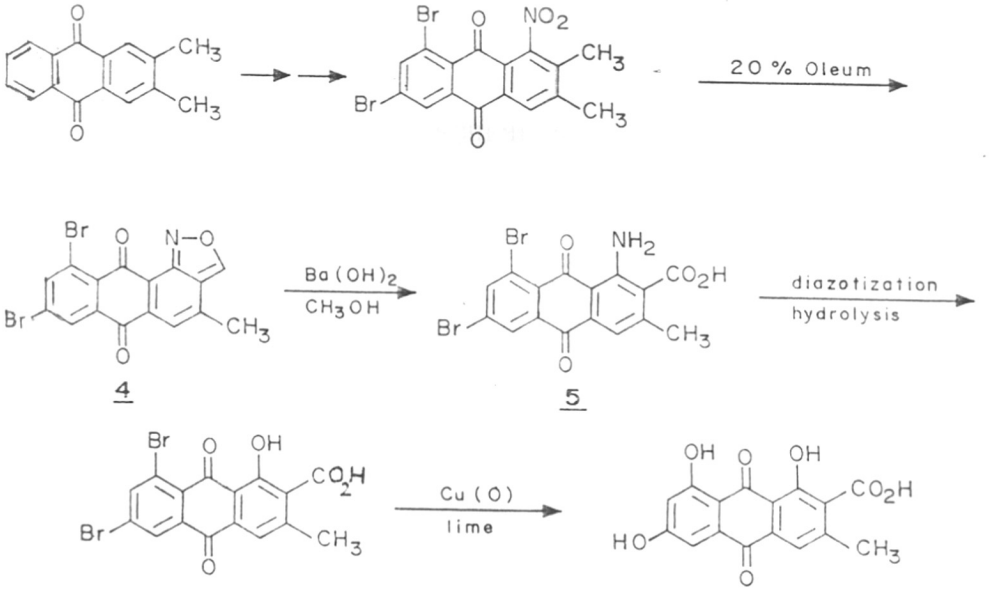
The first synthesis of endocrocin (3) was reported in 1962 by Venkataraman et al.[4] (SCHEME-5.1) In this approach isoxazole 4, a key intermediate was synthesised by selective oxidation of methyl group ortho to nitro group in 4a and nitro group was reduced to amino group through isoxazole 4 as a key intermediate to give acid 5. Replacement of amino function by hydroxy group and bromo substituents by hydroxyl yielded endocrocin (3).

Alternatively, endocrocin was also synthesised from hydroxy trinitroanthraquinone 6 (SCHEME-5.2). Reduction, diazotization, and hydrolysis OF 6 gave tetrahydroxyanthra-

quinone 7. Dehydroxylation with alkaline dithionite and aeration furnished trihydroxyanthraquinone 8. Acetylation, side chain bromination of 8, followed by displacement of benzylic bromide by -OAc yielded tetraacetate 9. Silver

SCHEME-5.1

VENKATARAMAN et al.[4]



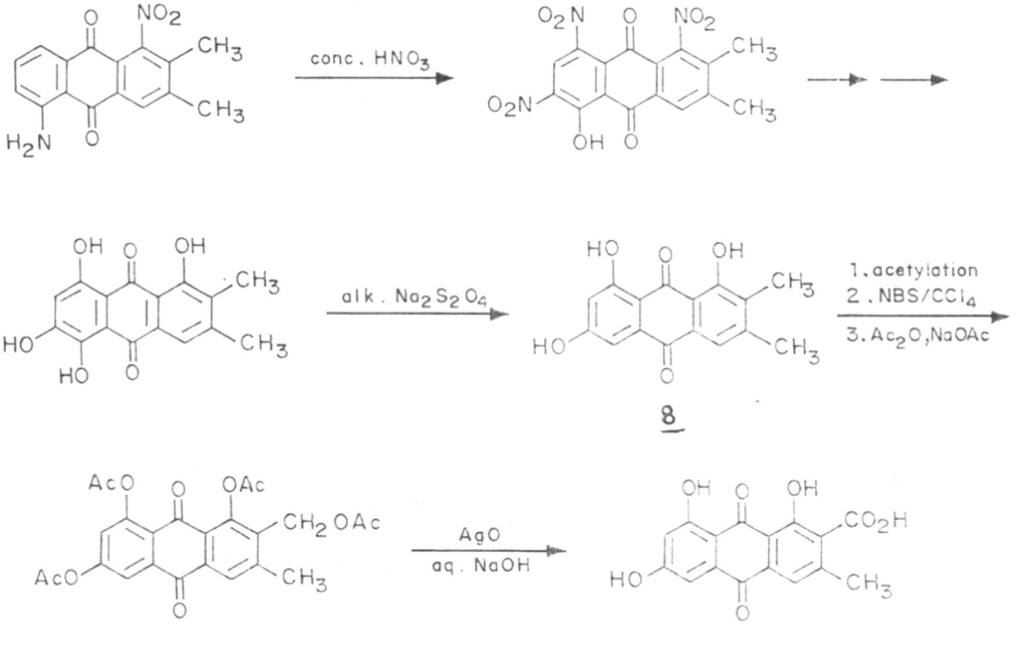
oxide oxidation and hydrolysis[4] of 9 afforded endocrocin (3).

Total synthesis of endocrocin (3)was reported by Frank et al.[5] based on Friedel-Crafts condensation of 3,5-dimethoxyphthalic anhydride (10) and 2,3-dimethylphenol (11) (SCHEME-5.3). Cycliacylation of keto-acid 12 gave trihydroxyanthraquinone 8. The latter was converted to

endocrocin (3) by a known sequence of reactions reported by Venkataraman et al.[4] (SCHEME 5.2).

An efficient synthesis of endocrocin (3) was reported by steglich and Reiningen[6] (SCHEME-5.4), wherein the dicarboxylic acid **14** was synthesised by condensation of diketone 13 with dimethylacetone dicarboxylate. Cycliacylation of the diacid 14 with PPA gave anthrone 15. Oxidation and demethylation of 15 afforded endocrocin (3).

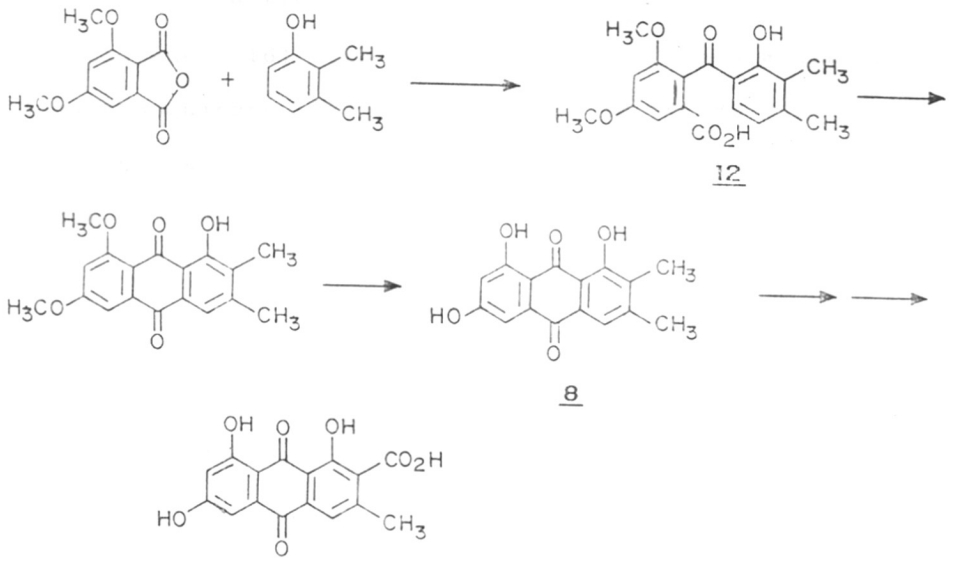
SCHEME-5.2



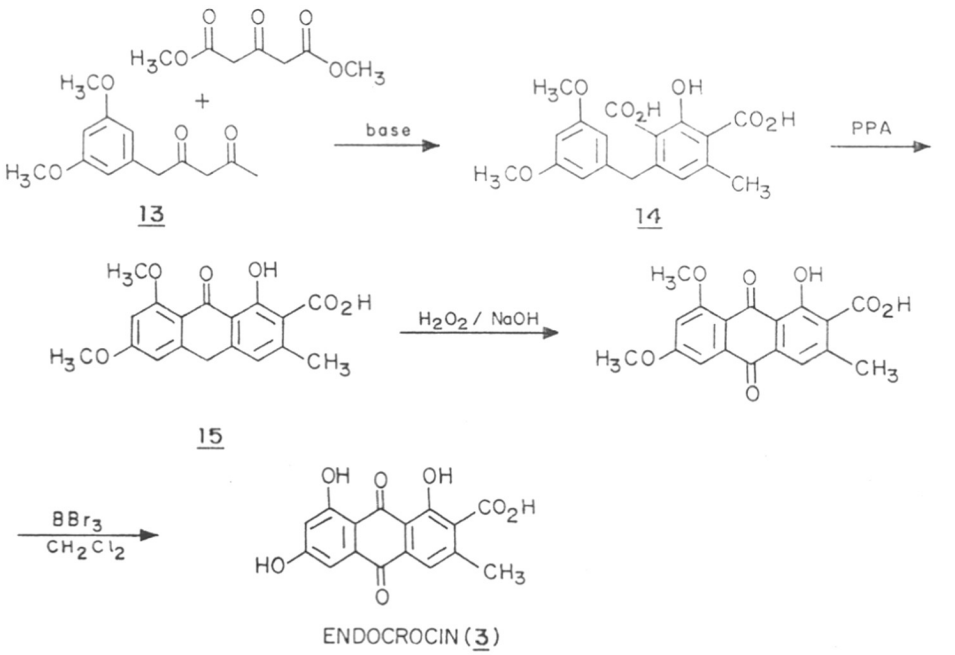
8

ENDOCROCIN (3)

SCHEME-5.3



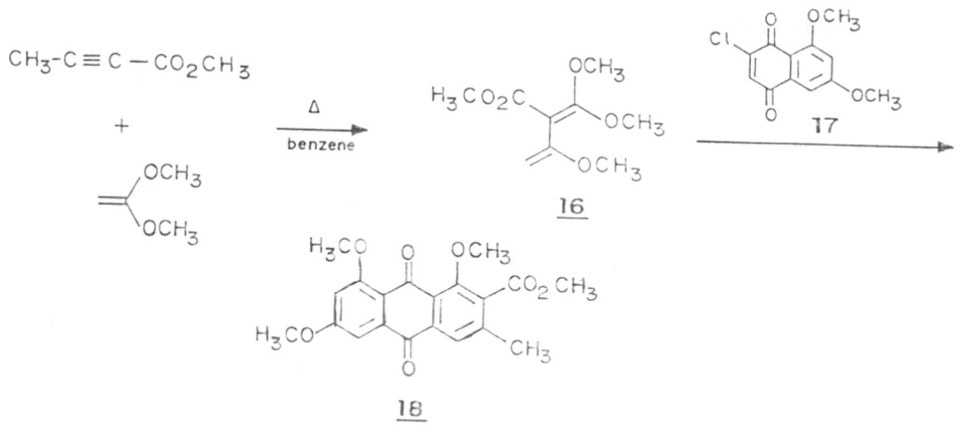
SCHEME-5.4



ENDOCROCIN (3)

Methyl ester of endocrocin trimethyl ether (18) was synthesised in one step by Bonville and Brassard[7] based on Diels-Alder reaction. Diels-Alder cycloaddition of dimethoxybutadiene (16) with the known[8] 2-chloro-6,8-dimethoxy-1,4-naphthoquinone (17) gave directly 18 in 48% yield. The diene 16 was prepared by heating methyl propiolate with 1,1-dimethoxyethene (SCHEME-5.5).

SCHEME-5.5



PRESENT WORK

Austrocorticin (1) and austrocorticinic acid (2) are the first endocrocin type naturally occurring anthraquinones bearing a C_2 side chain at C-3 in the anthraquinone nucleus. Retrosynthetic analysis, as shown in SCHEME-5.6 clearly indicates that 1 and 2 can be synthesised from the methyl orsellinate dimethyl ether (19) and 6-ethyl-4-methoxy-2-pyrone (22). The latter could be obtained by the methylation of the pyrone 21, which in turn is available from dehydroacetic acid.

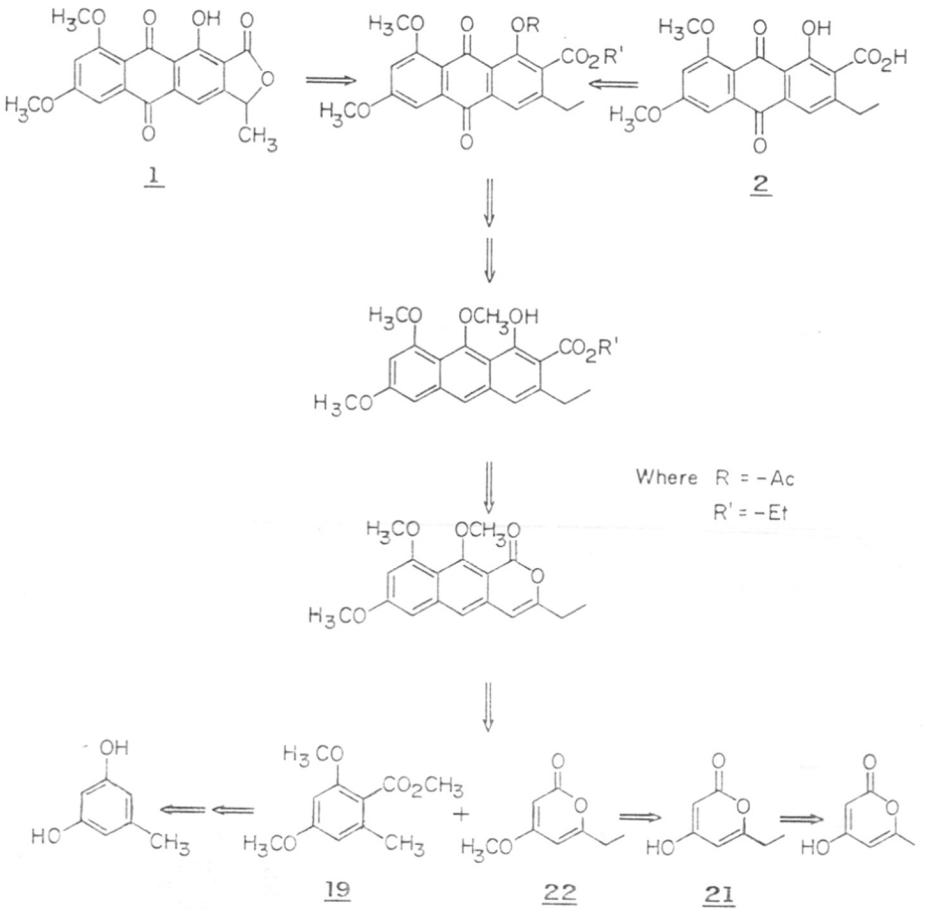
Thus, C-methylation[9] of the dianion ($NaNH_2$ in liquid NH_3) of 4-hydroxy-6-methyl-2-pyrone (20) (triacetic lactone) with methyl iodide yielded compound 21, which was O-methylated[10] by refluxing an acetone solution of 21 and dimethyl sulphate in presence of potassium carbonate to give the methoxypyrone (22). The assigned structure of 22 was consistent with its spectroscopic data (FIG.II).

The methyl 2,4-dimethoxy-6-methylbenzoate (19), whose synthesis has already been described in CHAPTER-II of this thesis was lithiated[11] at -78°C with LDA and treated with 6-ethyl-4-methoxy-2-pyrone (22) to give naphthopyrone 23. It showed fluorescence when exposed to UV light. The ^{1}H-NMR spectrum (FIG.III) revealed three aromatic protons appearing as a pair of meta-coupled doublets (δ 6.55 and 6.63; J = 2 Hz) and a singlet (δ 6.68). The remainder of ^{1}H-NMR spectrum consisted of a triplet at δ 1.24 and quartet at

δ 2.51. It further identified a chelated hydroxyl at

SCHEME-5.6

RETROSYNTHETIC ANALYSIS



δ 13.22 and olefinic proton of pyrone ring at δ 6.13. Its IR spectrum showed absorption bands at 1680, 1625 and 1580 cm^{-1}.

