THE CHEMISTRY OF SOME EXTRACTIVES FROM PLANTS OF THE FAMILY RUTACEAE

A Thesis

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by

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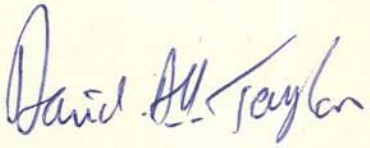
I certify that this work was carried out under my supervision by Mr. Marcus Olumuyiwa Abe in the Department of Chemistry, University of Ibadan, Nigeria.



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ABSTRACT

Chemically, the Rutaceae family is probably the most versatile of all higher family of plants. Three main groups of compounds, namely, limonoids, coumarins and quinoline alkaloids have been obtained from this family. The introductory part of this work reviews very briefly the chemistry of each of these groups.

In the main work, three plants of the West African genera of the Rutaceae were investigated. The wood of Afraegle paniculata (Schum and Thonn) yielded the furocoumarin, imperatorin which was isolated earlier from a number of Rutaceous plants and in addition, a furoquinoline alkaloid, dictamnine which had also been isolated from a large number of other genera of the family. The root of Clausena anisata was shown to contain imperatorin along with a new coumarin (coumarrayin) which was shown almost at the same time by Dreyer to be a constituent of Murraya paniculata.

From the wood of Oricia suaveolens was isolated a new alkaloid related to Flindersine (an alkaloid from an Australian Rutaceae plant) The structure of the new alkaloid was elucidated from spectroscopic

studies to be 1-methyl-6,7-dimethoxy-flindersine and this structure was confirmed synthetically.

ACKNOWLEDGEMENTS

I hereby express my indebtedness and profound gratitude to Professor D. A. H. Taylor for his keen and untiring supervision throughout the course of this study.

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Deepest gratitude is due to my father (whom I lost during this course of study) and my mother, for my early education. I am also

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C O N T E N T S

GUIDE TO SPECTRA REPRODUCED

INTRODUCTION

Since work started on wood products in this department, attention has been focussed more on the investigation of the family Meliaceae than any other family of plants. From this family, a large number of limonoids have been obtained. These limonoids are a class of C_{26} degraded triterpenes believed to be derivable from apo-euphol type of compound and they are now referred to as the 'meliacins'.[1]

Very closely related to the family Meliaceae is the Rutaceae family. Comprising of the members of this large family are about one hundred and fifty genera and over a thousand species, consisting mainly of evergreen, sweet scented trees and shrubs. They have their widest distribution in the tropical and sub-tropical habitats and are particularly abundant in Australia, South Africa and West Africa.

The Rutaceae family is morphologically similar to the Meliaceae family. Both families are shrubs or trees, but rarely herbaceous. From the close morphological relationships that exist between these two familites of plants, it is not too surprising, therefore, that their chemical constituents are very similar. This has been borne out by the large number of closely related limonoids extracted from both families.

Some of the well-known genera of the Rutaceae are:

Citrus : This forms a very large genus containing about sixteen species of which the following cultivated species form very good examples : C. Sinensis (Sweet organge), C. paradisi (grape fruit) C. lemon (lemon), C. auratifolia (lime tree) and C. reticulata (Tangerine).

Fagera consisting of F. zanthoxyloides, F. pubens, F. macrophylla, F. parvifolia and many others.

Aegle which include A. mildbraedii, A. paniculata and some others

Clausena typified by Clausena anisata. Oricia of which O. suaveolens and C. trifoliata form good examples.

Dictamnus exemplified by Dictamnus albus and Dictamnus dasycarpus.

Murraya typified by Murraya paniculata.

From purely chemical point of view, the Rutaceae family is a fascinating group and in respect of the compounds it produces, it is probably the most versatile of all families of higher plants. This family of plants has been found to contain three main groups of chemical compounds namely :

(i) Limonoids (ii) Quinoline alkaloids and (iii) coumarins.

An attempt is hereby made to review very briefly some of each of these groups of compounds.

(i) LIMONOIDS

The limonoids occurring in both the Meliaceae and the Rutaceae

families are a group of oxidised triterpenes believed to be derived genetically by the catabolism of a normal steroid side chain and formation of a β-substituted furan ring with loss of four carbon atoms. The limonoids occurring in the Meliaceae show, in general, much greater structural variation than the limonoids of the plants of the family Rutaceae. While the limonoids of the plants of the Rutaceae family very often have their A-rings as well as their D-rings expanded into δ-lactones, the limonoids of the Meliaceae family (the meliacins) are observed to be mainly D-ring lactones and their A-rings remain carbocyclic except methyl ivorensate which was isolated recently by E. K. Adesogan and D.A.H. Taylor[2] from Khaya ivorenses (Meliaceae). This meliacin is the only and the first limonoid from the Meliaceae family known to be both A- and D-rings opened to δ-lactones. The limonoids of the Rutaceae plants are much more interconvertible than those of the plants of the Meliaceae and they are, for the most part, reasonable intermediates in the biogenesis of limonin(I) (the parent compound) or are closely related biogenetically.

Limonin(I) : This is the parent limonoid of the Rutaceae and is the major constituent of Citrus seeds. It is the first furanoid triterpene to be isolated and has been known for over a hundred years[3]. Its structural determination was reported in 1960 by Arigoni et al[4] and later confirmed by X-ray crystallographic studies on the Iodoacetate

of epilimonol[5,6]. D. L. Dreyer[6] has recently shown from photochemical studies on limonin that it can be converted to photolimonin A (II) which has properties very similar to limonin but appears to be a C-8 stereo-isomer and photolimonin B (III) which is very similar structurally to methyl angolensate and andirobin which are rings B-Seco occurring naturally in the Meliaceae plants.

Deoxylimonin (IV) :

Deoxylimonin was isolated[8] from Citrus paradisi (grape fruit). It is a 14,15 deoxy-Δ^{14}-14,15-limonin. The origin of deoxylimonin was regarded to be a result of incompleteness of the epoxidation step in the biogenesis of limonin rather than the reduction of limonin to deoxylimonin. It could be prepared chemically from limonin by treatment with chromous chloride or with hydriodic acid under controlled conditions. (Scheme 1).

Limonin diosphenol (Evodol) (V)

Evodol is a highly oxidised limonoid which has been found[7] co-occurring with limonin (I) and rutaevin (XI) in three genera of the Rutaceae, namely, Evodia, Calodendrum and Dictamnus. Limonin diosphenol (evodol) is easily prepared directly from limonin by reacting limonin with oxygen in presence of potassium t-butoxide in t-butyl alcohol presumably via the hydroperoxide (Va)[9]

Rutaevin (XI)

Rutaevin was first isolated by Fujita et al[10], from dried fruit of Evodia rutaecarpa. It has also been isolated from Evodia hupenhensis by Dreyer[7]. It has been found that the seeds of Cape Chestnut Calodendrum carpense (Lf) Thumb, a native of South Africa are a good source of rutaevin and co-occur in these seeds with limonin and limonin diosphenol.

The structure of rutaevin has been formulated to be 6-keto epilimonol[11]. It forms a monoacetate, a monobenzoate and an oxime derivatives. The n.m.r. spectra of rutaevin and its acetate showed many features in common with those of limonin. Thus resonances were present for a 3-substituted furan ring, H-17, and epoxy H-15 and C_{19} methylene group.

Treatment of rutaevin with a base gives limonin diosphenol, indicating that both the hydroxy and the keto groups of rutaevin are located in the B-ring. Chromic acid oxidation of rutaevin gives a yellow α-diketone formulated as 6-Ketolimonin (XIII). Treatment of the last compound with hot sodium hydroxide converts it to limonin diosphenol (V) Like all limonoids with α-epoxy carbonyl groups, chromous chloride reduces rutaevin to deoxy rutaevin (XII).

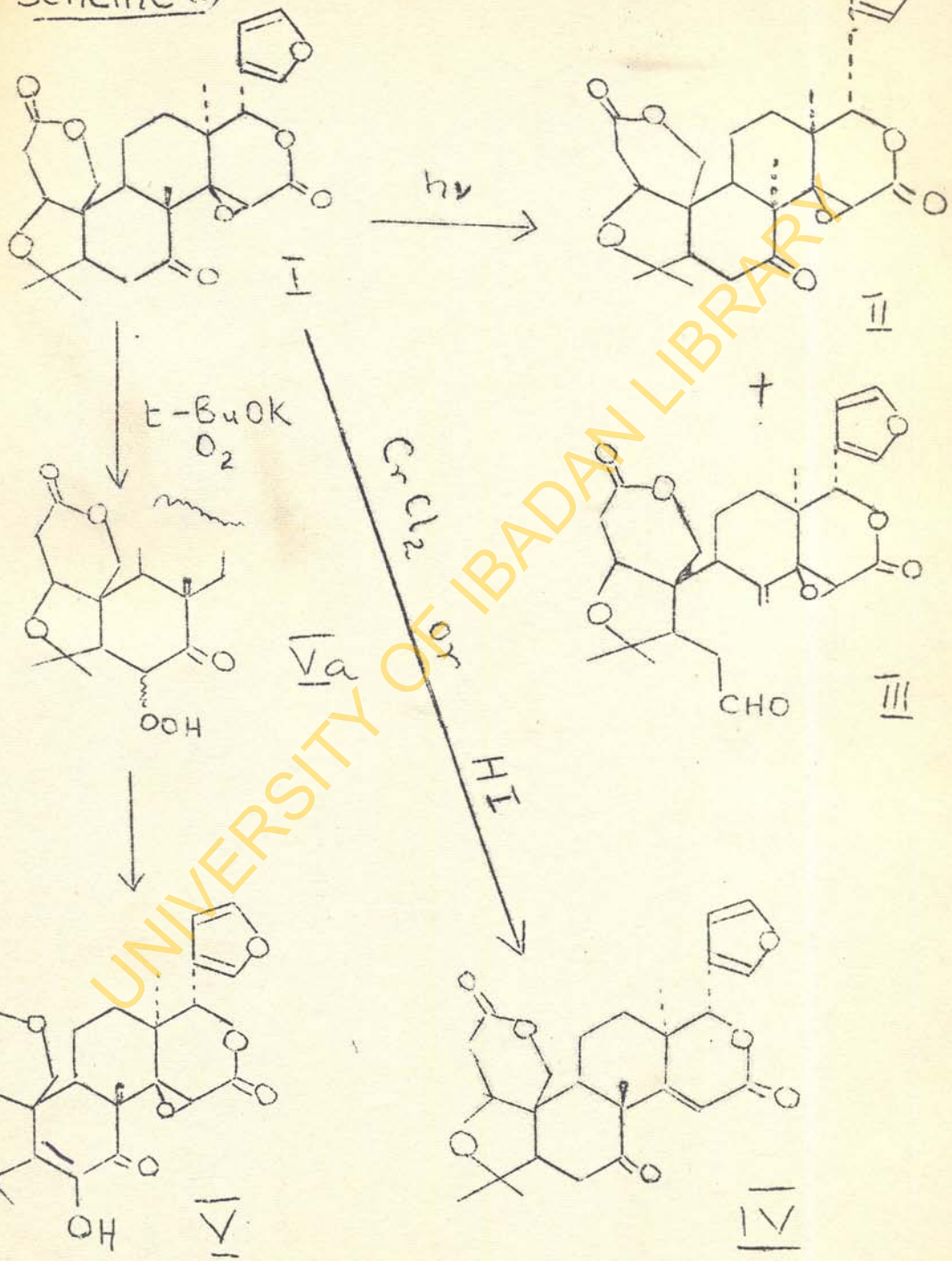
It seems likely that rutaevin is identical with dictamnolide[11,12] occurring in Dictamnus albus. The reported physical properties for

dictamnolide[12], its apparent non identity with limonin and its conversion to an acidic material having physical properties consistent with those of limonin diosphenol all point to the fact that diotamnolide is identical with rutaevin.

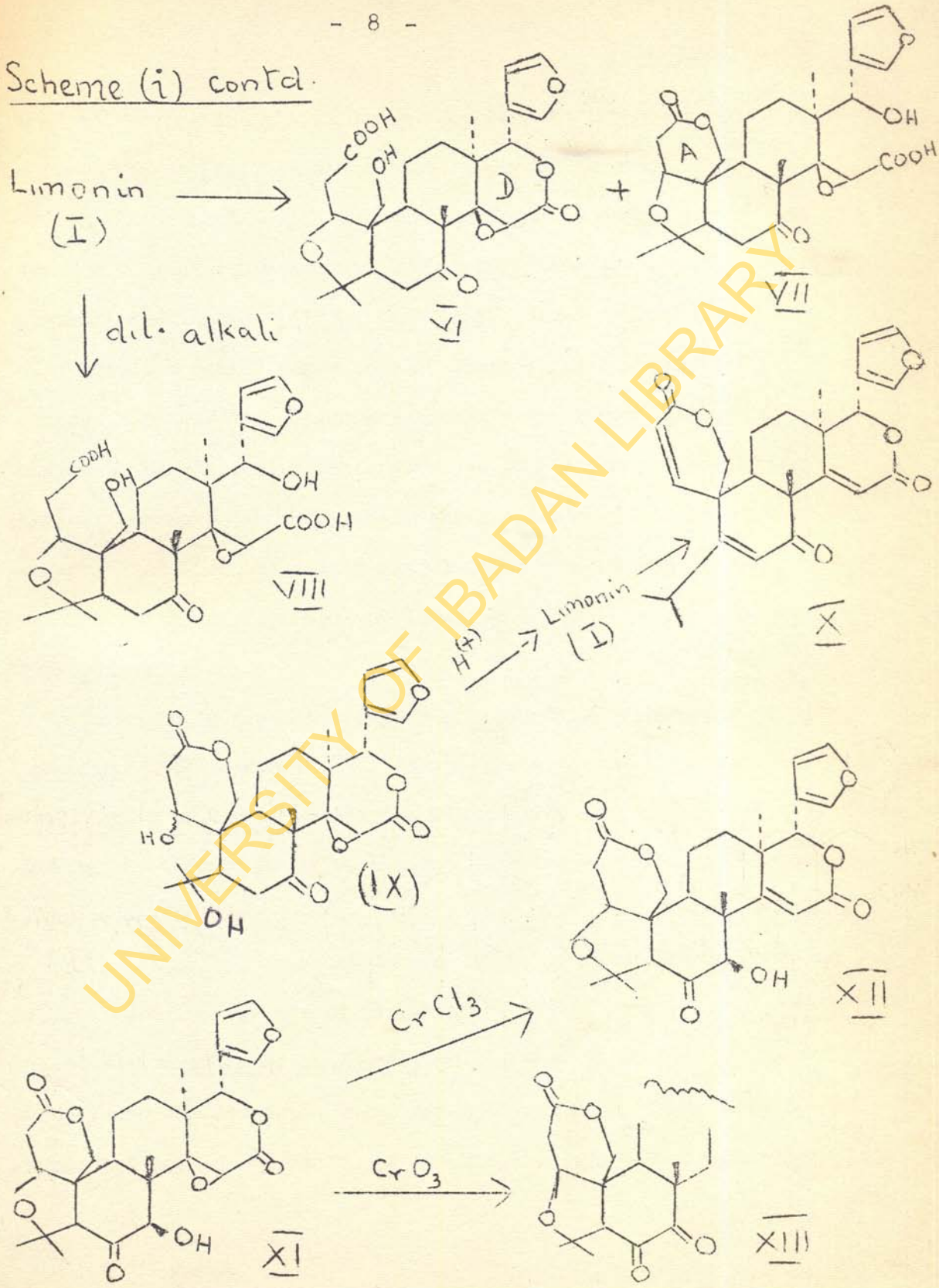
Limonoic acid A-ring lactone (VII)

V.P. Maier and D.A. Margileth have just reported[13] the isolation of a derivative of limonin for which the name limonoic acid A-ring lactone (VII) was proposed. This compound is one of the two possible monolactones which can be obtained from limonin by partial hydrolysis. It was identified as A-ring monolactone by thin layer chromatography and paper electrophoretic comparison with the authentic compound obtained synthetically and its facile conversion to limonin. There were indications of an enzyme in tissue extracts which converts limonoic acid A-ring lactone into limonin. The structure of limonin has been elucidated[4] as a tetracyclic triterpenoid dilactone with rings A & D δ-lactones and these lactones can be reversibly opened with dilute alkali. Maier and Margileth proposed the name limonoic acid to the dihydroxy diacid (VIII) derived from limonin by complete hydrolysis of these two lactones in limonin. This dihydroxy-diacid can lead to two monolactone forms namely limonoic acid A-ring lactone (VII) and limonoic acid D-ring lactone (VI). Maier and Margileth developed methods of separating

Scheme (i)



Scheme (i) contd.



and identifying the two acids and reported that the limonoic acid A-ring lactone (VII) is the naturally occurring monolactone.

Limonoic acid A-ring lactone was found to occur along with limonin in the orange membranes (Citrus sinensis) and grape fruit membranes and albedo (Citrus paradisi).

From the facile conversion of limonoic acid A-ring lactone to limonin and from the evidence suggesting the presence of a lactonizing enzyme in the tissues which accumulate both limonin and limonoic acid A-ring lactone as shown by Maier and Margileth, it is reasonable to suggest that limonoic acid A-ring lactone could be an immediate precursor in the biogenesis of limonin.

Ichangin IX

Ichangin is another congener of limonin. It is found in Citrus ichanges and its hybrids[14]. It appears to arise biogenetically from cyclisation of C-3 of deacetyl nomilin (XIV) into the C-19 methyl group and has been found under conditions where de-acetylnomilin occurs in large concentrations.

It is easily converted to limonin by trifluoroacetic acid and hydriodic acid converts it to citrolin (X).

Obacunone and related compounds.

These are limonoids which accompany limonin (I) in most Citrus seeds and some other genera of the Rutaceae[7]. They are closely related

to limonin, and a correlation between obacunone and limonin has been shown[15].

Obacunone (XVI)

Obacunone occurs together with nomilin (XV) in widely distributed species of the Rutaceae. For example, both nomilin and obacunone were found in Casimiroa edulis. Obacunone was reported[7] to occur with limonin (I) in the seeds of Fortunella margeritia and also in the bark of Phellodendron amurense.

The correlation between obacunone and limonin was effected through a lengthy series of transformations by T. Kubota and collaborators[15]. The end product of the transformations of both limonin and obacunone was the compound identified as methyl tetrahydro anhydro-epi-meroobacunone (XXI).

Obacunoic acid (XVII)

This acid, together with limonin was isolated from the powdered roots of Dictamnus dasycarpus by Nikonov[16]. The co-occurrence of limonin and obacunoic acid in Dictamnus dasycarpus on one hand and of limonin and obacunone in the two genera Fortunella and Phellodendron on the other hand supports the view that both compounds play some part in the biogenesis of limonin. Circumstantial evidence[7,8] has shown that both obacunone and obacunoic acid are precursors in the limonin biogenesis.

Obacunone is very easily converted chemically to obacunoic acid with a base. Obacunoic acid could be converted into isoobacunoic acid (XVIIIa) and epi-isoobacunoic acid (XVIIIb).

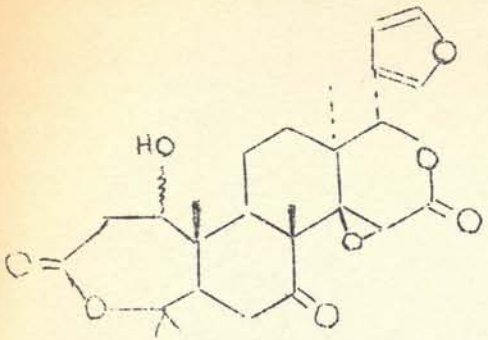
Veprisone (XIX)

Veprisone is the methyl ester of epi-isoobacunoic acid. It was isolated by T. R. Govindachari et al.[17] together with a number of furoquinoline alkaloids from Vepris biloculoris. From spectroscopic studies, the structure of veprisone was elucidated as methyl epi-isoobacunoate. This limonoid shows a close relationship to limonin and obacunone as borne out by the presence in its n.m.r. spectrum of signals at δ 5.6 (singlet, corresponding to the proton at C_{17} in limonin) and δ 4.25 (singlet, corresponding to the proton at C_{15} in limonin).

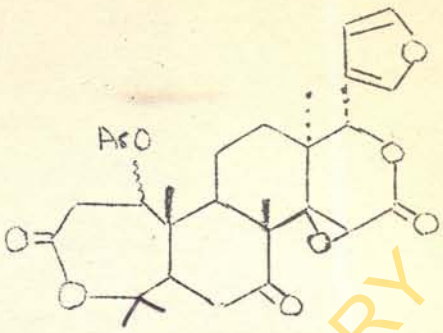
Reaction of veprisone with hydriodic acid in acetic acid gives an acid which, on treatment with diazomethane gives deoxy veprisone (XX). This shows that hydriodic acid is capable of de-epoxidising as well as hydrolysing veprisone. Hydrolysis of veprisone with methanolic caustic potash gives isoobacunoic acid (XVIIIa).

Nomilin (XV) and deacetyl-nomilin (XIV)

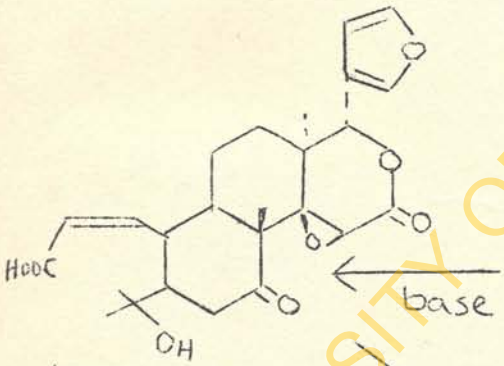
Nomilin (XV) occurs widely together with obacunone in many species of the Rutaceae. They were isolated together from the seeds of Casimiroa edulis[7]. Nomilin is easily converted[8] to obacunone by the



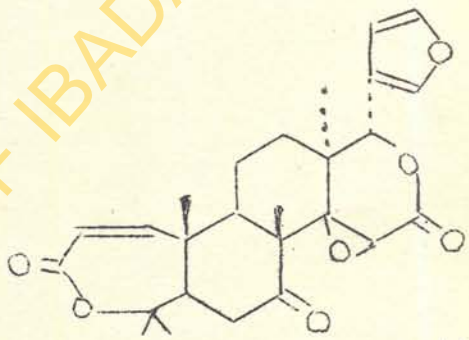
XIV



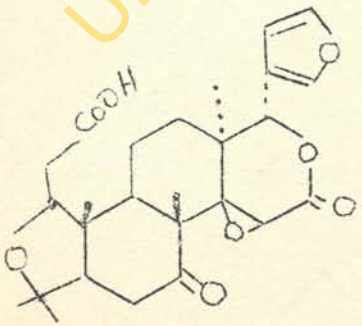
XV



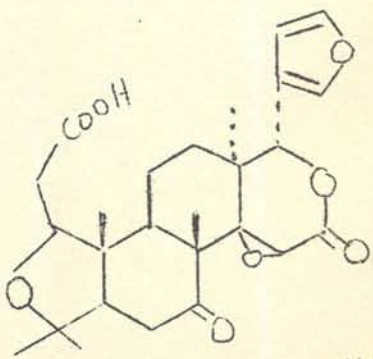
(XVII)



XVI

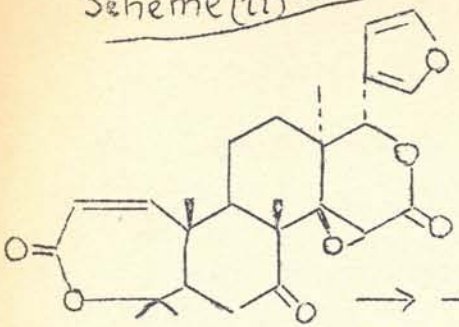


XVIIIa

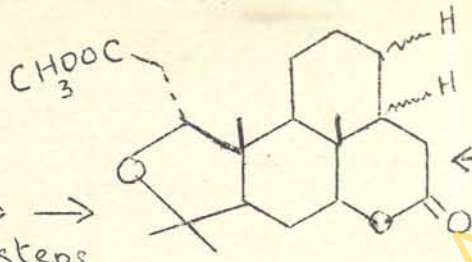


XVIIIb

Scheme (ii) contd.



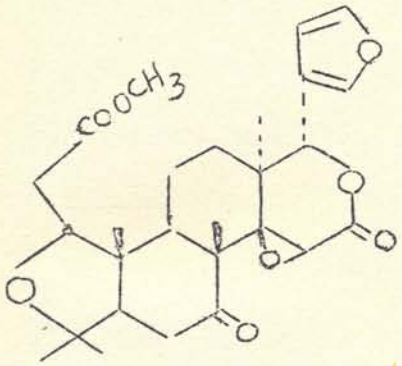
many steps



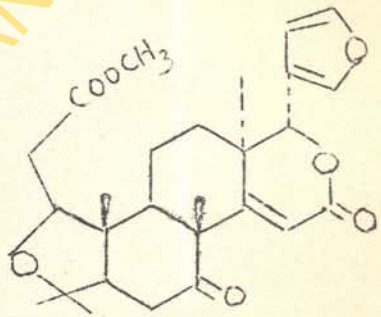
← ← ← Limonin (I)
many steps

XVI

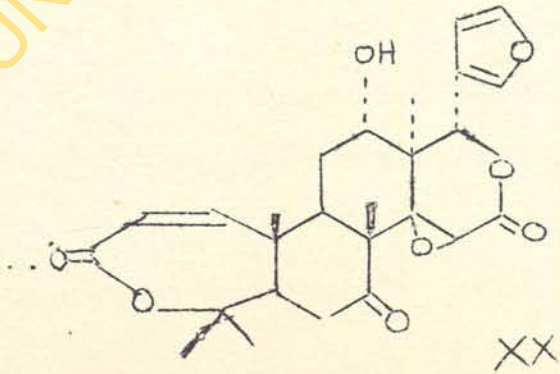
XXI



XIX



XX



XXII

action of acetic anhydride and pyridine.

Deacetylnomilin (XIV) was isolated by Dreyer from four Citrus species and from Poncirus trifoliata. Its structure was shown by spectroscopic studies and by its facile conversion to obacunone and nomilin.

From the interrelationships of the limonoids, nomilin, deacetylnomilin, obacunone and its acids, it appears, and evidence[7,8] suggests that the final stages in the formation of limonin are as follows:

deacetylnomilin (XIV) ⟶ nomilin (XV) ⟶ obacunone (XVI) ⟶ obacunoic acid (XVII) ⟶ isoobacunoic acid (XVIIIa) ⟶ limonin (I).

Zapoterin (XXII)

Zapoterin is closely related to obacunone. The isolation was reported in the original work of Kincl et al. on Casimiroa edulis[18]. The structure of zapoterin has been worked out[19a] from spectroscopic properties. Its infra red spectrum shows a hydroxy band and three well resolved carbonyl bands as well as bands due to a β-substituted furan ring. The n.m.r. spectrum showed resonances attributed to a β-substituted furan ring, an H-17 furfurylic singlet (δ 5.45) and an H-15 epoxy proton, an AB doublet identical with that of H-1 and H-2 of obacunone and five C- methyl groups. In addition, the n.m.r. spectrum showed a one-proton triplet at (δ 4.97). The sum of these

spectroscopic evidence indicates that zapoterin is a hydroxy-obacunone derivative having the structure (XXII).

But later, from the n.m.r. studies of Zapoterin and its acetate, Murphy et al.[19b] confirmed the structure of zapoterin to be an 11β-OH compound rather than the 12α- OH compound as earlier proposed by Dreyer.

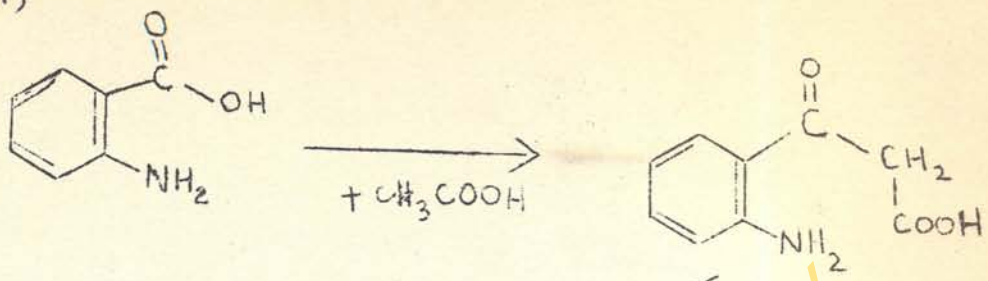
(ii) ALKALOIDS

From the point of view of alkaloid chemistry, the Rutaceae family is characterised by having a large number of bases of the anthranilic family. Biogenetically, most alkaloids isolated from the family Rutaceae could possibly be regarded as being derived from the amino acid, anthranilic acid, as postulated by Price[20] in the table shown in Scheme (iii).

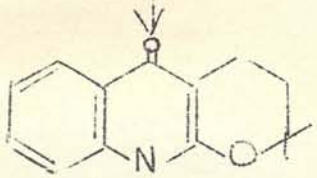
Price[21] has drawn the attention to the circumstance that the capability to add an isopentenyl unit to a wide variety of molecular types appears to be a biochemical characteristic of the Rutaceae family. This is supported to a large extent, considering the fact that not only the alkaloids, but also most of the coumarins isolated from this family of plants have been found to contain the isopentenyl group.

The Rutaceae family abounds in various types of furoquinoline alkaloids. The biogenetic pattern of these furoquinoline alkaloids is

Scheme (iii)



+ Isopentenyl radical



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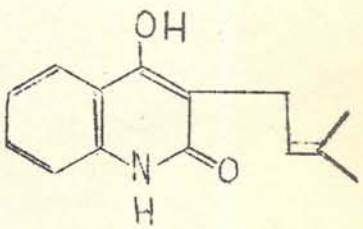
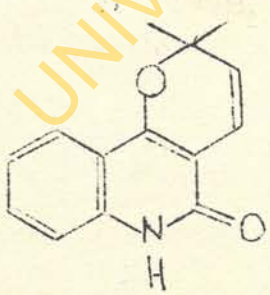
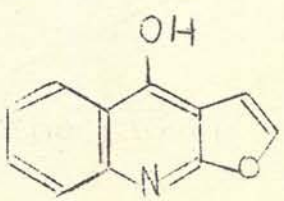




Flindersine group exemplified by Flindersine, Oricine



Furoquinoline group e.g. Dictamnine, the Fagarines

difficult to unravel. For instance, there is no good clue to the origin of the furan group. Robinson[22] suggests some possibilities (a) that the furan ring is a residue of the tryptophan side chain (b) that it is obtained by the degradation of an aromatic ring of the acridones or (c) that it arises in a manner analogous to the probable biogenesis of furo-coumarins (that is, condensation of a suitable intermediate with a 2,4-dihydroxy-quinoline derivatives).

The chemistry of some of these closely related alkaloids of the Rutaceae family is hereby briefly reviewed.

FUROQUINOLINE GROUP

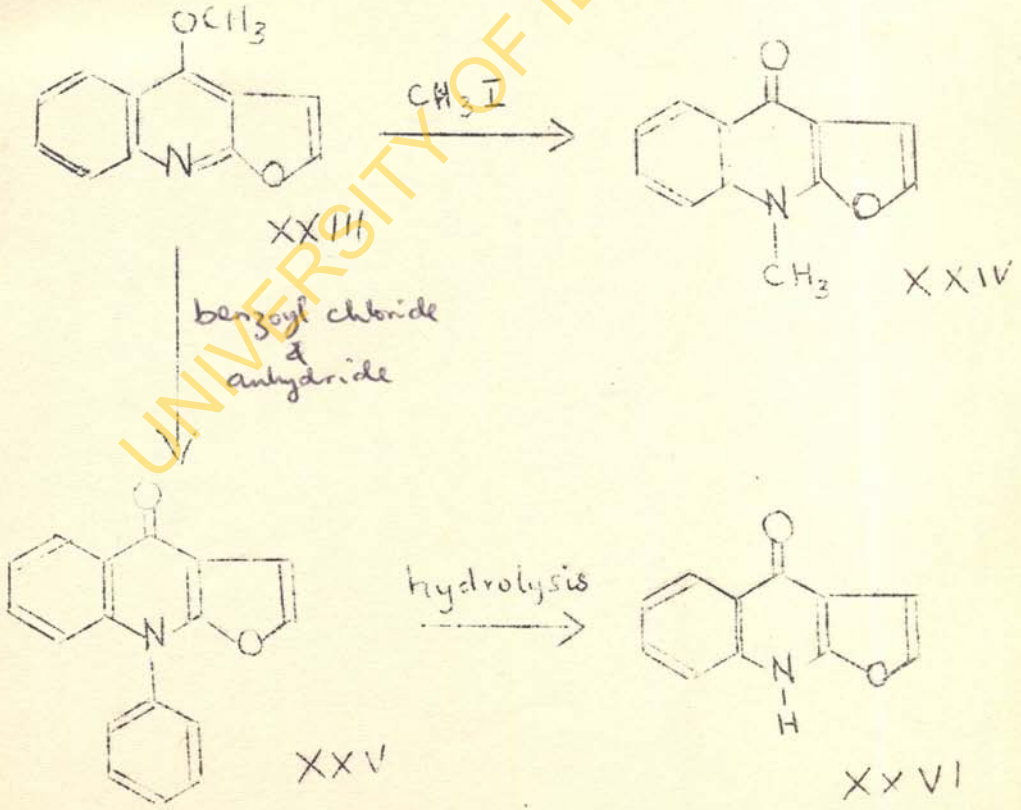
Dictamnine (XXIII) $C_{12}H_9O_2N$.

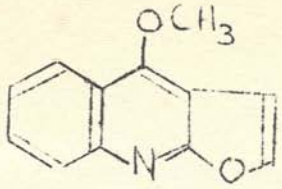
Dictamnine was first isolated by Thoms[23] from dittany root (Dictamnus albus Linn.). It crystallises in prisms m.p. 132°C-3°C. It was subsequently found in Skimmia repens by Asahina, Ohta and Inubuse[24] who showed that it contained one methoxy group and transformed at 80°C by methyl iodide into isodictamnine (XXIV) m.p. 188°C. Isodictamnine contains no methoxy group, a change recalling that of α- and γ-alkoxy quinolines to N-alkyl-quinolones[25]. With benzoyl chloride and anhydride, dictamnine yields N-benzoyl-nordictamnine (XXV) from which nor-dictamnine (XXVI) is obtained by hydrolysis. Oxidation of dictamnine by permanganate in acetone affords dictamnal (XXVII) and dictamnic acid (XXVIII). Dictamnic acid is converted by

hydrochloric acid into 2,4-dihydroxy quinoline.

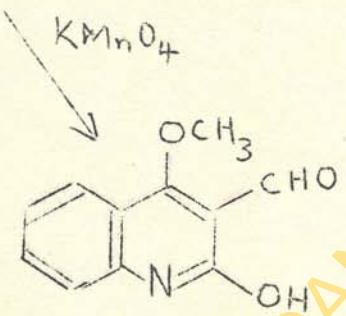
Dictamnal was shown[26] to be converted by hydrobromic acid in acetic acid into nor-dictamnal (XXIX), identical with 2,4-dihydroxy-3-aldehyde quinoline. The latter was synthesised and used to prepare Ψ -dictamnine (XXX).

Dictamnine occurs very widely in the plants of the Rutaceae family. It occurs in the Fagara genus (Fagara acumunata, Fagara dissoperma, Fagara maculosa), in the Casimiroa genus (Casimiroa edulis), in the Aegle genus (Aegle marmelos) and in the Afraegle genus (Afraegle paniculata) which would be discussed later in this work.

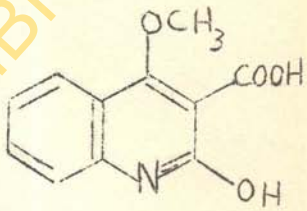




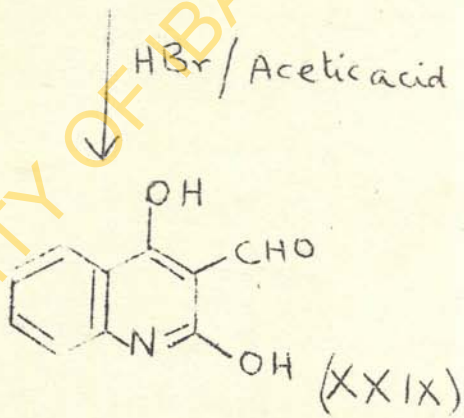
XXIII



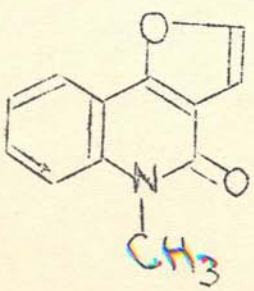
(XXVII)



(XXVIII)



(XXIX)

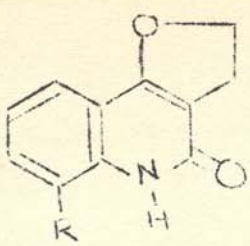


(XXX)

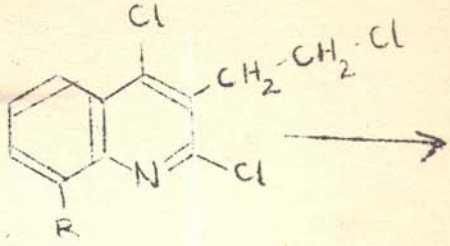
Dictamnine alongside with γ-fagarine (XXXVII) was synthesised in 1957 by Grundon and McCorkindale[27] by the series of reactions (XXXI) ——→ (XXXVI) in the scheme (V). Grundon and McCorkindale had shown[28] that the reaction of aniline or o-anisidine with ethyl-(2-ethoxy ethyl)-malonate gave exclusively the angular dihydrofurano-quinolones (XXXI, R=H, OCH_3) probably via 2,4-dihydroxy quinolines. Treatment of the angular dihydrofuranoquinolone (XXXI) with phosphorus oxychloride afforded 2,4-dichloro-3-(2')-chloroethyl-quinoline (XXXII, R=H, OCH_3). The trichloro compound (XXXII) was hydrolysed by an acid to give dichloro derivatives (XXXIII, R=H, OCH_3).

Chromatography of the chloroquinoline (XXXIII, R=H) on alkaline alumina effected cyclisation into the linear dihydrofuroquinoline (XXXIV, R=H) in about 40% yield but a more quantitative yield of (XXXIV, R=H) was obtained by reacting the chloroquinoline (XXXIII, R=H) with silver oxide in aqueous methanol. Both the dihydro-furanoquinolines (XXXIV, R=H, OCH_3) were prepared by the last method. Reaction of XXXIV with N-bromosuccinimide and treatment of the crude intermediate with diethyl aniline gave high yields of (XXXV, R=H,-OCH_3). Reaction of (XXXV, R=H) with sodium methoxide afforded the methoxy furoquinoline (XXXVI, R=H) identical in all respects with dictamnine.

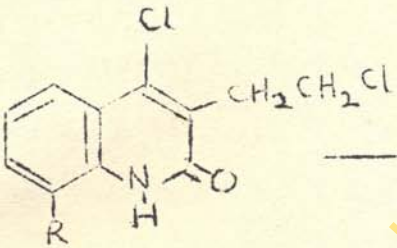
The chlorofuranoquinoline (XXXV, R= -OCH_3) was also converted by sodium methoxide into the dimethoxy compound (XXXVI, R= -OCH_3)



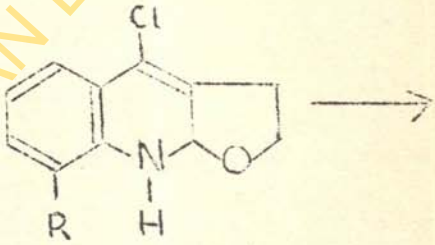
(XXXI)



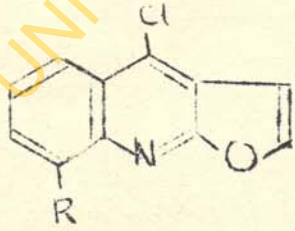
(XXXII)



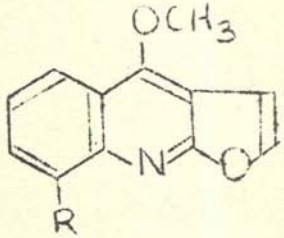
(XXXIII)



(XXXIV)



(XXXV)



(XXXVI)

indistinguishable from γ-fagarine (XXXVII) the isolation of which is discussed below.

The Fagarines

From the leaves of Fagara ooco (Gill) Engl., five alkaloids were isolated by Stuckert[29]. Two of these, β- and γ-fagarines, are discussed below. β-fagarine has been shown[30] to be identical with skimmianine.

γ-fagarine (XXXVII) $C_{13}H_{11}O_3N$

γ-fagarine (m.p. 139° - 140°) was obtained also from the mature bark of the bael fruit tree, Aegle marmelos (Correa)[31]. Its reactions are very similar to the reactions of dictamnine. Thus, like dictamnine, γ-fagarine is converted by methyl iodide at 100° into γ-isofagarine. The structure of γ-fagarine has been shown[32] to be 8-methoxy dictamnine.

The synthesis of γ-fagarine was done alongside with dictamnine by Grundon and McCorkindale[27].

β-fagarine (Skimmianine) (XXXVIII) $C_{14}H_{13}O_4N$

β-fagarine is the most wide-spread member of the group of alkaloids of the Rutaceae. It was first isolated from the leaves of Skimmia japonica (Thumb) by Honda.[33]. It occurs also in Chloroxylon swietenia D.C. (East Indian Satinwood).

Skimmianine crystallises out in colourless pyramids (m.p. 176°).

It was shown to contain 3-methoxy group and unreactive oxygen by Asahina and Inubuse[34] and a linear structure was assigned to the compound on the basis of the similarity of its ultra violet spectrum to that of dictamnine.

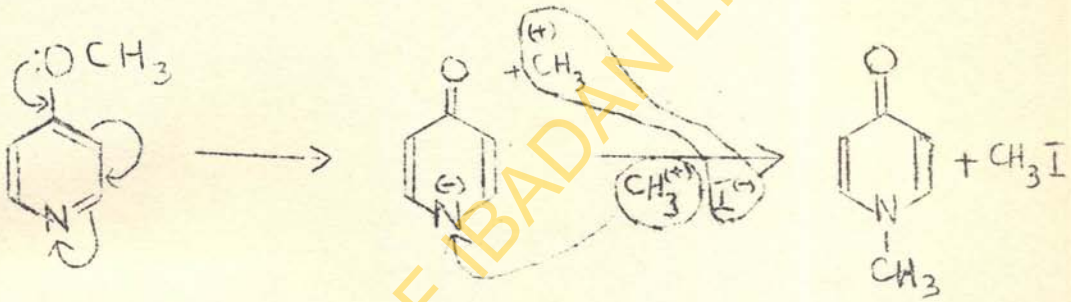
The reactions of skimmianine are very similar to those of dictamnine and Y-fagarine.

