Khaya senegalensis planted by Professor D.H.R. Barton F.R.S. on 13th January, 1967 in front of the New Chemistry Buildings University of Ibadan.

EXTRACTIVES FROM *KHAYA* SPECIES

A Thesis

Submitted in partial fulfilment of the

Requirements for the award of the degree

of

DOCTOR OF PHILOSOPHY

in the

University of Ibadan

by

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Professor in the Department of Chemistry,
University of Ibadan,
Nigeria.

March, 1968.

"..... God revealing Himself for those with eyes to see."

C. A. Coulson.

"Great are the works of the Lord, studied by all who have pleasure in them."

Psalm 111 : 2.

A B S T R A C T

The chemistry of β-furan-containing extractives obtained from trees of the family Meliaceae (and one tree from the family Rutaceae) is briefly reviewed and their biogenesis is discussed.

In continuation of our study of the extractives from the family Meliaceae in this department, five species of the genus Khaya have been examined. The seed, timber, bark, root, and root-bark of three species, K. senegalensis, K. ivorensis, and K. grandifoliola, and the seeds of the two others, K. anthotheca, and K. nyasica were examined. The extracts are mainly the tetranortriterpenes with a β-substituted furan, and about thirty of these were isolated and structures were assigned to nearly all of them. The known ones include khivorin, 7-deacetoxy-7-oxo-khivorin, 7-deacetoxy-7-oxogedunin, methyl angolensate, mexicanolide, and deacetylgedunin. Those characterised and reported for the first time include khayasin, 6-deoxy-3β-tigloyloxyswietenolide, 6-deoxy-3β-benzoyloxyswietenolide, khayanthone, 3-deacetylkhivorin, 3-deacetyl-7-deacetoxy-7-oxokhivorin, methyl 6-hydroxyangolensate, grandifoliolin, 3-destigloyl-6-deoxyswietenine, 3-destigloyl-6-deoxy-3β-acetoxyswietenine, 3β-dihydrocarapin, and 3-destigloyl-6-deoxy-3β,12β-diacetoxyswietenine. Others prepared before, but

isolated as natural products for the first time include deoxy-andirobin, and 6-deoxyswietenolide. In addition two substances, A and B from K. ivorensis root-bark have structures proposed for them which are still to be confirmed, while not much is known of the structures of a few others especially methyl senegalensate.

Most of these extracts contain glycosides and steroids, β-sitosterol in particular. Of these only the steroid hormone 20β-acetoxy-3-oxopregn-4-ene, a new compound, was sufficiently studied to be assigned a structure which was confirmed.

The structural elucidation of these compounds have depended almost entirely on their spectral properties including those of their chemical transformation products. Obviously physical properties played a great part especially in confirming a known compound by comparison of data.

The co-occurence of some of these compounds have strengthened the argument for the biogenesis proposed. The chemotaxonomic implication was also discussed.

A number of interesting reactions including some rearrangements are discussed and mechanism for some of them have been suggested.

ACKNOWLEDGEMENTS

I would like to express my indebtedness and gratitude to Dr. J. W. Powell for a most useful and an unselfish supervision in the early stages of this work, to Professor D. A. H. Taylor for his untiring efforts and efficient supervision in the later stages, to Professor J. Hirst for very useful discussions; to Professor C. W. L. Bevan for his encouragement and his being very understanding, and to Professor D. E. U. Ekong for very useful discussions.

I also wish to thank the wood chemistry group for useful discussions, the entire technical, and the secretarial staff for their invaluable assistance, and Mr. A. K. Fasina for "chemistry fellowship" in "E3."

I am very grateful to the University of Ibadan for the award of a three-year postgraduate scholarship.

Finally, I would like to thank my wife for her much-needed loving understanding and support throughout the duration of this study.

CONTENTS

GUIDE TO SPECTRA REPRODUCED

FOREWARD

In view of the fact that there has not yet emerged a universally accepted system of naming the many tetranortriterpenes in this fast-growing field of natural products chemistry, no restriction apart from that ensuring consistency, has been imposed in the various names used throughout this thesis. Names used in the original papers have been used especially where they provide shorter words. Mexicanolide has been used rather than C.O.B. (*Cedrela odorata* substance B) while its transformation products have been named C.O.C., C.O.D., and C.O.E. for the respective substances C, D, and E. Khayasin has been used rather than 6-deoxy-3β-isobutyrylswietenolide and this has led to khayasin C, and D, parallel to C.O.C., and C.O.D. However, the corresponding benzoates and tiglates are named as derivatives of swietenolide.

Mexicanolide has been treated separately because the discussion of its chemistry in one section may be disproportionate compared with the rest, especially as it was not identified as a new product as a result of the present study. Moreover, the earlier part of the time during which this work was done was spent on mexicanolide (= C.O.B.) obtained from *Cedrela odorata* extract.

INTRODUCTION

The great array of chemically very interesting secondary metabolites isolated from wood has been a major incentive to their study. Moreover there is the probability of (i) obtaining physiologically active compounds (a number of trees find great use in native medicinal practice), (ii) getting a correlation between various botanical species and their chemical constituents and thereby supplementing botanical taxonomy with chemical taxonomy. All these make it reasonable to presume that the study may not only be chemically rewarding but may well serve a wider circle.

A systematic survey of wood extractives has been going on in this department for over eight years. One of the families we have studied closely is the Meliaceae (closely related to the families Rutaceae and Simarubaceae). The Meliaceae family comprises some 40 genera and 600 species.[1] They are trees or shrubs and rarely herbaceous. The presence of a class of C-26 degraded triterpenes known as the limonoid bitter principles, after limonin (XXI), is a characteristic feature of the Meliaceae and some related Rutaceae.

BIOGENESIS

There has not been much biochemical work aimed at finding the biogenetic pathway to the furanoid (limonoid) triterpenes. However, the great number of different compounds found in the same species and in some cases in the same tree which must represent intermediate stages in the pathway give compelling evidence that the limonoid triterpenes are formed from a euphol (Ia) or a tirucallol (Ib) type nucleus and particularly from butyrospermol IIa (≡ eupha-7,24-diene-3β-ol), as has been noted before.[2]

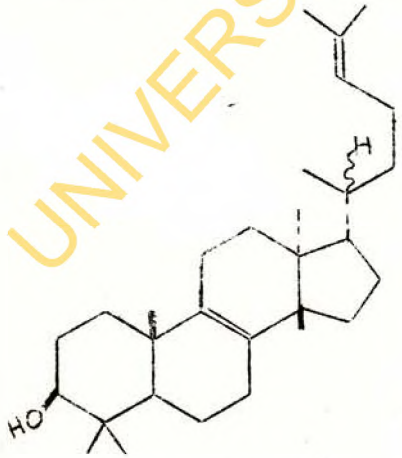
Birch et al.[3] suggested that a tirucalla-7,24-diene-3α-ol might be the precursor for these tetranortriterpenes and more recently Halsall et al.[4] gave similar proposition. These fix the structure of such a precursor as (IIb) (stereochemistry at C-3 and C-21 being unspecified). The probable steps from (IIb) to the limonoids as summarised in scheme 1 is as follows.

In view of the greater reactivity of the Δ^{24}-double bond over the Δ^{7}-double bond, there must first be a saturation of the former bond by epoxidation before oxidation of (IIb) can take place to give III (cf. Barton et al.[2,15]). This idea is supported by the fact that many compounds have been isolated with different functional groups between C-20 and C-27 while the nucleus of (IIb) remains unchanged. Furthermore, some of the compounds characterised suggest

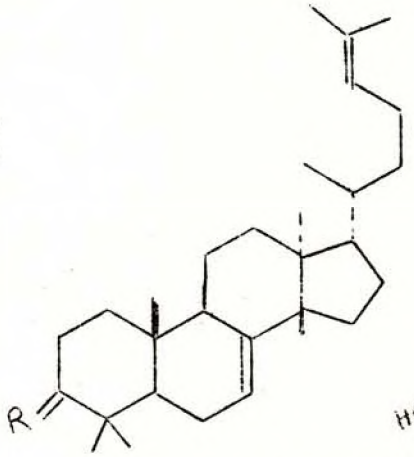
a stepwise oxidation of (IV) at C-21 (as in the elemi acids[3,5]), and at C-23. Making use of the ideas of Halsall[7] et al. the following can be deduced.

The diol (V) can cyclise in the way shown to give the bourjotinolone[8] series of type (VI); (VI) in turn can undergo oxidation to give grandifoliolenone trione[9] (VII).

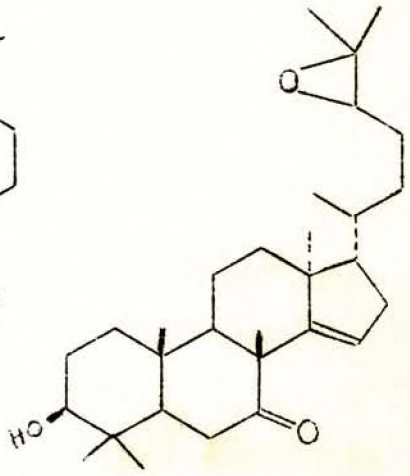
The acid portion of (VIII) can cyclise with the -OH at C-23 to give (IX) by a mechanism analogous to ether formation from alcohols by acid catalysis. Reduction of the lactone in (IX) will give the hemiacetal (XI) from which flindissol[3,8], melianone[10,11,12] and turraenthin[7] may be derived. In addition, there is the possibility of having the C-22 hydroxyl group (of a C_{22}, C_{23}, C_{24}-triol) cylising on C-25 to give compounds like odoratone,[14] odoratol[14] = mexicanol.[13]



I (a) 20-βH
(b) 20-αH

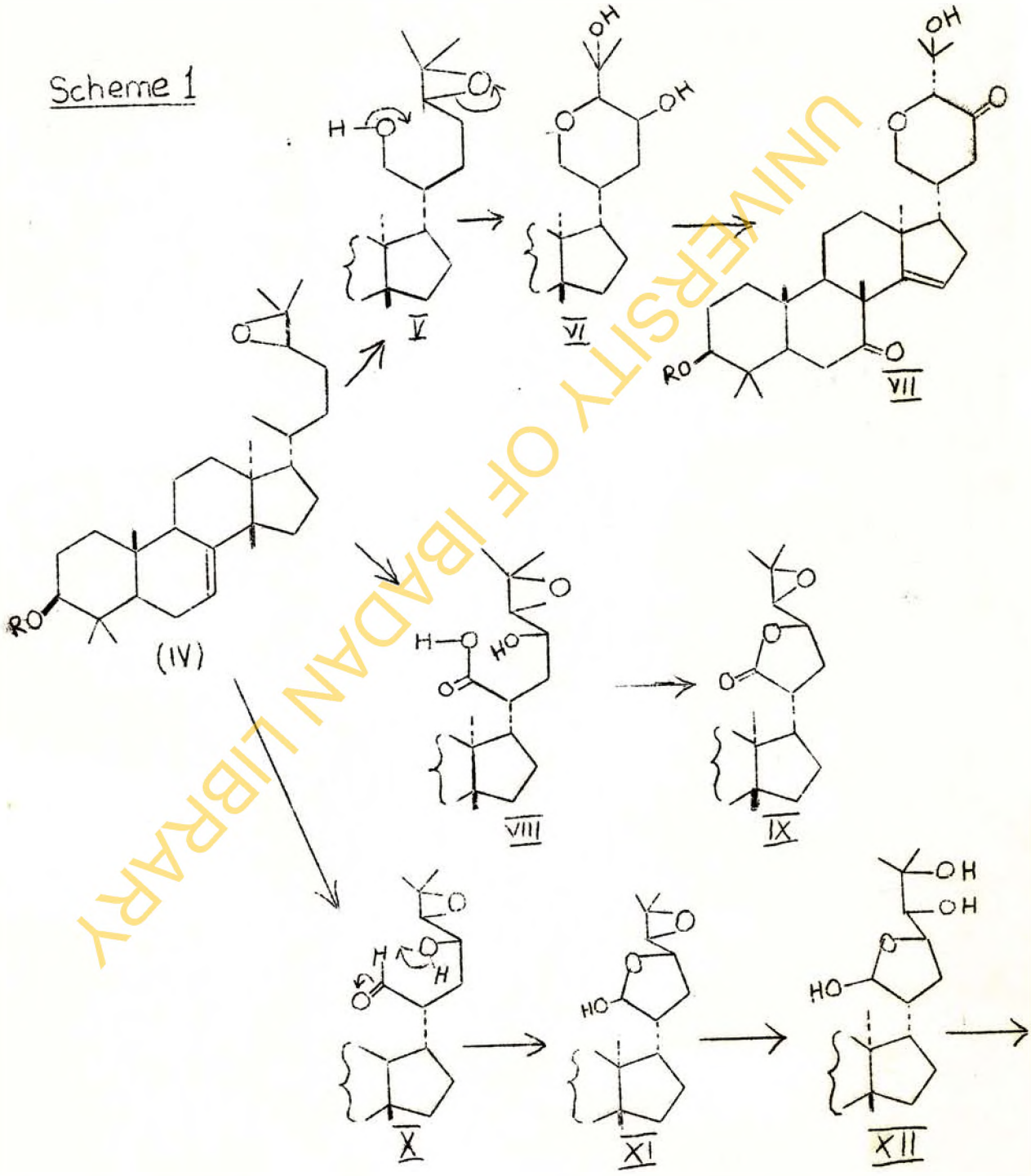


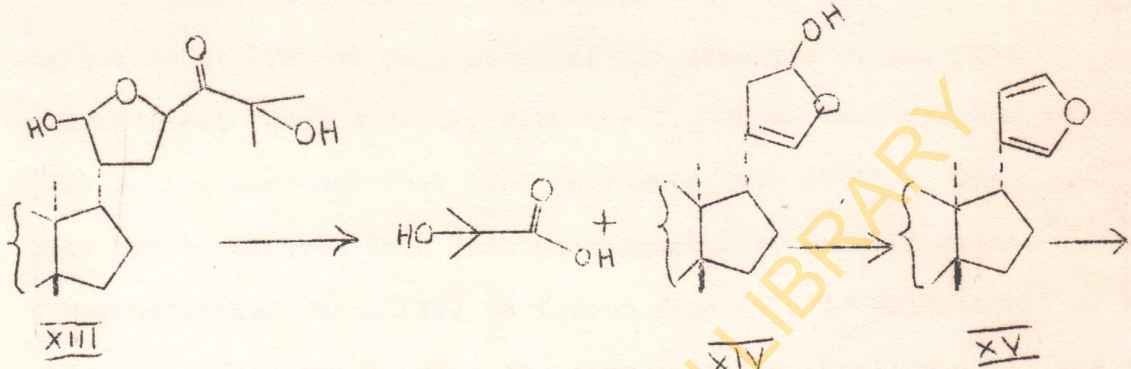
II (a) R = 3β-OH, αH
(b) R = α- or β-OAlkyl, (βH or αH)
or =O



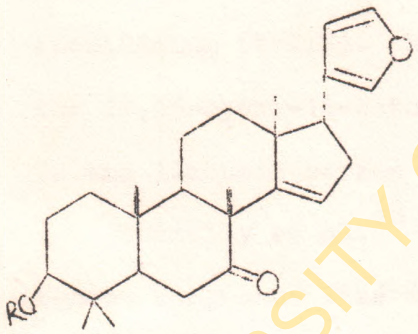
III

Scheme 1

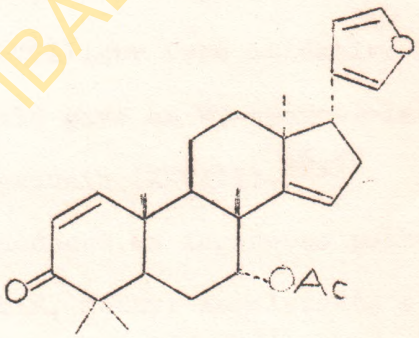




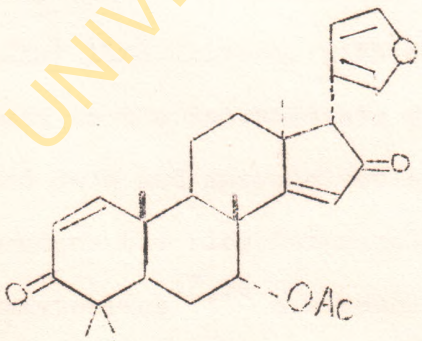
XIII XIV XV



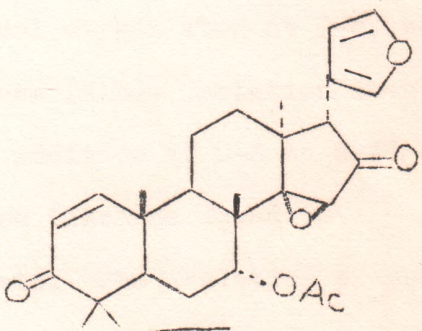
XVI



XVII



XVIII

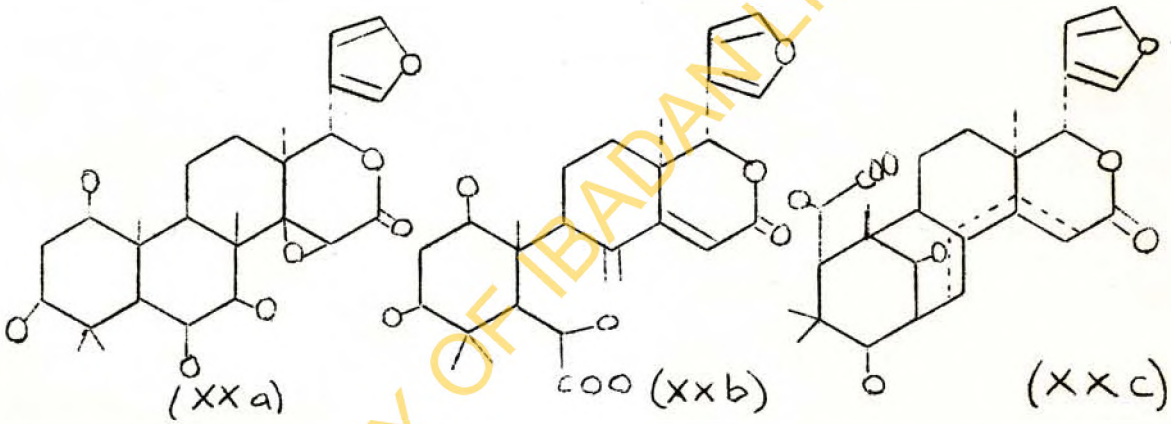


XIX

In plants the process of forming (XI) may be shorter if the oxidation of (IV) at C-21 stops at the aldehyde stage. The aldehyde can react directly with the C_{23}-OH to form the hemiacetal (XI) in the same way that (IX) is formed from (VIII). The C_{23}-C_{24}-bond can be cleaved in a fashion suggested by Halsall et al.[7], thus a β-substituted furan (XV) is formed from (XII). Oxidation[15] of (XV) will give (XVI) which after the necessary modification will lead to Lavie's series of compounds:[6] azadirone (XVII); which on oxidation at C-16 gives azadiradione (XVIII) and epoxiazadiradione (XIX) on epoxidising (XVIII). Baeyer-Villiger type oxidative cleavage of the 14,15-epoxy-16-ketone would give an αβ-epoxy-δ-lactone as found in the limonoid series e.g. gedunin (XXVIII).[16,17]

Connolly et al.[18] have adduced an ingeneous pathway for ring B-seco compounds like andirobin, methyl angolensate etc. and the bicyclononanolides, by making use of the Biogenetic Isoprene Rule.[19] They said that fission of ring B between C-7 and C-8 of a precursor (XXa) like khivorin with an additional oxygen atom at C-6, could lead to the intermediate diene-lactone (XXb). Rotation about C-9 and C-10 and intramolecular Michael addition of C-2 to C-30 would produce the bicyclononanolides system (XXc) as found in swieteni¢ne[18,20] mexicanolide[21,22] etc. The isolation of methyl

angolensate,[23] andirobin[24] etc. that fit the intermediate postulated, plus the important fact that the three series - the 7-oxo, Ring B-seco and bicyclononanolides often do co-occur in the same tree gave good evidence for the proposition.



Because of the possibility of (a) epimerization, (b) cleavage of each of rings A, B, and C and probably D, and (c) many feasible variations of the functional groups, there is certainly a very wide range to their structural possibilities. A large number of naturally occuring triterpenes have been isolated and characterised. An excellent review of these principles that have been described in literature to June 1967 has been written by D. L. Dreyer.[25]

Rather than attempting to give an exhaustive introduction to the known limonoid bitter principles, only salient features of a

few of them directly relevant to this thesis will be described.

LIMONIN-SERIES (DEGRADED RING A)

LIMONIN Although this occurs not in the Meliaceae but in the Rutaceae, it is pertinent to mention it here because of its historical interest as the first furanoid triterpene to be characterised. Limonin (XXI), a bitter principle from Citrus fruits, was isolated by Bernay in 1841. The chemical structure was determined in 1960 as a result of studies by three groups of workers: Arigoni et al., Barton et al., and Corey et al.[2,20] The structure was confirmed by the use of X-ray crystallography.[27]

All the oxygen functions of limonin $C_{26}H_{30}O_8$ were accounted for in 2 δ-lactones, 1 β-substituted furan, a ketonic oxygen probably in a six-membered ring and two ethereal oxygen atoms. Most of the reactions that led to its partial structure are base-catalysed; some of the interesting and important reactions are:

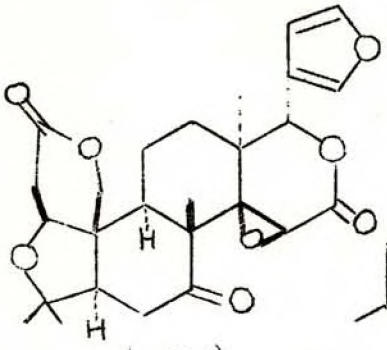
(i) Reduction of limonin by the Meerwein-Pondorff method to give limonol with an axial hydroxyl group at C-7. On alkaline treatment, limonol gave merolimonol (XXVII) with a loss of 5 carbons eliminated as β-furfuraldehyde. This gave a powerful guide to the relationship between ring D, the furan ring and the C_7-hydroxyl

group. In fact, it was asserted that the reaction took place between the 7α-hydroxyl group, the epoxide ring and the δ-lactone. The part structure (XXII) was thus written.

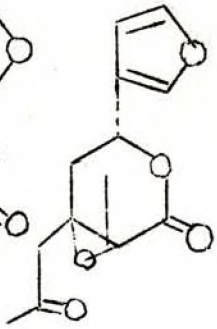
(ii) Autoxidation of the anion from the saturated ketone in the presence of dry t-butyl alcohol containing potassium t-butoxide to give a diosphenol (XXIa). This enabled the environment of C-7 in limonin to be written as $-CH.CH_2.CO$.

(iii) Oxidation of an alkaline solution of limonin with hypoidodite gives limonilic acid. When the reaction was performed on hexahydrolimonin, a dicarboxylic acid was formed. The second carboxylic acid was said to come from the second δ-lactone which must be in ring A and the important conclusion was drawn that the alkyl oxygen in lactone A must be of the type $-CH_2.O.CO-$. Ozonolysis of the diosphenol from tetrahydro limonin gave a nor-acid which was shown to have the grouping $-CO.O.CH_2.C-C=O$.

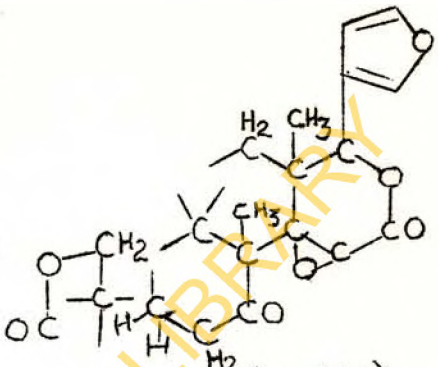
The combination of these facts led to a partial formula (XXIII). (XXIII) was expanded to (XXIV) or (XXV) by taking into account the bicarbocyclic nature of the system, its functional group and its biogenesis. The X-ray crystallography work showed that limonin could be (XXI) or (XXVI); thus limonin must be (XXI).



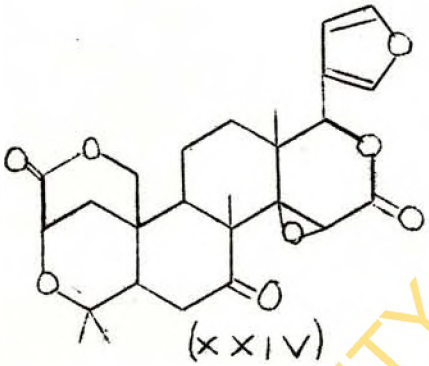
(XXI)



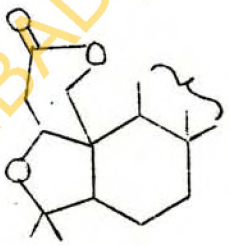
(XXII)



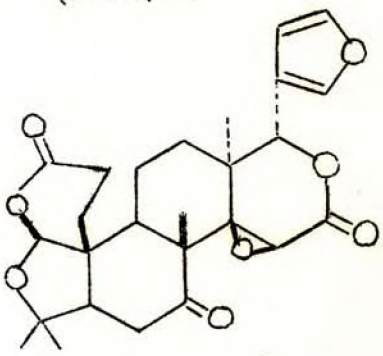
(XXIII)



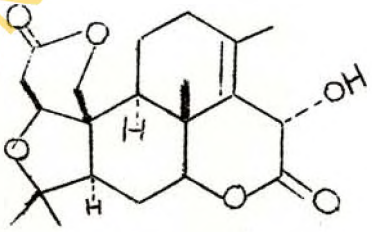
(XXIV)



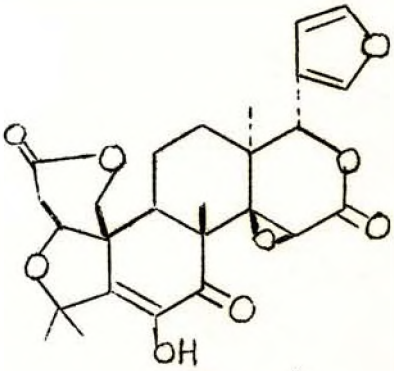
(XXV)



(XXVI)



(XXVII)

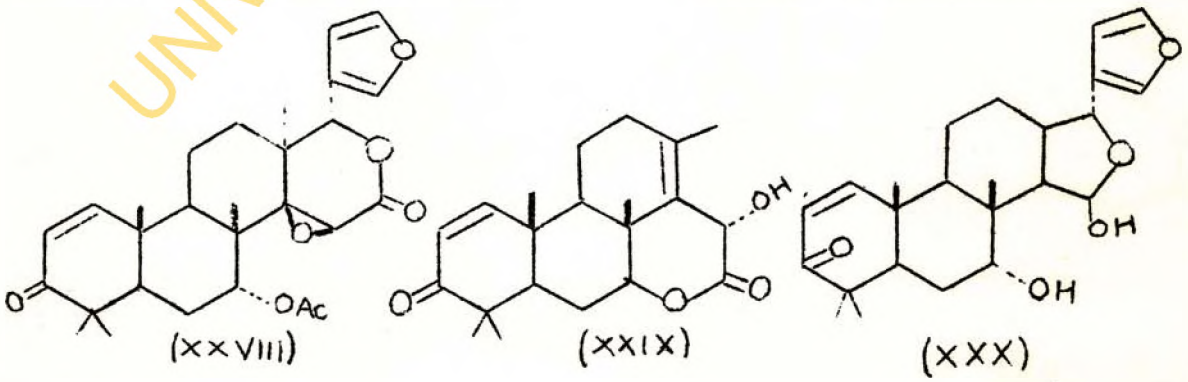


(XXIa)

Other ring A degraded compounds include obacunone,[28] obacunoic acid,[29] nomilin,[30] veprisone,[31] ichangin[32] and rutaevin.[33] All these with their ring A cleaved occur only in the family Rutaceae.

GEDUNIN[10]

The chemical work of Akisanya et al.[16,17,34] and the X-ray crystallographical investigation of Robertson[35] and his group on 1,2-dihydrogedunin have fixed the constitution and stereochemistry of gedunin as (XXVIII). The seven oxygen atoms in gedunin are accounted for in an αβ-unsaturated ketone, a β-substituted furan, an acetate group, a δ-lactone and an ethylene oxide ring alpha to the lactone. Gedunin undergoes the limonol → merolimonol change on hydrolysis to give merogedunin (XXIX), β-furfuraldehyde and in addition a hemiacetal (XXX) said to result from a glycidic acid type decarboxylation.[36] This again defines the relationship between the furan, αβ-epoxy-δ-lactone and the 7α-acetoxyl group in gedunin.



(XXVIII) (XXIX) (XXX)

Mild hydrogenation of gedunin gives 1,2-dihydrogedunin. Ozonolysis of dihydrogedunin followed by steam distillation gave an acid which was reduced to a hydroxy acid. Methylation with diazomethane of the hydroxyacid followed by dehydration with phosphorous pentachloride and ozonolysis gave acetone. This series of reactions shows that gedunin is a 4,4-dimethyl-Δ1-3oxo-compound.[73] The constitution of gedunin can be written when the above facts are combined with the tricarbocyclic nature of gedunin.

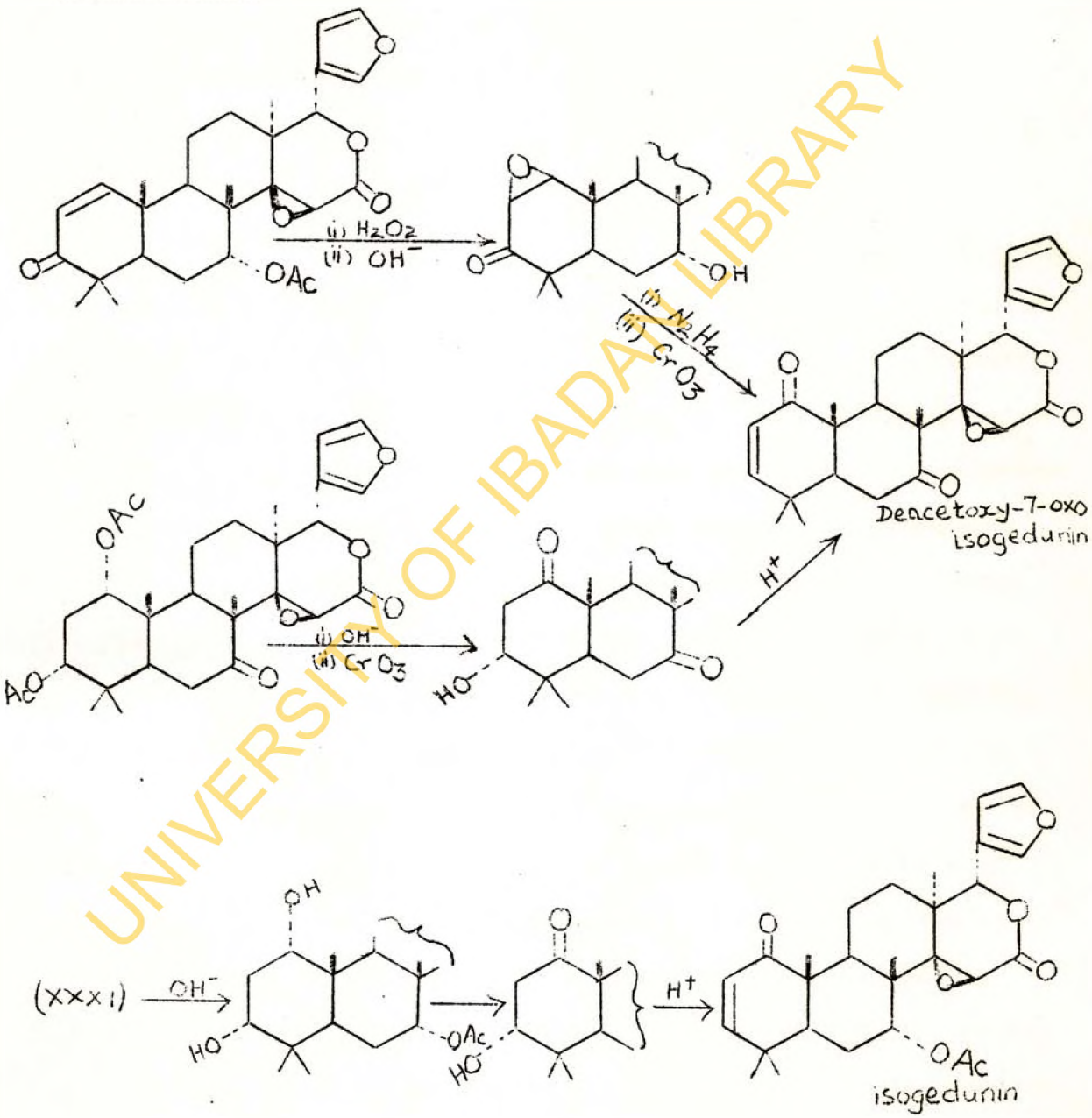
KHIVORIN

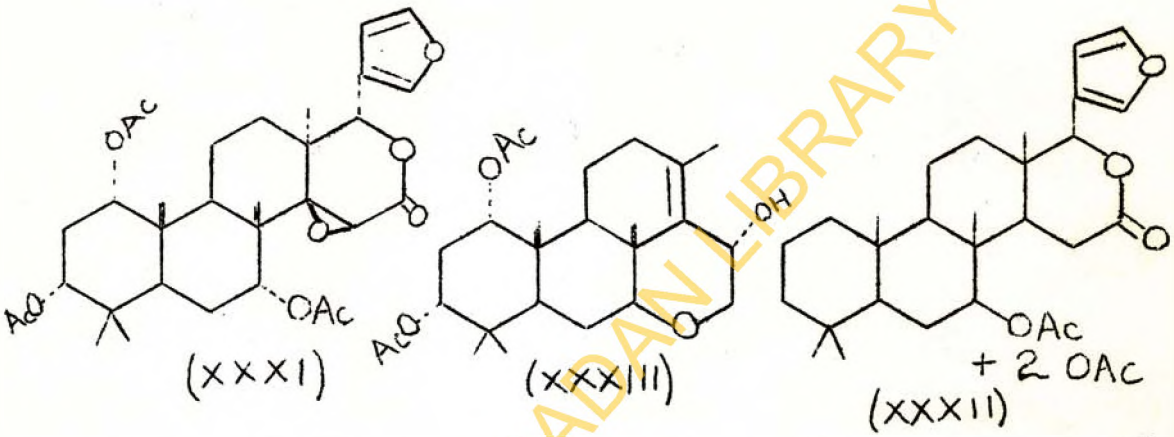
Khivorin (XXXI), $C_{32}H_{42}O_{10}$ is closely related to gedunin (XXVIII). The chemical structure was determined by Nwaji et al.[37,38] The presence of three acetoxyl groups, an αβ-epoxy-δ-lactone and a β-substituted furan, account for all the ten oxygen atoms in the molecule and this implies a tricarbocyclic skeleton for khivorin since there is no double bond in the molecule. Khivorin, like gedunin, undergoes the limonol → merolimonol reaction to give khivol (XXXIII) on hydrolysis. When these facts are taken together, a partial structure (XXXII) can be written for khivorin. Only the positions of the two acetoxyl groups remain to be fixed.

Failure of periodic acid to react with khivol was taken as

evidence that the acetoxyl groups could not be vicinal. That they are at C-1 and C-3 was shown by hydrolysing deoxykhivorin to trisdeacetyldeoxykhivorin. The chromic acid oxidation product of this gave an enolic triketone ($\lambda_{max.}$ 285 mμ; ε = 24,100) in ethanol containing a drop of 2N potassium hydroxide. The absorption was regarded as owing to a β-diketone system by comparison with dimedone[39] ($\lambda_{max.}$ 255 mμ, ε = 16,900 in ethanol but shifting to $\lambda_{max.}$ 282 mμ, ε = 27,700 with a drop of potassium hydroxide). Since a β-diketone cannot be accommodated in ring B or C, the two keto groups can only be at C-1 and C-3. The structural formulation of khivorin therefore follows, but the stereochemistry at C-1 and C-3 was undetermined. The observation by Dr. Melera of the Varian Associates Laboratory in Zurich on the n.m.r. spectrum of 7-deacetoxy-7-oxokhivorin that C-1 and C-3 protons did not show large coupling constants with the adjacent C-2 protons led him to conclude that the protons at C-1 and C-3 must be equatorial since one of the protons at C-2 must be axial. (Axial-axial interaction of vicinal protons usually have large coupling constant of the order of 10-13 c./sec.[69]). We have,[40] by looking at the n.m.r. spectrum of 3-deacetylkhivorin and 3-deacetyl-7-deacetoxy-7-oxo-khivorin, obtained further support for the equatorial orientations of the protons at C-1 and C-3. Khivorin is therefore the 1α, 3α, 7α-triacetoxy compound.

Scheme 2





Gedunin and khivorin have been interelated through isogedunin;[28] scheme 2 gives the essential steps. Here again we[40] have shown another sequence that interrelates khivorin and gedunin and this will be discussed below.

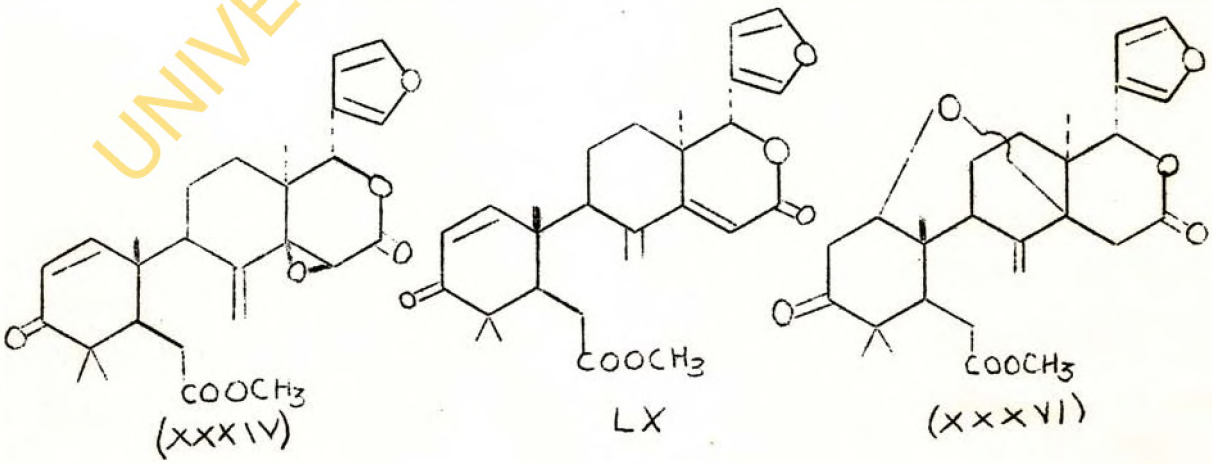
ANDIROBIN GROUP

This is a ring B-seco group consisting of andirobin (XXXIV), methyl angolensate (XXXVI), and a few others.