Methylation of hydroxynaphthopyrone 23 with dimethyl sulphate-potassium carbonate afforded trimethoxynaphthopy-

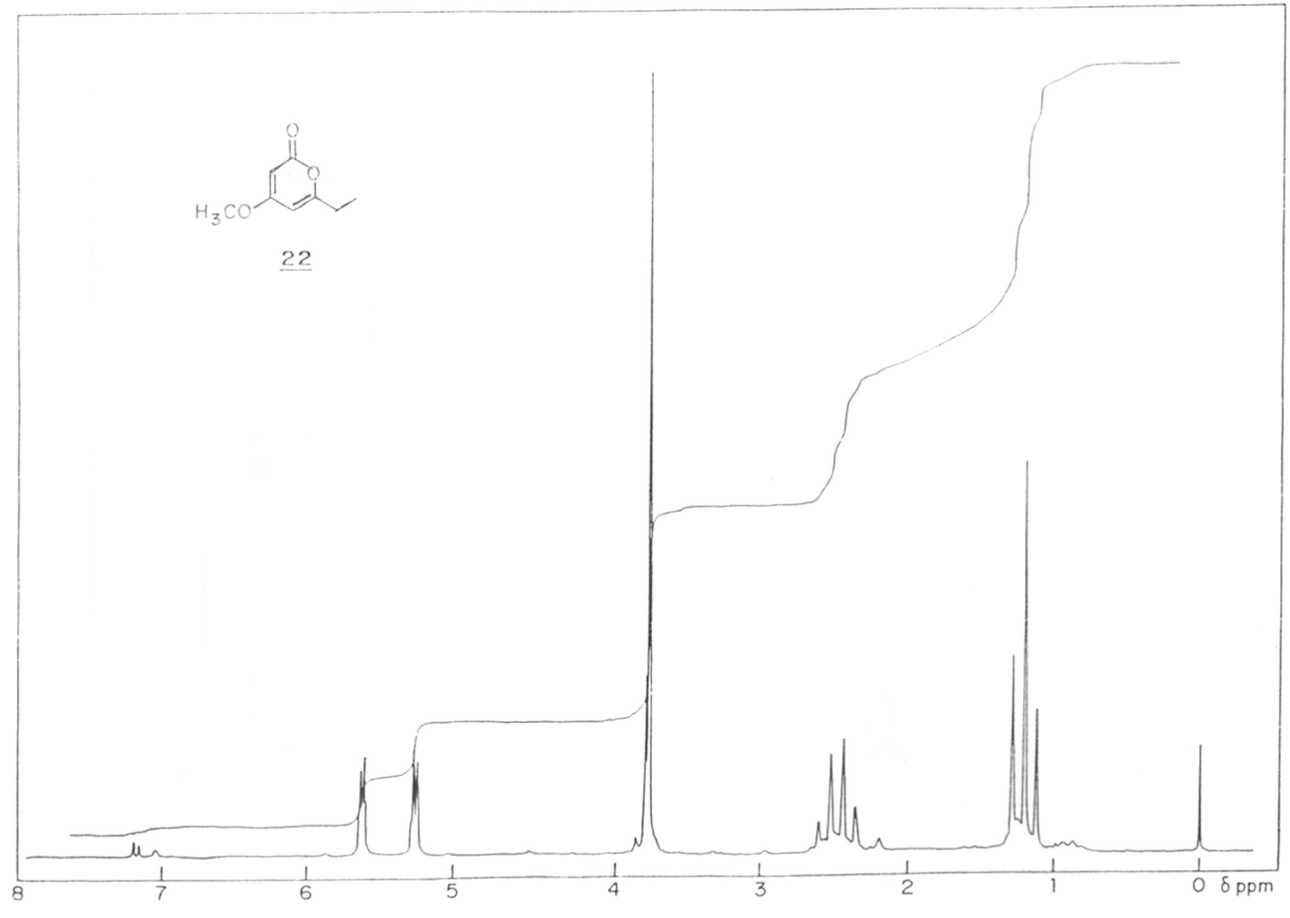


FIG. II : ^{1}H-NMR SPECTRUM OF THE COMPOUND (22) IN $CDCl_3$

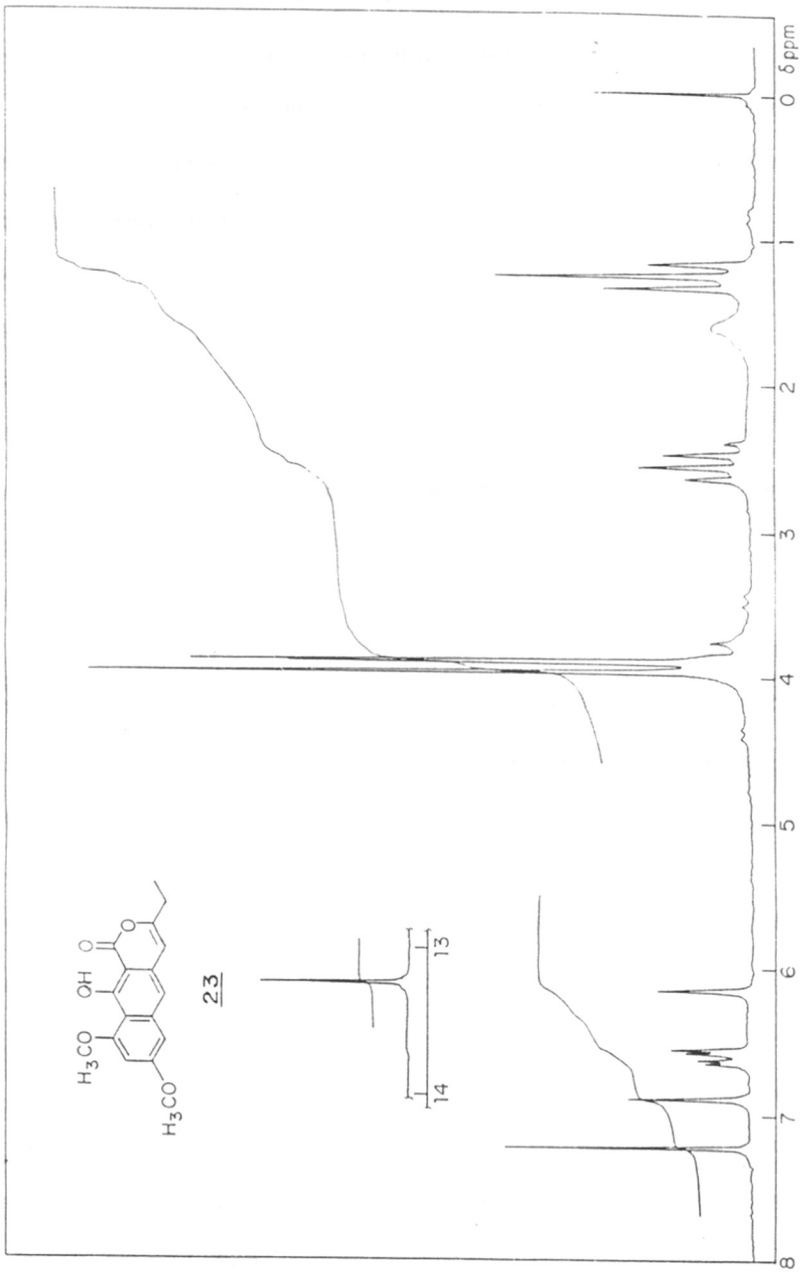
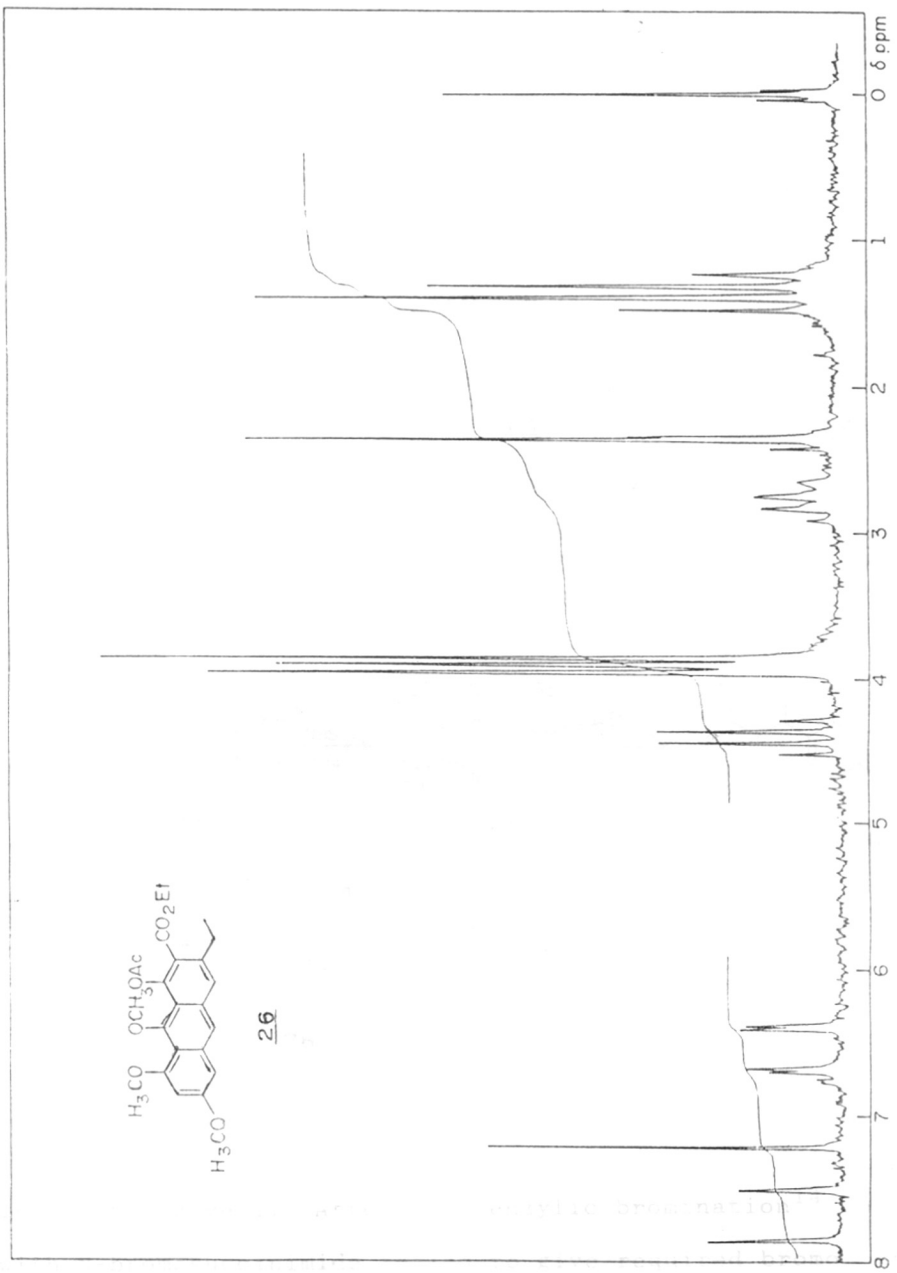


FIG III : ^{1}H-NMR SPECTRUM OF THE COMPOUND (23) IN $CDCl_3$

rone 24. Its structure was confirmed by spectral data. Reformatsky reaction[11] on naphthopyrone 24 with zinc and ethyl bromoacetate resulted in anthracene derivative 25 although in poor yield. Its structure was confirmed by spectral and physical properties. The ^{1}H-NMR spectrum showed four aromatic protons appearing as a pair of meta coupled doublets (δ 6.41 and δ 6.65; J = 2 Hz) and two singlets (δ 7.13 and 7.78). It also revealed chelated hydroxyl group at δ 10.93. The IR spectrum showed absorption at 1725 and 1620 cm^{-1}. The structure of 25 was further confirmed by mass spectrum which showed molecular ion peak at m/e 384.

The hydroxyl group of compound 25 was protected as acetate by treating it with acetic anhydride and pyridine to give 26 (FIG.IV). Oxidation[13] of 26 with potassium dichromate in acetic acid yielded the anthraquinone 27. Spectral data of compound 27 was in good agreement with the assigned structure. Its IR spectrum showed absorption bands due to quinonoid carbonyl at 1670 and 1660 cm^{-1} with a third carbonyl absorption at 1720 cm^{-1}. The ^{1}H-NMR spectrum consisted of a pair of meta coupled doublets (δ 6.40 and 7.6, J = 2.2 Hz) and two singlets at δ 7.61 and 2.32 for Ar$\underline{H}$ and -COC$\underline{H}_3$, respectively. Mass spectrum showed molecular ion peak at m/e 426.

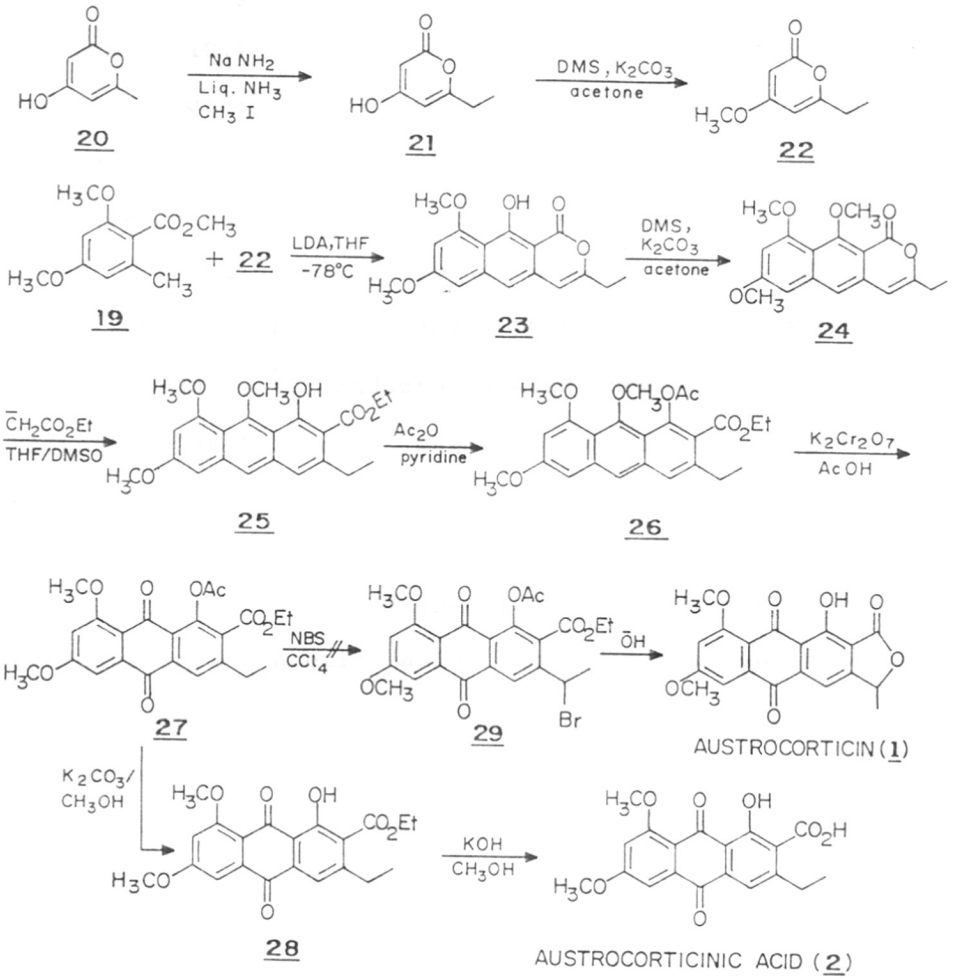
Synthesis of austrocorticin (1) requires introduction of bromine atom in compound 27 at the benzylic position of the C-3 ethyl group which could be replaced by hydroxyl



26

FIG IV : ^1H-NMR SPECTRUM OF THE COMPOUND (26) IN $CDCl_3$

SCHEME-5.7



group to give 1. Attempted benzylic bromination[14] of 27 with N-bromosuccinimide failed to give required bromo ester 29 and resulted into a mixture of products.

The partial hydrolysis of ethyl O-acetyl austrocorticinate (27) was effected by methanolic potassium carbonate to afford ethyl austrocorticinate (28), which showed a peak due to chelated hydroxyl proton at δ 13.35 in the ^{1}H-NMR spectrum (FIG.V). The hydrolysis of 28 with methanolic potassium hydroxide afforded austrocorticinic acid (2). The spectral characteristics of 2 were in full agreement with those reported[3] for it in the literature. The pigment 2 showed absorption bands due to carbonyl at 1665 (free) and 1625 (chelated with -OH) and a third acid carbonyl absorption at 1720 cm^{-1}. Endocrocin also shows an acid carbonyl absorption at 1720 cm^{-1}, which is rather at a higher frequency than the one expected for aryl carboxylic acids such as 1,6,8-trihydroxy-9,10-anthraquinone-2-carboxylic acid (3). Alternative structure i.e. 1,6,8-trihydroxy-9,10-anthraquinonyl-2-acetic acid for endocrocin was ruled out by it synthesis and direct comparison[15]. The ^{1}H-NMR spectrum revealed methoxy proton singlet at δ 3.98 and 4.01 and three aromatic protons appeared as meta-coupled doublets (δ 6.77 and 7.43, J = 2.2 Hz) and a singlet (δ 7.63). It was also confirmed by mass spectrum (M^+; 356).