Kokusagine (XXXIX)

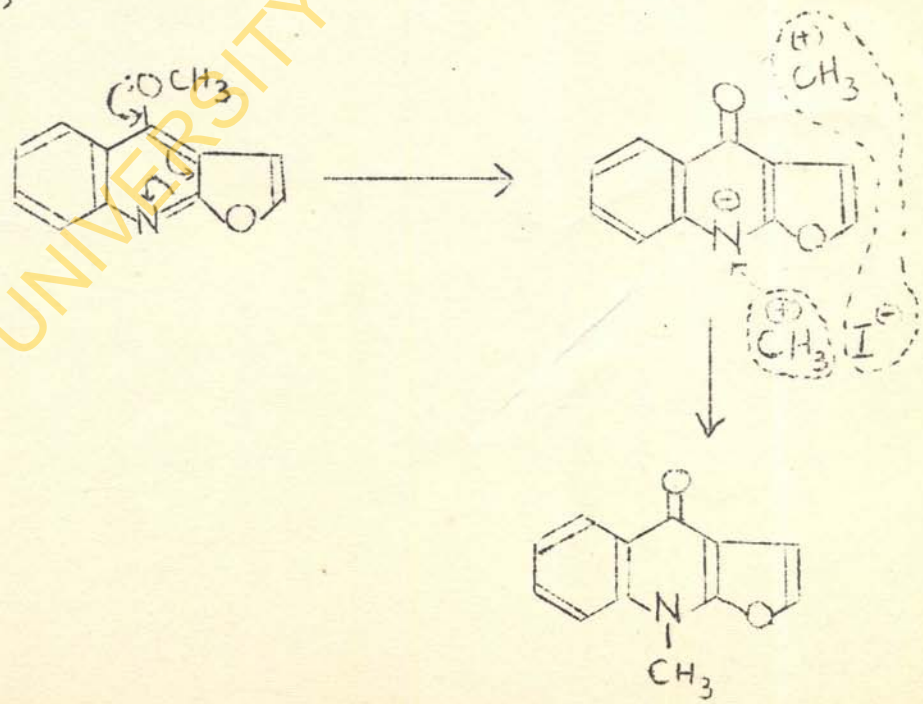
Kokusagine was first isolated from the root bark of Orixia japonica (Thumb) by Toresaka in 1933[35]. It was later found along with flindersiamine in the bark of Flindersia maculosa Lindl[36]. The structure of kokusagine (4,6,7-trimethoxy furoquinoline) (XXXIX) rests on its degradation to 6,7-dimethoxy-4-hydroxy-2-quinolone and by way of hydrogenolysis to 6,7-dimethoxy-3-ethyl-4-hydroxy-2-quinolone (XL). The hydrogenolysis reaction is similar to what was encountered when hydrogenation of dictamnine was attempted as would be seen later in this work. (The product of the attempted hydrogenation of dictamnine was 4-methoxy-3-ethyl-2-quinolone).

Kokusagine also undergoes reactions typical of the other linear furoquinoline alkaloids. Thus, like dictamnine, kokusagine is converted to isokokusagine by boiling with methyl iodide.

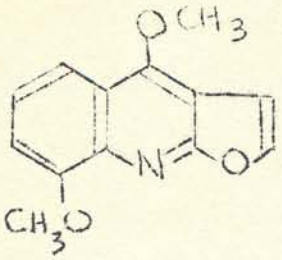
The mechanism of this reaction could be explained probably by the assumption that the methoxy quinoline group rearranges to give N-methyl quinolone as shown below. This rearrangement is parallel to the rearrangement of 4-methoxypyridine by methyl iodide to give N-methyl-γ-pyridone.



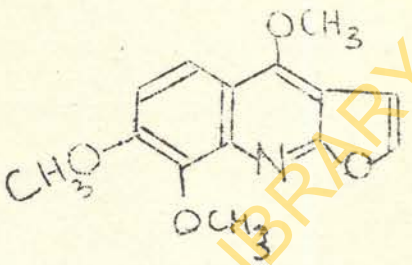
So, with dictamnine



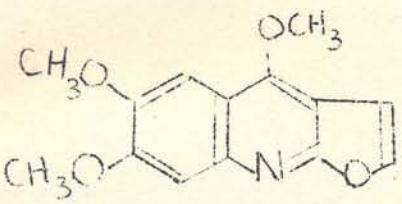
Scheme vi



(XXXVII)

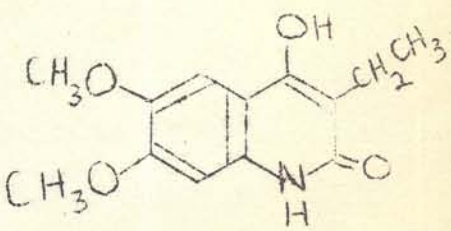


(XXXVIII)

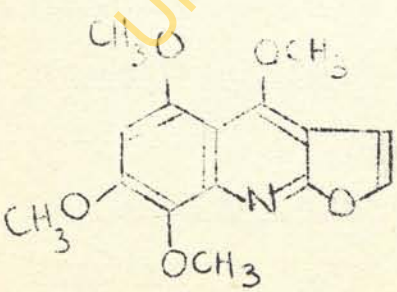


(XXXIX)

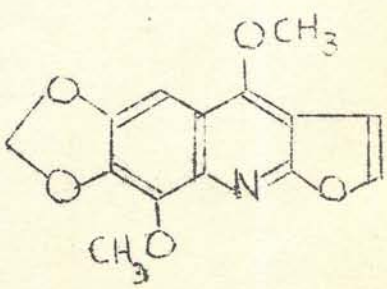
hydrogenolysis



XL



(XLI)



(XLII)

Acronycidine (XLI)

This is 4,5,7,8 -tetramethoxy furoquinoline first isolated from the bark of Melicope fareana[37]. Like dictamnine or kokusagine, acronycidine is converted to iso-acronycidine when boiled with methyl iodide. The most characteristic property of acronycidine and its derivatives is the ease with which they undergo oxidative demethylation with either nitric or nitrous acid to give 1,4-quinones.

Flindersiamine (XLII)

This alkaloid has the structure 6,7-methylene dioxy-8-methoxy dictamnine (XLII). It is degraded to 6,7-methylene dioxy-8-methoxy-4-hydroxy-2-quinolone and it undergoes the usual reactions of dictamnine, that is, conversion to iso-flindersiamine with methyl iodide and probably the rupture of the furan ring by permanganate.

Flindersiamine was first isolated by Cannon et al. in 1952 from Flindersia bourjotiana F. Muell[38]. Cannon and co-workers encountered flindersiamine as a constant melting point mixture with skimmianine. The alkaloid was later found along with kokusagine in the bark of Flindersia maculosa Lindl.[36]

THE LUNASIA ALKALOIDS

Lunacridine $C_{17}H_{23}O_4N$ (XLIII)

Lunacridine is a secondary alcohol which exists with its

quinolinium salt, lunasine (XLVI) in Lunasia amara Blanco[39]. It was first isolated by Boorsma in 1904[40] and subsequently Steldt and Chen in 1943[41]. Lunacridine gives large colourless needles from ethyl acetate m.p. 83.5°C. It contains two methoxy groups and one methylimino group. The ultraviolet absorption spectrum is characteristic of a 2-quinolone. The infra-red spectrum is also consistent with a quinolone structure, with the carbonyl frequency at ν_{max} 1633 cm^{-1}. Lunacridine is insoluble in alkali but contains a hydroxyl group as shown by infra-red absorption at 3370 cm^{-1} and by the formation of a monoacetate derivative.

Vigorous treatment with acid converts lunacridine in part to a more basic substance identical with the alkaloid lunacrine (XLIV) in infra-red spectrum and other physical properties, but differing in optical rotation. Lunacridine is optically active.

Goodwin and Horning[39] showed lunacridine to be 4,8-dimethoxy-3(3'-methyl-2'-hydroxy-butyl)- 1-methyl-2-quinolone (XLIII) by its formation when 8-methoxy-4-hydroxy-3-(3'-methyl-2'-hydroxy-butyl)-1-methyl-2-quinolone (XLV) obtained by the action of ethanolic potassium hydroxide on lunacrine was methylated with diazomethane.

Acid catalysed cyclisation of lunacridine gives rise to lunacrine.

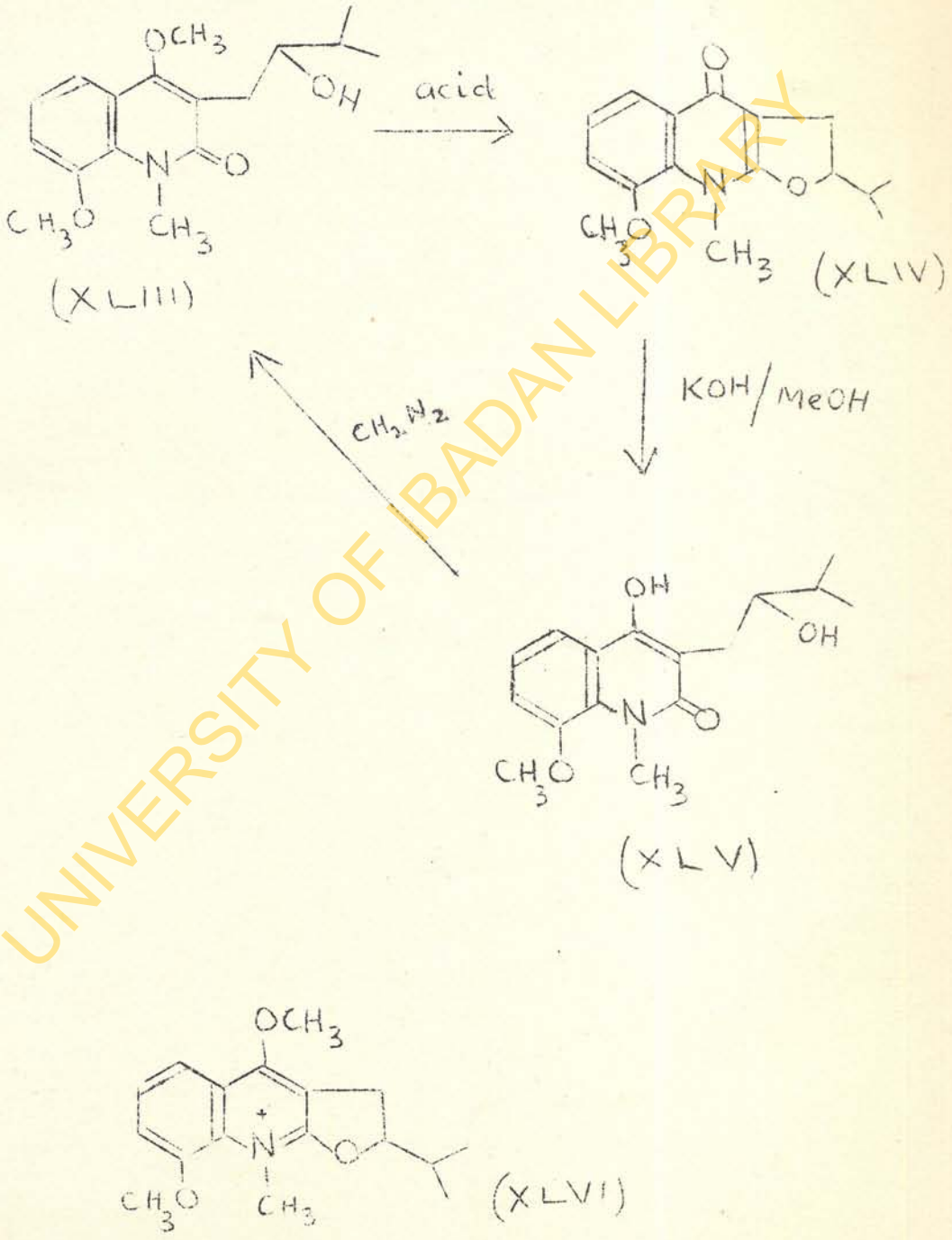
Lunacrine (XLIV)

Lunacrine $C_{16}H_{19}O_3N$ m.p. 114° was first isolated by Boorsma[39] in 1900 from the bark of Lunasia costulata Miq. It exists in other Lunasia species such as Lunasia amara Blanco[39], Lunasia quercifolia[39]. Like lunacridine, lunacrine is optically active and the naturally occurring isomer is (-) lunacrine. The ultraviolet spectrum of lunacrine in methanol was unaffected by the addition of alkali, but a marked change occurred on acidification, the long wave length bands (313 mμ and 326 mμ) exhibiting a hypsochromic shift (300 mμ), thus showing that the nitrogen atom is a part of the chromophore.

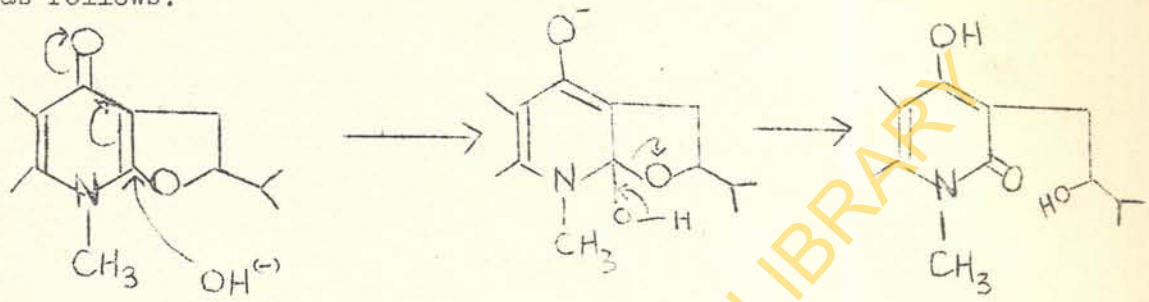
Lunacrine, on refluxing with 15% aqueous alcoholic potassium hydroxide solution, was converted in good yield to an alkali-soluble substance having the same number of carbon atoms as lunacrine but differing empirically by the addition of water. The produot contained one methoxy group and one methylimino group and was identified as (XLV).

Treatment of (XLV) with ethereal diazomethane gave a non-crystallizable oil which was converted to a crystalline hydroperchlorate. The orystalline base obtained from the hydroperchlorate was found to contain one methoxy group more than lunacrine and its alkaline transformation product. The empirical formula and physical constants of the new base were nearly the same as given for lunacridine (XLIII).

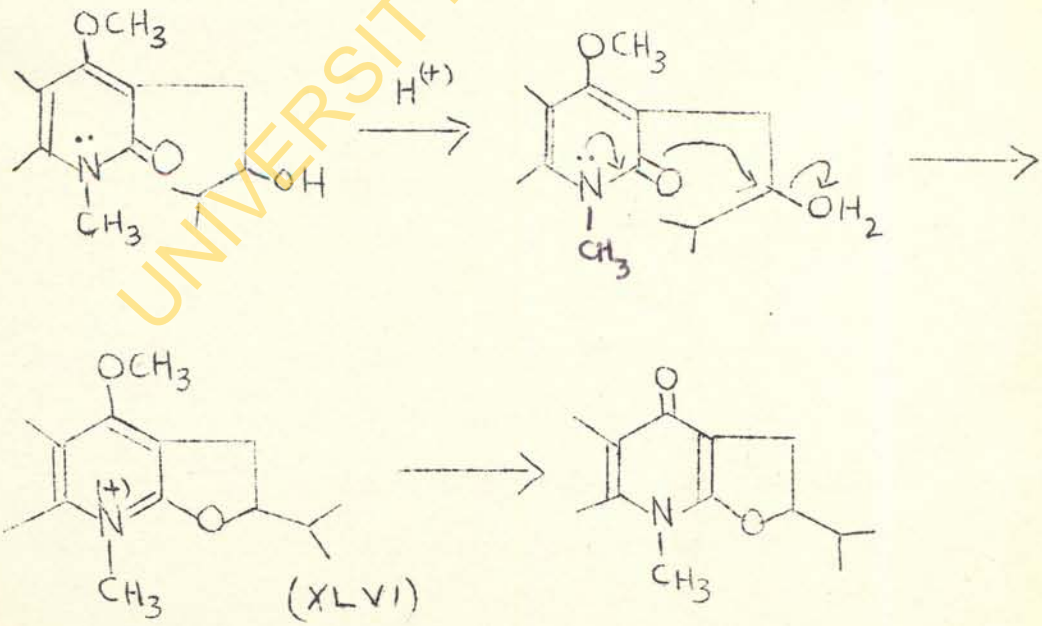
Scheme (vii)



Goodwin and Horning[39] suggested a mechanism for the alkaline hydrolysis of lunacrine to the 3-alkyl-4-hydroxy-2-quinolone (XLV) as follows:



And the acid cyclisation of lunacridine to lunacrine as going through the quartenary 4-methoxy-1-methyl quinolinium structure (XLVI) as follows:



Lunasine (XLVI)

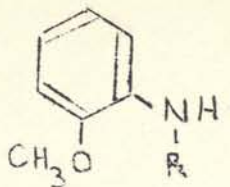
Lunasine is the quartenary 4-methoxy-1-methyl quinolinium structure (XLVI) corresponding to the 1-methyl-4-quinolone alkaloid, lunacrine (XLIV). It is the main constituent of the water-soluble alkaloids of Lunasia queroifolia[39]. The structure and properties of the 4-methoxy quinolinium salts obtained from 4-quinolones are of interest in connection with the conversion of 4-alkoxy quinolines to N-alkyl quinolones. For example, the well-known conversion of the furoquinoline alkaloids (4-methoxy compounds) to the iso-alkaloids (1-methyl-4-quinolones) by the action of methyl iodide might, by analogy with lunacrine, have been expected to give rise to a quartenary quinolinium iodide analogous to the methyl lunacrium salts. The conversion of dictamnine and its congeners into their iso-forms when heated with methyl iodide is an example of the above reaction which possibly goes via the quarternary ion as previously discussed.

Lunacridine and Lunacrine Syntheses

The syntheses of both lunacridine and lunacrine alkaloids were undertaken by Clarke and Grundon (1964)[41].

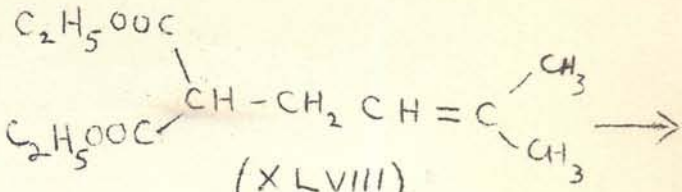
3-substituted-2, 4-dihydroxy quinolines and their 1-methyl derivatives can be prepared conveniently from aromatic amines and substituted malonic esters in diphenyl ether[42]. It was found that

Scheme (viii)

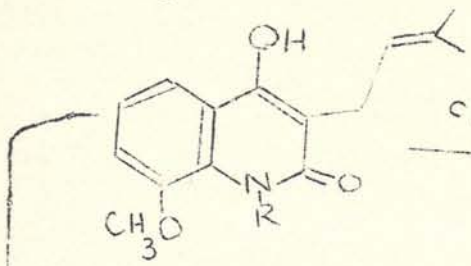


(XLVII)

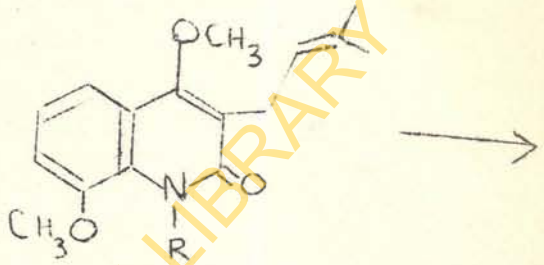
+



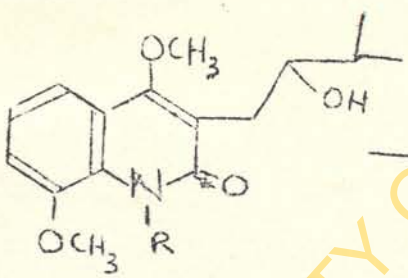
(XLVIII)



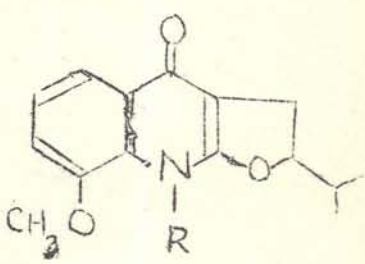
(XLIX)



(L)

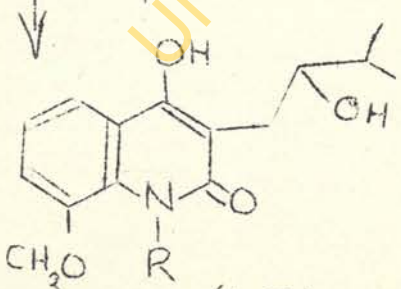


(XLIII, R = CH_3)

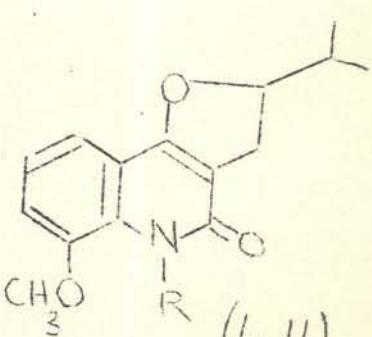


XLIV, R = CH_3

+



(LI)



(LII)

diethyl-(3-methyl but-2-enyl)-malonate (XIVIII) reacts in refluxing diphenyl ether with N-methyl-o-anisidine (XIVII, R=CH_3) to give the unsaturated 4-hydroxy-2-quinolone compound (XLIX). The series of reactions leading to the quinolones is shown in scheme (viii).

The conversion of the 1-methyl quinolone (XLIX, R = CH_3) to the secondary alcohol (LI, R = CH_3) was effected by diborane followed by alkaline hydrogen peroxide. Treatment of the 4-hydroxy quinolone (LI, R = CH_3) with diazomethane gave (±) lunacridine (XLIII). Lunacridine was then cyclised to lunacrine by methods of Goodwin and Horning[39].

FLINDERSINE GROUP

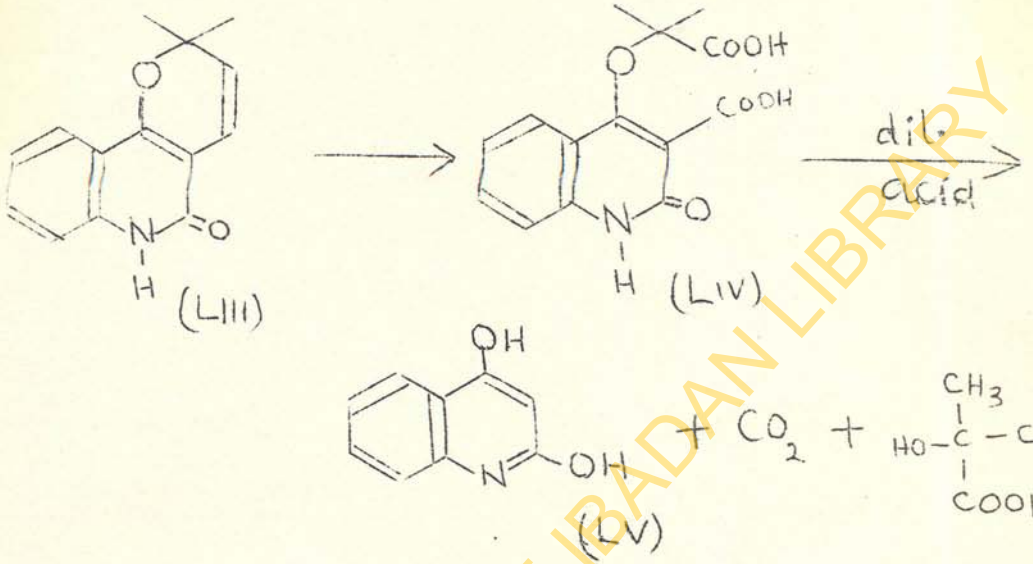
Flindersine (LIII) $C_{14}H_{13}O_2N$.

Flindersine was first isolated from the wood of Flindersia australis by Mathes and Schreiber[43] who assigned the molecular formula $C_{23}H_{26}O_7N_2$ to the compound, but later, Brown, Hobbs, Hughes and Ritchie[43] showed the formula to be correctly represented as $C_{14}H_{13}O_2N$ and to possess the structure (LIII).

Permanganate oxidation of flindersine gave flindersinic acid (LIV) which was hydrolysed by dilute acid to give 4-hydroxy-2-quinolone, α-hydroxy-iso-butyric acid and carbon dioxide.

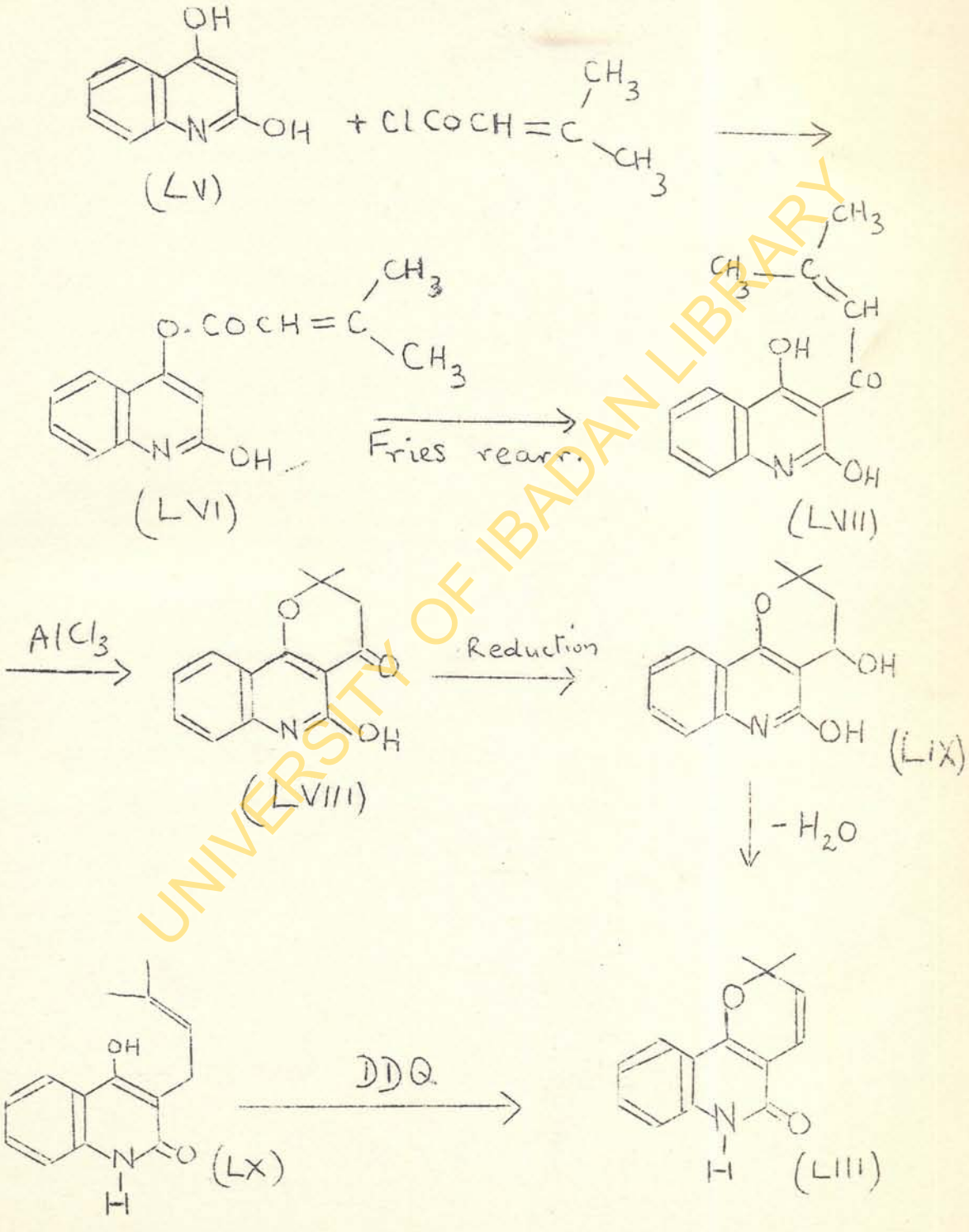
Flindersine is easily reduced to the dihydroderivative (LXII) by hydrogen in presence of platinum or Raney nickel but not easily reduced

in presence of 10% palladium on charcoal.



The synthesis of flindersine in poor yield was carried out by Brown, Hughes and Ritchie[44]. The synthesis involved the preparation of 2,4-dihydroxy quinoline (LV) by heating aniline with malonic ester in diphenyl ether. The quinoline was then esterified with ββ-dimethyl acryloyl chloride to give the ester (LVI) and Fries rearrangement gave probably the 3-acyl compound (LVIII) which was then isomerised by aluminium chloride in nitrobenzene to the cyclic ketone (LVIII). Reduction of the ketone gave the alcohol (LIX) which was then dehydrated by thionyl chloride or phosphorus pentoxide to give the alkaloid (LIII).

A more facile and shorter method of preparing flindersine was recently developed by Piozzi and co-workers[45].

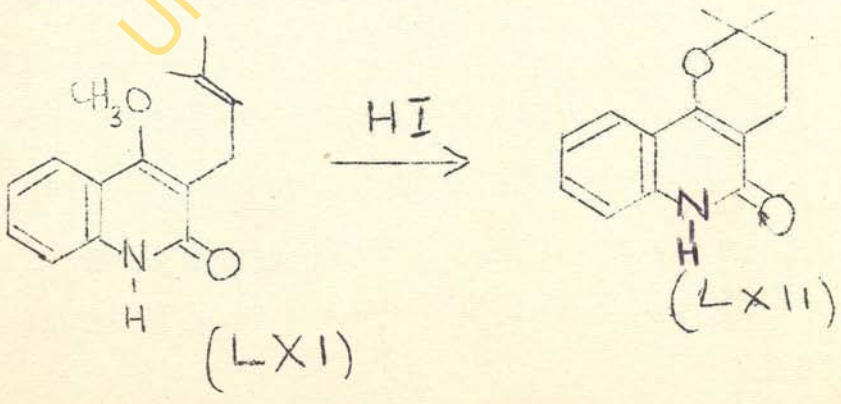


3-(γγ-dimethyl allyl)-4-hydroxy-2-quinolone (LX) was used as the starting material. Refluxing the last compound (LX) with 2,3-dichloro-5,6-dicyano benzoquinonone (DDQ) in dry benzene for just two hours gave the alkaloid (LIII) in 56% yield.

Atanine (LXI) $C_{15}H_{17}O_2N$ m.p. 133°C.

This new alkaloid was isolated by Eshiet and Taylor in 1966[46] from Fagara zanthoxyloides Lam. (Ata, Yoruba).

It was shown to be weakly basic and the infra-red spectrum showed a band at 1600 cm^{-1}, suggesting that the compound was a 2-quinolone compound. From the n.m.r. spectrum and on the basis of its close similarity to flindersine, the structure of the alkaloid was elucidated as 3-(3'-methyl but -2'-enyl)-4-methoxy-2-quinolone (LXI). That this structure was true for atanine was evident from the fact that treatment of atanine with hydriodic acid[46] afforded a compound, identical in properties with dihydro flindersine (LXII).



Atanine was hydrogenated to dihydroatanine and the dihydroatanine was synthesised by reacting 4-hydroxy-2-quinolone with isovaleryl chloride and aluminium chloride. The 3-isovaleryl-4-hydroxy-2-quinolone obtained was reduced by sodium borohydride to the 3-isoamyl-4-hydroxy-2-quinolone in accordance with the method of Huffman and Browder.[47] The 3-isoamyl-4-hydroxy-2-quinolone was methylated (diazomethane) to 4-methoxy compound, identical in properties with dihydroatanine

But atanine itself could possibly be prepared by the method of Clarke and Grundon[41]. Thus, heating aniline with diethyl-(3-methyl but- 2-enyl) malonate in diphenyl ether should give the 4-hydroxy-3-dimethyl allyl -2-quinolone which should then methylate to give 4-methoxy-3-dimethyl allyl-2-quinolone (atanine).

2 - ARYL - 4 - QUINOLONE GROUP

Apart from the 2-quinolone and the furanoquinoline alkaloids which exist in plants of the Rutaceae, a few 2-phenyl-4-quinolones have been reported isolated. Two examples of such alkaloids are:

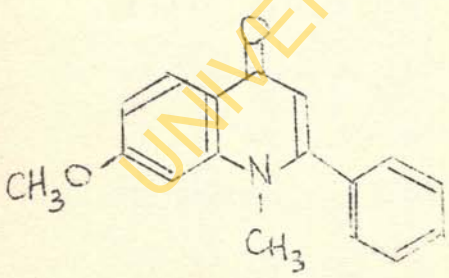
(a) Eduleine

Eduleine (7-methoxy-1-methyl-2-phenyl-4-quinolone) (LXIII) was first isolated by J. Iriarte and co-workers[48] from the bark of Casimiroa edulis Llave et Lex. and later from the bark of Lunasia quercifolia by Johnstone, Price and Todd[49].

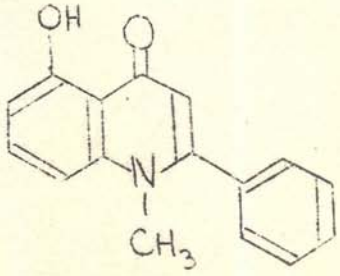
The alkaloid was shown to form mono and dibromo derivatives, but resistant to attack by acids, alkalis, oxidising and reducing agents. It was shown to contain one methoxy group and one methylimino group. It showed the characteristic 4-quinolone infra-red absorption at 1618 cm^{-1} and its infra-red absorption at 704 cm^{-1} was in accordance with a mono substituted benzenoid ring. On these spectral bases, the structure 7-methoxy-1-methyl-2-phenyl-4-quinolone (LXIII) was assigned to the alkaloid and this was confirmed by synthesis[49] from m-anisidine and ethyl-formyl-phenyl acetate.

(b) 5-hydroxy-1-methyl-2-phenyl-4-quinolone (LXIV)

This alkaloid has recently been isolated from Lunasia quercifolia by Hart, Johns and Lamberton[50] and its structural elucidation was based on the spectroscopic studies.



(LXIII)



(LXIV)

(iii) COUMARINS

Coumarins form one of the most important groups of natural products. All, but a few, are derived from plants especially Leguminosae, Rutaceae and Umbelliferae; the others come from animals and microorganisms. Some coumarins, for example, the simple coumarin itself, psoralene and dihydro coumarin occur as glycosides of the corresponding cinnamic acids. Although the simple coumarin is a natural product, it is believed[51] that the true parent of all naturally occurring coumarin is 7-hydroxy coumarin (umbelliferone).

The family Rutaceae is known to store a large number of coumarins. The Meliaceae family rarely stores coumarins, but during the course of the general survey of the Meliaceae, it was found[52] that a member of the family, Ekebergia senegalensis contained as a major product, a coumarin (8-methoxy-4-methyl coumarin). The occurrence of this coumarin in this plant of the Meliaceae further strengthens the view that the Rutaceae is very closely related to the Meliaceae.

A few of the very large number of the structurally related coumarins of the Rutaceae plants are hereby reviewed.

Bergapten (LXV)

Bergapten $C_{12}H_8O_4$ (m.p. 191°C) was isolated from bergamot oil as early as 1837 and it is wide-spread in the Rutaceae family, occurring in various species of Fagara, Ruta, Skimmia, Citrus,

Pimpinella and Casimiroa. Thoms and Baetche[53] showed that it is a furocoumarin with a linear type of molecule by nitrating bergapten. The nitro compound (LXVI) was reduced to the aminobergapten (LXVII) and the amino compound was oxidised to a compound identified as a 1,4-quinone, bergapten quinone (LXVIII).

Recently, Dreyer[8] reported a good yield of bergapten together with imperatorin (LXXIV) in Poncirus trifoliata.

Xanthotoxin (LXIX) $C_{12}H_8O_4$ (m.p. 146°)

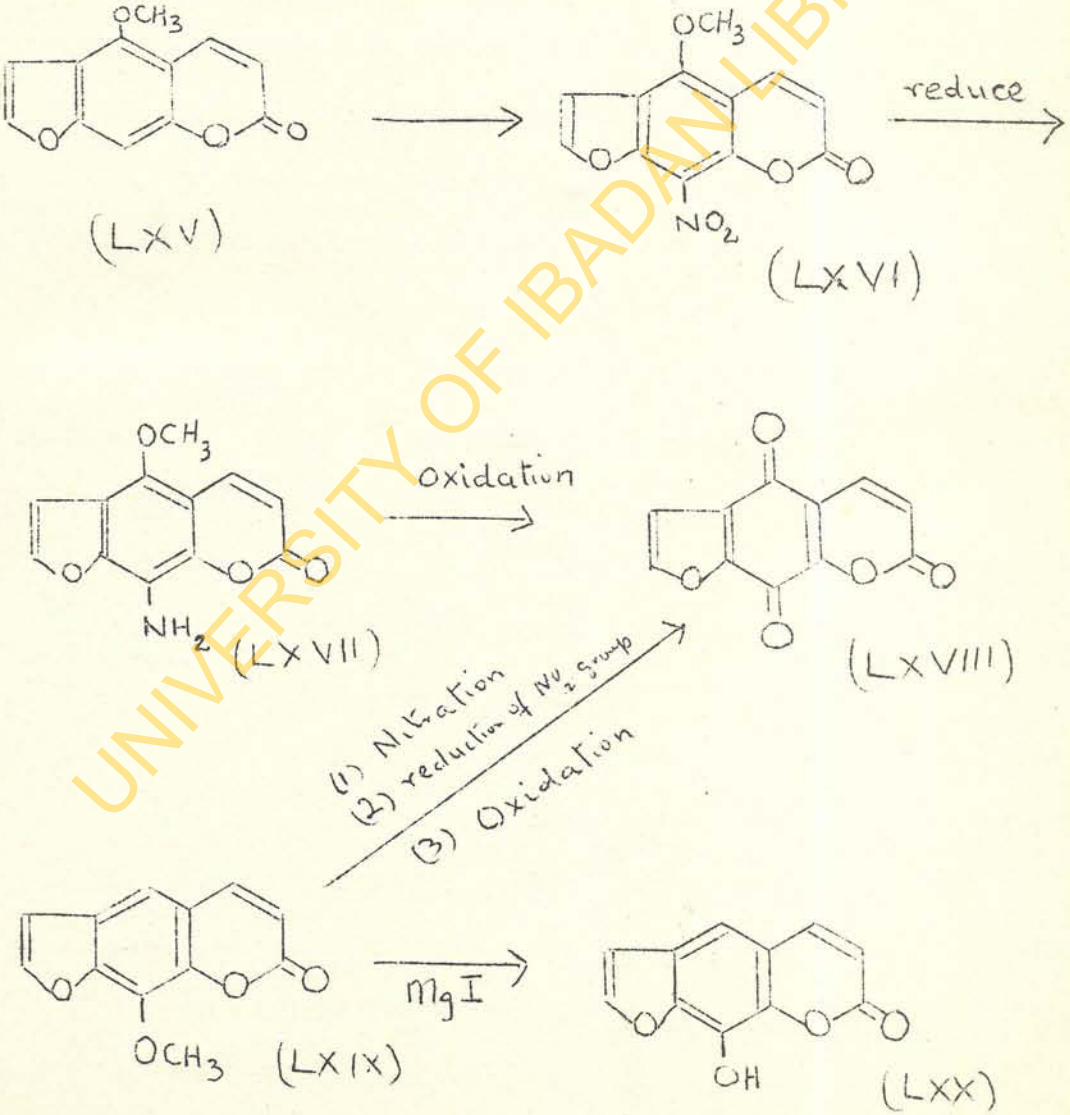
This is isomeric with bergapten and it has been isolated from a number of rutaceous plants, for example, from Fagara xanthoxyloides Lam; and various species of Ruta. Like bergapten, Thoms[54] recognised the presence of furan and coumarin rings and converted the compound to bergapten quinone by nitration, reduction of the nitro compound to the amino compound, followed by the oxidation of the amine.

Spath and Pailer[55] synthesised xanthotoxin from 6,7-dihydroxy coumarin by malic acid condensation to give dihydroxanthotoxol, followed by methylation and dehydrogenation on a palladium catalyst.

In the furocoumarin series, demethylation by the usual reagents is usually attended with difficulties owing to the sensitivity of the furan ring. However, demethylation can be effected by

magnesium iodide[56a] at 160° or by aluminium chloride in the absence of a solvent[56b].

Demethylation of xanthotoxin either by magnesium iodide or aluminium chloride afforded xanthotoxol (LXX) (m.p. 251°) $C_{11}H_6O_4$ which is itself a very minor component of the coumarin mixture of Angelica archangelica.



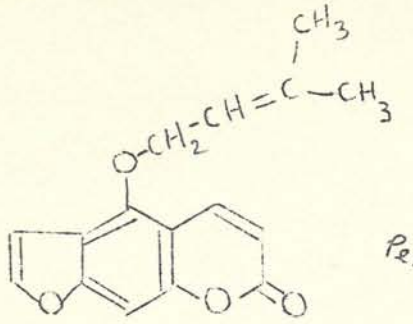
Isoimperatorin (LXXI)

Isoimperatorin $C_{16}H_{14}O_4$ (m.p. 109°) is the phloroglucinol based analogue of the pyrogallol derivative imperatorin (LXXIV). Isoimperatorin was isolated from Imperatoria ostruthium L. which yields several other coumarins. Spath and Kahovec[57] found that the acid hydrolysis of isoimperatorin yielded bergaptol (LXXII) (demethylated derivative of bergapten). Interaction of isoimperatorin with perbenzoic acid yielded an epoxide, identical with the natural coumarin, oxypeucedanin (LXXIII).

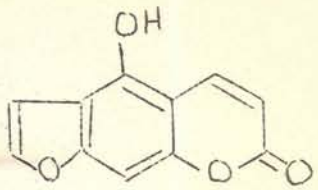
Spath and Dobrovolyny[58] synthesised isoimperatorin from bergaptol and γγ-dimethyl allyl bromide. They found that the hindered position of the hydroxy group made esterification usually difficult.

Imperatorin (LXXIV)

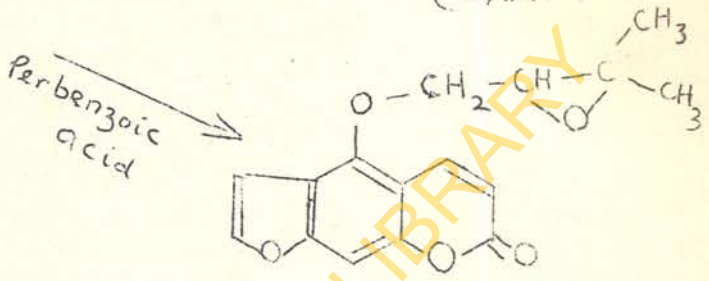
Imperatorin $C_{16}H_{14}O_4$ was identified as the γγ-dimethyl ether of xanthotoxol by Spath and Holzen[59]. They noted that this compound (LXXIV) on acid hydrolysis or hydrogenolysis yielded xanthotoxol (LXXV) and that oxidation with chromic acid yielded acetone. Imperatorin easily isomerises to allo-imperatorin (LXXVI). Imperatorin is a constituent of Imperatorin osthruthum L., Aegle marmelos (Correa), Poncirus trifoliata and, as would be seen later in this work, two West African rutaceous plants Afraegle paniculata and



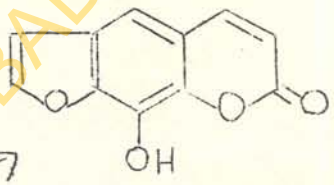
(LXXI)



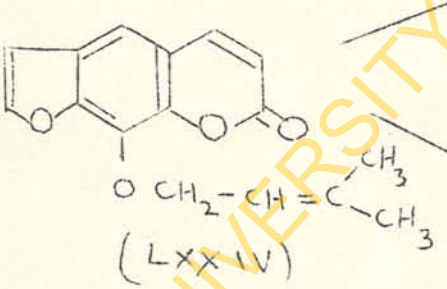
(LXXII)



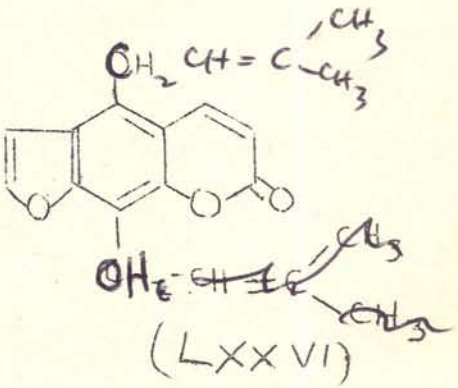
(LXXIII)



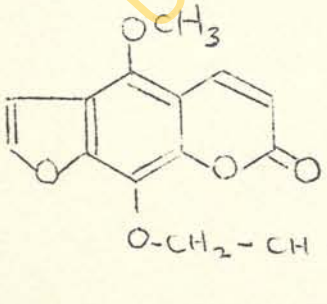
(LXXV)



(LXXIV)



(LXXVI)



(LXXVII)

Clausena anisata.