Andirobin[24] $C_{27}H_{32}O_7$ was isolated from the seeds of Carapa guayanensis Aubl. The structure was determined by Ollis, Ward and Zelnik as (XXXIV), largely as a result of the very informative spectroscopic properties (especially n.m.r.) of andirobin itself and

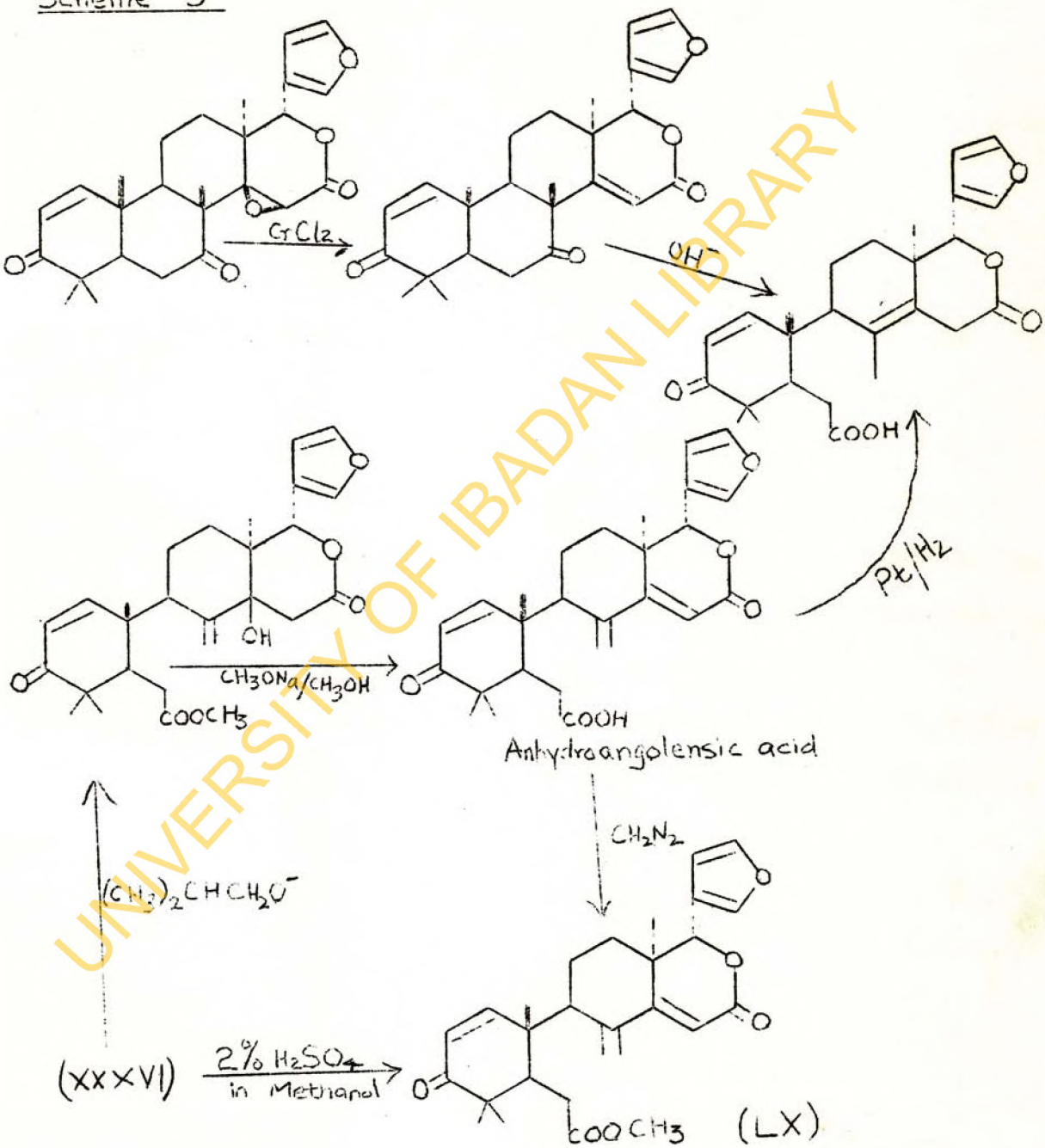
its derivatives. Phytochemical reasoning also played an important role in the process. The seven oxygen functions in andirobin are in a β-substituted furan, an αβ-epoxy-δ-lactone, a methoxycarbonyl group and an αβ-unsaturated ketone.

Sodium borohydride reduction of andirobin gives the tetrahydro derivative - andirobindiol, characterised as the diacetate. The two carbonyls reduced are shown by u.v. spectra to be in an αβ-unsaturated ketone and a δ-lactone. The n.m.r. spectra show a resemblance between the α,β-unsaturated systems of andirobin and gedunin; ring A in both compounds is regarded as being identical. Since chromous chloride reduction of andirobin gives deoxy-andirobin (LX), this enabled them to assert the presence of αβ-epoxy-δ-lactone. The stability of deoxyandirobin to acid and the additional spectral information from the αβ-γδ-unsaturated lactone enabled the constitution of andirobin and deoxyandirobin to be formulated unambiguously.



(XXXIV) LX (XXXVI)

Scheme 3



Methyl angolensate[23] (XXXVI) is closely related to andirobin. It has the same carbon skeleton as andirobin but has an ether bridge between C-1 and C-14 rather than 1,2-double bond and 14,15-epoxide.

Ekong and Olagbemi[41,42] have correlated gedunin with methyl angolensate and andirobin by cleaving ring B of 7-deacetyl-7-oxo-14, 15-deoxy gedunin with dilute alkali in a manner shown in scheme 3.

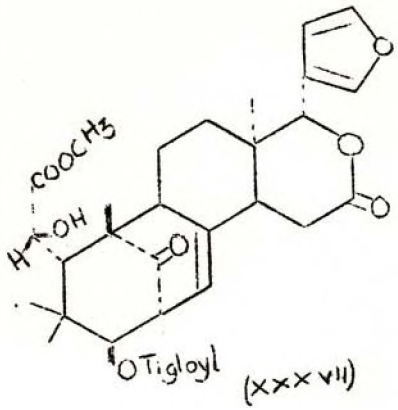
Bicyclononanolides

Swietenine $C_{34}H_{42}O_9$ is the first bicyclononanolide whose structure was determined. It occurs with swietenolide in the seeds of Swietenia macrophylla King, which grows in Central America. By a series of careful degradations and intensive use of n.m.r. data by Connolly et al.[18,20] and the X-ray investigation on the p-iodobenzoate of destigloyl-swietenine by McPhail and Sim,[74] the constitution and stereochemistry of swietenine was established as (XXXVII).

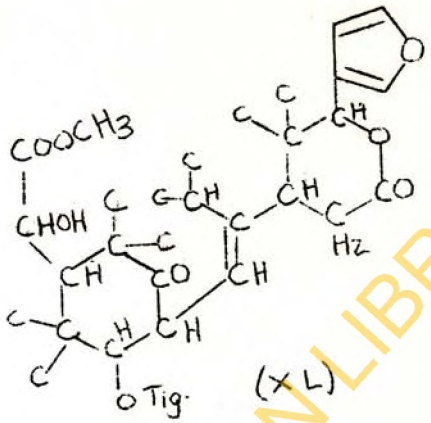
Swietenine was shown to have a β-substituted furan, a δ-lactone, a secondary tiglate ester, a $CH.OH.CO_2Me$ and a saturated ketone thus accounting for all the nine oxygen atoms in the molecule. The relationship between swietenine and limonin suggested itself when the spectra of the octahydro acid of swietenine and hexahydrolimoninic acid (both being catalytic hydrogenation products from the respective

parent compounds) were compared. A part structure (XXXVIII) was then written. A major reaction that led to the derivation of the constitution of swietenine is the alkaline hydrolysis on it to give a different series, the iso-series formed as a result of epimerization at C-3. Connolly et al. have explained the reaction in terms of retro-and re-aldolisation of the β-ketol system. They also interconverted the two series in the way shown in scheme 4. This supported the theory that inversion or epimerization is at C-3 and therefore a 1,3-relationship of the ketonic and tiglate ester functions.

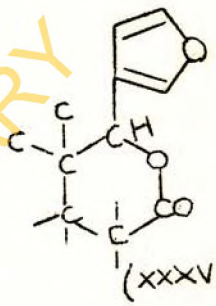
The α-hydroxy ester was related to the tiglate ester by oxidation of the α-hydroxy acid (XLI) with lead tetraacetate to give a nor-aldehyde (XLII). On chromic oxide oxidation,[90] a β-diketone (XLIII) was obtained, with the aldehydic function intact. When treated with base, the nor-aldehyde undergoes an intramolecular Cannizzaro reaction to give a γ-lactone (XLIV), the n.m.r. data of which made it possible to write a part structure (XXXIX). Nuclear magnetic double resonance studies at 100 M c./sec. gave additional information on the couplings in the system and a part structure (XL) was consequently written.



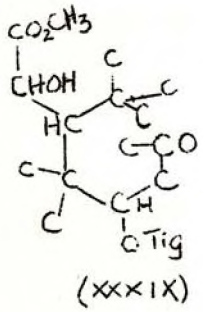
(XXXVII)



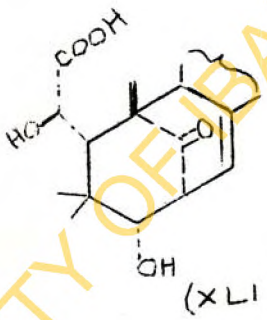
(XL)



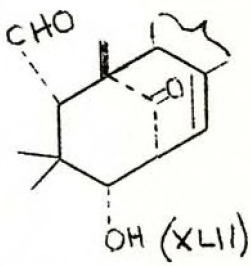
(XXXVIII)



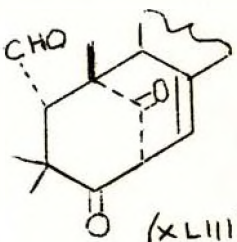
(XXXIX)



(XLI)

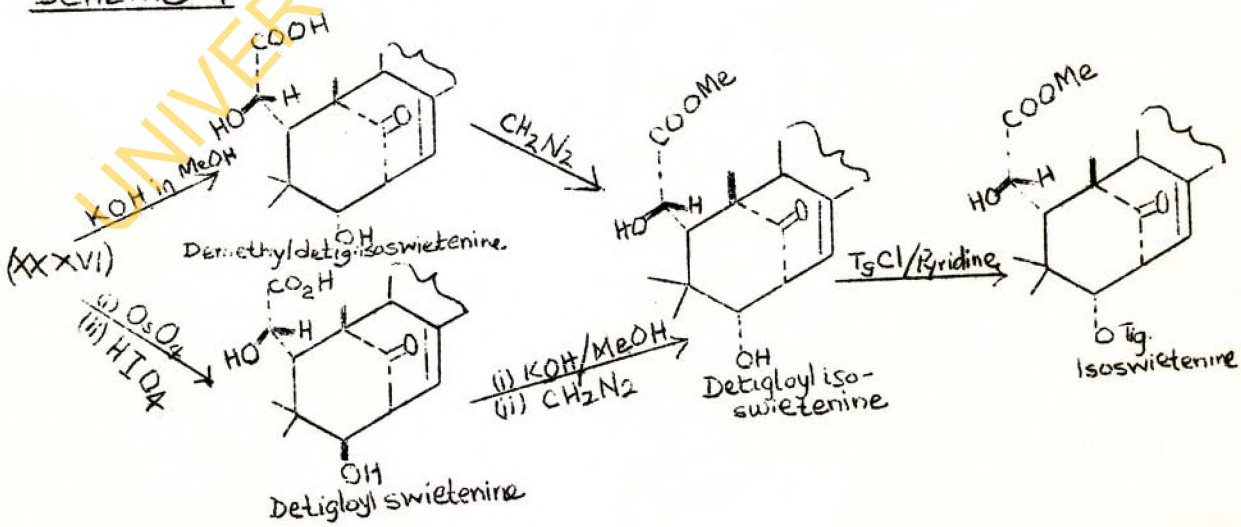


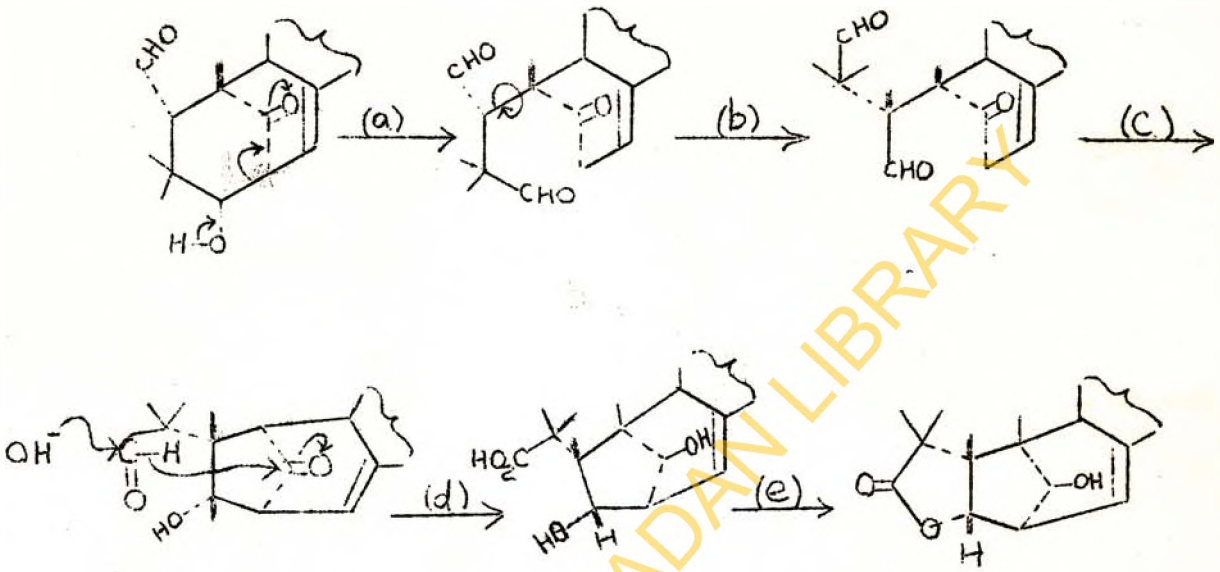
(XLII)



(XLIII)

Scheme 4





Scheme 5

The workers explained the formation of the γ-lactone in terms of (a) aldol reaction (b) inversion of configuration at C-5 (c) aldolisation (d) intra-molecular Cannizzaro reaction involving a hydride ion transfer and (e) lactonization of the γ-hydroxyacid obtained in (d). The sequence is illustrated in scheme 5. This evidence made it possible to account for the complete carbon skeleton.

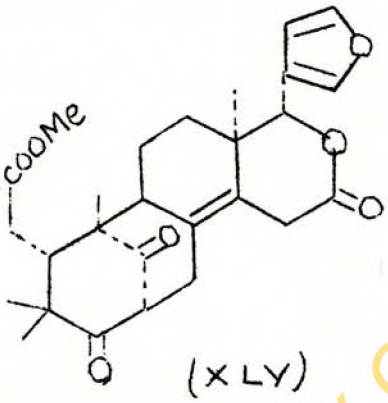
The double bond in swietenine is at 8,30 position. Many bicyclononanolides in which the double bonds are at the expected 8(14) or 14,15-positions have been found: the 8(14) double bond series include mexicanolide (XLV) and swietenolide[43,94] (XLVII) while the 14,15-series occur in the carapin[44] (XLVI) and its derivatives.

Carapin isomerises to mexicanolide on a column of alumina.[45]

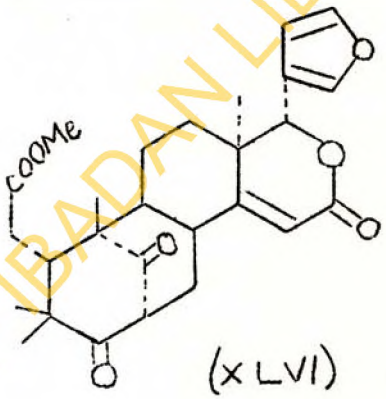
Bevan et al.,[22] and Connolly et al.[21,95] working independently on the structural determination of mexicanolide and the X-ray studies of Adeoye and Bekoe,[20,46] have fixed the constitution and stereochemistty as (XLV).

The most informative reaction of mexicanolide and carapin is its great sensitivity to base, when a complete transformation takes place in the molecule involving a ring opening to give an enolizable β-diketone (XLVa) as shown by spectroscopic studies. We[47] explained that the reaction proceeds by a concerted mechanism subject to frangomeric acceleration.[48] It is interesting that the 3β-acetate but not the 3β-ol (from sodium borohydride reduction of mexicanolide) will undergo the transformation. It is probably because OAc^- is a better leaving group than OH^-. Another way of expressing this is to attribute this difference to the polarisation of the carbonyl function which can under the reaction condition lead to the cleavage of the C_3-O bond leaving C_2-C_3 unsaturated and therefore resulting in its conjugation with the C-1 carbonyl. The effect will be to allow a delocalization of the π-electrons from C_{15}-C_3 in much the same way as in the β-diketone system. In the 3β-ol where there is little possibility of breaking the C_3-O bond, the reaction does not take plac

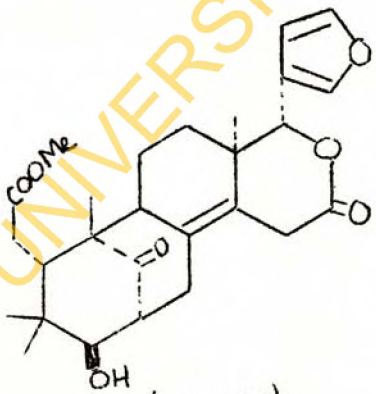
Another interesting reaction of mexicanolide but not of carapin - where the position of the double bond makes its δ-lactone rigid - is that it undergoes a ring D opening with methanolic sulphuric acid to give C.O.C. (LII) which in turn recyclises to mexicanolide on treatment with hydrochloric acid.



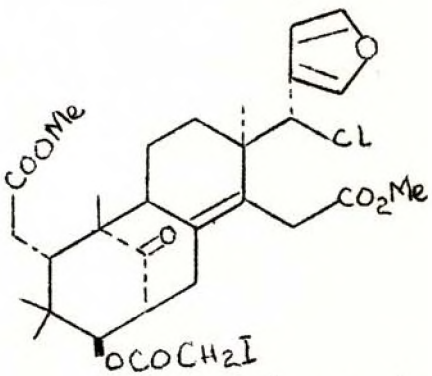
(XLV)



(XLVI)

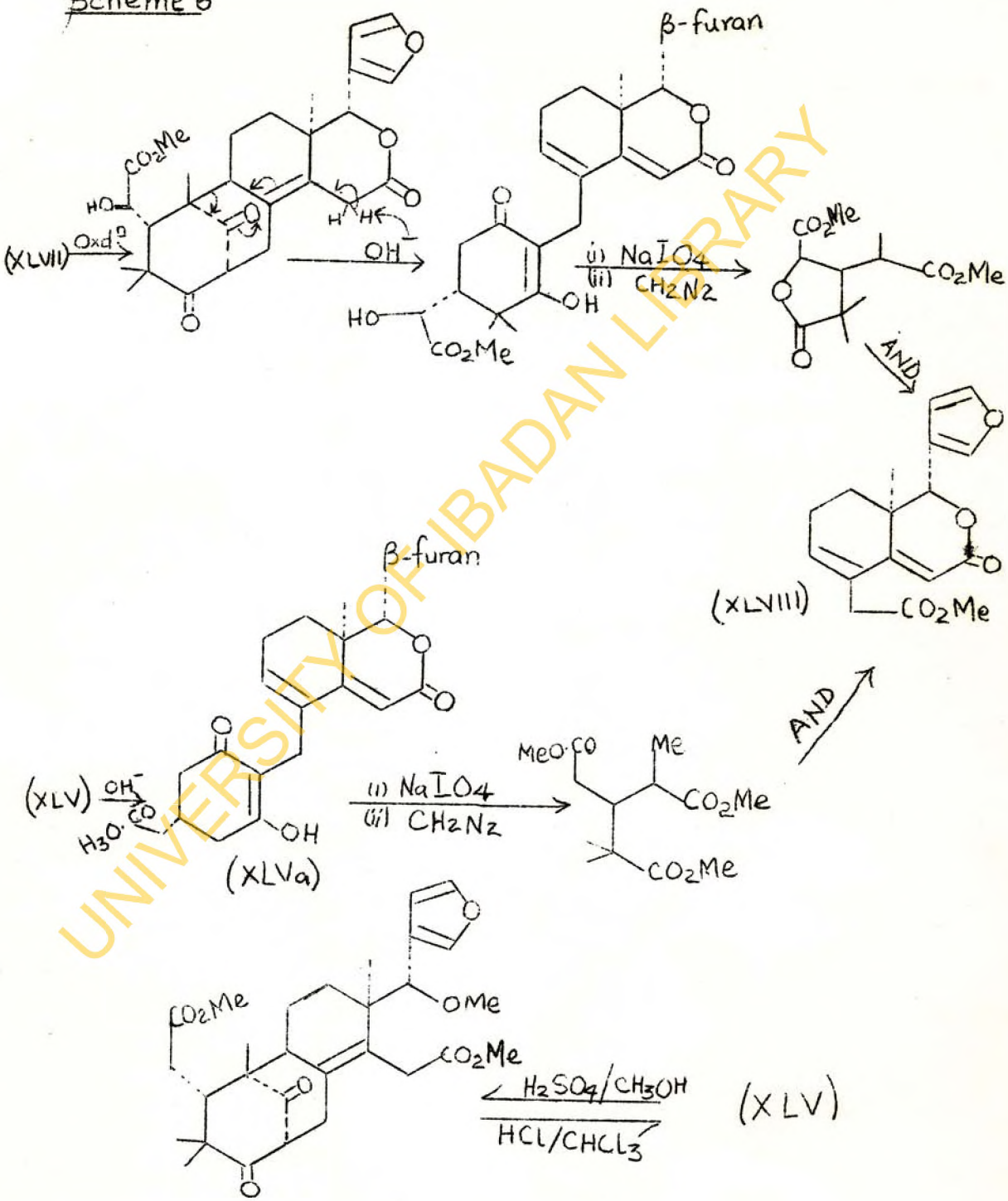


(XLVII)



(XLIX)

Scheme 6



Carapin and mexicanolide have been interrelated[42] to swietenolide by periodate oxidation of their base-catalysed transformation products. In each case a fragment (XLVIII) was obtained. This is illustrated in scheme 6.

ABNORMAL REACTIONS AND STEREOCHEMICAL CONFORMATIONS

Euphol or tirucallol, the assumed biogenetic precursors of these furanoid triterpenes, are by the very nature of their cyclizations from squalene of the form; rings A-chair, B-chair, C-chair and D-boat. However, many limonoids have ring conformations different from this and the difference would be reflected to some extent in the course and rate of the reactions in which they participate in view of the interactions of various functional groups in the different conformations. Interactions between functional groups do not only affect the course of a chemical reactions, but they sometimes lead to abnormal reactions. Some departures from normal behaviour are seen in;

(a) reduction of gedunin and anthothecol[49] to give the 1:2-dihydro products in either case and a further reduction of the 3-one to the 3-ol in gedunin

(b) failure of the 3-keto group in dihydrocedrelone[50] to undergo oxidation.

Hodges et al.[50] tried to explain the behaviour of dihydrocedrelone and cedrelone by suggesting that in order to prevent severe interaction of 4α-methyl and the 6-substituent, ring A must exist in the boat form. In this conformation the 3-keto group is shielded from attack on the β-face by the 10-methyl and on the α-face by the pseudo axial 4α and cannot therefore be very reactive. From this and deductions such as that of Narayanan and Pachapurkar in their work on nimbinic acid,[51] abnormal chemical reactions of this nature can be rationalised as the attempt of terpenoids to exist in a conformation which will minimize 1:3 nonbonded interactions.

PHYSIOLOGICAL ACTIVITY

Little work has been done to test many of the known limonoids for physiological or pharmacological activity. Many of these plants especially Khaya senegalensis are widely used in native medicine to treat diseases,[52,53] particularly in West Africa. Whether or not the curative powers attributed to these trees are intrinsic in the triterpenes is still to be determined. But even if it is, an obvious difficulty in these triterpenes finding their way to the clinical

stage lies in the insolubility in water of many of them. This property probably accounts for the rather slow interest shown by the pharmacologists to test them! It is true of course that drugs can be administered in emulsions and similar media but this is generally done when there is no available alternative of comparable activity which is water soluble. Some limonoid principles are bitter, mexicanolide for example is very bitter, while others are tasteless. If and when thorough pharmacological tests are carried out on these principles, it may be possible to give a broad correlation of taste with structure or even with activity in a particular series.

USES

(i) At present very little is known about the role of these secondary metabolites. In some cases they are found in large amounts as if to suggest they may be metabolic byproducts which are of no direct use to the plant whereas in some cases some of them do break down to other molecules e.g. lanosterol to cholesterol.[54]

(ii) CHEMOTAXONOMY

Correlation of classification with chemical constituents of particular Meliaceae species can be made only with great caution. It has been said[55] that general statements of taxonomic significance can be made only if a systematic and thorough survey has been made as opposed to chance isolation of a few substances in a few plants. Because the chemistry of the meliaceae is still in its infancy, a generalization that can be of taxonomic importance cannot be made at present and will have to await further study. Our studies on three Khaya species have shown us clearly that plants of the same species are often chemically variable. Indeed we have been led by our findings to conclude that chemical variation is not due to macroclimatic conditions alone. In addition, even under microclimatic conditions, it has been observed that two trees of the same species within a few yards from each other can vary chemically. However, this need not imply that a useful correlation will be impossible, for what is regarded as being absent may well be present - either in a small scale or not extracted in the usual way. Although successful isolation of chemical compounds depends largely on skill and method, there is nevertheless an element of chance involved. Since failure to detect a small concentration of a particular

compound present may obviously lead to a wrong conclusion, far reaching deductions that will be of taxonomic importance in this field may have to wait till better techniques are known which will lead to maximum identification of a mixture. It is encouraging to know that extensive studies of the cucurbitacins[56] (family Cucurbitaceae) have very usefully complemented some other methods of taxonomy. The distribution and structural relationship of the limonoids of the Rutaceae[62] have also enabled chemotaxonomic classification to be made.

The genus Khaya is the subject of this Thesis. There are six distinct Khaya species known to date and we have examined various parts of three of them (Khaya senegalensis,[40,47,57,58,75] Khaya ivorensis,[37] Khaya grandifoliola[59,60]), and only the seeds of two others (Khaya anthotheca[61] and Khaya nyasica).

The investigations carried out, the results obtained, and the deductions made, will be described for each of the five species in turn.

INVESTIGATION AND DEDUCTIONS

KHAYA SENEGALENSIS

Khaya senegalensis (Desr) A. Juss grows in the savannah regions. It is capable of attaining a height of over 100 ft. and a girth of nine feet. It is glabrous with grey scaly bark. The leaves are pinnate and the woody fruit encloses flat winged seed. The fruit which is four-carpelled seems capable of a subdivision into the thin-walled and the thick-walled carpels. The locus of the tree is the belt extending from Senegal to East Sudan and Uganda.

K. senegalensis has great reputation especially in West Africa as a potent drug to combat several diseases. The bark is the most commonly used. Several authors have described the various local uses of the tree and these can be summarised as follows:

Bark: Used as febrifuge, emmenagogue, vermifuge, emetic, anti-malarial, also for syphilis, ulcer and in local veterinary practice.

Flower: Used to treat stomach disorders and venereal diseases.

Seed: The crushed seed is used as an emmenagogue and the oil for anointing the body. Some early work on K. senegalensis has been reported but on the whole its chemistry has not been satisfactorily treated. Oliver[52] recorded that K. senegalensis contains mineral

substances, oxalate, sterols, sucrose, starch, catechuic tannins, a saponin, lipids, and a small amount of bitter principles, which he and some earlier authors presumed might be the alkaloid cailcedrine. Some of the substances mentioned are probably present as fragments of larger molecules e.g. sucrose and sterol from a glycoside. Dalziel[64] reported that the bark from Northern Nigeria was shown at the Imperial Institute (London) to contain no alkaloids, glucosides, or any resinous or crystalline neutral bodies. Ferreol[65] reported the isolation of nimbosterol, identical with β-sitosterol. Modern spectroscopic and analytical methods on which most of the work reported in this thesis depends have helped to clarify a lot of the rather confused picture in the literature. A lot of work in this direction will still be necessary before a full picture can emerge.

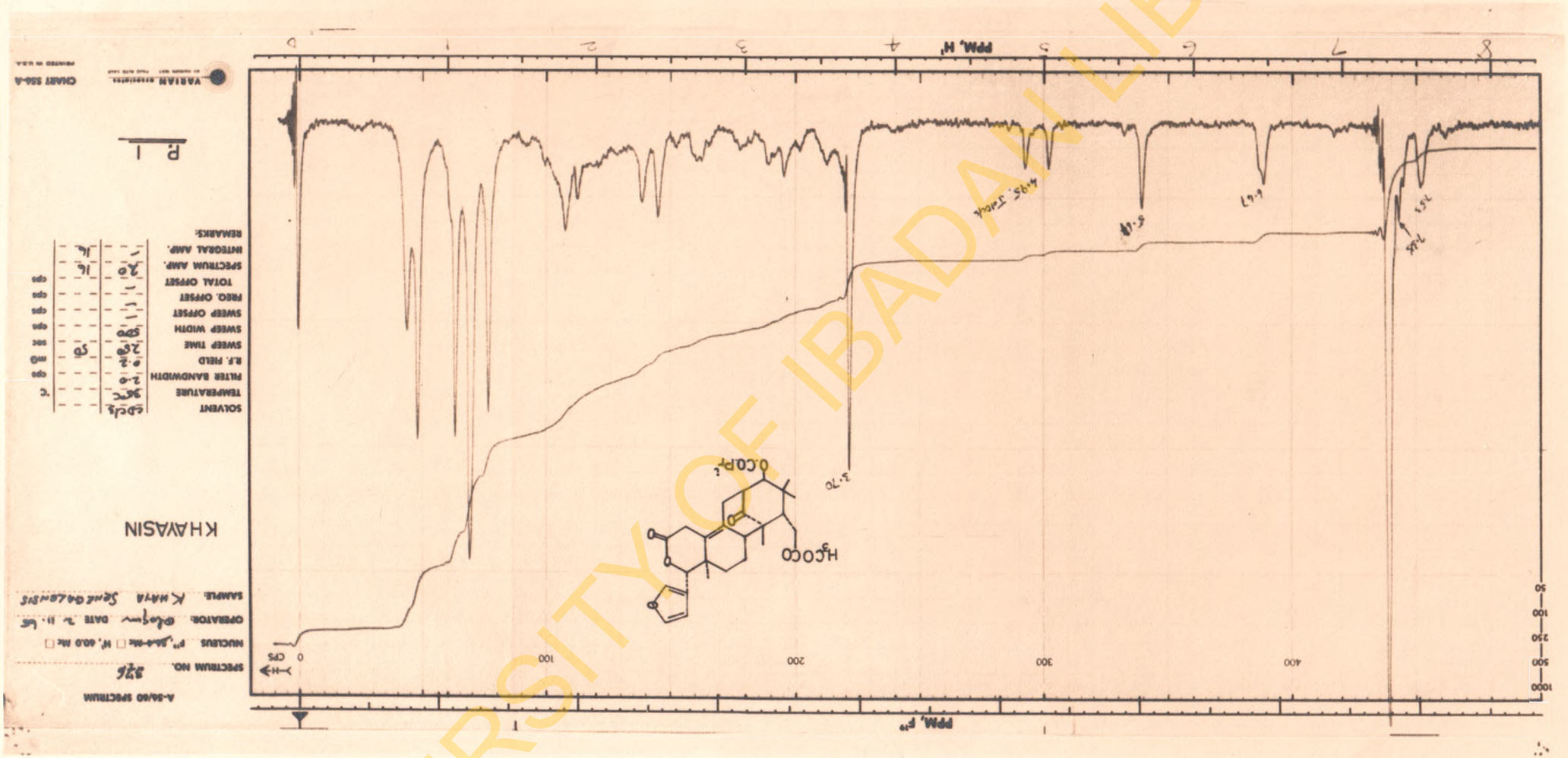
We have studied the extractives of various parts of trees of this species and have collected samples from different places.

TIMBER

Extraction of the timber of K. senegalensis with light petroleum gave a gum. From the chromatography of this gum, Bevan et al.[93] have obtained two crystalline compounds (i) 7-deacetoxy-7-oxokhivorin, and (ii) a compound melting at 88-100° $[\alpha]_D^{21}$ - 139°

($CHCl_3$). The chromatography on an old stock of extract obtained from the same tree was repeated. The gum was dissolved in benzene and adsorbed on alumina. Elution with benzene-ethyl acetate (4:1) brought down a mixture found later to be about 85% khayasin (= 6-deoxyswietenolide isobutyrate) (L). The mixture m.p. 114-116°, $[\alpha]_D^{25}$ - 165° was originally described as the low melting compound from K. seneganensis.[57] Elution with methanol gave 7-deacetyl-7-oxokhivorin m.p. 225° identical in every respect with an authentic sample.

The first indication that the khayasin-containing mixture was impure was given by the marked difference in its melting point when it was crystallised from different solvents. It had a melting point 114-116° when crystallised from benzene and 87-90° from methylated spirit. The fact that it crystallised in either case with the solvent of crystallisation, as shown by the i.r. and n.m.r. spectra, was not a satisfactory explanation for the difference. Molecular weight determination of a sample by the mass spectrometer confirmed the presence of impurities as there were still some peaks beyond 540, the molecular ion. The n.m.r. spectrum of the volatile acid showed the presence of what we originally thought was an acetate but which we now know to be a tiglate. This and another contaminant will be discussed.



The molecular weight 540 taken with the best fit from elemental analysis suggests a formula $C_{31}H_{40}O_8$ for khayasin. The compound has infra-red absorptions at 1733, 1721 (ester and or lactone); 1701 (saturated ketone); 1250 (ester); and 1499, 876 cm.$^{-1}$ (β substituted furan). The n.m.r. spectrum shows peaks attributable to a β-substituted furan (δ 7.38, 7.53 - 2α-protons and 6.47 β-proton); H-17 (δ 5.67), a three-proton singlet of the -CO.OMe (δ 3.70), a doublet at the base of a β-ester (δ 4.95, J = 9.5 c./sec.) recognised by comparison with the iodoacetate of C.O.C. reduction product (XLIX),[47] and four tertiary methyl groups.

Six of the eight oxygen atoms are accounted for in a β-substituted furan, an ester, a saturated ketone and a methoxycarbonyl group. The other two must be either in another ester or in a lactone (evidence from i.r. spectrum). The fairly characteristic fragmentation pattern at 96 and 124 in the mass spectrum (see p.103) suggest a δ-lactone allylically placed to the furan. Furthermore alkaline hydrolysis and methanolic sulphuric acid treatment of khayasin that find an exact parallel in mexicanolide confirm the presence of a ring D δ-lactone. All the eight oxygen atoms are therefore accounted for.

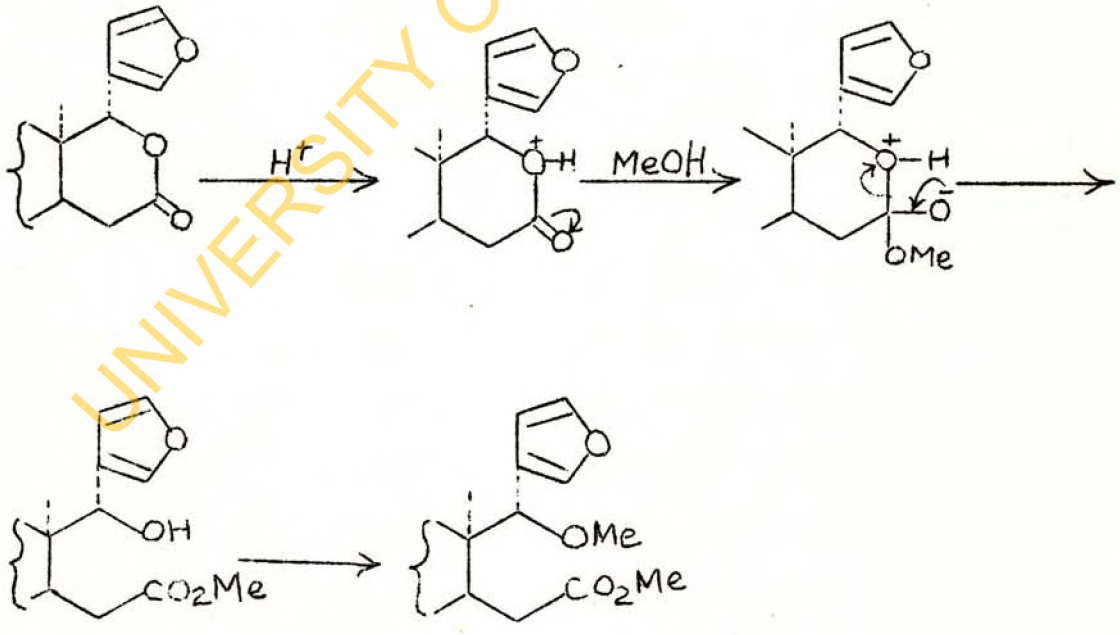
Alkaline hydrolysis of khayasin gave a volatile acid and a gum. The gum (Lb) did not crystallise but its ultraviolet spectrum showed

bands attributable to a furan ($\lambda_{max.}$ 214 mμ), and αβ-unsaturated ketone (230 mμ sh.) and an αβ-γδ-unsaturated lactone (276 mμ) a behaviour reminiscent of similar treatment of mexicanolide and the acetate of its reduction product.[14,15] The reaction has been suggested[22,47] to proceed by a concerted mechanism, subject to frangomeric acceleration,[48] (see in scheme 6). The volatile acid fraction was neutralised with sodium hydroxide and evaporated to dryness. The n.m.r. spectrum of the resulting sodium salts in deuterium oxide showed a six proton doublet (J = 7 c./sec.) at δ 1.1 and a one proton septet at δ 2.4. These peaks were those of sodium isobutyrate. There was also a peak at δ 1.8 from a tiglate. The p-phenylphenacyl derivative of the sodium salt was almost identical with an authentic sodium p-phenylphenacyl isobutyrate. This was taken as evidence for the presence of an isobutyrate, after making an allowance for the tiglate contaminant.