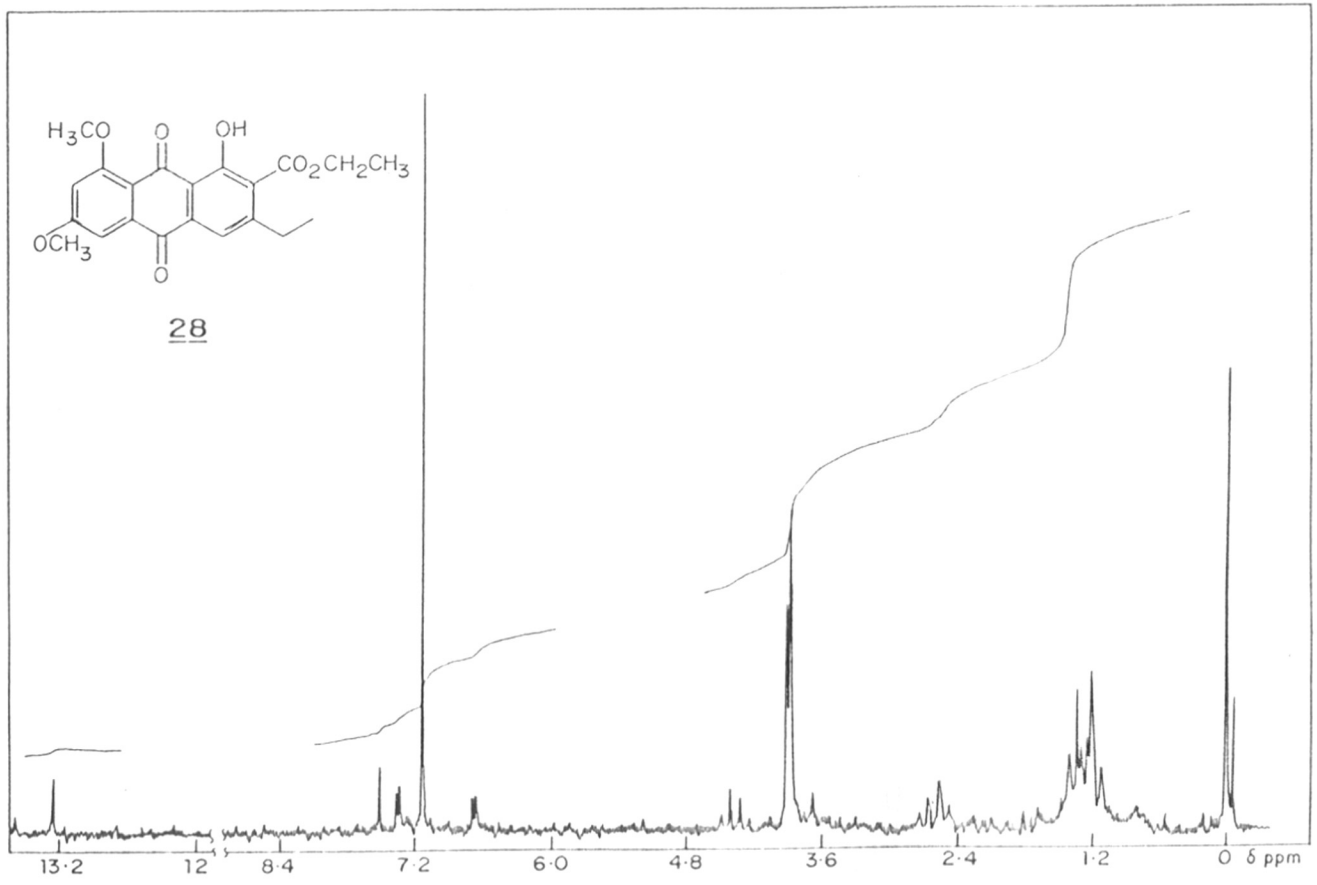


FIG. V : ^{1}H-NMR SPECTRUM OF THE COMPOUND (28) IN $CDCl_3$

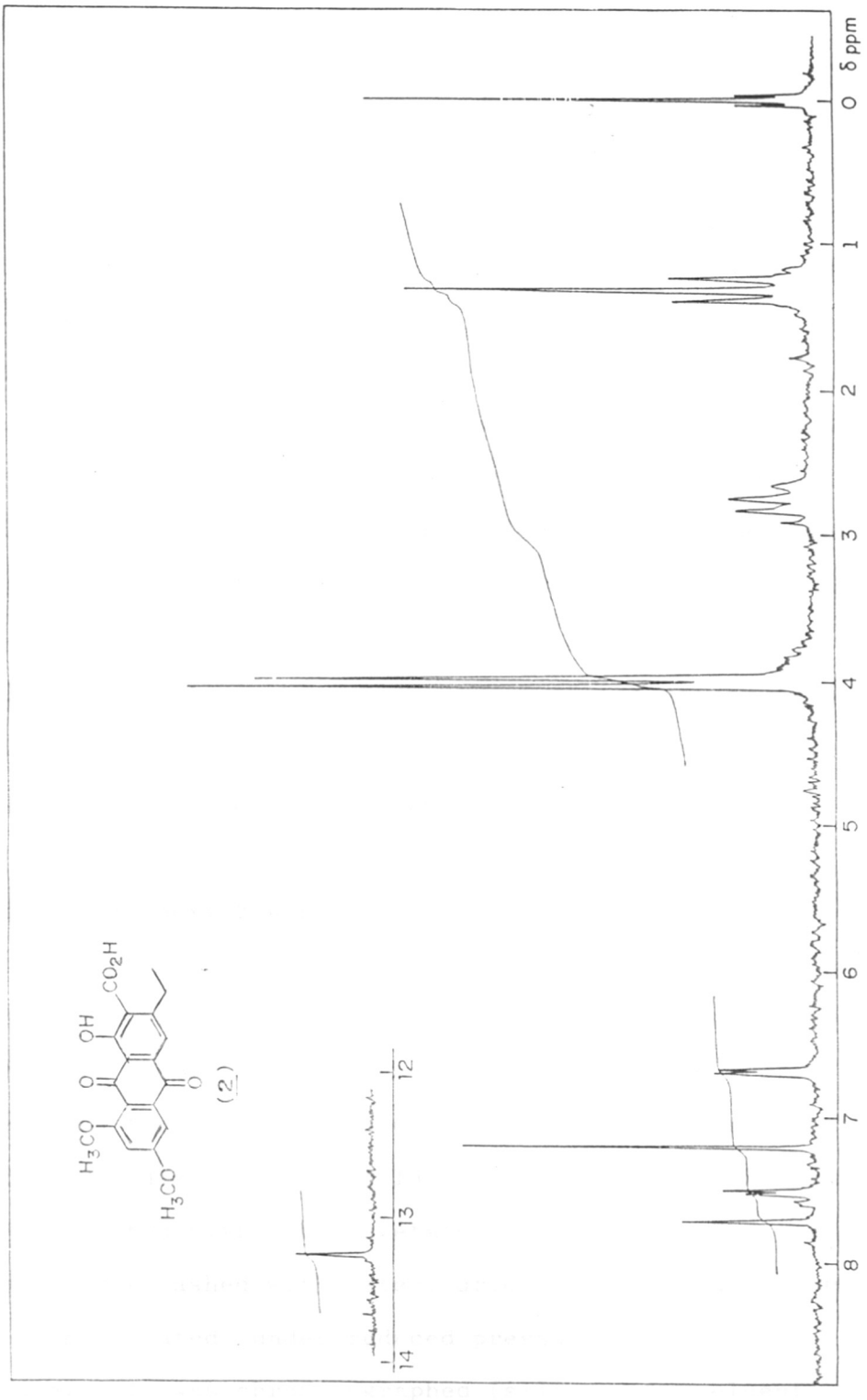


FIG. XI : ^{1}H-NMR SPECTRUM OF THE COMPOUND (2) IN $CDCl_3$

EXPERIMENTAL

6-Ethyl-2H-pyran-2,4-(3H)-dione (21):

To the stirred suspension of sodamide [prepared from 0.728 g of sodium] in liquid ammonia, (250 ml) was added portionwise triacetic lactone 20 (2.0 g, 15.88 mmol). After 30 min. methyl iodide (2.24 g, 15.88 mmol) was added to the resulting green suspension of dianion, ammonia was evaporated and diethyl ether (50 ml) and cold dilute hydrochloric acid were added to the reaction mixture. Insoluble material was removed by filtration, the ether solution dried (Na_2SO_4) and concentrated to give a white solid, which was purified by column chromatography on silica gel by eluting with 15% ethyl acetate-pet. ether to furnish compound 21 as a white crystalline solid (1.60 g, 72%); m.p. 183-184°C.

6-Ethyl-4-methoxy-2-pyrone (22):

A mixture of compound 21 (1.40 g, 10 mmol), dimethyl sulphate (1.63 g, 13 mmol) and anhydrous potassium carbonate (1.80 g, 13 mmol) in dry acetone was heated to reflux on water bath for 12 h. The acetone was removed from reaction mixture by distillation, cold water (50 ml) was introduced and extracted with ethyl acetate (2 x 25 ml). The organic extract was washed with water, dried over sodium sulphate and concentrated under reduced pressure to leave an oily residue. It was chromatographed (silica gel, eluent: 10% ethyl acetate-pet. ether) to yield 1.4 g of compound 22

(91%) as a white crystalline solid; m.p. 52°C.

IR (Nujol): ν max 1736 and 1722 cm^{-1}.

^{1}H-NMR : δ 1.20 (t, 3H), 2.46 (q, 2H), 3.75 (s, 3H), 5.26 (br d, 1H) and 5.62 (br d, 1H).

MS (m/e): 154 (M^+).

Analysis cal. for $C_8H_{10}O_3$: C, 62.33; H, 6.49;

Found : C, 62.20; H, 6.48%.

10-Hydroxy-7,9-dimethoxy-3-ethyl-1H-naphtho[2,3-c]pyran-1-one (23):

To the stirred solution of LDA [prepared from 1.6 M n-BuLi solution in n-hexane (6.25 ml) and diisopropyl amine (1.4 ml) at 0°C under argon atmosphere] in dry THF (20 ml) at -78°C was added methyl orsellinate dimethyl ether 19 (1.05 g, 5 mmol) in THF (5 ml). After 15 min. a solution of compound 22 (0.77 g, 5 mmol) in THF (5 ml) was injected to the resultant orange anionic solution and the reaction mixture was stirred for 30 min. at -78°C. It was allowed to warm to room temperature, stirred for 30 min. and poured into the mixture of water (25 ml) and conc. HCl (5 ml). The resulting solution was extracted with dichloromethane, dried (Na_2SO_4) and evaporated to give crude naphthopyrone, which was purified by column chromatography over silica gel (eluent: 5% acetone-pet. ether) to afford 23 as pale yellow needles (0.810 g 54%); m.p. 208-210°C (MeOH).

IR ($CHCl_3$): ν max 1680, 1625 and 1580 cm^{-1}.

^{1}H-NMR : δ 1.24 (t, 3H), 2.51 (q, 2H), 3.86 (s, 3H), 3.95

(s, 3H), 6.13 (s, 1H), 6.55 (d, J = 2 Hz, 1H), 6.63 (d, J = 2 Hz, 1H), 6.68 (s, 1H) and 13.22 (s, 1H).

MS (m/e): 300 (M^+).

Analysis cal. for $C_{17}H_{16}O_5$: C, 68.00; H, 5.33;

Found : C, 68.15; H, 5.33%.

7,9,10-Trimethoxy-3-ethyl-1H-naphtho[2,3-c]pyran-1-one (24):

A mixture of naphthopyrone **23** (0.450g, 1.5 mmol), dimethyl sulphate (0.283 g, 2.25 mmol) and anhydrous potassium carbonate in dry acetone (50 ml) was heated to reflux under anhydrous conditions for 11 h. The acetone was distilled off from the reaction mixture and water (50 ml) was introduced, whereby solid separated. It was filtered, washed with water and dried to obtain 0.465 g of compound **23** as white solid (98%). Recrystallization from methanol gave white needles, m.p. 158°C.

IR ($CHCl_3$): ν max 1730, 1680, 1628 and 1585 cm^{-1}.

^{1}H-NMR : δ 1.26 (t, 3H), 2.51 (q, 2H), 3.91 (s, 3H), 3.95 (s, 6H), 6.11 (s, 1H), 6.62 (d, J = 2 Hz, 1H), 6.44 (d, J = 2 Hz, 1H) and 7.22 (s, 1H).

MS (m/e): 314 (M^+).

Analysis cal. for $C_{18}H_{18}O_5$: C, 68.79; H, 5.73;

Found : C, 68.89; H, 5.72%.

Ethyl 1-hydroxy-6,8,9-trimethoxy-3-ethylanthracene-2-carboxylate (25):

Method A:

Into a vigorously stirred solution of compound 24 (0.100 g, 0.318 mmol) and freshly activated zinc dust (0.21 g, 32 mmol) in dry benzene (10 ml) heated at reflux, was dripped over a period of 45 min. a solution of ethyl bromoacetate (0.43 g, 2.6 mmol) in dry benzene (10 ml). After 2 h reaction mixture was cooled to room temperature, diethyl ether (30 ml) added and the mixture was washed successively with 1M H_2SO_4 (20 ml), 0.5 M H_2SO_4 solution (20 ml) (to dissolve the excess Zn), 5% aqueous sodium bicarbonate (15 ml), and saturated brine solution. The organic layer was then dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: 5% ethyl acetate-pet. ether) to give **25** as a yellow crystalline solid (0.027 g, 22%) ; m.p. 156°C (from hexane).

IR (Nujol): $\tilde{\nu}$ max 1725 and 1620 cm^{-1}.

^{1}H-NMR : δ 1.25 (t, 3H), 1.41 (t, 3H), 2.78 (q, 2H), 3.84 (s, 3H), 3.90 (s, 3H), 4.41 (q, 2H), 6.41 (d, J = 2 Hz, 1H), 6.65 (d, J = 2 Hz, 1H), 7.13 (s, 1H), 7.78 (s, 1H) and 10.93 (s, 1H).

MS (m/e): 384 (M^+).

Analysis cal. for $C_{22}H_{24}O_6$: C, 68.75; H, 6.77;

Found : C, 68.73; H, 6.78%.

Method B:

To the stirred solution of diisopropyl amine (0.320 g, 3.18 mmol) under nitrogen atmosphere in dry THF (5 ml) was added 1.6 M n-BuLi solution in n-hexane (2 ml) at $0^{o}C$ and stirred for 30 min. at $0^{o}C$ and 5 min at room temperature. It was then cooled to $-78^{o}C$ with dry ice-acetone bath. Dry ethyl acetate (0.280 g, 3.1 mmol) was injected dropwise and the solution was stirred for 30 min. at $-78^{o}C$. The anion of ethyl acetate was rapidly transferred to a stirred solution of naphthopyrone **24** (0.400 g, 1.27 mmol) in dry DMSO (4 ml) and dry THF (6 ml) at $0^{o}C$. After 30 min. the yellow mixture was quenched with acetic acid (6 ml) and stirred at room temperature for 48 h. Usual work up gave pure product 25 (0.450 g, 92%); m.p. $156^{o}C$.

Ethyl 1-acetoxy-6,8,9-trimethoxy-3-ethylanthracene-2-carboxy -late (26):

A mixture of anthracene **25** (0.4 g, 1.04 mmol) acetic anhydride (0.159 g, 1.56 mmol) and pyridine (2 ml) was stirred at room temperature for 24 h. Water (25 ml) was added and stirred for 30 min at room temperature. It was then extracted with dichloromethane (2 x 20 ml), the combined organic extracts were washed successively with dilute HCl, 5% aqueous bicarbonate and saturated brine and dried (Na_2SO_4). The dichloromethane was removed under reduced pressure to give acetate derivative **26** as yellow crystalline solid; (0.435 g, 98%); m.p. $180^{o}C$.

IR ($CHCl_3$): $\tilde{\nu}$ max 1725, 1620 and 1600 cm^{-1}.

^{1}H-NMR : δ 1.33 (t, 3H), 1.40 (t, 3H), 2.33 (s, 3H), 2.77 (q, 2H), 3.84 (s, 3H), 3.93 (s, 3H), 4.40 (q, 2H), 6.40 (d, J = 2 Hz, 1H), 6.63 (d, J = 2 Hz, 1H), 7.48 (s, 1H) and 7.84 (s, 1H).

MS (m/e): 426 (M^+).

Analysis cal. for $C_{24}H_{26}O_7$: C, 67.60; H, 6.10;

Found : C, 67.63; H, 6.10%.

6,8-Dimethoxy-2-ethoxycarbonyl-1-hydroxy-3-ethylanthracene-9,10-dione (Ethyl austrocorticinate) (28):

To the stirred solution of compound 26 (0.213 g, 0.5 mmol) in glacial acetic acid (5 ml) was added potassium dichromate (0.441 g, 1.5 mmol). After stirring for 8 h at room temperature, the acetic acid from the reaction mixture was evaporated under reduced pressure to leave the residue. It was dissolved in methanol (10 ml) and stirred with potassium carbonate (0.345 g, 2.5 mmol) for 15 h at room temperature. The methanol was evaporated under reduced pressure to give a residue which was dissolved in water and suspended particles were removed by filtration. The filtrate was made acidic with cold dilutehydrochloric acid and extracted with CH_2Cl_2 (2 x 20 ml). The combined extracts were washed with water, 5% aqueous sodium bicarbonate solution, dried (Na_2SO_4) and evaporated to afford ethyl austrocorticinate 28 (0.160 g, 83%); m.p. 208°C.

IR ($CHCl_3$): $\tilde{\nu}$ max 1720, 1670, 1630 and 1595 cm^{-1}.

^{1}H-NMR: δ 1.22 (t, 3H), 1.35 (t, 3H), 2.66 (q, 2H), 3.93 (s,

3H), 3.97 (s, 3H), 4.46 (q, 2H), 6.79 (d, J = 2.2 Hz, 1H), 7.66 (d, J = 2.2 Hz, 1H), 7.61 (s, 1H) and 13.35 (s, 1H).

MS (m/e): 384 (M^+).

Analysis cal. for $C_{21}H_{20}O_7$: C, 65.62; H, 5.21;

Found : C, 65.49; H, 5.20%.

Austrocorticinic acid (2):

The ethyl austrocorticinate **28** (0.100 g, 0.26 mmol) was dissolved in MeOH (10 ml) and refluxed with potassium hydroxide (0.100 g, 0.178 mmol) on water bath for 14 h. The methanol was distilled out under reduced pressure, water (20 ml) was introduced and the solution was filtered to remove insoluble impurities. The filtrate was cooled and acidified with dilute HCl. It was then extracted with chloroform (2 x 20 ml) and the extracts were untied, dried (Na_2SO_4) and evaporated to give pure austrocorticinic acid **2** (0.032 g, 35%) as a yellow crystalline solid; m.p. 279-280°C (lit.[3], m.p. 280°C).

IR ($CHCl_3$): ν max 3440, 1720, 1665, 1625 and 1595 cm^{-1}.

^{1}H-NMR : δ 1.13 (t, J = 7.3 Hz, 3H), 2.75 (q, J = 7.3 Hz, 2H), 3.98 (s, 3H), 4.01 (s, 3H), 6.77 (d, J = 2.2 Hz, 2H), 7.43 (d, J = 2.2 Hz, 2H), 7.63 (s, 1H) and 13.2 (s, 1H).

MS (m/e): 356 (M^+).