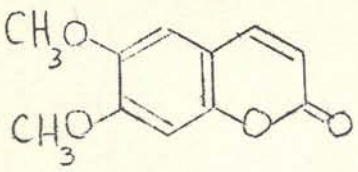
Phellopterin (LXXVII)

Phellopterin $C_{13}H_{16}O_5$ (m.p. 102°) was first isolated by Noguchi and Kawanami[60] from Phellopterus littoralis Benth, and later from the root of Angelica glabra. It differs from imperatorin only by the presence of an additional methoxy group and could be regarded as 5-methoxy imperatorin. Phellopterin has recently been shown by Dreyer[19] to co-exist with the limonoids zapoterin, 7α-obacunol, and deacetylnomilin in Casimiroa edulis Llave et Lex.

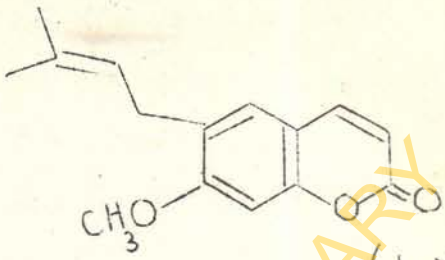
Some other known simple Coumarins from plants of the Rutaceae

Apart from the furocoumarins, the plants of the Rutaceae family abound in simple substituted coumarins. A few of these coumarins are:

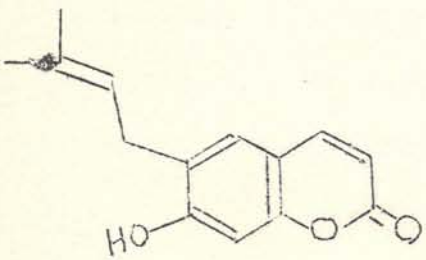
Aesculetin dimethyl ether (6,7-dimethoxy coumarin) (LXXVIII) from Fagara macrophylla,[61] Suberosin (7-methoxy-6-isopentenyl coumarin) (LXXIX) from Zanthoxylium flavium[61] and 7-demethyl-suberosin (LXXX) extracted from Chloroxylon swietenia.[61]. From the roots of Toddalia aculeata, Toddaculine (5,7-dimethoxy-6-isopentenyl-coumarin) (LXXXI) m.p. 95°C was extracted[62].



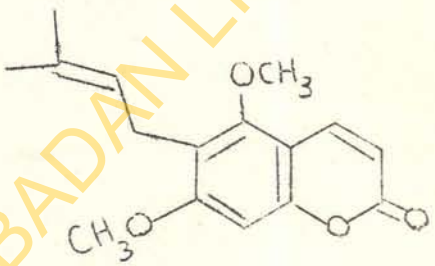
(LXXVIII)



(LXXIX)



(LXXX)



(LXXXI)

From the West African species of the Meliaceae family, a large number of limonoids have been isolated in this Department. From the Citrus genus of the Rutaceae family, many limonoids have been obtained and some plants of other genera in this family have been shown to contain limonoids as well as alkaloids with some coumarins as minor constituents. For example, Dictamnus albus has been found to be a source of the alkaloid dictamnine as well as the limonoid dictamnolide (identified as rutaevin). The alkaloids dictamnine and eduleine and the coumarin phellopterin have been obtained from

Casimiroa edulis which also stores the limonoid zapoterin. But no West African species of the Rutaceae has so far been shown to contain limonoids. It was, therefore, decided to investigate the West African species of some Rutaceae genera for their limonoid contents. Three West African species of the Fagara genus namely F. leprieurii, F. lamarei and F. zanthoxyloides have already been investigated and none of the three plants was shown to contain limonoids. We hoped that other genera would give some limonoids and we, therefore, decided to examine species of different genera.

INVESTIGATIONS AND DISCUSSIONS

In the course of this study, three West African species of three different genera of the family Rutaceae were investigated. They were:

(a) Afraegle paniculata (Schum and Thonn)

(b) Clausena anisata (Willd)

(c) Oricia suaveolens (Engl.)

AFRAEGLE PANICULATA (Schum and Thonn)

This plant was formerly classified under the genus Aegle on the basis of its close relationship to Aegle marmelos (Correa). It is commonly found in Ghana, Togo, Dahomey and Southern Nigeria. It is usually planted at the back of many houses in Oyo Province, Nigeria. The wood extracted was brought from Fiditi, (Oyo Province Nigeria).

It is a small tree, but said to occur wildly attaining 30 feet to 40 feet in height. The fruit is orange-like, but with a tough shell and is usually about 2 - 4 inches in diameter. The branchlets are grey-green and its flowers are white and fragrant. The Yoruba name is "Shanga".

Two crystalline substances A and B were isolated from the

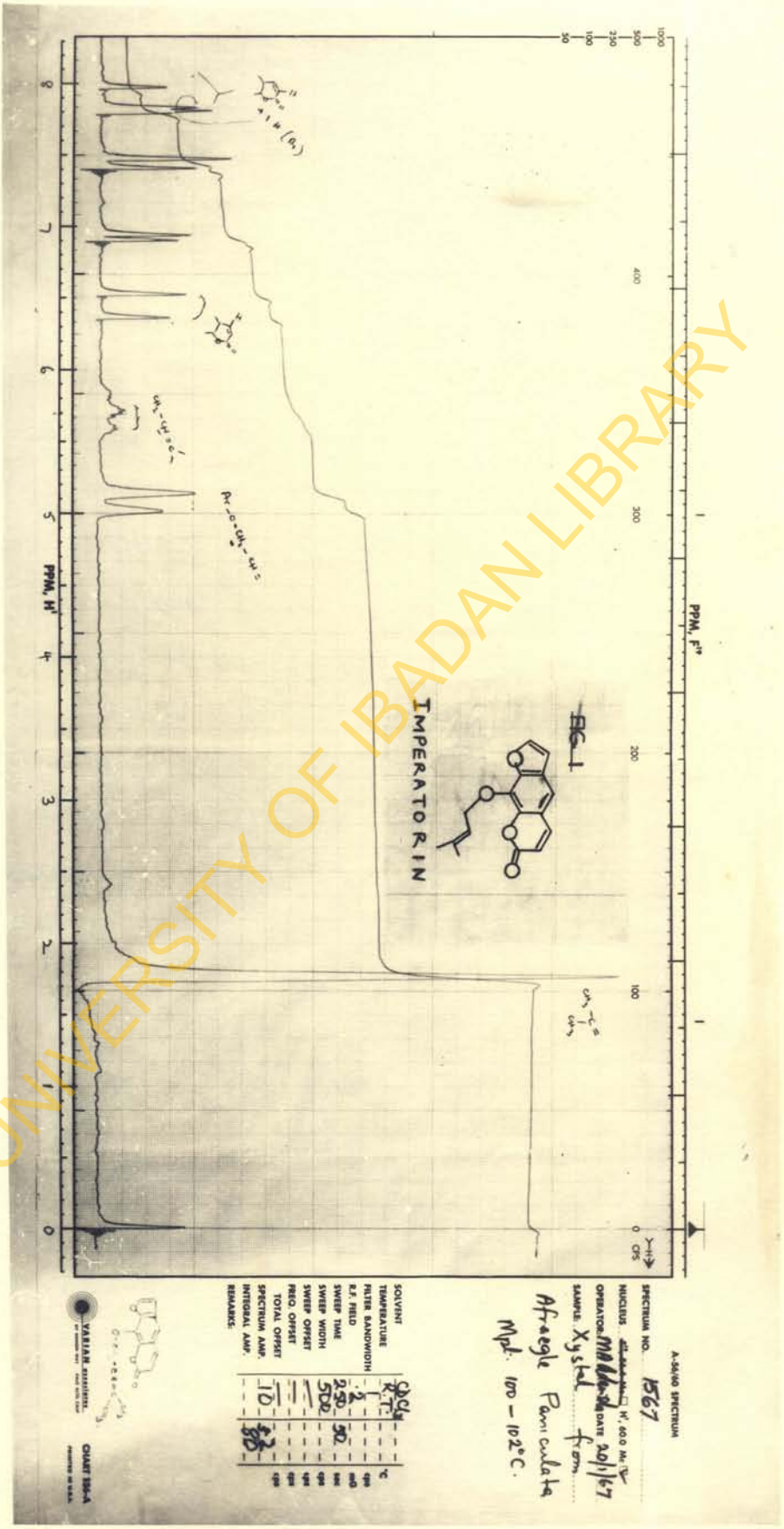
wood. A was found to be a known furocoumarin and B a known furoquinoline alkaloid.

Compound A m.p. 100° - 102°

The petroleum ether (60° - 80°) extract of the wood was concentrated and on allowing to stand overnight, some crystals appeared. The crystals were collected, washed with petroleum ether and recrystallised from methanol to give light yellow crystals m.p. 92°C. The n.m.r. spectrum of the crystalline substance showed that it was a mixture. The substance showed two spots on the thin layer chromatoplate indicating that it was probably a mixture of two substances. The mixture was then dissolved in benzene and put on alumina column. Benzene brought down a new crystalline substance A, recrystallised from methanol, m.p. 100°C - 102°C.

The other component did not come down from the column.

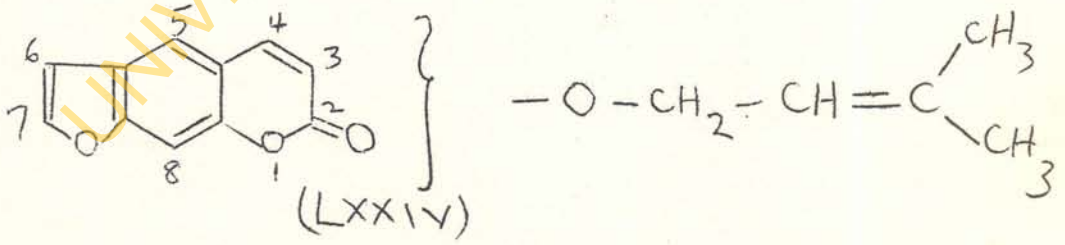
The n.m.r. spectrum of the substance A, (fig.1) showed the presence of two methyl groups on a double bond at δ 1.77 (singlet), an ethylenic proton showing as a triplet at δ 5.73 (J = 8 c/s), a methylene group centred at δ 5.09 as a doublet (J = 8 c/s). These signals indicated the presence of $-CH_2 - CH = C\begin{matrix}CH_3\\CH_3\end{matrix}$ group. The downfield position of the methylene group suggested that the isopentenyl group was probably joined through an ether oxygen to a



benzene ring rather than directly to the benzene ring. The n.m.r. spectrum also showed the presence of two furan protons at δ 7.45 (doublet, J = ~ 3 c/s) for the α-proton and at δ 6.93 (doublet, J = ~ 3 c/s) for the β-proton. There were two AB doublets at δ 6.44 (J = 9 c/s) and at δ 7.50 (J = 9 c/s) attributed to the two coumarin protons. There was a singlet at δ 7.83 attributed to a benzenoid proton. The infra red spectrum (fig. 2a) showed a strong carbonyl absorption at ν_{max} 1695, characteristic of the carbonyl band of a coumarin.

Elemental analysis (carbon and hydrogen analyses) combined with the molecular weight of 270 (from the mass spectrometer) suggested the molecular formula $C_{16}H_{14}O_4$.

It was evident from the spectral properties that compound A was a furocoumarin compound with an o-isopentenyl side chain. The partial structure (LXXIV) was, therefore, suggested for A.



(LXXIV)

The next problem was to determine which of the two possible positions in the benzenoid (5 and 8) the o-isopentenyl group was substituted.

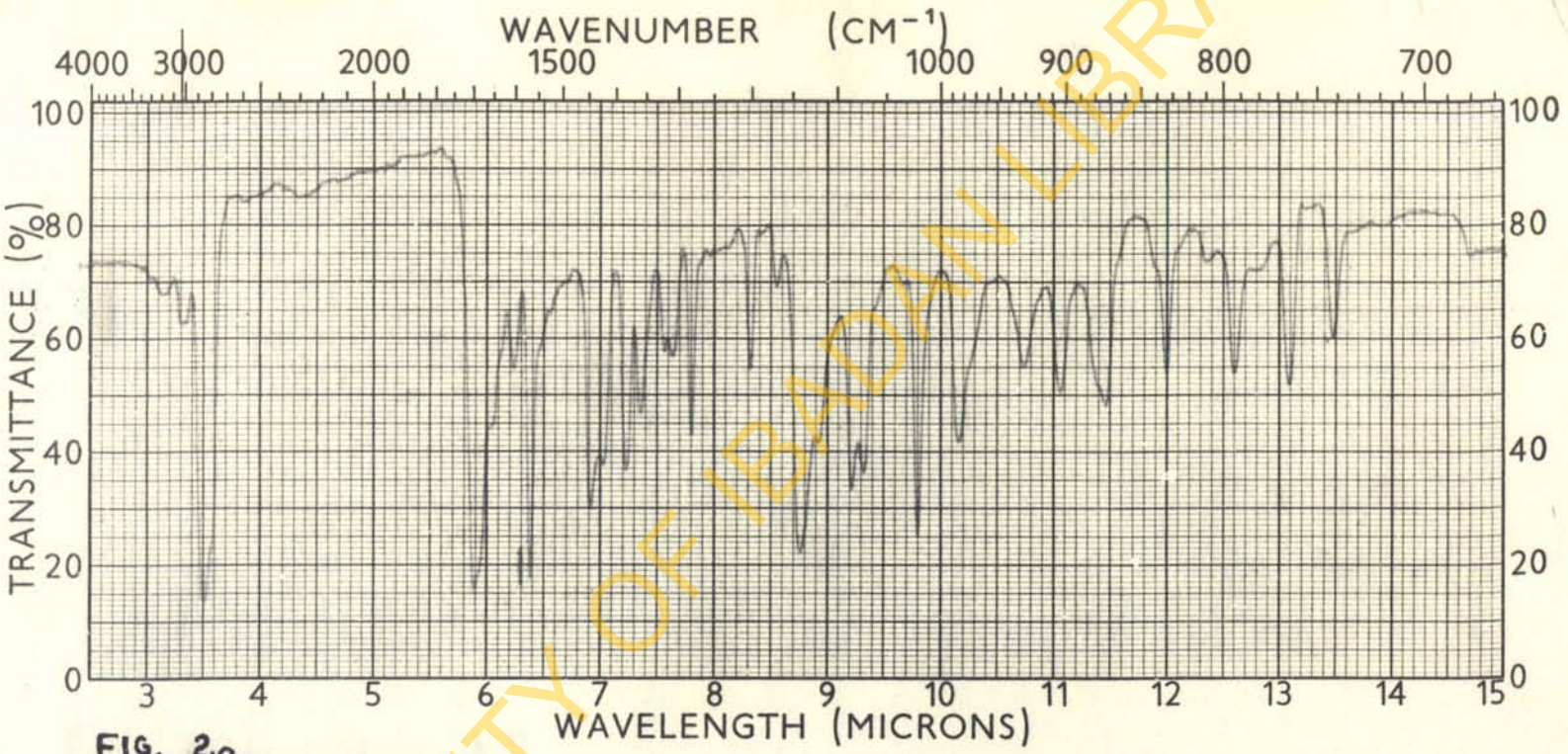
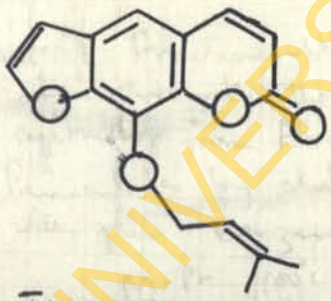
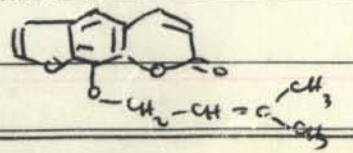


FIG. 2a



IMPERATORIN

PHASE N	SCAN SPEED Fast SLIT
SOLVENT	OPERATOR Abl DATE 18/1/67
CONC.	REMARKS
CELL PATH	
REFERENCE	



NO. 5263

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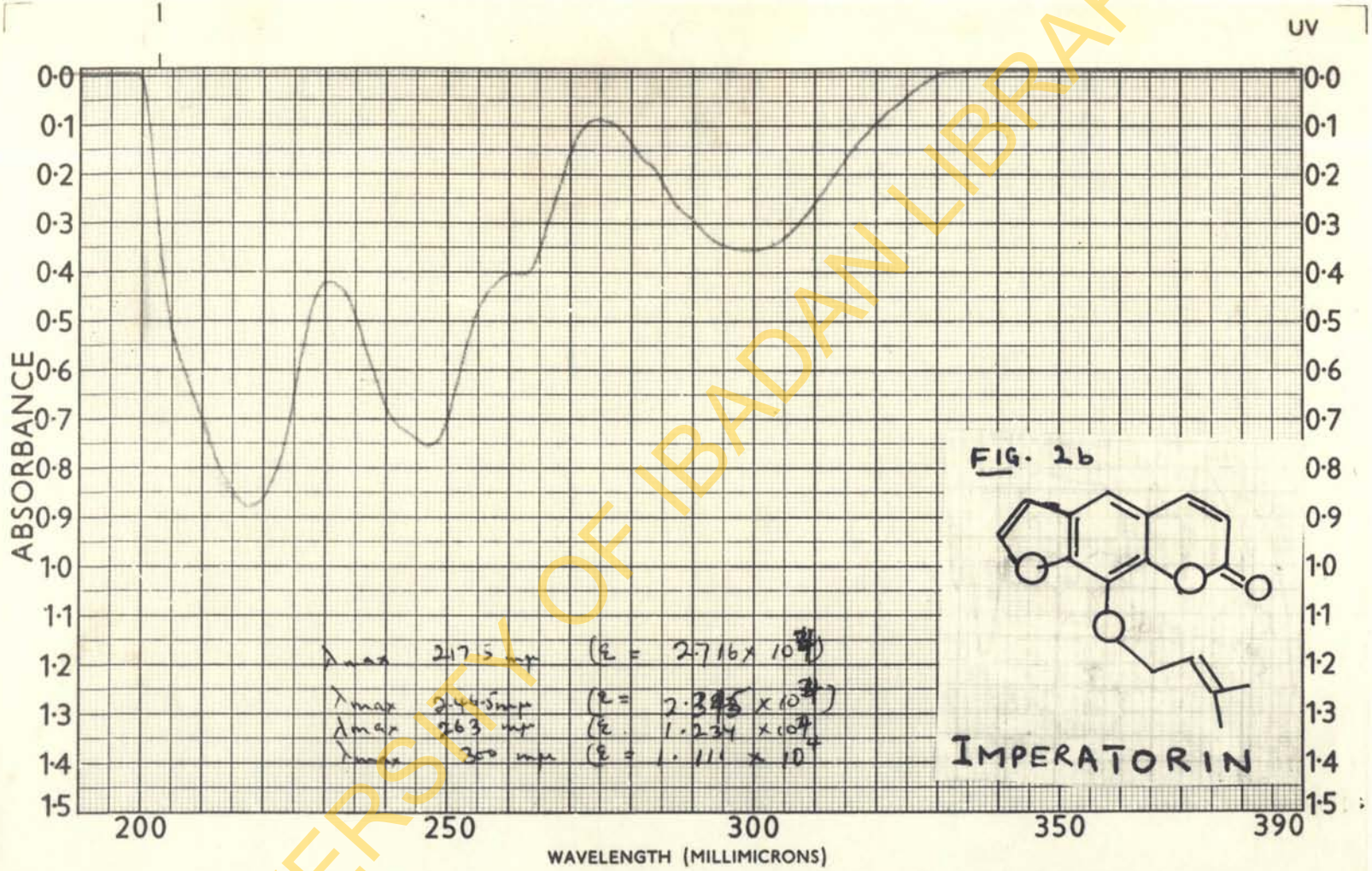
An attempt at hydrolysing A by refluxing with concentrated hydrochloric acid in methylated spirit gave a dark tar which did not crystallise.

On comparing the physical properties of compound A (m.p., infra-red spectra and ultra violet spectrum (fig. 2b) with the physical properties of some known furocoumarins reviewed by Dean[63], it was found that compound A was similar to both imperatorin (m.p. 105°) and isoimperatorin (m.p. 109°).

Imperatorin (LXXIV) is a furocoumarin extracted from the root of Imperatoria ostruthium[59], and its isoform (isoimperatorin) (LXX1) was extracted from the same plant.

Hydrolysis of imperatorin with acetic acid containing traces of sulphuric acid gave the hydroxy product xanthotoxol (LXXV) melting at 243°C[59]. Hydrolysis of isoimperatorin under the same condition gave bergaptol (LXXII) melting at 277°. Methylation of xanthotoxol with diazomethane gave the methyl ether of xanthotoxol, xanthotoxin (LXIX) m.p. 144° while methylation of bergaptol afforded bergapten (LXV) m.p. 188° - 189°[59].

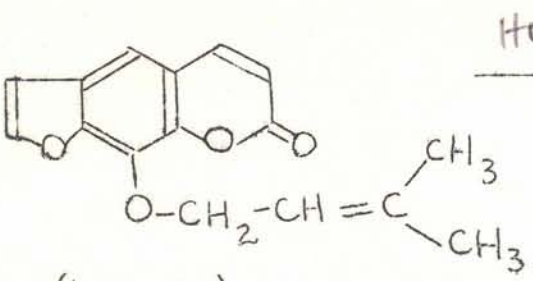
Since the two compounds imperatorin and isoimperatorin have very close melting points, it seemed that one way of differentiating between them was to hydrolyse them and then methylate the hydrolysed



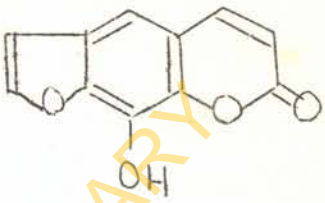
SAMPLE Crystal from Aframomum Paniculata M.P 100°-102°	CURVE NO.	SCAN SPEED fast	OPERATOR M. of Abe
	CONC 0.00875 mg/l	SLIT 25	DATE 21/1/67
ORIGIN Aframomum Paniculata	CELL PATH	REMARKS	
SOLVENT MeOH	REFERENCE MeOH		

PART NO. 202-1511

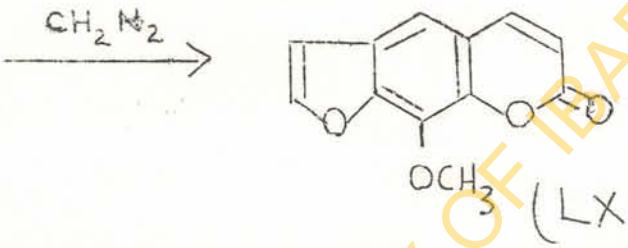
PERKIN - ELMER LIMITED



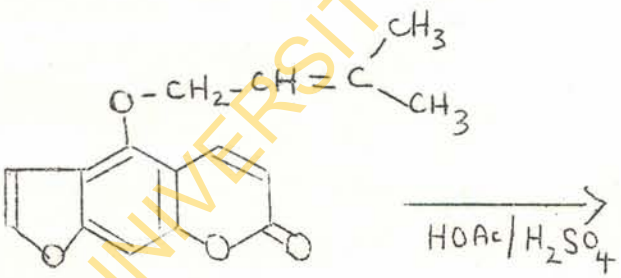
(LXXIV) m.p. 102°C



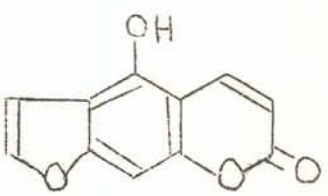
(LXXV) m.p. 243°C



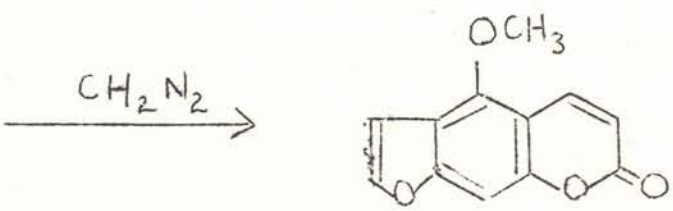
(LXIX) m.p. 144°C



(LXXI) m.p. 109°C



(LXXII) m.p. 277°C



(LXV) m.p. 188° – 189°

products and to compare the melting points of both the hydrolysed products and the methyl ether of the hydrolysed products.

In order to find out whether substance A was imperatorin or isoimperatorin, it was hydrolysed with acetic acid containing a few drops of sulphuric acid. The product was a white crystalline substance m.p. 240°C. This was very comparable with the melting point of xanthotoxol. Methylation of the white substance with ethereal diazomethane afforded a reddish crystalline substance m.p. 145°. This was very close to the melting point of xanthotoxin. These two experiments confirmed that substance A was imperatorin (LXXIV) and not isoimperatorin.

The oily portion of the extract was chromatographed on neutral alumina and a large quantity of β-sitosterol was eluted.

Compound B m.p. 130°C - 132°C.

Another extract of the same wood was investigated in order to get more of the crystalline mixture which melted at 92°C, and from which compound A was separated by chromatography. It was hoped that the second component with the lower R_f value on the t.l.c. plate would separate from compound A when the mixture was put on a column using perhaps silica gel as the absorbent. Unfortunately, this second extract gave no crystals, but a thick oil. A portion of

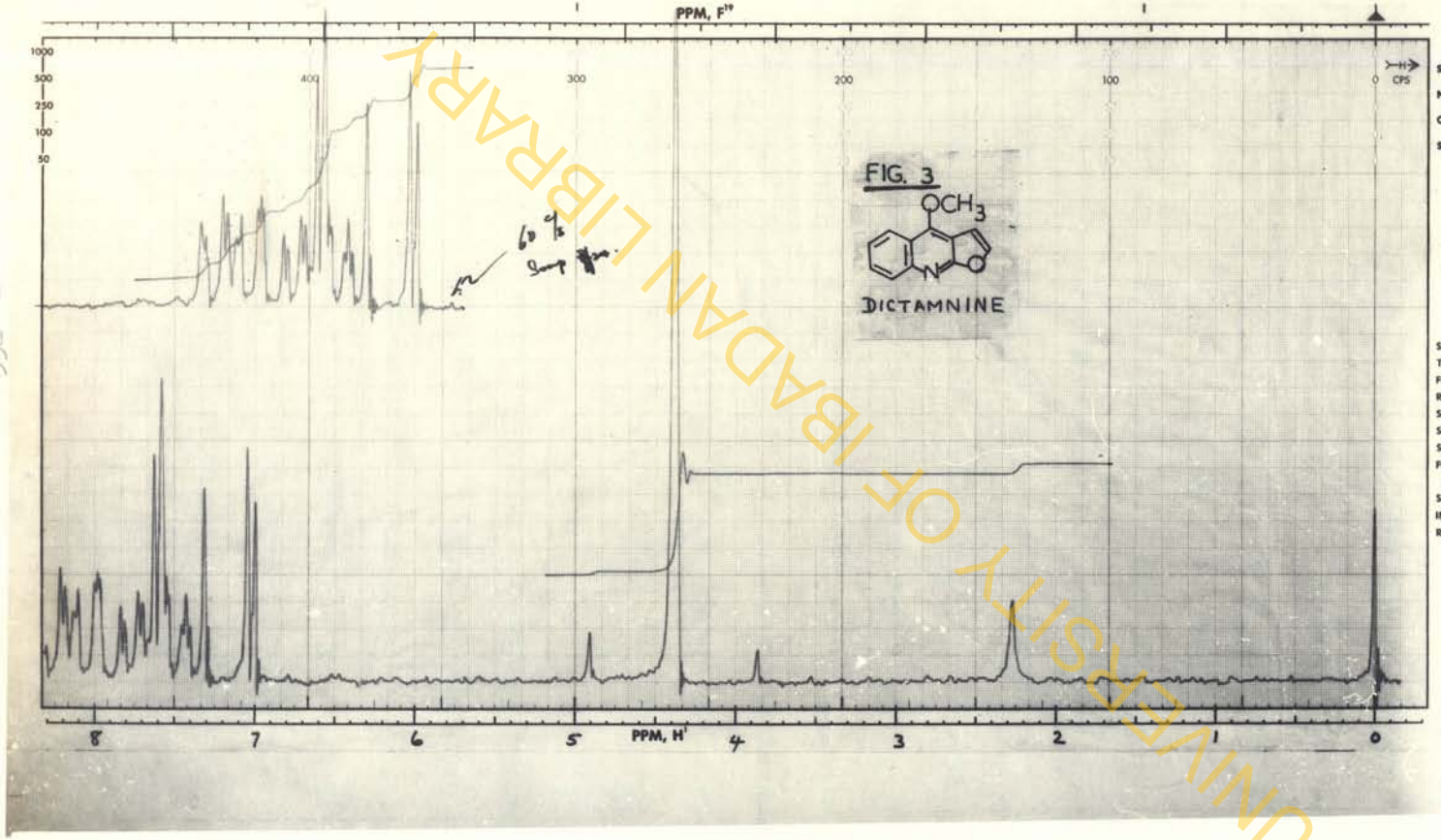
the oil was chromatographed first, on alumina, and then on silica gel. In both cases, a large quantity of β-sitosterol was obtained and no other crystalline substances came down even with the most polar mixture of solvents.

To the remaining portion of the oily extract, petroleum ether was added to precipitate most of the unwanted β-sitosterol. Then it was extracted with 10% water in methanol. To the methanolic extract, some quantity of water was added and then re-extracted with chloroform. The chloroform extract was concentrated and then redissolved in a little quantity of benzene. This was then chromatographed on alumina. A fraction eluted with 20% ether in benzene gave a crystalline substance, recrystallised from methanol to give large prism-like crystals of substance B m.p. 130°C - 132°

The molecular weight of 199 (from mass spectrometer) suggested that substance B contained a nitrogen atom (molecular weight odd). The infra-red spectrum showed no carbonyl band.

The elemental analysis combined with the molecular weight determination suggested the empirical formula $C_{12}H_9O_2N$ for the substance B.

The n.m.r. spectrum (fig. 3) showed signals at δ 2.23 (singlet) attributed to an NH proton, at δ 4.38 (singlet) for the $-OCH_3$ protons and complex multiplets between δ 7.0 and δ 8.0. Attempted



A-56/60 SPECTRUM

SPECTRUM NO. 1255

NUCLEUS ~~56.4 Mc~~ H¹, 60.0 Mc

OPERATOR MMAdesanth DATE 7/3/67

SAMPLE: Xystals from Afragle Plant
mpt. 130° - 132°C.

Dictamine

SOLVENT	CCl_4		
TEMPERATURE	R.T.		°C
FILTER BANDWIDTH	1		cps
R.F. FIELD	.2		mG
SWEEP TIME	250	50	sec
SWEEP WIDTH	500		cps
SWEEP OFFSET	—		cps
FREQ. OFFSET	—		cps
TOTAL OFFSET	—		cps
SPECTRUM AMP.	16	1.25	
INTEGRAL AMP.	—	20	
REMARKS:			

VARIAN associates

CHART 556-A

hydrolysis of B with methanolic hydrochloric acid was unsuccessful. Hydrogenation of substance B using platinum oxide as a catalyst in methanol afforded a crystalline substance m.p. 180° - 182°C with a lower t.l.c. R_f value than the starting material. Molecular weight of the hydrogenated product (from mass spectrometer) was found to be 203, two units higher than the molecular weight of the starting material.

The infra-red spectrum (fig.4) of the hydrogenated product showed a carbonyl band at ν_{max} 1653 cm^{-1}, characteristic of the carbonyl band of a 2-quinolone. The n.m.r. spectrum (fig.5) of the hydrogenated product showed signals at δ 1.28 (triplet, J = 7 c/s) attributed to the $-CH_3$ protons next to a methylene group and at δ 2.76 (quartet, J = 7 c/s) attributed to the methylene group, being split by the methyl group. This indicated that the hydrogenated product was a 2-quinolone with an ethyl group as a side chain. The n.m.r. spectrum of the hydrogenated product also showed the singlet at δ 4.0 attributed to the methoxy protons. It was suggested from the above spectral evidences that the hydrogenated product was probably a 3-ethyl-2-quinolone compound.

By comparing the physical properties, (melting point, molecular weight and the ultra violet spectrum) of some known alkaloids of the family Rutaceae with compound B, it was found that Compound B was

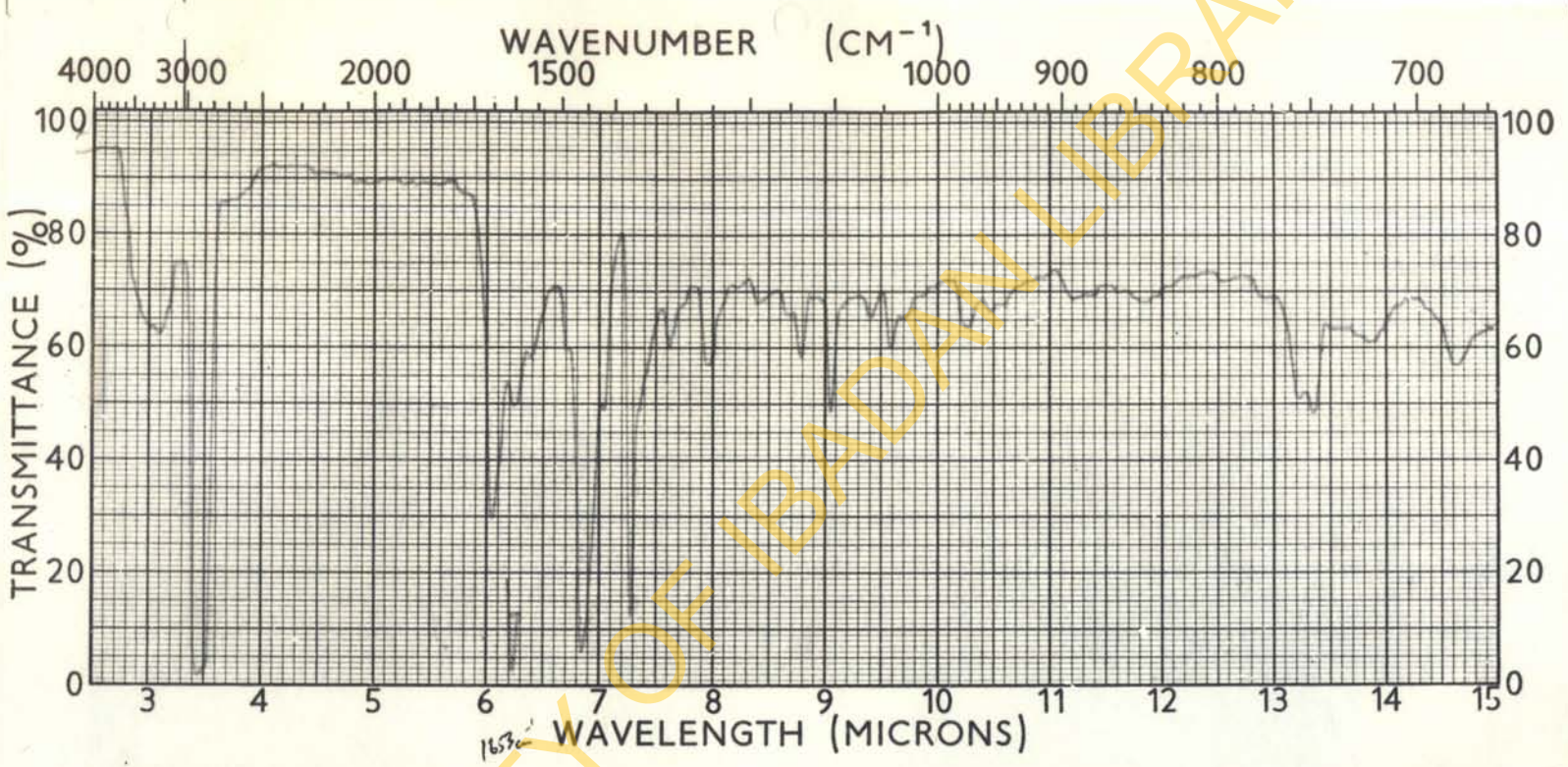


FIG. 4 SAMPLE 3-ethyl-4-methoxy-2-quinolone.

PHASE N

SOLVENT

CONC.

CELL PATH

REFERENCE

SCAN SPEED Fast SLIT Normal

OPERATOR Ade DATE 18/4/67

REMARKS m.p. 182° c

NO. 3489

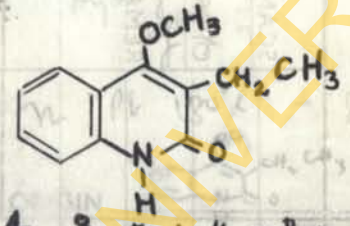


FIG. 4 3-ethyl-4-methoxy-2-quinolone

PART NO. 137E - 1281

PERKIN - ELMER LIMITED, BEACONSFIELD, BUCKS

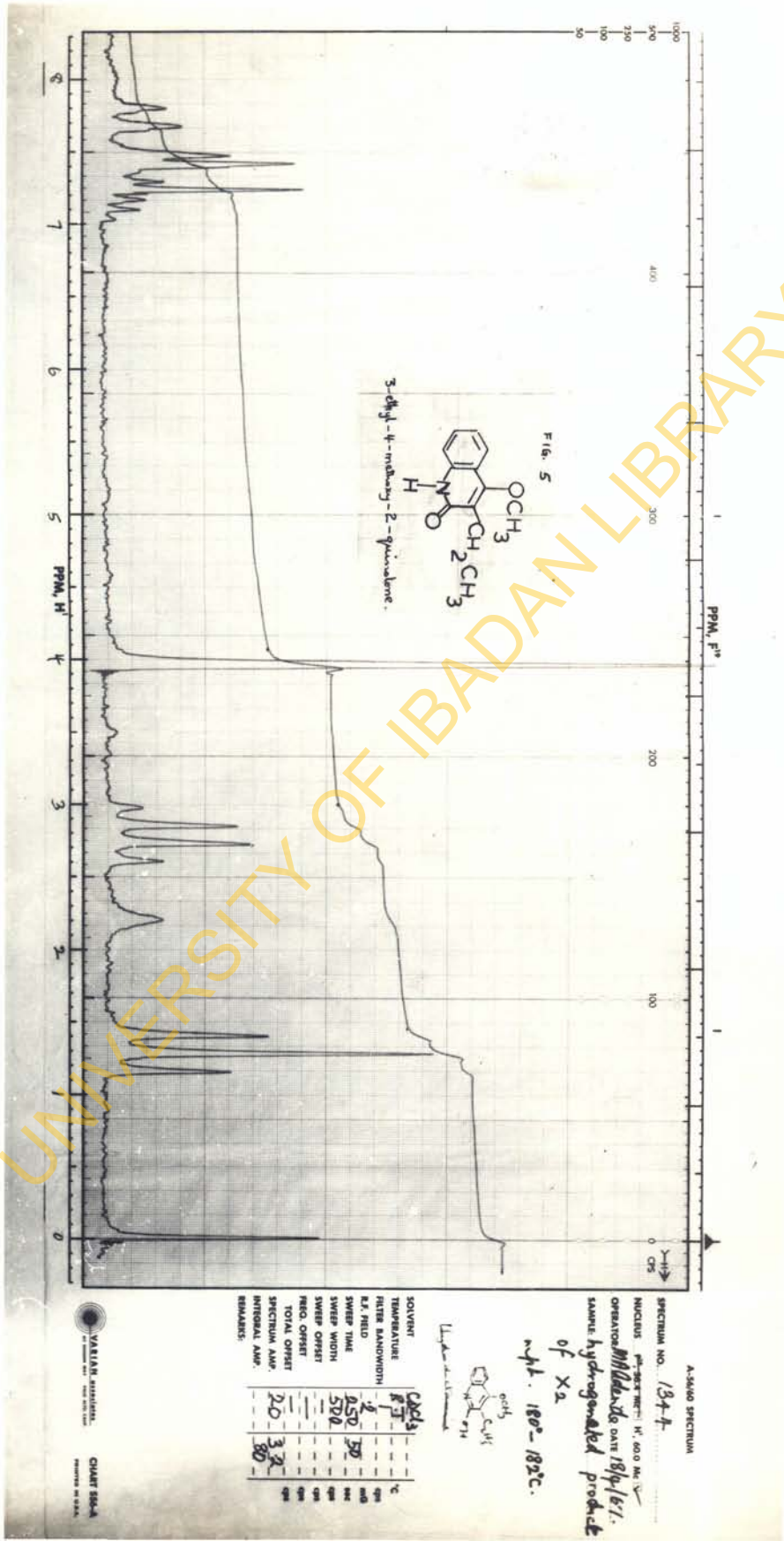
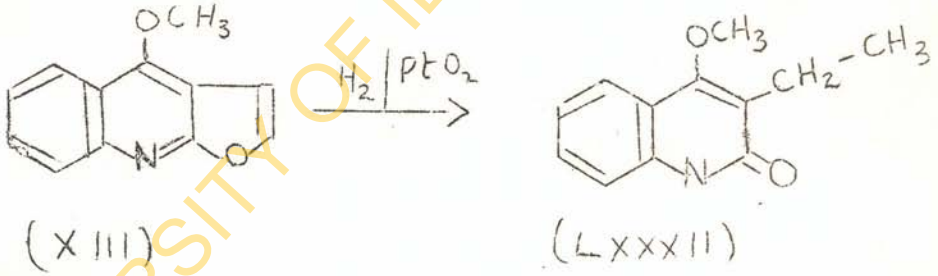


Fig. 5

identical with dictamnine.

Dictamnine is an alkaloid existing in many plants of the Rutaceae. It has a molecular weight of 199, the same as the molecular weight of compound B and its melting point 132°-133° is the same as the melting point of compound B. It was concluded, therefore, that Compound B was the known alkaloid dictamnine (XIII).

Hydrogenation ruptured the furan ring to give 3-ethyl-4-methoxy-2-quinolone, (LXXXII) (m.p. 180° - 182°), a reaction recalling the hydrogenolysis of kokusagine (XXXIX) to give 6,7-dimethoxy-3-ethyl-4-hydroxy-2-quinolone (XL)[36].



(XIII) (LXXXII)

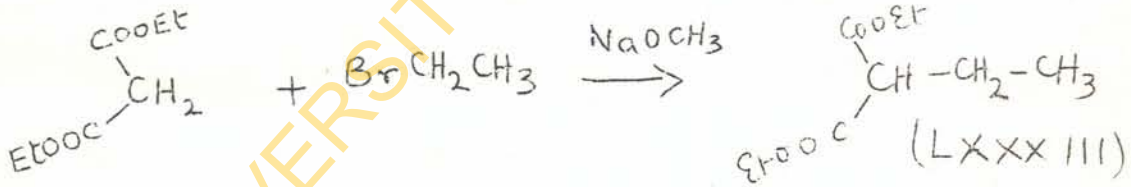
That the product of hydrogenation of dictamnine (compound B) was 3-ethyl-4-methoxy-2-quinolone was evident from the synthesis of the last compound.

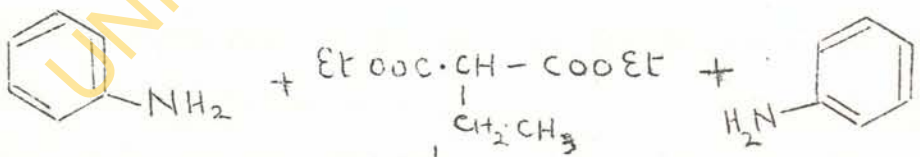
Synthesis of 3-ethyl-4-methoxy-2-quinolone

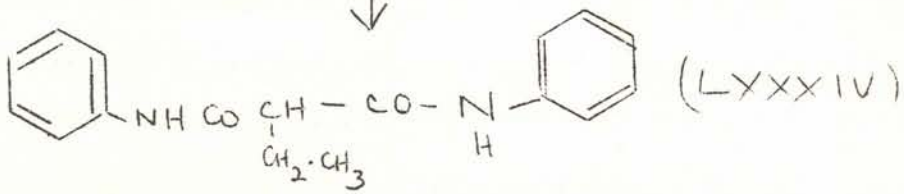
Baeker and co-workers[42b] had made a 3-substituted-4-hydroxy-2-quinolone by the reaction of aniline with a substituted malonic ester.