Another reaction that has a parallel in mexicanolide is the treatment of khayasin with 1% methanolic sulphuric acid to give khayasin C (LIVa) in which the ring D-δ-lactone is opened. It was this reaction that really paved the way for the elucidation of the structure of this compound since khayasin C crystallised out from the reaction products. The n.m.r. spectrum of the substance showed

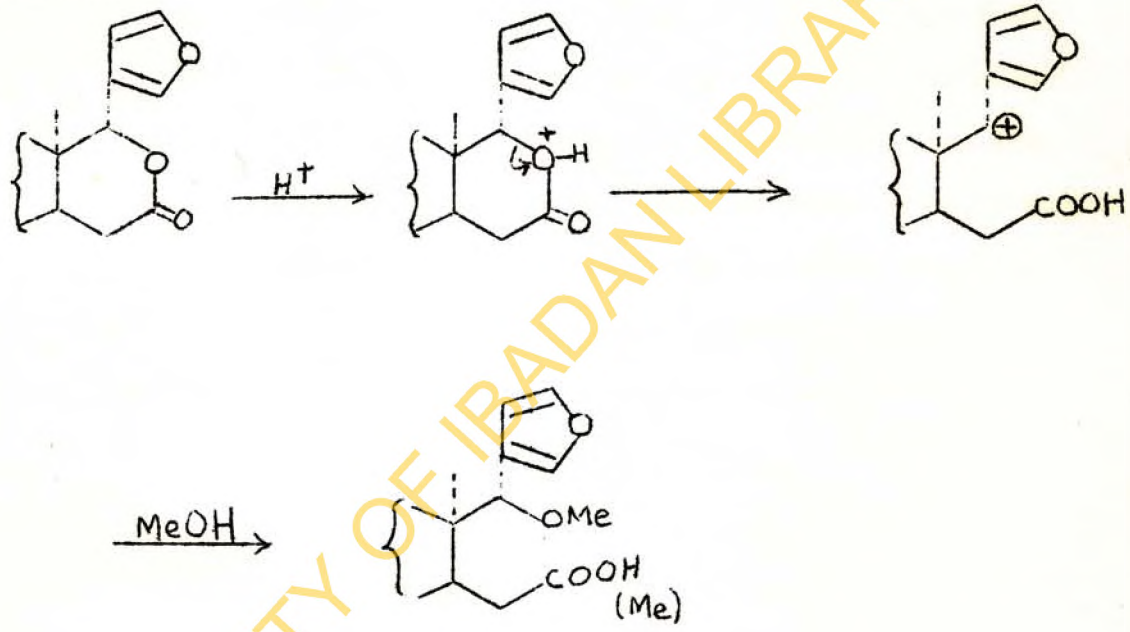
a new methoxyl (δ 3.2) and a second methoxycarbonyl (δ 3.6) groups at C-17 and C-16 respectively. The H-17 was observed to have undergone a diamagnetic shift from δ 5.67 to 4.67. The difference is in agreement with the chemical shifts of a proton from the base of an ester to an ether (>CH.OR is usually about 3.6 while >CH.OAc is about 5.1 p.p.m.). The lactone opening is acid induced and can go either of two ways. Protonation of the C-17 oxygen atom with a subsequent attack of a methanol molecule on C-16 leads to cleavage of the lactone. The C-17 is subsequently methylated under the reaction condition. Scheme 7 shows the essential steps.

Scheme 7

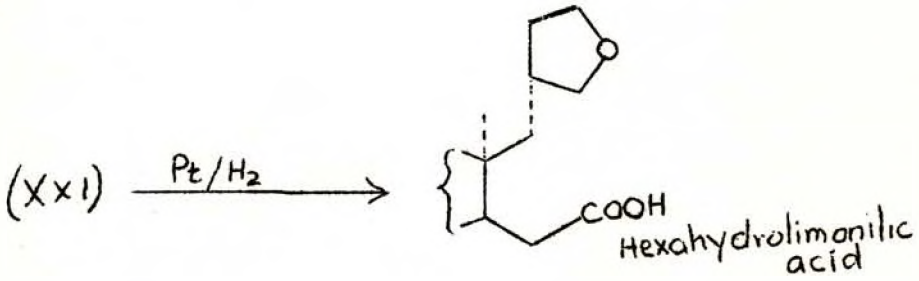


Alternatively, after protonation of the C-17 oxygen, fission can take place in a different way as shown in scheme 8.

Scheme 8



The latter scheme is favoured on the ground that hydrogenation of limonin gives hexahydrolimonilic acid, and this must have involved a C-17 oxygen fission.

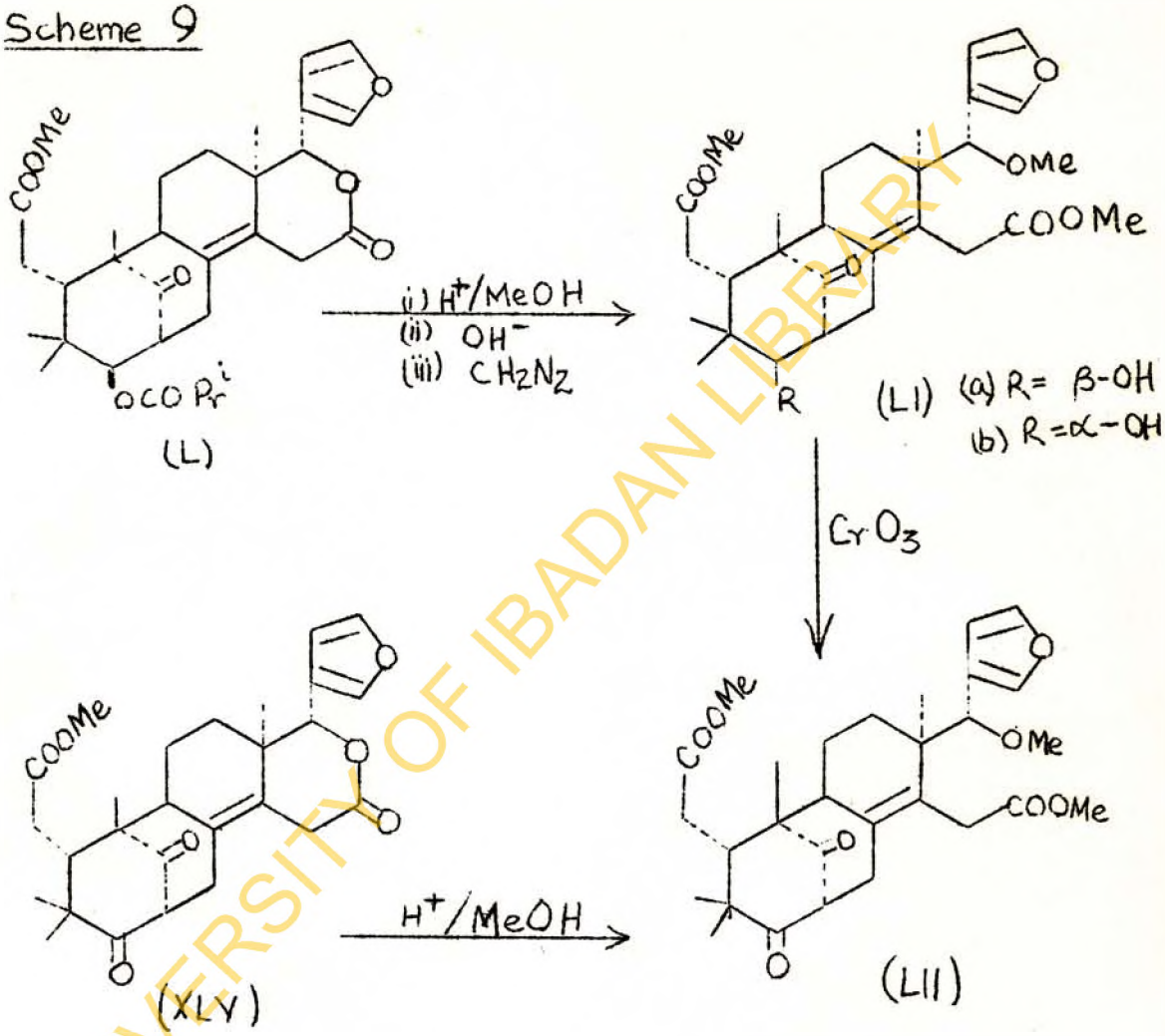


In addition, methylation of the acid in scheme 8 will take place much more readily than methylation of the C-17 alcohol in scheme (7). Lactonization normally takes place in the presence of an acid but it would appear it is prevented in this case because the $-CH_2CO.OMe$ formed is capable of free rotation about the C-14, C-15 bond. The free rotation is enhanced by the rigid stereochemistry of rings A, B and C forming as it were a hinge for the $-CH_2CO.OMe$. The effect is thus to make the ends of the two groups that might have cyclised come as far apart as possible, thus preventing recyclisation.

The molar rotation change for khayasin and the ring opened compound, $\Delta M = +663$ when compared with a similar change of mexicanolide and its substance C, $\Delta M = +686$ provide another striking illustration of the similarity between their nuclei.

Mexicanolide and khayasin were interelated via their ring D-opened compound (scheme 9). Methylation of the hydrolysis product of the latter followed by oxidation gave C.O.C. (LII) shown by i.r., t.l.c. and mixed m.p. to be identical with an authentic sample.

Scheme 9



The reaction cannot be carried out on the ring D-closed compounds because of the rearrangement such a system undergoes with alkali.

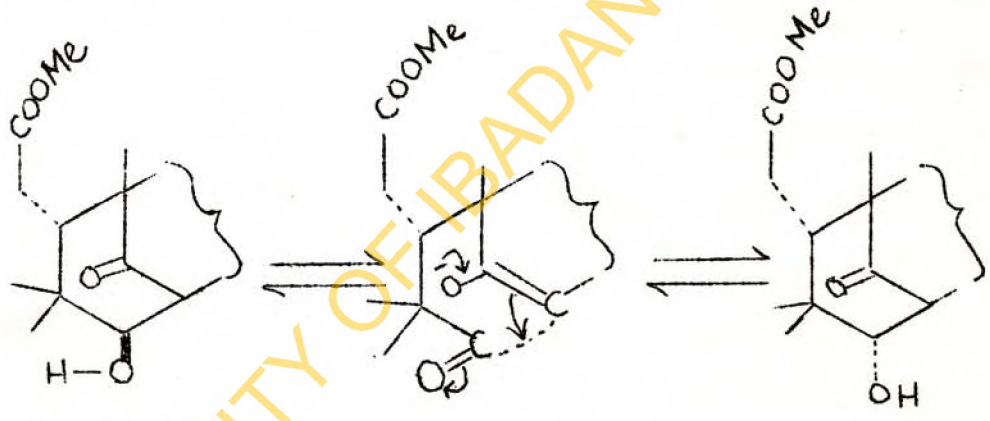
Careful examination of the n.m.r. spectra of khayasin and 17-chloro-3-iodoacetoxy-3-deoxy-derivative of C.O.C. (XLIX) prepared

by Dr. J. W. Powell show very striking resemblance and therefore suggest similar chemical environment. It is known from the X-ray work of Adeoye and Bekoe[46] that the iodoacetate group of (XLIX) has the β-configuration at C-3. In view of the fact that the H-3 peak in the isobutyrate (L) occurs at about the same place (δ 4.95) and with the same coupling constant (J = 10 c./sec.) as the iodoacetate (δ 4.91, J = 10 c./sec.) the β-configuration is proposed for the isobutyrate. An α-configuration would have a much smaller coupling constant since the resulting splitting between the C-3 equatorial hydrogen will have a coupling constant of the order 1-7 c./sec. with a neighbouring axial or equatorial hydrogen.[69] The β-configuration was confirmed by partial synthesis. Isobutyrylation of the 3β-alcohol (LIa) gave khayasin C (LIVa). Under the same conditions the 3α-alcohol (LIb) was not isobutyrylated. The constitution and absolute stereochemistry of khayasin must be (L).

The isobutyrate behaved in an anomalous manner on alkaline hydrolysis in giving not the expected β-alcohol (LIa) but the stereoisomer (LIb), which was also obtained in small yield together with (LIa) by the borohydride reduction of C.O.C. The iodoacetate under the same condition gave the 3β-alcohol as the major product and a small amount of the 3α-alcohol. Overton and his

collaborators[18] have reported a parallel reaction in the closely related swietenine (XXXVII). Alkaline hydrolysis gives epimerization at C-3 which they explained in terms of dealdolisation and realdolisation according to scheme 10.

Scheme 10

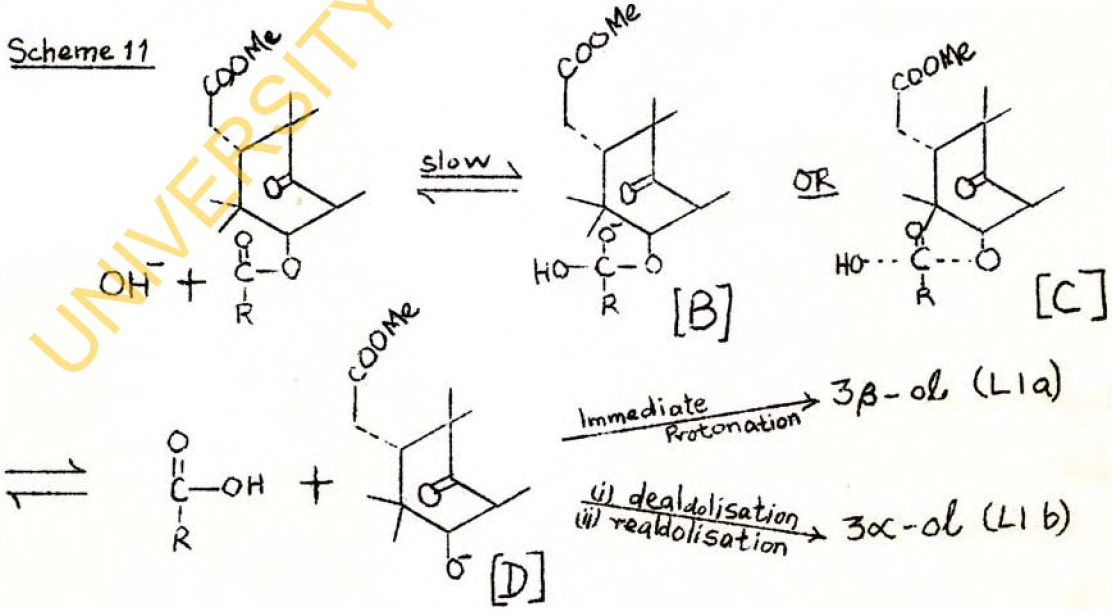


This would account for the observation of the epimerization with the isobutyrate but not the iodoacetate. Light was thrown on the problem by treatment of the 3β-ol (LIa) with alkali under the same condition as used for the isobutyrate and the iodoacetate. The

methylated product was shown by t.l.c., n.m.r. and i.r. spectra to be an equilibrium mixture of the two isomers in which the 3α-isomer predominates. These observations must mean that the mechanism of the reaction in the early stages is essentially the same in the iodoacetate and as it is in the isobutyrate. The course of the reaction is explained as follows.

In both esters alkaline hydrolysis involve acyl oxygen fission, a feature of carboxylic esters and hydroxide ion in aqueous solution.[66] The reaction is second order and on theoretical grounds, and by analogy with other esters, it must be bimolecular of the form $B_{AC}2$. The reaction can therefore be represented as shown in scheme 11.

Scheme 11



Because the intermediate complex, a mesomer between [B] and [C] is negatively charged it will be expected that electronegative substituents (-I effect) like iodine will accelerate its formation and electropositive substituents like the isopropyl will retard its formation. Steric bulk would also probably affect the rate of the formation of the complex. Courtauld atomic models show that the intermediate complex would be more difficult to form with the isobutyrate than the iodoacetate because the former's flanking methyls constitute a steric hindrance to the oncoming hydroxyl group. Both factors indicate that the formation of the intermediate complex which is the slow step will take place more readily with the iodoacetate than with the isobutyrate. Since the slow step of a reaction must largely determine the rate of reaction, one can conclude that the rate of hydrolysis of the iodoacetate will be greater than that of the isobutyrate.

Since both esters pass through [D], which could not have involved inversion of configuration, epimerization must therefore occur after stage [D]. This suggests competition reactions involving (a) direct protonation of [D] to give the 3β-ol, and (b) retro-and re-aldol reactions to give the 3α-ol. The reason for the difference in products would therefore seem to be that in

the iodoacetate the rate of formation of [D] is much faster than the rate of de-and re-aldolisation leaving most of it to undergo direct protonation to give the 3β-ol while only a few ions give the epimer. With the isobutyrate the rate of formation of [D] must be about the same as or even slower than the rate of dealdolisation and consequently the isobutyrate has greater chance of undergoing epimerisation. Clearly this must be an equilibrium reaction subject to kinetic control in which no single isomer is exclusively formed at the expense of the other. This has been observed experimentally. It can further be added that it would be expected that if the iodoacetate was hydrolysed long enough one would obtain the 3α-ol since the 3β-ol when formed would, in the presence of more alkali and with more time, undergo hydrogen abstraction and epimerize. The 3α compound is therefore the more stable epimer to alkali.

Khayasin C (LIVa) reacts with concentrated hydrochloric acid or hydrogen chloride gas to give the 17-chloro compound by replacement of the 17-methoxyl group. This is indicated by the loss of the ether methoxyl band in the n.m.r. spectrum and by the downshift of the H-17 absorption to 5.69 p.p.m. as in iodoacetate with a chlorine atom at C-17. Elemental analysis also shows the

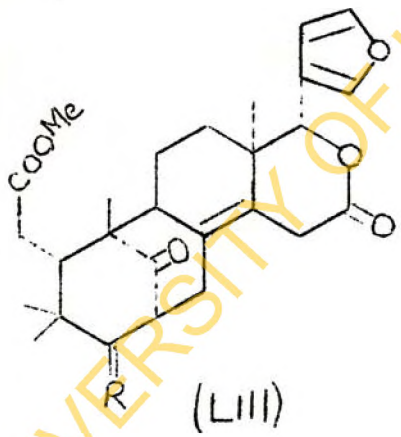
presence of an atom of chlorine per molecule of compound. Treatment of the isobutyrate with lithium aluminium hydride led to a break down of the molecule, presumably because of the several possible places of attack (C_1, C_3, δ-lactone etc.).

Second Extract

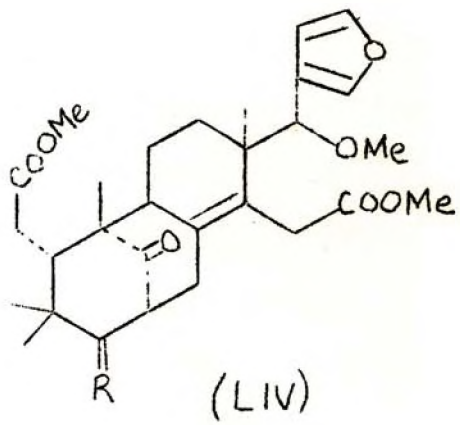
Extractives from the timber of K. senegalensis growing in a restricted area about 20 miles south of Ilorin gave a wide range of interesting products in which all the three main nuclei are present i.e. (i) rings A, B and C carbohexacyclic (ii) ring B seco, A and C carbohexacyclic and (iii) rings A, B, C carbohexacyclic with rings A and B 1:3 fused. The isolation of representatives of all three nuclei from the same tree provides powerful support for the biogenesis of these limonoids as outlined above (p. 3).

Light petroleum extraction gave an oily extract from which a large amount of solid separated. The solid fraction on crystallisation gave mainly methyl angolensate, plus a small amount of methyl 6-hydroxyangolensate. The mother liquor on chromatography gave a small amount of a new compound which we name methyl senegalensate, more methyl angolensate, and a mixture of methyl angolensate and methyl 6-acetoxyangolensate which could not be separated.

Chromatography of the oily residue of the extract gave a very nicely crystalline compound m.p. ca. 100° found later to be a mixture of the isobutyrate and two new compounds, the benzoate and the tiglate of 6-deoxyswietenolide. Other fractions from the chromatography gave mexicanolide, 7-deacetyl-7-oxogedunin, and a new compound we deduced to be 12β-acetoxy-6-deoxydestigloylswietenine acetate (LVIIc).



(LIII)



(LIV)

(a) R = αH, β - O.CO.CH.$(CH_3)_2$.

(b) R = αH, β - O.CO.Ph.

(c) R = αH, β - O.CO.C(=CH_3):CH_3.

Methyl angolensate, 7-deacetyl-7-oxogedunin (LV) and mexicanolide were readily identified from their spectral properties and by comparing some of their physical properties with those of the authentic samples. The evidence that led to the structure of methyl 6-hydroxyangolensate will be discussed later.

The isobutyrate, the tiglate and the benzoate derivatives of 6-deoxyswietenolide always came together as fine crystals. The mixture could have passed for a single compound from its t.l.c. in most solvents; however its m.p., mass spectra and n.m.r. spectra showed it was a mixture. All attempts to separate the mixture on alumina and silica gel MN were abortive and recourse had to be taken eventually in their varied stability to methanolic sulphuric acid. Chromatography of the product obtained by the methanolic sulphuric acid treatment gave two ring-opened compounds, the isobutyrate, and the benzoate C, while two later fractions gave two ring D-intact compounds, the tiglate and the benzoate. These were initially designated as compounds X, Y, M and N respectively. The products indicate that the order of sensitivity to methanolic sulphuric acid is $(CH_3)_2.CH.CO.O > Ph.CO.O > CH_3.CH:CH_3.CO.O$, in fact the tiglate appears not to undergo solvolysis under the reaction conditions.

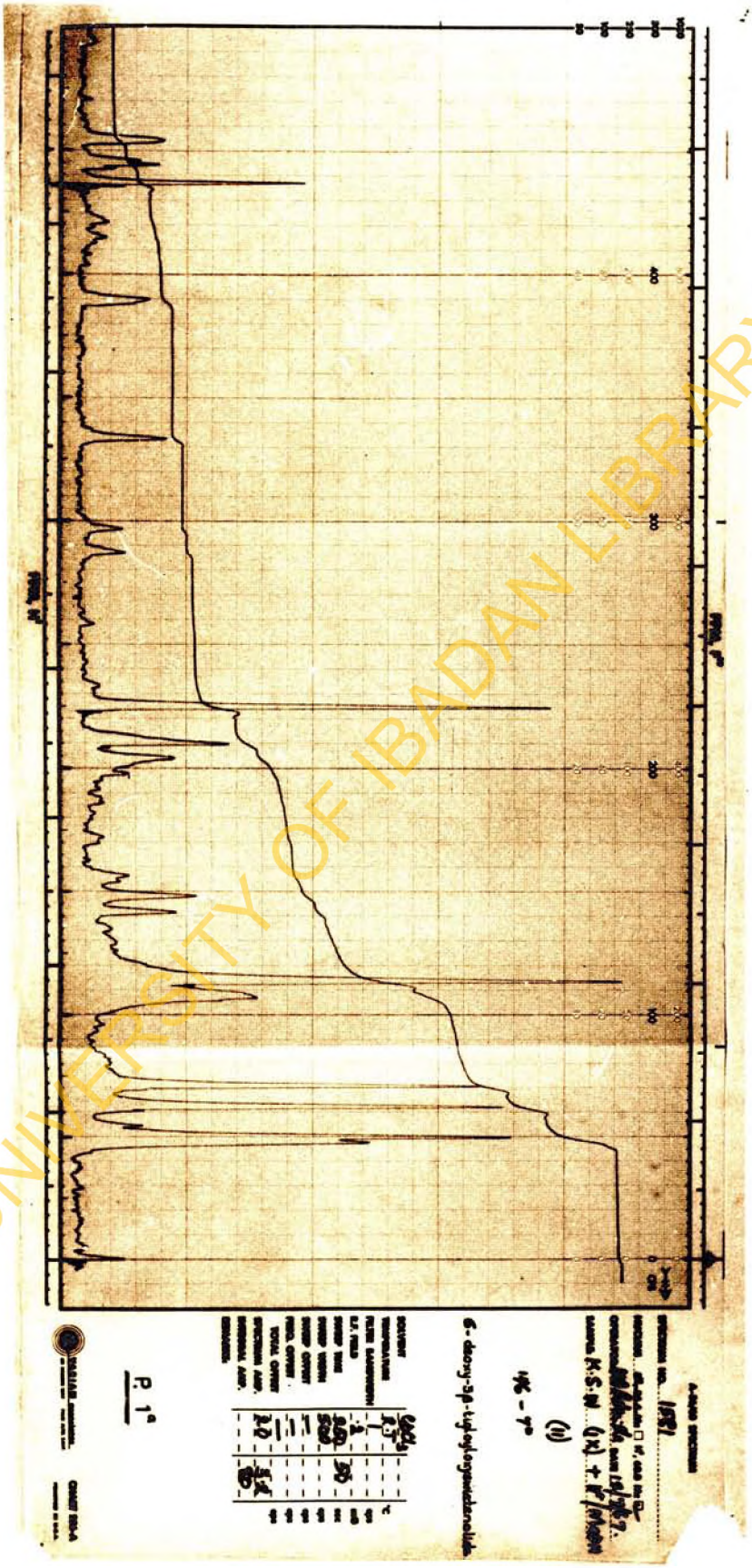
Compound X, m.p. 154-157°, was easily identified as khayasin C

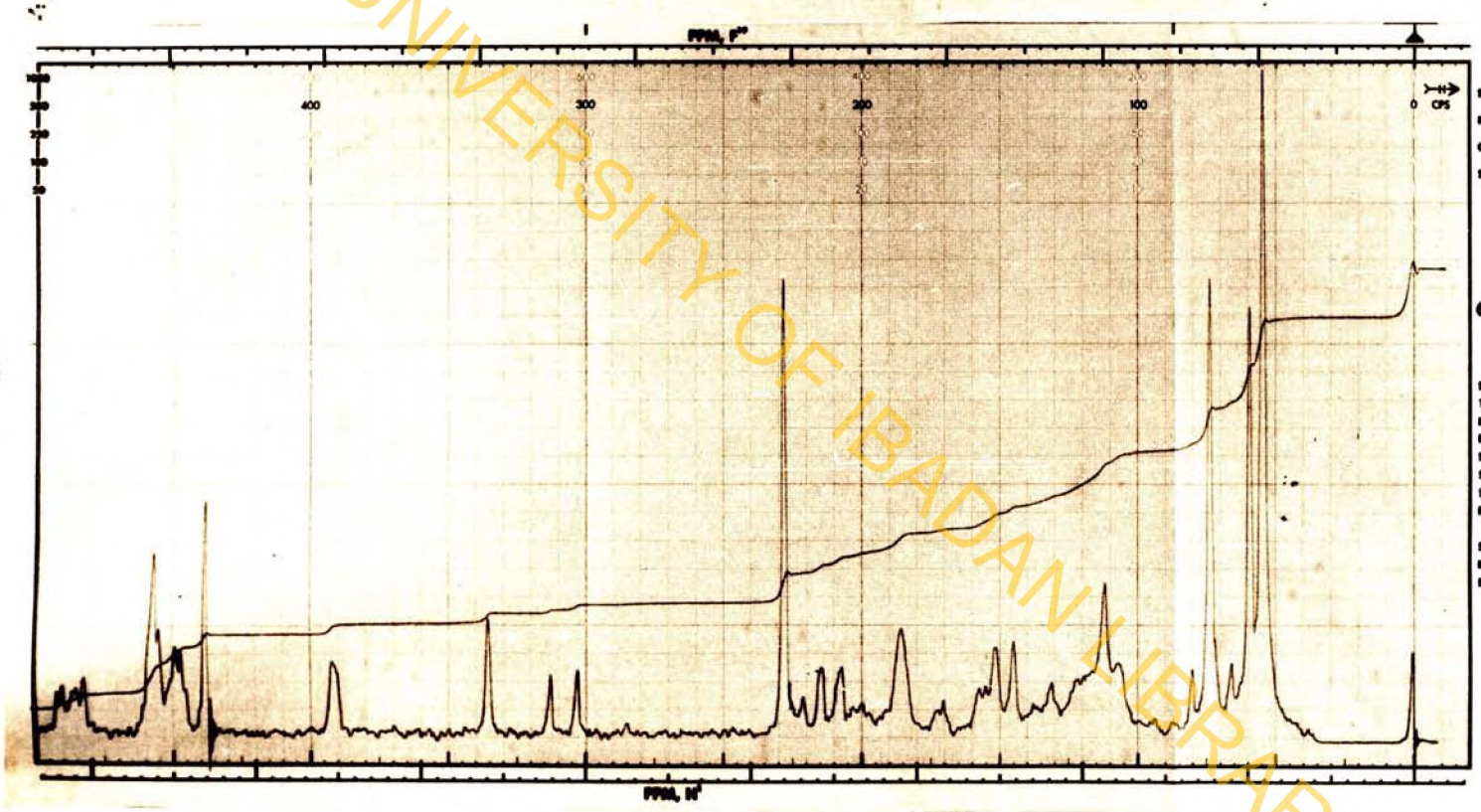
from its melting point and spectral properties. Compound Y m.p. 168° has a molecular weight 620 with formula $C_{36}H_{44}O_9$. The n.m.r. spectrum showed four tertiary methyl groups, two carbomethoxyl groups (δ 3.43, 3.70) and a methoxyl group (δ 3.17) suggesting a ring D-δ-lactone opened compound. There were also a one proton doublet at δ 5.11 (J = 9.5 c./sec.) indicating a β-ester as in the isobutyrate, and the usual protons of a β-substituted furan. However, instead of the usual two α-protons of the furan, there are seven protons absorbing in different positions between δ 7 and δ 8.2. The seven protons are due to the two α-protons of the furan, and five protons in a benzoate group. The base peak of the mass spectrum at 121 mass units is attributed to $C_6H_5CO.O^+$ while the next two strongest peaks at 105 and 77 are attributed to the $C_6H_5CO^+$ and $C_6H_5^+$ respectively. This evidence confirms that Y is a benzoate. Compound N, M.W. 574, $C_{34}H_{38}O_8$ m.p. 197-199°, was found to be related to Y in the same way as mexicanolide is to the ring-D-opened compound. Thus compounds N and Y were regarded as benzoates.

Alkaline hydrolysis of either N or Y, followed by neutralisation, gave the same volatile acid and the residual parent nucleus. Both were extracted with ether and gently evaporated. Sublimation of the mixture gave benzoic acid identical (i.r., m.p., mixed m.p) with an

authentic sample. Compound N must be 6-deoxy-3β-benzoyloxyswietenolide (LIIIb) and Y its ring-D-opened derivative (LIVb).

Compound M m.p. 146-7° which did not ring-open has a molecular weight 552 and a formula $C_{32}H_{40}O_8$. The n.m.r. showed the presence of four tertiary methyl groups, the usual β-and α-protons of a furan, a methoxycarbonyl group (δ 3.74) and a singlet due to H-17 at δ 5.56. The presence of a one proton doublet at δ 4.83, J = 10 c./sec. suggested equatorial ester. There were in addition a singlet methyl at δ 1.88 superimposed on a doublet methyl (δ 1.82, J = ca. 7 c./sec.) and a broad one-proton multiplet at δ 6.97; these were regarded as absorptions from a tiglate and compound M was tentatively taken to be 6-deoxyswietenolide tiglate. Here again the mass spectrum was informative. There was a very strong peak at m/e 88 corresponding to the tigloyl ion $C_4H_7CO^+$. Hydrolysis of compound M followed by steam distillation from the neutralised solution gave a volatile acid. The n.m.r. of its sodium salt was identical with that of an authentic sample of sodium tiglate. The n.m.r. spectrum was different from that of sodium angelate (trans methyl) prepared by Professor Taylor later has its doublet methyl slightly shifted downfield of the singlet methyl rather than upfield as in the tiglate. Compound M is therefore 6-deoxy-3β-tigloyloxyswietenolide (LIIIc).





A-56/60 SPECTRUM

SPECTRUM NO. 1589

NUCLEUS

OPERATOR [redacted] DATE 19/7/67.

SAMPLE K.S.W at fit fr 17

6-deoxy-3β-benzoyloxyswietenolide

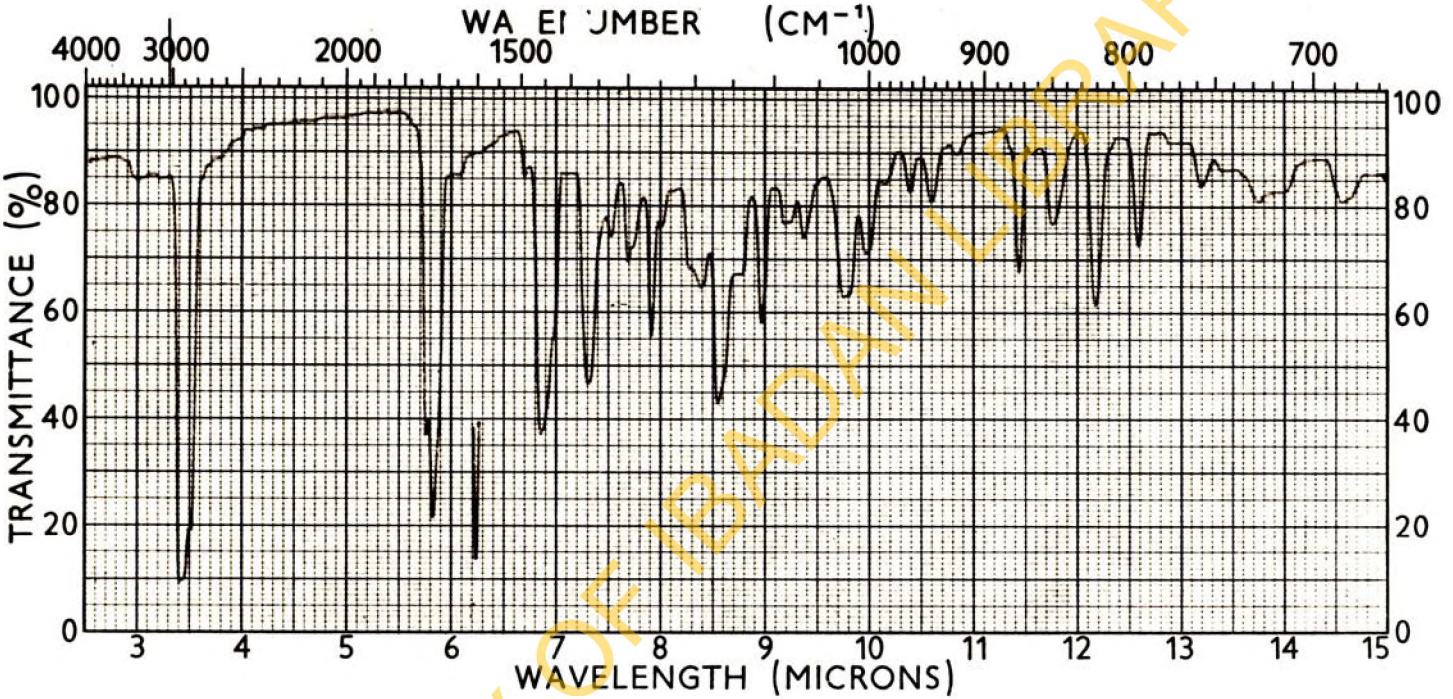
SOLVENT	$CaCl_3$		
TEMPERATURE	R.T		°C
FILTER BANDWIDTH	1		
R.F. FIELD	·2		
SWEEP TIME	0.60	50	
SWEEP WIDTH	500		
SWEEP OFFSET	—		
FREQ. OFFSET	—		
TOTAL OFFSET	—		
SPECTRUM AMP.	2·0	2·5	
INTEGRAL AMP.		30	

REMARKS

P. 1b

VARIAN associates

CHART 556-A

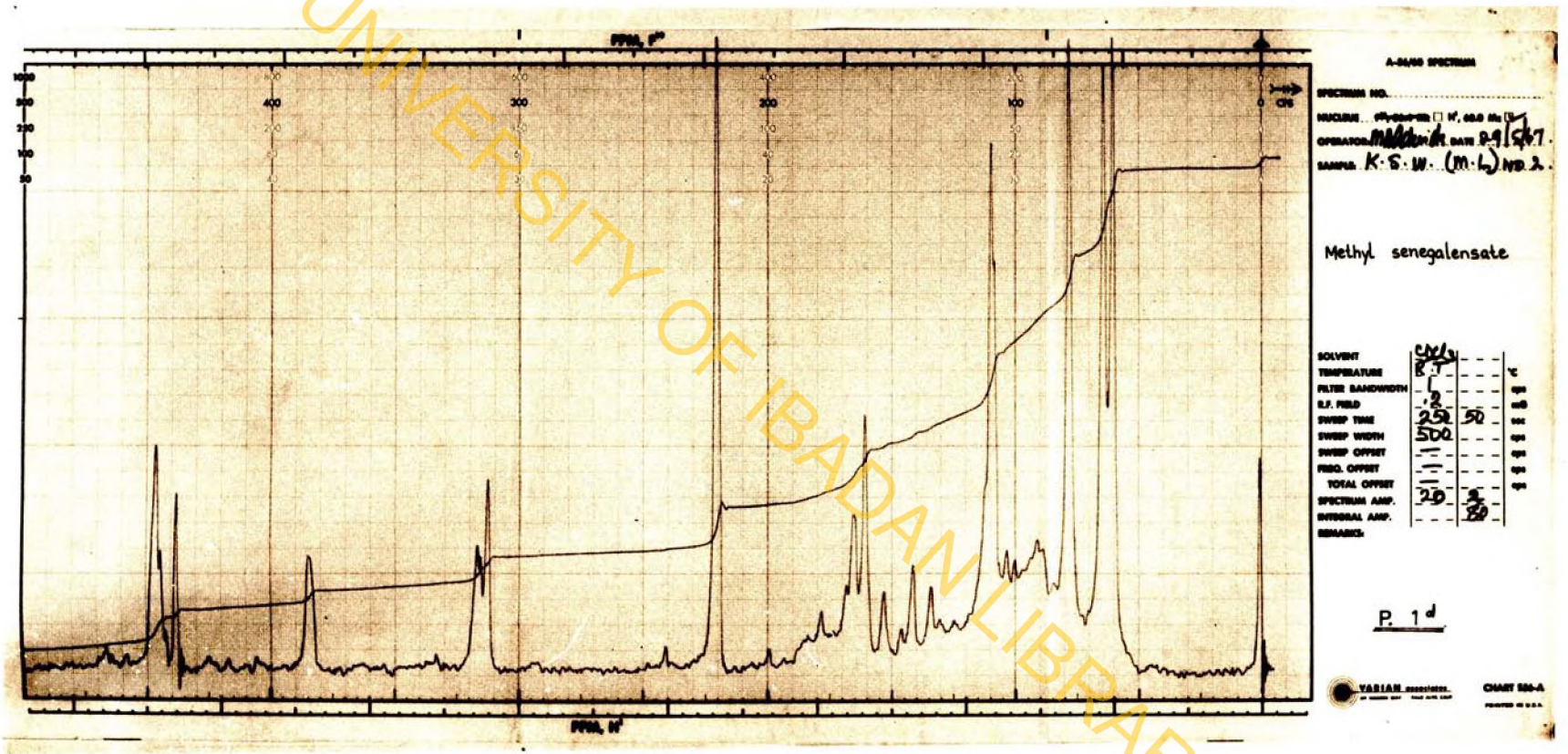


SAMPLE Frac^n 1 mL. of K.S.W. (Storin) mth. ester in Ether	PHASE	SCAN SPEED F SLIT
	SOLVENT	OPERATOR DATE 25/5/67
	CONC.	REMARKS
	CELL PATH	Methyl senegalensate
ORIGIN	REFERENCE	P. 1c

NO. M

PART NO. 137E - 1281

PERKIN - ELMER LIMITED, BEACONSFIELD, BUCKS



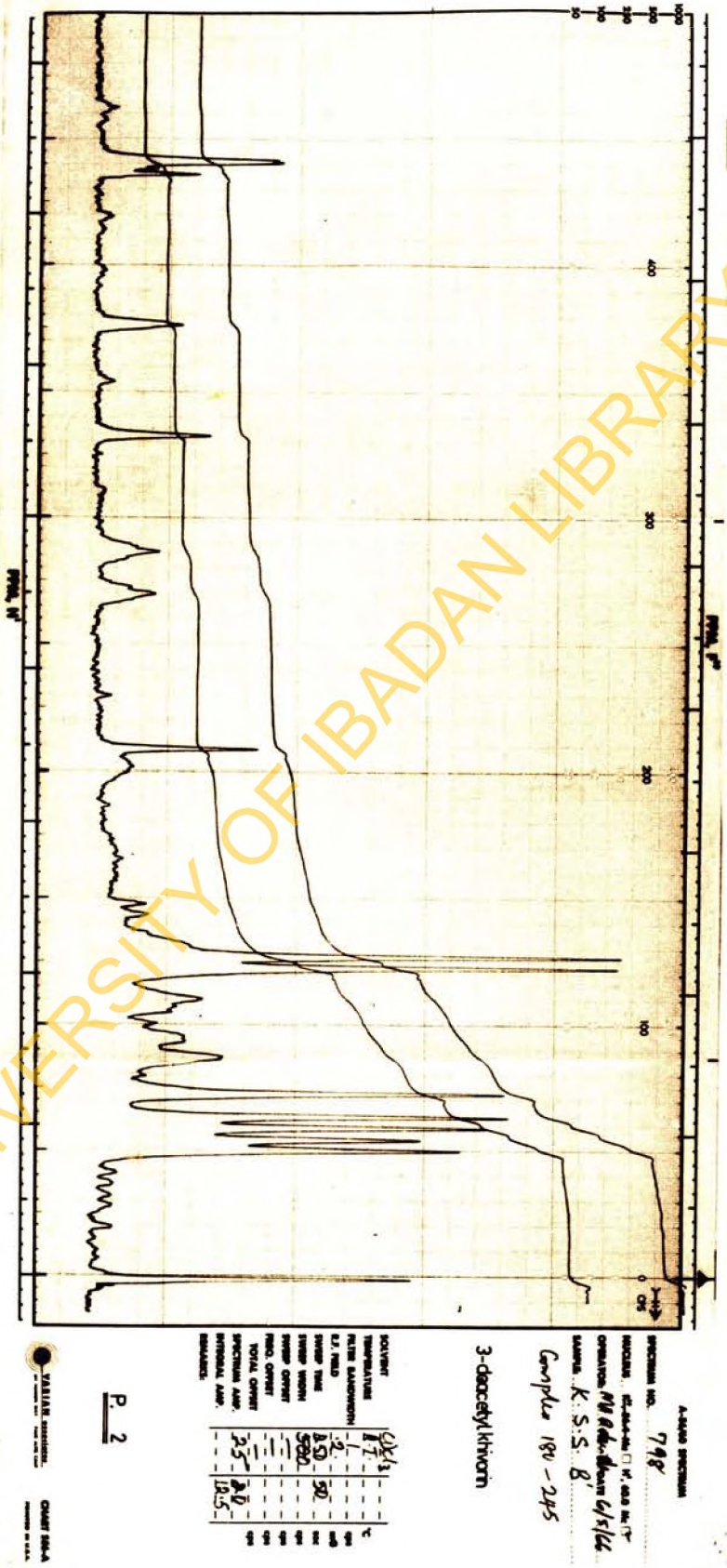
Two more new compounds were isolated from the timber. We have identified one of them as 6-deoxy-3-destigloyl-3β-12β-diacetoxyswietenine (LVIc). The other we have named methyl senegalensate, and its structure has not yet been determined owing to insufficiency of material. The first of these (LVIc) has m.p. 250-252° $[\alpha]_D^{20}$ - 131° M^+ 520 has a molecular formula $C_{31}H_{38}O_{10}$. It is also found in the bark of K. senegalensis and in Khaya nyasica seed. The evidence that led to its structural determination will be given after simpler compounds of identical nuclei have been discussed. Methyl senegalensate m.p. 197-198° $[\alpha]_D^{22}$ + 223° has a molecular weight 452 and molecular formula $C_{27}H_{32}O_6$. It has maximum absorptions at $\lambda_{max.}$ 218 mμ (ε = 11,700); $\lambda_{max.}$ 234 (ε = 9,900). The former suggests the presence of a β-furan which from its extinction coefficient must have a similar environment to that in mexicanolide. The latter suggests an αβ-unsaturated ketone system. Its infra red spectrum shows the presence of a lactone (1740), an ester (1721) and a β-substituted furan (1493, 875 $cm.^{-1}$). The n.m.r. reveals the presence of three tertiary methyls (δ 1.30, 1.07 and 1.00), a β-substituted furan (7.49, 2α-H; 6.47, 1β-H) and a methoxycarbonyl group (δ 3.70). In addition there are a doublet methyl (J = 1 c./sec. at δ 5.25 and an indistinct doublet at δ 5.31. The singlet is almost certainly the H-17 and the latter a vinyl proton. The vinyl proton

and the methyl on the double bond are probably not geminal as the coupling constant is too small (c.f. tiglate vinyl proton) and it is too far upfield to be conjugated to a deshielding nucleus like a carbonyl group. All attempts to write a structure that would fit the properties obtained were unsuccessful. Methyl senegalensate is almost certainly a seco-compound or one that has cyclised after ring opening but in any case it appears that the basic nucleus is different from any we have come across yet. It is hoped to get more of this compound in order to effect some chemical transformations that may eventually lead to the structural elucidation of this compound which may yet give another interesting biogenetic pathway in the limonoids.