Analysis cal. for $C_{19}H_{16}O_7$: C, 64.04; H, 4.49;

Found : C, 64.21; H, 4.50%..pa

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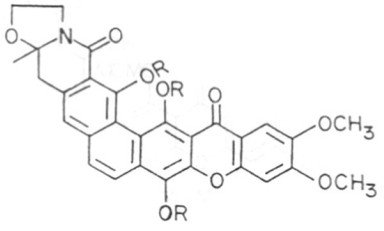
CHAPTER-VI

SYNTHETIC APPROACHES TOWARDS CERVINOMYCIN

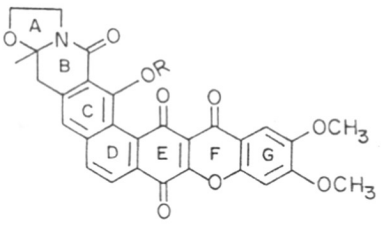
INTRODUCTION:

Cervinomycin is an anti-anearobic and anti-micoplasmal antibiotic produced by Streptomyces cervinus sp. nov.[1]. The antibiotic consists of two components, cervinomycin A_1(1) and A_2(2), which are insoluble in most of the solvents. However, triacetyl cervinomycin A_1(3) has high solubility and shows enhanced anti-anaerobic activity against Clostridium difficile, Reptococcus variabillis and Streptococcus mutans and anti-micoplasmal activity.[2] Cervinomycins and their acetyl derivatives afforded a monocrystal in appropriate solvents. However the X-ray crystallographic analyses were unsuccessful, because of extreme instability of the crystals on exposure to air. Therefore, the structure determination of cervinomycin was carried out by means of NMR spectroscopy of methyl derivatives[1]. Cervinomycin's[3] unique structure consists of a sensitive tetrahydrooxazolo-[2,3-b]benz[g]isoquinoline moiety fused angularly on a novel and highly functionalised xanthone unit.

FIGURE-I



1 ; R = H CERVINOMYCIN A_1
3 ; R = $-COCH_3$
4 ; R = CH_3



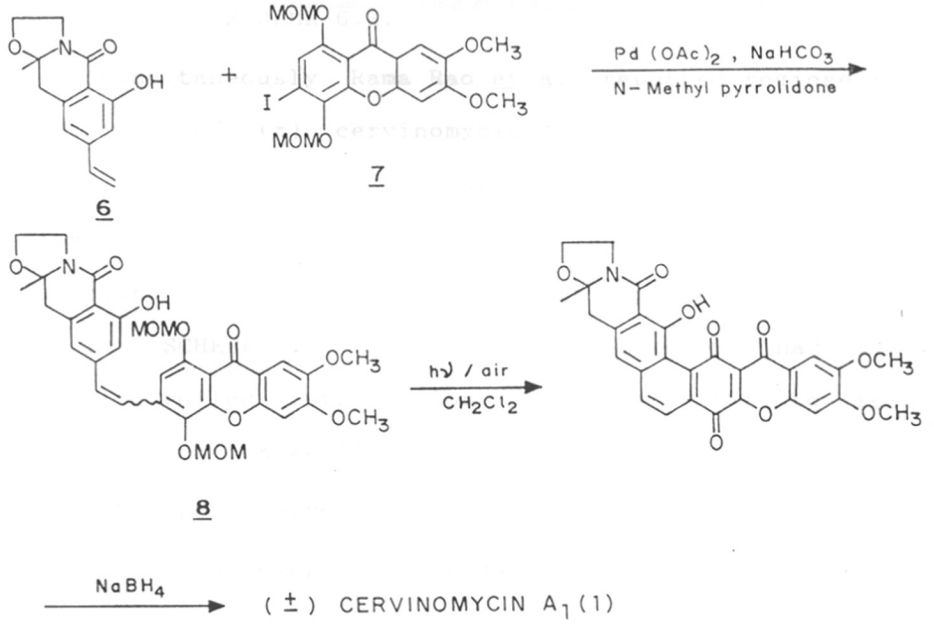
2 ; R = H CERVINOMYCIN A_2
5 ; R = CH_3

Owing to their skeletal novelty and potent activity, several groups[4] have attempted their syntheses. The first total synthesis of (±) cervinomycin A_1(1) and A_2(2) was reported by Kelly *et al*[5]. Since then to date two more total syntheses of cervinomycins have been reported. For the sake of brevity only the important strategies applied in these syntheses will be highlighted here.

The main strategy in the reaction sequence of Kelly's approach[5] (SCHEME-6.1) was the Pd (II) catalyzed bridging off isoquinolone 6 (ABC fragment) and xanthone (EFG fragment) moieties to give stilbene derivative 8. Irradiation of 8 in dichloromethane, while open to the air, not only resulted in cyclization but also led to cleavage of MOM

SCHEME-6.1

T.R. KELLY *et al*.[5]



6 7 8

ether and oxidation to afford (±) cervinomycin A_2 (2) directly in 36% yield. Reduction of (±) 2 with sodium borohydride gave (±) cervinomycin A_1(1).

Recently (1991), Mehta and Shah[6] reported total synthesis of (±) cervinomycin A_2-methyl ether (5), in which the key central ring D was constructed through a photochemical electrocyclization strategy. A model study[4b] was first executed for the construction of ring D. Thus the stilbene derivative 10 was irradiated, which yielded a mixture of two pentacyclic compounds in 10% yield. Using similar conditions the required pentacyclic compound 12 was synthesised by Wittig reaction of ylide derived from 9 and aldehyde 11 followed by photocyclization. The compound 12 was converted to (±) cervinomycin A_2-methyl ether (5) through cervinomycin A_1-trimethyl ether (4) in two steps as depicted in SCHEME-6.2.

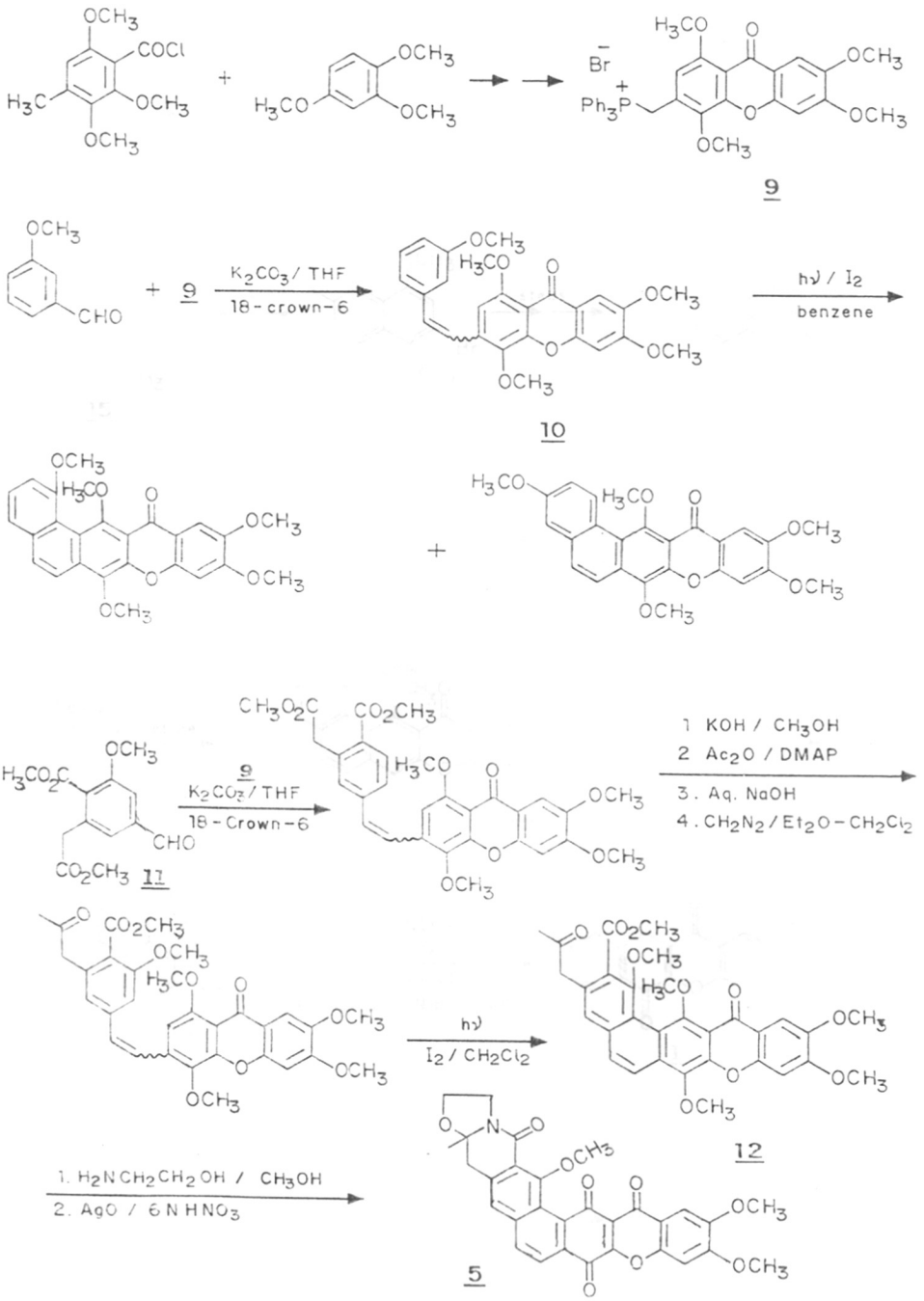
Simultaneously Rama Rao *et al*[7] reported regioselective syntheses of (±) cervinomycin A_1 (1) and A_2 (2). The strategy utilized centres around the key intermediate 15 constituting DE ring of cervinomycin. The acetyl functionality in 15 was used to build up isoquinolone moiety on it (SCHEME-6.3) while the bromine group had allowed regiocontrolled introduction of xanthone unit to furnish (±) cervinomycin A_1 (1) and A_2 (2).

In the synthetic study on cervinomycin, Rama Rao *et al*[4a] first developed a methodology for the construction of

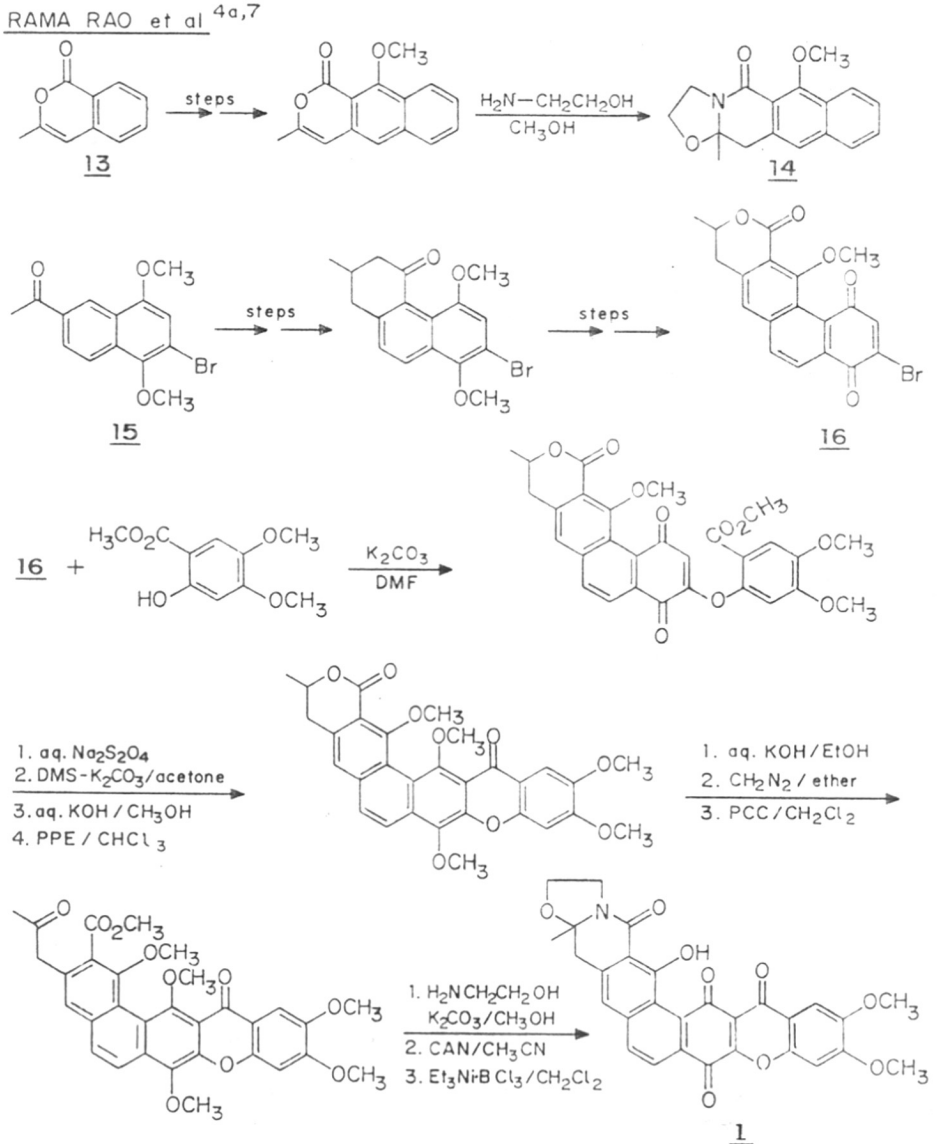
tetrahydrooxazolo[3,2-b]benz[9]isoquinolone 14 system from the known isocoumarin 13 as outlined in SCHEME-6.3.

MEHTA et. al.[4b,6]

SCHEME-6.2



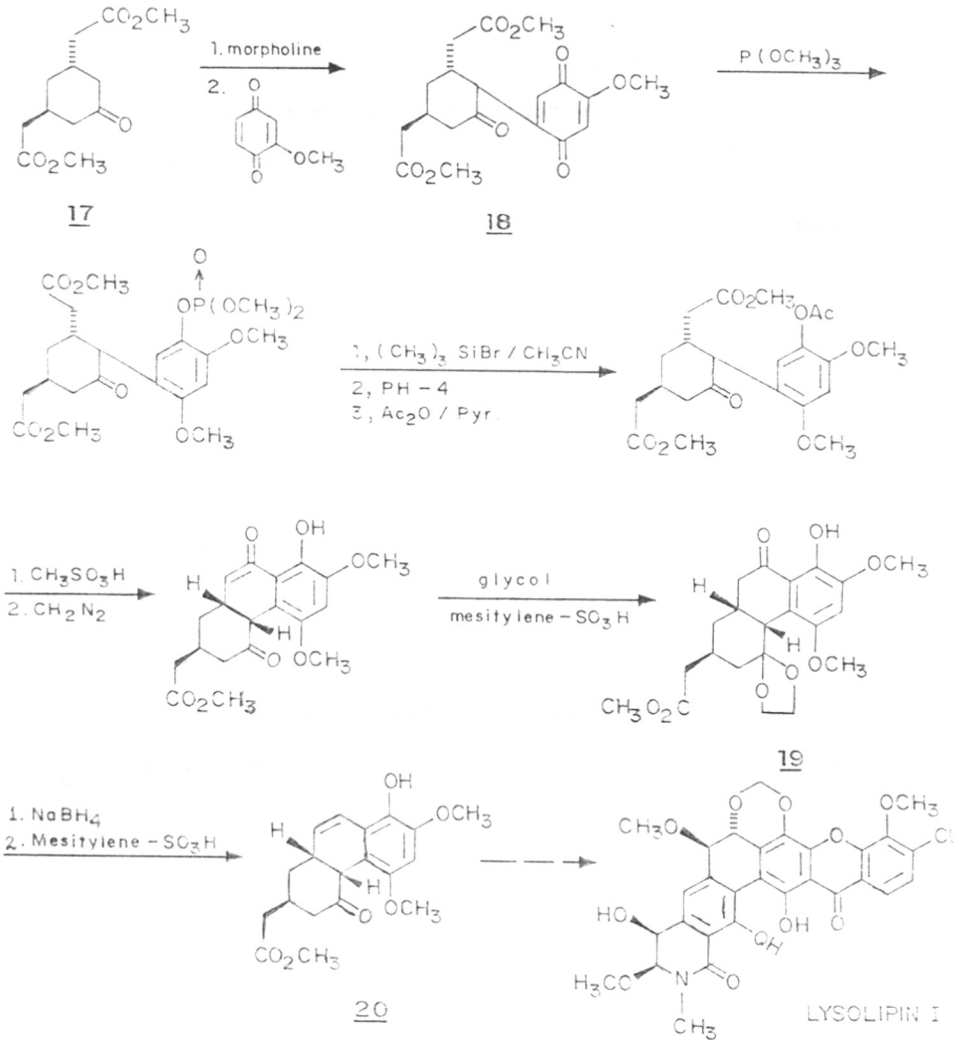
SCHEME-6.3


RAMA RAO et al 4a,7
steps
13
14
15
16
$H_2N-CH_2CH_2OH$
CH_3OH
K_2CO_3
DMF
1. aq. $Na_2S_2O_4$
2. DMS-K_2CO_3/acetone
3. aq. KOH / CH_3OH
4. PPE / $CHCl_3$
1. aq. KOH/EtOH
2. CH_2N_2 / ether
3. PCC/CH_2Cl_2
1. $H_2NCH_2CH_2OH$
K_2CO_3/CH_3OH
2. CAN/CH_3CN
3. Et_3NHBCl_3/CH_2Cl_2
1

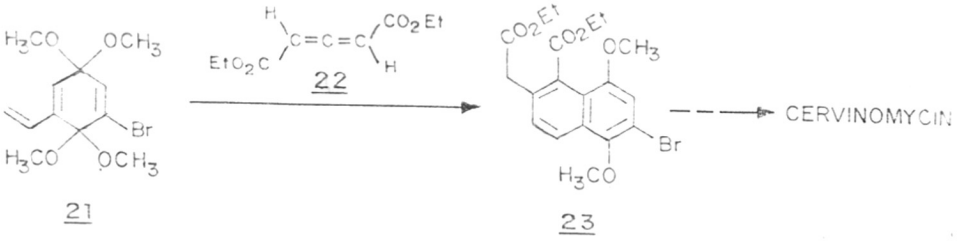
A summary of model studies directed towards the synthesis of lysolipin I[3a], a heptacyclic xanthone antibiotic, which is structurally related to cervinomycin was reported by Duthaler et al[4d]. In their approach cyclohexanone 17 was used as precursor for the phenolic ring F of lysolipin I (SCHEME-6.4). The scope and limitations of the access to 2-aryl-cyclohexanone derivatives by Michael-addition to p-quinones has been evaluated on a broad basis. A regiospecific mono protection of substituted hydroquinone was achieved by reductive phosphorylation of p-quinone 18 with trimethyl phosphite. Synthesis of the key intermediate 20 from compound 18 is illustrated in SCHEME-6.4. The tricyclic intermediate 20 can be elaborated to lysolipin I and can also be considered for the syntheses of cervinomycins.