This method was attempted in order to make the 3-ethyl-4-hydroxy-2-quinolone which, it was hoped, would methylate to the required 4-methoxy derivative.

Diethyl-ethyl-malonate (LXXXIII) was prepared by refluxing diethyl malonate and ethyl bromide with sodium methoxide in methanol[64a,b]. Condensation of this ester with aniline gave a substance (LXXXIV), m.p. 220° - 223°C, insoluble in chloroform and its n.m.r. spectrum in deuterochloroform could not be taken. The infra-red spectrum showed a carbonyl band at 1724 cm^{-1}. This band could not have been due to the carbonyl band of the 2-quinolone which we observed at ν_{max} 1653 cm^{-1}. This product was presumed to be a dianilide formed probably by the condensation of two moles of aniline with one mole of the substituted ester as shown below:-

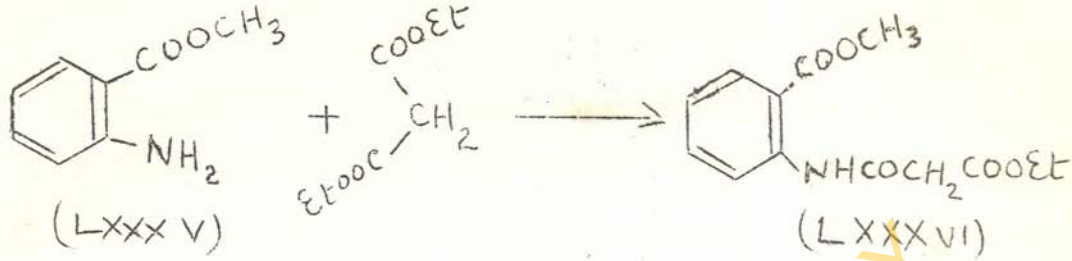




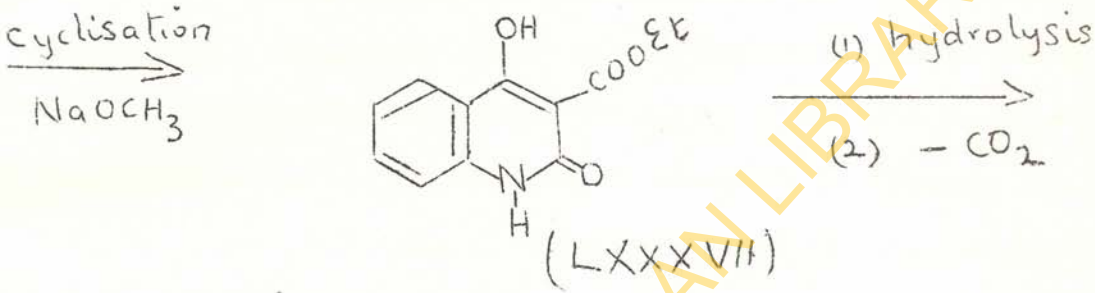


Another approach to the 3-ethyl-4-methoxy-2-quinolone (LXXXII) involved the Friedel Craft's method of introducing an acyl group to an aromatic ring. The reaction of 4-hydroxy-2-quinolone (LXXXVIII) with acetyl chloride and aluminium chloride gave 3-acetyl-4-hydroxy-2-quinolone (LXXXIX) which was reduced by sodium borohydride to give 3-ethyl-4-hydroxy-2-quinolone (XC). Methylation of this with ethereal diazomethane gave the required 3-ethyl-4-methoxy-2-quinolone (LXXXII), m.p. 182°. This was the method employed in preparing 3-isoamyl-4-methoxy-2-quinolone using isovaleryl chloride instead of acetyl chloride by Perkin Jr. (1909)[47]. The starting material, 4-hydroxy-2-quinolone was prepared by condensing methyl anthranilate (LXXXV) with diethyl malonate according to the method of Lutz et al[65]. The anthranilide (LXXXVI) thus obtained was cyclised using sodium methoxide. The resulting ester (LXXXVII) was hydrolysed with 40% sodium hydroxide and this was followed by decarboxylation to give the required 4-hydroxy-2-quinolone.

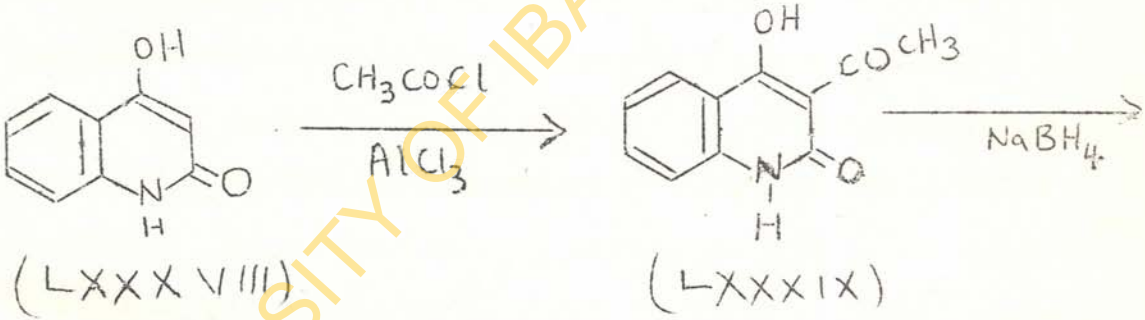
The n.m.r. spectra of both the synthetic 3-ethyl-4-methoxy-2-quinolone and the material obtained when dictamnine was hydrogenated were found to be identical in all respects. The infra-red spectra of both compounds were found to be superimposable. Their melting points were found to be the same and mixed melting points were found to be undepressed. It was concluded, therefore, that the product of the



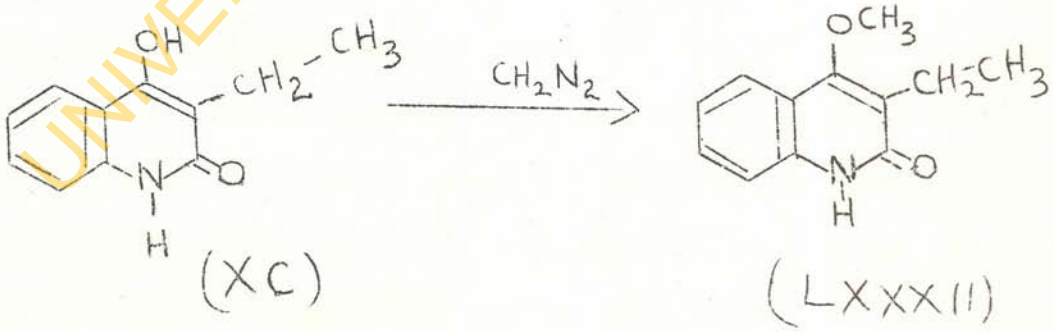
(LXXX V) (LXXX VI)



(LXXX VII)



(LXXX VIII) (LXXX IX)



(XC) (LXXX II)

hydrogenation of dictamnine with platinum oxide as a catalyst in methanol was 3-ethyl-4-methoxy-2-quinolone (LXXXII).

CLAUSENA ANISATA (Willd)

Clausena anisata is a very small shrub. It is found in Togo, Dahomey, Southern Nigeria and in Bauchi plateau in Northern Nigeria. It occurs as a small tree up to 20 ft. high in some areas.

The roots of the plant were extracted and the extract, after evaporating the solvent (petroleum ether) gave some crystals on standing. The crystals were separated from the oil by washing with petroleum ether and filtering. Recrystallisation from methanol gave light yellow crystals m.p. 98° - 100°C. The infra-red spectrum was found to be identical in all respects with the infra-red spectrum of imperatorin obtained from the wood of Afraegle paniculata . The n.m.r. spectrum of the crystalline substance was also identical with that of imperatorin. These facts showed that the crystalline substance from Clausena anisata was imperatorin.

The petroleum ether was evaporated off the filtrate and the residue was chromatographed on neutral alumina. Another crystalline substance C m.p. 150° - 153°C. was brought down from the column by 10% ether in benzene.

The infra-red spectrum (fig.6) showed a strong >C=O band at

1709 cm^{-1}. This appeared to be the carbonyl band of a coumarin rather than of a quinolone. The n.m.r. spectrum (fig. 7) showed signals at δ 1.67 (singlet) and δ 1.83 (singlet) attributed to the two methyl groups on a double bond, δ 3.45 (doublet, J = 6 c/s) assigned to the two protons of a methylene group and δ 5.22 as complex triplet attributed to the vinyl proton. This portion of the spectrum indicated the presence of an isopentenyl group $-CH_2-CH = C(CH_3)_2$ in the compound. The n.m.r. spectrum also showed signals at δ 3.93 as a singlet counting for 6 protons and this was assigned to two methoxy groups. There were two AB doublet at δ 6.13 (J = 10 c/s) and δ 7.97 (J = 10 c/s). These two doublets were characteristic of H-4 and H-3 protons of a coumarin and a singlet at δ 6.32 attributed to a benzenoid proton. Since the n.m.r. spectrum showed the presence of only one benzenoid proton, the benzenoid ring of the compound was likely to be highly substituted. From the above spectral properties, the partial structure (XCI) was suggested for the coumarin.

The next problem was to find out the positions of the two methoxy groups and the isopentenyl group in the benzenoid ring. Six possible structures (XCIa - XCIf) could be written down for the compound.

By comparing the ultra violet absorption of various dimethoxy coumarins reviewed by F. M. Dean in his book[66], it was found that the

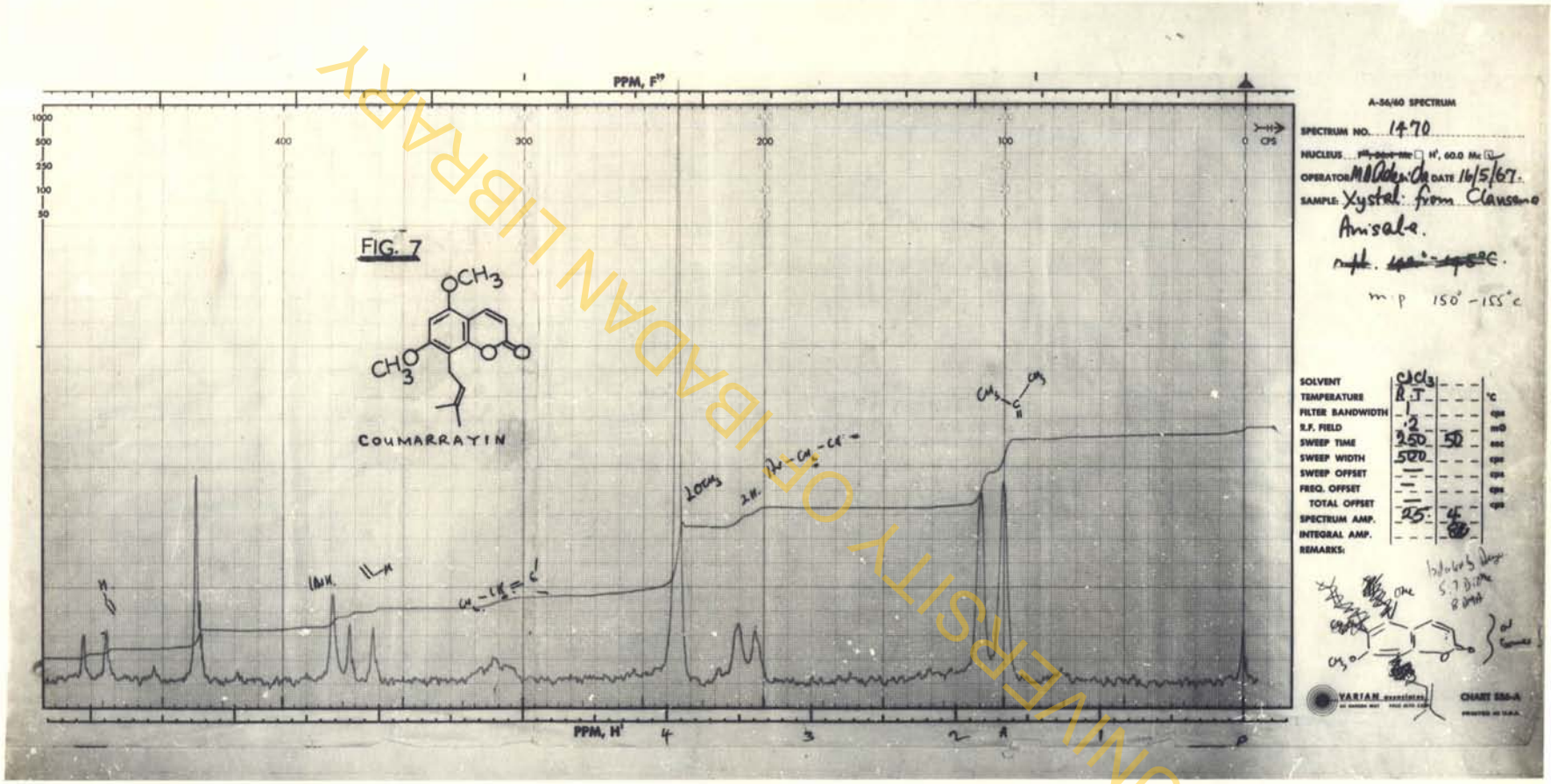
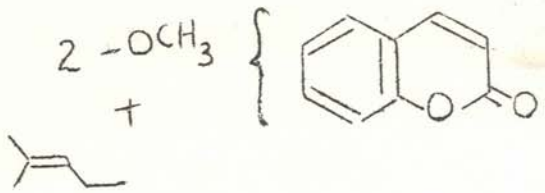
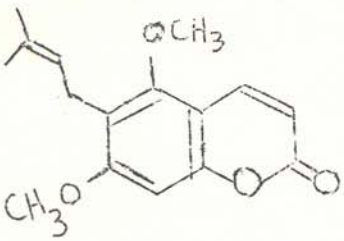


FIG. 7

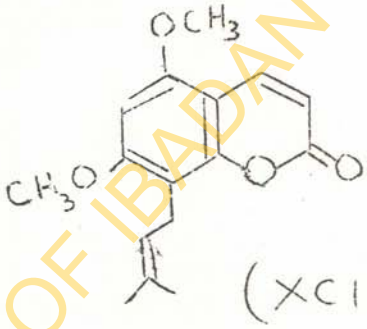
COUMARRAYIN



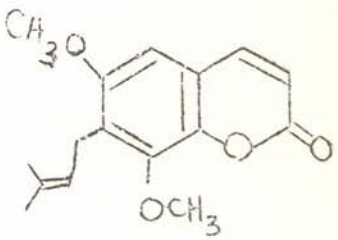
(XC1)



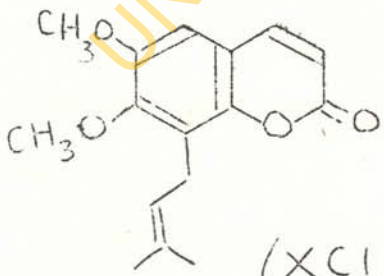
(XC1a)



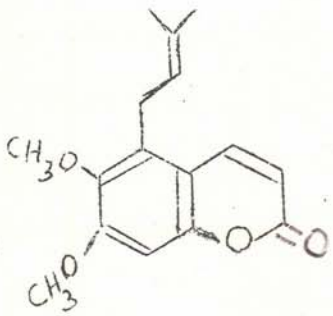
(XC1b)



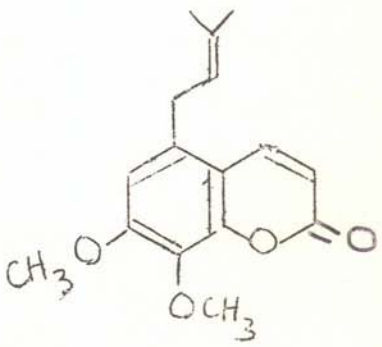
(XC1c)



(XC1d)



(XC1e)



(XC1f)

ultraviolet absorption of the new compound C (Fig.8) was much closer to the ultraviolet absorption of 5,7 dimethoxy coumarin than any of the other dimethoxy coumarins.

The ultra violet absorptions of some known dimethoxy coumarins and the new coumarin C are shown in the table below:

5,7-dimethoxy λmax	6,7-dimethoxy λmax	7,8-dimethoxy λmax	New Coumarin C λ max
246 mμ	235 mμ	250 mμ	213 mμ
254 mμ	296 mμ	318 mμ	260 mμ
323 mμ	342 mμ		323 mμ

It seemed, therefore, that the new coumarin C was probably either 5,7-dimethoxy-6-isopentenyl coumarin (XC1a) or 5,7-dimethoxy-8-isopentenyl coumarin (XC1b) and not any of the other structures (XC1c - XC1f).

But 5,7-dimethoxy-6-isopentenyl coumarin (XC1a) is a known compound, Toddaculine[62] whose melting point (95°) differs from the melting point of the new coumarin C. The only structure left for consideration, therefore, was 5,7-dimethoxy-8-isopentenyl coumarin (XC1b).

A confirmation of the structure of the coumarin C by the synthesis of (XC1b) was then aimed at.

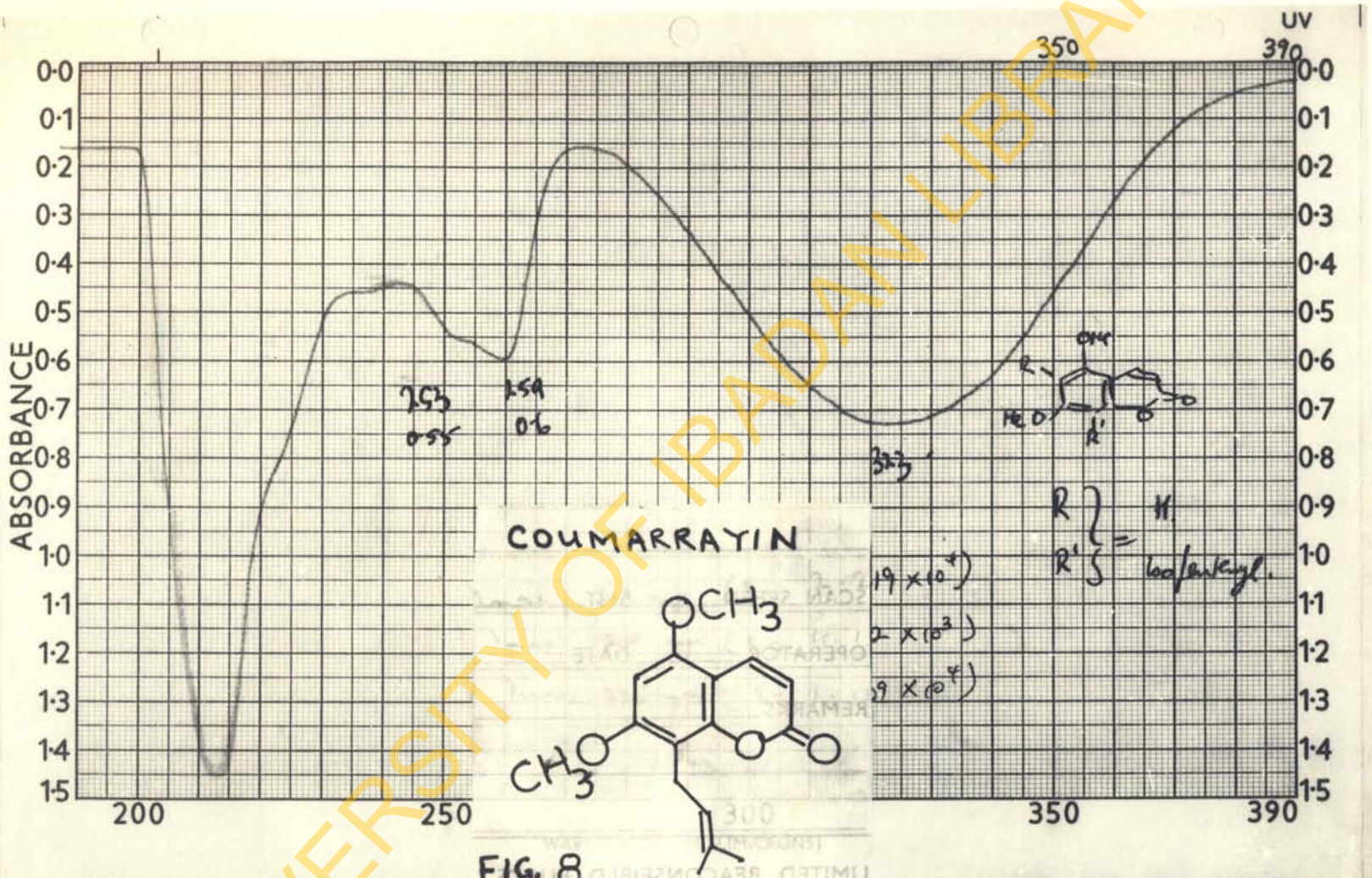


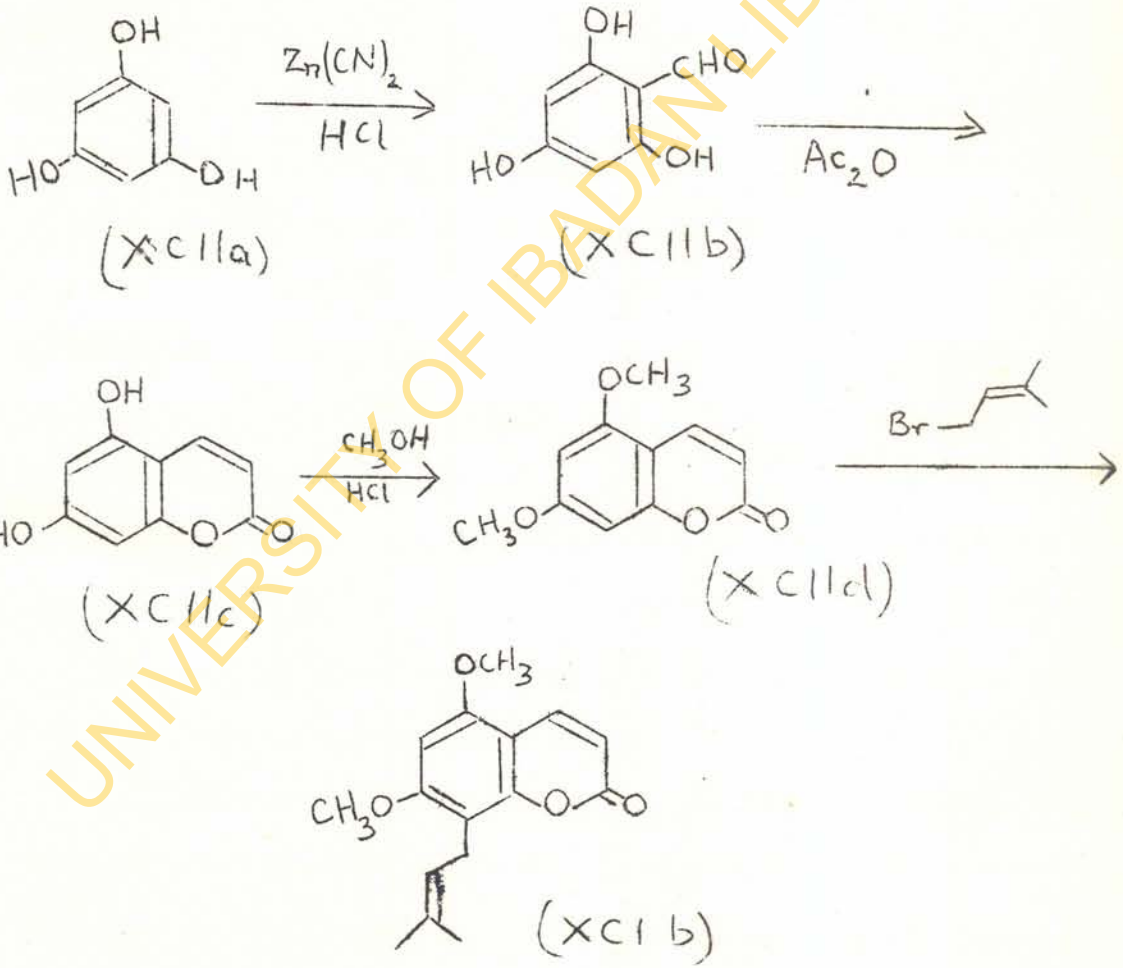
FIG. 8

SAMPLE Xystal from Clausena ~~from~~ Anisata m.Pt 145°C-147°C	CURVE NO.	SCAN SPEED Fast	OPERATOR Abe
ORIGIN Clausena Anisata	CONC 0·000153g/10ml i.e 0·015g/litre	SLIT Normal	DATE 16/5/67
SOLVENT MeOH	CELL PATH	REMARKS	
	REFERENCE		

PART NO. 202-1511

PERKIN - ELMER LIMITED

5,7-dimethoxy coumarin is a phloroglucinol based compound. The starting material for the synthesis of 5,7-dimethoxy-8-isopentenyl coumarin was, therefore, thought to be phloroglucinol. An attempt was made at making 5,7-dimethoxy coumarin before introducing the isopentenyl group according to the proposed scheme :



(XC11a) (XC11b) (XC11c) (XC11d) (XC1b)

Phloroglucinol (XCIIa) was formylated by a method modified by Malkin and Nierenstein[67]. This was done by passing dry hydrogen chloride gas into a solution of phloroglucinol in dry ether containing zinc cyanide.

Condensation of the phloroglucinaldehyde with acetic anhydride by the method of Heyes and Robertson[68], gave, instead of the expected 5,7-dihydroxy coumarin, a dirty brown oil which did not solidify. The infra-red spectrum did not show the characteristic α,β unsaturated carbonyl band of a coumarin.

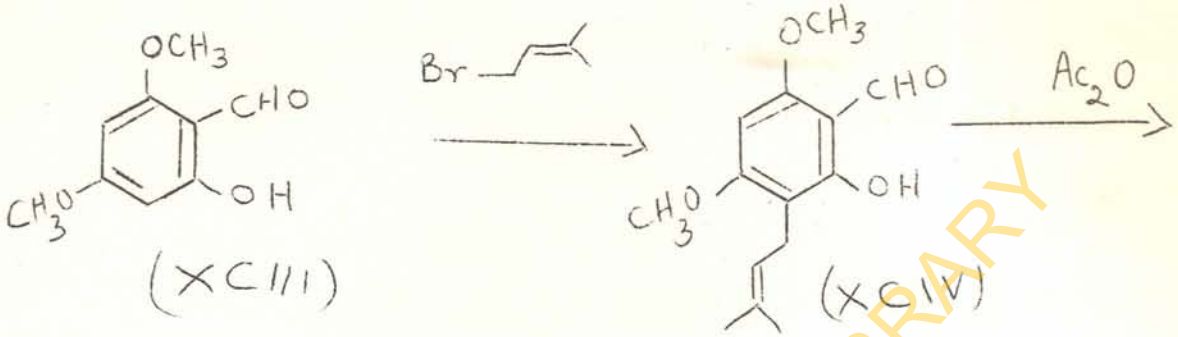
It was thought that the dimethyl ether of phloroglucinaldehyde might cyclise easily instead of the phloroglucinaldehyde. Phloroglucinol was di-methylated by a method modified by Pratt and Robinson[69]. This involved passing dry hydrogen chloride into the solution of phloroglucinol in analar methanol. The dimethyl ether of the phloroglucinol thus obtained was formylated using formanilide and phosphoryl chloride[69] to give the salt $\{(CH_3O)_2.C_6H_2.OH - CH = CH - Ph\ HCl\}$ which was hydrolysed to give a poor yield of the required dimethoxy phloroglucinaldehyde.

The experiment was repeated by passing hydrogen chloride into the solution of dimethyl ether of phloroglucinol in dry ether containing zinc cyanide as was done in the formylation of phloroglucinol. A much improved yield of dimethoxy phloroglucinaldehyde was obtained.

Vigorous acetylation of dimethoxy phloroglucinaldehyde with acetic anhydride and sodium acetate gave a dark green oil whose infra-red spectrum did not show any trace of a coumarin.

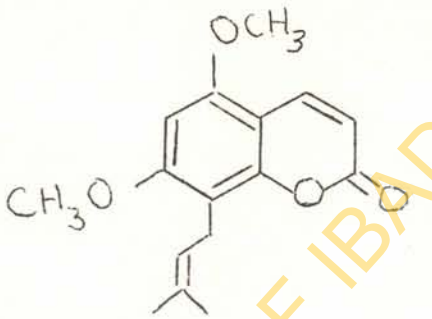
While the synthesis of the coumarin C was still being attempted, D.L. Dreyer [70] reported the isolation and synthetic confirmation of coumarrayin (m.p. 157° - 158°) from the dried foliage of Murraya paniculata, another rutaceous plant. The melting point of coumarrayin was very comparable to the melting point of the coumarin we called C. The n.m.r. spectra of the two compounds were very similar. The infra-red spectrum of coumarrayin kindly supplied by Dreyer himself was found to be superimposable on the infra-red spectrum of our coumarin C. It followed, therefore that our coumarin C was the same compound as coumarrayin. The structure of coumarrayin was elucidated and confirmed synthetically by Dreyer[70] as 5,7-dimethoxy-8-isopentenyl coumarin i.e. (XCIb). This was the structure proposed for our own coumarin C and which we set out to confirm by synthesis.

Dreyer synthesised his coumarrayin by a method analogous to our approach. Our plan was to make the 5,7-dimethoxy coumarin before introducing the isopentenyl group to the benzenoid ring, but Dreyer introduced the isopentenyl group to the dimethyl ether of the phloroglucinaldehyde before cyclisation to the coumarin as shown in the next page.



(XCIII)

(XCIV)



(XCIb)

ORICIA SUAVEOLENS (Engl.) Verdoon

Oricia suaveolens is a small under-storey plant locally abundant in and around the Gambari F.R., but has not been recorded elsewhere in Nigeria. It occurs in Sierra Leone, and Ivory Coast.

The wood of the plant was extracted with light petroleum ether (60° - 80°) to afford a large quantity of oily material.

Column chromatography of the oil on neutral alumina gave a yellow crystalline substance on eluting with 20% benzene in diethyl

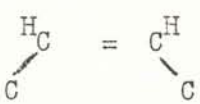
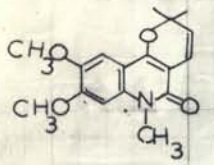
ether. Recrystallisation from benzene gave large, glassy prism-like crystals m.p. 150° - 155° which was optically inactive. The molecular weight from the mass spectrometer gave 301 and the fact that the molecular weight was odd suggested the presence of a nitrogen atom. The presence of a nitrogen atom was confirmed by Lassaigne's test. The elemental analysis (carbon and hydrogen analyses) combined with the molecular weight determination suggested the empirical formula $C_{17}H_{19}O_4N$ for the compound. The n.m.r. spectrum (fig.9) of the compound which we now refer to as oricine showed a sharp singlet counting for six protons at δ 1.53 and this was attributed to two methyl groups. There was a sharp singlet at δ 3.70 counting for three protons and this singlet was thought to be attributable to the protons of a methoxy group, but later found to be due to the protons of a methylimine group ($=NCH_3$). The singlets at δ 3.98 and δ 4.02 counting for three protons each were assigned to two methoxy groups. There were two doublets centred at about δ 5.48 (J = 10 c/s) and δ 6.75 (J = 10 c/s) which were not downfield enough to be attributed to the H-4 and H-3 of a coumarin. In fact, the infra-red spectrum of oricine (fig. 10a) did not indicate the presence of a coumarin. We thought, that the doublets were due to the ethylenic protons of such grouping as  with no hydrogen atoms on the contiguous

FIG. 9

ORICINE



A-56/60 SPECTRUM

SPECTRUM NO. 154-B

NUCLEUS ☐ H¹, 60.0 Mc ☐

OPERATOR MA Odeniyi DATE 27/6/67.

SAMPLE: Xystal from

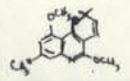
ORICIA

mpt. 150°C (158°C)

Oricin A

SOLVENT	$CDCl_3$			
TEMPERATURE	R.T			°C
FILTER BANDWIDTH	1			cps
R.F. FIELD	3			mG
SWEEP TIME	250	50		sec
SWEEP WIDTH	500			cps
SWEEP OFFSET	—			cps
FREQ. OFFSET	—			cps
TOTAL OFFSET	—			cps
SPECTRUM AMP.	25	6		
INTEGRAL AMP.		30		

REMARKS:



?

VARIAN associates

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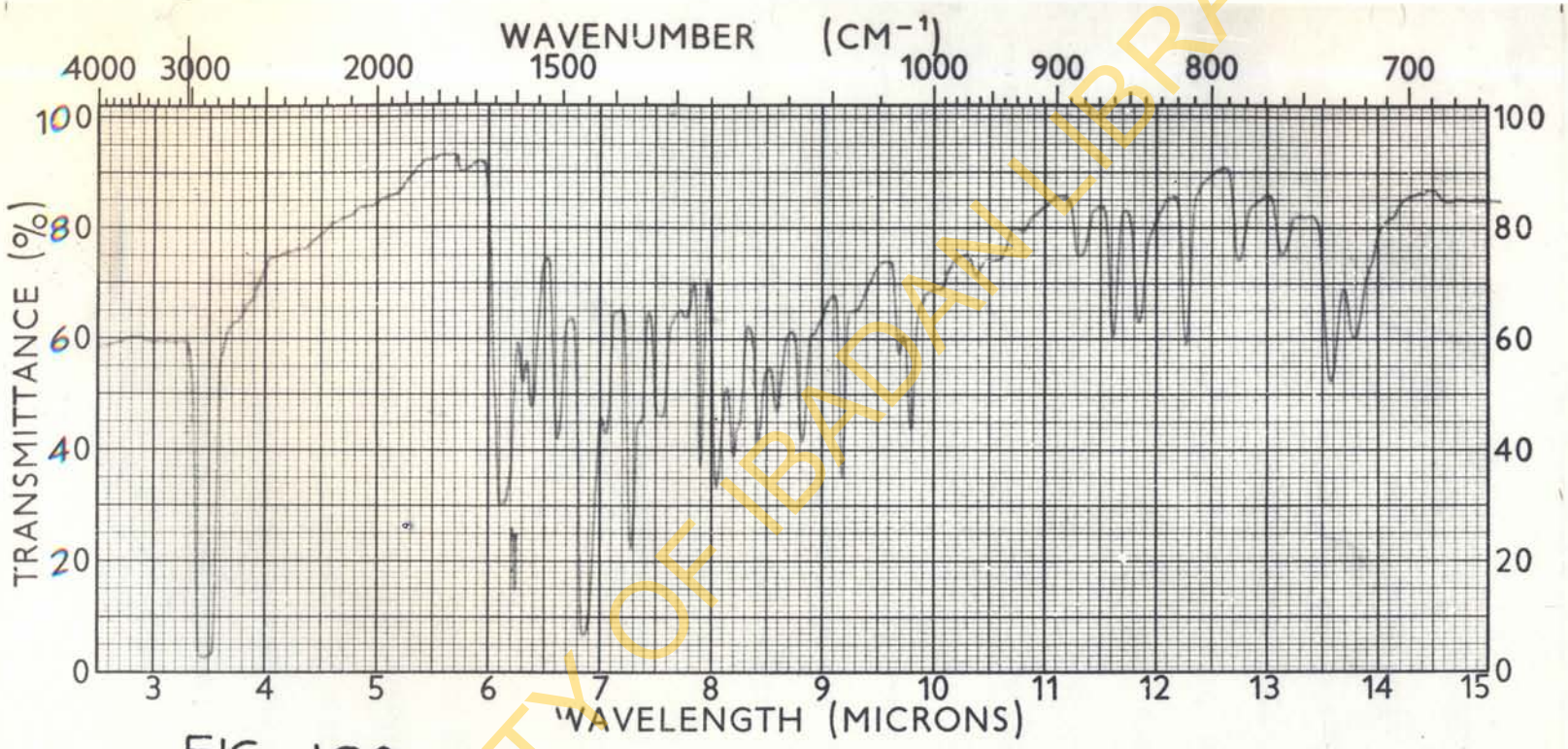
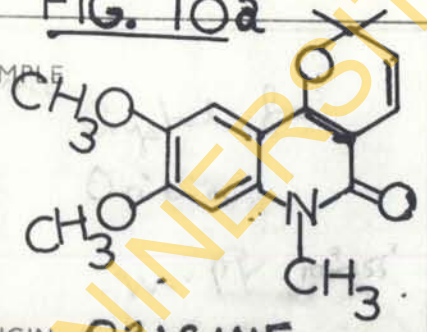


FIG. 10a

SAMPLE



ORIGIN ~~ORIGIN~~ ORICINE

PHASE Nujol

SOLVENT

CONC.

CELL PATH

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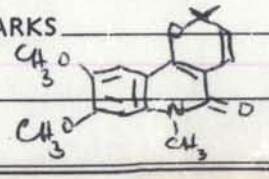
OPERATOR Abe DATE 25/6/67

REMARKS



NO. 11,711

PART NO. 137E - 1281 m.p 150°c—155°c

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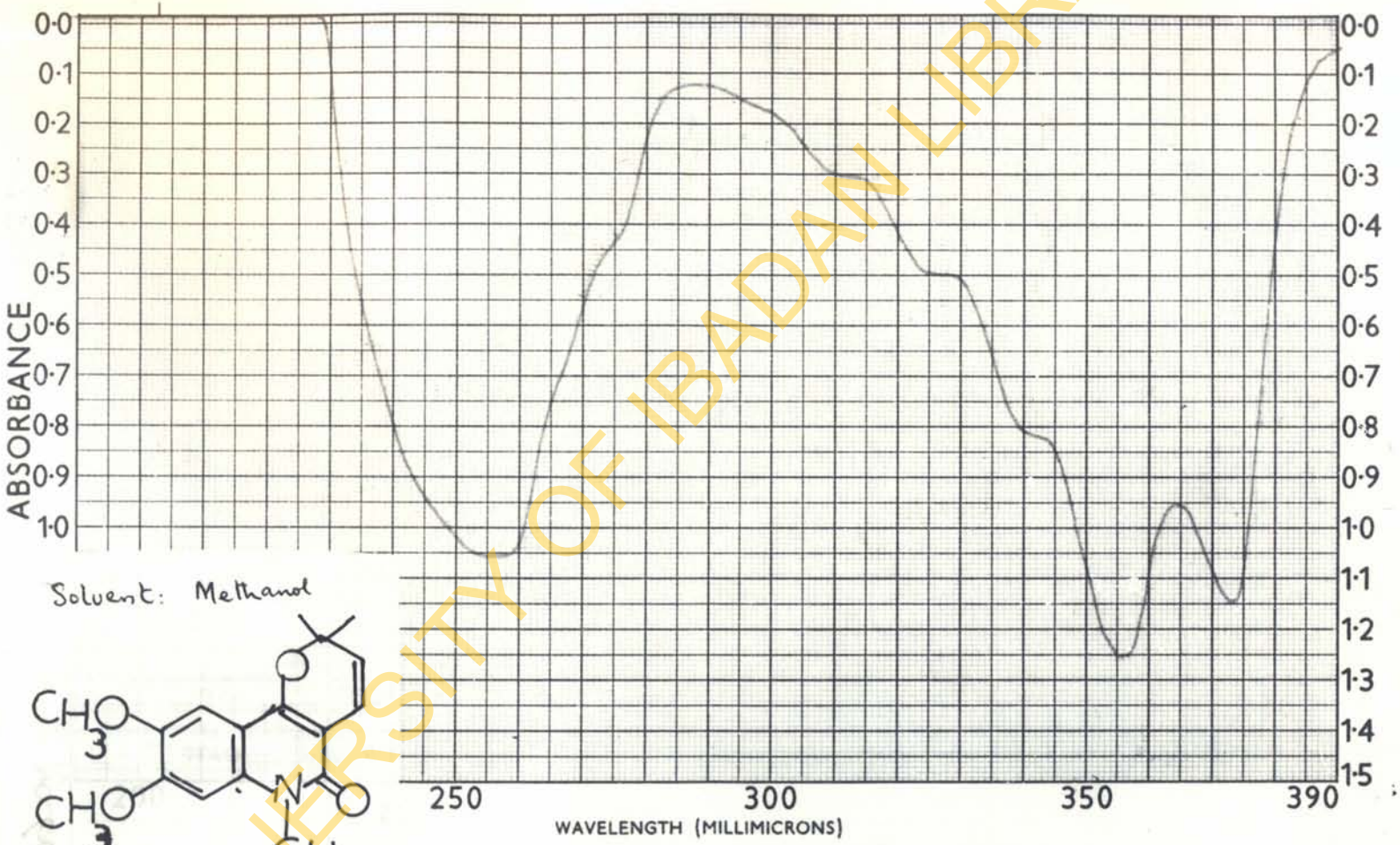
carbon atoms. The signals at δ 6.73 and δ 7.31 were attributed to two benzenoid protons and since they did not couple with each other, they were, perhaps, para to each other.

Hydrogenation of oricine with platinum oxide as a catalyst in methanol gave dihydro-oricine m.p. 150° . In the n.m.r. spectrum of the hydrogenated product, (fig. 11) i.e. dihydro-oricine, there were two triplets centred at about δ 1.83 (J = 7 c/s) and δ 2.65 (J = 7 c/s) which were not in the n.m.r. spectrum of oricine. The doublets at δ 5.48 and δ 6.75 in the n.m.r. spectrum of oricine were absent in the n.m.r. spectrum of the dihydro-derivative.

Molecular weight (from mass spectrometer) of the hydrogenated product was 303, an addition of two units to the molecular weight of oricine. This indicated that there was only one reducible ethylenic bond in oricine. The presence of the two triplets in the n.m.r. of the hydrogenated product and the absence of the doublets at δ 5.48 and δ 6.75 indicated that the $-\overset{H}{C} = CH-$ group was hydrogenated to a $-CH_2 - CH_2-$ group.