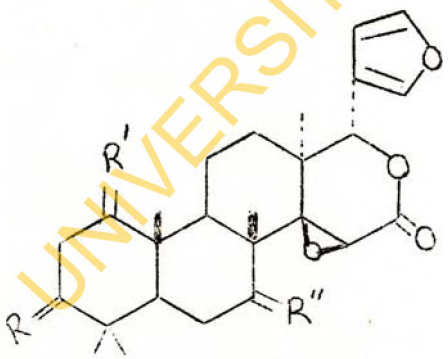
KHAYA SENEGALENSIS SEED

A sample of K. senegalensis seed from Gavva in the north of Nigeria was extracted with light petroleum. Chromatography and crystallisation enabled four crystalline compounds to be isolated. Two of these were recognised as khivorin (LVIa = XXXI) and 7-deacetyl-7-oxokhivorin (LVIc) from their spectral and physical properties. The i.r. spectrum of the third compound ($C_{30}H_{40}O_9$) showed absorptions at $\nu_{max.}$ 3534 (-OH), 1724, 1245 (ester); and 1495, 877 $cm.^{-1}$ (β-furan). The n.m.r. spectrum showed peaks attributable

to five tertiary methyl groups (δ 0.83, 0.88, 1.00, 1.07, 1.21); two acetate groups (δ 2.01, 2.12); and a β-substituted furan (7.38, 2α-H; 6.30, β-H). In addition there were two symmetrical triplets of the familiar ABX type at 4.78 (J = 5.4 c./sec.) and 4.52 (J = 4.0 c./sec.); these were regarded as base protons of the two acetates. Another broad and unresolved proton at 3.38 was resolved into an ABX triplet on addition of deuterium oxide. This must be the base proton of the hydroxyl group, the replacement of H in -OH by D allowed only the two almost equivalent protons (A and B) to couple with base proton to form the observed triplet. The n.m.r. spectrum data in conjunction with a prior identification of khivorin led us to suggest that the compound was a monodeacetylkhivorin; this was confirmed by acetylation to give khivorin. The hydroxyl group was shown to be at C-1 or C-3 by alkaline hydrolysis. Two products were obtained - the trisdeacetylkhivorin (LVIf) m.p. 319-324° insoluble in all common solvents except dioxan, was readily identified by comparison with the authentic sample from Dr. M. N. Nwaji. The second product was the dideacetyl derivative of khivorin (LVIe). Oxidation of this derivative gave a β-diketone as shown by its u.v. spectrum $\lambda_{max.}$ 211, and 256 mμ with a very intense absorption shifting to 285 mμ with alkali. The β-diketone could only arise from



the 1,3-dideacetyl compound. The monodeacetylkhivorin is therefore either 1-deacetylkhivorin or 3-deacetylkhivorin. The true position of the hydroxyl group was revealed by chromic acid oxidation. The ketone obtained (LVIg) was treated with dilute acid and gedunin (XXVIII) was obtained. The compound must therefore be 3-deacetylkhivorin (LVIb). A β-keto ester with the ketogroup at C-3 would readily lose acetic acid to give gedunin. On the other hand if the hydroxyl group were at C-1, isogedunin would be obtained from the resulting β-keto ester. A hydroxyl group at C-7 cannot form αβ-unsaturated ketone. The scheme of formation of gedunin is shown in scheme (12) and provides a way of interrelating khivorin and gedunin.



(LVI)

(g) $R' = R'' = \beta H$, αOAc; R = O.

(h) $R'' = \beta H$, αOAc; $R = R' = O$.

(a) $R = R' = R'' = \beta H$, αOAc.

(b) $R' = R'' = \beta H$, αOAc; $R = \beta H$, αOH.

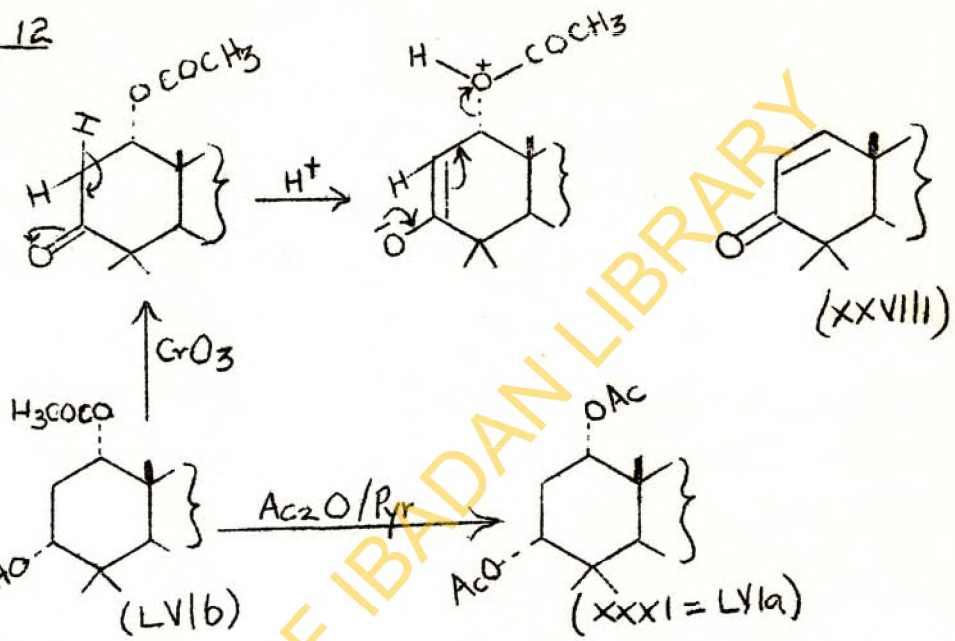
(c) $R = R' = \beta H$, αOAc, $R'' = O$.

(d) $R = \beta H$, αOH, $R' = \beta H$, αOAc, $R'' = O$.

(e) $R = R' = \alpha OH$, βH; $R'' = \alpha OAc$, βH.

(f) $R = R' = R'' = \alpha OH$, βH.

Scheme 12



The small coupling constants of the protons H-1, H-3 and H-7 ($J_{1-2\alpha} + J_{1-2\beta}$ = 5.4 c./sec.; $J_{3-2\alpha} + J_{3-2\beta}$ = 5.2 c./sec. and $J_{7-6\alpha} + J_{7-6\beta}$ = 4 c./sec. respectively) in 3-deacetylkhivorin have been used to infer the stereochemistry at C_1, C_3, C_7. They are not large enough to involve axial-axial coupling and since one of the two protons at C-2 and C-6 must be axial, H-1, H-3 and H-7 must all be equatorial and therefore the C-1 acetate, C-3 hydroxide and C-7 acetate must all be axial with α-configuration. Furthermore since acetylation of 3-deacetylkhivorin to khivorin could not have involved an inversion of configuration khivorin must be 1α, 3α, 7α - triacetoxy compound.

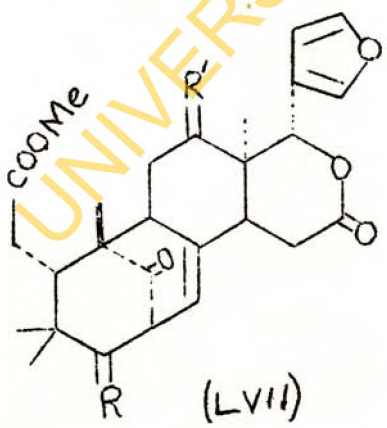
Evidence from spectra and analysis show that the fourth compound (LVId), also new, is almost certainly 3-deacetyl-7-deacetoxy-7-oxokhivorin though there was not enough of it to confirm the structure. The i.r. spectrum showed the presence of a hydroxyl group ($\nu_{max.}$ 3584 cm.$^{-1}$) in addition to an ester and or a lactone, a saturated ketone and a furan. The n.m.r. spectrum also suggested monodeacetyl 7-oxokhivorin (only one acetate group). The diamagnetic shift of the H-17 to δ 5.43 is in agreement with the observation of Powell[86] for a 7-keto compound. Acetylation gave a product which had the same R_f value (t.l.c.) as 7-deacetoxy-7-oxokhivorin, thus confirming the original supposition.

Careful comparison of the spectra of 3-deacetyl-7-deacetoxy-7-oxokhivorin, 3-deacetylkhivorin and their derivatives enabled the assignments of the various base protons of acetates at C_1, C_3, C_7 to be made. In 7-deacetoxy-7-oxokhivorin the two protons at C_1 and C_3 formed an unresolved broad peak at ca. δ 4.75. The fact that in khivorin all the three protons go from ca. δ 4.75 to as far up field as δ 4.5 and in 3-deacetylkhivorin the C_1 and C_7 protons are at δ 4.78 and 4.52 must mean that the C-1 proton absorbs at ca. δ 4.7 while C-7 absorbs at ca. δ 4.5. The fact that in 3-deacetyl-3-oxo-khivorin with a keto group beta to C-1 proton originally absorbing at δ 4.7 is now shifted down-field while the other is unaffected

supports the δ 4.7 - 4.8 position for C-1 proton and 4.5 for the C7 proton. Additional confirmation comes from 3-deacetyl-7-deacetoxy-7-oxokhivorin whose only acetate base proton (β- to a hydroxyl group) at C-1 or C-3 absorbs at δ 4.93 and must therefore be at C-1 or C-3 acetoxy compound. The reason for the difference in the chemical shifts of the acetate base-protons would seem to be due to a greater interaction (and therefore greater mutual deshielding) in the 1,3-diacetate than it is between the C-7 acetate and the ring D lactone.

The seed from the specimen of K. senegalensis collected near Ilorin was examined and found to contain khivorin (XXXI), 3-deacetylkhivorin, 7-deacetyl-7-oxokhivorin, and methyl angolensate, which have already been described. Two new compounds were also isolated and identified as 6-deoxydestigloylswietenine (LVIIa) m.p. 250-265° M^+ 470 and the corresponding acetate (LVIIb). The i.r. spectrum of the former shows the presence of a hydroxyl group ($\nu_{max.}$ 3472 $cm.^{-1}$) a β-substituted furan, ester and/or lactone. The n.m.r. spectrum of the second compound $C_{29}H_{36}O_8$ (M^+ 512) m.p. 223 - 226° shows the presence of four tertiary methyl groups (1.13, 1.08, 0.82(2)), β-furan protons (7.78, 7.40 - 2α-H; 6.48, β-H), a methoxy-carbonyl group (δ 3.73) a C-17 proton (δ 5.7) and a one proton doublet (δ 4.74, J 9.5 c./sec.) reminiscent of base protons of 3β-esters in the bicyclononanolides. The three-proton singlet at δ 2.09 indicates

that the ester is an acetate. The n.m.r. spectrum further reveals the presence of a pair of confused triplets W/2 = 3 c./sec. at δ 5.35 with a separation of 7 c./sec. similar to the vinyl proton at C-30 of swietenine and its derivatives. The compound was therefore identified as 6-deoxydestigloylswietenine acetate. Further support for this assignment came from the alkaline hydrolysis of the acetate which, as would be expected from similar reaction on swietenine, led to epimerisation at C-3. Acetylation of the epi-alcohol (LVId) gave an isomeric acetate (LVIIe) m.p. 209-212° $[\alpha]_D^{20}$ - 86° with the base proton of the acetate collapsing to a broad singlet (W/2 = 2 c./sec.) at δ 4.65. An axial acetate at C-3 would have an equatorial H-3 and will therefore account for the small coupling constant with neighbouring axial or equatorial H-2.



(LVII)

(a) R′ = αH, βH; R = αH, βOH.

(b) R′ = αH, βH; R = αH, β-OAc.

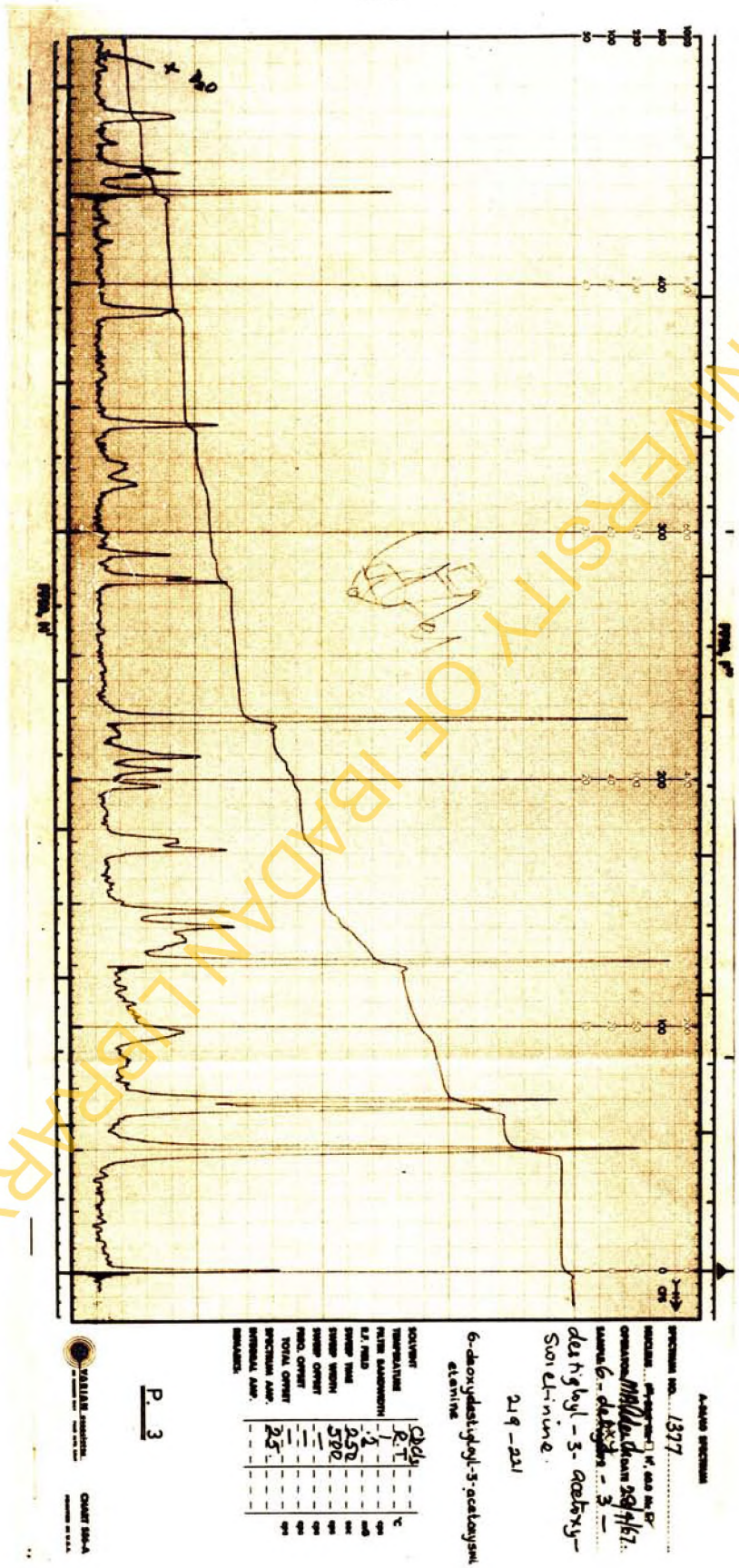
(c) R′ = αH, βOAc; R = αH, β-OAc.

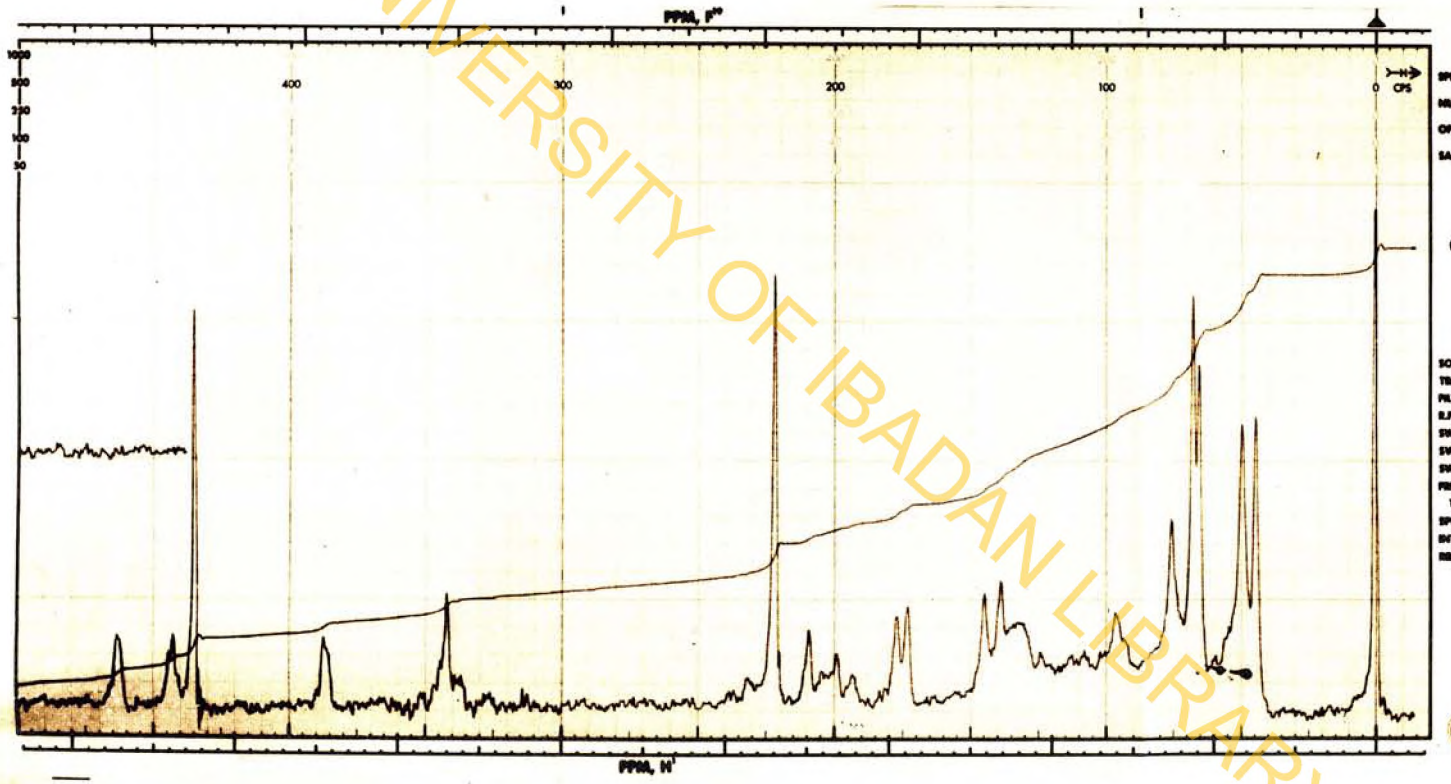
(d) R′ = αH, βH; R = βH, αOH.

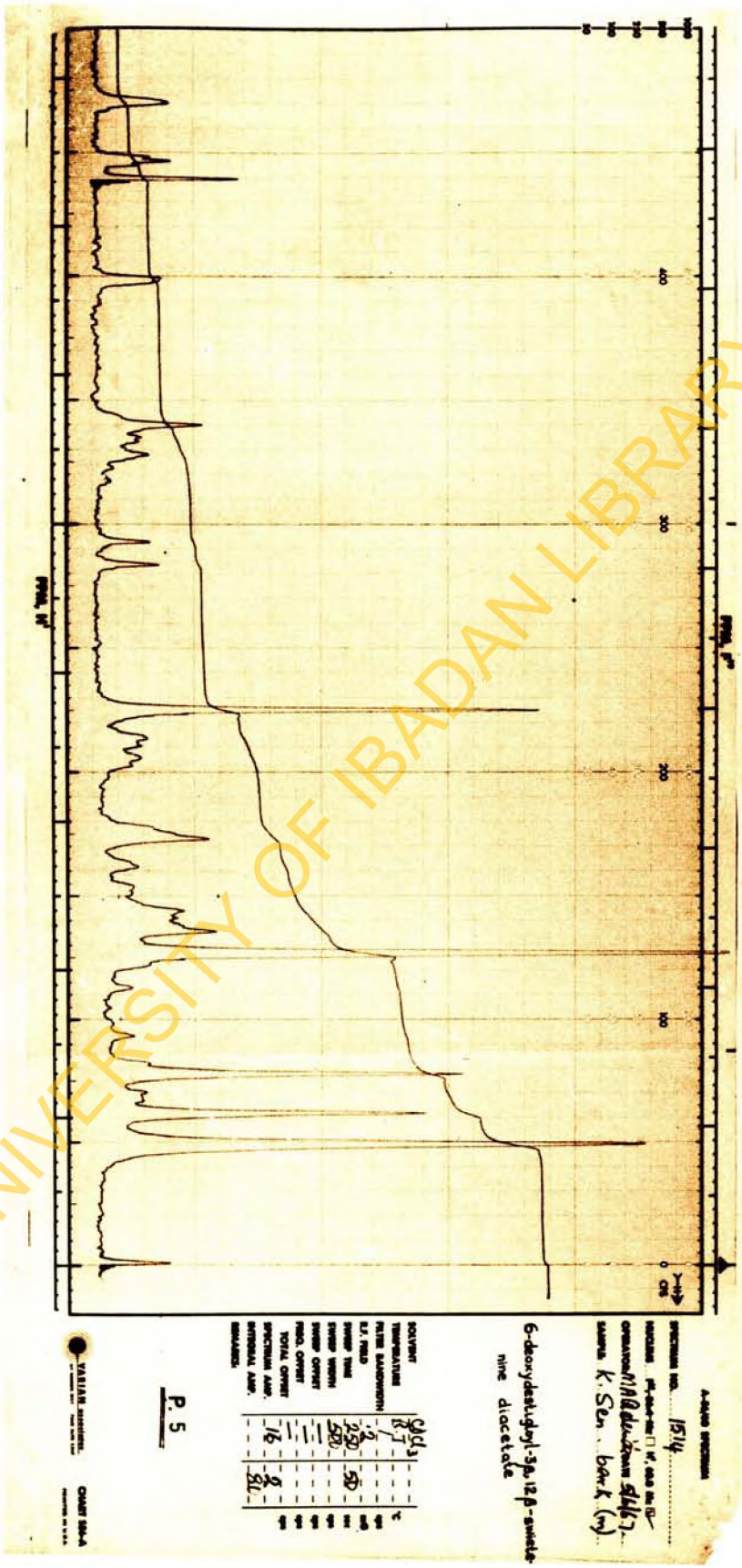
(e) R′ = αH, βH; R = βH, αOAc.

(f) R′ = αH, βOAc, R = αH, βOAc.

(g) R′ = αH, βH; R = O.







One interesting change that was also shown in the iso-swietenine series was the down-field shift of the H-30 absorption peaks to δ 5.9 compared to 5.35 in the normal series. The epi-alcohol was found to be isomeric with the second new product and their n.m.r. spectra are related in much the same way as the natural acetate is to its epimer. The second compound is therefore 6-deoxydestigloylswietenine. That the natural hydroxy compound and the alcohol from the acetate are epimers have been shown by chromic acid oxidation of either of them to give the same crystalline 3-keto compound (LVIIg).

When benzene, a more polar solvent than light petroleum, was used for extracting the timber that has been extracted with the latter, the gum obtained contained no furan and was not investigated further.

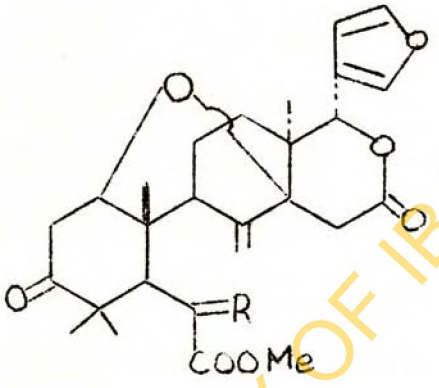
KHAYA SENEGALENSIS BARK

The bark which is by far the most widely used part of the plant for curative purposes is very bitter. Extraction with light petroleum gave methyl angolensate, 7-deacetoxy-7-oxogedunin, a large amount of a new compound $C_{27}H_{34}O_7$, m.p. 252° $[\alpha]_D^{20}$ - 83° known as methyl 6-hydroxyangolensate, and a sterol probably β-sitosterol.

The mother liquor of the fraction containing the sterol gave what we now regard as 6-deoxydestigloyl-3β,12β-swietenine diacetate (LVIIc) previously obtained from the timber.

Methyl 6-hydroxyangolensate (LVIIIb) was first isolated but not described by Overton and his co-workers.[9] Its identification was simplified by its very similar n.m.r. spectrum to that of methyl angolensate. This suggested a methyl angolensate-type skeleton for the new compound. All assignable low-field peaks of methyl angolensate were present except for a new doublet at δ 4.5 (J = 3 c./sec.) which became a broad singlet on addition of deuterium oxide, and still integrating for a proton. This must be a proton at the base of a hydroxyl group, >CH.OH. The infra-red spectrum had also indicated the presence of a hydroxyl group ($\nu_{max.}$ 3497 cm.$^{-1}$). The compound was regarded as a hydroxy derivative of methyl angolensate. The low pKa 4.85 of the acid obtained after hydrolysis suggested an α-hydroxyacid and therefore possibly a 6-hydroxy compound. The 6-position was confirmed by lead tetraacetate oxidation of the hydroxyacid (carried out by Professor Taylor). A non-crystalline substance was obtained which showed a doublet at δ 10.0 (J = 2 c./sec.). This was an aldehydic proton from a nor-aldehyde that would come from a hydroxyl group at

C-6, alpha to the carboxylic acid. The compound is therefore methyl 6-hydroxyangolensate (LVIIIb). Acetylation with acetic anhydride in pyridine readily converts it to the 6-acetoxy derivative , (LVIIIc) crystallising from methanol with a molecule of the solvent, m.p. 170-174° $[\alpha]_D^{20}$ - 84°.



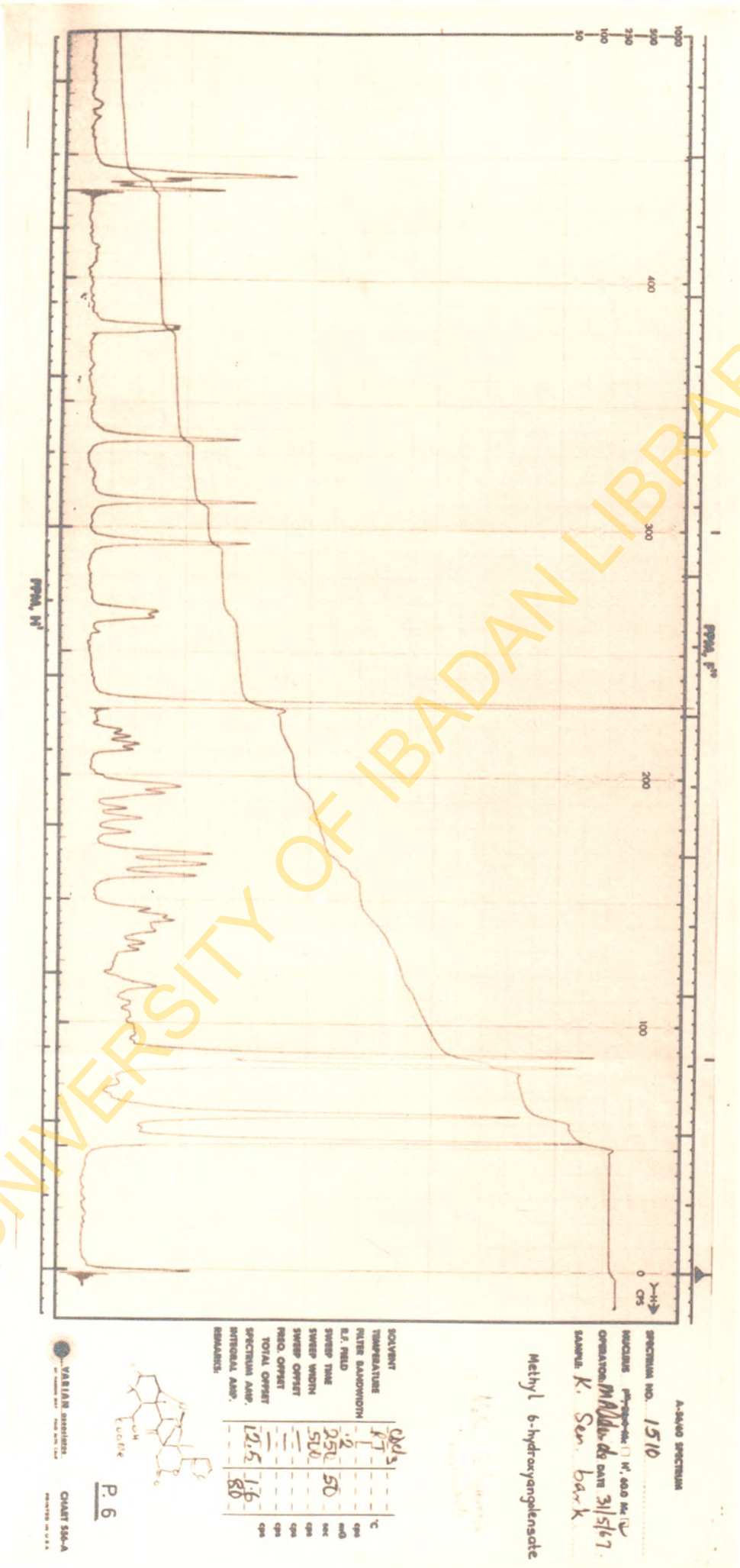
(LVIII)

(a) R = αH, βH.

(b) R = αH, βOH.

(c) R = αH, β,OAc.

The configuration of the hydroxyl group at C-6 is of interest. By taking the n.m.r. spectra of methyl angolensate, the 6-hydroxy-, the 6-acetoxy- and their 3-deoxy-derivatives plus the nor-ester and applying Zurcher's principle[68] of additivity of methyl resonance frequencies and their neighbouring functional groups we have arrived at a β-configuration for the C-6 hydroxyl group. By analogy with the steroid side chain,[68] the configuration at C-6 becomes beta because writing the structure of the compound with the C-6 above ring A, and the methoxycarbonyl group backwards makes the C-6 hydroxyl group



come to the left hand side. The deduction was made possible by using the above in conjunction with a consideration of various conformations and with the help of Courtauld atomic models choosing a conformation that was sterically favourable as well as giving the correct H_5-H_6 dihedral angle and therefore the right coupling constant between the two. A lengthy discussion on this has already been reported.[75]

The other compound $C_{31}H_{38}O_{10}$ M^+ 570 m.p. 250-252° $[\alpha]_D^{20}$ = -131° has already been obtained from the seed. The n.m.r. spectrum is very similar to 6-deoxydestigloylswietinine acetate except for the presence of an extra acetate group - a singlet integrating for six protons at δ 2.10. The methoxycarbonyl group at δ 3.73, the acetates, the H-3 down-field doublets (δ 4.79, J = 9.5 c./sec.) are almost all exactly at the same place as in the monoacetate. However the pair of triplets of H-30 which in the monoacetate is at δ 5.35 seems to be lost in a three proton complex signal at ca. δ 5.5. The other two protons are the base proton of the second acetate and the H-17, the latter may be the singlet that appears to stand out clearly in the 'jumble.' These observations led us to think that the compound was the 3,6-diacetate of destigloylswietenine. However alkaline hydrolysis followed by methylation gave a compound m.p. 223-226°, $[\alpha]_D^{20}$ - 88° which was different in the recorded physical data from

either destigloylswietenine or destigloylisoswietenine.[18] The compound was either isomeric at C-6 with swietenine or the second acetoxyl group was in another place in the molecule. Because of insufficienty of material it was not possible to get conclusive evidence as to whether it is an α-hydroxy ester. Closer examination of the n.m.r. spectrum of the diacetoxy compound showed that the β-furan, the C-30 proton and one methyl had undergone a paramagnetic shift while the H-17 of opposite stereochemistry to the C-13 methyl and the furan had undergone a very small diamagnetic shift. These suggested the presence of a group that deshielded the first three but shielded the last; in any case the group must be close to the group whose resonance frequencies it affected. The acetate group could not therefore be in the 6-position but must either be at C-11 or C-12. The observation that H-30 and the β-furan protons are deshilded while the H-17 and C-13 are shielded can therefore probably be explained in terms of the anisotropy of the carbonyl group of the ester. Such anisotropy effects, being field effects acting through space, are known to cause deshielding and shielding of protons depending on the position of such protons relative to the carbonyl group. If the base proton of this second acetate could be singled out, it would require only a measurement of the coupling constant

to fix its position. A β-acetate at C-11 on a chair conformation must be axial and have an equatorial hydrogen whose coupling constant with the neighbouring proton either the axial or the equatorial at C-12 or that at C-9 will only be of the order of 1-7 c./sec. (contrast 11β-acetate of gedunin, ring C boat[70]). On the other hand a β-substituent on C-12 would be equatorial and its axial α-hydrogen would have a coupling constant of 8-14 c./sec. from the axial hydrogen at C-11. It had already been noted that the H-30 of the iso-series of swietenine or 6-deoxyswietenine is paramagnetically shifted compared with the normal series. Use was made of this and in the isomeric 3α-acetate (LVIIf) with a broad singlet due to H_3 at δ 4.57 (W/2 = 2 c./sec.), the hitherto complex region at δ 5.5 was slightly resolved, the H-30 had moved downfield to δ 6.05 forming the familiar pair of triplets (W/2 = 3 c./sec., separation 7 c./sec.). This left a two proton signal due to H-17 (singlet at δ 5.5) and a quadruplet (W/2 = 16 c./sec.) at ca. δ 5.45. Evidently second order splittings and interactions have made it difficult to get the exact coupling constant. The observed value is however consistent with an equatorial acetate at C-12 and not at C-11. Taking the H-30 signal as strong evidence for a swietenine nucleus, the compound must be 3-destigloyl-3β,12β-diacetoxyswietenine (LVIIc).

KHAYA SENEGALENSIS ROOT

Extraction of the ground root in the usual way gave a little solid and much gum. The solid was chromatographed to give mainly β-sitosterol and a little methyl angolensate. The gum on chromatography, gave khayasin and a non-furanoid oil which was not investigated further.

KHAYA SENEGALENSIS ROOT BARK

The macerated root bark on light petroleum extraction gave methyl 6-hydroxy angolensate readily characterised by comparison of its physical properties with those of an authentic specimen.