Parker and Ruder[4c] developed a classical approach for the preparation of phenanthrene building block 23, which might be considered for the synthesis of the structures similar to cervinomycin 1. Naphthalene 23, functionalized on both rings, was considered as desirable intermediate for the regiospecific elaboration to the cervinomycin 1 and was synthesised directly in one step by Diels-Alder condensation of vinylquinone bis-ketal 21 and allene dicarboxylate 22 in 37% yield (scheme-6.5). The elaboration of intermediate 23 and the exploration of the other strategies for the preparation of nonlinear polyketides such as cervinomycin are their subjects of further study[4c].

SCHEME-6.4



SCHEME-6.5



PRESENT WORK:

In 1986, Omura et al[1b] elucidated the structures of novel xanthone antibiotics cervinomycin A_1 (1) and A_2 (2), isolated earlier[1a] by them from Streptomyces cervinus sp. nov. Cervinomycin's skeletal novelty and promising activity[2] against anoerobic bacteria, mycoplasma and gram positive bacteria have attracted the attention towards its synthesis. No synthesis or synthetic study directed towards these antibiotics was reported when its synthesis was initiated in early 1988.

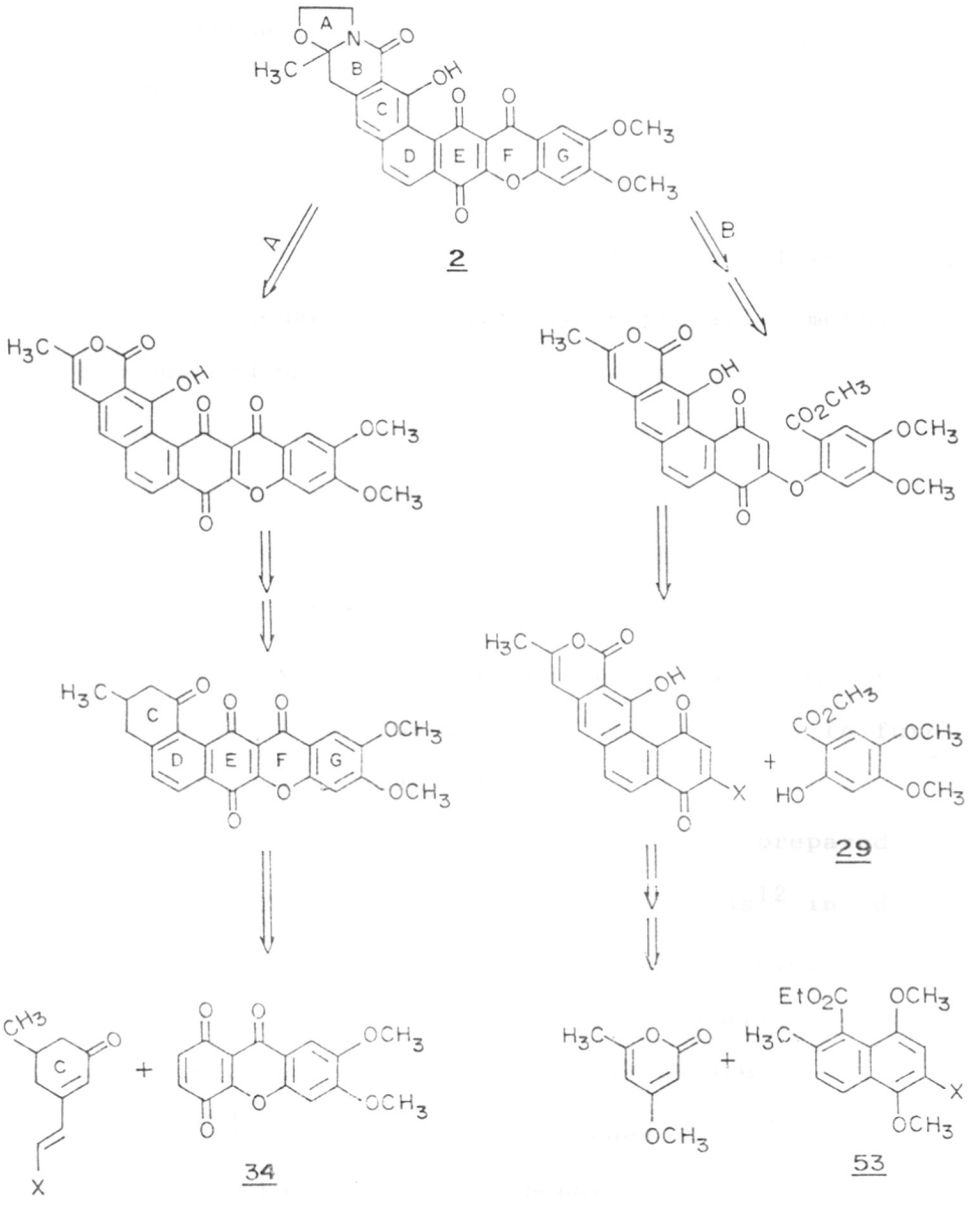
A retrosynthetic protocol indicated (SCHEME-6.6) xanthoquinone **34** (EFG fragment) and diene **39** (c fragment) as the key intermediates. These intermediates on Diels-Alder condensation (route A) were expected to result in the formation of CDEFG ring system **40**, which could be further elaborated to cervinomycin. In another approach (route B) the naphthalene derivative **53** was considered as a desirable starting intermediate for the regiospecific elaboration to the cervinomycins through phenanthropyrone **55** as a key intermediate.

DIELS-ALDER APPROACH (ROUTE A):

In this approach it was considered that the key intermediates diene **39** and the dienophile 6,7-dimethoxyxanthene-1,4,9-trione (**34**) could be condensed under Diels-Alder reaction to construct an important CDEFG ring skeleton **40**, which could be further elaborated to cervinomycins.

SCHEME-6.6

RETROSYNTHETIC ANALYSIS



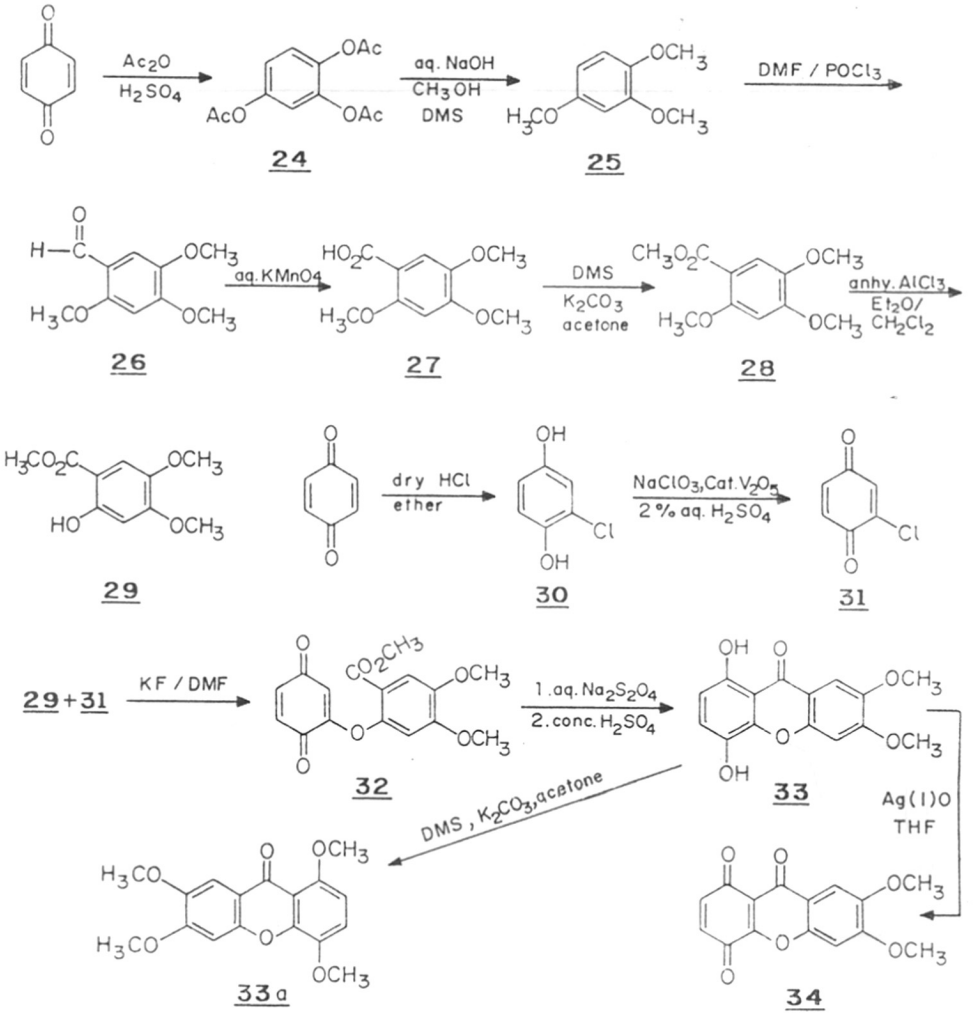
Although a number of natural and unnatural xanthones are known, none of them are having the desired 1,4,6,7-tetrasubstituted oxygen pattern in the xanthone nucleus. Therefore, there was a need to develop a suitable methodology for the synthesis of 1,4-dihydroxy-6,7-dimethoxyxanthone (33). The synthesis of 33 was accomplished starting from easily accessible 1,4-benzoquinone as depicted in SCHEME-6.7.

1,2,4-Triacetoxybenzene (24), obtained by Thiele acetylation[8] of p-benzoquinone was hydrolytically methylated[9] with aqueous sodium hydroxide and dimethyl sulphate to give 1,2,4-trimethoxybenzene (25). Vilsmeier-Haack formylation[9] (DMF/$POCl_3$) of 25 followed by oxidation[10] of the corresponding aldehyde 26 with aqueous potassium permanganate yielded acid 27. It was esterified (DMS-K_2CO_3, acetone) and selectively monodemethylated[11] with anhydrous aluminium chloride in a mixture of dichloromethane and diethyl ether to furnish methyl 2-hydroxy-4,5-dimethoxybenzoate (29).

2-Chloro-1,4-benzoquinone (31) was also prepared from p-benzoquinone by treating it with dry HCl gas[12] in diethyl ether followed by oxidation[13] of resulting 2-chlorohydroquinone (30) using sodium chlorate and catalytic vanadium pentaoxide in 2% aqueous sulphuric acid (SCHEME-6.7).

Coupling[14] of 29 and 31 proceeded *via* an addition/elimination mechanism to give phenoxyquinone 32, which was reduced with aqueous sodium dithionite and cyclized by treating it with concentrated sulphuric acid at 60°C to give

SCHEME-6.7



1,4-dihydroxy-6,7-dimethoxyxanthone (33). Compound 33 was oxidized[14] to xanthoquinone 34 with silver (I) oxide in THF (SCHEME 6.7). Spectral data of 34 was in good agreement with the assigned structure.

With the key intermediate 34 in hand, the next aim was to prepare diene 39 which was required for the Diels-Alder

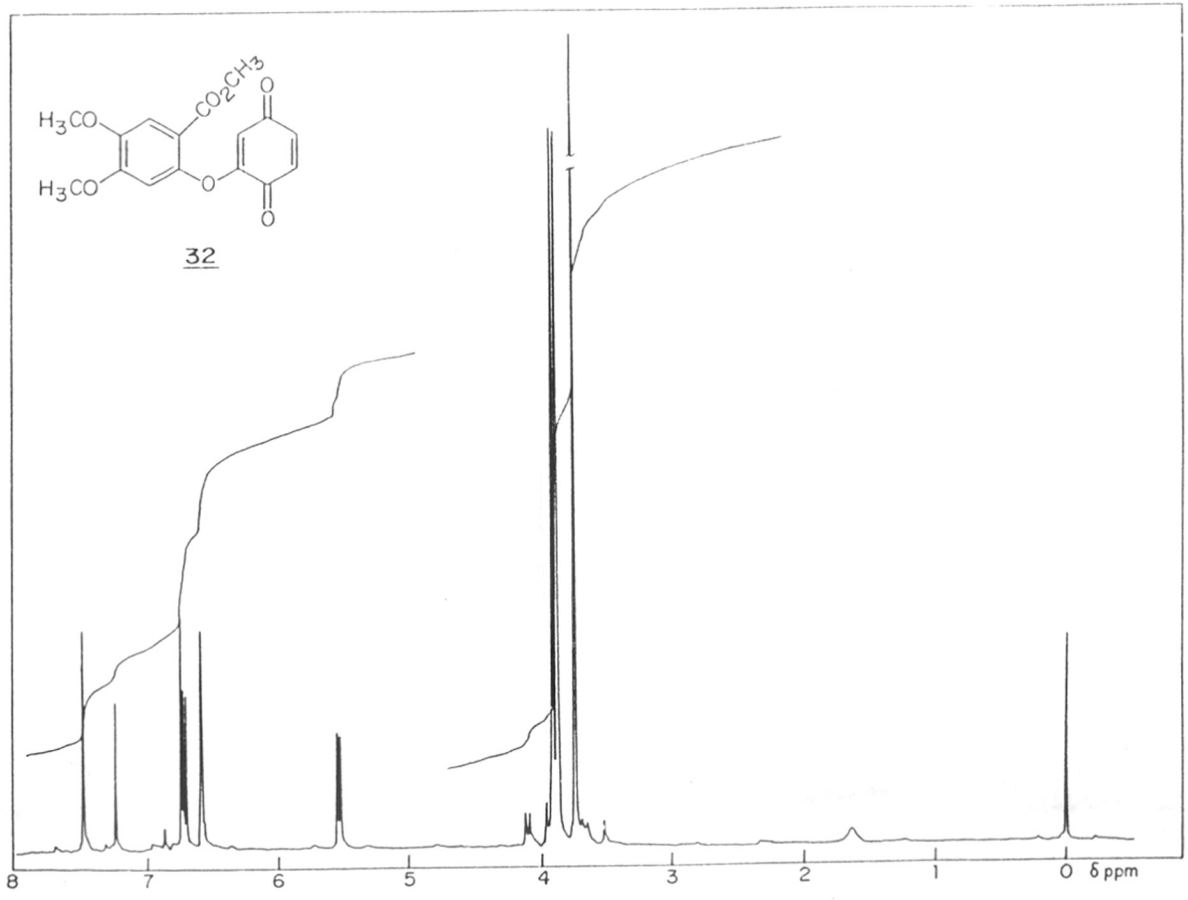


FIG. II : ^{1}H-NMR SPECTRUM OF THE COMPOUND (32) IN $CDCl_3$

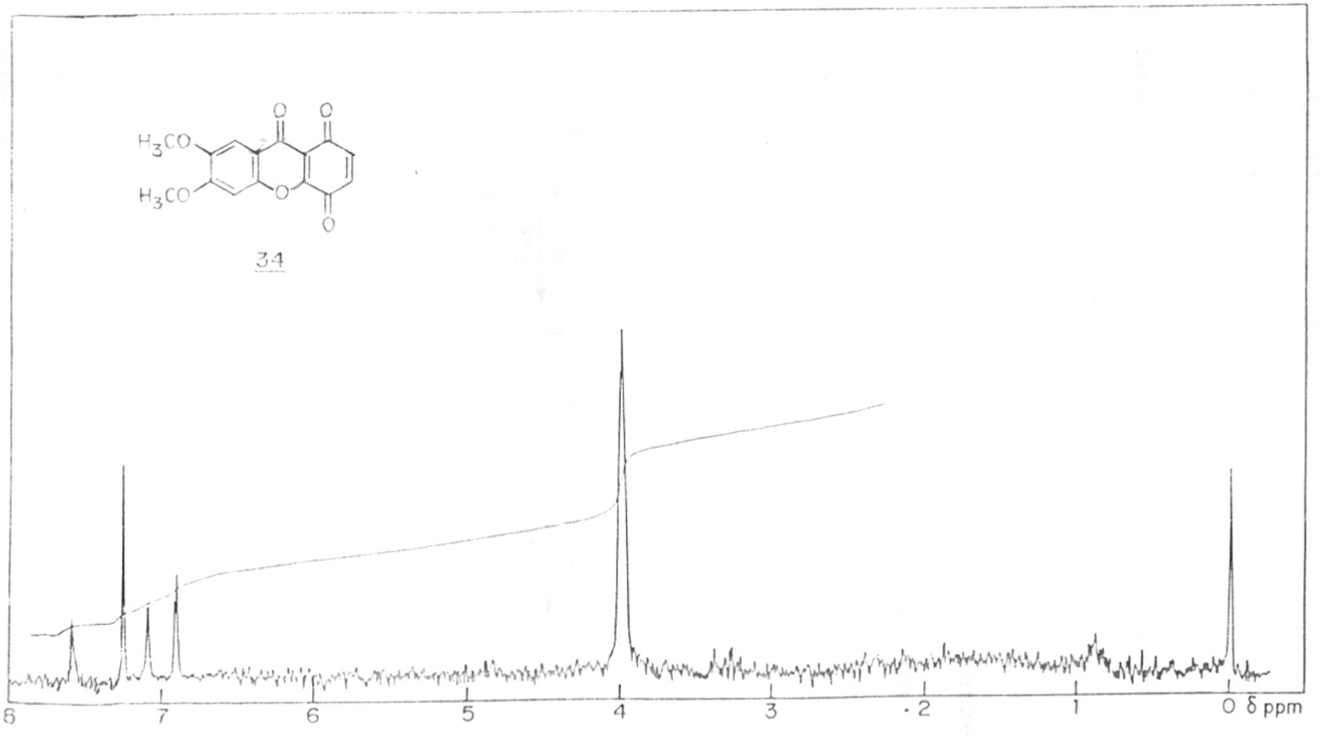
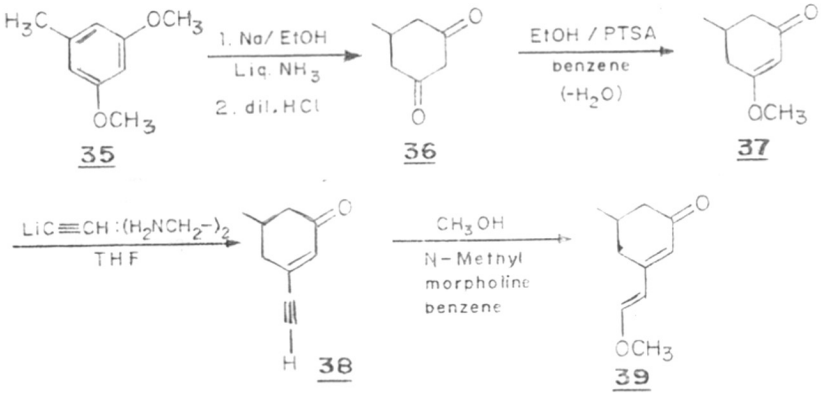


FIG. III : ^{1}H-NMR SPECTRUM OF THE COMPOUND (34) IN $CDCl_3$

reaction. The diene 39 was synthesised[16] from 3,5-dimethoxytoluene (35) in four steps (SCHEME 6.8). Birch reduction (Na/liq. NH_3, EtOH) of compound 35 gave 5-methylcyclohexane-1,3-dione (36) which was converted to ethyl enol ether 37 by refluxing it with benzene and ethanol in presence of catalytic PTSA and removing water azeotropically[16]. Ynone 38 obtained by the reaction of compound 37 with lithium acetylide-ethylenediamine complex[17] in THF was treated with methanol and N-methylmorpholine in benzene to give dienone 39 as the sole EE stereoisomer[16]. The ^{1}H-NMR and IR spectra of the diene 39 were identical with those reported in the literature[16].