Comparing the ultraviolet spectrum of oricine (fig. 10b) with the ultraviolet spectra of some known alkaloids of the Rutaceae plants, it was found that the ultraviolet absorption of oricine was very similar to the ultraviolet absorption of flindersine, an alkaloid from the wood of Flindersia australis[43]. It appeared, therefore, that

UV



Solvent: Methanol

FIG. 10b

U.V. of ORICINE in methanol solution

PART NO. 202-1511

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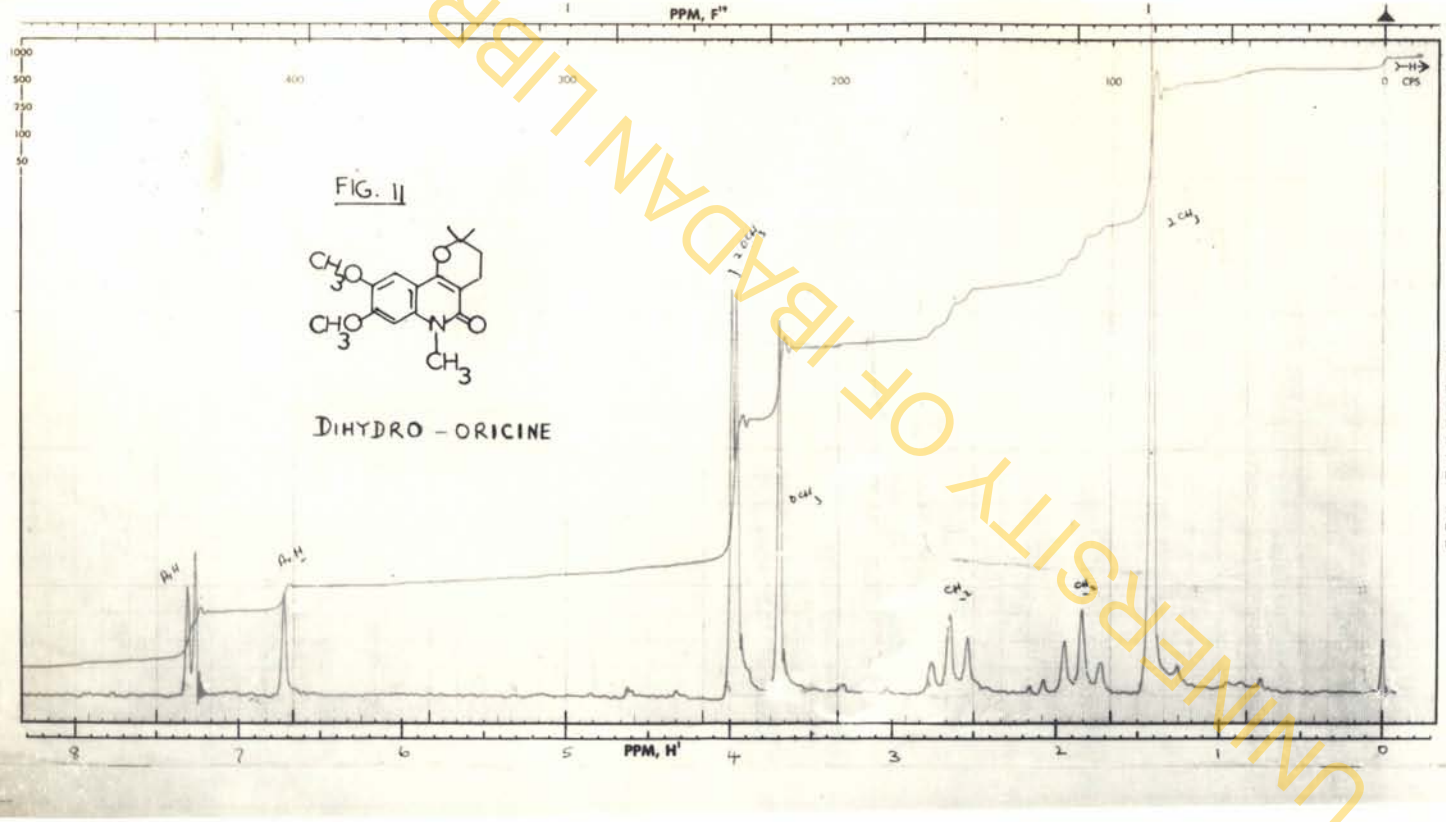
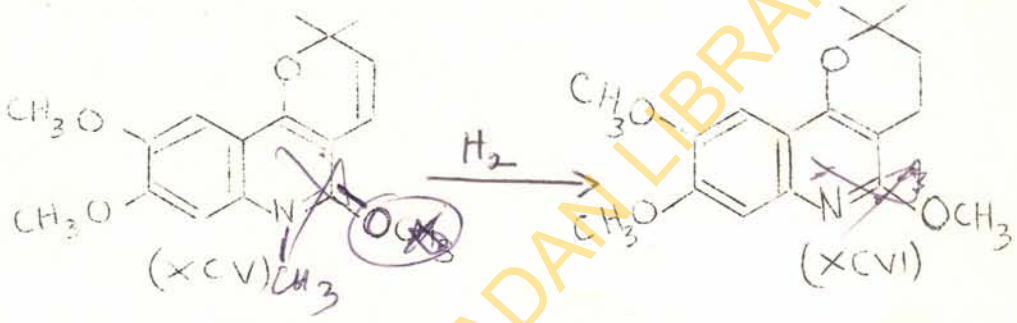
PERKIN-ELMER LIMITED.



oricine had the same nucleus as flindersine and the structures (XCV) and (XCVI) were suggested for the new alkaloid oricine and its dihydro derivative.



The three-proton signal at δ 3.70 in the n.m.r. spectrum of oricine was thought to be due to the protons of a methoxy group. If so, we wondered why the protons of the methoxy group should resonate at a higher field than the protons of the other two methoxy groups. We assumed, therefore, that for these protons to give a signal at such a high field, it should be substituted in the heteocyclic ring and very close to the hetero atom. The methoxy group was, therefore, thought to be in the 2-position of the alkaloid.

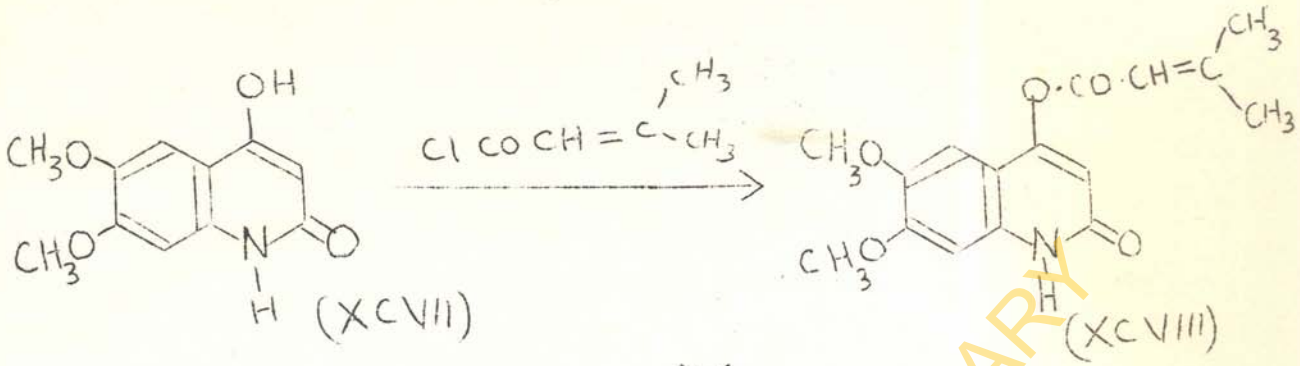
The quantity of oricine obtained from the extract was so small that degradative work on it in order to confirm this structure was impossible. It was decided, therefore, to confirm the structure of the new alkaloid by synthesis.

SYNTHESIS OF ORICINE

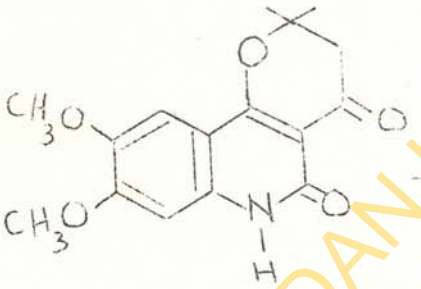
A possible intermediate in the synthesis of oricine was thought to be 6,7-dimethoxy-4-hydroxy-2-quinolone (XCVII). Reaction of this compound with ββ-dimethyl acrylcyl chloride (by the method of Brown et al.[44] in the synthesis of flindersine) would give, it was hoped, the ester (XCVIII) which would then isomerise and cyclise to give the ketone (XCIX). Reduction of the ketone followed by dehydration was expected to give the compound (C) which should be converted to (XCV) by methylation with diazo methane.

Various Attempts at the Synthesis of 6,7-dimethoxy-4-hydroxy-2-quinolone

A method of preparing a 4-hydroxy-2-quinolone is by refluxing an arylamine with malonic ester in a high boiling solvent. The arylamine required in the synthesis of the 6,7-dimethoxy-4-hydroxy-2-quinolone was 6-aminoveratrole and this was made from catechol[71]. Catechol was methylated with a mixture of dimethyl sulphate and caustic potash at below 0°C. The veratrole (CI) formed was nitrated with a mixture of nitric acid (D 1.42) and water (1:1) by the method of Cardwell and Robinson[72]. Attempted catalytic reduction of the nitroveratrole (CII) using 10% palladised charcoal at 3 atmospheres was unsuccessful. Reduction of the nitroveratrole to the aminoveratrole (CIII) was effected chemically by refluxing the nitro compound with

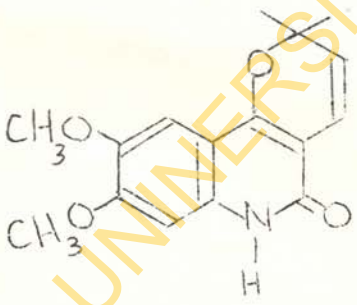


(1) isomerise
(2) cyclise



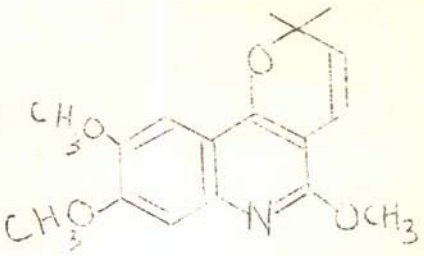
(XCIX)

(1) reduce
(2) dehydrate

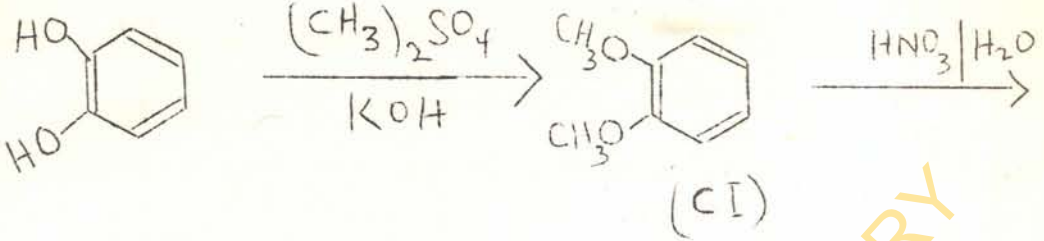


(C)

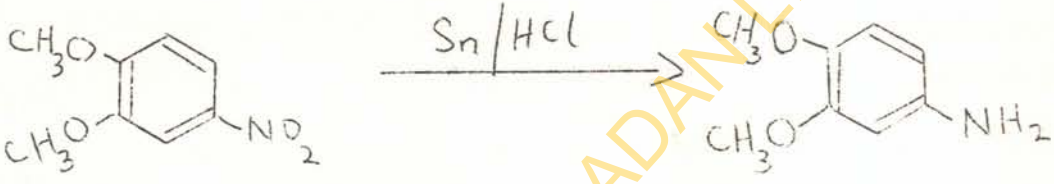
CH_2N_2



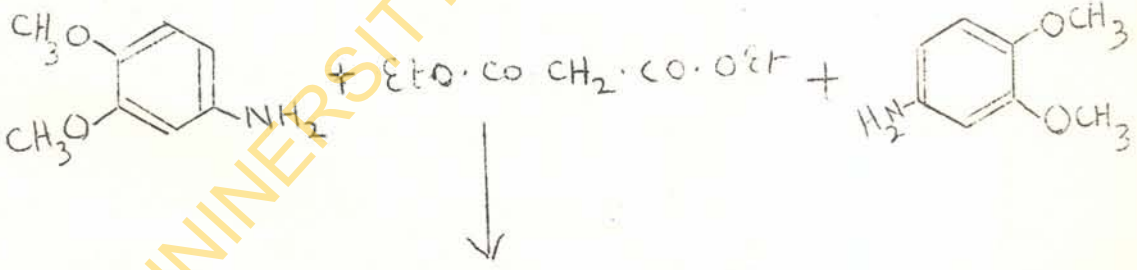
(XCV)

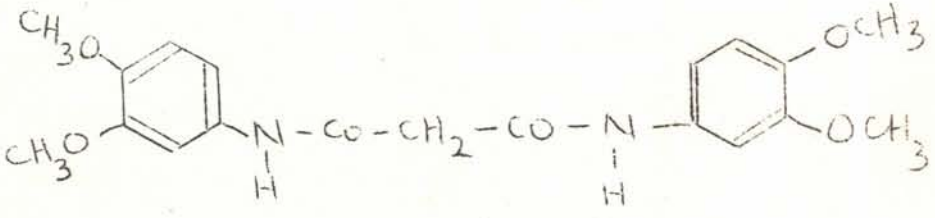


(CI)



(CII) (CIII)





(CIV)

tin in 50% hydrochloric acid[73]. The aminoveratrole was a low melting solid (m.p. 76°) which quickly darkened on exposure to air. The infra-red spectrum showed the characteristic absorption for the $-NH_2$ group as a doublet at ν_{max} 3333 cm^{-1}.

Attempted condensation of the amino-veratrole with diethyl malonate by refluxing the mixture in diphenyl ether gave, on cooling, a greyish solid, m.p. 210°C.

Molecular weight from the mass spectrometer was found to be 360. The fact that the molecular weight was even suggested that either there was no nitrogen atom in the molecule of the product or that there were two nitrogen atoms in the product. The solid was insoluble in chloro-form and its n.m.r. spectrum in deutero-chloroform could not be taken. That the compound contained two nitrogen atoms was proved by Lassaigne's test.

It was, likely, that the solid formed was a di-anilide (CIV) formed probably by the condensation of two moles of dimethoxy-aniline (6-aminoveratrole) and one mole of malonic ester.

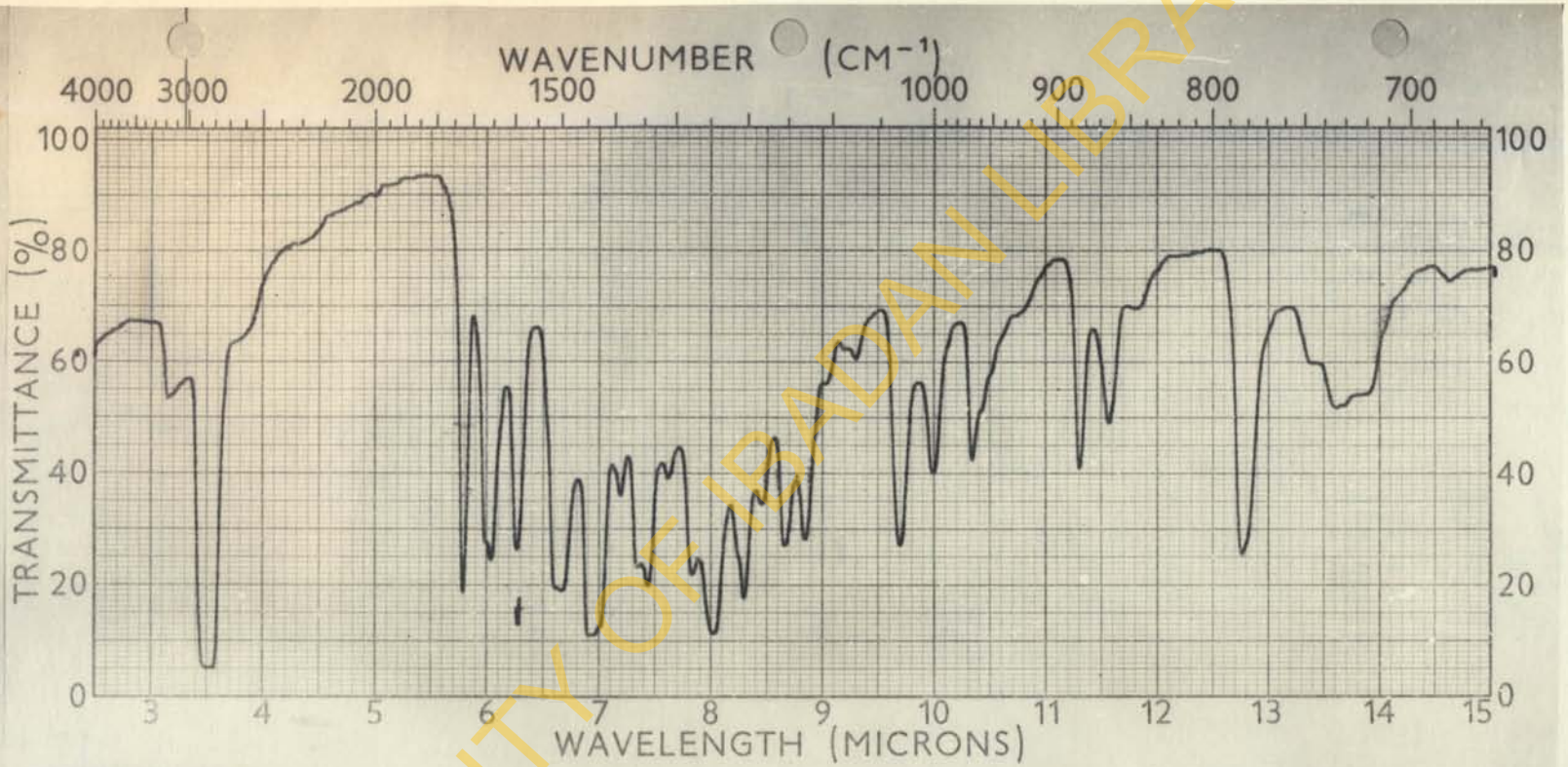
Another approach to the 6,7-dimethoxy-4-hydroxy-2-quinolone by the way of an anthranilate was sought. Lutz et al.[65] had made 4-hydroxy-2-quinolone by heating methyl anthranilate with malonic ester and the resulting anthranilide was cyclised with sodium methoxide.

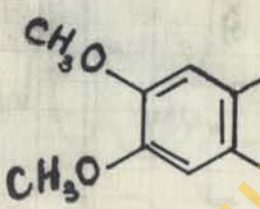
The resulting 3-carboxyl-4-hydroxy-2-quinolone, after hydrolysis, was decarboxylated to the required 4-hydroxy-2-quinolone.

The synthesis of 6,7-dimethoxy-4-hydroxy-2-quinolone was attempted by adopting the above method. This involved making methyl veratrate (methyl 3,4-dimethoxy anthranilate) (CXI) from vanillin (CV).

Vanillin was methylated with dimethyl sulphate and caustic soda to give veratraldehyde (CVI). This was converted into veratraldoxime (CVII) which was dehydrated with acetic anhydride to give veratronitrile (CVIII)[74a]. The nitrile was hydrolysed by 10% caustic soda solution[74b] and the resulting veratric acid was methylated with methanol containing a few millilitres of sulphuric acid[74c] to give methyl veratrate (CIX). Nitration of the methyl veratrate with a mixture of nitric acid and acetic acid[75] gave methyl 6-nitro veratrate (CX) which was reduced chemically with stannous chloride and hydrochloric acid[75] to give methyl 6-amino-veratrate (CXI) n.p. 127°C.

Condensation of the methyl 6-amino veratrate (methyl 3,4-dimethoxy anthranilate)(CXI) with malonic ester gave a solid material, m.p. 75°C, soluble in chloroform. The infra-red spectrum (fig. 12) showed a sharp ester band at ν_{max} 1724 cm^{-1} and a carbonyl band of probably an amide at 1667 cm^{-1}. The n.m.r. spectrum (fig. 13) showed the presence of an ethoxy group $-OCH_2CH_3$ [triplets at δ 1.32





m. p. 75°C

FIG. 12

Nujol

NT

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REMARKS This is the product obtained when [illegible] was condensed with malonic ester

NO.

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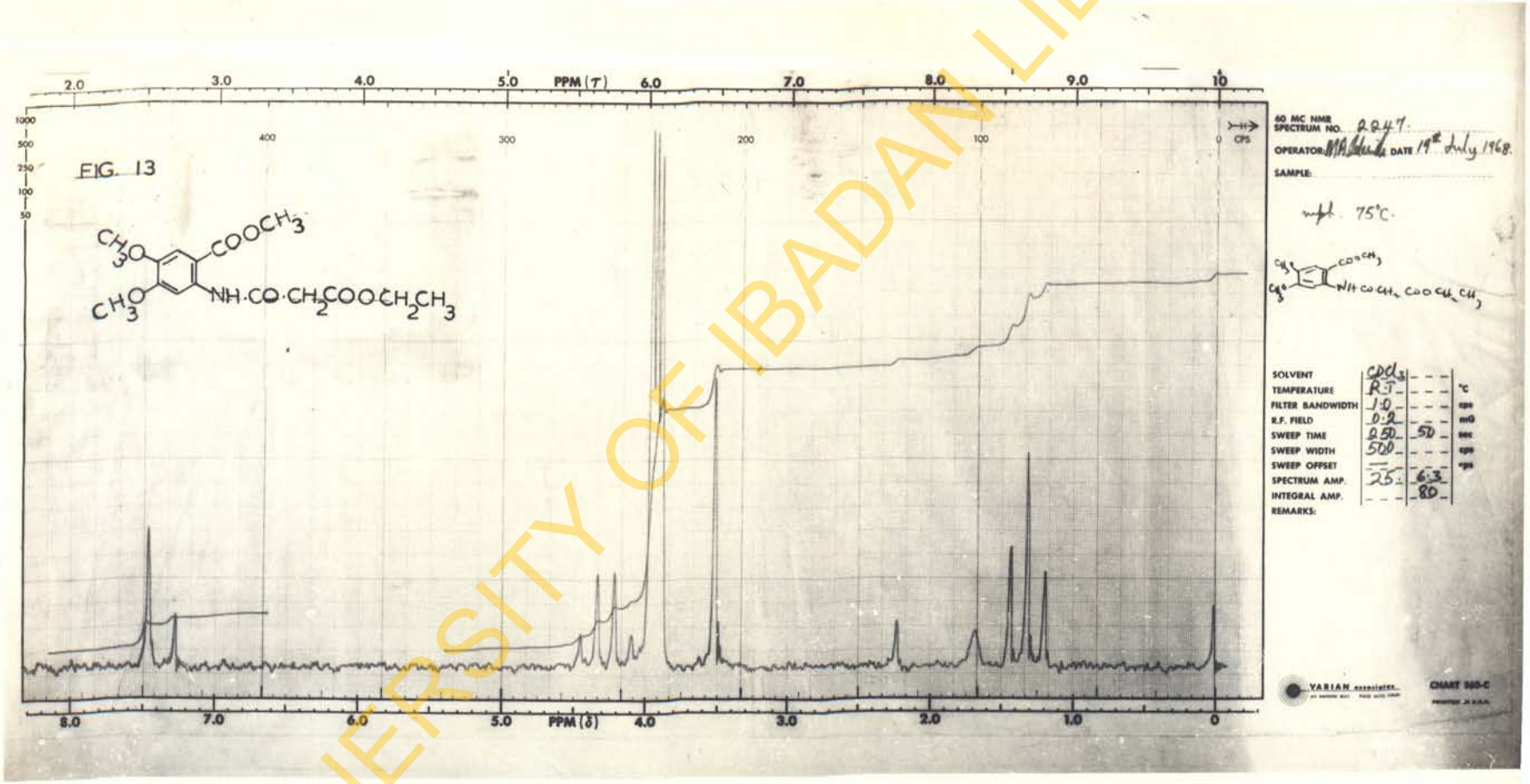
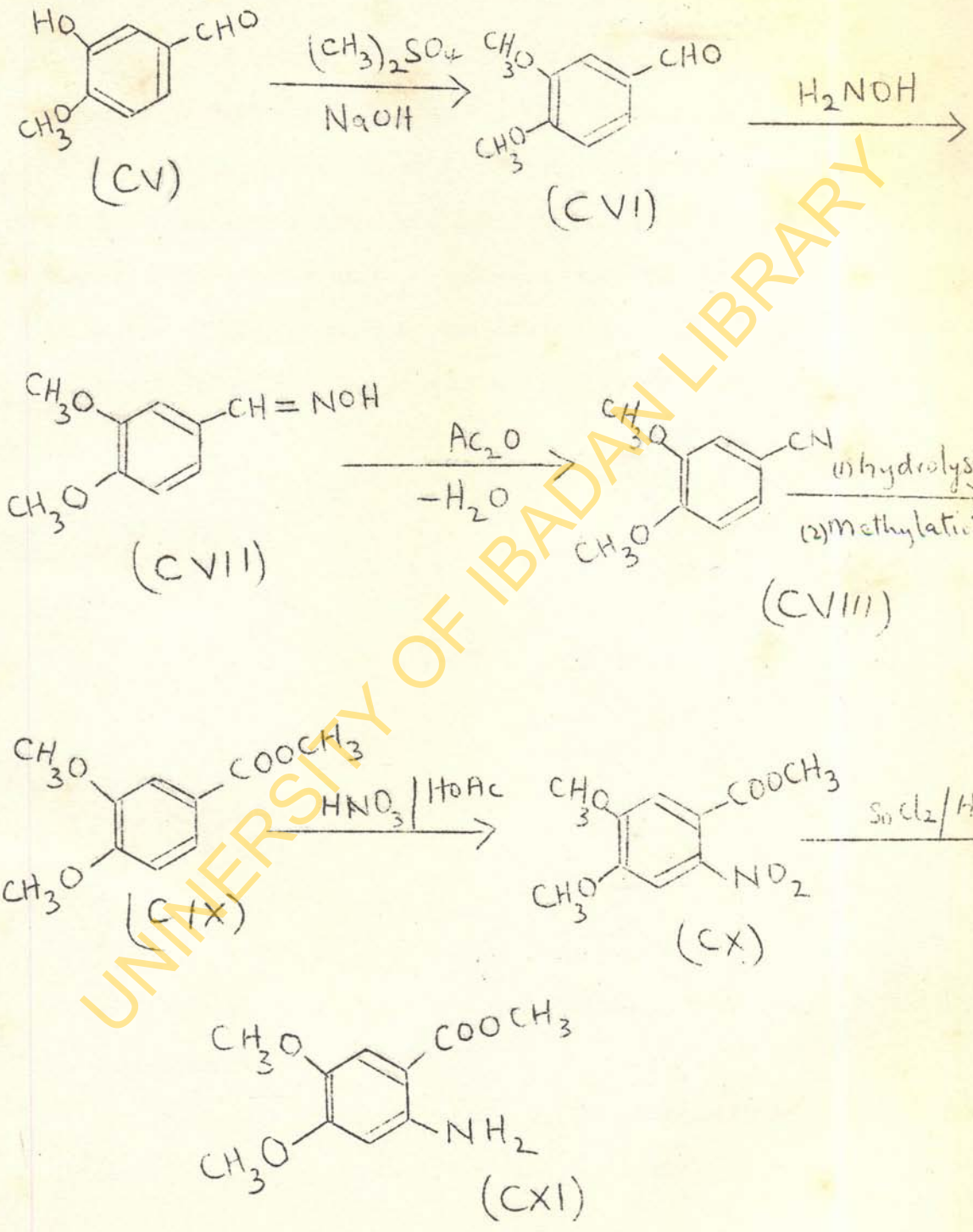
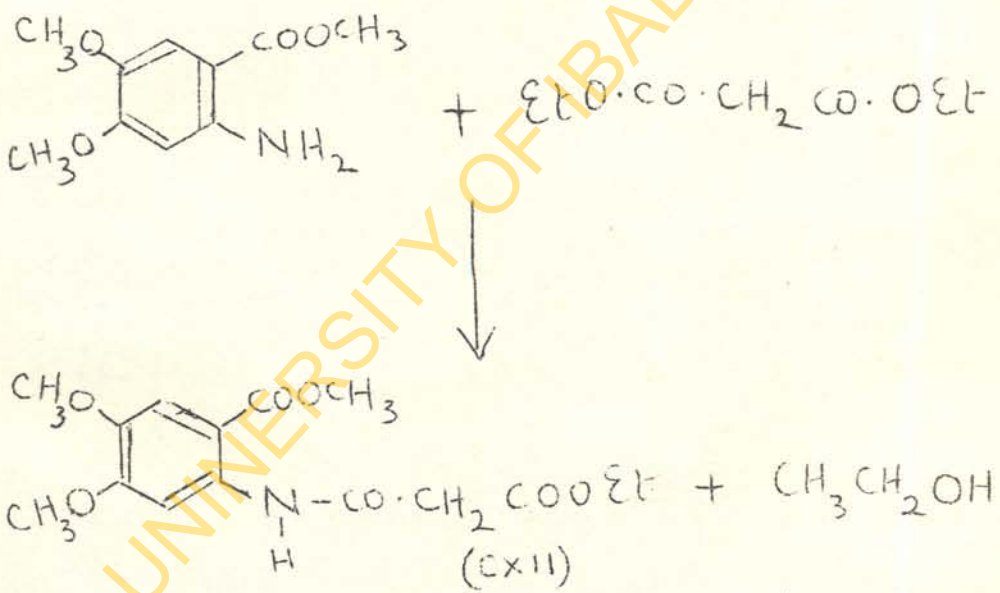




(J = 7 c/s) and quartet at δ 4.29 (J = 7 c/s) , three $-OCH_3$ groups at δ 3.90, δ 3.93 and δ 3.97. There was a sharp singlet at δ 3.52 counting for two protons. The molecular weight of the compound from the mass spectrometer was found to be 335. From these spectral evidences, we arrived at the conclusion that the product was the mono-malonamide (CXII) formed by the condensation of 1 mole of methyl 6-aminoveratrate with one mole of malonic ester thus:

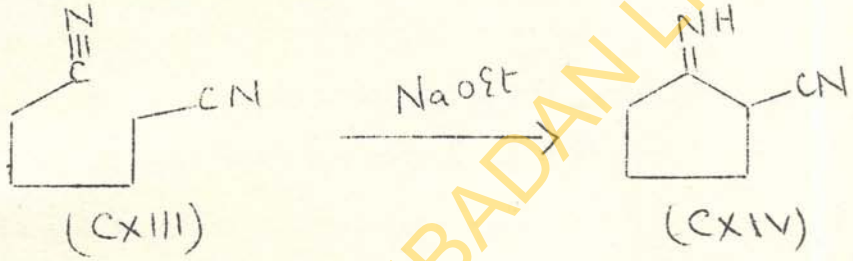


Attempted cyclisation of the mono-malonamide . with sodium methoxide was unsuccessful.

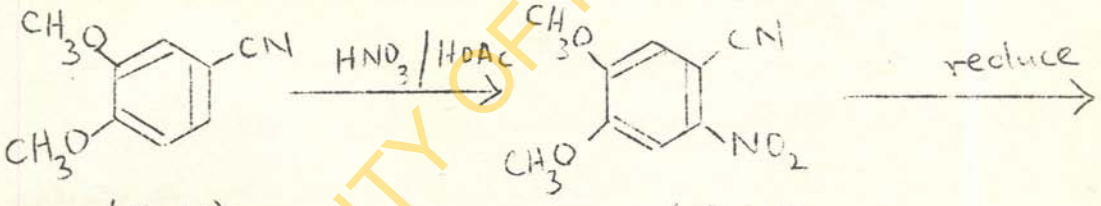
Another attempt at making the 6,7-dimethoxy-4-hydroxy-2-quinolone was sought via N-acetyl veratronitrile. Thorpe had reported[76]

the formation of 1-imino-2-cyano-cyclo-pentane (CXIV) by the cyclisation of adiponitrile (CXIII) with sodium ethoxide.

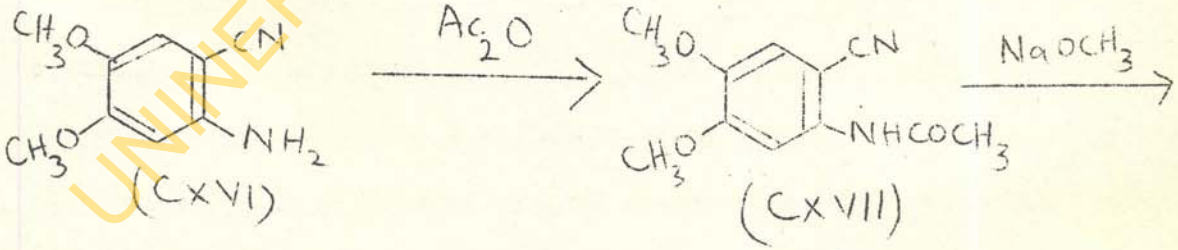
It was hoped that a similar cyclisation of 6-N-acetyl veratronitrile (CXVII) would give 6,7-dimethoxy-4-imino-2-quinolone (CXVIII) which should then hydrolyse to the required 6,7-dimethoxy-4-hydroxy-2-quinolone (XCVII) as shown below :



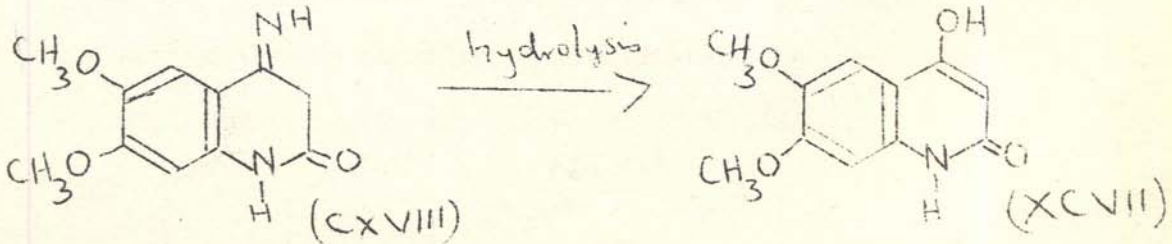
(CXIII) (CXIV)



(CVI) (CXV)



(CXVI) (CXVII)



(CXVIII) (XCVII)

The 6-N-acetyl veratronitrile was prepared from veratronitrile (CVI). Nitration of veratronitrile with a mixture of acetic acid and nitric acid (D 1.42) at room temperature gave a quantitative yield of 6-nitroveratronitrile (CXV) which was reduced with stannous chloride and methanolic hydrochloric acid to give a quantitative yield of 6-aminoveratronitrile (CXVI) m.p. 90°C - 92°C.

The reduction of 6-nitroveratronitrile to the amino compound was found to be much more facile and gave more quantitative yield of the product than the reduction of methyl 6-nitroveratrate. That this was so could be explained by the fact that the nitro group in the 6-nitroveratronitrile was less sterically hindered than the nitro group of the methyl 6-nitroveratrate.

Acetylation of 6-amino veratronitrile (CXVI) with acetic anhydride and a few drops of sulphuric acid at room temperature gave the N-acetyl veratronitrile (CXVII) as a white crystalline substance m.p. 195°C - 196°C.

Cyclisation of N-acetyl veratronitrile was attempted by refluxing the nitrile with sodium ethoxide in absolute ethanol. On adding the reaction mixture to cold water, fine, cream-coloured crystalline substance (m.p. 138°) which was soluble in chloroform was obtained. The infra-red spectrum did not show any carbonyl band. The n.m.r. spectrum in deutero-chloroform (fig. 14) showed the

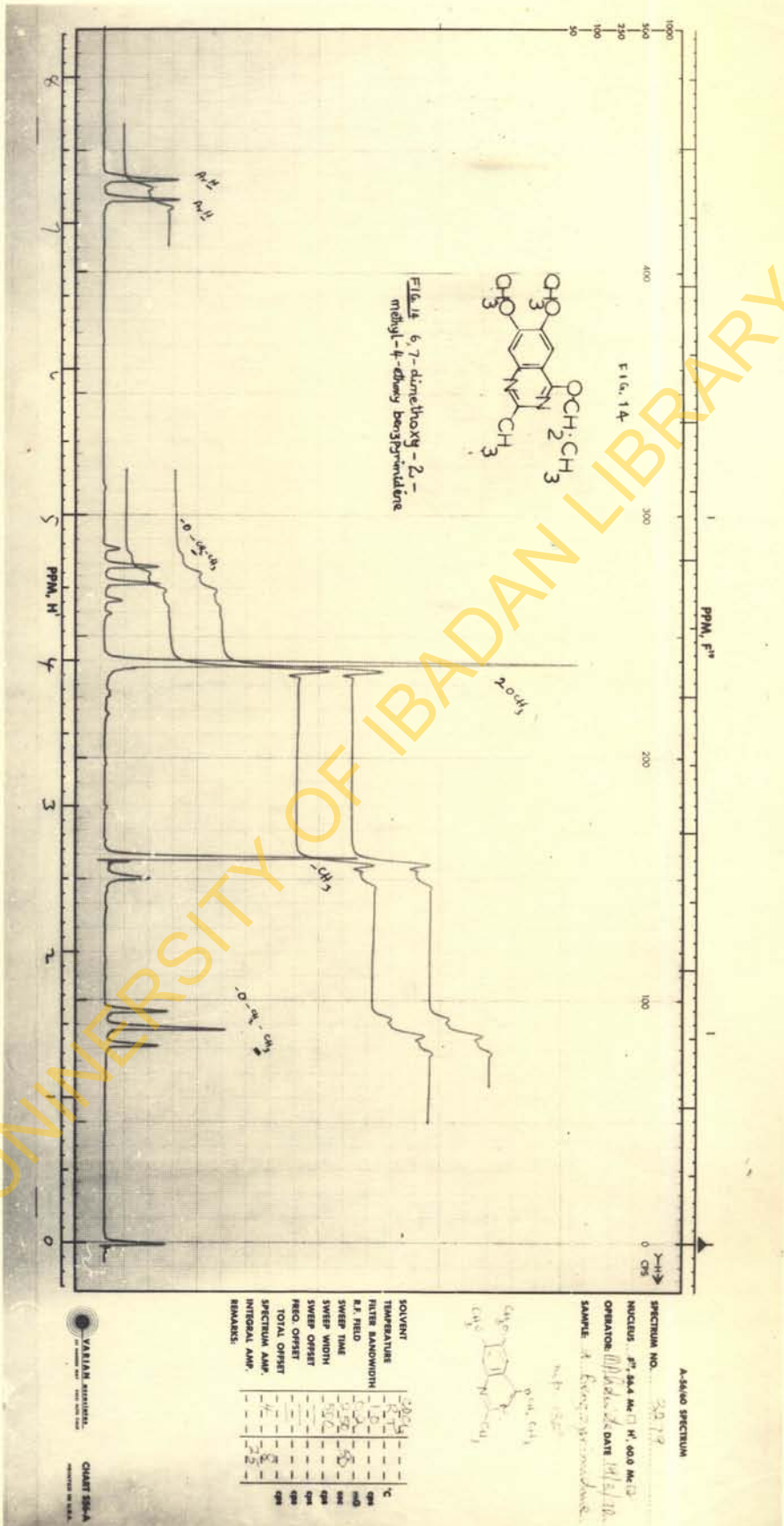
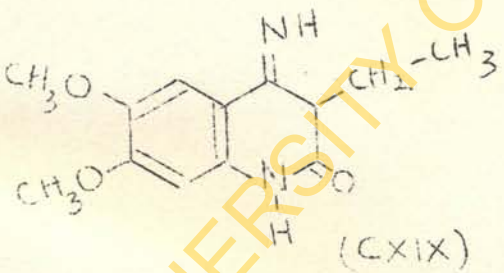


FIG. 14

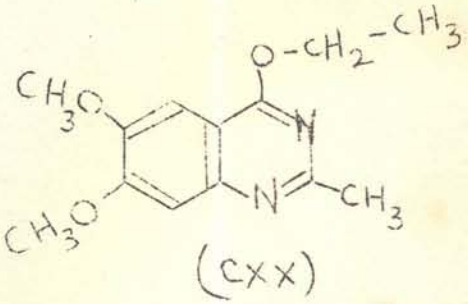
FIG. 14 6,7-dimethoxy-2-methyl-4-ethoxy benzpyrimidine

presence of an ethoxy group $-OCH_2CH_3$ [triplet at δ 1.45 (J = 7 c/s) and a quartet at δ 4.59 (J = 7 c/s)]. There was a singlet at δ 2.65 counting for three protons and this was attributed to a methyl group. The singlet at δ 3.98 counting for six protons was attributed to two methoxy groups and there were two aromatic proton signals at δ 7.17 and δ 7.30. The molecular weight was found to be 248 from mass spectrometer and this combined with the elemental analysis suggested the molecular formula $C_{13}H_{16}O_3N_2$ for the product.

From the n.m.r. spectrum, two possible structures could be written down for this compound, the quinolone structure (CXIX) or the benz - pyrimidine (CXX).



(CXIX)

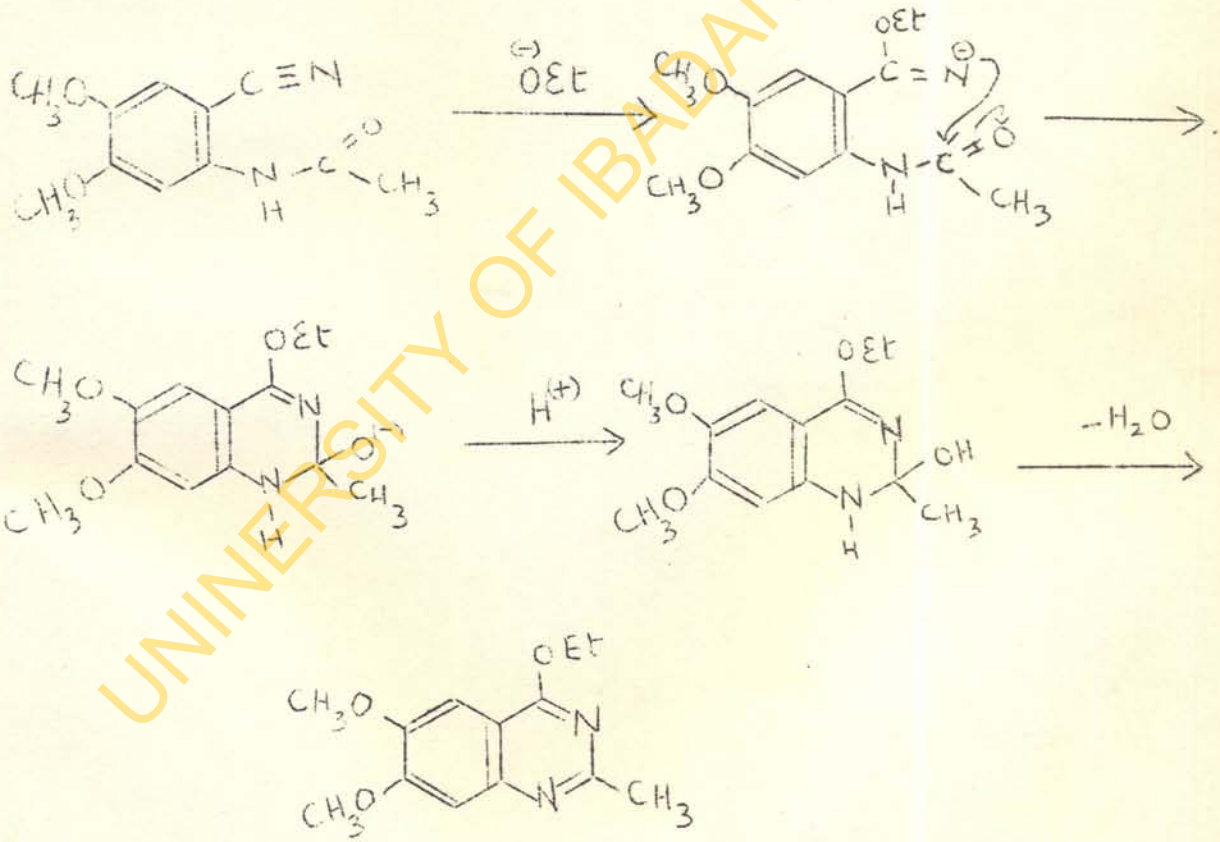


(CXX)

The quinolone structure (CXIX) could not have been the true structure of the compound because infra-red spectrum did not show the presence of a carbonyl band. The n.m.r. spectrum indicated the presence of $-OCH_2CH_3$ and not $C-CH_2\ CH_3$ because of the downfield chemical shift of the quartet attributed to the methylene group. The methyl signal

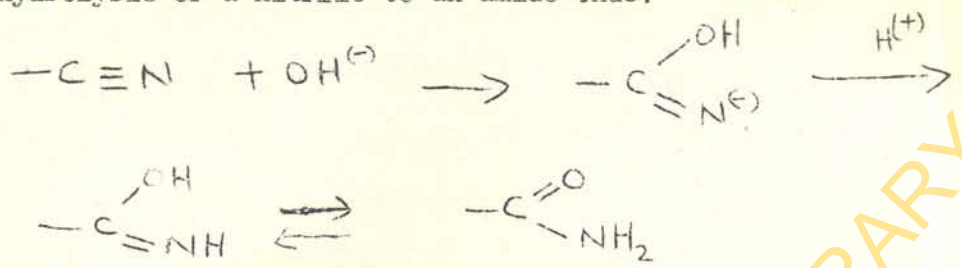
at δ 2.65 in the n.m.r. spectrum of the product was not accounted for in this structure. The structure of the compound was, therefore, likely to be (CXX). The fact that the three-proton signals at δ 2.65 was a sharp singlet justified its position in the benz-pyrimidine structure.