KHAYA GRANDIFOLIOLA

K. grandifoliola C.DC. grows in slightly wetter areas than K. senegalensis. It is a tree of drier parts of forest regions and forest outliers in the savannah, capable of attaining a height of 130 ft. It has grey scaly bark. Like K. senegalensis it carries woody fruit but has five rather than four valves. The fruit is bigger and the leaf broader than those of K. senegalensis. It is one of the sources of African mahogany, useful for carpentry, joinery,

cabinet making and for canoes. It enjoys considerable use as a source of native drugs though it is not as popular as K. senegalensis. Some of the uses in this direction have been reported.

Bark Used as fish-poison in Uganda. In Central Africa, the decoction is taken by mouth to relieve postpartum pains.

Root-bark - Used for blenorrhagia and as a local application to dermititis.

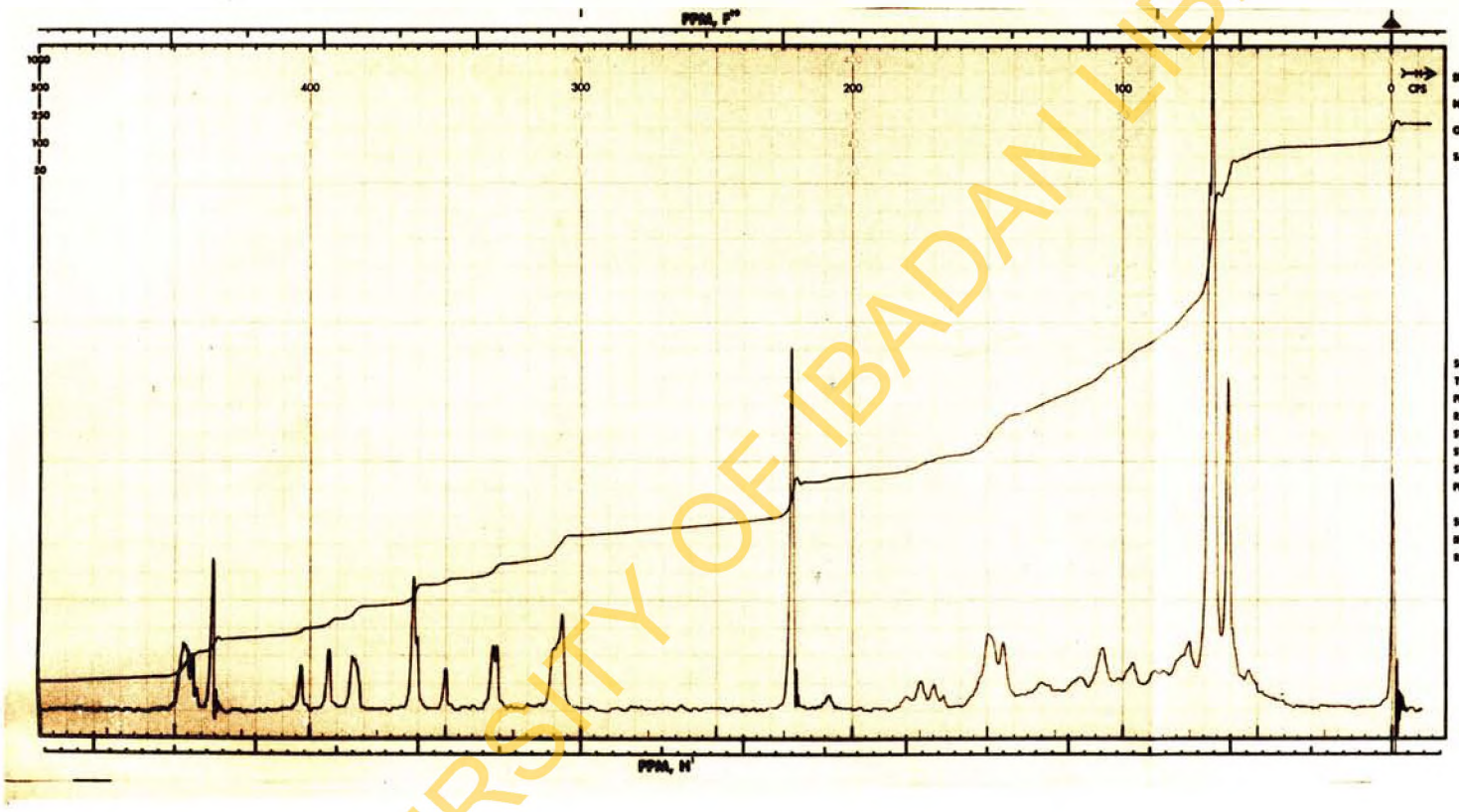
The chemical constituents of the various extractives isolated from the different parts of the plant are discussed.

EXTRACTIVES FROM THE TIMBER

A sample of K. grandifoliola (F.H.I. No.54740) collected from Balogun Village near Ibadan has been shown to contain methyl angolensate and mexicanolide. We examined another sample from Ife and chromatographed the gum over neutral alumina. Elution with benzene-ethylacetate (1:1) gave mexicanolide; ethyl acetate gave methyl angolensate and an earlier fraction from benzene-ethyl acetate (3:1) gave deoxyandirobin (LX).

Methyl angolensate and mexicanolide were readily identified by their spectral and other physical data. Deoxyandirobin m.p. 182 - 184° $[\alpha]_D$ + 392° was recognised from its n.m.r. and i.r. spectra.

- 65a -



A-56/60 SPECTRUM

SPECTRUM NO. 1341

NUCLEUS ... H¹, 60.0 Mc

OPERATOR MA Rahman DATE 18/7/67

SAMPLE K·G·W· (9 ex. MeOH)

179 – 181°

Deoxyandirobin

SOLVENT	CCl4		
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.	12.5	2.5	
INTEGRAL AMP.		80	

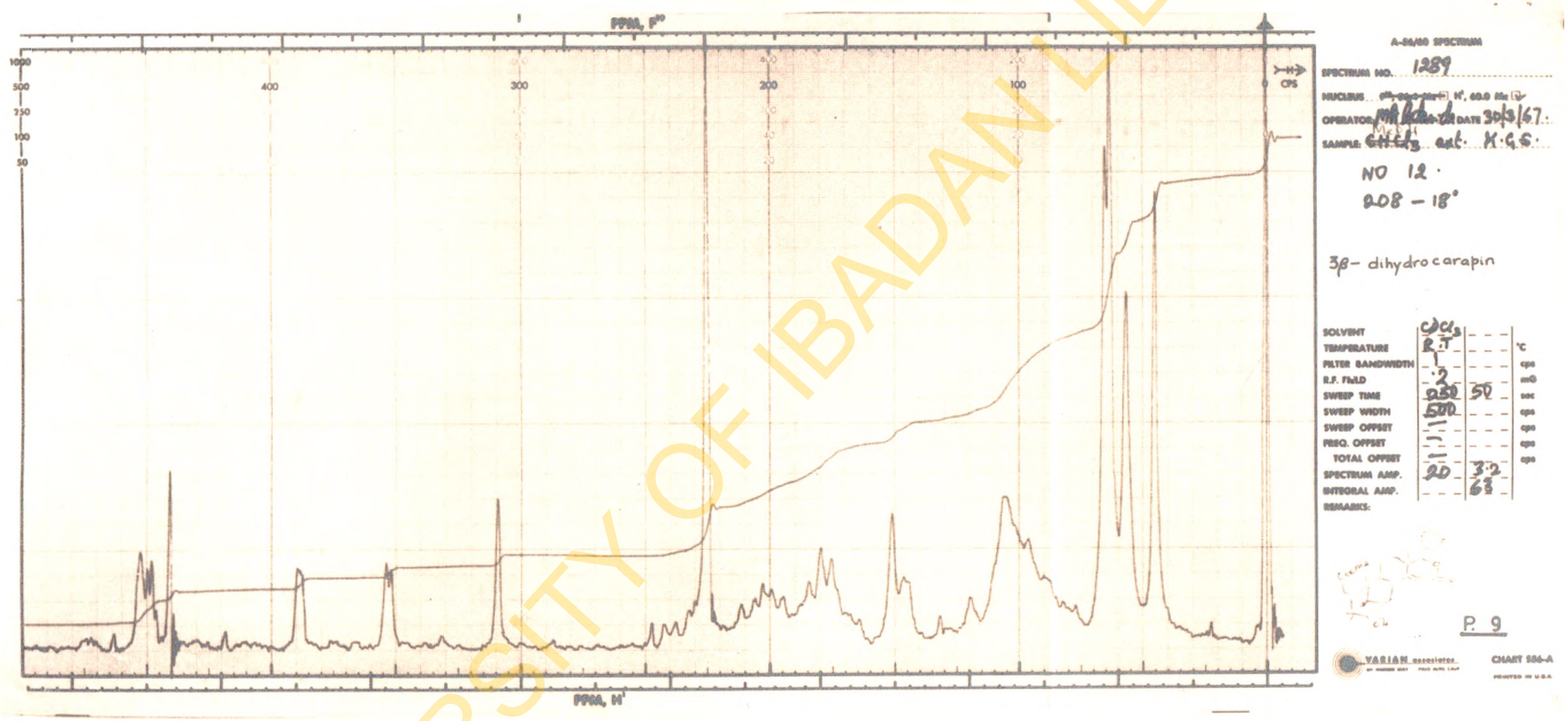
REMARKS:

P 7

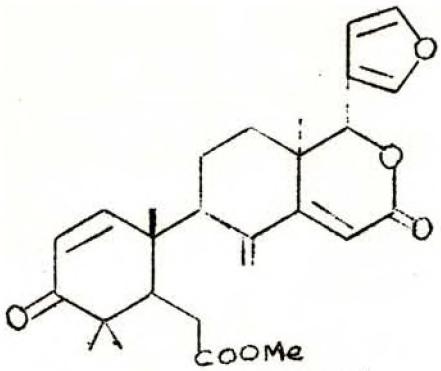
YARIAN ASSOCIATES

CHART 556-A

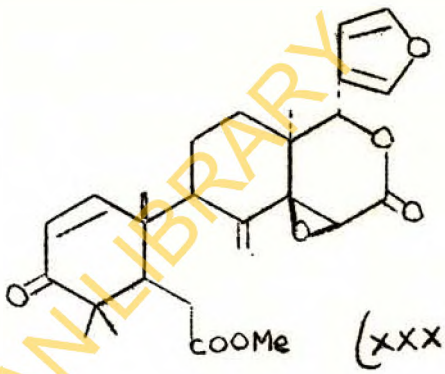
In the infra-red spectrum there were bands at 1724 (ester); 1661 ($\alpha\beta$-unsaturated ketone), 1613 ($>C=H_2$) and 1493, 875 $cm.^{-1}$ (β-furan). The u.v. spectrum, $\lambda_{max.}$ 217 mμ, ϵ = 17,500; $\lambda_{max.}$ 234 mμ, ϵ = 17,000, suggested a conjugated system. The n.m.r. spectrum showed peaks attributable to four methyls, two exocyclic methylene protons (δ 6.64, 5.92; J = 10.5 c./sec.), a singlet vinyl proton (δ 6.03), two other vinyl protons coupled together (δ 5.15, 5.53; J = 2 c./sec.); the usual H-17 (δ 5.15); a CO.OMe (3.71) and the β-substituted furan protons. The presence of a methoxycarbonyl group suggested the presence of a ring-opened compound as in methyl angolensate or a compound that has cyclised by a different route from that by which it opened as in mexicanolide. The presence of the exocyclic methylene group and the vinyl proton suggested the compound to be deoxyandirobin (LX). Comparison of these data with those of an authentic deoxyandirobin showed exact identity. There was no depression in a mixed melting point determination. The compound must therefore be deoxyandirobin previously prepared by Zelnik et al.[24] by the reduction of andirobin. But it had never been obtained as a natural product before.



66b



(LX)



(XXXIV)

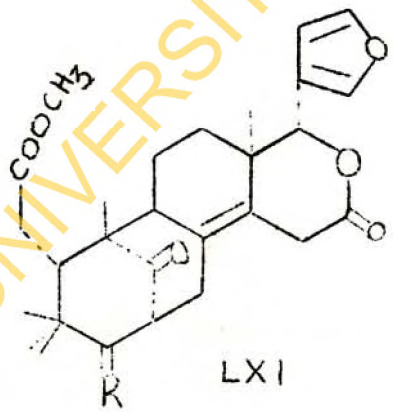
The isolation of deoxyandirobin is biogenetically very interesting as it can conceivably be regarded as a potential intermediate for a number of isolated triterpenes. For (1) epoxidation at C-14, 15 will give andirobin, (2) hydroxylation at C-1 and subsequent attack of the oxygen at C-1 on C-14 will give methyl angolensate and (3) oxidation of the hydroxyl group at C-1 in (2) can invoke a Michael addition of the C-30 terminal methylene group on to the β-diketone-activated C-2 protons to give the bicyclononanolides.

EXTRACTIVES FROM THE SEED

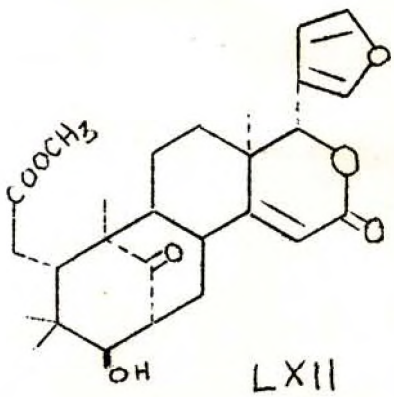
The seed of K. grandifoliola from a single tree at Balogun Village near Ibadan (Herbarium specimens retained as DAHT 157 at Forest Herbarium Oxford) was extracted with light petroleum. From this sample we have obtained a very small quantity of

3β-dihydrocarapin (LXII) 6-deoxyswietenolide (LXIb) and the corresponding acetate (= fissinolide[71] = grandifoliolin[60]). These three which are new compounds were isolated along with the known mexicanolide and methyl angolensate, and a sterol, probably β-sitosterol.

The n.m.r. spectrum of grandifoliolin (LXIa) showed the presence of four tertiary methyls, a methoxycarbonyl group, one β- and two α-furan protons and a singlet assignable to H-17. These facts, plus the absence of a vinyl proton, led to the suggestion of a mexicanolide nucleus. The presence of a one-proton singlet at δ 5.03 (J = 10 c./sec.) indicated the presence of an acetate which if in a mexicanolide-type nucleus would probably be a 3β-acetate.



LXI

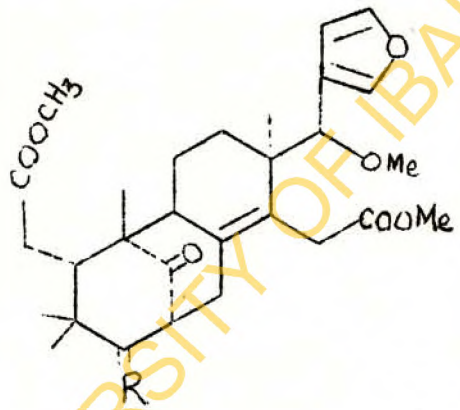


LXII

(a) R = αH, β-O.$COCH_3$

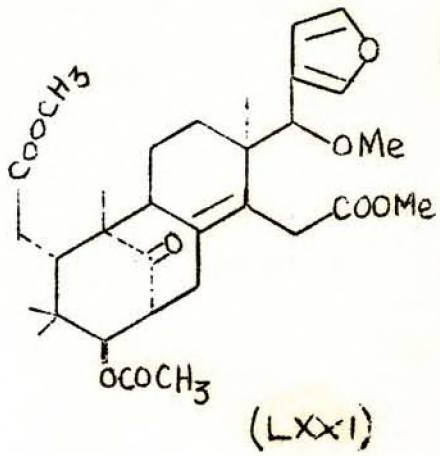
(b) R = αH, β-OH.

Grandifoliolin was confirmed to be 6-deoxyswietenolide acetate by treatment with methanolic sulphuric acid to give a ring-opened compound (LXXI); m.p. 195-198°. This compound, on alkaline hydrolysis, gave an equilibrium mixture (m.p. 189-192°) of the known and previously described 3α-and β-ols (LIa and b) in which the 3α-ol was predominant.



(LI) (a) R = αH, β-OH

(b) R = α-OH, βH



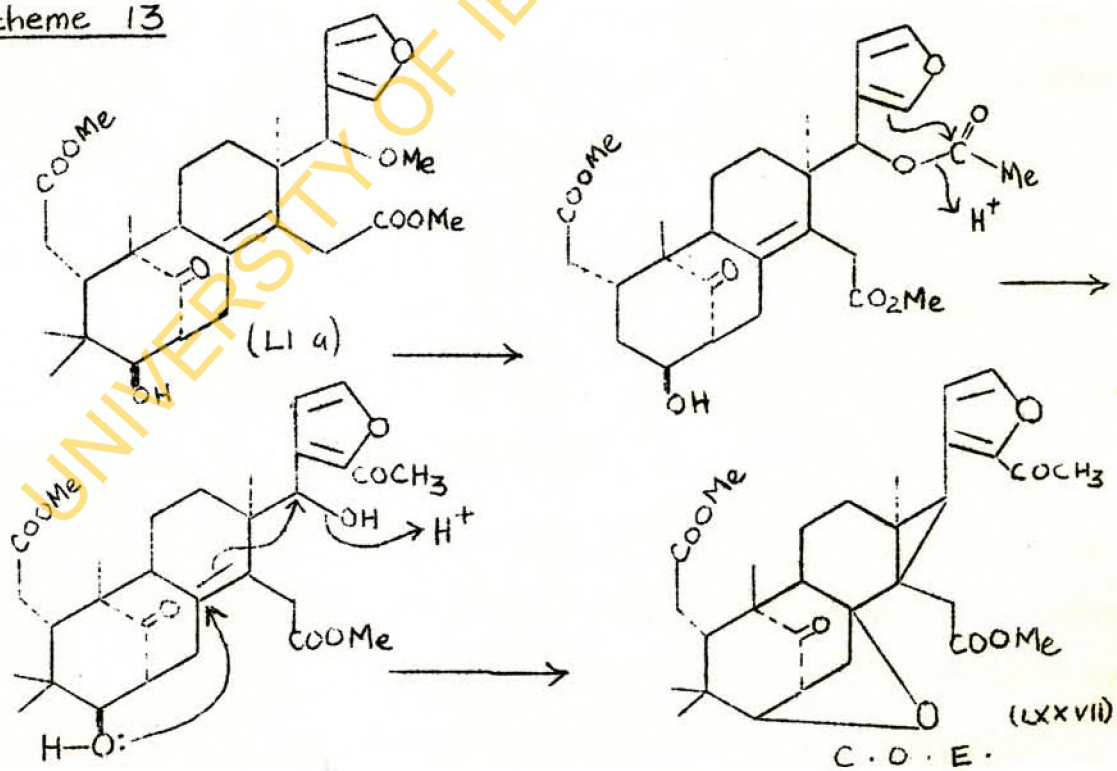
(LXXI)

Grandifoliolin has been obtained by Connolly and co-workers by acetylation of 3β-dihydromexicanolide (LXIb), a borohydride reduction product of mexicanolide. A sample of fissinolide kindly supplied by Dr. R. Zelnik, who had previously obtained it from Cedrela fissilis

Vell.,[71] had an identical i.r. spectrum, the same R_f (t.l.c.) and gave no depression on mixed melting point with our sample. Grandifoliolin must therefore be 6-deoxyswietenolide acetate (LXIa).

The formation of (LXXI) is of some interest. Previous attempts[47] to make it by acetylation of the 3β-alcohol (LIa) always led to the interesting rearrangement in which the furan was acetylated. This was followed by an attack of the C-3 oxygen on C-8 and a C-14, C-17 linkage to give C.O.E. (LXXVII) (see scheme 13). Grandifoliolin therefore provides the unique way of making (LXXI).

Scheme 13



6-deoxyswietenolide (LXIa) came down as a gum and did not crystallise from any common solvent. T.l.c. showed it to be homogeneous. The n.m.r. was so similar to that of fissinolide that nearly all the signals of one were almost superimposible on the signals of the other. The only significant difference was the absence of the acetate peak and its base proton. But whereas grandifoliolin did not change on addition of deuterium oxide, the gum was affected; the proton at δ 2.9 disappeared and the broad peak at 4.2 was reduced to a narrow peak. This indicated an alcohol and the gum was regarded as the 3β-alcohol of grandifoliolin. This structure was confirmed by acetylation of the gum to give grandifoliolin. The gum on oxidation also gave mexicanolide. Therefore the compound must be 6-deoxyswietenolide (LXIa).

The compound with m.p. 215-220°, $C_{27}H_{34}O_7$ M^+ 470, has been characterised on the basis of the i.r. and n.m.r. spectra as 3β-dihydrocarapin (LXIII). The presence of -OH was indicated by its i.r. spectrum $\nu_{max.}$ 3480 $cm.^{-1}$ and the total collapse of a doublet at δ 3.0 in its n.m.r. spectrum on addition of deuterium oxide. The n.m.r. spectrum revealed the presence of four tertiary methyls, a methoxycarbonyl group (δ 3.75), the usual β-substituted furan protons and H-17 (5.12). These were indicative of a

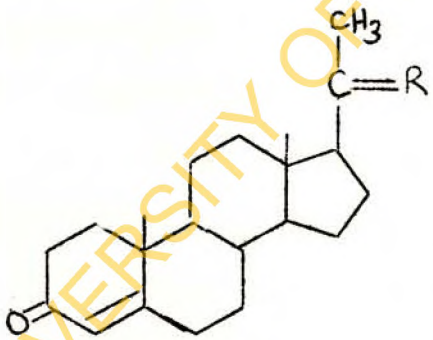
bicyclononanolide system. The doublet proton signal at δ 5.88 (J = 2 c./sec.) was taken to be H-15 of αβ-unsaturated lactone being split as in a few Δ^{14}-compounds e.g. carapin by an allylic coupling with H_7. On this basis, structure (LXII) was ascribed to 3β-dihydrocarapin. There was not enough material to confirm the structure by, for example, oxidation to give carapin.

The sterol obtained was almost certainly β-sitosterol but its chemistry was not investigated further.

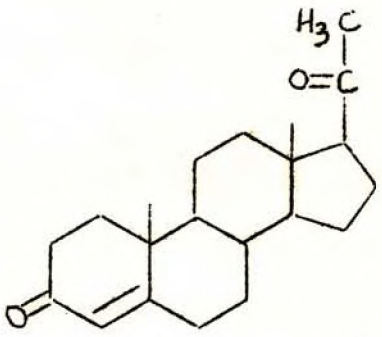
EXTRACTION OF THE STEM BARK

Chromatography of the bark extract gave methyl angolensate, methyl 6-hydroxyangolensate and a mixture of methyl angolensate and methyl 6-acetoxyangolensate which, as before, could not be separated. In addition a crystalline solid, m.p. 150° $[\alpha]_D^{20}$ + 120°, identified as a steroid hormone was isolated. The infra red spectrum of the new compound was different from any of the limonoid triterpenes, in particular both the i.r. and n.m.r. spectra indicated the absence of a furan. The n.m.r. showed the presence of two tertiary methyls at δ 0.69 and 1.20; one secondary methyl at δ 1.15, J = 6 c./sec., a vinyl proton at δ 5.72; a one proton multiplet at δ 4.5-5.0 and an acetate group at δ 2.02. The i.r. spectrum showed the presence

of an acetate (1722, 1248 cm.$^{-1}$), αβ-unsaturated ketone (1650) while $\lambda_{max.}$ 240 mμ, ε = 11,500 in the u.v. indicated αβ-unsaturated ketone. These properties were taken as indicative of 20β-acetoxy-3-oxopregn-4-ene (LXVa) (a progesterone derivative). This was confirmed by hydrolysis to the alcohol, which on oxidation gave progesterone (LXVI). An authentic sample of 20β-hydroxy-3-oxopregn-4-ene, kindly supplied by Professor Reichstein, was identical in all respects with our alcohol (LXVb). This confirmed structure (LXVa) for the steroid.



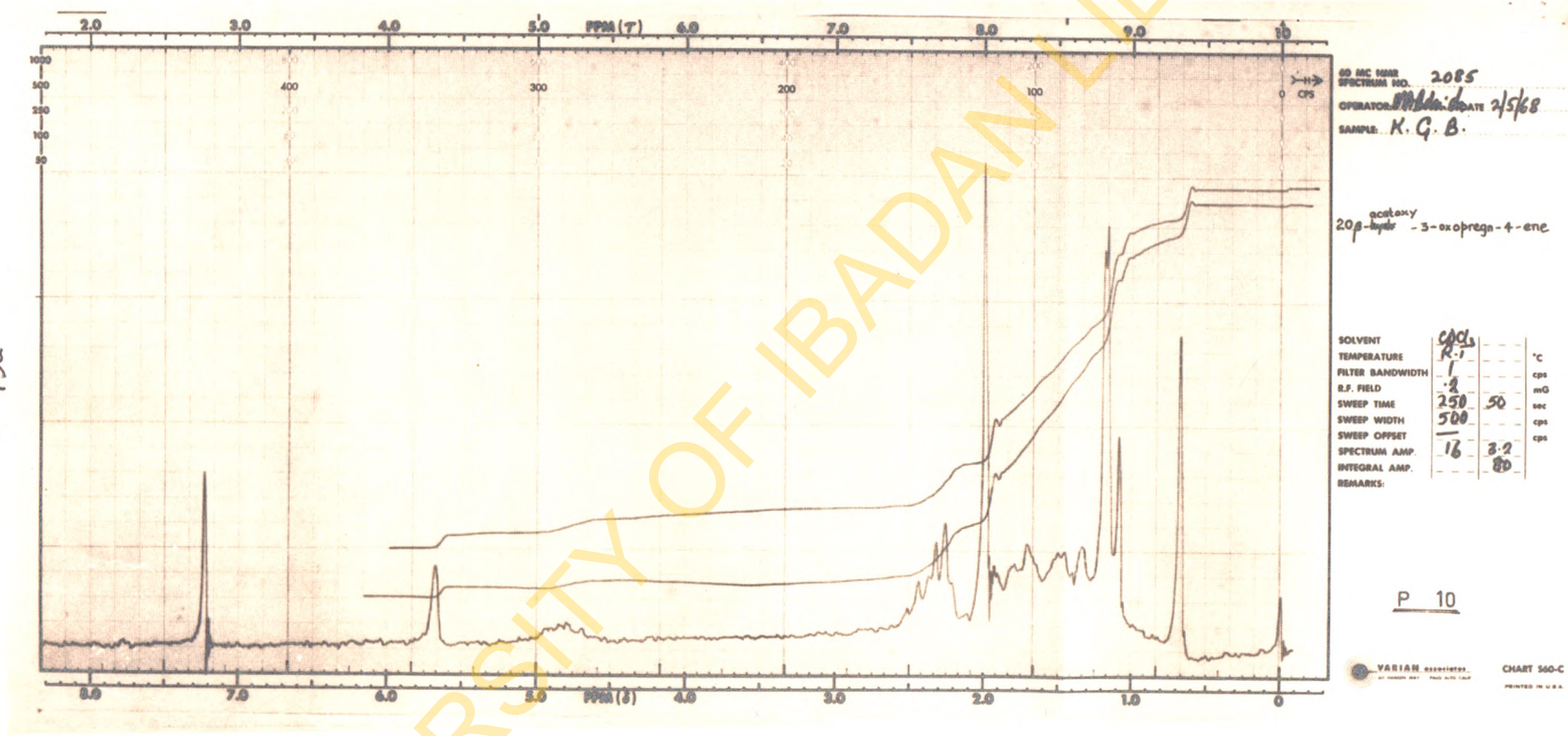
(LXV)



(LXVI)

(a) R = β-OAc, αH.

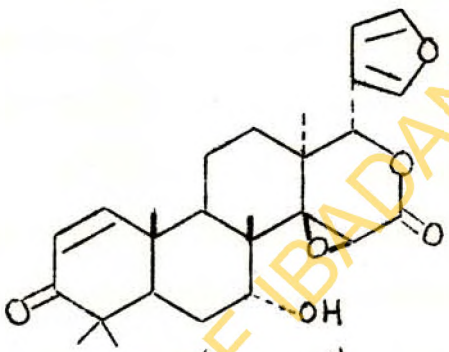
(b) R = β-OH, αH.



EXTRACT FROM THE ROOT BARK

Light petroleum extraction of the root-bark gave a gum which on chromatography yielded the known 7-deacetoxy-7-oxokhivorin, methyl angolensate and methyl 6-hydroxy angolensate. There was also a mixture of methyl angolensate and methyl 6-acetoxy angolensate obtained previously and deacetylgedunin (LXIV). The latter compound has been prepared previously and has been isolated as a natural product by Ekong and Olagbemi.[72] Deacetylgedunin was identified from its spectral properties. The i.r. spectrum showed bands at $\nu_{max.}$ 3450 (-OH), 1750 (δ-lactone); 1650 (αβ-unsaturated ketone) and 1500, 876 cm.$^{-1}$ (β-substituted furan). The n.m.r. spectrum confirmed the presence of a hydroxyl group. A broad peak at δ 2.6 disappeared on addition of deuterium oxide while the poorly resolved ABX triplet integrating for one proton at 3.6 became better resolved. This indicated the presence of $-CH_2-CH-OH$. The pair of doublets at δ 5.82 and 7.18 which were spin-coupled (J = 10 c./sec.) and the i.r. band at 1650 cm.$^{-1}$ suggested the presence of an αβ-unsaturated ketone of gedunin type. Other n.m.r. signals occurred at 7.4 (2α-furan) and 6.3 (1β-furan), 5.6 (H 17) and a singlet at 3.94 due to H-15.

The compound was confirmed to be deacetylgedunin by comparison of its spectral and physical properties with those of the authentic sample. Partial synthesis of gedunin by acetylation of deacetyl-gedunin confirmed its structure.



(LXXIV)

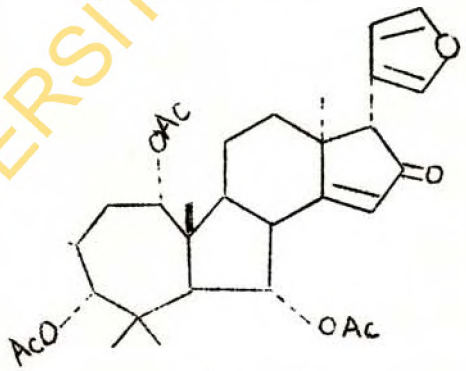
KHAYA IVORENSIS

Khaya ivorensis A. Chev. grows in the wetter part of the Forest regions. It is a large forest tree strongly buttressed and capable of attaining a height of 180 ft. and with a bole of up to 90 ft. Unlike K. grandifoliola and K. senegalensis, there is no record of any medicinal uses for the plant despite the fact that the bark is very bitter. However the wood is used for making canoes, building and furniture work. It was used for aviation purposes during the second world war.

(I) EXTRACT FROM THE TIMBER.

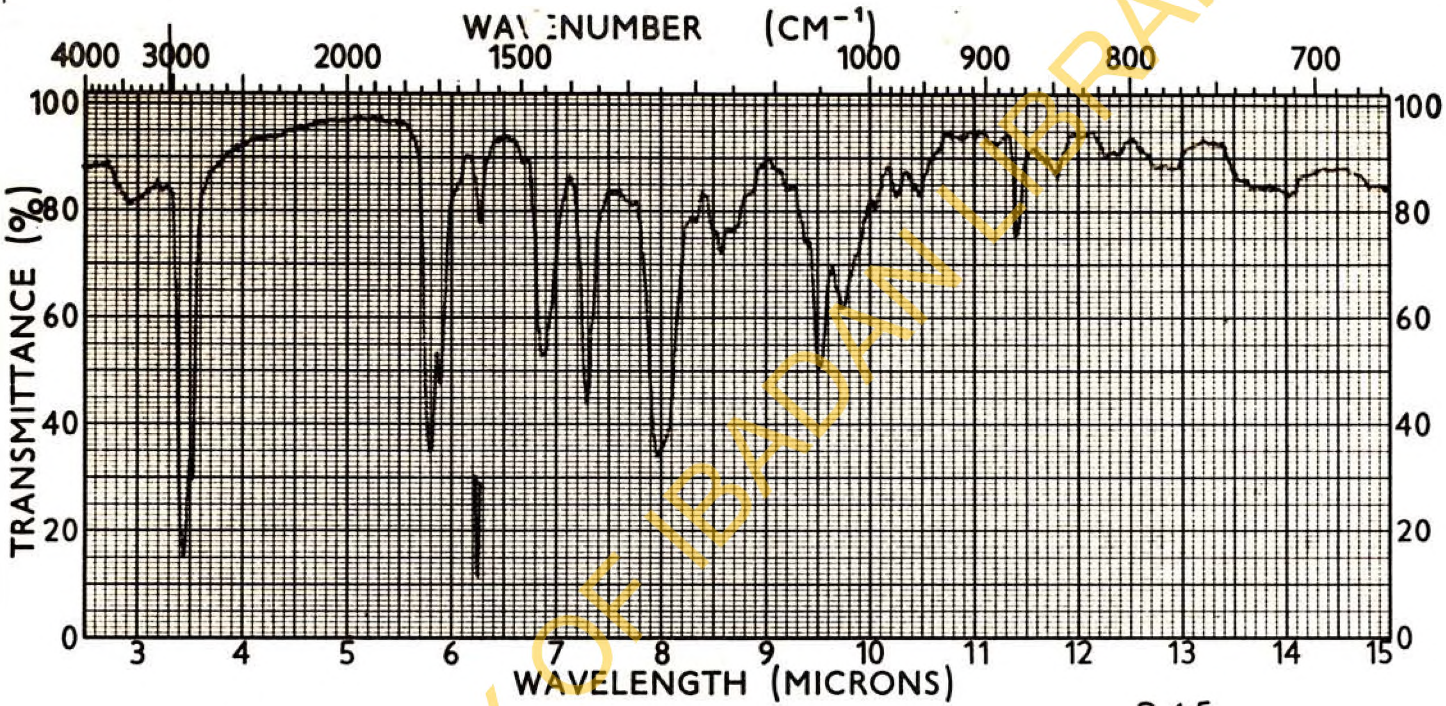
The timber of K. ivorensis from Omo River Forest Reserve, Ijebu, was percolated with light petroleum and the crude solid that separated gave khivorin. The mother liquor gave more khivorin and in all, over 90% of the solid extract was khivorin. The remaining extract was separated by thin-layer chromatography to give very small amounts of 3-deacetylkhivorin, methyl angolensate and a new compound m.p. 100-105°, M^+ 554. The new compound has i.r. absorptions attributable to an ester (1725, 1252); cyclopentenone of type >C=CH.CO (1700); a >C=C< (1542), and β-substituted furan (1500, 878 $cm.^{-1}$) $\lambda_{max.}$ 215 and 237 mμ in the u.v. spectra also confirm the presence of αβ-unsaturated ketone system. These facts when taken together with the presence of three acetates (one nine proton signal at ca. δ 2.03) as deducible from the n.m.r. spectrum could lead to structure (LXIX) for the compound. Compound (LXIX) which has been prepared from khayanthone by chromous chloride reduction[76] of the epoxide ring however has a different spectrum from the new compound. Additional evidence that show the two compounds dissimilar comes from the base protons of the acetates. In the new compound these are represented by two proton - ABX triplet at δ 4.70 and the third proton as a singlet at δ 4.55. The other low field protons are at

δ 5.28 (probably H-15 in a Δ^{14}-system), and 4.08 (probably H-17). Whichever of these three singlet protons is the base proton of the third acetate, its singlet nature is difficult to explain. A β-acetate at C-7 or any of the other two places will give even larger coupling constant than in the triplet because of an axial-axial interaction. A possible structure is (LXVII) where ring B has contracted into a cyclopentane and ring A enlarged into a cycloheptane systems. This will account for almost all the spectral properties known so far except that H-7 should be a doublet, but the strong argument against it is the lack of a biogenetic justification for such a system.



(LXVII)

77a



P 15

SAMPLE
Khaya ivorensis wood M.L.
4th fraction no 5.
Note low intensity of 1700 band
cf. Kamath CrCl$_2$.
ORIGIN

PHASE N

SOLVENT

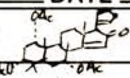
CONC.

CELL PATH

REFERENCE

SCAN SPEED slow SLIT

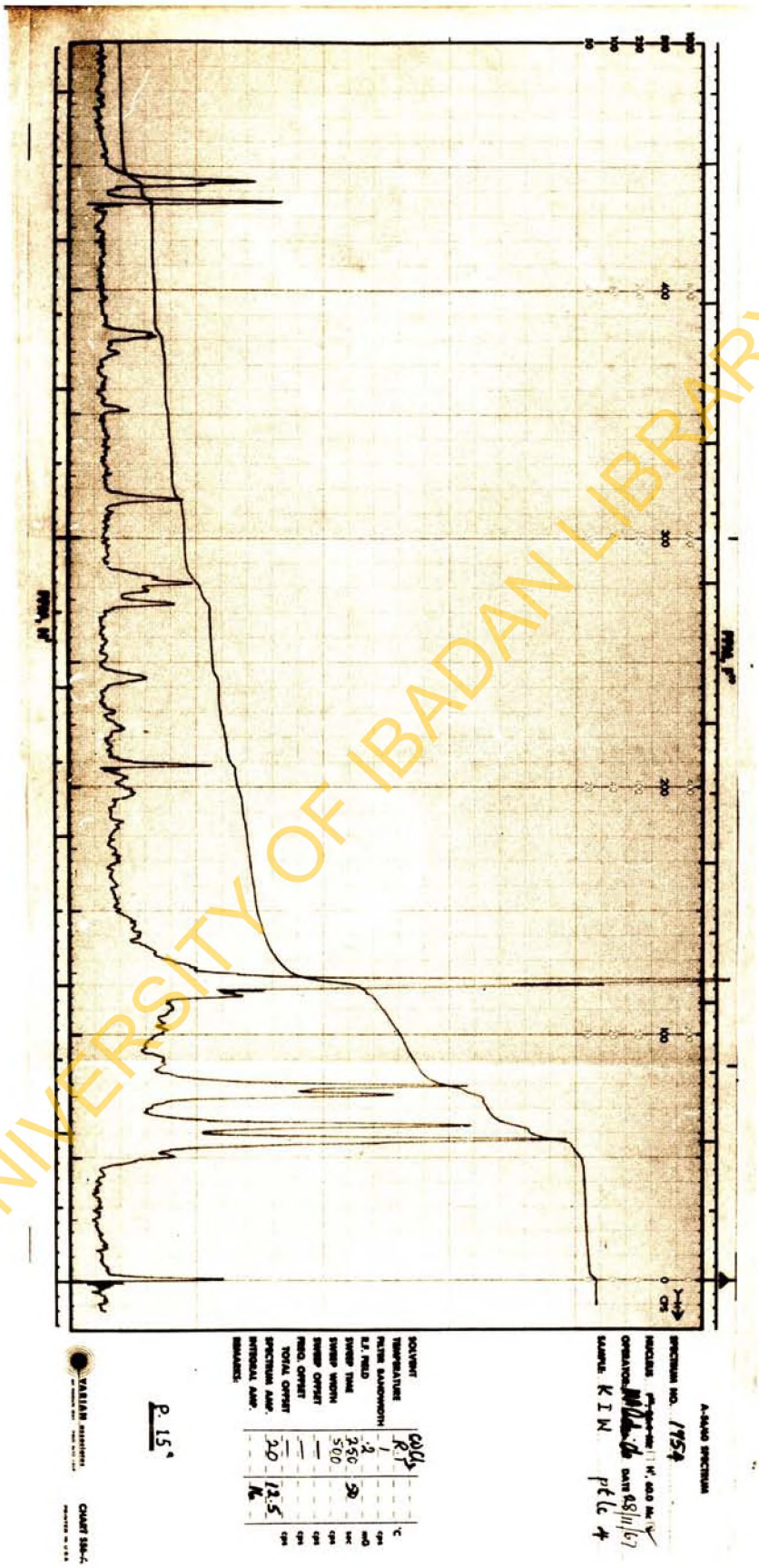
OPERATOR DATE 23/11/67

REMARKS Probably  see u.v.
m.p. 100 – 5° (not v. pure)
melts sluggishly.