SCHEME-6.8



Having obtained the diene 39 and dienophile 34, a stage was set for the Diels-Alder reaction. Thus, the compound 34 was treated with diene 39 in presence of boron triacetate[16] in dichloromethane at room temperature. However, this reaction failed to give desired cycloadduct 40. The Diels-

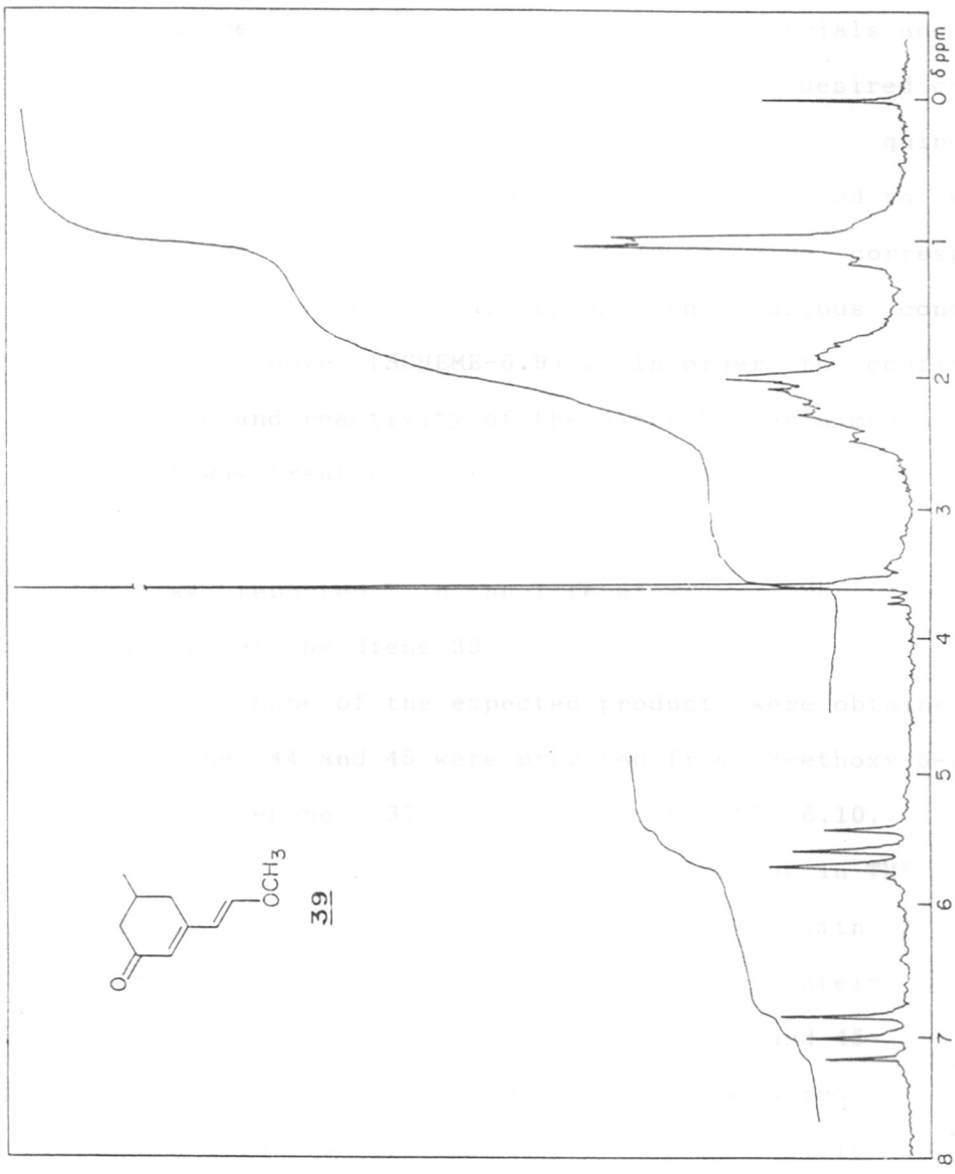


FIG. IV : ^{1}H-NMR SPECTRUM OF THE COMPOUND (39) IN $CDCl_3$

Alder reaction between 34 and 39 was attempted with different Lewis acid catalysts (anhy. $AlCl_3$[18], $TiCl_4$[19], $BF_3:OEt_2$[20] and $SnCl_4$[20]), with or without solvent and different temperatures[21]. In addition to this, many trials and variations in reaction conditions failed to give desired cycloadduct 40. Similarly the intermediate phenoxy- quinone 32, benzoquinone and chlorobenzoquinones also failed to undergo Diels-Alder reaction with diene 39 to give corresponding cycloadducts using catalysts and the various conditions mentioned above (SCHEME-6.9) . In order to confirm the structure and reactivity of the diene 39, as a model experiment it was treated with juglone (41) in dichloromethane in presence of $B(OAc)_3$. This reaction gave (±) ochromycinone (42) as reported[16] in the literature and reconfirmed the structure of the diene 39.

When none of the expected products were obtained, two more dienes 44 and 45 were prepared from 3-ethoxy-5-methylcyclohex-2-enone (37) as shown in SCHEME 6.10. Grignard reaction of 37 with vinyl magnesium bromide in THF yielded dienone 44, which was reduced to dienol 45 with diisobutylaluminium hydride in toluene. Unfortunately attempted Diels-Alder reaction of these dienes (44 and 45) with quinone 34 or 32 also failed to give desired cycloadduct (SCHEME-6.10) under the various conditions. It should be mentioned here that the Diels-Alder reactions under high pressure conditions (15-17 K bar)[16b] and under ultrasonication conditions have not been attempted[16c].

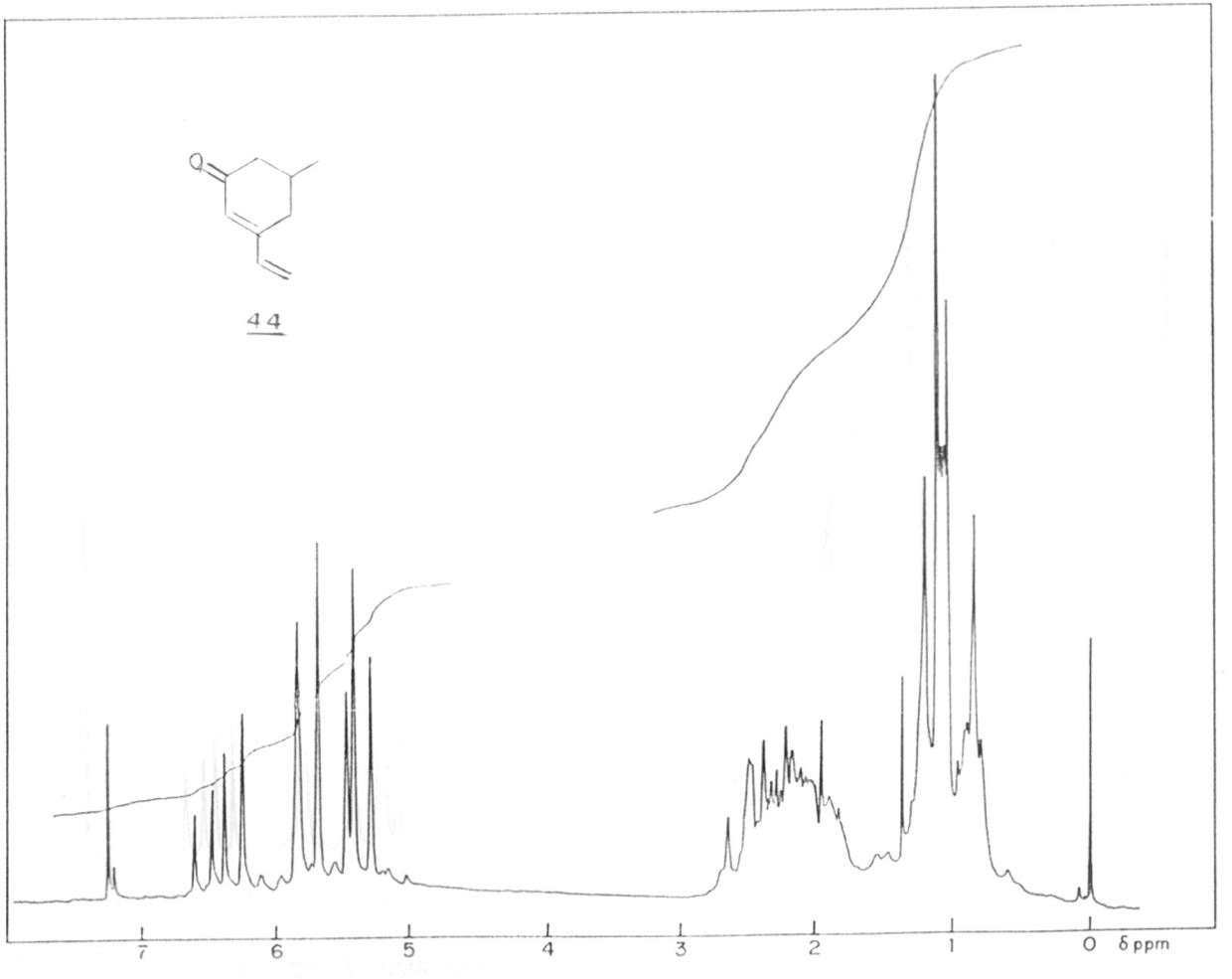


FIG. V : ^{1}H-NMR SPECTRUM OF THE COMPOUND (44) IN $CDCl_3$

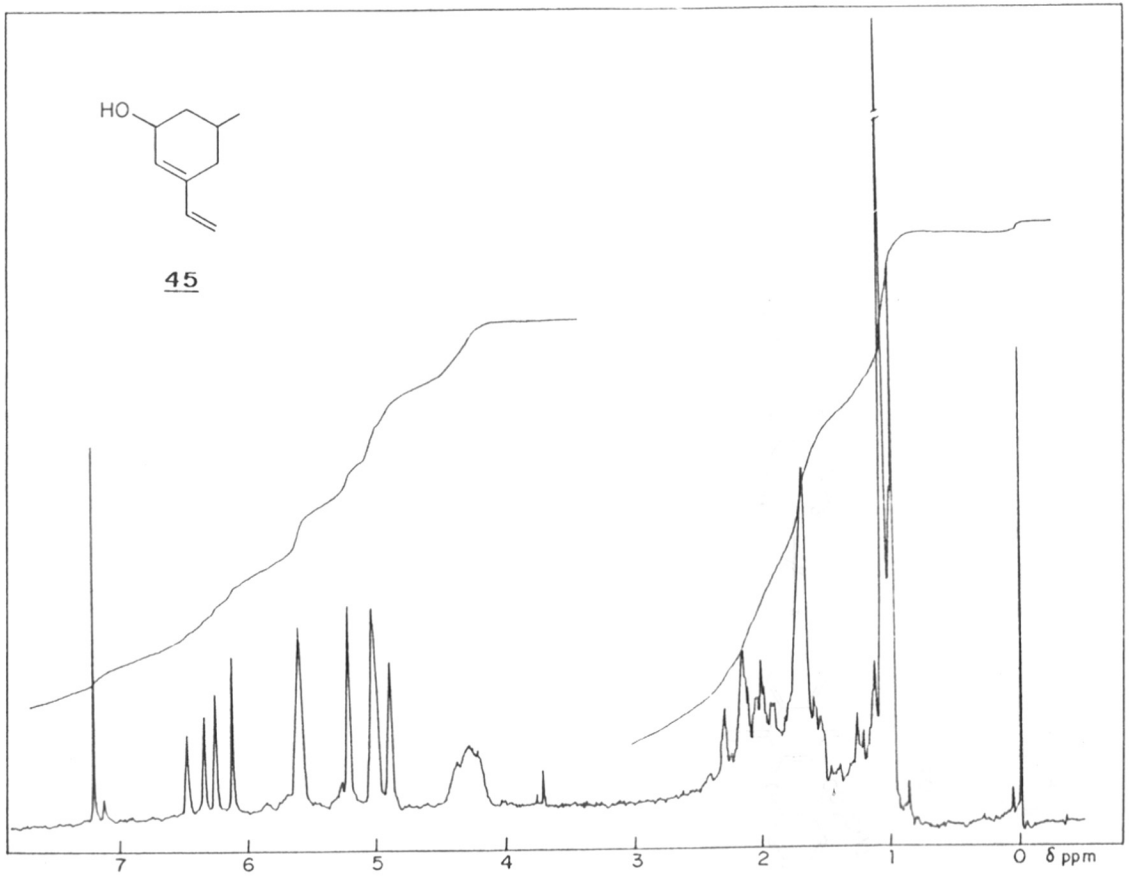
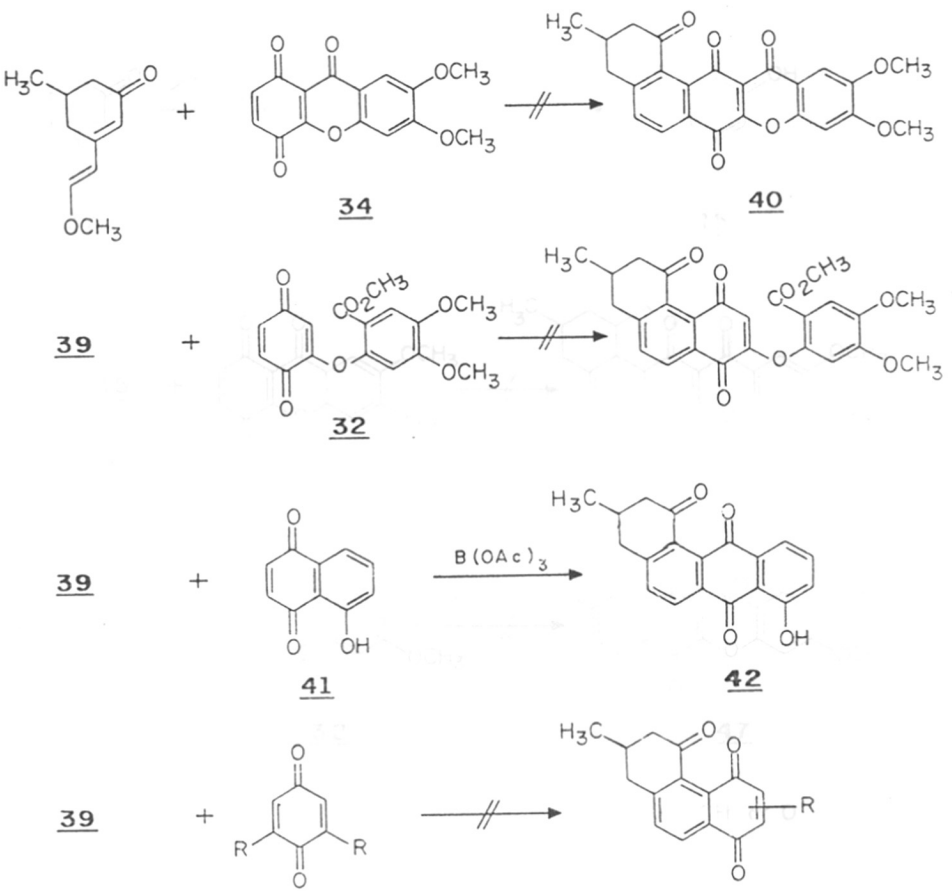