The cyclisation of N-acetyl veratronitrile to the dimethoxy benz-pyrimidine (CXX) took place probably by the mechanism below:

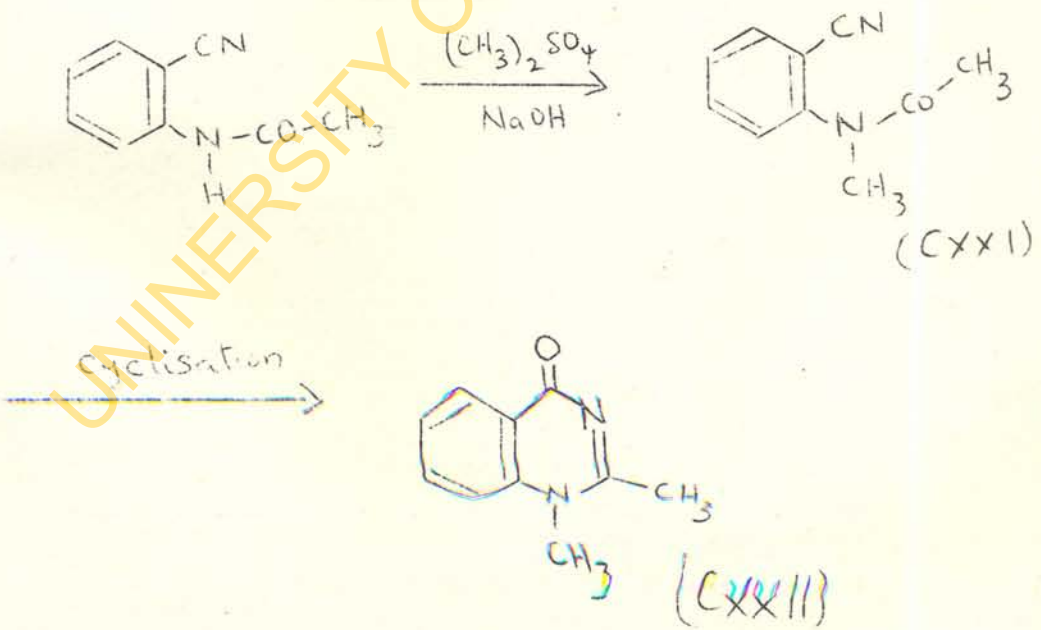


The cyclisation reaction is very similar to the mechanism of the

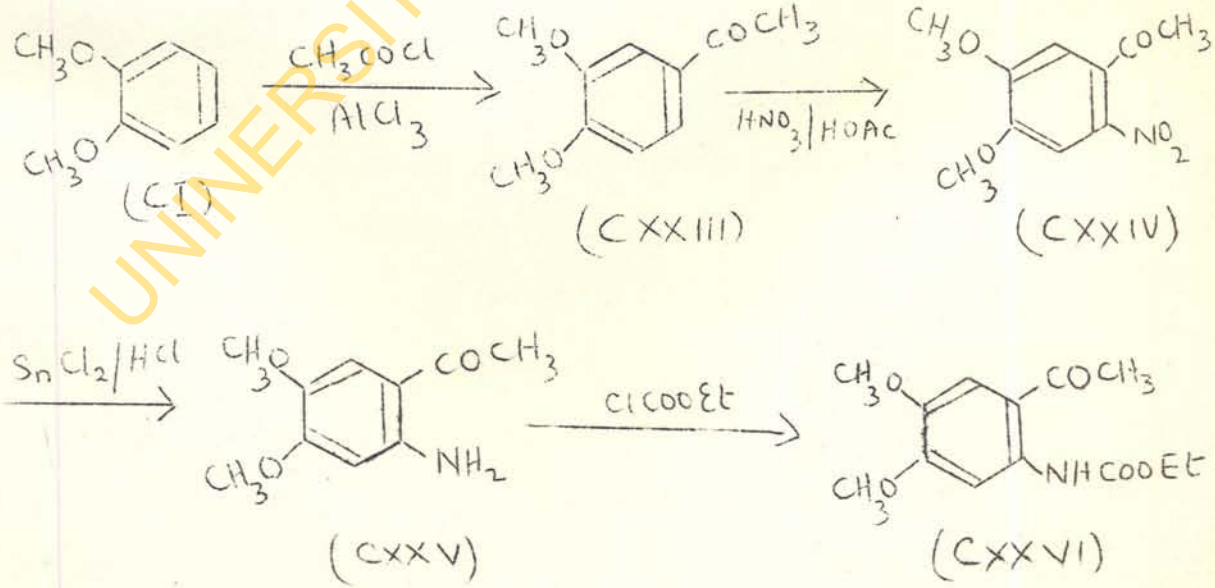
hydrolysis of a nitrile to an amide thus:



The accidental cyclisation of N-acetyl veratronitrile (CXVII) to 2-methyl-4-ethoxy-6,7-dimethoxy benz-pyrimidine (CXX) is similar to the cyclisation of N-methyl-N-acetyl anthranilonitrile (CXXI) to 1-methyl-2-methyl benz-pyrimidine (CXXII) with hydrogen chloride gas in dry methanol recently reported by E. C. Taylor and Y. Shvo[78].



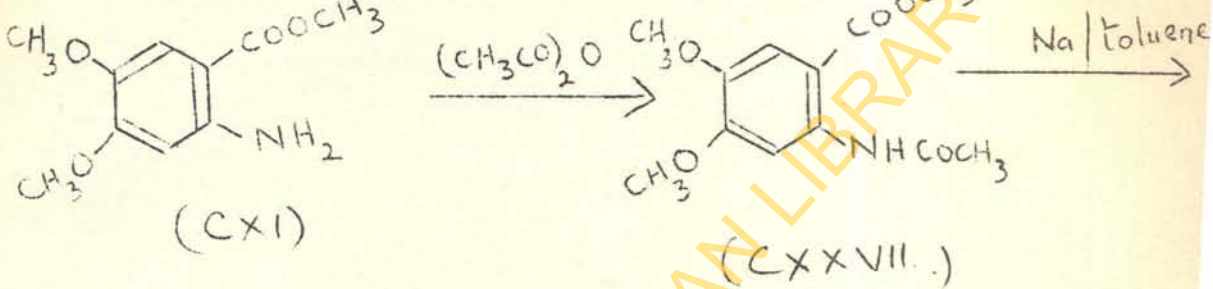
In search of a suitable intermediate that would cyclise to the required 6,7-dimethoxy-4-hydroxy-2-quinolone, N-ethyl-acetoveratrone formate (CXXVI) was thought of as a possibility. This was made from veratrole thus : Friedel-Crafts acylation of veratrole[79] gave a good yield of acetoveratrole (CXXIII) which was nitrated with a mixture of acetic acid and nitric acid (D.1.42). The nitro compound was reduced by stannous chloride and methanolic hydrochloric acid to give 6-amino acetoveratrone (CXXV). Reaction of the 6-amino acetoveratrone with ethyl formate gave the required N-ethyl acetoveratrone formate (CXXVI) recognised by its n.m.r. spectrum. Attempted cyclisation of the N-ethyl acetoveratrone formate with sodium ethoxide was unsuccessful; the starting material identified by the infra-red and n.m.r. spectra was recovered.



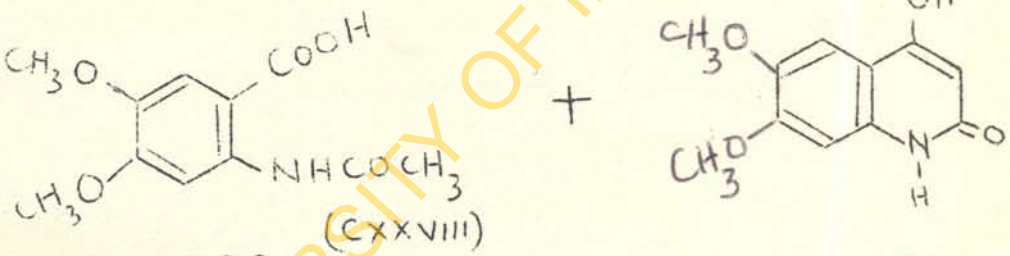
It was thought that, perhaps, methyl N-acetyl veratrate (CXXVII) might cyclise with sodium hydride to the required 6,7-dimethoxy quinolone. methyl 6-amino veratrate (CXI) was converted to methyl N-acetyl-veratrate by acetic anhydride and a few drops of sulphuric acid at room temperature. The methyl N-acetyl veratrate was refluxed with sodium hydride in benzene and the product obtained after destroying the excess sodium hydride was a high melting solid, (m.p. $> 300^{\circ}$) insoluble in chloroform. Methylation of the solid with ethereal diazomethane gave a crystalline substance whose n.m.r. spectrum in deutero chloroform was found to be identical in all respects with the n.m.r. spectrum of methyl N-acetyl veratrate, the starting material. The high melting solid was likely to be N-acetyl veratric acid (CXXVIII). It seemed that the hydrolysis of the ester group of the methyl N-acetyl veratrate to the carboxyl group took place and this could have happened only if there was any trace of water in the reaction mixture.

The cyclisation was repeated using metallic sodium in toluene instead of sodium hydride in benzene. A solid (m.p. $233^{\circ}C$ - $236^{\circ}C$) which was insoluble in chloroform was obtained. The mass spectrum gave very sharp peaks at M^+ 239 and M^+ 221. It seemed from the mass spectrum that the solid was a mixture of two substances with the above molecular weights. The required 6,7-dimethoxy-4-hydroxy-2-quinolone ($C_{11}H_{11}O_4N$) should have a molecular weight of 221, and 239 could be

the molecular weight of the N-acetyl veratric acid (CXXVIII) ($C_{11}H_{13}O_5N$).



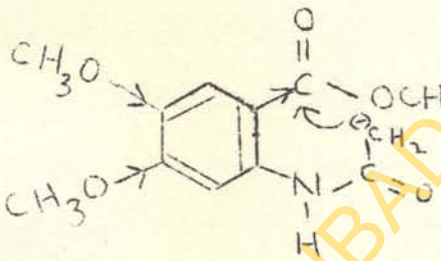
(CXI) (CXXVII.)



239 (CXXVIII) 221

The difficulty in cyclising methyl N-acetyl veratrate could be explained by the fact that cyclisation depends on the attack of $\overset{(-)}{-}CH_2$ on the carbon joined directly to the benzene ring in the ester group of the veratrate. There are two electron-donating methoxy groups,

supplying electrons to the benzene ring, thus making the methyl 6-N-acetyl veratrate less reactive than methyl N-acetyl anthranilate (which has none of such electron donating groups). With electron donation to this carbon atom of the ester group of the methyl N-acetyl veratrate as shown below, the attack of the $\overset{(-)}{-CH_2}$ on it becomes difficult

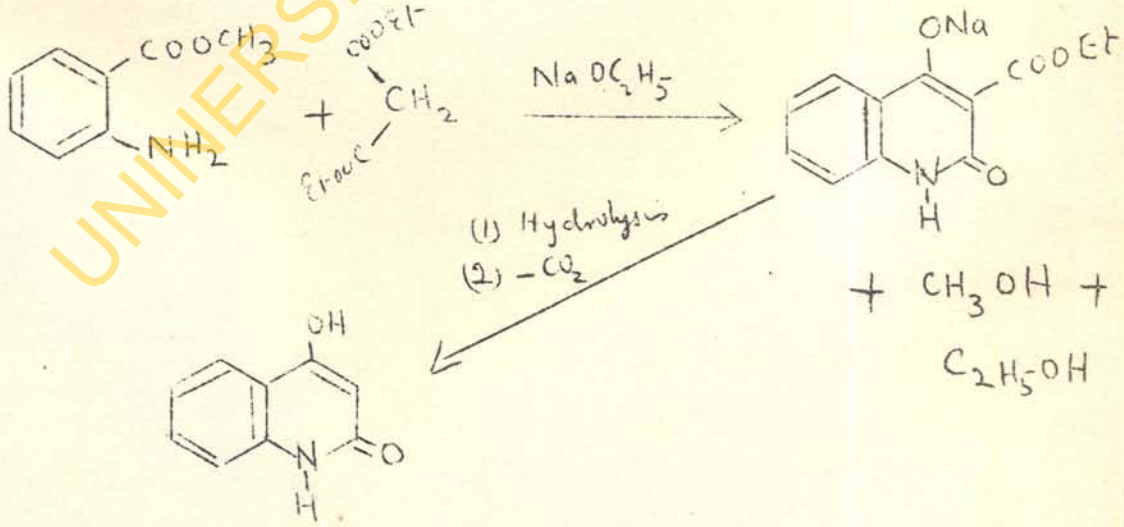


and if there is any competing reaction such as hydrolysis, it would be preferred. With any slight trace of water either in the solvent of the reaction or in the reactants, hydrolysis would preferrentially take place.

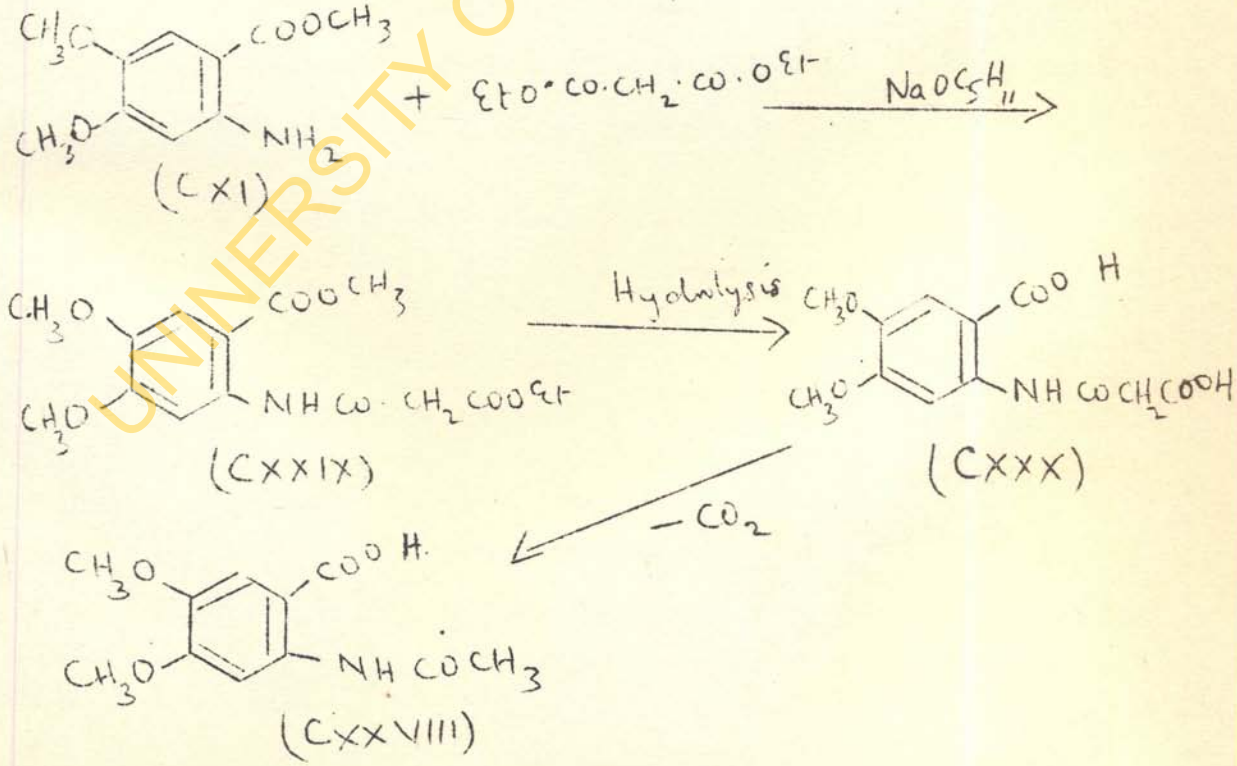
The experiment was, therefore, repeated using dried toluene. A solid was obtained and this again gave two peaks in the mass spectrum at 221 and 239, but the 221 peak was much stronger than the 239 peak, indicating a larger proportion of the required 6,7-dimethoxy-4-hydroxy-2-quinolone in the mixture. Since the mixture was insoluble in most common organic solvents, separation of the two substances either by column chromatography or preparative thin layer chromatography was not attempted.

Ashley, Perkin Jr. and Robinson[81] used sodium granules instead of chips in a high boiling solvent (toluene) to cyclise methyl N-acetyl-anthranilate to 4-hydroxy-2-quinolone. The use of sodium granules instead of chips provided a larger reaction surface area than the sodium chips. This method was adopted in another effort to cyclise methyl N-acetyl-veratrate. Refluxing the methyl N-acetyl-veratrate with sodium granules in toluene gave a solid which was believed to be mainly N-methyl veratric acid (mass spectrum gave a strong peak at 239, but the 221 was much weaker).

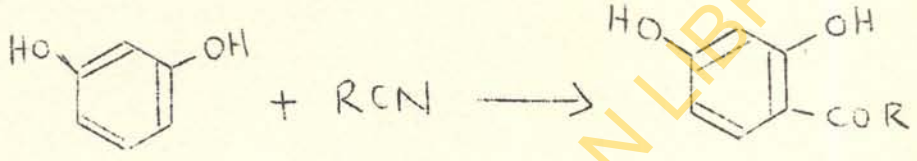
George Koller[82] had prepared 4-hydroxy-2-quinolone by the Claisen condensation of methyl anthranilate with diethyl malonate using sodium ethoxide in a sealed tube at a temperature of above 140°C. The resulting 3-carboxyl-2-quinolone was hydrolysed and decarboxylated to the required quinolone according to the scheme below:



The foregoing method was tried on 6-amino veratrate using sodium amyloxide. A yellow solid, insoluble in chloroform was obtained. The molecular weight from the mass spectrum was 239. Methylation of the solid with ethereal diazomethane gave a crystalline substance recognized as the methyl N-acetyl veratrate by the infra-red spectrum and the melting point. This meant that the yellow solid obtained as a product of the condensation was N-acetyl veratric acid. The condensation of the amino compound and malonic ester probably resulted in the formation of a malonanilide (CXXIX) which was then hydrolysed to the dicarboxylic acid (CXXX). Loss of one of the carboxyl groups of the acid then afforded the N-acetyl veratric acid (CXXVIII).

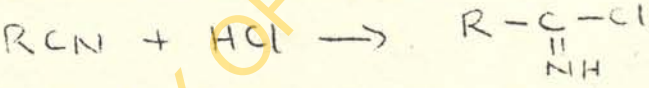


Another route to the 6,7-dimethoxy-4-hydroxy-2-quinolone via Hoesch reaction[83] was explored. The Hoesch reaction consists of the condensation of a nitrile with a phenol, a polyhydric phenol or a phenolic ether to form a hydroxy aryl or an alkoxyaryl ketone, for example :

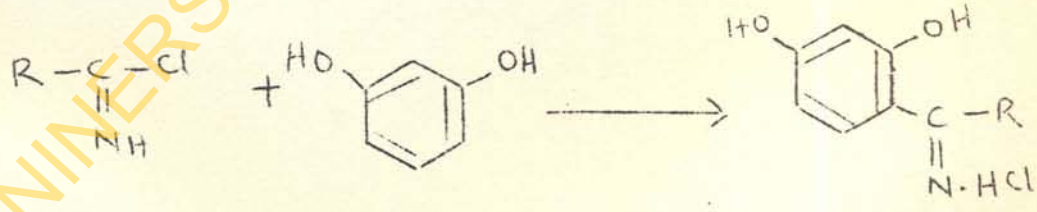


The mechanism of this reaction was assumed by Hoesch as involving three separate steps:

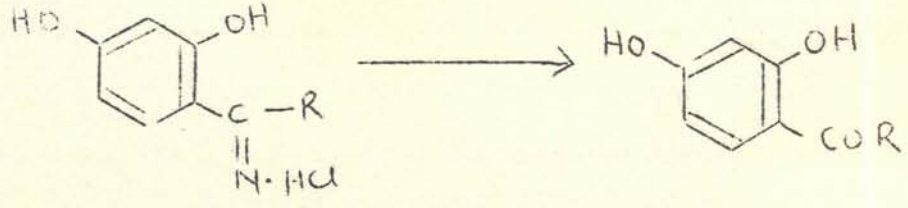
(i) Formation of imino chlorides



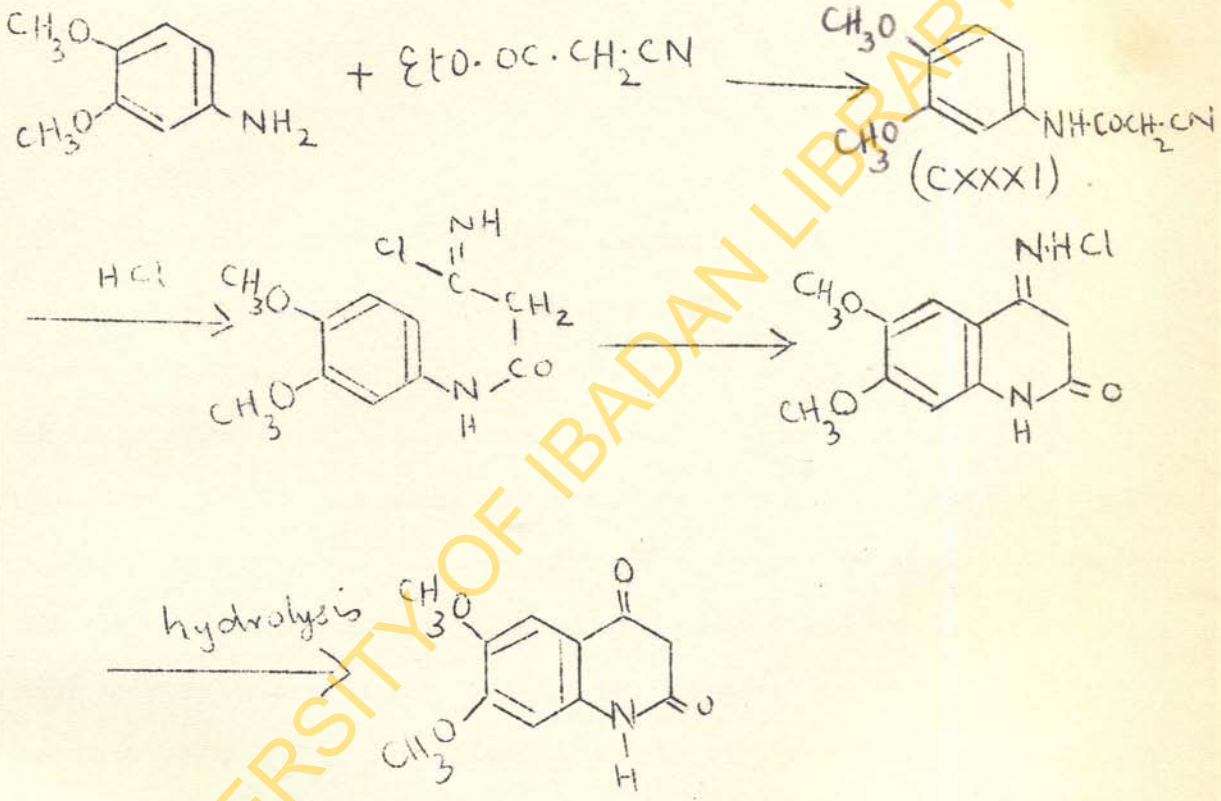
(ii) Interaction of imino chlorides with the phenol or phenol ether to give Ketimine hydrochloride



(iii) Hydrolysis of the Ketimine hydrochloride to the ketone.



It was thought that by a sort of "intramolecular" Hoesch reaction shown below, the 6,7-dimethoxy-4-hydroxy-2-quinolone could be obtained.



The reaction of the amino veratrole with the ethyl cyanoacetate gave the required N-substituted compound (CXXXI) as a yellow amorphous solid, m.p. 232°C - 233°C. It was insoluble in chloroform and hence its n.m.r. spectrum in deuterochloroform was not taken.

Its molecular weight from mass spectrometer (220) agreed with the molecular weight of the expected product. The infra-red spectrum showed the sharp >NH band at ν_{max} 3226 cm^{-1} and the -CN band at ν_{max} 2222 cm^{-1} and the >C = O band at ν_{max} 1653 cm^{-1}. The attempted Hoesch reaction on the solid was unsuccessful. The starting material was recovered.

The condensation of the amino compound, amino veratrole with malonic ester already attempted was repeated. This time, a large excess of malonic ester was refluxed with the amino veratrole in diphenyl ether using a short air condenser to give a solid material m.p. above 300°C. The solid was insoluble in chloroform, but the mass spectrum gave a strong peak at 221 and a relatively weaker peak at 289. Boiling the substance with caustic potash and reprecipitation with hydrochloric acid gave a solid whose molecular weight from mass spectrum gave 221, the molecular weight of the expected 6,7-dimethoxy-4-hydroxy-2-quinolone. The infra-red spectrum (fig. 15) gave the characteristic sharp >NH band at ν_{max} 3448 cm^{-1} and the carbonyl band of a 2-quinolone at 1639 cm^{-1}. It seemed, therefore, that the 6,7-dimethoxy-4-hydroxy-2-quinolone was obtained.

Various attempts to react this with ββ-dimethyl acryloyl chloride according to the method of Brown et al.[44] in the synthesis of flindersine were unsuccessful.

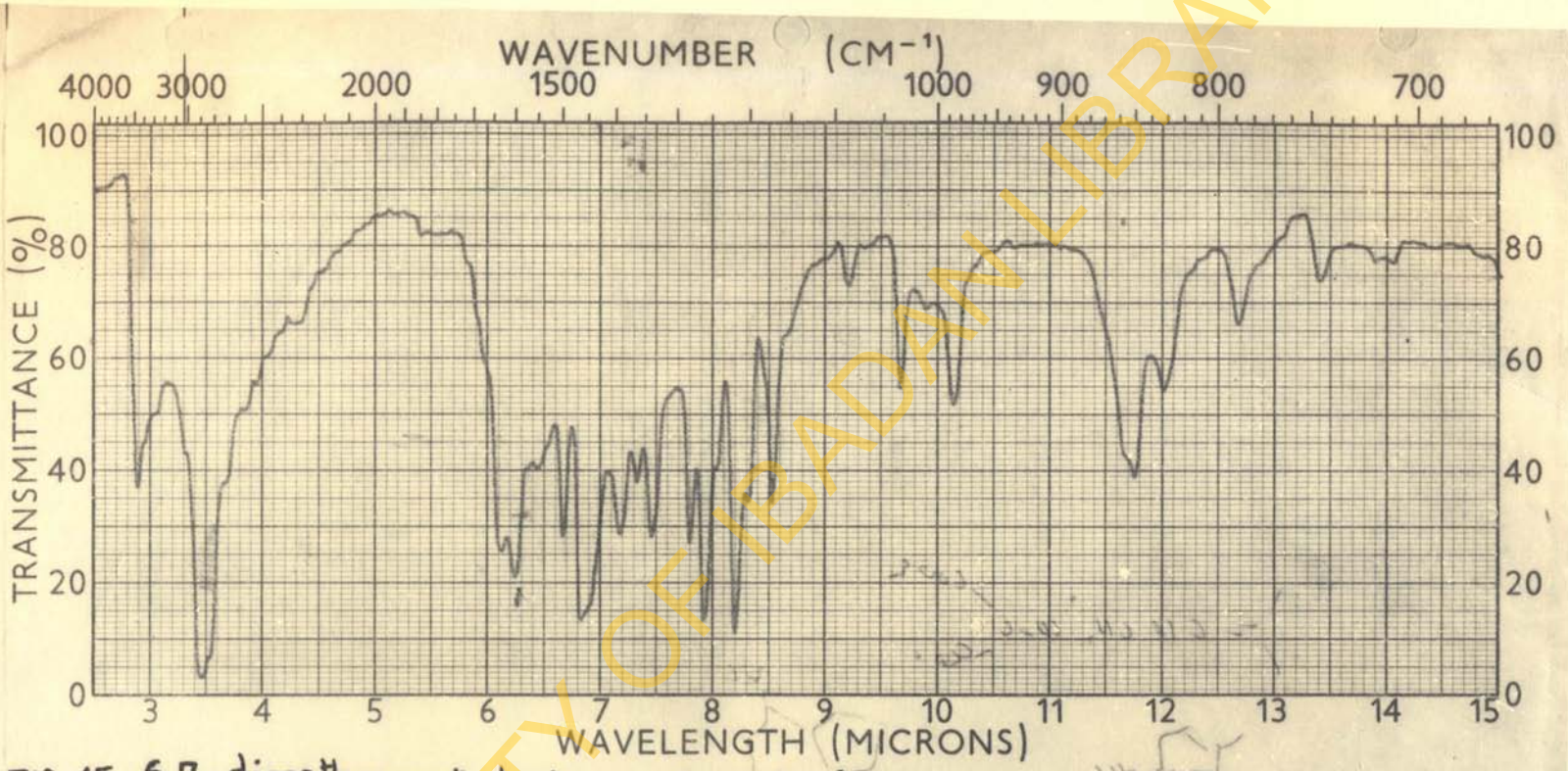


FIG. 15 6,7-dimethoxy-4-hydroxy-2-quinolone

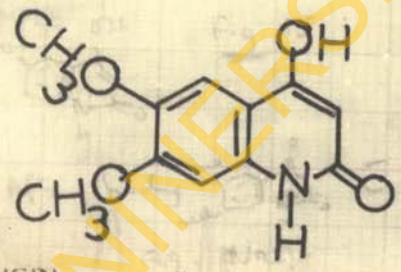


FIG. 15

Nujol

SCAN SPEED Fast SLIT Normal

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REMARKS

ORIGIN v REFERENCE

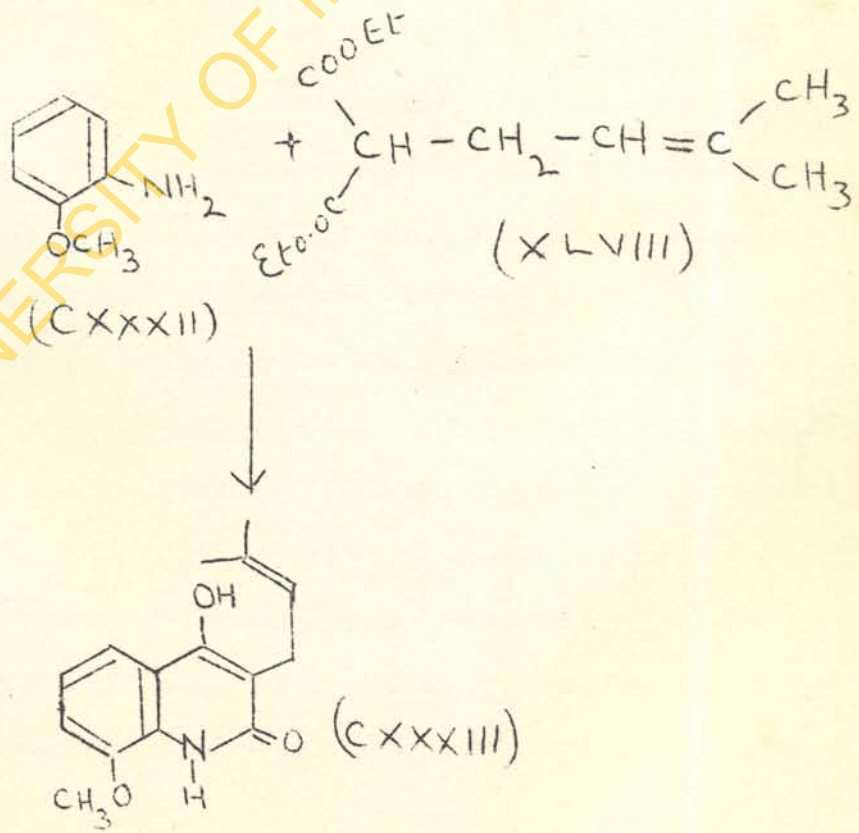
NO.

PART NO. 137E - 1281

PERKIN - ELMER LIMITED, BEACONSFIELD, BUCKS

3-Substituted 4-hydroxy-2-quinolones.

In the syntheses of the Lunasia alkaloids, Clarke and Grundon[41] made a number of 3-substituted 4-hydroxy-2-quinolones by heating arylamines with appropriately substituted malonic esters in high boiling solvents. For instance, 8-methoxy-4-hydroxy-3-(γγ-dimethyl-allyl)-2-quinolone (CXXXIII) was synthesised by refluxing o-anisidine (CXXXII) with diethyl-(γγ-dimethyl allyl) malonate (XLVIII) in diphenyl ether in a blanket of nitrogen. These workers suggested that the 4-hydroxy-3-(γγ-dimethyl allyl)-2-quinolones would cyclise easily to the flindersine-related compounds.

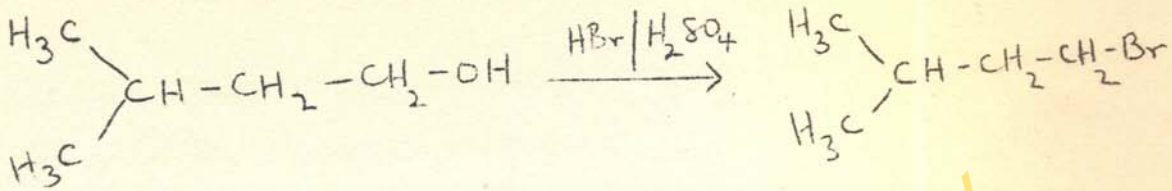


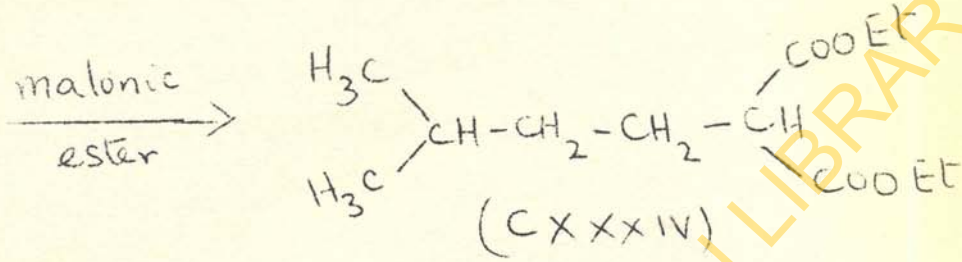
As a check on this malonic ester condensation : 6,7-dimethoxy-4-hydroxy-3-isoamyl-2-quinolone (CXXXV) was prepared. This involved the preparation of isoamyl bromide which was condensed with diethyl malonate to give diethyl-isoamyl-malonate (CXXXIV).

Isoamyl alcohol was brominated by boiling with hydrobromic acid containing a few millilitres of sulphuric acid[84]. The resulting isoamyl bromide b.p. 117° - 120° was condensed with malonic ester by refluxing with sodium methoxide in dried methanol for over six hours[64b]. The substituted malonic ester was refluxed with amino veratrole (CIII) in diphenyl ether to give a good yield of a greyish solid material m.p. 130°C - 135°C.

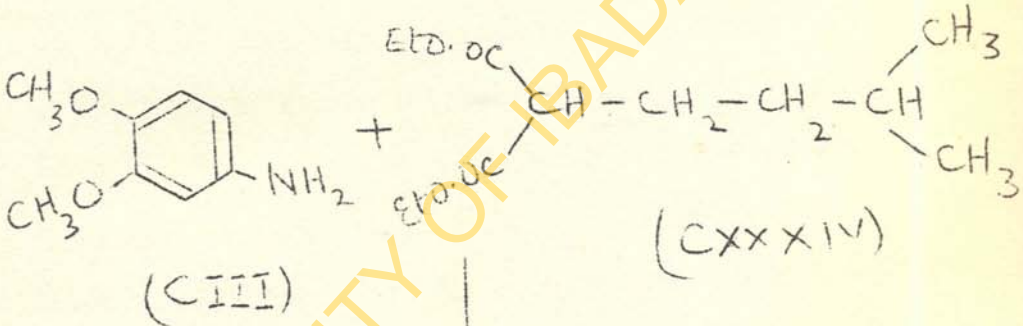
The infra-red spectrum showed the characteristic imino band (>NH) at ν_{max} 3509 cm^{-1} and the carbonyl band of a 2-quinolone at ν_{max} 1639 cm^{-1}. The solid material was insoluble in chloroform, but methylation with ethereal diazomethane converted it into a chloroform-soluble derivative (m.p. 182°C - 184°C). On inspection of the n.m.r. spectrum of the methylated product, it was recognised as the 4,6,7-trimethoxy-3-isoamyl-2-quinolone (CXXXVI). Therefore, the chloroform-insoluble material (m.p. 130° - 135°) was the required 6,7-dimethoxy-4-hydroxy-3-isoamyl-2-quinolone (CXXXV).

It appeared very hopeful, from the above reactions that 6,7-dimethoxy-3-(3'-methyl but -2'-enyl)-4-hydroxy-2-quinolone would be



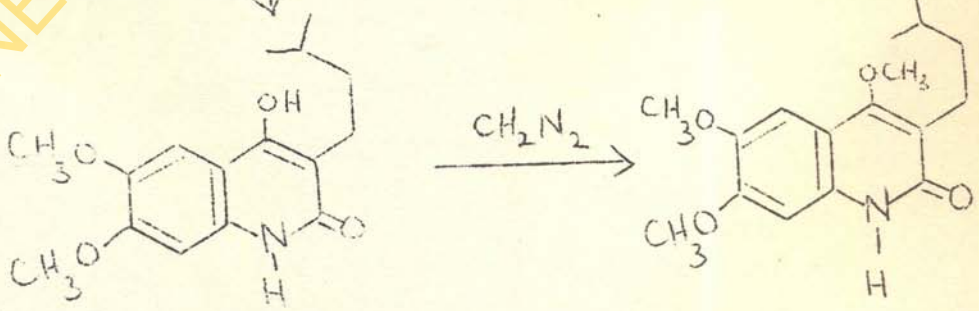


(CXXXIV)



(CIII)

(CXXXIV)

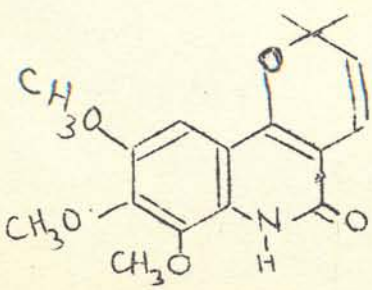


(CXXXV)

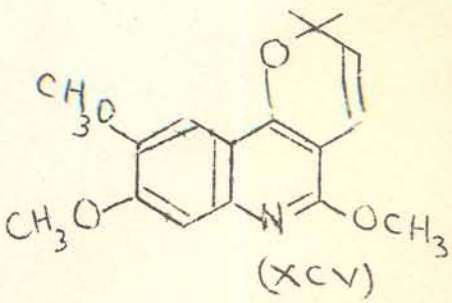
(CXXXVI)

obtained if diethyl-(YY-dimethyl-allyl)-malonate (XLVIII) were used instead of diethyl-isoamyl-malonate.

M. F. Grundon and his colleagues[85] had already synthesised a number of flindersine-related alkaloids in their unpublished work. In one of such alkaloids, the 2-position was o-methylated. From the n.m.r. spectrum of this 2-methoxy alkaloid kindly supplied by Grundon, it was found that the 2-OCH_3 protons showed a sharp signal at a position very similar to the positions of the two methoxy groups in the benzenoid ring of oricine. This meant that the singlet at δ 3.70 in the n.m.r. spectrum of oricine (fig. 9) which was thought to be due to the 2-OCH_3 protons was not in fact due to the 2-OCH_3 protons. If this signal was due to a methoxy group, it was suggested that it could be due to the methoxy group in the 8-position of the alkaloid and that the 8-OCH_3 group being very close to the nitrogen atom at the 1-position could have a different chemical shift from the other methoxy groups in the benzenoid ring. It was, therefore, suggested that the alkaloid, oricine, could have the structure (CXXXVII) rather than the structure (XCV) which was earlier proposed.



(CXXXVII)



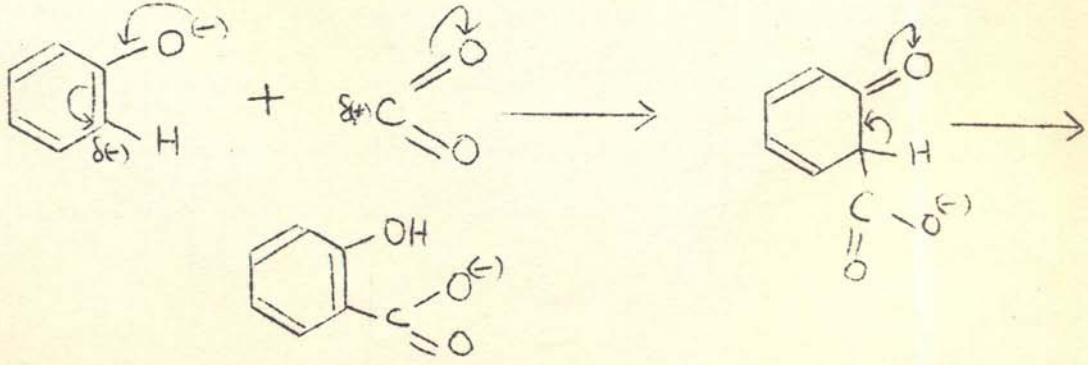
(XCV)

An attempt was, therefore, made to synthesise the 6,7,8-trimethoxy flindersine or its dihydro derivative and compare the physical properties with the natural alkaloid oricine, or dihydro-oricine.

This involved the preparation of 2,3,4-trimethoxy aniline. Condensation of this with diethyl-(3-methyl but-2-enyl) malonate should give 6,7,8-trimethoxy-3-isopentenyl-4-hydroxy-2-quinolone which would then cyclise, perhaps, under acid conditions, to give 6,7,8-trimethoxy dihydro flindersine.

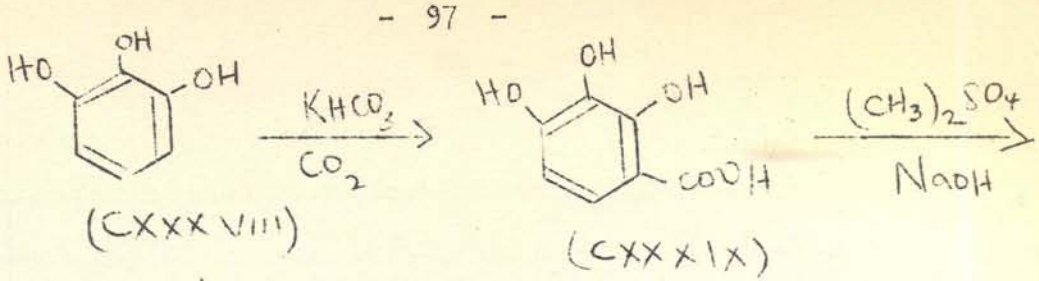
The 2,3,4-trimethoxy aniline was prepared from pyrogallol. Pyrogallol was carboxylated by the method of Kolbe-Schmidt[86]. This is a method of introducing a carboxyl group directly into a phenol nucleus by passing carbon dioxide into a solution of the sodium or potassium salt of the phenol at above 100°C. The reaction is particularly facile with di- and tri-hydric phenols.

The mechanism of the reaction appears to involve the attack by an activated carbon dioxide molecule at the activated ortho position in the phenoxide ion.