NO. 4605

PART NO. 137E - 1281

PERKIN - ELMER LIMITED, BEACONSFIELD, BUCKS



EXTRACT FROM THE SEED

K. ivorensis seed collected from Sapoba Forest Herbarium was extracted and chromatographed to give methyl angolensate and mexicanolide. Some gum was obtained which partially crystallised from petroleum-ether mixture had m.p. 116-119°. The gum was identified from its spectral properties as 6-deoxyswietenolide, previously obtained from K. grandifoliola seed. The structure was confirmed by acetylation to give grandifoliolin and by oxidation to give mexicanolide.

EXTRACT FROM THE ROOT-BARK

Extractives from K. ivorensis root-bark may well provide the most chemically interesting series. At least eight compounds have been isolated, and all but methyl angolensate are obtained in very small yield and their structures have either not been determined or not confirmed. Methyl angolensate was readily identified from its spectral and physical properties. The three substances A, B, and C, obtained in sufficient quantity for useful information about their structural formulae are discussed.

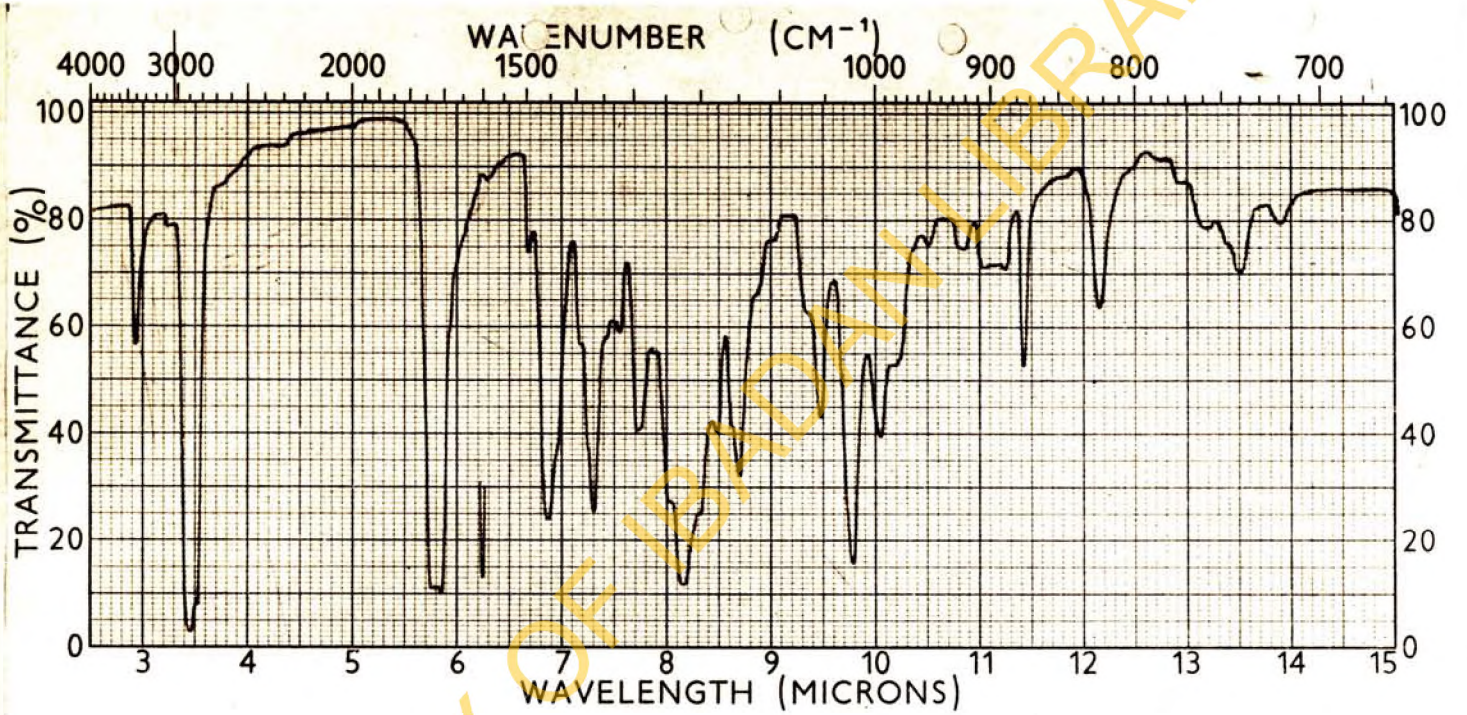
Substance A m.p. 196-198°, $[\alpha]_D$ - 123°; $\lambda_{max.}$ 219 mμ (ϵ = 9,000) has molecular weight 528. Elemental analysis and molecular weight

suggest the formula of A to be $C_{29}H_{37}O_9$. The i.r. spectrum suggests the presence of a hydroxyl group $\nu_{max.}$ 3560 cm^{-1} while the n.m.r. spectrum shows the hydroxyl group at δ 4.20 (disappears with D_2O), is not spin-coupled with any other proton. The latter observation is in agreement with the resistance of the hydroxyl group to oxidation by Jones reagent,[90] and to acetylation by acetic anhydride with p-toluene sulphonic acid.[77] The two reactions only take place under drastic conditions and then they do so with a rearrangement. Substance A therefore contains a tertiary hydroxyl group. Other functional groups shown by the n.m.r. spectrum are a β-substituted furan, a methoxycarbonyl, and an acetate. The absence of exocyclic methylene protons and the presence of four tertiary methyl groups suggest a bicyclomonanolide skeleton. Substance A undergoes ring-opening with methanolic sulphuric acid and must therefore contain a ring D δ-lactone. The one-proton signal at δ 5.10 must be the base proton of the acetoxyl group, and its singlet nature suggests that either there is no hydrogen atom on any adjacent carbon atom or, of there is, the dihedral angle between them must be about 90°. Using the assumption that the substance has mexicanolide skeleton, and bearing in mind the tertiary nature of the -OH, the singlet nature of the acetate, and the molecular formula, structure (LXIII) is

proposed for substance A. All the assignable peaks in the n.m.r. can be explained in terms of this structure. The hydroxyl group is put at C-2 because putting it in any other place would give rise to the familiar doublet (J = 10 c./sec.) of the 3β-esters as a result of the coupling between H-2 and H-3.

Prolonged treatment with p-toluene sulphonic acid and acetic anhydride in acetic acid (with boiling) gave an extra acetate at δ 2.13 with no base proton. The drastic condition under which the reaction was carried out suggests that this second acetate did not arise by direct acetylation. Acetylation of the hydroxyl group almost certainly took place after a rearrangement. This is supported by the low molecular mass M^+ 510, lower than that of the starting material. The hydroxyl group at C-2 can be abstracted in the acid medium with a tendency to form a double bond at C-2. This will be resisted in accordance to Bredt's rule[82] that double bonds are not formed at bridge-heads. A bond then breaks which may provide the driving force for the reaction that leads to the elimination of some part of the skeleton. It is interesting that this product (M^+ 510) occurs in the same root-bark as a natural product.

Oxidation of substance A under conditions more drastic than normal for Jones' reaction gave a gum whose ultraviolet absorption

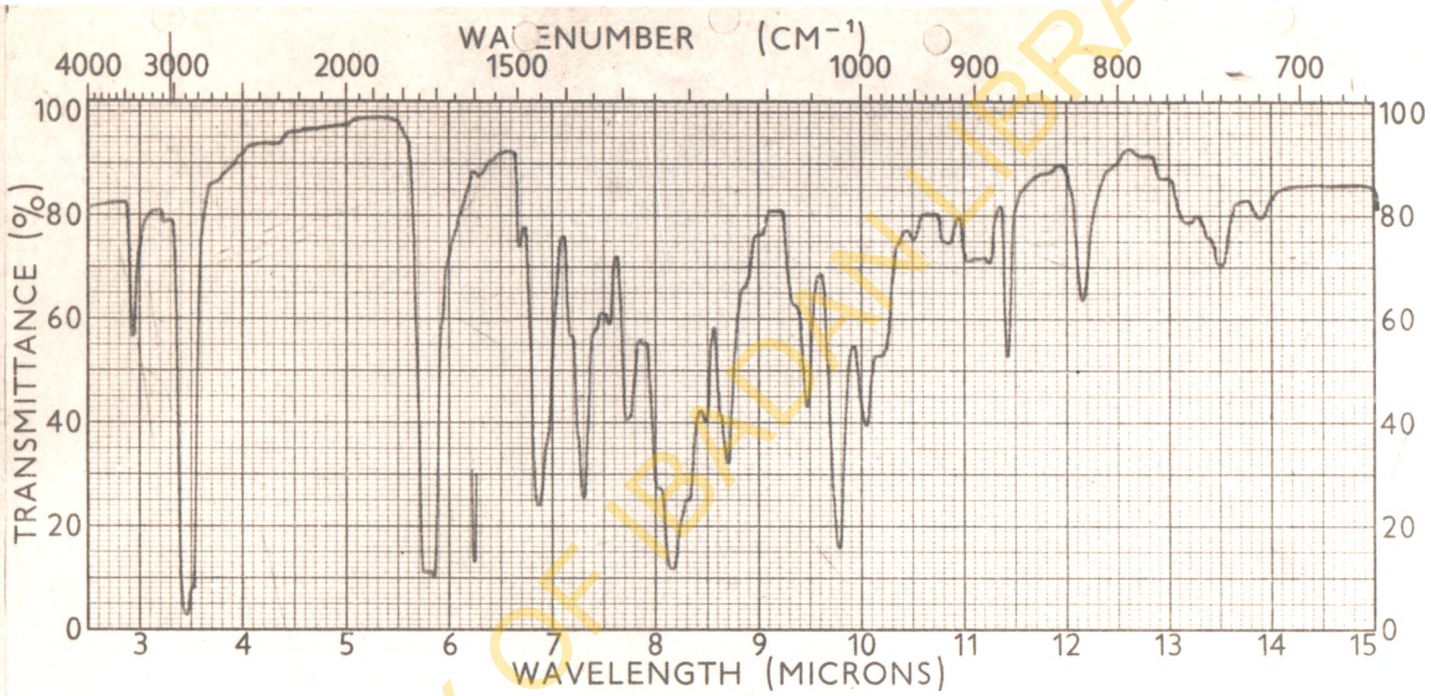


SAMPLE KIRB (26-28) recrom. [Eluted with Ether from B. ex Ether]	PHASE	SCAN SPEED 5 SLIT
	SOLVENT	OPERATOR DATE 4/1/67
	CONC.	REMARKS 0.69 g.
	CELL PATH	P. 11.
ORIGIN	REFERENCE	

NO. 4900

PART NO. 137E - 1281

PERKIN - ELMER LIMITED, BEACONSFIELD, BUCKS

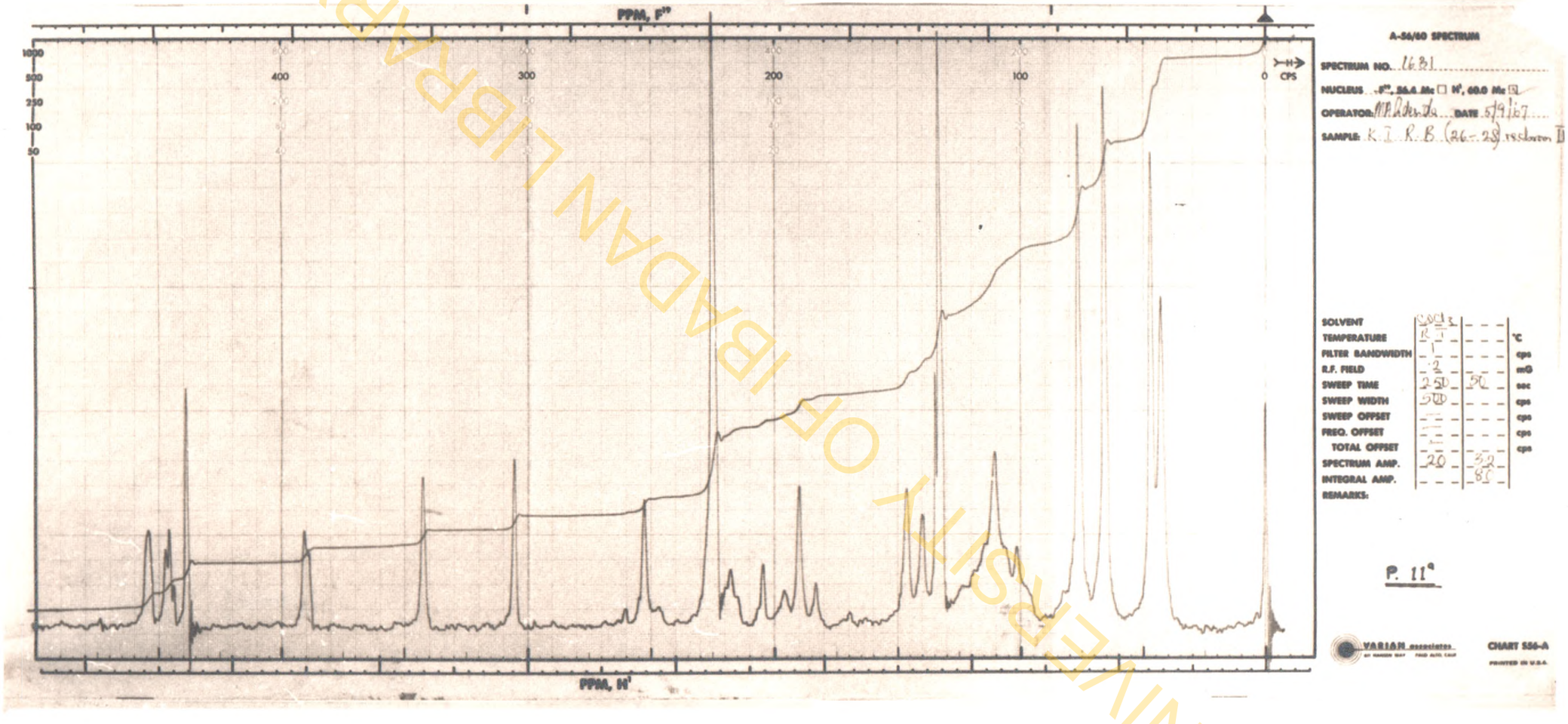


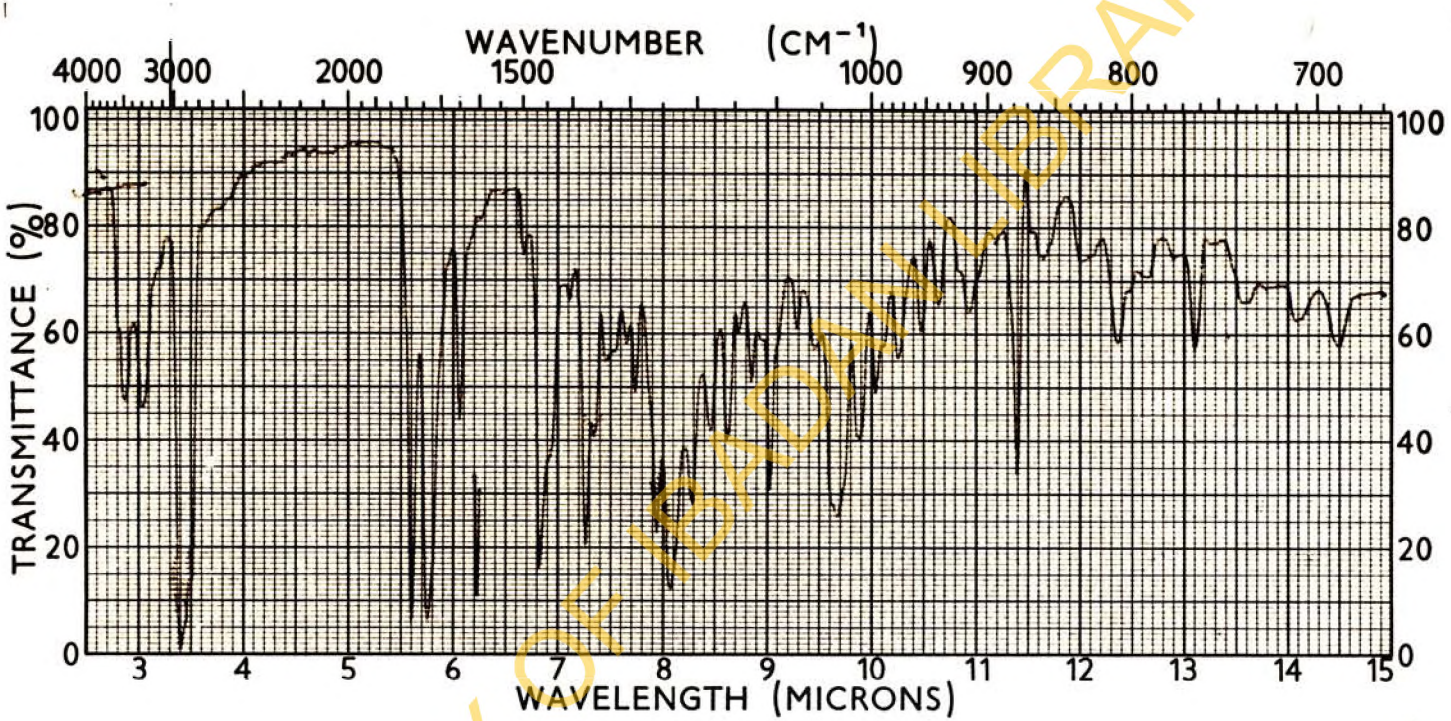
SAMPLE KIRB (26-28) rechrom. [Eluted with Ether fr. B. xtl's ex Ether]	PHASE	SCAN SPEED S SLIT
	SOLVENT	OPERATOR DATE 4/5/67
	CONC.	REMARKS 0.69g.
	CELL PATH	
ORIGIN	REFERENCE	P. 11.

PART NO. 137E - 1281

PERKIN - ELMER LIMITED, BEACONSFIELD, BUCKS

a09b





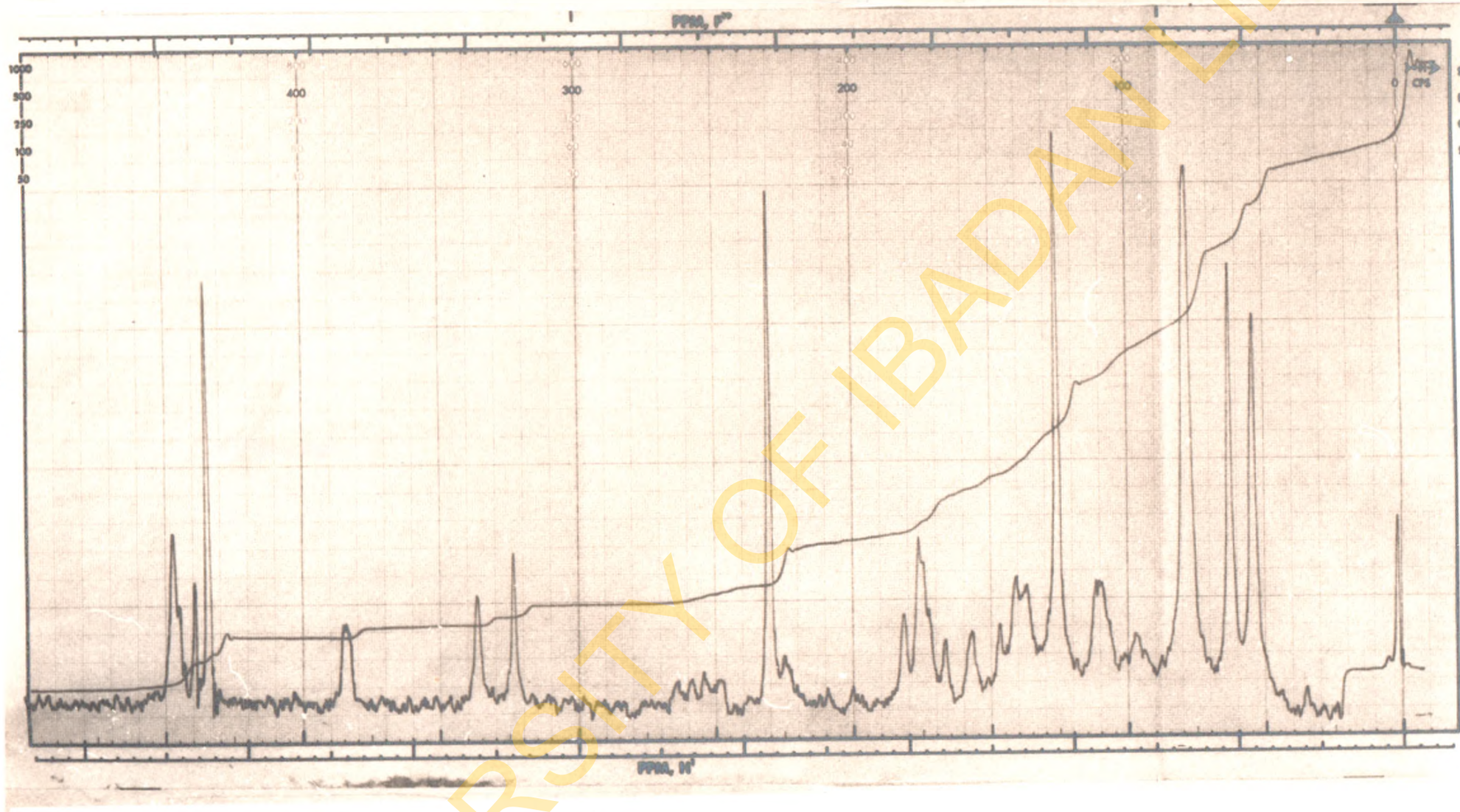
SAMPLE RICB (18) (6b)	PHASE N	SCAN SPEED ____ SLIT ____
	SOLVENT ____	OPERATOR ____ DATE 31/1/68
	CONC. ____	REMARKS ____
	CELL PATH ____	
ORIGIN ____	REFERENCE ____	P. 12

NO. 2587

PART NO. 137E - 1281

PERKIN - ELMER LIMITED, BEACONSFIELD, BUCKS

- 80c -



A-56/60 SPECTRUM

SPECTRUM NO. 1826

NUCLEUS [illegible] MHz ☐ H¹, 60.0 Mc ☑

OPERATOR: MAAdeide DATE 19/12/67

SAMPLE: K·I R B i Pr₂O (New)

m.p. 150 - 160°!

SOLVENT	$CDCl_3$			
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.	40	10		
INTEGRAL AMP.		40		

REMARKS:

P. 12ᵃ

VARIAN associates

CHART 556-A

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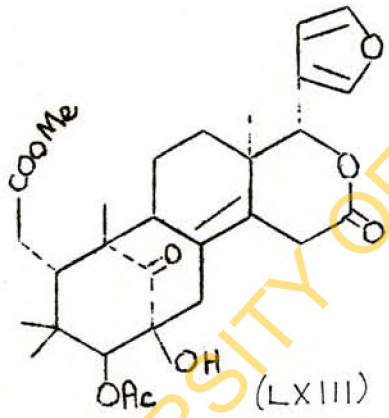
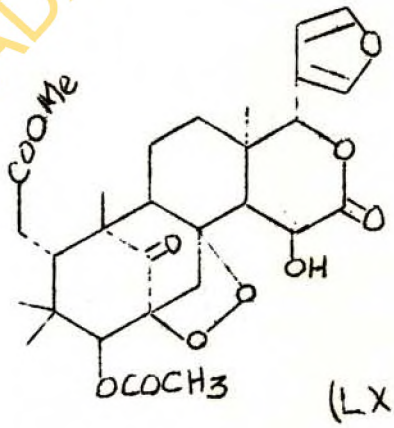
has $\lambda_{max.}$ 221 and 284 mμ (unaffected by sodium hydroxide), although the mass spectrum of the gum does not give a good molecular ion, it is clear that this is less than m/e 500.

The two reactions are understandable in the light of the structure proposed. It is hoped to isolate more of this substance, to confirm the structure and to find the rearranged products and the mode of transformations.



(LXIII)



(LXIV)

Substance B m.p. 150 - 160 and sharply at 172°, crystallises out with very great difficulty and only a very small amount of it has been obtained. The i.r. and the n.m.r. spectra show the presence of a β-substituted furan, an acetoxyl group, a methoxycarbonyl, and four tertiary methyls. A singlet proton at δ 5.57

is attributed to H-17 of the usual ring D-δ-lactone. Another singlet proton at δ 5.35 is assigned to the base proton of the acetate, which is therefore assumed to be in the same chemical environment as that in substance A: both substances A and B occur alongside each other and are therefore likely to be biogenetically closely related. A one proton quartet (doublet of a doublet) at ca. 4.1 - 4.4 p.p.m. collapses to a clean doublet δ 4.27 (J = 11 c./sec.) on addition of deuterium oxide. This suggests the presence of $>CH_{(a)}\cdot CH_{(x)}OH$ in the molecule, while the large coupling constant after addition of D_2O suggests an axial-axial interaction between H_a and H_x.

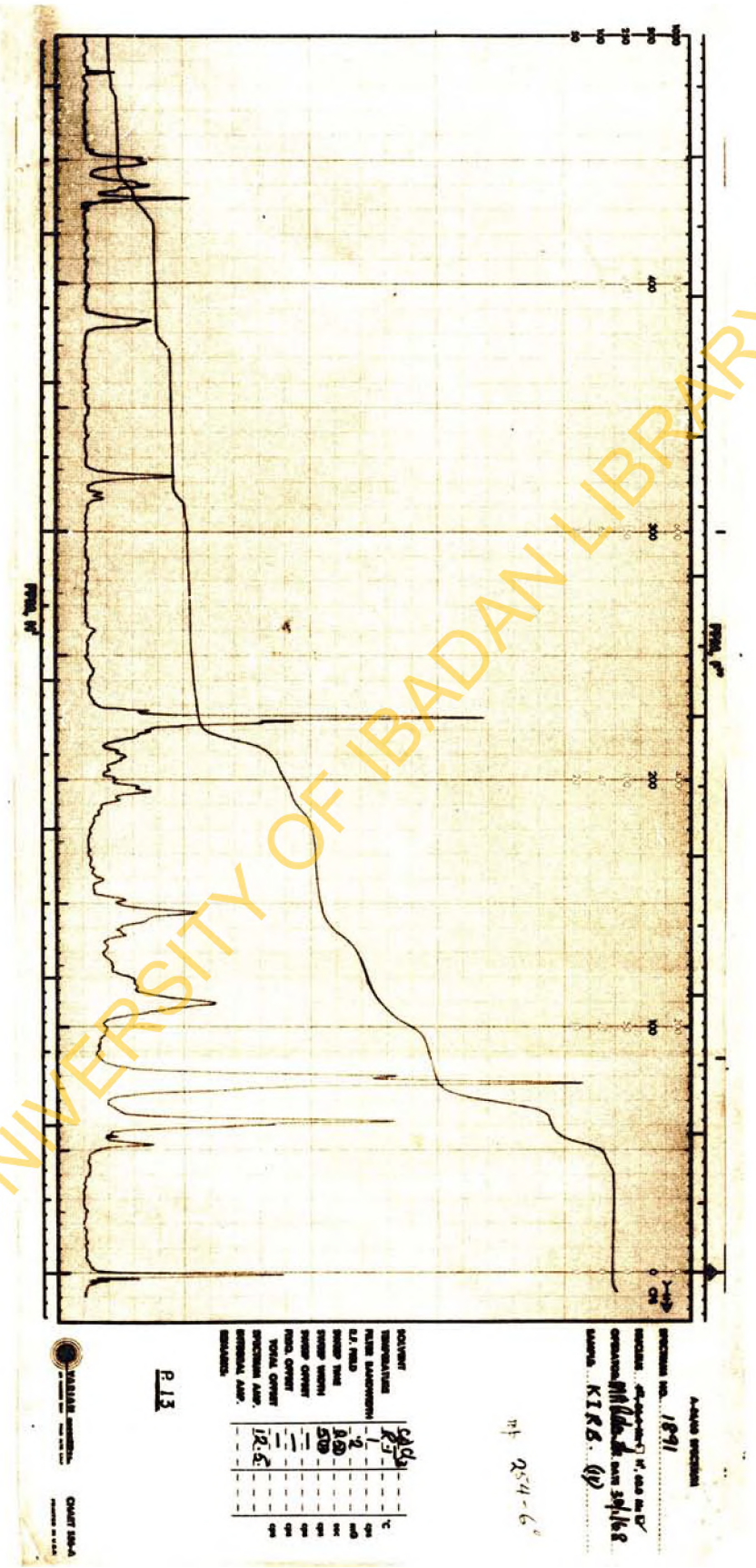
Molecular weight determination (M^+ 560) and elemental analysis agree with a molecular formula $C_{29}H_{36}O_{11}$ for substance B. The appearance of M-96 ion (see p. 103) is taken as evidence of a ring D-δ-lactone. The infra-red peak at $\nu_{max.}$ 1790 cm.$^{-1}$ that suggests a peroxide,[78] the difference of 32 mass units (= O-O or CH_4O) between substances A and B, and the foregoing deductions were combined to arrive at structure (LXIV) for substance B. The structure satisfactorily explains all the assignable peaks in the n.m.r. spectrum. The quartet nature of H-15 is not only explicable but its downfield position is also consistent with its position

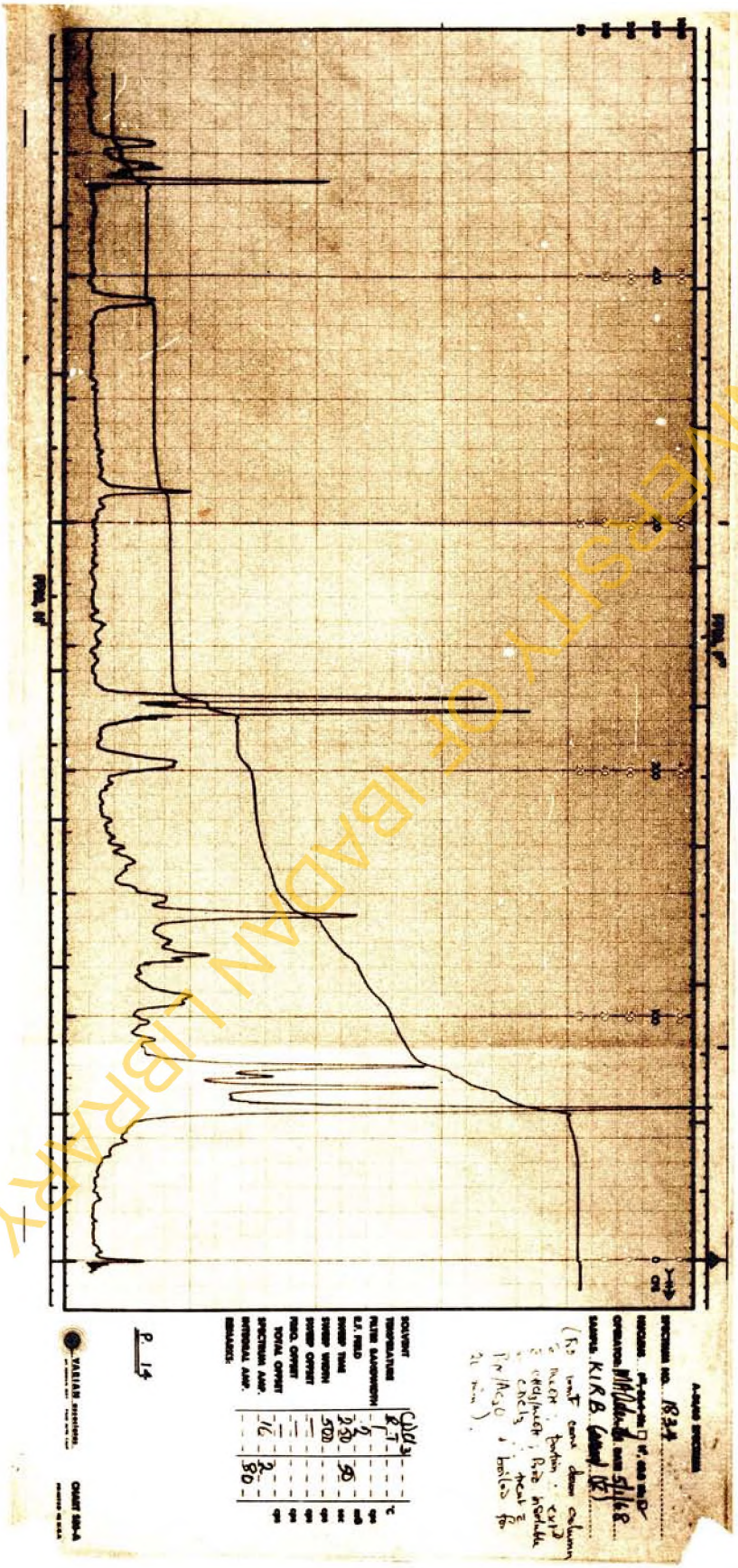
alpha to a lactone (c.f. methyl 6-hydroxyangolensate >CH OH alpha to an ester, at δ 4.41).

Moreover the structure explains why the substance does not undergo the usual rearrangement of the mexicanolide-type compounds on addition of alkali in a spectrophotometric cell. Even if H-15 can be abstracted by base, there is no 8,14-double bond to effect the transformation. Substance B is however not stable to alkaline hydrolysis that employs refluxing; the n.m.r. spectrum of the reaction product shows a complete break down of the nucleus. Cold hydrolysis technique[79] has been used with some success, but the n.m.r. of the reaction product was not clean enough to be interpretable especially in the methyl region. Treatment with methanolic sulphuric acid gave back the starting material. It is not known for sure whether the reaction will not go because the additional functional groups cause steric inhibition or whether conditions for the reactions need some modification.

Substance C crystallises nicely m.p. 230-235° but it is a mixture consisting mainly of mexicanolide. The other component has not been identified.

Other substances isolated of which there is very little information are summarised:





Three substances never come off an alumina column even with methanol. Extraction of a portion containing one of them gave a compound with two methoxycarbonyl groups. The second methoxycarbonyl could possibly arise by the opening of a ring D lactone.

Diisopropyl ether extract gave a glycoside which was not characterised; and methylated spirit extract gave a large quantity of a gum whose infra red spectrum suggests the presence of an aromatic compound.

Investigation into these outstanding substances is continuing.

EXTRACT FROM THE ROOT

The petroleum ether extract of K. ivorensis root on chromatography yielded khivorin and methylangolensate. These were readily characterised by their physical and spectral properties. T.l.c. showed the presence of minor constituents which are still to be isolated.

KHAYA ANTHOTHECA

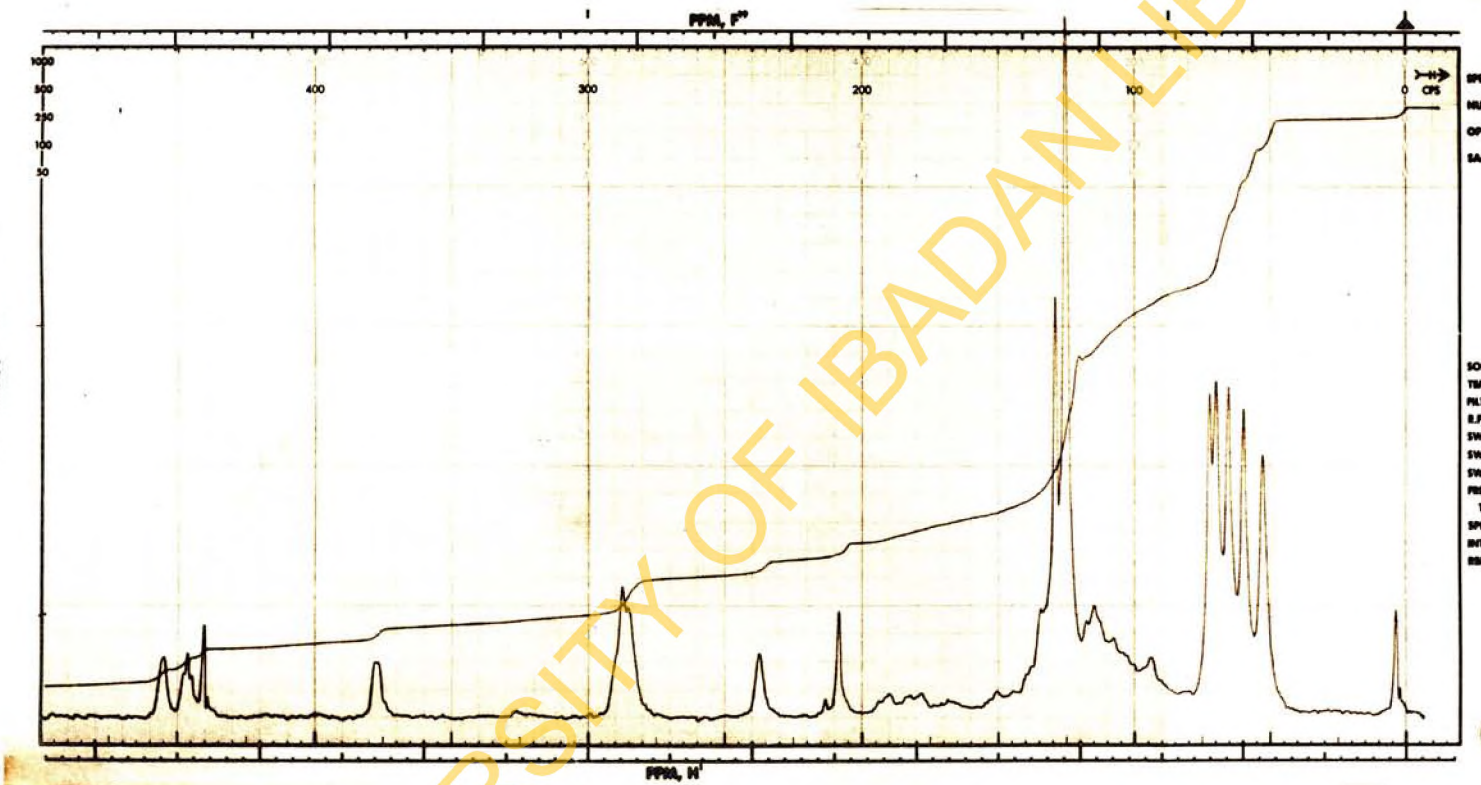
K. anthotheca (Welw.) C.DC. grows in the drier parts of the Forest Regions. It is a large tree capable of attaining a height of 180 ft. It does not appear to grow in Nigeria except near

Obubra. The root is said to be poisonous and the bark which is bitter is used as a febrifuge in Angola. The timber, which is not attacked by insects, is used for furniture and other similar work.