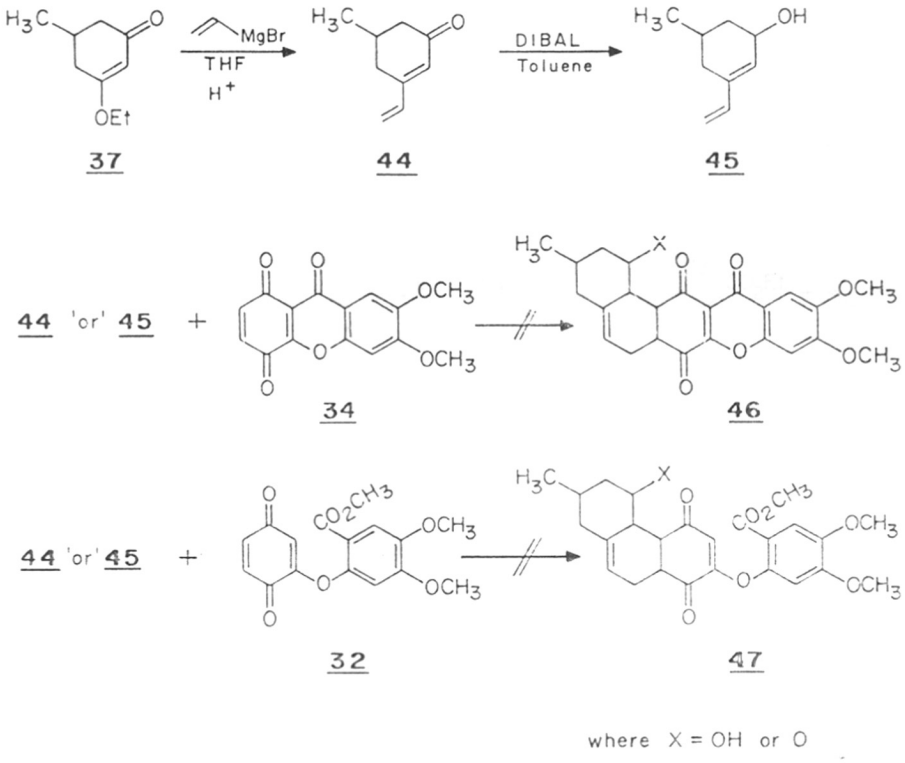
FIG. VI : ^{1}H-NMR SPECTRUM OF THE COMPOUND (45) IN $CDCl_3$

SCHEME-6.9



Where R = H or Cl

SCHEME-6.10

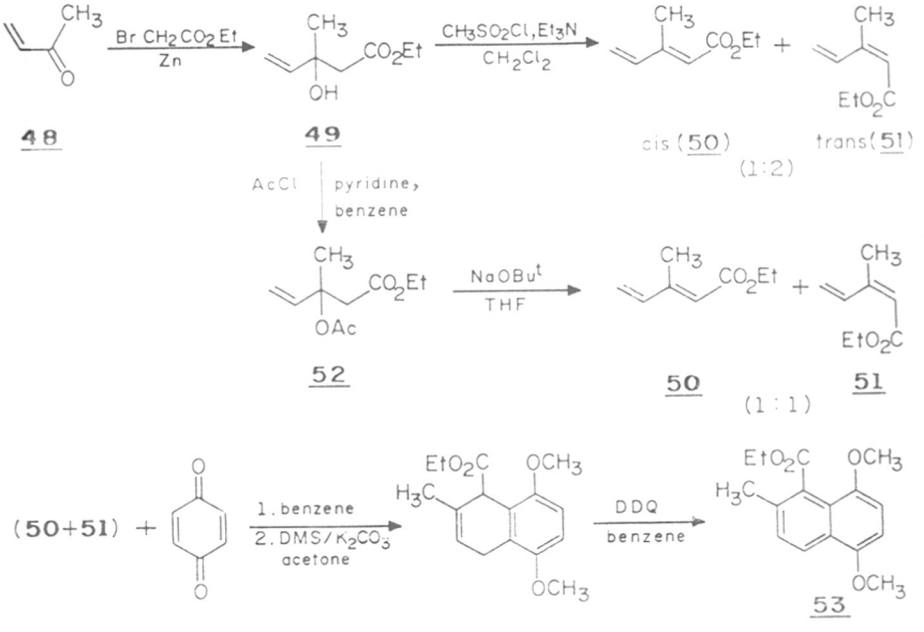


PHENANTHRENE INTERMEDIATE APPROACH (ROUTE B):

In this approach it was considered that the key intermediate like phenanthropyrone 55 could be elaborated regiospecifically to cervinomycin. The compound 55 could be synthesised in one step from the naphthoate 53 and 2-pyrone derivative 54 using heteroatom directed lithiation methodology.[22].

The synthesis of phenanthropyrone 55 was planned from naphthoate derivative 53, which was in turn synthesised (SCHEME 6.11) by Diels-Alder reaction of dienoate 51 with

SCHEME-6.11



benzoquinone followed by methylation (DMS, K_2CO_3, acetone reflux) and aromatization (DDQ, benzene)[23]. The required trans-dienoate 51 was obtained alongwith cis-dienoate 50 by using known literature procedure[24,25]. Reformatsky reaction of methyl vinyl ketone 48 and ethyl bromoacetate in diethyl ether gave hydroxy-ester 49. Dehydration of hydroxy-ester 49 by acetylation (AcCl-pyridine, benzene) followed by elimination (t-BuONa, THF) afforded a mixture of cis- and trans-dienoates 50 and 51 in an approximate 1:1 ratio.

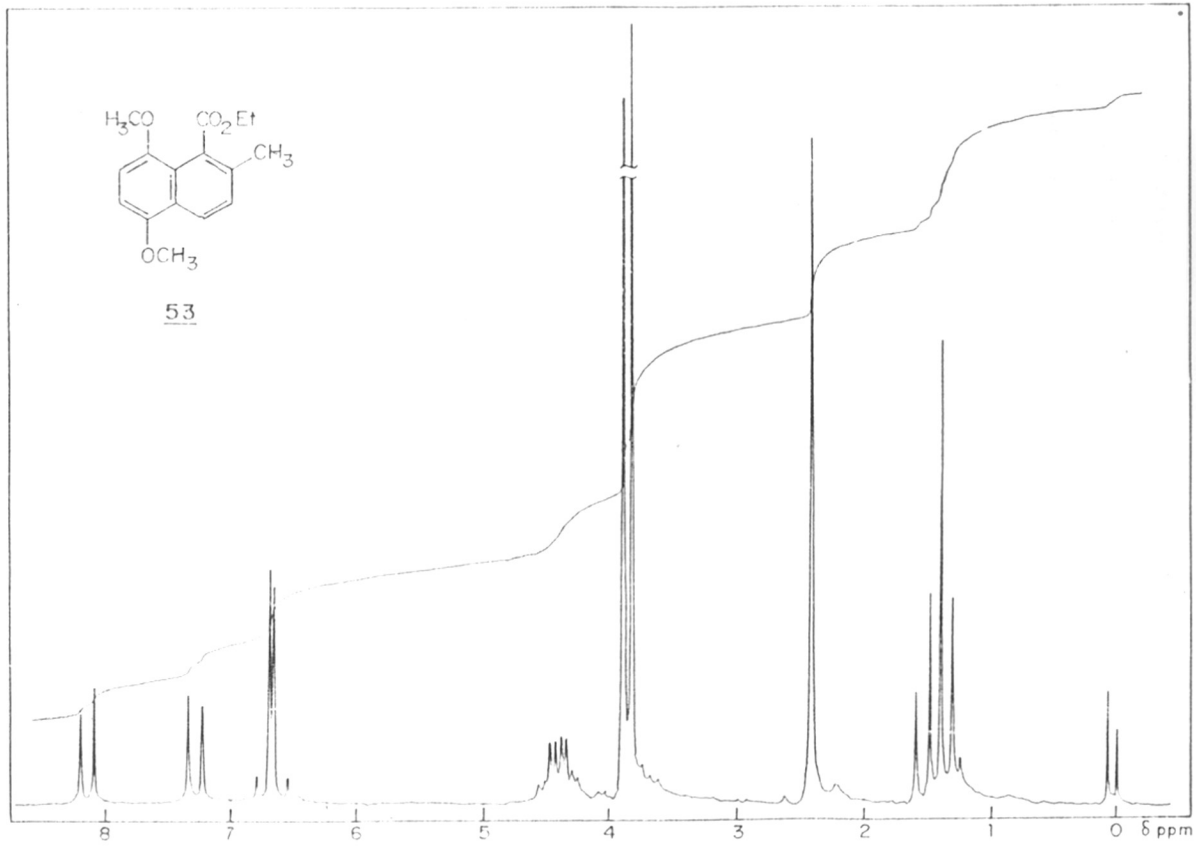
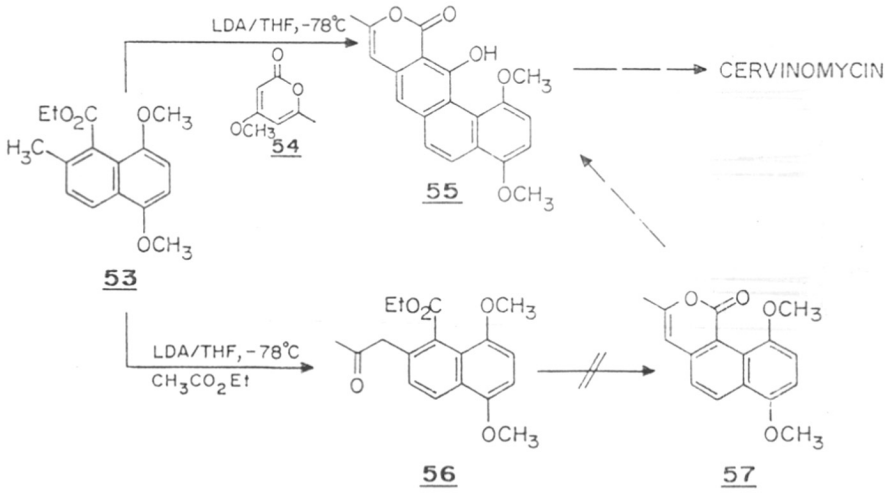


FIG. VII : ^{1}H-NMR SPECTRUM OF THE COMPOUND (53) IN $CDCl_3$

While the dehydration of the ester 49 with mesyl chloride and triethyl amine in dichloromethane as reported by Yadav and Mysoreker[25] gave a mixture of cis and trans-dienoates 50 and 51 in 1:2 ratio. The spectral and physical properties of the dienoates 50 and 51 were in good agreement with those reported in the literature[24].

After obtaining the compound 53, the next task was to condense it with 4-methoxy-6-methyl-2-pyrone 54 (triacetic lactone methyl ether) whose synthesis has already been described in CHAPTER-III of this thesis. Thus, the naphthoate 53 was lithiated[22] with LDA at -78°C and was treated with 54, unfortunately this reaction failed to give desired pheananthropyrone 55 and only starting materials were recovered. Therefore, an alternate approach (SCHEME-6.12) for the synthesis of compound 55 was attempted. Thus, the anion of 53 (prepared with LDA at -78°C in THF) was treated with ethyl acetate at -78°C to give keto-ester 56. The yield of

SCHEME-6.12



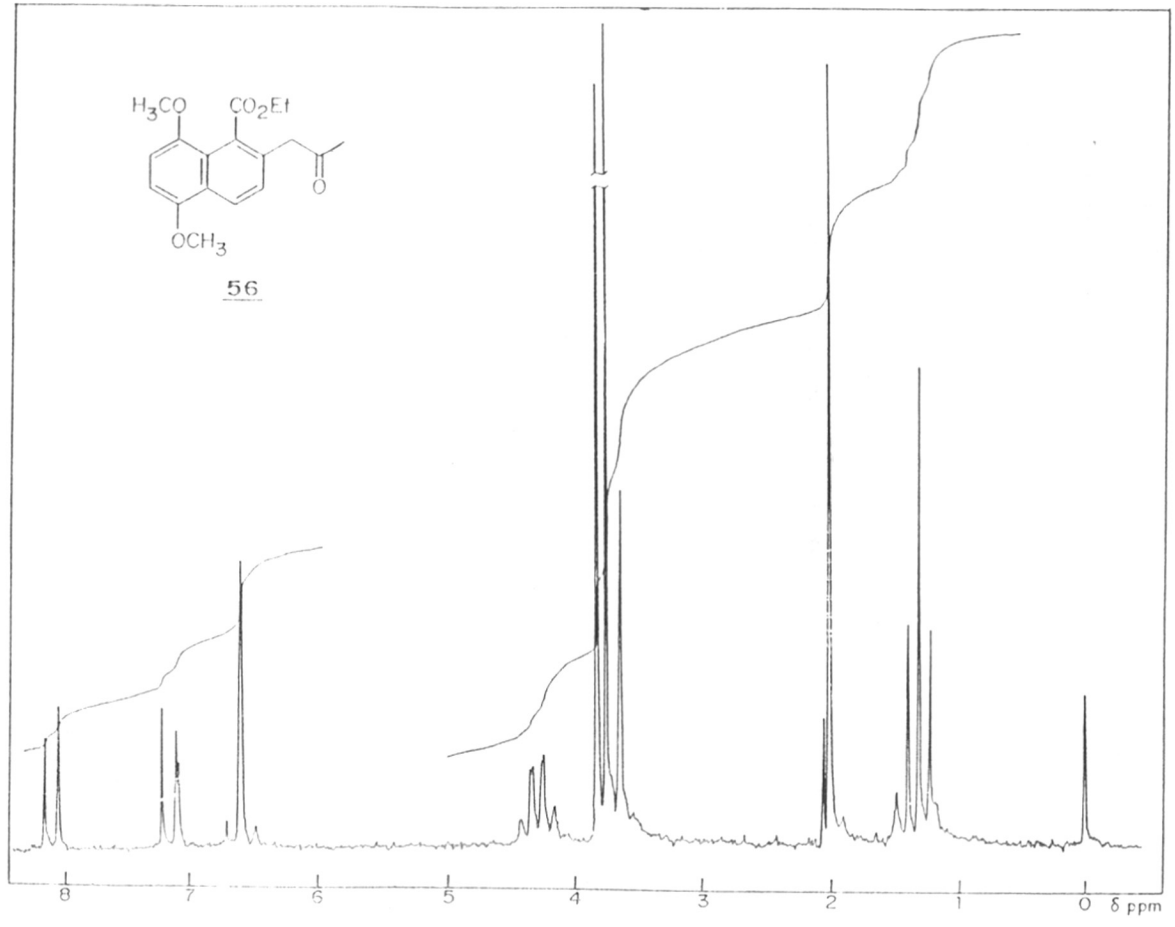


FIG VIII : ^1H-NMR SPECTRUM OF THE COMPOUND (56) IN $CDCl_3$

this reaction was poor (32%) and no improvement in the yield of 56 was achieved by changing reaction conditions. The ^{1}H-NMR spectrum of **56** revealed two singlets at δ 2.03 (-CO-$\underline{CH}_3$) and δ 3.62 (Ar-$\underline{CH}_2$-CO) along with the other required peaks. Its IR spectrum showed absorption bands at 1735, 1680 and 1615 cm^{-1}. The structure of **56** was further confirmed by mass spectrum which showed molecular ion peak at m/e 274.

The attempted cyclization of **56** under basic conditions (NaH, Cat.t-BuOH, toluene)[27] as well as basic hydrolysis and/or acidic cyclization ($HClO_4$, Ac_2O)[4a,48] failed to give required naphthopyrone **57** which, if available, could be converted to phenanthropyrone **55** (SCHEME-6.12).

EXPERIMENTAL

1,2,4-Triacetoxybenzene (24):

To a mechanically stirred mixture of sulphuric acid (0.25 ml) was added p-benzoquinone (11 g, 0.1 mol) in small portions. The temperature of the reaction mixture rose to 40-45°C and was kept within this range by regulating the rate of addition of the quinone. When the addition was complete, the solution was allowed to cool to about 25°C and poured into cold water (150 ml). The precipitated solid was collected by filtration and recrystallized from rectified spirit to give **24** (22 g, 86%); m.p. 97°C (lit.[8], m.p. 97°C).

1,2,4-Trimethoxybenzene (25):

The triacetate **24** (22 g, 0.131 mol) was stirred vigorously with dimethyl sulphate (138.6 g, 1.09 mol) in methanol (45 ml) at 10°C, and slowly treated with aqueous solution of sodium hydroxide (90 gm NaOH in 90 ml of water). Water (200 ml) was added after 1 h and extracted with diethyl ether (3 x 30 ml). The organic extracts were dried (Na_2SO_4) and evaporated to give dark brown oil, which was distilled under reduced pressure to give the compound **25** (11 g, 86%) as a colourless oil; b.p. 130-135°C/15 mm Hg (lit.[9], b.p. 247°C/760 mm Hg).

2,4,5-Trimethoxybenzaldehyde (26):

A complex was prepared from $POCl_3$ (19.16 g, 0.125 mmol) and DMF (9.13 g, 0.125 mmol) at 0°C and to this complex was added 1,2,4-trimethoxybenzene **25** (10 g, 0.059 mmol) with cooling (0°C). The mixture was allowed to warm to room temperature and stirring was continued for 5 h. It was cooled to 5°C and decomposed with 25% aqueous solution of sodium hydroxide (500 ml). The separated colourless solid was filtered, washed with cold water and dried. Recrystallization from hot water yielded 9.5 g of the required aldehyde **26** as a colourless crystalline solid (95%); m.p. 115°C (lit.[9], m.p. 115°C).

2,4,5-Trimethoxybenzoic acid (27):

To a stirred solution of aldehyde **26** (9 g, 0.046 mmol) in water (50 ml) at 85-90°C was added an aqueous solution of potassium permanganate (8%, 200 ml), till the colour of solution persisted. The mixture was stirred for 2 h at room temperature. The MnO_2 formed during the reaction was filtered and washed with water (50 ml). Acidification of the aqueous filtrate with dilute hydrochloric acid (1 N, 50 ml) gave colourless solid, which was filtered, washed with cold water and dried do afford acid **27** (7.1 g, 92%); m.p. 144°C (Lit.[10], 144-145°C).