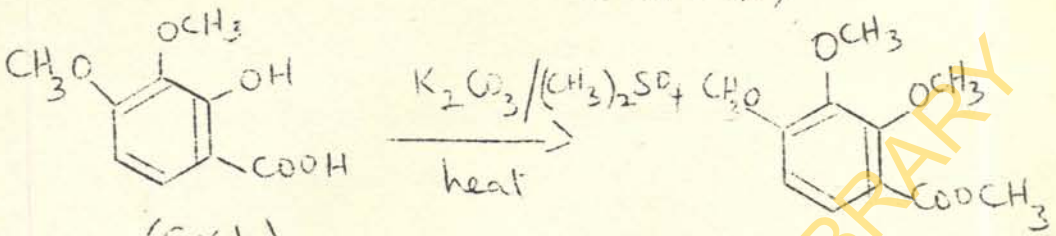


The pyrogallol-carboxylic acid (CXXXIX) obtained was methylated[87] by shaking with a mixture of dimethyl sulphate and caustic soda. Only two of the three hydroxyl groups were methylated by this method to give 3,4-dimethoxy-2-hydroxy benzoic acid (CXL) (m.p. 160°C-164°C). It gave a very intense colour with ferric chloride showing that there was still a free phenolic -OH group. It seemed that the third hydroxyl group next to the carboxy group could not easily be methylated because it was sterically hindered. One method of overcoming sterical hindrance in organic reactions is to increase the temperature of the reaction. At a high temperature, caustic soda could decompose dimethyl sulphate before methylation could take place.

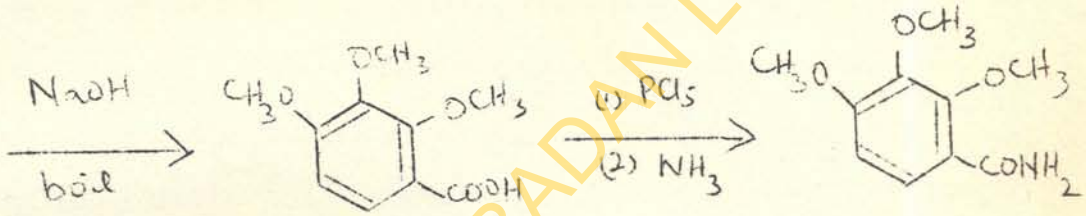
Dimethyl sulphate - potassium carbonate combination in dry acetone had been found to be useful for the methylation of plant phenols[88]. The methylation of the sterically hindered phenolic -OH group in the 3,4-dimethoxy-2-hydroxy benzoic acid (CXL) was effected by boiling the acid with dimethyl sulphate - potassium carbonate (anhydrous) in methyl ethyl ketone (higher boiling solvent than acetone) to give the methyl 2,3,4-trimethoxy benzoate (CXLI) as an oil, which was hyrolysed to the required 2,3,4-trimethoxy benzoic acid (CXLII) (m.p. 90°). It gave no colour change with ferric chloride solution showing that all the phenolic hydroxyl groups had been methylated. The acid (CXLII) was converted to the amide (CXLIII) by reacting the



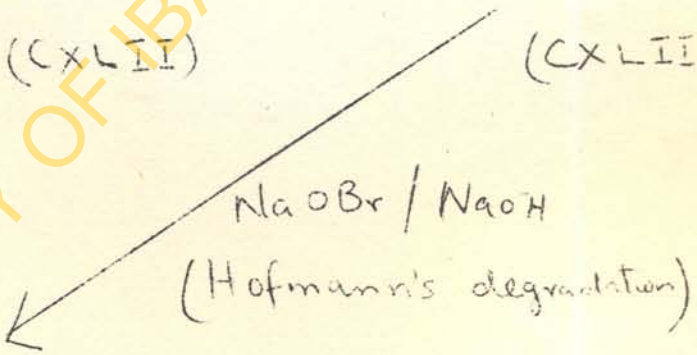
(CXXX VIII) (CXXXIX)

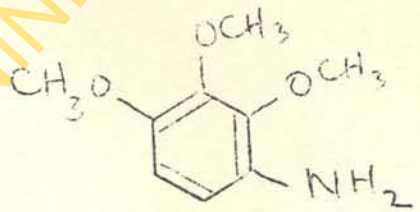


(CXL) (CXLI)



(CXLII) (CXLIII)



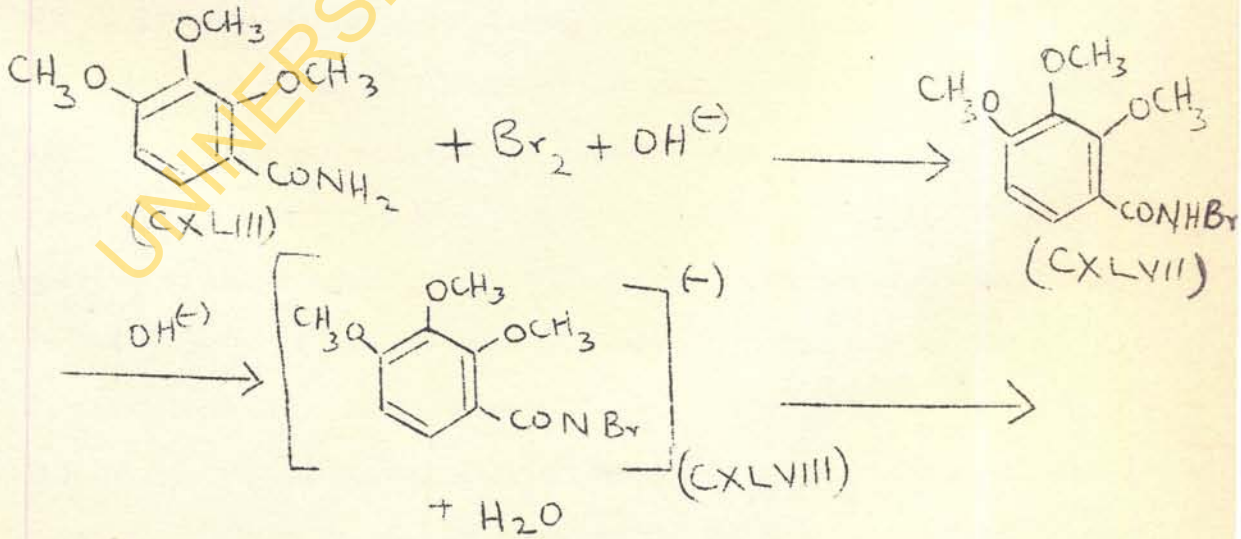


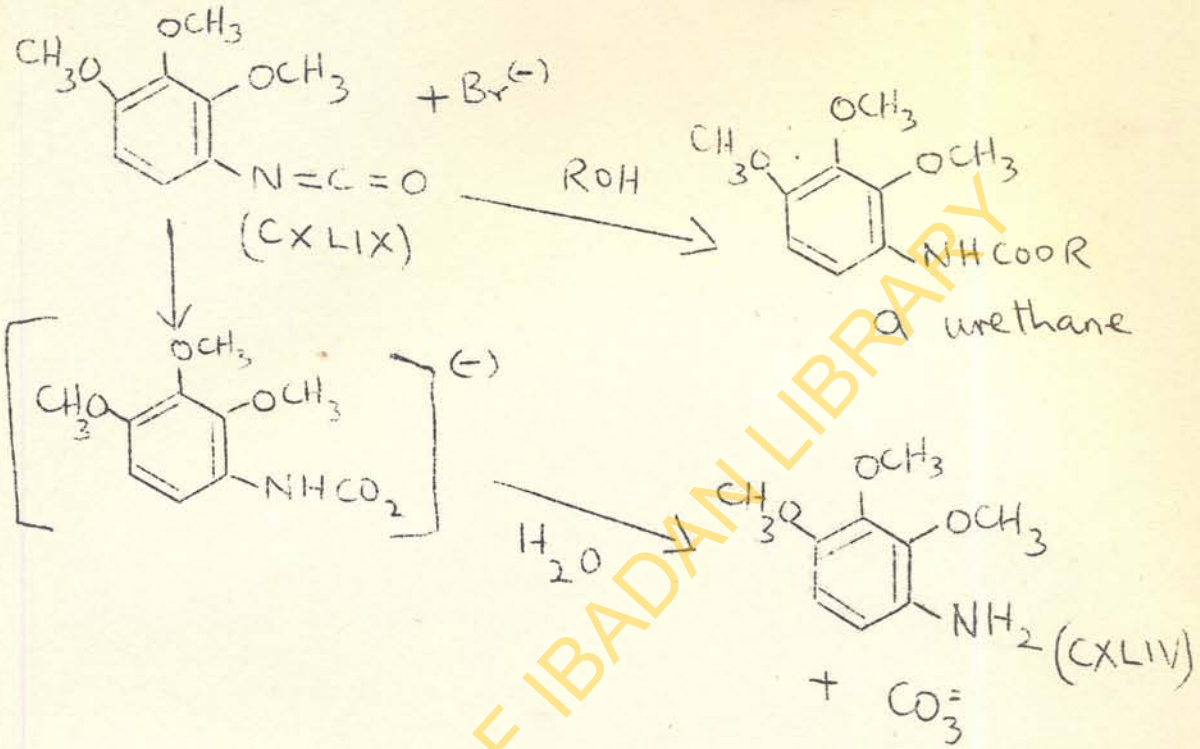
(CXLIV)

acid first, with phosphorus pentachloride to afford the acid chloride which was then shaken with ammonia solution. The amide was converted to the arylamine (CXLIV) by Hofmann's degradation method[87].

The mechanism of Hofmann's degradation is explained as follows:[89]

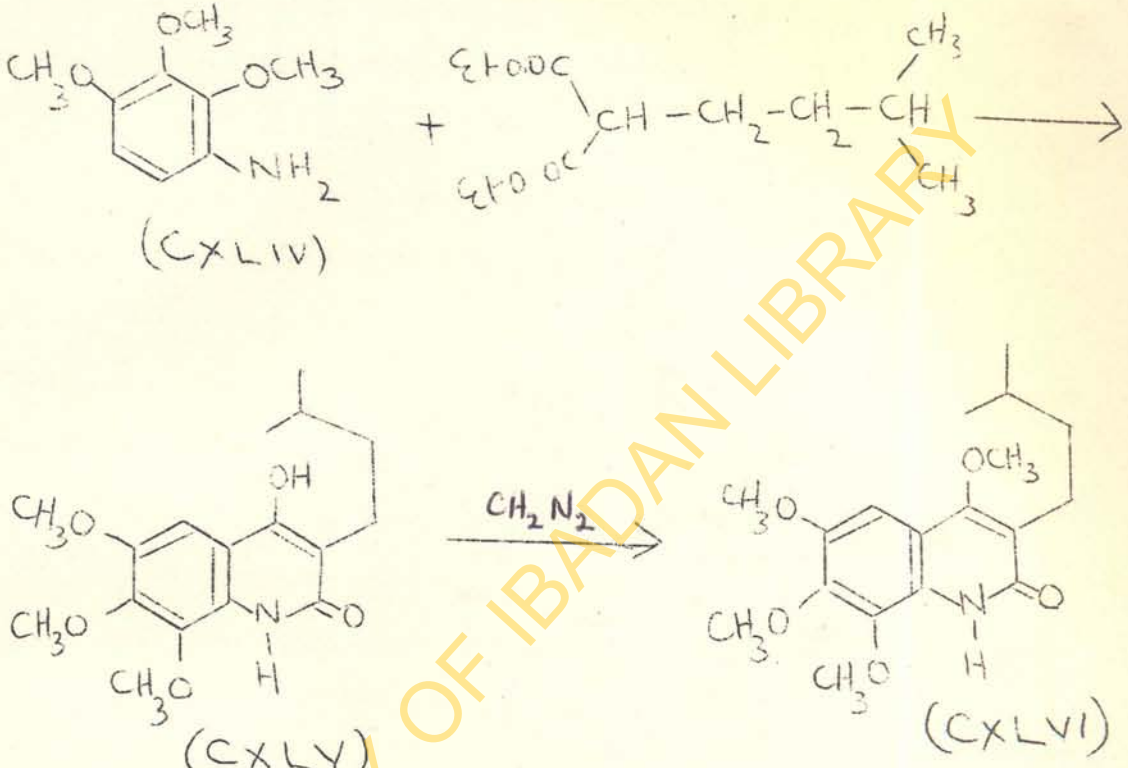
Hypobromite solution reacts with the acid amide (CXLIII) to give N-haloamide (CXLVII) which reacts with the alkali solution to afford an unstable salt (CXLVIII). In the dry state, the salt undergoes decomposition wherein the organic residue migrates from the carbon atom to the nitrogen atom, the products being the isocyanate (CXLIX) and an alkali metal halide. In the presence of water and an excess alkali, the isocyanate is hydrolysed to the amine (CXLIV). In alcoholic solution, the isocyanate would be converted to a urethane.





It was decided to make the 6,7,8-trimethoxy-4-hydroxy-2-quinolone with a saturated side chain at the 3-position before preparing 6,7,8-trimethoxy-3-isopentenyl-4-hydroxy-2-quinolone.

The arylamine (2,3,4-trimethoxy aniline) (CXLIV) was refluxed with diethyl-isoamyl-malonate in diphenyl ether in the usual way to give 6,7,8-trimethoxy-3-isoamyl-4-hydroxy-2-quinolone (CXLV) as a greyish substance(m.p. 155°C - 157°C.) The infra-red spectrum showed the usual imino (>NH) band at ν_{max} 3333 cm^{-1} and a characteristic carbonyl band of a 2-quinolone at ν_{max} 1639 cm^{-1}. Methylation of the substance with diazomethane afforded the 4,6,7,8-tetramethoxy-2-quinolone (CXLVI) which was readily soluble in chloroform.

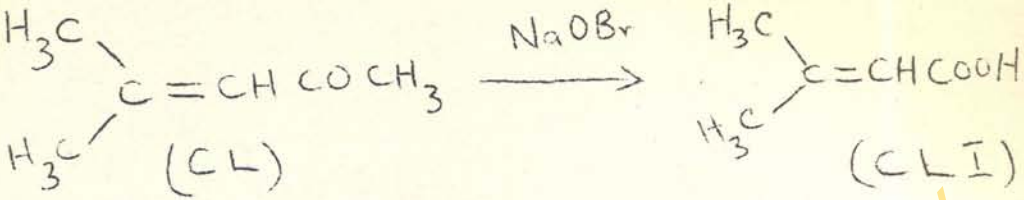


The n.m.r. spectrum of the tetramethoxy compound in deutero-chloroform showed, "inter alia", four very close peaks at 235 c/s, 236 c/s, 237 c/s and 241 c/s for the 6,7,8-and 4-methoxy groups. This showed that the 8-methoxy protons had almost the same chemical shifts as the other two methoxy groups in the 6,7-positions in the benzenoid ring. Therefore, the supposition that the signal at δ 3.70 (223 c/s) (fig. 9) for three protons in the natural alkaloid, might be for the 8-methoxy group could not be true.

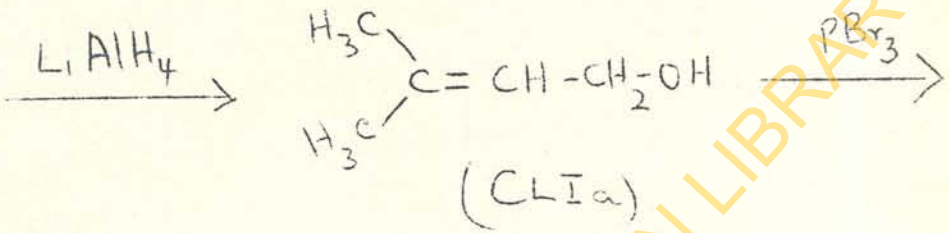
On a close inspection of the infra-red spectrum (fig. 10) of oricine, it was found that the characteristic >NH band expected at ν_{max} 3333 cm^{-1} was absent. This showed that, perhaps, the alkaloid was N-methylated. Again, the characteristic carbonyl band at ν_{max} 1639 cm^{-1} for a 2-quinolone was very prominent, showing that the natural alkaloid could not have been 2-o-methylated. The n.m.r. spectrum of oricine showed two aromatic singlets indicating that the benzenoid ring of the alkaloid had two free positions and not just one as we had in the proposed structure (CXXXVII).

It was suggested, therefore, that the true structure of oricine was 1-methyl-6,7-dimethoxy flindersine (CLVII) and the synthesis discussed in the rest of this work confirmed this structure to be true.

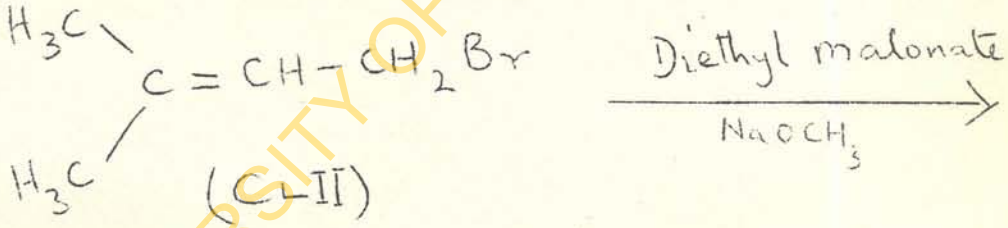
The intermediate 6,7-dimethoxy-3-isopentenyl-4-hydroxy-2-quinolone (CLIII) required for the synthesis of the 1-N-methyl compound (CLVII) was prepared from amino-veratrole (CIII) and diethyl-isopentenyl malonate (XLVIII). The preparation of the substituted malonate (XLVIII) was carried out by oxidising mesityl oxide (CL) with sodium hypobromite to ββ-dimethyl-acrylic acid[90] (CLI). Lithium aluminium hydride reduction of the acid gave the γγ-dimethyl-allyl-alcohol[91] (CLIa) which was brominated with phosphorus tribromide containing a few drops of pyridine in a low boiling petroleum ether[91]. The resulting γγ-dimethyl-allyl-



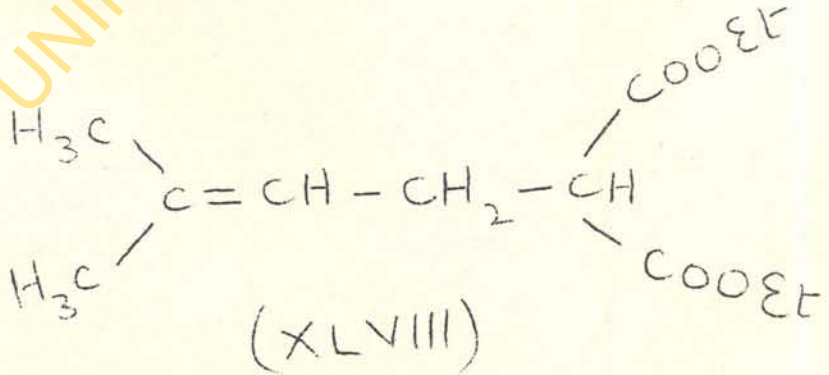
(CLI)



(CLIa)



(CLII)

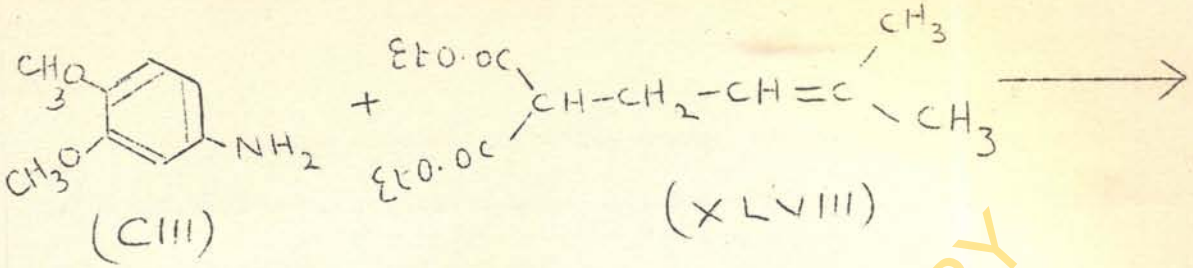


(XLVIII)

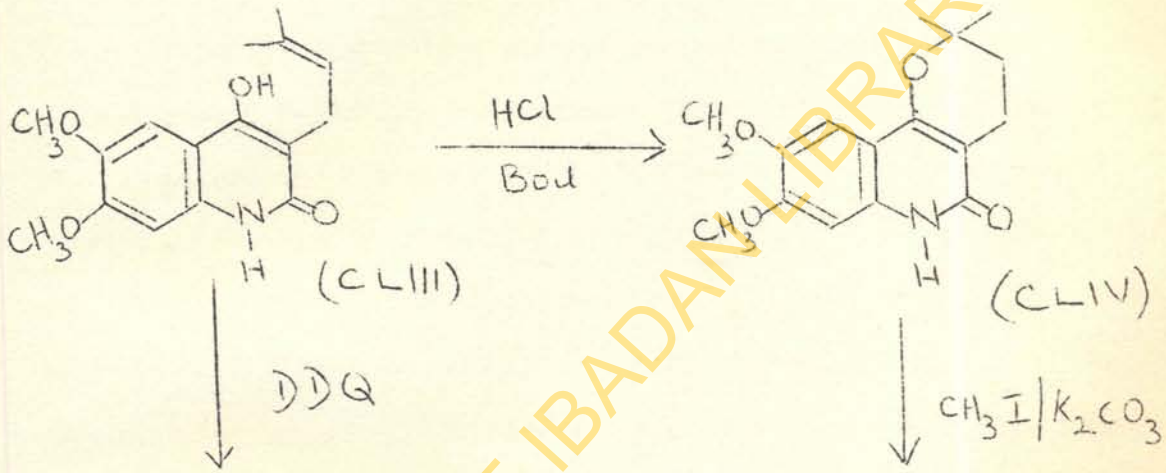
bromide (CLII) was condensed with redistilled malonic ester using sodium methoxide in dried methanol[64b] to give the required diethyl-isopentenyl-malonate (XLVIII).

Refluxing an excess amount of the substituted malonate with amino veratrole under nitrogen for over six hours[41] gave the desired intermediate 6,7-dimethoxy-3-isopentenyl-4-hydroxy-2-quinolone (CLIII) (m.p. 200°C - 201°C). Its infra-red spectrum gave the characteristic carbonyl band of a 2-quinolone (1639 cm^{-1}). The material was insoluble in chloroform, hence its n.mr. spectrum in deutero-chloroform was not taken. Its molecular weight from the mass spectrum was 289, the molecular weight of the expected compound. The carbon, hydrogen and nitrogen analyses agreed with the molecular formula of the expected 3-substituted quinolone (CLIII).

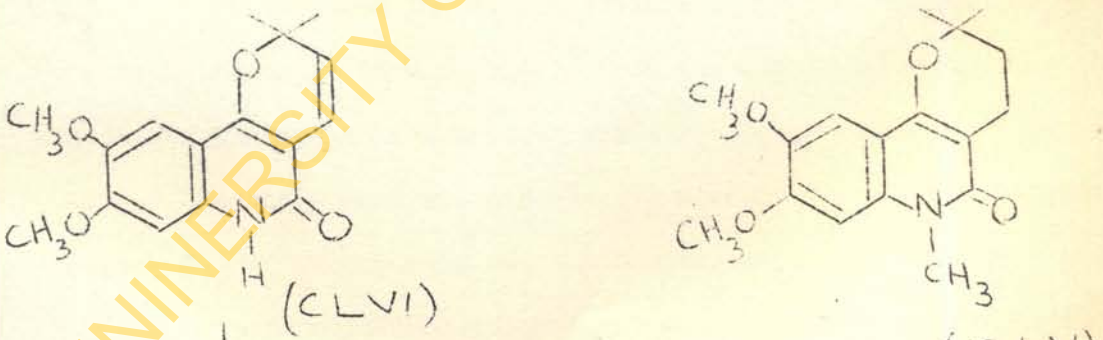
The substance (CLIII) was cyclised to the 6,7-dimethoxy dihydro-flindersine (demethyl-dihydro-oricine) (CLIV) m.p. 220° - 221°C by refluxing with hydrochloric acid in accordance with the method of Eshiet and Taylor[92] in the conversion of atanine to dihydro - flindersine. N-methylation of the demethyl dihydro oricine with methyl iodide and potassium carbonate in acetone[43] gave the dihydro-oricine (CLV) whose n.m.r. spectrum was similar to the n.m.r. spectrum of the substance obtained by hydrogenating the natural oricine.



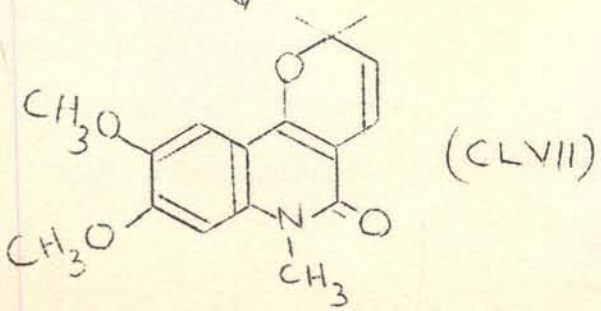
(CIII) (XLVIII)



(CLIII) (CLIV)



(CLVI) (CLV)



(CLVII)

Oricine was obtained directly by the cyclohydrogenation of 6,7-dimethoxy-3-isopentenyl-4-hydroxy-2-quinolone using DDQ, followed by N-methylation.

Refluxing the 3-isopentenyl-2-quinolone compound (CLIII) with 2,3-dicyano-5,6-dichloro benzoquinone (DDQ) in dry benzene according to the method of Poizzi et al. in the preparation of flindersine[44] gave a crystalline substance, m.p. 210°C - 212°C, readily soluble in chloroform. The infra-red spectrum (fig.16) gave a sharp characteristic carbonyl band of a 2-quinolone at about ν_{max} 1650 cm^{-1}. The n.m.r. spectrum (fig. 17) differed from the n.m.r. spectrum of the natural oricine (fig. 9) only in the absence of the three-proton singlet at δ 3.70 and the slight downfield shift of one of the benzenoid protons. It was obvious from the n.m.r. spectrum that the product of the cyclohydrogenation was the expected demethyloricine (CLVI). Elemental analysis was also in agreement with the molecular formula $C_{16}H_{17}O_4N$ expected for the demethyloricine.

DDQ is an excellent reagent for dehydrogenation. It has found very considerable importance in the synthesis of natural chromenes. The choice of benzene as the solvent in the dehydrogenation reaction of DDQ has the advantage that while DDQ dissolves readily in benzene (solubility ~ 68g/litre at 25°C), the 2,3-dicyano-5,6-dichlorohydroquinone produced after the dehydrogenation reaction is

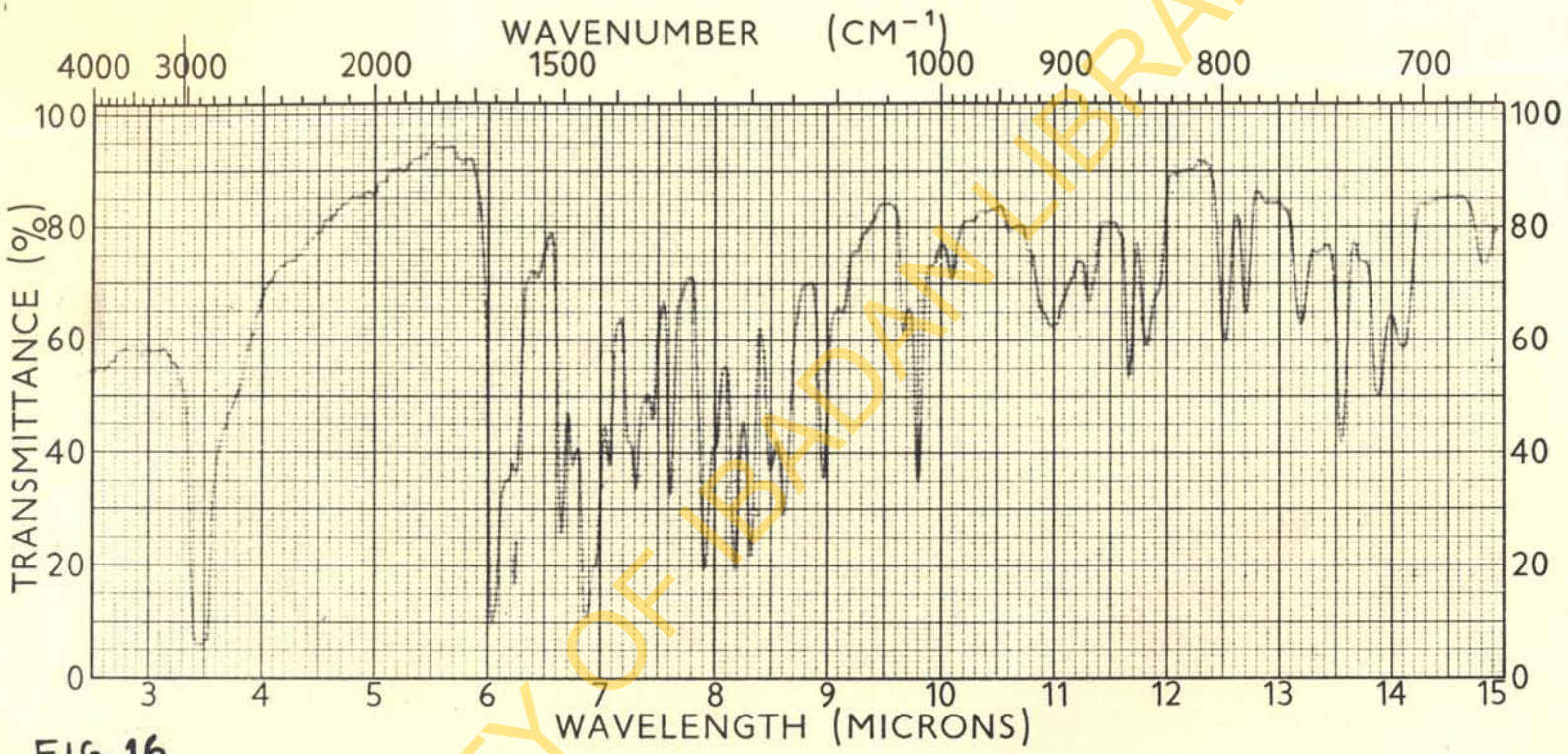
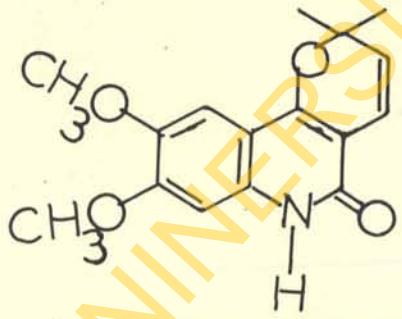


FIG. 16



N-demethyl-oricine.

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SOLVENT	OPERATOR Ale DATE 1/4/70
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PERKIN - ELMER LIMITED. BEACONSFIELD. BUCKS

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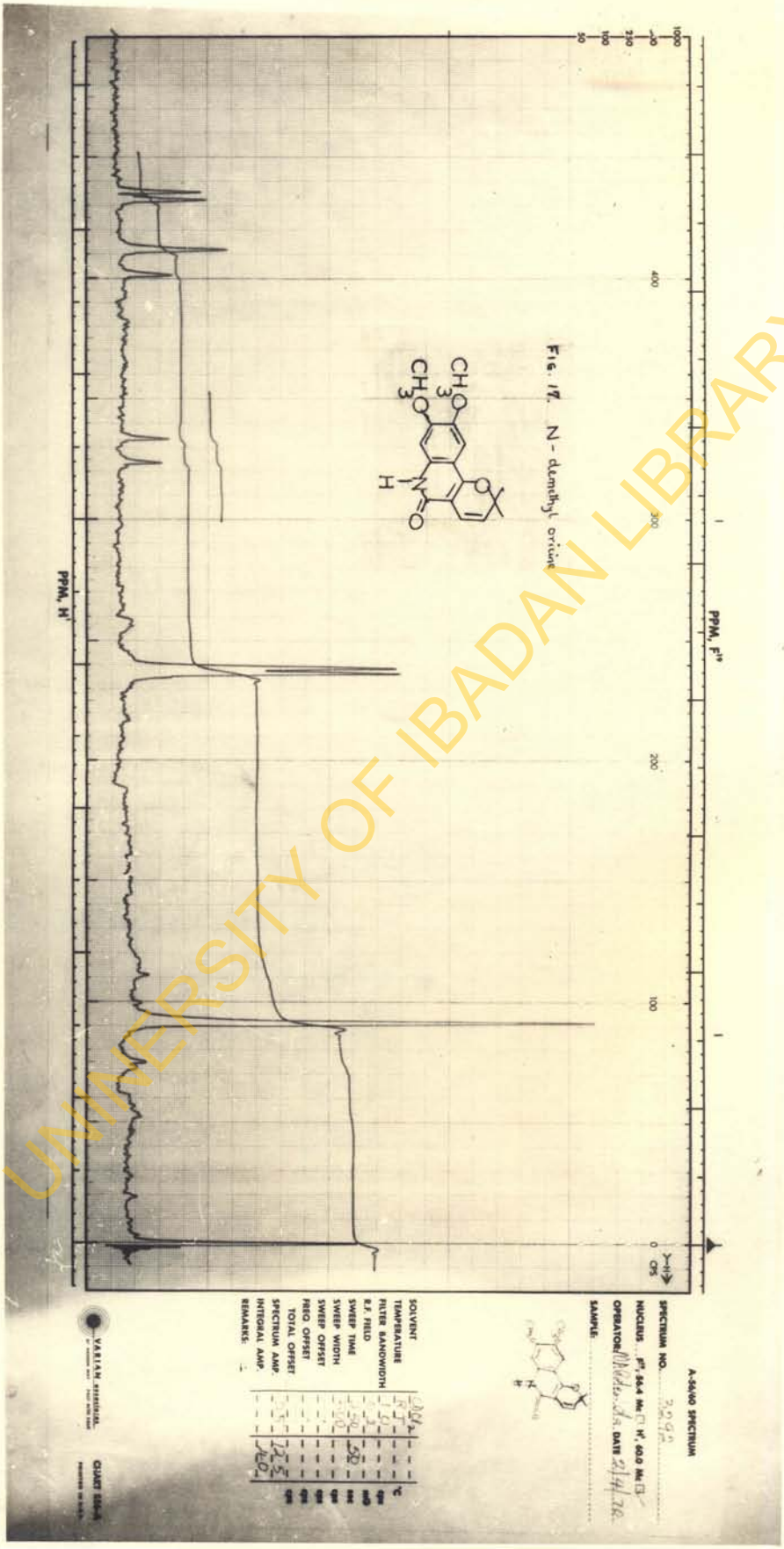

FIG. 17. N - dimethyl orione

reasonably insoluble (solubility ~ 0.6g/litre at 25°C) and may be filtered off[93].

N-methylation of demethyloricine (CLVI) with methyl iodide and potassium carbonate (anhydrous) in dry acetone gave oricine (CLVII) whose melting point and infra-red spectrum were found to be identical in all respects with the natural oricine. Both the natural oricine and the synthetic compound had the same R_f values on the t.l.c. plate. The n.m.r. spectra of both compounds were superimposable. This proved that the natural alkaloid from Oricia suaveolens has the structure 1-methyl-6,7-dimethoxy-flindersine (CLVII) related to flindersine and atanine isolated from other genera of the Rutaceae family.

CONCLUSIONS AND COMMENTS

From the West African plants of the Rutaceae so far examined, no limonoid has been isolated, but it is interesting to note that in these plants, coumarins and alkaloids whose structures are similar to coumarins and alkaloids of other plants of the same family were isolated.

For instance, Afraegle paniculata which is believed to be native to West Africa and India was found to contain dictamnine which has earlier been isolated from Dictamnus albus, an Australian

Rutaceous plant. The coumarin imperatorin which exists in Imperatoria ostruthium was found in two genera of West African Rutaceae, Afraegle and Clausena. From the root of Clausena anisata was isolated a coumarin which was isolated at the same time from Murraya paniculata. Oricia suaveolens was shown to be a source of the alkaloid oricine which is closely related structurally to flindersine, obtained from the Australian Rutaceae plant Flindersia australis.

Most of the limonoids obtained from the family Rutaceae exist in the seeds. Usually, in cases where dictamnine is extracted in the plants of the Rutaceae, it is usually accompanied by a limonoid. It is not unlikely, therefore, that the Citrus-like plant, Afraegle paniculata which has been shown to contain dictamnine may contain limonoids which would, perhaps, be similar in structure to limonin in its seeds.

E X P E R I M E N T A L

All melting points (m.p.) were taken on a Kofler hot-stage microscope and were not corrected. The infra-red (i.r.) spectra of solids (Nujol mulls) were taken on a Perkin-Elmer model 137 instrument and ultra violet (u.v.) spectra were determined in methanolic solutions on a Perkin-Elmer model 137 u.v. instrument. Nuclear Magnetic Resonance (n.m.r.) were taken on a Varian A.56/60 Mc/sec spectrophotometer, in deutero-chloroform solution against tetramethylsilane as internal standard. The units quoted for n.m.r. are δ values. Mass spectra were obtained with a Perkin-Elmer Hitachi R.M.U. 6E instrument.

Silica gel refers to Merck, mesh 0.05 mm - 0.2 mm. Alumina refers to the activated type, Peter Spence H-type. Thin plate chromatograms for thin-layer chromatography (t.l.c.) were run on plates made by spreading an aqueous slurry of Merck silica gel G on glass plates and drying at 130° in an oven for about one hour. The chromatoplates were developed with benzene-ethyl acetate (3:1) otherwise stated. After drying, the spots showing the positions of the components of the material spotted were detected by exposing the plates to iodine vapour inside an iodine tank for a few minutes.

Light petroleum refers to the fraction b.p. 60° - 80°.

EXTRACTION OF THE WOOD OF AFRAEGLE PANICULATA

The powdered wood was continuously extracted with boiling light petroleum ether for 24 hours. The solvent was evaporated off and on keeping the residue overnight, crystals mixed with oil were obtained. The crystals were washed with light petroleum ether and filtered. Recrystallisation from methanol gave light yellow crystals (m.p. 92°) as a mixture (shown on t.l.c.).

Chromatography of the mixture on activated alumina gave, on elution with pure benzene, a crystalline substance identified as imperatorin m.p. 100°-102° (from methanol) (found C, 71.86; H, 5.06; $C_{16}H_{14}O_4$ requires C, 71.11 ; H, 5.2) M^+, 270. ν_{max} 1695 cm^{-1} (carbonyl) λ_{max} 217 mμ ($\epsilon = 2.716 \times 10^4$), 246 mμ ($\epsilon = 2.2345 \times 10^4$), 263 mμ ($\epsilon = 1.234 \times 10^4$), 300 mμ ($\epsilon = 1.111 \times 10^4$).

Attempted Hydrolysis of Imperatorin with HCl

Imperatorin (0.45 g.) in methylated spirit (5 ml.) and hydrochloric acid (5 ml.) were refluxed for half an hour. Water was added and the organic portion extracted with diethyl ether. The ethereal layer was extracted again with caustic soda and the aqueous layer was acidified with hydrochloric acid and re-extracted with ether. Evaporation of the ether gave a dark tar as a residue. The infra-red spectrum was uninteresting.

Hydrolysis of Imperatorin to Xanthotoxol

Imperatorin (1.0089 g.) was dissolved in acetic acid (10 c.c.) and one drop of concentrated sulphuric acid was added. The mixture was allowed to stand at room temperature for over 40 hrs. The product (white crystalline substance) was washed with water and dried on the filter paper.

m. p. 240° (Lit.[59] 243°).

Methylation of Xanthotoxol

Xanthotoxol (0.8g.) was dissolved in a mixture of methanol (5 ml.) and diethyl ether (20 c.c.) in a 100 ml. round bottomed flask. Diazomethane was bubbled into the solution until the solution attained a permanent yellow colour. The mixture was left in the fume cupboard overnight until the excess diazomethane escaped (when the solution became colourless) Evaporation of the solvent gave a solid, recrystallised from methanol

m.p. 145° (Lit.[59] 144°).

Isolation of Dictamnine

To the oil obtained from another extract of the wood of Afraegle paniculata, light petroleum ether (50 c.c.) was added then extracted with 10% water in methanol (150 c.c.). To the methanolic extract, some quantity of water was added and then re-extracted with chloroform.

Evaporation of the chloroform gave a gummy material which was chromatographed on alumina.

A fraction eluted with 20% ether in benzene gave a light yellow prism-like crystals from methanol m.p. 130° - 132°C (Found C, 72.46; H, 4.54 ; $C_{12}H_9O_2N$ requires C, 72.35 ; H, 4.55) M^+ 199 λ_{max} 235 mμ ($\epsilon = 4.4 \times 10^4$), 310 mμ ($\epsilon = 6.5 \times 10^3$).

Attempted Hydrolysis of Dictamnine with hydrochloric acid

Dictamnine (0.63 g.) was refluxed with hydrochloric acid (6 ml.) for one hour. The mixture was diluted with water, then extracted with ether. The ether solution was dried with anhydrous sodium sulphate and evaporated to give a solid, identified as the starting material by the m.p. and t.l.c.

Hydrogenation of Dictamnine

Dictamnine (0.3025 g.) was dissolved in methanol (50 c.c.) and platinum oxide (0.1 g) was added. The mixture was shaken up with hydrogen at 1 atmospheric pressure until no more hydrogen uptake. Then the catalyst was filtered off and the solvent evaporated from the filtrate to give white crystals m.p. 180°C - 182°C M^+ 203. (Found C, 69.24; H, 6.04 ; $C_{12}H_{13}O_2N$ requires C, 70.94; H, 6.40) ν_{max} 1653 cm^{-1} (carbonyl of a 2-quinolone).

Synthesis of the hydrogenated Product of Dictamnine
(i.e. 3-ethyl-4-hydroxy-2-quinolone)

Preparation of diethyl-ethyl-malonate

Sodium (9g.) was dissolved in methanol (150 c.c.) and cooled. To the sodium methoxide solution was added diethyl malonate (57.5 ml.) and ethyl bromide (45 ml.). The mixture was refluxed for over 24 hours. After adding water, the product was extracted with ether and the ethereal layer was well washed with water, and dried over anhydrous sodium sulphate. Evaporation of the ether and re-distillation of the residue gave the substituted malonate collected at above 180°C
Yield 20g.

Attempted condensation of diethyl-ethyl-malonate with aniline

The diethyl-ethyl-malonate (10 ml.) was added to aniline (10 ml.) in diphenyl ether (50 ml.) and the mixture was refluxed for one hour. On cooling, a solid appeared, and this was collected and washed with hexane to give an ashy crystalline substance. m.p. 220° - 225° insoluble in chloroform. ν_{max} 1724 cm^{-1}.

Attempted methylation of the solid was unsuccessful.

4-hydroxy-2-quinolone

(a) Condensation of methyl anthranilate with malonic ester.

A solution of methyl anthranilate (40 ml.) in diethyl malonate (250 ml.) was heated in an oil bath rapidly at 165°C and then gradually up to 195°C over a period of 90 minutes and kept at 195° - 198° refluxing for one hour longer. During this time, some quantity of ethanol distilled through a partial reflux condenser. The excess diethyl malonate was distilled ~~in~~ under a reduced pressure and mechanical stirring. On cooling, a solid precipitated which dissolved on addition of about one litre of sodium-dried ether. The resulting solution of the anthranilide was used directly in the cyclisation below:

(b) Cyclisation

A solution of metallic sodium (8g.) in dried methyl alcohol (150 ml.) was added dropwise to the stirred and refluxing ether solution of crude mono-anthranilide over a period of 2½ hours. The resulting thick suspension was allowed to cool by standing overnight. The ether was evaporated.

(c) Hydrolysis was carried out without isolating the ester by adding 40% caustic potash (140g.) to the mixture and heating at 60° - 70° for one hour.

(d) Decarboxylation : The acid, without being isolated was decarboxylated thus:

The temperature of the warm alkaline solution from the preceeding step was raised from 70° to 95°C over a period of three and a half hours; alcohol distilled out slowly. After cooling to 70°C, the alkali-insoluble material was filtered, slurried in 400 ml. of 10% caustic soda at 70°C and refiltered; then washed with water.

The 4-hydroxy carbostyril was precipitated from the combined alkali filtrates by acidifying with hydrochloric acid. The resulting gelatinous precipitate was filtered, washed by stirring in about 10 litres of 5% sodium bi-carbonate. It was then filtered and dried in an oven

m.p. $>$ 300°C (Lit[44] 354°C)

yield ~ 7.5g.