EXTRACT FROM THE SEED

A sample of K. anthotheca seed, kindly supplied by the Uganda Forestry Department in Siba C.F.R., Uganda, was extracted and chromatographed to give three crystalline products. Two of these were easily recognised as khivorin (LVIa) and 3-deacetylkhivorin (LVIg). The third compound M^+ 570, m.p. 215-217° $[\alpha]_D$ - 57° with a molecular formula $C_{32}H_{42}O_9$ is a new compound named khayanthone (= grandifolione acetate) (LXVIII). It has a very similar i.r. spectrum to khivorin. The presence of three acetoxyl groups (a six proton singlet at δ 2.01 and a three proton singlet at δ 2.08) with their base protons in a diffuse peak at ca. 4.81-4.64 and a β-furan as seen in the n.m.r. spectrum suggest the compound must be very similar to khivorin. The striking difference between the two is the absence of H_{17} at δ 5.58. This was taken as evidence for either a ring D-δ-lactone opened compound as in C.O.C., or a cyclic compound with no C-17 oxygen allylically placed to the furan. The two singlet protons at δ 3.40 and 3.89 were ascribed to

H-15 at the base of an epoxide ring, and H-17 respectively. The three acetates, the epoxide and the furan rings account for eight of the nine oxygen atoms. If the ninth oxygen is assumed to be a ketone at C-16 the position of H-15 is readily explained by analogy with khivorin where H-15 is at δ 3.55. The presence of an epoxide ring and its relationship to the ketone were confirmed by chromous chloride reduction to give a clean but non-crystalline compound whose $\lambda_{max.}$ at 237 mμ indicated the presence of an αβ-unsaturated ketone. The i.r. spectrum of this product at $\nu_{max.}$ 1570 $cm.^{-1}$ also indicate a C=C stretching frequency. The n.m.r. of the compound show the presence of the acetate groups, their base protons, β-furan protons, and H-17; all in about the same place as in the epoxy-compound. The conspicuous paramagnetic shift of H-15 from δ 3.40 in the epoxy-compound to 5.85 in the desoxy compound is consistent with changes in such a system as proposed in structures LXVIII and LXIX (c.f: Khivorin and deoxykhivorin the positions of H-15 being at δ 3.55 and 5.68 respectively). The absence of an ether signal e.g. -OMe in the n.m.r. spectrum was used to confirm a ketone at C-16. The monodeacetyl product of grandifolione acetate named grandifolione was isolated by Overton et al. from K. grandifoliola.[9] The prepared acetate was not obtained crystalline but the recorded spectral data



- 86a -

A-56/60 SPECTRUM

SPECTRUM NO. 1225

NUCLEUS F, [illegible] H, 60.0 Mc

OPERATOR: [illegible] DATE 2/12/67

SAMPLE: Khaya Anthotheca Seeds

213 - 5

Khayanthone

SOLVENT	$CDCl_3$		
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.	12.5	3.2	
INTEGRAL AMP.		40	

REMARKS:

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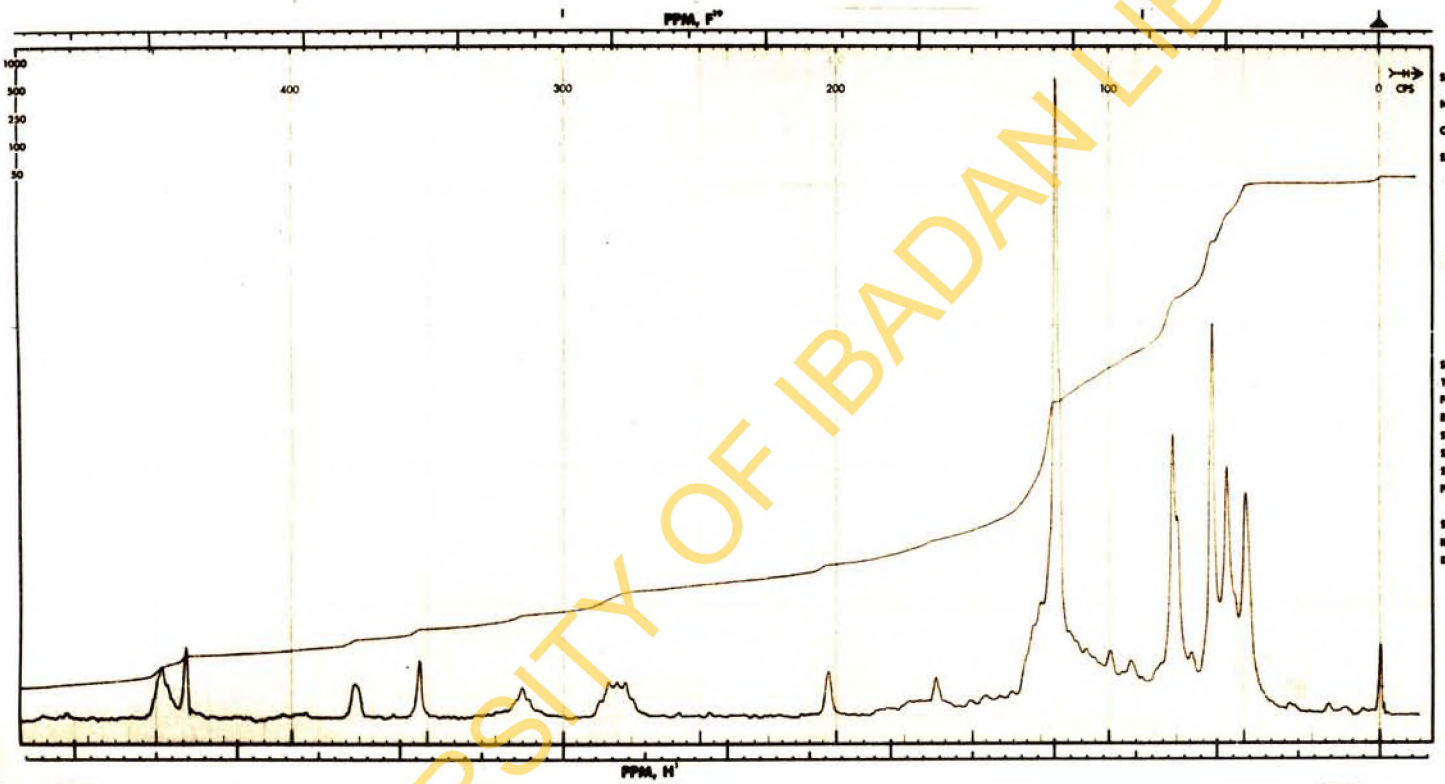
VARIAN associates

CHART 556-A

- 86b -



A-56/60 SPECTRUM

SPECTRUM NO. 1257

NUCLEUS F¹⁹, 56.4 Mc H¹, 60.0 Mc

OPERATOR: MPRabideau DATE 24/2/67.

SAMPLE: K. Anthocleista (A) + CCl_4

Deoxykhayanthone

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.		3·2	
INTEGRAL AMP.		4·0	

REMARKS:

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YARIAN associates

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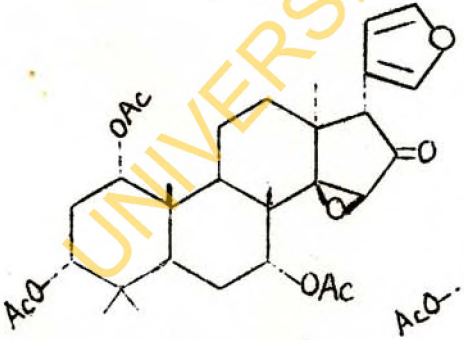
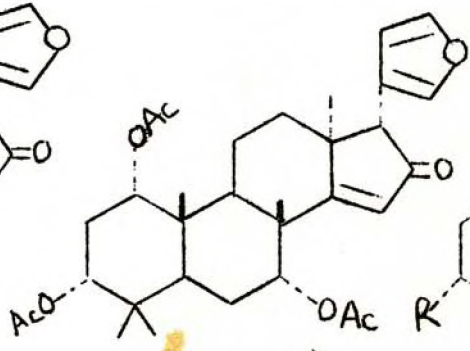
show exact identity with our natural acetate.

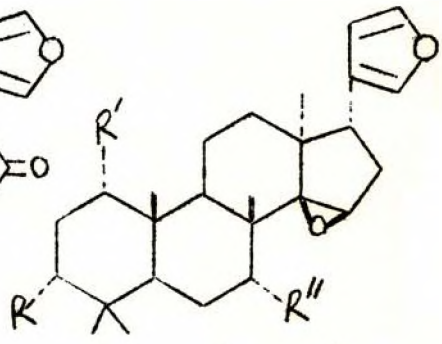
Khayanthone is the most primitive triterpene isolated during the course of this investigation. Baeyer-Villiger type oxidation will readily change the αβ-epoxycyclopentanone into a δ-lactone as in khivorin. It is interesting that Professor Taylor has got a series of the havanensins[80] (LXX) from another lot of K. anthotheca seed from Ghana. These are even more primitive than khayanthone. Anthothecol,[49] an extract from K. anthotheca timber has a five membered ring D. It is therefore primitive in the same sense that it has no ring D δ-lactone. It thus appears that K. anthotheca has fewer of the enzymes that effect a Baeyer-Villiger type oxidation than the other Khaya species examined.



(LXVIII)



(LXIX)



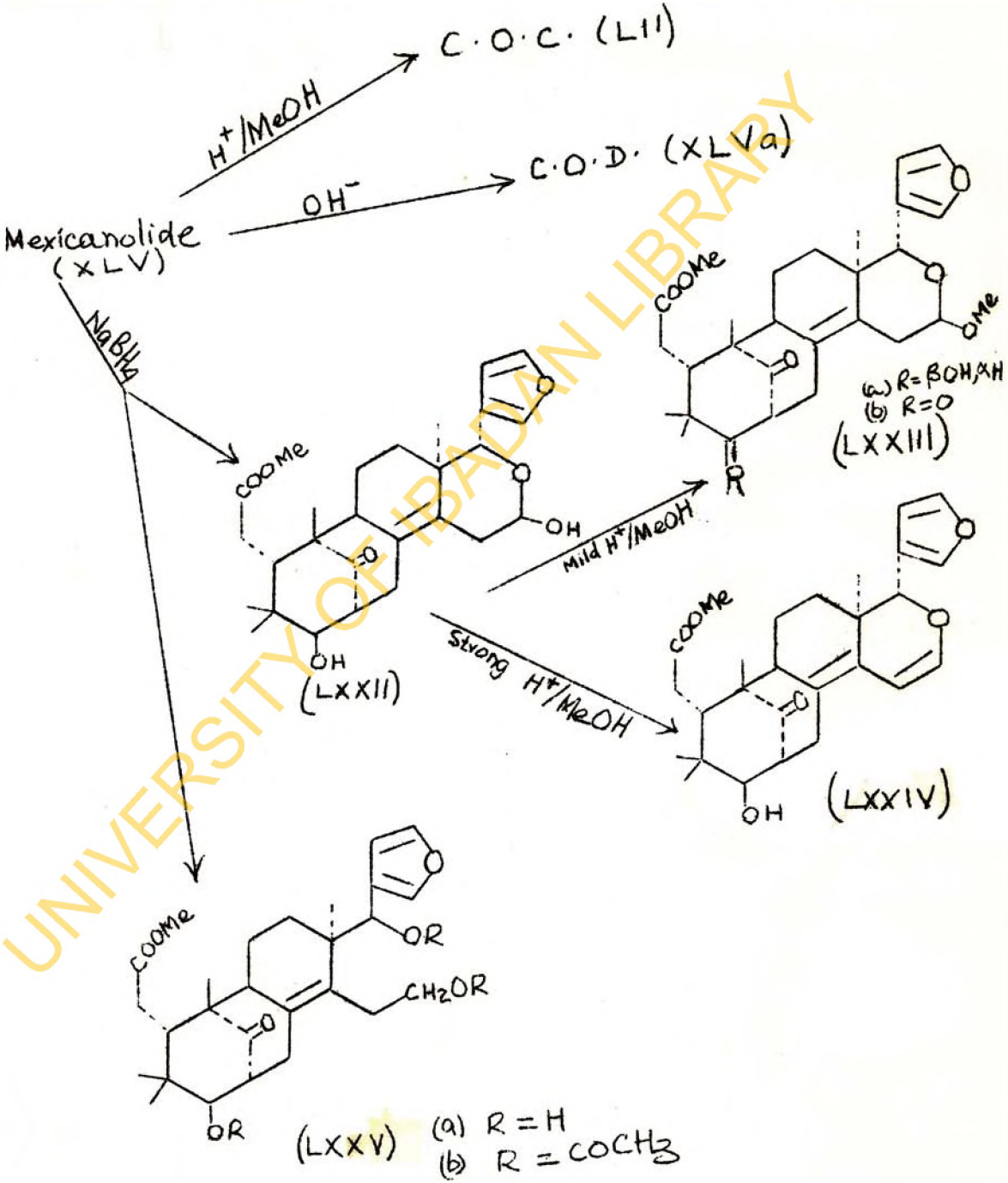
(LXX)

KHAYA NYASICA

The minced seed of K. nyasica Stapf. from Mingoli Forest Reserve (Zambia) was extracted and chromatographed. Three known compounds were isolated; khivorin, 3-deacetyl-khivorin and 6-deoxy-3β,12β-diacetoxyswietenolide. The wood of this species has been previously reported[81] to contain nyasin.

MEXICANOLIDE

Mexicanolide, (= C.O.B), occurs in most of the Khaya species and in Cedrela odorata. The latter was the first source from which the compound was explored in this department. All the reactions of mexicanolide described in this thesis have been carried on samples from the Cedrela odorata extract. Structure (XLV) has been ascribed to mexicanolide. The main reactions that led to the elucidation of its structure have already been summarised in the introduction. Some other reactions of the compound have been mentioned in verious places in the thesis, but the borohydride reduction is now discussed separately.



Connolly et al.[21] have been able to reduce mexicanolide with sodium borohydride to the 3β-alcohol (LXIb). Our reduction product was a mixture of six or more compounds (t.l.c.) from which we have been able to isolate two compounds A and B none of which was the 3β-alcohol. We have since learnt that they obtained this alcohol by working at a much lower temperature and over a shorter time.

The two compounds A and B have been ascribed structures (LXXII) and (LXXVa) respectively on the following evidence:

Compound A

The two peaks at $\nu_{max.}$ 3356 and 3236 cm.$^{-1}$ suggested the presence of at least two hydroxyl groups. The n.m.r. spectrum revealed essentially the same features as in mexicanolide, the presence of H-17 at δ 5.52 suggested that the C-17 oxygen was still in a closed ring. Careful examination of the n.m.r. spectrum revealed four very broad peaks at ca. δ 5.4, 5.0 and 4.4, 3.6; each peak integrating for one proton. The peaks at 5.0 and 4.4 disappeared on addition of deuterium oxide and were therefore regarded as the hydroxyl protons. At the same time the broad peak at δ 5.4 became narrower and the multiplet at 3.6 was replaced by a doublet (J = 10 c./sec.) surrounding the methoxycarbonyl group at δ 3.7. The latter was regarded as the axial base proton of a C-3 hydroxyl group. These

observations suggest that the two hydroxyl groupings are at C-3 and C-16, since the methoxycarbonyl group was intact and the cyclohexanone band in the infra-red would be impossible to account for with another -OH on C-1. Compound A was therefore formulated as (LXXII). Treatment of the hemiacetal A with mild acid in methanol lead to the addition of a molecule of methanol under the acid condition to form an acetal (LXXIIIa). The i.r. spectrum of the acetal still showed the presence of a hydroxyl group ($\nu_{max.}$ 3484 $cm.^{-1}$). But the n.m.r. showed an additional three-proton singlet at δ 3.41. It was rather far downfield for a methyl-ether; this is probably due to the influence of the geminal C-17 oxygen atom. The C-16 proton as would be expected, was not much affected. There was only a very little diamagnetic shift (due to the more shielding methyl now replacing the hydrogen atom) from ca. δ 5.0 to 4.9. It was still a multiplet as a result of the interaction with the C-15 protons but was better resolved because of the absence of the hydroxyl proton. Oxidation of (LXXIIIa) gave a β-diketone (LXXIIIb) in which the C-16 proton was almost completely resolved into an ABX triplet at ca. δ 4.9.

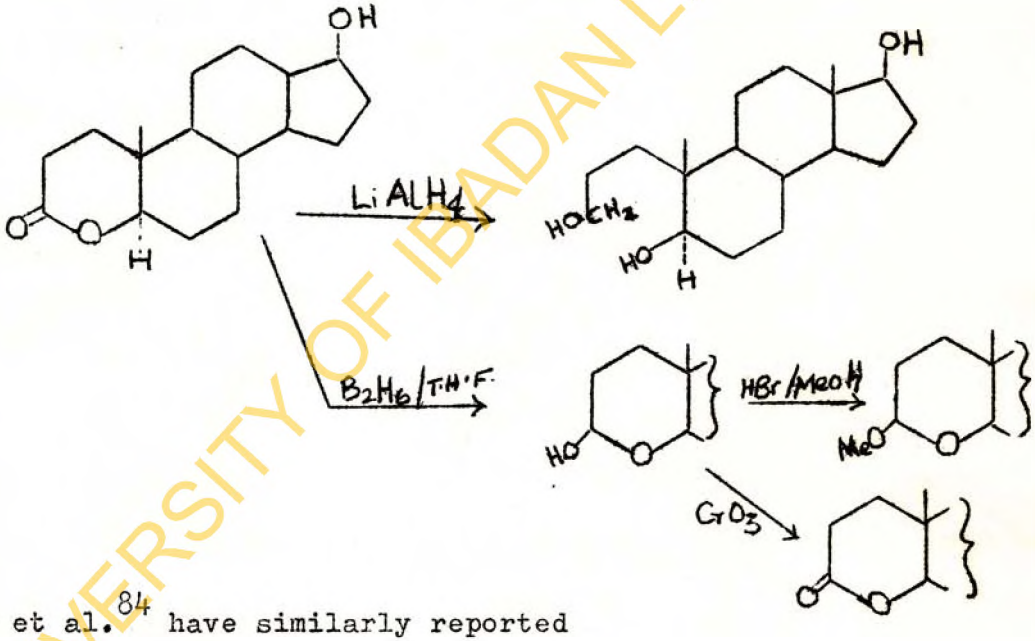
Further confirmation of structure (LXXII) for A came from subjecting A to stronger acid treatment. This led to the dehydration of the hemiacetal to form an $\alpha\beta$-unsaturated ether (LXXIV).

The product was recognised by its i.r. absorption at 1603 $cm.^{-1}$ (typical of C=C stretching frequency) and an intense absorption $\lambda_{max.}$ 263 mμ, ε = 15,400 in the u.v. spectrum which is typical of a conjugated system and will therefore explain the system >C:CH.CH:CH.O in (LXXIV). The presence of this system was confirmed by the n.m.r. spectrum which showed a pair of cleanly coupled vinyl protons at δ 6.67 and 5.72 (J = 6 c./sec.). These were the C-$\overset{15}{16}$ and C-16 protons respectively.

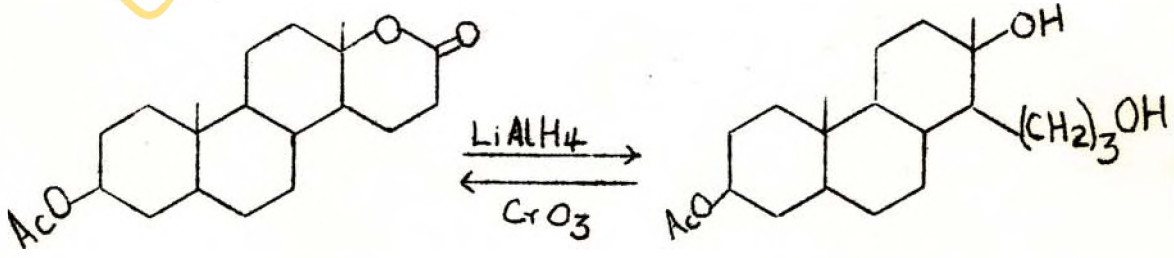
Compound B

Compound B was insoluble in any of the common solvents. An intense peak at 3356 $cm.^{-1}$ in the i.r. spectrum indicated the presence of a hydroxyl group while the sharp peaks at 1724 and 1250 $cm.^{-1}$ were indicative of an ester. Another sharp absorption at 1672 $cm.^{-1}$ suggested an unsaturated ketone but the n.m.r. spectrum of the acetylated product showed no vinyl protons. It however showed three acetates which must have come from three hydroxyl groups i.e. Compound B is trihydroxylic. On the ground that the methoxycarbonyl was intact and that the 1672 $cm.^{-1}$ was from a ketone (n.m.r. and i.r. spectra evidence), it follows that the three hydroxyl groups could only be at 3, 16 and 17 positions and Compound B must be (LXXVa) and the acetate (LXXVb).

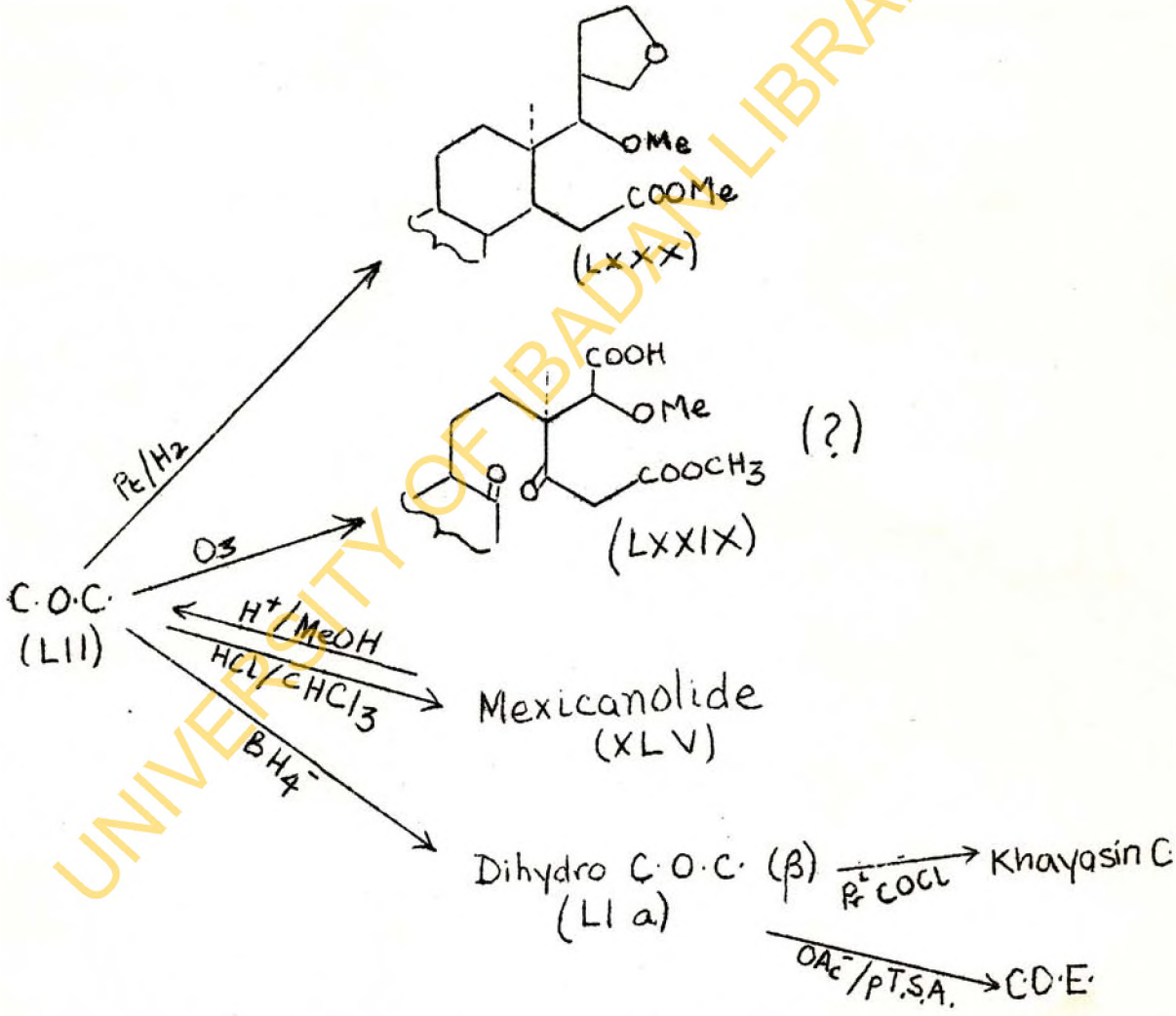
The behaviour of D-ring lactone in the reduction of mexicanolide to give compounds A and B is well known in the steroid field and therefore gives additional support for the assignment of these structures. In his work on the synthesis of oxasteroids, Pettit and Kasturi reported[83] the following:



Murray et al.[84] have similarly reported



We have also found that either B or A and in fact the mixture of the reduction products was readily oxidised to mexicanolide.



The main reactions carried out on C.O.C., itself a transformation product of mexicanolide, is summarised in the scheme above.

D I S C U S S I O N

During the course of this work, about thirty different compounds from the various Khaya species were isolated, less than ten of them have previously been characterised and reported. About fifteen of them are characterised and described for the first time while the structures of about five are either not yet known or are still awaiting confirmation. All the tetracyclic nor-triterpenes with known structures agree with the biogenesis proposed for them (see Introduction). It is interesting to note that whereas the only acyl group found in the khivorin type compounds is the acetoxyl group, the mexicanolide-type compounds are known to have the acetoxy-, the tigloyloxy- and the benzoyloxy- groups. 6-deoxybenzoyloxyswietenolide is the first limonoid triterpene with an aromatic side chain to be reported. Recently Fasina[85] has isolated a limonoid triterpene with a cinnamate side chain.

PHYTOCHEMISTRY

The distribution of the various compounds in the different Khaya species are shown in Table 1. The table only gives a rough basis for differentiating the various species because of the random

nature of the collections. However, the samples of the various species were not collected in the same area, neither were they from trees of about the same age.

The table shows that in general, in one tree, a given secondary metabolite can be found anywhere from the seed to the root. Although there is a great overlap it appears that the seed often contain biogenetically more primitive metabolites than the lower parts. Examination of K. senegalensis in particular shows that a khivorin-type nucleus is found in the wood and stem-bark, but it is absent in the root and root-bark. This shows that more primitive nuclei are more common as one goes up in the tree. However, the fact that isolation of all chemical constituents are not yet possible, and the fact that the opposite effect seems to be found in the seed and root of K. ivorensis show again that such broad generalisations can only be made with reservation. Most of the extractions were done with light petroleum alone; in order to get a broader spectrum of the chemical constituents present, it is envisaged that solvents of different polarity will be used.

Comparison of corresponding parts of different species again shows great overlap. The most obvious deduction therefore is that the grouping of these species under one genus is chemically valid.

Table 1.

SPECIES	SEED	WOOD	BARK	ROOT	ROOT-BARK
K. senegalensis	Khivorin 6-deacetoxy-7-oxo-khivorin 3-deacetylkhivorin 3-deacetyl-7-deacetoxy-7-oxokhivorin Methyl angolensate 3-destigloyl-6-deoxyswietenine 3-destigloyl-6-deoxyswietenine acetate	Khayasin 6-deoxyswietenolide tiglate 6-deoxyswietenolide benzoate Mexicanolide 7-deacetoxy-7-oxogedunin 7-deacetoxy-7-oxokhivorin Methyl angolensate methyl 6-hydroxy-angolensate methyl senegalensate 3-destigloyl-6-deoxy-3β,12β-acetoxy-swietenine	Methyl angolensate Methyl 6-hydroxy-angolensate 7-deacetoxy-7-oxokhivorin 7-deacetoxy-7-oxogedunin 3-destigloyl-6-deoxy-3β,12β-acetoxy-swietenine	Khayasin Methyl angolensate	Methyl angolensate Methyl 6-hydroxy-angolensate
K. grandifoliola	3-Dihydrocarapin methyl angolensate mexicanolide Dihydromexicanolide Grandifoliolin	Deoxyandirobin Mexicanolide Methyl angolensate	Methyl 6-hydroxy angolensate 20β-acetoxy-3-oxopregn-4-ene		Methyl angolensate Methyl 6-hydroxyangolensate 7-deacetoxy-7-oxokhivorin Deacetylgedunin
K. Ivorensis	Mexicanolide Dihydromexicanolide methyl angolensate	Khivorin 3 deacetykhivorin Methyl angolensate "Deoxykhayanthone"		Khivorin Methyl angolensate	Methyl angolensate mexicanolide "Substance A" "Substance B"
K. anthotheca	Khayathone Khivorin 3-deacetylkhivorin				
K. nyasica	3-deacetylkhivorin Khivorin 3-destigloyl-6-deoxy-3β,12β-acetoxyswietenine				

Moreover, the co-occurence of many of these compounds in the different species indicate that their biogenesis is the same and therefore emphasizes the phylogenetic relationship of the Khaya species.

It must be mentioned that contrary to previous ideas, we find that the sapwood of these species do contain secondary metabolites. While the heartwood of a particular K. senegalensis tree gave methyl angolensate and 7-ketokhivorin in large yield, the sapwood gave mexicanolide in comparable yield. However it is not yet determined how close to the heartwood, a sapwood must be to have a secondary metabolite, in other words it is still to be ascertained whether the secondary metabolites are formed during or before the transformation of sapwood into heartwood.

REACTIONS

The main reactions of these triterpenes can be broadly grouped into two:

1. Those involving the functional groups and side chains

In general all the functional groups behave as would be expected of them in their particular conformation. However, non-bonded

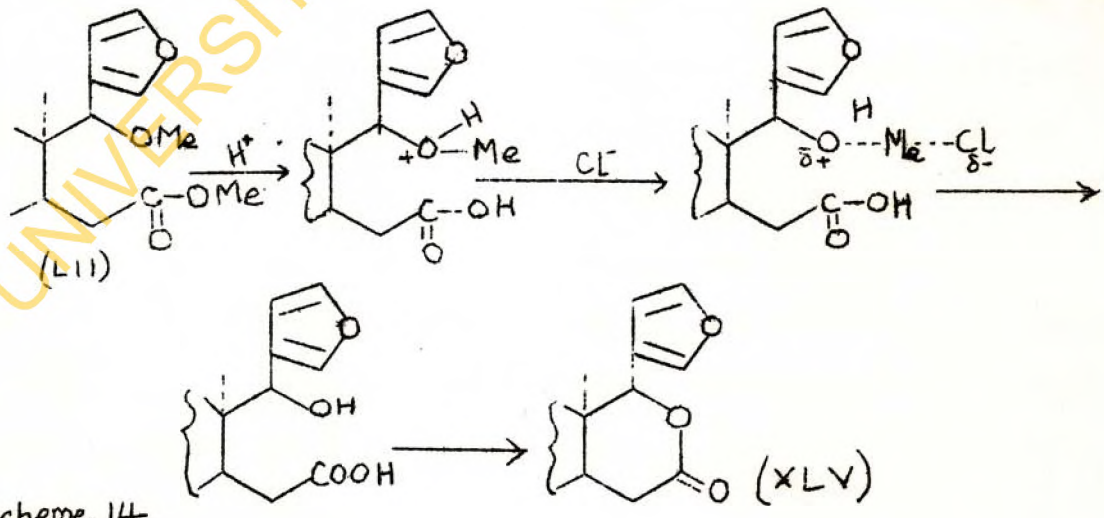
interactions as has been mentioned (see introduction) do result in some abnormal reactions.

2. Those involving the nucleus

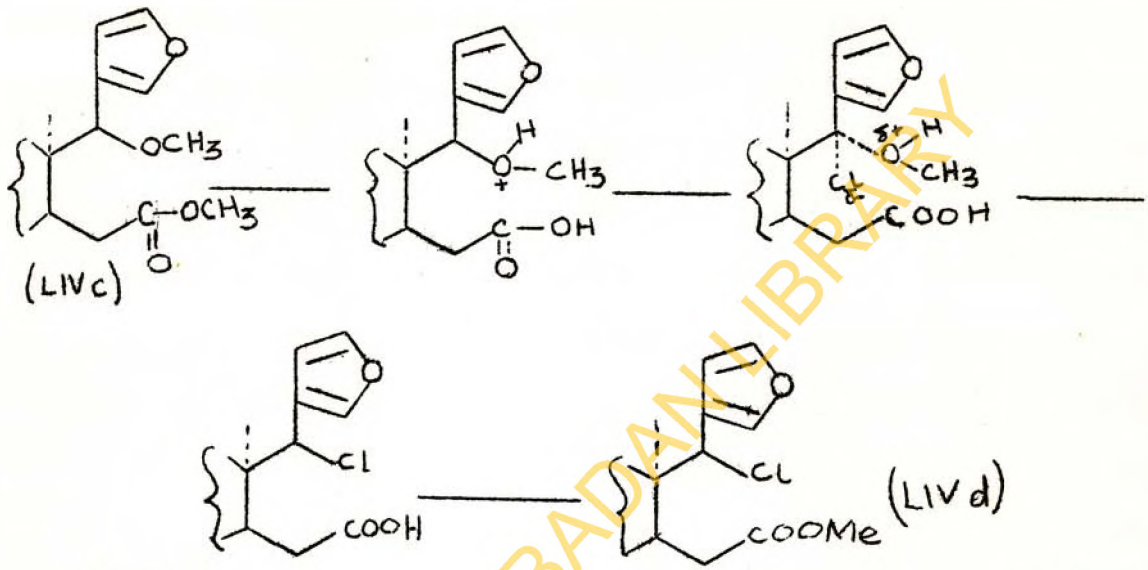
The khivorin nucleus is generally very stable. The 14,15-epoxide or double bond makes the ring D-δ-lactone stable to methanolic sulphuric acid treatment. However, ring B of this nucleus can be cleaved to give a ring B-seco compound on treatment with base,[42] while ring A will undergo ring contraction with PCl_5 as has been mentioned for gedunin.

The nuclei of the bicyclononanolides undergo three very interesting reactions. The $\Delta^{8,14}$-compounds readily undergo a ring D δ-lactone opening with methanolic sulphuric acid and a reversible ring closure with hydrochloric acid in chloroform. The mechanism of the former step has been discussed. The latter is almost certainly due to the protonation of the methoxycarbonyl group. The oxonium ion formed provides the driving force for the series of steps that lead to the ring closure as shown in scheme 14. It has been reported[18] that a $\Delta^{8,30}$-compound undergoes ring D-δ-lactone opening with methanolic hydrogen chloride although the reversible reaction was not recorded. The two reports show how solvents can alter the

course of chemical reactions. Ring closure is therefore probably the result of the fission of the methoxyl ether with the formation of methyl chloride and a C-17 hydroxy compound. (Cf. Zeisel method of estimation of methoxyl groups[91]). The steps leading to the δ-hydroxyacid, almost certainly by S_N2 mechanism is shown in scheme 14. The δ-hydroxyacid under the reaction conditions undergoes internal esterification to give the δ-lactone. It would be expected that a mixture of the C_{17}-OH and C_{17}-Cl compounds will be produced. While the former is produced with C.C.C. (with a 3-oxo), the latter is formed in khayasin C (3-isobutyrate). These reaction products support the mechanism suggested. The difference in reaction products is probably due to changes in the conformation at C-3 and the subsequent effect on the stereochemistry at C-17.



Scheme 14



In the ring opening either with hydrochloric acid or sulphuric acid, in methanol, the solvent is the nucleophile. Since chloroform cannot effect this nucleophilic attack, the lactone is not reversibly opened once it cyclises. The double bond makes the ring D of $\Delta^{14,15}$-compounds rigid and ring opening is resisted.

Both the $\Delta^{8,14}$- and $\Delta^{14,15}$-compounds undergo interesting transformations with base. This rearrangement which leads to the cleavage of the C_9-C_{10} bond has been described earlier.[18] The $\Delta^{8,30}$-compounds do not undergo this reaction because the double bond is too far away to conjugate with the anion at C-15 if it is formed.

A reaction common to all the bicyclononanolides is the

epimerization at C-3 on treatment with alkali and this has been discussed earlier (p. 40).

SPECTRA

N.m.r.

The n.m.r. spectra for all new compounds are reproduced while the n.m.r. data for all isolated compounds and their derivatives are given in Table 2. The significance of the peaks for each compound have been described in the appropriate places. It has been noted[86] that H-17 is one of the most characteristic features of the n.m.r. spectra of these triterpenoids. The general pattern remains the same namely:

1. The H-17 of compounds with a ring D-δ-lactone absorbs at low field, with the 14,15-double bond compounds absorbing at a slightly higher field than their 14,15-epoxy or 8,14-double bond compounds.