Methyl-2,4,5-trimethoxybenzoate (28):

A mixture of acid 27 (7 g, 33 mmol), dimethyl sulphate (4.99 g, 39.6 mmol) and potassium carbonate (6.8 g, 49.5 mmol) in dry acetone (100 ml) was refluxed with stirring for 5.5 h. The acetone was distilled out from reaction mixture, cold water (100 ml) was added to the residue and kept standing for 2 h at room temperature. The solid separated was collected by filtration, washed with cold water and dried to give 7.1 g of ester 28 (95%); m.p. 97°C (lit.[29], m.p. 97°C).

Methyl 2-hydroxy-4,5-dimethoxybenzoate (29):

A solution of methyl 2,4,5-trimethoxybenzoate 28 (5 g, 22.1 mmol) in dichloromethane (30 ml) was added dropwise to a stirred solution of anhydrous aluminium chloride (4.42 g, 33.2 mmol) in anhydrous ether (20 ml) at 0°C. The reaction mixture was stirred at room temperature for 4 h. It was then poured slowly into ice cold dilute hydrochloric acid (50 ml) and then warmed on water bath. The solid separated was filtered, washed with water and dried. Recrystallization from benzene pet. ether afforded 4.45 g of ortho-hydroxybenzoate 29 as colourless needles (95%);
m.p. 95°C (lit.[30], m.p. 95°C).

2-Chloro-1,4-benzenediol (30):

p-Benzoquinone (5 g, 46 mmol) was gradually added over 30 to 40 min to the stirred anhydrous ether (25 g) saturated at 0°C with dry hydrogen chloride gas (3 g). The reaction

mixture was stirred for 30 min at room temperature and the ether was evaporated under reduced pressure to give 6.6 g of 2-chlorohydroquinone **30** (100%) as a colourless solid; m.p. 105°C (lit.[12], m.p. 105°C).

2-chloro-1,4-benzoquinone (31):

A mixture of 2-chlorohydroquinone **30** (6 g, 41 mmol), sodium chlorate (2.43 g, 22.9 mmol) and vanadium pentoxide (0.1 g) was stirred vigorously in dilute sulphuric acid (2%, 50 ml) for 4 h. The temperature of the reaction was maintained below 40°C by cooling the flask in running water. The reaction mixture was filtered, washed with cold water and dried. The crude product was purified by recrystallization from light petroleum (b.,p. 60-80°C) to give **31** as a yellow crystalline solid (4.7 g, 80%); m.p. 57°C, (lit.[31], m.p. 57°C).

2-(4,5-Dimethoxy-2-methoxycarbonylphenoxy)-1,4-benzoquinone (32)

To the fine suspension of anhydrous potassium fluoride (3.48 g, 60 mmol) in dry DMF (50 ml) containing the ortho-hydroxy ester **29** (4.24 g, 20 mmol) added a solution of 2-chlorobenzoquinone **31** (3.16 g, 20 mmol) in the same solvent (50 ml) over 10 min. The reaction mixture was kept at 75°C for 4 h, poured into water (200 ml) and extracted with dichloromethane. The organic extract was washed with dilute hydrochloric acid, dried Na_2SO_4) and evaporated under re-

duced pressure. Purification of the crude product was carried out by column chromatography on silica gel (eluent: 25% ethyl acetate-pet. ether) to give phenoxyquinone 32 (5.61 g, 85%); m.p. 165°C.

IR (Nujol): ν max 1780, 1740, 1680 and 1600 cm^{-1}.

^1H NMR : δ 3.75 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 5.52 (d, 1H), 6.56 (s, 1H), 6.68 (d, 1H), 6.75 (s, 1H) and 7.47 (s, 1H).

MS (m/e): 318 (M^+).

Analysis cal. for $C_{16}H_{14}O_7$: C, 61.53; H, 4.40;

Found : C, 61.38; H, 4.35%.

1,4-Dihydroxy-6,7-dimethoxyxanthone (33):

A solution of phenoxyquinone 32 (5 g, 15.7 mmol) in dichloromethane (200 ml) was shaken with an aqueous solution of sodium dithionite (16 g, 200 ml), until the mixture became colourless. The organic extract and washings, after being dried (Na_2SO_4), were evaporated and the residue was stirred with concentrated sulphuric acid (30 ml) for 5 min. at room temperature then at 60°C for 20 min. The reaction mixture was cooled and cautiously poured over crushed ice (100 gm). The solid was filtered, washed with ice cold water and dried. Recrystallization of the crude product from methanol afforded 3.17 g of xanthone 33 (70%); m.p. 335°C.

IR (Nujol): ν max 3320, 1650, 1620 and 1585 cm^{-1}.

MS (m/e): 288 (M^+).

Since compound 33 was found to be insoluble in $CDCl_3$

and acetone d_6 it was characterized by converting it to dimethyl ether **33a** using dimethyl sulphate-potassium carbonate in refluxing acetone; m.p. 229°C.

IR (Nujol); max 1635, 1620 and 1600 cm^{-1}.

^{1}H-NMR : δ 3.95 (s, 3H), 3.97 (s, 9H), 6.68 (d, J = 8.4 Hz, 1H), 6.97 (s, 1H), 7.15 (d, J = 8.4 Hz, 1H) and 7.64 (s, 1H).

MS (m/e): 316 (M^+).

6,7-Dimethoxyxanthene-1,4,9-trione (34):

A mixture of the dihydroxyxanthone **33** (2.88 g, 10 mmol), silver (I) oxide (4.63 g, 20 mmol) and anhydrous $MgSO_4$ (5 g) in tetrahydrofuran (25 ml) was stirred for 3 h and filtered. Evaporation of the filtrate gave 6,7-dimethoxyxanthene-1,4,9-trione **34** (2.70 g, 94%); m.p. 274-275°C (decomp.).

IR ($CHCl_3$): ν max 1695, 1680, 1625 and 1595 cm^{-1}.

^{1}H-NMR: δ 3.97 (s, 3H), 6.91 (s, 1H), 6.92 (s, 1H), 7.08 (s, 1H) and 7.57 (s, 1H).

Ms (m/e): 286 (M^+).

Analysis cal. for $C_{15}H_{10}O_6$: C, 62.94; H, 3.49;

Found : C, 63.01; H, 3.45%.

5-Methyl-cyclohexan-1,3-dione (36):

Orcinol dimethyl ether **35** (17.6 g, 0.116 mmol) in ethanol (50 ml) was reduced in liquid ammonia (250 ml) by adding sodium (11.9 g, 0.51 mmol) in small pieces over

10 min. and was stirred for 30 min. Ammonia was evaporated, methanol (25 ml) followed by water (100 ml) were added and the product was taken in ether. The ether extract was dried over potassium carbonate, and evaporated. The residue was heated on steam bath for 10 min with 1N hydrochloric acid (20 ml), product was taken in ether and extracted with aq. NaOH solution (5%). Acidification and filtration gave 5-methyl-cyclohexane-1,3-dione **36** as a colourless crystalline solid (11 g, 72%); m.p. 128°C (lit.[15], m.p. 127-8°C).

3-Ethoxy-5-methylcyclohex-2-enone (37):

To the stirred solution of 5-methyl-cyclohex-1,3-dione **36** (10 g, 0.079 mmol) in benzene (500 ml) and ethanol (50 ml) was added a catalytic amount of p-toluenesulfonic acid and refluxed under azeotropic conditions for 8 h. Excess ethanol and benzene were distilled out. The reaction product was taken in benzene and washed successively with 10% aqueous sodium hydroxide solution, saturated brine solution, dried over sodium sulphate and concentrated under reduced pressure to give compound **37** (14 g) in 91% yield as a colourless oil.

IR (Neat): ν max 1665 and 1615 cm^{-1}.

^{1}H-NMR: δ 1.03 (br d, 3H), 1.31 (t, J = 2.5 Hz, 1H), 2-2.5 (m, 5H), 3.87 (q, J = 7.5 Hz, 2H) and 5.25 (s, 1H).

MS (m/e); 154 (M^+).

3-Acetylene-5-methylcyclohex-2-enone (38):

To the stirred lithium metal powder (0.406 g, 58 mmol) in THF (50 ml). Under argon atmosphere ethylene diamine (3.48 g, 58 mmol) was added dropwise over a period of 30 min. The temperature rose quickly to the reflux during the addition and was maintained at reflux by gentle heating for 2h. The reaction mixture was cooled to room temperature, vigorous stirring was initiated and acetylene was introduced over a period of 30 min. The temperature of the reaction was maintained at 25°C by external cooling. The compound 37 (2 g, 12.9 mmol) was injected to the resultant slurry and the reaction mixture was stirred for 24 h at room temperature. It was poured into ice cold 2.5 N H_2SO_4) (25 ml) and extracted with dichloromethane. The organic extract was washed with 5% aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated to give crude product (1.7 g). Which was purified by column chromatography (silica gel, eluent; 2% ethyl acetate-pet. ether) as a colourless oil (1.5 g, 86%).

IR (Neat): $\bar{\nu}$ max 2080, 1660 and 1590 cm^{-1}.

^{1}H-NMR : δ 1.12 (d, J = 5 Hz, 3H), 1.94 - 2.68 (m, 5H), 3.50 (s, 1H) and 6.22 (d, J = 1.8 Hz, 1H).

MS (m/e): 134 (M^+).

3-Methoxymethylidene-5-methylcyclohex-2-enone (39):

A mixture of compound 38 (1.34 g, 10 mmol), N-methylmorpholine (1.01 g, 10 mmol) and methanol (1.28 g, 40 mmol) in dry benzene (20 ml) was stirred at room temperature for 24 h. It was then added to cold 1N H_2SO_4 solution (50 ml) and extracted with dichloromethane (3 x 25 ml). The organic extract was washed successively with water, 5% aqueous sodium bicarbonate, saturated solution of brine, dried (Na_2SO_4) and evaporated to give diene **39** as a dark yellow oil. It was purified by chromatography (silica gel, eluent: 5% ethyl acetate - pet ether) to give 1.2 g of diene as a sole EE stereoisomer in 72% yield.

IR (Neat): $\tilde{\nu}$ max 1695, 1650, 1620 and 1580 cm^{-1}.

^{1}H-NMR : δ 1.97 (d, J = 6 Hz, 3H), 1.78-2.566 (m, 5H), 3.59 (s, 3H), 5.50 (d, J = 16 Hz, 1H), 5.69 (s, 1H) and 7.00 (d, J = 16 Hz, 1H).

MS (m/e): 166 (M^+).

3-Vinyl-5-methylcyclohex-2-enone (44):

To the vigorously stirred magnesium turning (0.29 g, 12 mmol) in THF (25 ml) at 0°C a solution of vinyl bromide (1.28 g, 12 mmol) in THF (10 ml) was added dropwise over 15 min and stirred for 30 min at room temperature. The solution was cooled to 0°C and a solution of compound 37 (1.54 g, 10 mmol) in THF (10 ml) was added dropwise over 10 min. After complete addition the reaction mixture was allowed to warm to room temperature and stirred further for

2 h. The reaction mixture was slowly added to the saturated solution of ammonium chloride (25 ml) and extracted with ether. The ether extract dried over sodium sulphate and evaporated. Chromatographic purification of the product on silica gel afforded 1.1 g of dienone 44 (79%) as a colourless oil.

IR (Neat): ν max 1670, 1628 and 1590 cm^{-1}.

^{1}H-NMR: δ 1.1 (d, J = 6.25, 3H), 1.78-2.78 (m, 5H) and 5.15 - 6.25 (m, 4H).

MS (m/e): 136 (M^+).

3-Vinyl-5-methylcyclohex-1-enol (45):

A solution of diisobutyl aluminium hydride in toluene (7.9 ml, 1.5 M) was injected dropwise to the stirred solution of dienone 44 (1.00 g, 7.35 mmol) in toluene (15 ml) at -78°C and the reaction mixture was stirred for 1 h at -78°C. It was then allowed to warm to room temperature and stirred further for 30 min. The methanol was added to decompose aluminium complex. The solid separated was filtered, washed with toluene and the filtrate was concentrated under reduced pressure to give sufficiently pure dienol 45 (1 g, 98%) as a colourless oil.

IR (Neat): ν max 3320, 1640 and 1610 cm^{-1}.

^{1}H-NMR : δ 1.06 (d, J = 6.25 Hz, 3H), 2.47 - 2.34 (m, 5H), 4.31 (m, 1H) and 4.81 - 6.56 (m, 4H).

MS (m/e): 138 (M^+).

Analysis cal. for $C_9H_{14}O$: C, 78.26; H, 10.14;

Found : C, 78.31; H, 10.15%.

Ethyl-3-methyl-3-hydroxypent-4-enoate (49):

A portion of solution of ethyl bromoacetate (22 g, 0.131 mmol) and methyl vinyl ketone 48 (9.1 g, 0.13 mol) in ether (65 ml) was added to activated zinc (15.3 g, 0.234 mol) and once the reaction had commenced, the remainder of the solution was added at a rate allowing gently refluxing. When the addition was complete the mixture was heated under reflux for 1h, cooled and excess of zinc was removed by filtration. The filtrate was treated with 1.7 N acetic acid (100 ml) and the aqueous layer was saturated with ammonium chloride. The ether layer was separated and the aqueous phase repeatedly extracted with ether. The combined extracts were washed with aqueous sodium bicarbonate and water, and dried (Na_2SO_4). The ether was evaporated and the residue was distilled under reduced pressure to give the hydroxy-enoate 49 (15.5 g, 76%); b.p. 75-78°C/10 mm Hg (lit.[24], b.p. 82°C/ at 15 mm Hg).

cis and trans-Ethyl 3-methylpenta-2,4-dienoates (50 and 51):

To a stirred solution of alcohol 4 (5 g, 31.6 mmol) in dichloromethane (30 ml) was added triethylamine (9.6 g, 94.9 mmol, 13.23 ml) and 4-dimethylaminopyridine (DMAP, 0.100 g). The mixture was cooled to 0°C and methanesulfonyl chloride (5.43 g, 47.5 mmol, 3.67 ml) was added dropwise to it. The mixture was stirred for 1 h at room temperature. Then crushed ice was added and the mixture was stirred for 1h,

after which, it was extracted with dichloromethane (3 x 25 ml). The organic extracts were combined, washed with water (3 x 20 ml) and dried (Na_2SO_4). Evaporation of the solvent and distillation of residue under reduced pressure furnished a mixture of cis and trans dienoates **50** and 51 (3.32 g, 75%) in an approximately 1:2 ratio; b.p. 68-70°C/10 mm Hg (lit.[24], 70-74°C/14 mm Hg).

Ethyl 5,8-dimethyl-2-methylnaphthoate (53):

A solution of benzoquinone (1.08 g, 10 mmol) and a mixture of dienoate **50** and **51** (2.2 g, 15.7 mmol) in dry benzene (30 ml) was refluxed under argon atmosphere for 8 h. The benzene was distilled out and the crude adduct was methylated by refluxing in dry acetone (30 ml) with dimethyl sulphate 3.78 g, 30 mmol) and anhydrous potassium carbonate (4.14 g, 30 mmol) for 10 h. The reaction mixture was filtered, washed with acetone and the filtrate concentrated to give the corresponding dimethyl ether as gummy product (2 g), It was aromatized by refluxing in dry benzene (25 ml) with DDQ (6.8 g, 30 mmol) for 5 h. $DDQH_2$ formed in the reaction was filtered and washed with benzene. The filtrate and the washings were combined, dried (Na_2SO_4) and concentrated. It was chromatographed (basic alumina, eluent: benzene) to give compound 53 (1.5 g, 54%) as a colourless semi-solid.

IR (Nujol): ν max 1736, 1615 and 1600 cm^{-1}.

^{1}**H-NMR**: δ 1.41 (s, 3H), 2.41 (s, 3H), 3.84 (s, 3H), 3.90 (s, 3H), 4.41 (m, 2H), 6.59 (d, J = 10 Hz, 1H), 6.75

(d, J = 10 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H) and 8.15 (d, J = 8.7 Hz, 1H).

MS (m/e): 274 (M^+).

Analysis cal. for $C_{16}H_{18}O_4$: C, 70.07; H, 6.57;

Found : C, 70.18; H, 6.50%.

5,8-dimethoxy-2-(2'-oxopropyl)-1-naphthoate (56):

Into the flask containing LDA [prepared from a n-hexane solution n-BuLi (1.6 M, 0.79 ml) and diisopropyl amine (0.16 ml) at 0°C under argon atmosphere] in dry THF (5 ml) at -78°C, a solution of the compound 53 (0.274 g, 1 mmol) in THF (5 ml) was injected. After 15 min. the resultant dark-red anionic solution was treated with ethyl acetate (0.104 ml, 1.22 mmol) in THF (1 ml). The reaction mixture was stirred further for 30 min. at -78°C and allowed to warm to room temperature. It was then poured slowly to ice cold dilute hydrochloric acid (50 ml) and extracted with dichloromethane (2 x 20 ml). The combined dichloromethane extracts were washed with brine solution, dried (Na_2SO_4) and evaporated. The pure keto-ester **50** (.100 g, 32%) was obtained as a semisolid by column chromatography on silica gel (eluent: 15% ethyl acetate-pet ether).

IR (Nujol): ν max 1735, 1680, 1615 and 1595 cm^{-1}.

^{1}H-NMR: δ 1.31 (t, 3H), 2.03 (s, 3H), 3.62 (s, 2H), 3.75 (s, 3H), 3.84 (s, 3H), 4.31 (q, 2H), 6.56 (d, J = 8.7 Hz,

1H), 6.68 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 8.7 Hz, 1H) and 8.13 (d, J = 8.7 Hz, 1H).

MS (m/e): 316 (M^+).

Analysis cal. for $C_{18}H_{20}O_5$: C, 68.35; H, 6.33;

Found : C, 68.41; H, 6.39%.

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6. Synthesis of Bostrycoidin
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7. Total synthesis of austrocorticinic acid
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