Synthesis of 3-acetyl-4-hydroxy-2-quinolone

To a suspension of 4-hydroxy-2-quinolone (6 g.) in carbon disulphide (90 ml.) was added acetyl chloride (6.25 ml.). The mixture was heated under reflux for thirty minutes, cooled to below 0° in ice-salt mixture and treated with aluminium chloride (16.5g) with mechanical stirring. The mixture was poured over ice-HCl and left in the fume cupboard for another day to allow the carbon disulphide escape.

The crude product was collected and recrystallised from acetic acid-water

Yield ~ 5g.

m.p. 254°C - 255°C (Lit[44] 255°C - 256°C).

Sodium borohydride reduction of 3-acetyl-4-hydroxy-2-quinolone

To 3-acetyl-4-hydroxy-2-quinolone (2.18g.) in isopropyl alcohol (75 ml.) was added sodium borohydride ($NaBH_4$) (4.0g.). The mixture was refluxed for seven hours; then carefully treated with hydrochloric acid to decompose the excess sodium borohydride, diluted with water and extracted three times with dichloromethane (3 x 100 c.c.). The organic extracts were evaporated to dryness and the crude product was recrystallised from methanol-water

Yield ~ 1.15g.

m. p. 240° - 245°C.

Methylation of 3-ethyl-4-hydroxy-2-quinolone to 3-ethyl-4-methoxy-2-quinolone

To a mixture of 3-ethyl-4-hydroxy-2-quinolone (1.0g.) in sodium-dried ether (20 ml.) containing methanol (5 ml.) was bubbled diazomethane. The material dissolved as methylation took place. The solution was allowed to stand overnight in the fume cupboard. The solvent was evaporated to dryness and the residue was recrystallised

from aqueous methanol m.p. 182°.

Yield 0.452 g.

The i.r. spectrum and n.m.r. spectrum were identical with the i.r. and n.m.r. spectra of the hydrogenated product of dictamnine.

EXTRACTION OF THE ROOT OF CLAUSENA ANISATA

The root of Clausena anisata (6.75 kg.) was continously extracted with light petroleum ether overnight. The solvent was evaporated to give some crystals embedded in oil.

The crystals were separated from the oil, recrystallised from methanol to give a solid m.p. 95° - 98°. The i.r. and n.m.r. spectra of the solid were identical in all respects with the n.m.r. and i.r. of imperatorin.

Chromatography of the oily portion

The oil (17.7425 g.) was chromatographed on alumina (800 g.) The fraction eluted with 10% ether in benzene gave white crystals (coumarin C). m.p. 150° - 155°C yield 1.3 g. (Found C, 71.34 ; H, 6.83, $C_{16}H_{18}O_4$ requires C, 70.04; H, 6.60) ν_{max} 1709 cm^{-1} λ_{max} 213 mμ (ϵ = 2.219 x 10^4), 260 mμ (ϵ = 9.12 x 10^3) and 325 mμ (ϵ = 1.109 x 10^4). The n.m.r. spectrum showed signals at δ 1.67 (Singlet) and δ 1.83 (Singlet, $= C\begin{matrix}CH_3\\CH_3\end{matrix}$) ; δ 3.45 (doublet, J = 6 c/s methylene), δ 5.22 (triplet, vinyl proton),

δ 3.39 (Singlet, 2-OCH_3) δ 6.13 (doublet J = 10 c/s), δ 7.97 (doublet J = 10 c/s), δ 6.32 (Singlet).

Attempted Synthesis of Coumarin C (Coumarrayin).

Formylation of Phloroglucinol:

Into a solution of anhydrous phloroglucinol (20 g.) in dry ether (250 c.c.) containing zinc cyanide (12 g.), a stream of dry hydrogen chloride was passed. [The dry hydrogen chloride gas was generated in Kipp's apparatus from ammonium chloride and sulphuric acid and dried by passing through a wash bottle containing sulphuric acid]. The bubbling of hydrogen chloride gas continued until the oil formed solidified. After standing overnight, the solid was collected, washed with ether and the imide salt formed was dissolved in water (400 c.c.) and hydrolysed by warming on the water bath. The solid obtained on cooling was dissolved in ether, filtered from traces of red-coloured by-product and the ether was evaporated. Phloroglucinaldehyde thus obtained was recrystallised many times from water saturated with sulphur dioxide to give orange-coloured needle-like crystals. No definite melting point[67]. Yield 10.5 g.

Attempted condensation of Phloroglucinaldehyde with acetic anhydride

A mixture of phloroglucinaldehyde (8 g.), sodium acetate (8 g.) and acetic anhydride (40c.c.) was heated on an oil bath for over

15 hours. The mixture was added to water to give a dirty brown oil. This oil was taken up in ether and evaporation of the ether gave a dark oil as residue whose infra-red spectrum did not show a carbonyl band.

Methylation of Phloroglucinol

Into a solution of anhydrous phloroglucinol (25 g.) in analar methanol (150 c.c.) was passed a stream of dry hydrogen chloride gas for one hour at such a rate as to raise the temperature of the solvent to its boiling point. The solution was boiled for one hour under reflux and, after saturating with hydrogen chloride once more for another hour, was allowed to stand overnight.

The greater part of the alcohol was removed by distillation and the heavy oil which precipitated on the addition of water was taken up in ether. The ethereal solution was washed with water, dried with anhydrous sodium sulphate and evaporated. Redistillation gave a yellow oil at above 300°C.

Yield 20 g.

Formylation of Dimethoxy phloroglucinol

The mixture of phloroglucinol dimethyl ether (20 g.), formanilide (17.4 g.) and phosphoryl chloride (7.4 g.) in sodium-dry ether (150 c.c.) was heated gently on a steam bath and after half an hour, a heavy oil began to separate from the dark liquid. After a

total of one and a half hours from the commencement of the reaction, heating was discontinued and the containing vessel was stoppered and allowed to stand for 24 hours. The ether was decanted from the hard solid mass and the latter was broken up and washed thoroughly with fresh ether. The product (a salt of the composition $MeO_2C_6H_2OH \cdot CH{=}CHPh$) was hydrolysed by repeated and prolonged stirring (mechanical) with a large quantity of water and a large volume of ether. After a few hours, the ethereal layer was separated and fresh ether was added. The combined ethereal layer was washed with dilute hydrochloric acid, dried with sodium sulphate and after the removal of the solvent, the residue was distilled under reduced pressure. The yellow oil obtained gave crystals and recrystallisation from methanol gave pure crystals.

m.p. 68° - 69°C. (Lit.[69] 70°C)

Yield 0.5 g.

Alternative method of Formylation of dimethoxy-phloroglucinol giving a quantitative yield

Dimethoxy phloroglucinol (10g.) was dissolved in dry ether 250 c.c.) and zinc cyanide (12g.) was added. A stream of hydrogen chloride was passed into the mixture and after sometime, an oil was formed. The oil solidified on allowing to stand overnight. The ether remaining was decanted from the solid, water was added and the mixture was warmed on a water bath for 30 minutes. The oil which separated

was collected in ether and the ethereal layer was dried with anhydrous sodium sulphate and evaporated. The residue (a solid) was recrystallised from methanol :

m. p. 68°C - 69°C.

Yield ~ 6 g.

Attempted condensation of dimethoxy phloroglucinaldehyde with acetic anhydride

Dimethoxy phloroglucinaldehyde (3g.), sodium acetate (3g.) and acetic anhydride (15 c.c.) in a 100 ml. flask were refluxed for about 20 hours. On adding the mixture to water, a green oil was obtained. This again did not give the infra-red absorption expected at about ν_{max} 1700 cm^{-1} for the γ-lactone of a coumarin.

EXTRACTION OF ORICIA SUAVEOLENS

The wood (14.75 kg.) was pulverised and extracted continuously for over two days with light petroleum ether. Evaporation of the solvent afforded an oily material (~ 300g.) as the residue.

The oil was chromatographed on alumina and a fraction eluted with 20% benzene in diethyl ether gave a yellow crystalline substance, oricine.

Recrystallisation from benzene gave large prism-like crystals

(~ 1.5g.) m.p. 150°C - 155°C, optically inactive (Found C, 67.05 ; H, 6.2 ; $C_{17}H_{19}O_4N$ requires, C, 67.76 ; H, 6.34). Lassaigne test for nitrogen was positive. M^+ (from mass spectrum) 301 ; ν_{max} 1639 cm^{-1} (carbonyl of a 2-quinolone). The n.m.r. spectrum showed signals at δ 1.53 (singlet, 6H for 2 methyl groups), δ 3.70 (singlet, 3H for $\rangle NCH_3$), δ 3.98 (singlet) and δ 4.02 (singlet) [both for 6H of 2-OCH_3 groups], δ 5.48 (doublet, J = 10 c/s) and δ 6.75 (doublet J = 10 c/s), δ 6.73 (singlet ArH) and δ 7.31 (singlet ArH).

Hydrogenation of Oricine

Oricine (0.135g.) was dissolved in methanol (about 50 ml.) and platinum oxide (~ 0.1g.) was added. The mixture was shaken up with hydrogen at atmospheric pressure. until there was no more uptake of hydrogen. The catalyst was filtered off and the filtrate evaporated to give a white crystalline substance, dihydrooricine. m.p. 150°C. (Found C, 67.02 ; H, 6.81 ; $C_{17}H_{21}O_4N$ requires C, 67.32, H, 6.93) M^+ (mass spectrum) 303. The n.m.r. spectrum showed signals at δ 1.54 (singlet 6H for 2 methyl groups) δ 3.70 (singlet 3H for $\rangle NCH_3$) δ 3.98 (singlet) and δ 4.02 (singlet) [both for 6H of 2-OCH_3 groups], δ 1.83 (doublet, J = 7 c/s) and δ 2.65 (doublet, J = 7 c/s) each for the methylene group.

Methylation of Catechol to Veratrole

A solution of catechol (75 g.) in methanol (150 c.c.) was mixed with dimethyl sulphate (188 ml.). After cooling to -5°C, a solution of potassium hydroxide (113g.) in water (263 ml.) was added all at once. A vigorous reaction took place and the reaction subsided after about three minutes. On allowing to cool, the mixture was diluted with water and extracted with ether. The ether solution was dried with anhydrous sodium sulphate and evaporated. The residue was re-distilled to give a colourless oil at 200°C - 206°C (760mm.)

Yield 65 g.

Nitration of Veratrole

Veratrole (30g.) was gradually added with careful cooling (in iced water) to a mixture of nitric acid D. 1.42 (35 c.c.) and water (35 c.c.). A solid appeared immediately. This was filtered and recrystallised from methylated spirit to give needle-like bright yellow crystals :

m. p. 95°C - 96°C

Yield 28 g.

Reduction of nitroveratrole to aminoveratrole

Nitroveratrole (20g.) was mixed with tin (48 g.) and after adding a trace of animal charcoal, 50% hydrochloric acid (200 c.c.)

was added and the mixture was heated on a water bath for three hours. The mixture was cooled, and diluted with water. Sodium hydroxide solution was added until the white precipitate of tin chloride formed redissolved, and then extracted with ether. The ethereal layer was dried with anhydrous magnesium sulphate and evaporated to give a low melting substance, 4-aminoveratrole.

m.p. 78° - 80° (darkens on exposure to light)

Yield 12 g.

Attempted Condensation of 4-aminoveratrole with diethyl malonate

Aminoveratrole (10g.) and diethyl malonate (10g.) were dissolved in diphenyl ether (100 c.c.) and the solution was refluxed for about $1\frac{1}{2}$ hours. On cooling, a solid appeared. This was filtered and washed with hexane to give a greyish powder of the malonanilide m.p. 210°C. M^{+} (from mass spectrum) 360. The solid was insoluble in chloroform. ν_{max} 1724 cm^{-1} (carbonyl group of an amide).

Preparation of Veratraldehyde

Vanillin (76g.) was placed in a three-necked 500 ml. flask equipped with a reflux condenser and two separating funnels. The vanillin was melted by warming on a water bath and stirred vigorously. Potassium hydroxide solution (41 g. in 60 ml. of water) was run in

from one of the dropping funnels and after about 40 drops had been run in, dimethyl sulphate (60 ml.) was run in through the other dropping funnel at the same rate as the potassium hydroxide solution. The external heating was stopped after a few minutes and the mixture was allowed to reflux gently from the heat of the reaction. As soon as all the reagents had been run in, the reaction mixture (yellow) was poured into a large porcelain basin and allowed to cool overnight. The hard crystalline mass of the aldehyde was filtered and ground in a mortar with 150 c.c. of ice cold water. It was filtered and dried in a vacuum desiccator.

Yield 64 g.

m.p. 46°C.

Veratronitrile:

Veratraldehyde (60 g.) was dissolved in warm methylated spirit (150 ml.) in a beaker and a warm solution of hydroxylamine hydrochloride (31 g.) in water (35 ml.) was added. A solution of sodium hydroxide (22.5g.) in water (30 ml.) was run into the mixture and the mixture was allowed to stand for about 2 hours. Crushed ice was added and then saturated with carbon dioxide. The mixture was allowed to stand in the refrigerator overnight. The crystalline aldoxime was filtered and washed with cold water and dried in air

Yield 54 g., m.p. 82°C.

The aldoxime was placed in a 500 ml. round bottomed flask equipped with a reflux condenser. Redistilled acetic anhydride (56 ml) was added and the mixture was heated cautiously. Immediately the reaction became vigorous, the external heating was stopped. When the vigorous reaction subsided, the solution was boiled for 20 minutes more and then carefully poured into ice-cold water (150 ml.). The veratronitrile crystals formed were filtered and dried in the air

Yield 50 g.

m.p. 60°C.

Veratric acid

The veratronitrile (50 g.) was boiled with about one litre of 10% sodium hydroxide solution under reflux until the condensed liquid contained no oily drops. (about 1 hour). The condenser was removed and the solution was boiled in the open flask in order to allow off the free ammonia. The boiling was stopped when no more ammonia was being evolved. The solution was poured into a large beaker, cooled, and enough concentrated hydrochloric acid was added to precipitate the acid. The acid was filtered and dried in the air

Yield 40 g., m.p. 182°C.

Methyl Veratrate

The veratric acid (30 g.) was placed in a 500 ml. round bottomed

flask. Methyl alcohol (100 ml.) and concentrated sulphuric (3 ml.) were added and the mixture was refluxed for over 6 hours. On cooling, the mixture was added to about 250 ml. of ice-cold water and the white ester crystals were collected on a buckner funnel, washed well with water and allowed to dry in the air. m.p. 52°C - 55°C
Yield ~ 22 g.

Nitration of methyl veratrate

Methyl veratrate (15 g.) was dissolved in glacial acetic acid (20 ml.) and the solution was added gently to nitric acid D 1.42 (about 20 ml.) in the fume cupboard with shaking. The mixture was left for a couple of minutes and the crystals of the methyl 6-nitro veratrate appeared. This was collected and washed with water and allowed to dry on the filter paper.

Yield 10 g. ; m.p. 142°C - 144°C.

Reduction of methyl 6-nitro veratrate to the amino compound.

Methyl 6-nitro veratrate (10g.) was added to a solution of stannous chloride (16 g.) in 50% methanolic hydrochloric acid (100 ml) and the solution was refluxed for one hour on the steam bath. The reaction mixture was diluted with ice-cold water, and made alkaline. Extraction with ether gave, after evaporation, light yellow crystals,

recrystallised from methanol to give large prism-like crystals.

Yield ~ 3.5 g. m.p. 127°C.

ν_{max} ~ 3333 cm^{-1} as doublet for the $-NH_2$ group.

Condensation of aminoveratrate with diethyl malonate

Methyl 6-amino-veratrate (3g.) and diethyl malonate (5g.) were heated together in an oil - bath at 190°C - 200°C for one hour. On distilling off the excess diethyl malonate, a solid, 6,7-dimethoxy-malon-anthranilide m.p. 75° was obtained.

Yield less than 1 g.

(Found C, 55.32 ; H, 6.21 ; $C_{15}H_{21}O_7N$ requires C, 55.05 ; H, 6.42) M^+ (from mass spectrum) 327 ν_{max} 1724 cm^{-1} (ester band) 1669 cm^{-1} (ester) 1658 cm^{-1} (carbonyl of an amide).

Nitration of Veratronitrile to 6-nitroveratronitrile

The veratronitrile (10g.) was dissolved in glacial acetic acid (20 c.c.). Nitric acid D 1.42 (10 c.c.) was added with careful shaking. On allowing to stand at room temperature for about 30 minutes, bright yellow crystals appeared. The crystals were collected and washed well with water. The crude nitro compound was recrystallised from methylated spirit to give fine yellow needle-like crystals.

Yield ~ 9.5 g. m.p. 166° - 168°.

Reduction of the nitro compound to 6-amino-veratronitrile

The nitro compound (10.5g.) was added to a solution of stannous chloride (32g.) in 50:50 methanolic hydrochloric acid (200ml) and refluxed for over 4 hours. The solution was diluted with water and basified with sodium hydroxide solution until the gelatinous precipitate of tin chloride formed redissolved. The product was taken up in chloroform. The chloroform solution was dried with anhydrous magnesium sulphate and evaporated to give a deep yellow oil which solidified on cooling. M.P. $90^{o}C - 92^{o}C$, yield (9.5g.)

ν_{max} 3333 cm^{-1} and 3175 cm^{-1} (amino group), 2410 cm^{-1} (-CN group)

Acetylation of 6-aminoveratronitrile

6-aminoveratronitrile (5g.) was dissolved in acetic anhydride (100 c.c.) and about 10 drops of concentrated sulphuric acid were added and the mixture was allowed to stand for about 20 minutes. The white crystals of the N-acetyl-veratronitrile appeared. This was collected, washed with water and allowed to dry on the filter paper.

m.p. $195^{o}C - 196^{o}C$.

Yield 3g.

6,7-dimethoxy-2-methyl-4-ethoxy- benz pyrimidine

6-N-acetyl-veratronitrile (3g.) was dissolved in absolute ethanol (30 ml.) and a small piece of metallic sodium (~ 1g.) was dropped. When all the sodium had dissolved, the mixture was refluxed for over $1\frac{1}{2}$ hours. A dark solution was obtained. This solution, on pouring into 150 ml. of cold water, gave white crystals. m.p. 138°C. Yield 2.2.g. (Found C, 60.82; H, 6.72; $C_{13}H_{16}O_3N_2$ requires C, 62.90 ; H, 6.45 ;) M^+ (mass spectrum) 248. The n.m.r. spectrum showed signals at δ 1.45 (triplet J = 7 c/s) and δ 4.59 (quartet, J = 7 c/s) both for the ethoxy protons; δ 2.65 (singlet, methyl protons) ; δ 3.98 (singlet, 6H of the two methoxy groups) ; δ 7.17 (Singlet) and δ 7.30 (Singlet) for two aromatic protons.

Friedel - Craft's acetylation of Veratrole

Finely powdered aluminium chloride (25g.) was added to an ice-cooled mixture of veratrole (25g.) and acetyl chloride (17g.) in carbon disulphide (63 c.c.). A vigorous reaction occurred and the purple mixture obtained was warmed for about 10 minutes on a water bath and allowed to stand overnight. The reaction mixture was treated with much ice-cold water and the lower organic layer was separated, washed with sodium hydroxide solution, then three times

with water. The organic layer was dried with anhydrous magnesium sulphate and the solvent was evaporated on the water bath in the fume cupboard. The residue was distilled and the product (yellow oil) was collected at 184°C under reduced pressure. On allowing to stand at room temperature, the yellow oil solidified to shinning prism-like crystals of acetoveratrone

Yield 18 g.

m.p. 47°C (Lit.[79] 48°C).

Nitration of Acetoveratrone

Acetoveratrone (3.67g.) was dissolved in glacial acetic acid (2 ml.) and cooled. To the cooled solution, concentrated nitric acid D, 1.42 (2 ml.) was added dropwise with shaking. On allowing the mixture to stand for a couple of minutes, a solid appeared. This was collected and recrystallised from methylated spirit to give needle-like crystals of the 6-nitro-acetovaratrone. Yield 2 g. m.p. 136°C. ν_{max} 1667 cm^{-1} (ketone).

Reduction of Nitroacetoveratrone to aminoacetoveratrone

The nitroacetoveratrone (8g.) was added to stannous chloride (24g.) in 50:50 methanolic hydrochloric acid (160 ml.). The mixture was refluxed for 4 hours, cooled and diluted with water. It was made alkaline with sodium hydroxide solution and extracted

with chloroform. The chloroform was evaporated to give an oil as a residue. Yield 3g. ν_{max} 1616 cm^{-1} (ketone), 3333 cm^{-1} and 3279 cm^{-1} (doublet, $-NH_2$ group).

Reaction of Aminoacetoveratrone with ethyl chloroformate

6-aminoacetoveratrone (1g.) was added to ethyl chloroformate (1 ml.) in 100 ml. round bottomed flask. To the mixture, sodium hydroxide (5g.) in ice-cold water (20 ml.) was added. There was a vigorous reaction and a deep brown oil floated on the aqueous layer. After sometime, the oil solidified to give dark crystals. The crystals were collected and recrystallised from methanol to give light brown crystals of the urethane m.p. 95°C. Yield (~ 1 g.) ν_{max} 1695 cm^{-1} (ester), 1639 cm^{-1} (ketone).

Attempted Cyclisation of the Urethane

Metallic sodium cut into small pieces (0.529g.) was dissolved in absolute ethanol (99%) (20 ml.). When all the sodium had dissolved, the solid urethane (1g.) was added and refluxed for two hours. On adding the reaction mixture to water, a solid appeared and this solid was found to be identical in melting point and i.r. with the starting material.

Acetylation of methyl 6-aminoveratrate

Methyl 6-aminoveratrate (2g.) was added to acetic anhydride (10 ml.). After a while, when all the ester had dissolved, a white solid appeared. The solid was washed well with water and dried on the filter paper giving fine needle-like crystals of N-acetyl methyl veratrate. Yield (~ 2g.) m.p. 163°C.

Attempted Cyclisation of the methyl N-acetyl veratrate with sodium hydride

Methyl N-acetyl veratrate (1g.) was dissolved in benzene (10 ml.) and sodium hydride (1g.) was added and the mixture was refluxed for 2 hours on a water bath. It was cooled and methanol was added to decompose the excess hydride. It was diluted with water and on making slightly acidic with hydrochloric acid, a solid appeared. This was filtered and dried in the oven. The solid was insoluble in chloroform . m.p. above 300°C. Yield of material (~ 0.5g.).

Methylation of the solid material was done by suspending it in a mixture of methanol (5 ml.) and diethyl ether (15 ml.) and diazomethane was bubbled into the mixture. As methylation occurred, the material gradually dissolved until a permanent yellow clear solution was obtained. The yellow solution was kept in the fume cupboard overnight. The solvent was evaporated to give a solid m.p. 160°-164°C.

identified as the methyl N-acetyl veratrate by the i.r. spectrum.

(This showed that the reaction of sodium hydride with methyl N-acetyl veratrate resulted in the hydrolysis of the ester group to the carboxyl group).

Second Attempted Cyclisation of methyl N-acetyl veratrate with sodium in toluene.

Methyl 6-amino veratrate (0.5g.) was added to toluene (10 ml.) in which metallic sodium (0.01g.) had been suspended. The mixture was refluxed for about four hours on an oil-bath. The toluene was decanted from the solid and it was dissolved in water. The aqueous solution was made just acidic with hydrochloric acid and the solid precipitated was filtered. m.p. 240°, insoluble in chloroform. Mass peaks at 253, 239 and 221 corresponding to the compounds methyl N-acetyl veratrate, N-acetyl veratric acid and 6,7-dimethoxy-4-hydroxy-2-quinolone.

Repeat of the attempted cyclisation of methyl N-acetyl veratrate using Sodium and dried toluene

(a) Drying Toluene

Toluene (100 ml.) was shaken with fused calcium chloride (20g.) for about one hour and then filtered into dry clean flask

into which sodium wire was pressed. The solution was allowed to stand over the sodium wire overnight and then distilled into another dry flask.

(b) Attempted cyclisation

With the toluene thus dried (20 ml.) methyl N-acetyl veratrate (1g.) was dissolved. The solution was distilled until about half of the solvent distilled off, (to ensure that there was no trace of water in the reaction mixture). Chipped metallic sodium (0.5g.) was added into the remaining solution and the mixture was refluxed for over four hours. The excess toluene was decanted and the solid left in the flask was dissolved in water. On acidifying the aqueous solution a solid was obtained with mass peaks at 221 and 239, again indicating that the solid was a mixture of N-acetyl veratric acid and the required 6,7-dimethoxy-4-hydroxy-2-quinolone.

Attempted Cyclisation of methyl N-acetyl veratrate with sodium granules (Method of Ashley and Co.[81])

Sodium (3g.) was placed in about 100 ml. of high boiling petroleum ether (100°-120°) in a round bottomed flask. The sodium was melted under this liquid by heating gently on a flame below the boiling point of the liquid. As soon as all the sodium melted, it was shaken vigorously until it had broken into fine granules. The

pet. ether was then carefully decanted and the sodium washed with dry toluene. Then dry toluene (100 ml.) was added. To this, methyl N-acetyl-veratrate (25g.) was added. Reaction occurred immediately and the yellow mixture boiled spontaneously. The mixture was refluxed on an oil-bath for 6 hours and after six hours, a solid was formed. The solid was collected and then redissolved in warm water(about 400 ml) On acidifying the aqueous solution with hydrochloric acid, a light yellow solid appeared. This was filtered and dried in the oven. m.p. 232°C - 235°C, Yield 17g.

The solid dissolved in sodium bicarbonate with effervescence, showing that it was a carboxylic acid.

Mass peak 239 (strong) 221 (weak).

Attempted Condensation of methyl N-acetyl veratrate with diethyl malonate and sodium amyloxide in accordance with the method of Georg Koller[82].

Methyl N-acetyl veratrate (16g.) was placed in a Clarius tube and diethyl malonate (15g.) was added. A solution of sodium (0.7g.) in n-amyl alcohol (20 ml.) was added and the tube was sealed. The tube was heated in a furnace at 140° - 150° for over 15 hours.

A solid was formed, and this was insoluble in water and chloroform. The solid gave a mass peak of 239. Yield 12 g.

The solid was methylated by suspending it in ether (100 ml) and saturated with diazomethane as usual. On allowing the diazomethane to escape and evaporating the solvent, a solid was obtained m.p. 162°C. Yield 10 g.

The solid was identified as the methyl N-acetyl veratrate by the i.r. spectrum.

Reaction of amino veratrole with ethyl cyanoacetate

Amino veratrole (15g.) was added to excess ethyl cyanoacetate (100 ml.) and the pink solution obtained was boiled on a heating mantle for 3 hours. The excess ethyl cyanoacetate was distilled off under pressure and the residue was allowed to cool. A solid was formed. This was collected and washed with ether to give a deep yellow powdery substance m.p. 232°C - 233°C. Yield 10 g. (Found C, 54.81 ; H, 5.56 ; $C_{11}H_{12}O_3N$ requires C, 55.00, H, 5.45) M^+ 220. ν_{max} 1750 cm^{-1} (carbonyl band of an amide), 2225 cm^{-1} (- CN group).

An attempted Hoesch reaction on the solid was abortive.

The synthesis of 6,7-dimethoxy-4-hydroxy-2-quinolone

Aminoveratrole (20g.) was added to excess diethyl malonate (40g.) in diphenyl ether (100 c.c.) in a 250 ml. round bottomed flask

equipped with a short air condenser and the mixture was refluxed for about 2 hours. On cooling, a solid appeared. This was filtered and the solid was washed with petroleum ether to give a powdery substance m.p. above 300°C. Yield 12.5 g. Mass peak at 221 and a very weak peak at 289.

The solid was boiled with 10% caustic soda (20 ml.) and on reprecipitation with hydrochloric acid gave light yellow crystals, which was collected and dried in the oven. m.p. above 300°C. Yield ~5g. mass peak 221 (very sharp) (Found C, 60.11 ; H, 4.72 ; $C_{11}H_{11}O_4N$ requires C, 59.73, H, 4.99) ν_{max} 3448 cm^{-1} (imino band), 1639 cm^{-1} (carbonyl band of a 2-quinolone).

Attempted esterification of the 6,7-dimethoxy-4-hydroxy-2-quinolone with ββ-dimethyl acryloyl chloride according to the method of Brown et al. was unsuccessful.

Preparation of Isoamyl bromide

48% hydrobromic acid (142 ml.) was put in a 500 ml. flask and concentrated sulphuric acid (33 ml.) was added in portions with shaking. When cold, isoamyl alcohol (109 ml.) was added and the apparatus was assembled for distillation with a dropping funnel for adding more sulphuric acid. The end of the condenser was connected to an adapter dipping into water contained in a 500 ml. flask

surrounded by ice. More concentrated sulphuric acid (5.5.ml) was added slowly from the tap of the funnel and the mixture was distilled slowly. The distillate, a heavy liquid below the water level in the flask was washed well with water, then with an equal volume of concentrated hydrochloric acid (volume equal to the volume of the distillate), with water, then with a small quantity of sodium bi-carbonate and finally with water. It was dried with fused calcium chloride and the dried bromide was distilled between 117° - 120°

Yield 65 g.

Condensation of Isoamyl bromide with diethyl malonate

Metallic sodium (3.8g) was dissolved in dried methanol (100 ml) and the sodium methoxide solution was allowed to cool. Diethyl malonate (25 ml.) and isoamyl bromide (20 g.) were added and the mixture was refluxed for over six hours. After about one hour, a white solid of sodium bromide started to appear causing much bumping. The excess methanol was distilled off and to the residue, water (100 ml.) was added and the ester formed as oily drops was extracted with ether (100 mls x 3). The combined ether extracts were washed well with water and dried with sodium sulphate (anhydrous). Evaporation of the ether and distillation of the residue gave the diethyl-isoamyl-malonate as a colourless oil, collected above 200° at atmospheric pressure.

Yield 15 g.

Preparation of 6,7-dimethoxy-4-hydroxy-3-isoamyl-2-quinolone

A solution of diethyl-isoamyl-malonate (10g.) and aminoveratrole (5g.) in diphenyl ether (50 c.c.) was refluxed in a blanket of nitrogen for 3 hours in 100 ml. flask fitted with a short air condenser to allow off the ethanol formed.

On allowing to cool, the 2-quinolone crystallised out. This was collected and washed well with n-hexane to remove the diphenyl ether. The cream-coloured solid was insoluble in chloroform but soluble in methanol. m.p. 130° - 135°C, Yield 3.5g. (Found C, 62.76 ; H, 8.07 ; $C_{16}H_{22}O_4N$ requires C, 65.75 ; H, 7.54) M^+ 291 ν_{max} 3448 cm^{-1} (imino band), 1639 cm^{-1} ($>c = o$ of a 2-quinolone).

Methylation of 6,7-dimethoxy-4-hydroxy-3-isoamyl-2-quinolone

6,7-dimethoxy-4-hydroxy-3-isoamyl-2-quinolone (0.5g.) was dissolved in methanol (10 ml.) and diethyl ether (20 ml.) was added. The solution was saturated with diazomethane until the solution attained a permanent yellow colouration. The solution was then allowed to stand in the fume cupboard overnight until the excess diazomethane had escaped (when the solution became colourless). The solution was evaporated and the residue crystallised to give the 6,7,4-trimethoxy-3-isoamyl-2-quinolone m.p. 182° - 184°. Yield 0.3g.

The methylated product was identified by its n.m.r. spectrum.

Pyrogallol carboxylic acid

A solution containing pyrogallol (40g.) and potassium bi-carbonate (200g.) in water (400 ml.) was placed in a litre 2-necked flask. The solution was heated gently on a steam bath for 4 hours. Then it was refluxed vigorously over a flame for half an hour while a rapid stream of carbon dioxide was being passed. The solution was acidified while still hot with hydrochloric acid, the acid being delivered to the bottom of the flask with a long tube connected to the tap of the separating funnel. The solution was allowed to cool and the acid crystals appeared on cooling. The crystals were collected by filteration and recrystallised by boiling with 200 ml. of water containing a little decolourising charcoal to give light yellow needle-like crystals. Yield 35g.
m.p. 224° - 225°.

3,4-dimethoxy-2-hydroxy-benzoic acid

Pyrogallol carboxylic acid (30g.) was dissolved in sodium hydroxide solution (35 g. of NaOH in 250 ml. of water) and dimethyl sulphate (60 ml.) was added and the mixture was shaken up while cooling under tap water for 30 minutes. The dark-brown mixture was then refluxed for 2 hours while more sodium hydroxide solution (5 g. of NaOH in about 15 ml. of water) was being added through the

condenser, to hydrolyse any ester that might be formed. On allowing to cool, the 3,4-dimethoxy-2-hydroxy benzoic acid was precipitated with concentrated hydrochloric acid. m.p. 160°C - 164°C (Lit.[87] 164°C). Yield (about 16g.).

An attempt at shaking the 3,4-dimethoxy-2-hydroxy benzoic acid with more sodium hydroxide and dimethyl sulphate to give the trimethoxy benzoic acid was unsuccessful.

2,3,4-trimethoxy benzoic acid

3,4-dimethoxy-2-hydroxy benzoic acid (38g.) was dissolved in methyl ethyl ketone (300 ml.) and anhydrous potassium carbonate (30g.) was added.[88] To the mixture, dimethyl sulphate (40 ml.) was added and the mixture was refluxed on a heating mantle for over 5 hours. The mixture was filtered and the solvent was distilled off the filtrate. The residue, an oil, presumably 2,3,4-trimethoxy methyl benzoate was boiled with 20% caustic soda (100 ml.) on a flame for 2 hours to hydrolyse the ester. The solution was allowed to cool and acidification with hydrochloric acid gave the 2,3,4-trimethoxy benzoic acid as white needle-like crystals (after recrystallisation from hot water containing a little charcoal).

Yield 15 g.

m.p. 98°C - 100°C. (Lit[87] 99°C).

2,3,4-trimethoxy benzamide

2,3,4-trimethoxy benzoic acid (25g.) was dissolved in benzene (375 ml.) and to the solution, phosphorus pentachloride (25g.) was added. The solution was refluxed for over one hour until there was no more evolution of hydrogen chloride gas. The undissolved material was filtered off and the filtrate was cooled well in ice-salt mixture. Concentrated ammonia solution (250 ml.) was added gently. The benzene was then steam distilled and the aqueous solution left as residue gave cream-coloured prism-like crystals on cooling. This was filtered and dried in the desiccator. m.p. $134^{\circ} - 136^{\circ}$ (Lit[87] $130^{\circ} - 131^{\circ}$).

Conversion of the 2,3,4-trimethoxy benzamide to 2,3,4-trimethoxy aniline (Hofmann's degradation method)

2,3,4-trimethoxy benzamide (14g, ~ 0.06 mole) was dissolved in methanol, then reprecipitated with water and filtered as fine granules; it was washed well with water to remove all traces of alcohol. This was suspended in sodium hypobromite solution. The hypobromite solution was prepared at $0^{\circ}C$ by adding bromine (4 c.c., ~ 0.08 mole) to a solution of sodium hydroxide (16 g., ~ 0.4 mole) in 133 ml. of water. The mixture was stirred (mechanical stirring) for over two hours. Then it was diluted with water and the pink oil formed was taken up in ether. The ethereal solution was dried with anhydrous magnesium sulphate and

evaporated. The residue was a thick pinkish oil. Yield : 8g. The i.r. spectrum showed the doublet of the amino group at ν_{max} 3333 cm^{-1} and 3448 cm^{-1}.

6,7,8-trimethoxy-3-isoamyl-4-hydroxy-2-quinolone

2,3,4-trimethoxy aniline (2g.) was added to diethyl-isoamyl-malonate (5g.) in diphenyl ether (50 c.c.). The mixture was refluxed for two hours under nitrogen. On cooling, the 3-substituted-2-quinolone compound was precipitated when titurated with petroleum ether (40^{o} - 60^{o}). This was filtered and washed well with petroleum ether (40^{o} - 60^{o}) until all the diphenyl ether had been washed off. It was dried on the filter paper. Yield (1.2g.) m.p. $155^{o}C$ - 157^{o}. (Found C, 62.58; H, 7.58 ; $C_{17}H_{23}O_5N$ requires C, 63.54 ; H, 7.16). ν_{max} 1639 cm^{-1} (carbonyl of a 2-quinolone) and 3333 cm^{-1} (imino band).

Methylation of 6,7,8-trimethoxy-3-isoamyl-4-hydroxy-2-quinolone

6,7,8-trimethoxy-3-isoamyl-4-hydroxy-2-quinolone (0.2g.) was suspended in dry diethyl ether (20 ml) and diazomethane was bubbled into the solution until it attained a permanent yellow colouration. The excess diazomethane was allowed to escape by leaving the solution in the fume-cupboard overnight. On evaporating the solvent, an oil was obtained. The n.m.r. of the oil showed the presence of the four

methoxy groups of 4,6,7,8-tetramethoxy-3-isoamyl-2-quinolone.

Preparation of ββ-dimethylacrylic acid :

In a 5l. round bottomed flask fitted with a stirrer, re-distilled mesityl oxide (100g.) dissolved in dioxan (200 ml) was added. A cold solution of sodium hypobromite was prepared at 0^{o} by adding bromine (100 ml) gently from a dropping funnel into a solution of sodium hydroxide (200 g. of NaOH in 1 Litre of water and 1 kg. of ice) with vigorous stirring. The cold solution of sodium hypobromite thus prepared was added all at once to the solution of mesityl oxide in dioxan and stirring was started immediately. After a short while, the mixture warmed up and the yellow mixture turned milky. The stirring continued for about 3 hours after which the milky mixture turned to a light yellow clear solution. The solution was tested with acidified potassium iodide solution and no iodine was liberated showing that all the hypobromite had decomposed. The solution was then acidified with 50% sulphuric acid (250 ml) until it was acid to Congo red. The whitish mixture formed was then extracted with ether in bits (100 ml of the aqueous mixture to 500 ml. of ether) with vigorous shaking during each extraction. The ether extracts were combined and dried with anhydrous magnesium sulphate and the ether was evaporated to give an oil as a residue. The residue was distilled

under reduced pressure to give a light yellow thick oil which solidified on cooling. Recrystallisation of the solid from pet. ether gave pure white long needles of the acid which was dried in air. Yield 25 g. m.p. 65°C - 66°C (Lit[90] 68°C).

YY-dimethyl-allyl alcohol

ββ-dimethylacrylic acid (18g.) dissolved in dry ether (50 ml) was added slowly for about one hour to a stirred slurry of Lithium aluminium hydride (10g.) in dry ether (100 c.c.). The mixture was stirred overnight at room temperature. The excess lithium aluminium hydride was destroyed by carefully adding first, wet ether, then ice chips bit by bit to the mixture cooled below 0°C. The complex formed after all the hydride had been destroyed was decomposed with dilute sulphuric acid (75 ml. of sulphuric acid in 225 ml. of water). The liberated alcohol was extracted with ether and the ethereal solution was dried with anhydrous magnesium sulphate and evaporated. The residue was re-distilled under reduced pressure to give a colourless liquid.

Yield 12 g.

YY-dimethylallyl bromide :

YY-dimethylallyl alcohol (12g.) was dissolved in low boiling

petroleum ether (40° - 60°) (40 ml) and added slowly to a stirred mixture of phosphorus tribromide (13g.) and pyridine (1.9g.) in petroleum ether (40° - 60°) (35 ml) at a temperature below -10°C. for about half an hour. The mixture was stirred overnight and ice-cold water was added. The oil formed was well extracted with petroleum ether (40° - 60°); the pet. ether extract was dried with anhydrous sodium sulphate and evaporated. The residue was distilled to give the γγ-dimethylallyl bromide as a light yellow fuming liquid. Yield 10 g.

Dimethyl -(γγ-dimethylallyl)-malonate :

Freshly cut sodium (2g.) was added to dried methanol (100 ml) [dried by refluxing with calcium hydride and distilling over it into another clean dry flask]. Redistilled diethyl malonate (9g.), and γγ-dimethylallyl bromide (10g.) were added to the sodium methoxide solution and the mixture was refluxed for about six hours. The excess methanol was distilled off and the residue was taken up in diethyl ether. The ethereal extract was dried with anhydrous sodium sulphate and the solvent was distilled off. The residue was redistilled and the substituted malonic ester was collected above 200°C. as a colourless liquid.

Yield 6g.

6,7-dimethoxy-3-isopentenyl-4-hydroxy-2-quinolone

A mixture of aminoveratrole (3g.) and diethyl-(γγ-dimethylallyl)-malonate (6g.) in diphenyl ether (50c.c.) was refluxed in a blanket of nitrogen for five hours. When cool, the solid 2-quinolone was precipitated with petroleum ether (40^{o}-60^{o}), collected and washed with petroleum ether. The solid was shaken well with chloroform and filtered to give an ash-coloured powder. Yield 1.8g.
m.p. $200^{o}C$ - $201^{o}C$. (Found C, 66.51 ; H, 6.84 ; $C_{16}H_{19}O_4N$ requires C, 66.42 ; H, 6.58) M^{+} (mass spectrum) 289. ν_{max} 1639 cm^{-1} (carbonyl of a 2-quinolone).

Demethyl dihydro-oricine :

6,7-dimethoxy-3-isopentenyl-4-hydroxy-2-quinolone (50 mg.) was refluxed with concentrated hydrochloric acid (2 ml.) for about 2 hours. It was diluted with water and extracted with chloroform. The chloroform extract was dried with anhydrous sodium sulphate and evaporated to give a solid residue of the demethyl dihydro-oricine. Yield 10 mg. m.p. $222^{o}C$ - $226^{o}C$.

Methylation of demethyl dihydro-oricine to dihydro-oricine

A mixture of demethyl dihydro-oricine (10 mg.) methyl iodide (5 ml.) and anhydrous potassium carbonate (10g.) in analar acetone

(80 ml) was refluxed overnight (over 12 hours) and then filtered. The solvent (acetone) was evaporated off the filtrate and the residue was extracted with chloroform. On evaporation of the chloroform, a gummy material was obtained. The n.m.r. spectrum of the gummy material indicated that methylation took place but there were lots of impurities. The gummy material showed mainly three spots on the t.l.c. and the fastest spot corresponded to the dihydro-oricine (obtained by the hydrogenation of the natural oricine).

The gummy material was too small for column chromatography. Preparative thin layer chromatography was done and a slightly purer material, still uncrystalline, was obtained. The n.m.r. of the last gummy material was very similar to the n.m.r. of the dihydro-oricine

N-demethyl-oricine

6,7-dimethoxy-3-isopentenyl-4-hydroxy-2-quinolone (0.1042g.) and 2,3-dicyano-5,6-dichloro benzoquinone (DDQ) (0.1056g.) in dry benzene (100 ml) was refluxed for about 4 hours. The mixture was cooled and filtered. The benzene was evaporated and the residue was extracted with chloroform, then washed with 10% sodium bicarbonate solution (about 500 ml.), then with water. The chloroform extract was dried with anhydrous sodium sulphate and evaporated

to give a crystalline substance. m.p. 210° - 212°C. Yield ~ 0.1 g. (Found C, 68.01 ; H, 6.01 ; $C_{16}H_{17}O_4N$ requires C, 67.20 ; H, 5.92.) M^+ (mass spectrum) 287.

Methylation of N-demethyloricine to Oricine :

A mixture of N-demethyloricine (0.05g.) methyl iodide (2 ml) and anhydrous potassium carbonate (5g.) in analar acetone (40 ml) was refluxed for 6 hours on a steam bath. The mixture was filtered and the filtrate was evaporated to give a residue which was taken up in chloroform. The chloroform extract was washed with water, then dried with anhydrous sodium sulphate and evaporated to give the crystalline substance, oricine, recrystallised from benzene. m.p. 150°C. Yield 0.03 g. (Found C, 67.51 ; H, 6.30 ; $C_{17}H_{19}O_4N$ requires C, 67.76 ; H, 6.34. The i.r. and n.m.r. spectra were identical with the i.r. and n.m.r. spectra of the natural oricine.

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