2. The H-17 of all the ring-D-opened compounds except those with chlorine at C-17 (subjected to the -I effect and therefore has great deshielding effect as opposed to +I effect of -OMe), absorb at higher field than the ring-closed counterparts. This is consistent with the change from an ester to an ether as mentioned

Table 2

Khayanthone, khivorin, gedunin, and methyl angolensate (δ values)

No.	Compound		H-1	H-3	H-7(1-12) or C_{13}-H(13-16)	H-15	H-17	$-CO_2Me$	-OAc	β-furan	α-furan	Methyl Groups
1.	Khayanthone (LXVIII)		(4.81 - 4.65 d.p.)			3.40	3.89		2.08 2.01(2)	6.23	7.38 7.53	1.13, 1.10, 1.03, 0.94, 0.82
2.	(1) + $CrCl_3$		4.78-4.57dp.		5.25$_t$	5.88	3.89		2.00(3)	6.28	7.43(2)	1.28, 1.03(2), 0.94, 0.82
3.	Khivorin (XXI)		ca. 4.75 - 4.5 d.p.			3.51	5.58		2.02(2) 2.12	6.30	7.38(2)	1.25, 1.10, 1.02, 0.92, 0.81
4.	7-deacetoxy-7-oxokhivorin		ca. 4.75 d.p.			3.63	5.43		1.95 2.00	6.33	7.37 7.39	1.25, 1.10, 1.02, 0.92, 0.81
5.	3-deacetylkhivorin		4.78 J°=5.4	3.38 J°=8.2	4.52 J°=4.0	3.51	5.58		2.01 2.12	6.30	7.38(2)	1.21, 1.07, 1.00, 0.88, 0.83
6.	1,3-dideacetyl-khivorin		3.4-3.65 d.p.		4.50	3.50	5.58		2.18	6.31	7.35 7.38	1.28, 1.25, 1.08, 0.92, 0.83
7.	Trideacetylkhivorin (D.M.S.O. solvent)					3.82	5.48			6.46	7.65(2)	1.11, 0.85, 0.78, 0.75, 0.70
8.	3-deacetoxy-3-oxo-khivorin		5.05 J°=6.0		4.53 J°=5.0	3.51	5.58		2.01 2.12	6.30	7.38(2)	1.20(2), 1.15, 1.05(2)
9.	Gedunin (8 + H^+) (XXVIII)		7.07 d J = 10	5.81d. J = 10	4.5m	3.50	5.51		2.07	6.30	7.37(2)	1.23, 1.20, 1.13, 1.04(2)
10.	Deacetylgedunin	OH 2.65	7.12d. J = 10	5.84d. J = 10	3.59m	3.97	5.60			6.39	7.39(2)	1.27, 1.24, 1.17, 1.12(2)
11.	7-deacetoxy-7-oxo-gedunin		7.09d. J = 10	5.88d. J = 10		3.85	5.44			6.34	7.45(2)	1.35, 1.22, 1.14(3)
12.	3-deacetyl of (4)		4.93	3.47		3.78	5.43		2.01	6.32	7.37 7.39	1.15(3), 1.01, 0.93
13.	Methyl angolensate (XXXVI)	$>C=CH_2$ 4.88 5.12	3.48dd			3.65	3.71			6.36	7.38(2)	1.20, 1.05, 0.95, 0.86
14.	Methyl 6-hydroxy-angolensate	$>C=CH_2$ 4.91 5.22					5.61	3.83		6.34	7.39(2)	1.47, 1.41, 1.06, 0.89
15.	(14) + OAc^-	$>C=CH_2$ 4.90 5.17				47	5.61	3.77		6.36	7.38(2)	1.47, 1.12(2), 0.88
16.	Deoxyandirobin (LX)	$>C=CH_2$ 5.15 5.53 J=2	H_6: 5.92d. J=10.5			6.03	5.15	3.71		6.40	7.43(2)	1.13, 1.11(2), 1.01

Mexicanolide and cuietenine (δ values)

No.	Compound		H-3	Hm45	H-17	-OAc	$-CO_2Me$	-O.CO.R	β-furan	α-furan		Methyl Groups
17.	Mexicanolide (XLV)			3.5m	4.27		3.73		6.48	7.38 7.57		1.27, 1.02(2), 0.88
18.	Compound A of (17) (LXIII) (LXII)	C_{14}-OH ca.4.5dp	ca.3.5		5.53		3.82		6.39	7.50(2)	H-16,5.39m C_{14}-OH,5-1dp	1.10, 1.05, 0.80, 0.71
19.	(18) + 0.6S H^+				5.43	3.42	3.70		6.45	7.40(2)	H-16,4.92m.	1.12(2), 0.87, 0.77
20.	(18) + 90S H^+			6.67 J=6	4.97		3.70		6.48	7.35 7.52	H-16,5.72 J = 6	1.15, 1.05, 0.82, 0.75
21.	C.O.D. (XLVa)	H_9,5.93m		5.93m	5.10		3.70		6.41	7.43(2)		1.28, 1.18, 1.05, 1.00
22.	C.O.D. acetate	H_9,5.90m			5.10		3.71	Me,2.23	6.43	7.43(2)		1.18, 1.10(2), 1.01
23.	C.O.C. (LII)				4.45	3.22	3.57 3.68		6.37	7.30 7.42		1.23, 1.08, 0.93, 0.89
24.	3-ol of (23)				4.65	3.22	3.58 3.69		6.48	7.47(2)		1.10, 1.03, 0.97, 0.81
25.	3β-ol of (23)						4.62	3.23	3.58 3.65		6.53	7.45		1.13, 1.00, 0.93, 0.77
26.	C.O.C. + H_2/Pt.							3.50	3.70 3.73					1.27, 1.10, 0.96, 0.92
27.	C.O.E. (LXXVII)					3.97d J=5.5	2.78		3.62 3.68		6.38d	7.43d J = 2		1.08, 0.92, 0.90, 0.62
28.	3β-dihydromexicanolide						5.62		3.70		6.52	7.42 7.58		1.13, 1.03, 0.82, 0.72
29.	Grandifoliolin (LXIa)					5.03d J=10	5.74		3.75	Me,2.20	6.52	7.45 7.60		1.17, 1.08, 0.82, 0.73
30.	(29) + H^+/MeOH					4.82d J=10	4.76	3.22	3.58 3.68	Me,2.18	6.63	7.52 7.68		1.15, 1.07, 0.83(2)
31.	3β-dihydrocarapin (LXII)						5.12		3.75		6.48	7.47 7.55		1.08, 1.05, 0.94, 0.73
32.	Khayasin (L)					4.95d J=10	5.67		3.70		6.47	7.38 7.53		N. A.
33.	Khayasin C					4.83d J=10	4.67	3.17	3.53 3.65		6.55	7.45 7.62		N. A.
34.	(32) + HCl					4.86 J=10	5.69		3.57 3.70		6.70	7.45 7.69		N. A.
35.	The benzoate (LIIIa)					5.11 J=10	5.58		3.80		6.51	N.A.	7H-2o-furan and 5 benz. H	1.22, 0.96, 0.90(2)
36.	The benzoate C					5.03 J=10	4.58	3.17	3.43 3.70		6.50	N.A.	"	1.17, 0.97(2), 0.88
37.	The tiglate (LIIIb)	>C=C-H 6.97m.				4.83 J=10	5.56		3.74	1.89m(3H) 1.85d(3H) J = 7	6.50	7.41 7.57		1.17, 1.03, 0.83, 0.80
38.	6-deoxydestigloy-cuietenine	H_{30},3.70m J = 9					5.70		3.70		6.46	7.37 7.72	OH, 3.48	1.13, 1.09, 0.83, 0.73
39.	3-iso of (38)	H_{30},5.86m J = 7	3.83				5.67		[illegible]3		6.48	7.75(2)	OH,2.62	1.15, 1.10, 0.91, 0.72
40.	(38) acetate (LVIIb)	H_{30},5.35m J = 7	4.74 J=9.5				5.71		[illegible]	2.09	6.48	7.40 7.78		1.15, 1.09, 0.82(2)
41.	3-iso of (40)	H_{30},5.95m J = 7	4.68				5.63		[illegible]		[illegible]5	7.38 7.70		1.15, 1.10, 0.85, 0.80
42.	12β-acetate of (40)		4.79 J=9.5				5.65		[illegible]		[illegible]62	7.43 7.82	H_{30}& H-COAc ca5.72-5.40	1.28, 1.01, 0.8(2)
43.	Substance A (LXIII)	OH 4.20				3.25(?)	5.72		[illegible]			7.43 7.57	H.C.OAc 5.10$_s$	1.28, 1.10, 0.72
44.	(43) + H^+/MeOH	OH 4.12					4.69	3.20	[illegible]			7.43 7.58	H.COAc 5.13$_s$	1.25, 1.08, 0.81(2)
45.	(43) + OAc^- (H^+)						5.72		3.[illegible]	2.2[illegible]	6.45	7.38 7.52	H.C.OAc 5.52$_s$	1.25, 1.10, 0.97, 0.72
46.	Substance B (LXIV)					ca.4.1-4.4dd.	5.57		3.80	[illegible]0	6.37	7.40(2)	H.C. OAc 5.35$_s$	1.2(2), 1.02, 0.88
47.	(46) + cold OH^-						5.58		3.83		6.35	7.66(2)		N. A.
48.							5.67		3.72	2.20	6.43	7.40 7.50	H.C.OAc 5.06	1.25, 1.08, 0.77, 0.70

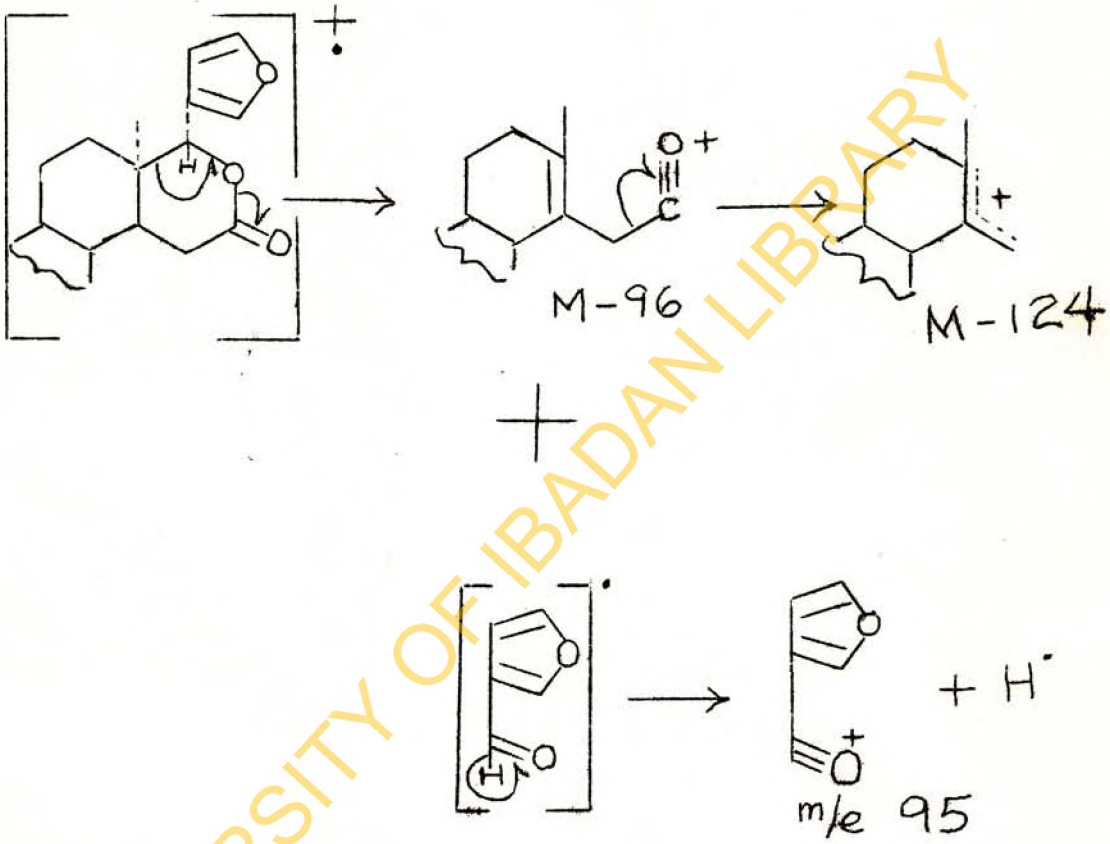
Abbreviations : s = singlet; d = doublet; dd = doublet of doublets; m = multiplet.
dp = diffuse peak; N.A. = [illegible] assigned; $J^\circ = J_{AX} + J_{BX}$ for an ABX system.
J in c./sec.

earlier. In khayanthone with no α-oxygen to the H-17, the signal is further upfield than it is in any of these compounds containing an oxygen atom allylically placed with the furan.

Mass Spectra

Throughout this work the mass spectrophotometer was only used as a means of obtaining molecular mass. However certain fragmentation patterns are observed which are characteristic of this group of compounds. Most of them give prominent peaks at M-96 and M-124. When both occur, the latter is usually the stronger of the two peaks. However in a few compounds these peaks are absent and in these cases it is the m/e 95 ions (usually m/e 123 is not conspicuous) that show up prominently. Without exception, all the compounds with ring D δ-lactone either give M-96, M-124 or m/e 95 peak. In a number of cases all these peaks are observed. Fragmentations within the molecule leading to the production of these ions are summarised in scheme 15. This observation has been useful in the structural determination of at least two substances, khayanthone (absence of these peaks) and the diacetoxy-compound of destigloylswietenine.

Scheme 15



Mass spectra also played an important role in the confirmation of the structures of the tiglate, and the benzoate of 3-dihydromexicanolide. In each case the molecular ion minus part of whole of these ester groups gave the base peak in the respective spectrum.

A detailed account of the mass spectra of gedunin and its derivatives has been published.[87]

Ultraviolet

The u.v. spectra of all the compounds show that all of them have an absorption in the region $\lambda_{max.}$ 208-215, and this is attributed to the β-substituted furan. U.v. spectra were useful in confirming the structure of 3-deacetylkhivorin: the oxidation product of the 1,3-dideacetyl compound has the characteristic absorption of a β-diketone.

Infrared

This was the most commonly used and has been particularly useful in revealing non-furanoid compounds with which we are not principally concerned.

BIOGENETIC AND PHARMACOLOGICAL APPLICATIONS

1. The compounds isolated and characterised have strengthened the proposed biogenesis of these compounds. Some novel compounds and novel reactions were also described. In addition, it is possible to predict the existence of some hitherto unisolated natural products. For example we have isolated three isomeric monoalcohols with the double bond in the 8-30, 8-14, and 14-15 positions; two

isomeric acetates ($\Delta^{8,14}$-and $\Delta^{8,30}$-) and two isomeric diketones ($\Delta^{8,14}$-and $\Delta^{14,15}$-) in the bicyclononanolide series. It is therefore reasonable to predict that the third isomeric diketone ($\Delta^{8,30}$-) and the third isomeric acetate ($\Delta^{14,15}$) are natural products still to be isolated. Recently the isolation of this third isomeric acetate (3-deoxo-3β-acetoxy carapin) was reported.[88]

2. All these compounds are insoluble in water and have therefore not been particularly attractive to pharmacologists. Several of them have been tested and shown to be physiologically inactive. The test on methyl angolensate shows it to be analgesic at low dose levels (in mice) while mexicanolide is shown to be antidiabetic. Work is going on in the department to increase the activity of the latter compound.

The isolation of the new steroid hormone 20β-acetoxy-3-oxopregn-4-ene, a progesterone derivation is significant although no pharmacological tests have yet been carried out on it to determine its activity. The fact that it is a product of plant metabolism is not only interesting but it means that commercial exploitation would be relatively easy should it turn out to be medicinally useful.

COMMENT

Because of the overlap of the chemical constituents known so far in the various Khaya species, it is not possible now to make a generalisation that will be of any great taxonomic significance. Moreover, some compounds isolated from one tree are not obtained from another tree of the same species. Apart from seeds which come at a definite and about the same time of the year, collections of various parts of trees were made any time they were required.

However, the results of this work supports the classification of the various Khaya species under one group - the genus Khaya. For a more far-reaching generalisation of chemotaxonomic importance, future work on the genus must be directed at solving problems arising from seasonal variation, age differences, chance isolation, climatic conditions, and the kinds of solvents employed for extraction.

On the other hand, other chemical constituents like the steroids, or the glycosides etc., rather than the tetracyclicnor-terpenes, may in fact provide the satisfactory basis for such a classification.

The immediate relevance of this work is neither chemotaxonomic nor does it lie in the potential medicinal value of the chemical constituents isolated; it is in the chemistry of those constituents.

EXPERIMENTAL

All melting points were taken on a hot-stage microscope, and are uncorrected. Infrared spectra quoted are for Nujol mull unless otherwise stated, and were taken on a Perkin-Elmer model 137 instrument. Ultraviolet spectra were taken, in methanol solution, on a Perkin-Elmer model 137 UV, or Unicam S.P. 700, instrument. Nuclear magnetic resonance (n.m.r.) spectra were taken on a Varian A 56/60 Mc./sec. spectrophotometer, in deutrochloroform solution, unless otherwise stated, against tetramethylsilane as internal standard. N.m.r. absorptions are quoted in δ units. Optical rotations were taken on Hilger standard polarimeter, or Perkin-Elmer model 141 instrument, in chloroform solution. Mass spectra were taken on a Hitachi Perkin-Elmer R.M.U.-6E instrument.

"Deactivated alumina" refers to Peter Spence type H, shaken with 5% by volume of 10% acetic acid. Silica gel refers to Merck or MN (Machery, Nagel and Co.), mesh 0.05 mm. - 0.2 mm.

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

Thin plate chromatograms (t.l.c.) were run on plates made by spreading an aqueous slurry of Merk Silica gel G on glass plates, and drying the plates at 120° for 1 hour. The chromatoplates were developed in one of the following solvent mixtures; chloroform-

diisopropyl ether (1:1); chloroform-methanol (10:1); and benzene-ethyl acetate (5:3). Spots showing the positions of the compent compounds in a sample were detected by leaving the developed plates in a tank of iodine vapour for about five minutes.

The first stage in the extraction of wood and bark is to percolate hot solvent through chopped wood, or bark, in aspirators continuously for about 20 hr. The resulting solution was concentrated to give the crude extracts. These initial stages were carried out by Mr. George Adesida in this department.

(I) Extractives From the Timber Khaya Senegalensis

(A) First Extract

The crude light-petroleum extract (50 g.) that had been standing for some years was dissolved in benzene (80 ml.) and chromatographed on deactivated alumina (1.5 l.). Elution with 25% benzene-light petroleum yielded a new compound, khayasin (L) (ca. 5% of the total extract), while elution with 100% methanol yielded the known 7-deacetyl-7-oxokhivorin (LVIc), m.p. 225°, previously characterized. Recrystallisation of the former from benzene gave crystals (2.48 g.), m.p. 114-116°; $[\alpha]_D^{25}$ - 165° $\lambda_{max.}$ 209 mμ, ε = 12,500 (furan). $\nu_{max.}$ 1738 (ester or lactone);

1700 (ketone); 1500, 875 cm.$^{-1}$ (furan). (Found: C, 72.0; H, 7.6. $C_{31}H_{40}O_8 \cdot C_6H_6$ requires C, 71.8, 7.5%).

The presence of benzene of crystallisation was confirmed by spectral evidence (infrared, n.m.r. and mass spectra.) Recrystallisation from methylated spirit lowered the melting point (87-90°) and resulted in the benzene of crystallisation being replaced by ethanol.

Mild Hydrolysis of Khayasin (L)

Khayasin (0.36 g.) in methanol (40 ml.) was treated with 2N-sodium hydroxide (3 ml.) under reflux, for 10 min. (The solution immediately turned pale yellow on adding the alkali). After cooling, water (40 ml.) was added, the solution acidified (dil. sulphuric acid) and the product extracted with chloroform (3 x 20 ml.). Washing and evaporation yielded a gum, which would not crystallise in any of the common solvents.

$\lambda_{max.}$ 214 (furan); 230 sh. ($\alpha\beta$-unsaturated carbonyl); and 276 mμ ($\alpha\beta$, $\gamma\delta$-unsaturated lactone).

Vigorous Hydrolysis of khayasin

Khayasin (1.1 g.) in methanol (80 ml.) was heated under reflux with 2N-sodium hydroxide solution (50 ml.) for 2 hr. The solution was just neutralised with sulphuric acid, and the mixture distilled to dryness. Water (10 ml.) was added to the residue, and the solution distilled to dryness. The combined distillate was titrated with 2N-sodium hydroxide (2.01 ml.) using phenolphthalein as indicator. The resulting sodium salt solution was evaporated to dryness, the residue was taken up in deuterium oxide, and the n.m.r. spectrum taken. This showed a mixture of sodium isobutyrate (ca. 85%) and sodium tiglate (ca. 15%). The p-phenylphenacyl derivative of the acid was prepared, m.p. 74-77°, and shown to be identical, within the limit of its purity, with that from authentic isobutyric acid, (Literature[36a,96] m.p. 89°). The peaks in their i.r. spectra were superimposible on one another.

Khayasin C (LIVa)

Khayasin (0.58 g.) was heated under reflux with methanolic sulphuric acid (1%, 100 ml.) for 20 min. Water (100 ml.) was added, and the product extracted with chloroform (3 x 20 ml.). Evaporation yielded a gum which crystallised from methanol to give khayasin C

(LIVa) (0.39 g. m.p. 146-156°). Recrystallisation from methanol raised the m.p. to 154-157°. $[\alpha]_D^{25}$ - 39° (Found: C, 67.8; H, 7.9. $C_{33}H_{46}O_9$ requires C, 67.55; H, 7.9%). $\lambda_{max.}$ 209 mμ, ε = 10,000 (furan). $\nu_{max.}$ 1740 (esters); 1710 (ketone); 1505 and 875 $cm.^{-1}$ (furan).

Hydrolysis of Khayasin C

Khayasin C (LIVa) (0.45 g.) in methanol (50 ml.) and 2N-sodium hydroxide was refluxed for 2 hr. After acidification with dil. sulphuric acid, the hydrolysis product was extracted into chloroform (3 x 20 ml.) and washed several times with water. Evaporation yielded a gum. The gum was treated with ethereal diazomethane to give the two alcohols (3α-and β-ols identical with those from C.O.C. (LIa and b), (0.31 g. m.p. 179-181°) as a solid from ether-methanol. T.l.c. and i.r. spectra showed the product to be mainly the 3α-ol; this was confirmed by the observed rotation $[\alpha]_D^{25}$ + 69° [cf. α-ol, $[\alpha]_D^{25}$ = +93°; β-ol, $[\alpha]_D^{25}$ = -6°].

Jones Oxidation[73] of Hydrolysis Product from Khayasin C

The methylated hydrolysis product from khayasin C (0.31 g.) in acetone (25 ml.) was treated dropwise with chromic acid solution

(8N) until a yellow colour persisted for five min. Saturated aqueous potassium carbonate (25 ml.) was then added, and the product extracted into ether (3 x 30 ml.). The organic product, recrystallised from methanol had m.p. 169-170°; it was shown by infrared and n.m.r. spectra plus t.l.c. to be identical with authentic C.O.C. (LII).

Preparation of Isobutyryl Chloride[92]

Isobutyric acid (70 ml.) was put in a dry flask immersed in a bath of tap water, and phosphorous trichloride (25 ml.) was slowly added for 15 min. The mixture was left to stand for a further 15 min. Then the mixture was left on the water bath (now raised to 40-60°) for 70 min. A gentle flame was used to drive off all the hydrogen chloride gas. Isobutyryl chloride (58 g.) was collected between 89° and 92°

Isobutyrylation of the 3β-ol (LIa)

The 3β-ol (0.67 g.) was heated under reflux (6 hr.) with isobutyryl chloride (20 ml.) and pyridine (3 drops) in chloroform (50 ml.). After cooling, the solution was thoroughly washed; (water, 2N-sodium carbonate, and water); and then dried.

Evaporation gave a semi-crystalline solid which when taken up in methanol gave the isobutyrate (0.61 g.; m.p. 153-155°, $[\alpha]_D^{25}$ - 40°). This product was shown to be identical with khayasin C by t.l.c.; infrared and n.m.r. spectra.

The Action of Alkali on the 3β-ol

The 3β-ol (0.15 g.) in methanol (50 ml.) was treated with 2N-sodium hydroxide, under reflux for 2 hr. After cooling, water (50 ml.) was added and the solution acidified with dil. sulphuric acid. The organic product was taken in chloroform (3 x 20); washed and evaporated to give a gum. The gum was methylated with diazomethane. Crystallisation from methanol gave a microcrystalline product (0.07 g.) which was shown by t.l.c. to be predominantly the 3α-ol. This was confirmed by both i.r. and n.m.r. spectra.

Hydrolysis of 6-deoxy-17-chloroswietenolide iodoacetate

The iodoacetate (XLIX) (0.23 g.; from Dr. J. W. Powell) in methanol (45 ml.) and chloroform (10 ml.) was treated with 2N-sodium hydroxide (25 ml.) under reflux (2 hr.). After acidification with dilute sulphuric acid, the product was extracted into chloroform (4 x 20 ml.) and the extract washed and evaporated. Treatment with

diazomethane, followed by crystallisation from methanol, yielded a microcrystalline solid (0.13 g.). T.l.c. of this showed two spots, corresponding to the 3α- and 3β-ols respectively; the latter spot predominated. The i.r. and n.m.r. spectra also showed the product to be mainly the 3β-compound.

Treatment of Khayasin C with conc. Hydrochloric Acid

Khayasin C (100 mg.) in chloroform (15 ml.) and conc. hydrochloric acid (2 ml.) was heated under reflux for 10 hr. Water (25 ml.) was added after cooling, and the organic layer separated and washed. After evaporation and crystallisation from ethanol, crystals of 6-deoxy-17-demethoxy-17-chloroswietenolide isobutyrate C (LIVd) (50 mg., m.p. 188-192°) were obtained. (Found: Cl, 6.4. $C_{32}H_{43}O_8Cl$ requires Cl, 6.0%).

Reduction of Khayasin with Lithium Aluminium Hydride

Khayasin (1.96 g.) was dissolved in dry tetrahydrofuran (150 ml.; previously dried by adding calcium hydride (10 g.) to the solvent (600 ml.), and allowing to stand for about 2 hr. before distilling into a dry flask protected from moisture with calcium chloride guard tubes. Lithium aluminium hydride (2.05 g.) suspended in dry

tetrahydrofuran (150 ml.) was added dropwise and with stirring to the solution, over 10 min. The mixture was left to stand, with stirring, for 3 hr.; then poured in ice-water (50 ml.) and dilute sulphuric acid (10%; 200 ml.) added. The homogeneous solution was extracted into chloroform (2 x 40 ml.); and the chloroform layer was washed with water, sodium bicarbonate and water before evaporation.

The aqueous layer was treated with chloroform and evaporated. In either case no interesting product was obtained.

(B) SECOND EXTRACT

The heartwood of the specimen of Khaya senegalensis collected at mile 170, south of Ilorin on the Lagos road was examined. In the first lot examined, 45 gm. of gum came down after extraction by percolation of the heartwood (13 Kg.) with hot light petroleum. The gum was taken up in benzene (200 ml.) and chromatographed over deactivated alumina (1.5 Kg.). Elution with ethyl acetate gave methyl angolensate (3.65 g.).

In another extraction, the heartwood (25.25 Kg.) gave a solid (57.5 g.) from which methyl angolensate (45.0 g.) separated when left to stand in methanol. The mother liquor was evaporated to dryness and the gum taken in benzene and chromatographed over

deactivated alumina (400 ml.). Elution with 75% benzene-ethyl acetate gave

(i) methyl senegalensate (160 mg.) m.p. 197-8° $[\alpha]_D^{20}$ + 223°, M^+ 452 $\nu_{max.}$: 1740 (lactone); 1721 (ester); 1493, 875 $cm.^{-1}$ (Furan). (Found: C, 71.1; 71.6, 71.3; H, 6.4, 6.9, 6.4. $C_{27}H_{32}O_6$ requires C, 71.71, H, 7.7.11%)

(ii) methyl angolensate (XXXVI) (5.0 g.) and

(iii) a mixture of probably methyl angolensate and methyl 6-hydroxyangolensate (LVIIIb) that could not be separated.

(C) THIRD EXTRACT

In an attempt to get more "methyl senegalensate", the ether filtrate gum, after the main residue had been chromatographed [see (B)], was investigated.

The gum (175 g.) was taken up in benzene (500 ml.) and chromatographed over deactivated alumina. The results are as shown. Elution with:

(i) Benzene gave a mixture that crystallises very readily from ether-light petroleum mixture, m.p. 80-100°

(ii) ethyl acetate gave methyl angolensate (14.0 g.) which was crystallised out of methanol. The mother liquor gave 6-deoxy-3β,12β-diacetoxyswietenolide (LVIIc) (0.1 g.)

(iii) 20% ethyl acetate-methanol gave 7-deacetoxy-7-oxogedunin (LV) (80 mg.).

Mexicanolide which was present did not come down the column not even with methanol. In order to isolate it, the alumina was ejected and extracted with chloroform. It crystallised from methanol (0.26 g.) m.p. 223-226°. Attempts to separate the mixture (m.p. 80-100°) by a more careful chromatography were unsuccessful. Separation was effected thus:

Methanolic Sulphuric Acid on the Mixture

The solid mixture (1.06 g.) was treated with sulphuric acid (2.0 ml.) in methanol (150 ml.) under reflux for 15 min.

Khayasin C was produced while the remainder appeared to be the starting material.

Repetition of the experiment was made with 5 g. of the substance. Again two spots were noticed on t.l.c. (benzene/ethyl acetate, 5:3) and more spots were noticed when the development was in chloroform/disopropyl ether (1:1).

The entire crude gum was dissolved in diisopropyl ether and chromatographed over deactivated alumina (200 ml.). Elution results are:

(i) Diisopropyl ether gave khayasin C (180 mg.).

(ii) Diisopropyl ether-chloroform (1:1) gave 6-deoxyswietenolide benzoate C (LIVc) (0.53 g.) m.p. 168° $[\alpha]_D$ - 20°; $\lambda_{max.}$ 226 mμ (ε = 14,800) $\nu_{max.}$ 1742 (lactone); 1724, (ester) 1709 (ketone); 1500, 877 $cm.^{-1}$ (furan). (Found: C, 70.0; H. 7.1. $C_{34}H_{44}O_9$ requires C, 69.7; H, 7.15%).

(iii) Methanol -

(a) 6-deoxyswietenolide tiglate (LIIIc) (0.24 g.) m.p. 146-147° $[\alpha]_D$ - 146°; $\lambda_{max.}$ 230 mμ (ε = 13,500) $\nu_{max.}$ 1742 (lactone); 1724, 1250 (ester); 1500, 877 $cm.^{-1}$ (furan). (Found: C, 69.0; H, 7.1. $C_{32}H_{40}O_8$ requires C, 69.5, H, 7.3).

(b) 6-deoxyswietenolide benzoate (LIIIb) (20 mg.) m.p. 197-199° $[\alpha]_D$ - 156; $\lambda_{max.}$ 230 mμ (ε = 11,700) $\nu_{max.}$ 1748 (lactone); $1724^{sh.}$ (ester) 1712 (ketone); 1595, 716s. (aromatic); 1506, 877 $cm.^{-1}$ (furan). (Found: C, 71.2, 71.3; H, 6.6, 6.5. $C_{34}H_{38}O_8$ requires C, 71.1; H, 6.7%).

A third rechromatography over a very long column of deactivated alumina afforded the isolation of 6-deoxyswietenolide benzoate m.p. 197-199°.

Identification of the Volatile Acids from 6-deoxyswietenolide Esters

(i) Benzoic Acid

6-deoxyswietenolide benzoate (LIIIb) (0.5 g.) was hydrolysed vigorously in the manner described. The solution was treated with dil. sulphuric acid until it was just acid to litmus. Extraction with ether followed by gentle evaporation gave two acids - the benzoic acid and the resulting dihydromexicanolide acid. The mixture was sublimed and benzoic acid was obtained on a cold surface m.p. 115-120°. Mixed m.p. = 117°. (Literature:[89] m.p.121°). The i.r. spectrum is identical with that of an authentic sample.

(ii) Tiglic Acid

The tiglate (LIIIc) 0.8 g.) was similarly hydrolysed. The solution was treated with dil. sulphuric acid until it was just acid to litmus. The resulting solution was distilled. The distillate (acid and water) was neutralised with sodium hydroxide (2N) and evaporated to dryness. The n.m.r. spectrum of the sodium salt

showed it to be sodium tiglate. The p-phenylphenacyl derivative was prepared and chromatographed. One of the purest fractions melted at 89-94°.

(II) Extractives from the Seed

(A) First Extract

Khaya senegalensis seed (1.6 kg.), collected by Professor D. A. H. Taylor from a single tree at Gavva in the Mandara mountains region of the former Northern Cameroons, was minced and extracted with light petroleum in a Soxhlet extractor. Solid material (38 g.) henceforth referred to as (I) separated from the petroleum extract (II). Crystallisation of (I) from benzene afforded 7-deacetoxy-7-oxokhivorin (1.4 g.); m.p. 225°, $[\alpha]_D^{25}$ = -99°; t.l.c., infrared and n.m.r. spectra show it to be identical with an authentic sample. Concentration of the mother-liquor gave more crystalline material (0.82 g.), m.p. 196-238° shown by t.l.c. to be a mixture of two compounds neither of which is 7-deacetyl-7-oxokhivorin. Chromatography of this mixture (10.3 g.) on deactivated alumina afforded two materials. The first (0.18 g.) m.p. 250-254° $[\alpha]_D^{25}$ - 40° was identical (t.l.c., i.r. and n.m.r.) with an authentic sample of khivorin. The second (0.08 g.); double

m.p. 210-214 and 240°, has been suggested to be 7-deacetoxy-3-deacetyl-7-oxokhivorin (LVId). (Found: C, 67.2; H, 7.3. $C_{28}H_{36}O_8$ requires C, 67.2; H, 7.25%. $\lambda_{max.}$ 209 mμ, (ε = 4,600) $\nu_{max.}$ 3584 -OH; 1730 (ester and lactone) 1704 (ketone); 1495, 877 $cm.^{-1}$ (furan). Acetylation of this substance with acetic anhydride in pyridine gave a different substance indistinguishable from 7-deacetyl-7-oxokhivorin by t.l.c.

The original petroleum extract liquid (II) was extracted in a separating funnel with methanol containing a trace of water. The petroleum layer after evaporation gave the seed oil. The methanol layer was evaporated, and the residue chromatographed on deactivated alumina. Three crystalline fractions were obtained. Elution with 50% benzene-ethyl acetate yielded the first crystals (2.45 g.) characterized as 7-deacetoxy-7-oxokhivorin by t.l.c., i.r. and n.m.r. spectra to be khivorin. The second lot of crystals (2.77 g.), double m.p. 180 and 245°, $[\alpha]_D^{25}$ - 38° came down with 10-50% ethyl acetate - methanol. It was shown to be 3-deacetyl-khivorin (LVIb). (Found: C, 66.0, H, 7.5. $C_{30}H_{40}O_9$ requires C, 66.15; H, 7.4%). $\lambda_{max.}$ 210 mμ; (ε = 3,600); $\nu_{max.}$ 3534 (OH); 1724 (carbonyl); 1495, 877 (furan) 1245 $cm.^{-1}$ (ester).

3-Deacetoxy-3-oxokhivorin

3-Deacetylkhivorin (LVIb) (82 mg.) was dissolved in acetone (5 ml.) and oxidised with chromic acid solution in the usual way. The ethereal layer was washed and evaporated. The residue crystallised from methanol to give 3-deacetoxy-3-oxokhivorin (LVIg) (62 mg.) m.p. 216-218° $[\alpha]_D^{25}$ - 18° (Found: C, 66.5; H, 7.3. $C_{30}H_{38}O_9$ requires C, 66.4; H, 7.1%). $\lambda_{max.}$ 214 mμ, ε = 4,500. $\nu_{max.}$ 1730 (ester and lactone); 1701 (ketone); 1497, 876 (furan) 1240 $cm.^{-1}$ (ester).

Gedunin (XXVIII)

3-Deacetylkhivorin (200 mg.) was oxidised to 3-deacetoxy-3-oxokhivorin as before. The crude product was dissolved in methanol (35 ml.) containing sulphuric acid (1.4 ml.) and the solution was heated under reflux for ½ hr. After dilution with water the product was extracted with chloroform and chromatographed on deactivated alumina. The crystalline eluate recrystallised from methanol to give gedunin (XXVIII) (67 mg.) double m.p. 156-159 and 195°. T.l.c., infrared and n.m.r. show it to be identical with an authentic sample.

1,3-Dideacetylkhivorin (LVIe)

3-Deacetylkhivorin (103 mg.) was dissolved in boiling methanol and 2N-sodium hydroxide (2.5 ml.) was added. After heating under reflux for 10 min., the solution was acidified with dilute hydrochloric acid and extracted into chloroform (3 x 20 ml.). After washing and evaporation of the extract, a gum shown by t.l.c. to contain two substances was obtained. The gum was taken in methanol fromwhich some crystals separated (19 mg.) m.p. 319-324°. This was shown to be identical (i.r. mixed m.p.) with an authentic sample of trideacetylkhivorin (LVIf). The mother-liquor gave 1,3-dideacetylkhivorin as large prisms, m.p. 261-269°, $[\alpha]_D^{25}$ - 16°, $\lambda_{max.}$ 213, ε = 9,300. (Found: C, 67.2; H, 7.3. $C_{28}H_{38}O_8$ requires C, 66.9; H, 7.6%). $\nu_{max.}$ 3546, 3460 (2 - OH); 1727 (ketone); 1497, 877 (furan); 1247 $cm.^{-1}$ (acetate). Oxidation of a sample, with chromic acid in acetone, gave 1,3-dideacetoxy-1,3-dioxokhivorin (LVIh) not obtained crystalline but had the characteristic absorption spectrum of a β-diketone. [$\lambda_{max.}$ 211 and 256 mμ (very strong); with the 256 mμ peak shifting to 285 mμ with 1 drop NaOH].

(B) Second Extract

Khaya Senegalensis Seed (80 g.) collected from a single tree south of Ilorin and close to the trees that gave the third extract was minced and extracted as previously described. The solid which separated and the product from the methanol layer were taken in benzene and chromatographed over deactivated alumina. Elution with (i) 75% benzene - ethyl acetate afforded methyl angolensate (1.02 g.); (ii) 50% benzene-ethylacetate gave 3-deacetylkhivorin (0.64 g.). Concentration of the mother liquor gave 6-deoxy-3-destigloylswietenine (LVIIa) (30 mg.) m.p. 260-265° $\nu_{max.}$ 3450 (OH); 1718 (ester); 1493, 875 $cm.^{-1}$ (furan).

(C) Third Extract

Khaya senegalensis seed (500 g.) collected near Ilorin was minced and extracted as usual. The gum (ca. 30 g.), obtained after treating the light-petroleum extract with methanol and evaporating the methanol layer, was taken in benzene and chromatographed on deactivated alumina. Elution with ethyl acetate gave a product shown by t.l.c. to contain three substances. They were separated by fractional crystallisation from methanol to give (a) khivorin

(1.0 g.), (b) methyl angolensate (0.36 g.) confirmed by t.l.c., i.r. and n.m.r. and (c) 6-deoxy-3-destigloyl-3-acetoxyswietenine (LVIIb), (3.4 g.) m.p. 223-226°, $\lambda_{max.}$ 210, (ϵ = 8,000) $[\alpha]_D^{20}$ - 150° (Found: C, 68.3; H, 7.1 $C_{29}H_{36}O_8$ requires C, 68.0; H, 7.1%). $\nu_{max.}$ 1727 (ester and lactone); 1502, 876 (furan); and 1233 $cm.^{-1}$ (ester).

Further elution with 50% ethyl acetate-methanol afforded a mixture shown by t.l.c. to contain two compounds which were separated by fractional crystallisation from methanol. The first was 7-deacetoxy-7-oxokhivorin (1.12 g.) and the other methyl angolensate (1.0 g.).

Hydrolysis of 6-deoxy-3-destigloyl-3-acetoxyswietenine

6-deoxy-3-destigloyl-3-acetoxyswietenine (LVIIb) (1.0 g.) was refluxed in ethanolic potassium hydroxide (5%; 100 ml.) for 15 min. (The solution turned pale yellow immediately). After cooling, the solution was poured into water (500 ml.), neutralised with hydrochloric acid (50% w/v) and extracted into chloroform. After evaporation and methylation of the extract with ethereal diazomethane the product obtained (t.l.c. showed several spots but one was major) was fractionally crystallised from benzene/light

petroleum. Some solid came down which was recrystallised from benzene to give the 3 epi-hydroxy compound i.e. 6-deoxy-3-destigloyl-isoswietenine (0.26 g.) m.p. 193-195°; $[\alpha]_D^{20}$ - 89°. $\nu_{max.}$ 3484 (OH); 1727 (ester and lactone); 1709 (ketone); 1502 877 $cm.^{-1}$ (furan), $\lambda_{max.}$ 210 mμ (ε = 8,000).

6-deoxy-3-destigloyl-3-epiacetoxyswietenine

6-deoxy-3-epidestigloylswietenine (70 mg.) was acetylated overnight using acetic anhydride (4 ml.) in pyridine (5 ml.). The product was worked up in the usual way to give crystals of 6-deoxy-3-destigloyl-3-epiacetoxyswietenine (60 mg.) m.p. 209-212° $[\alpha]_D^{20}$ - 86° $\lambda_{max.}$ 210 mμ (ε = 16,400). $\nu_{max.}$ 1725 (ester and lactone); 1495, 873 $cm.^{-1}$ (furan).

6-deoxy-3-destigloyl-3-oxoswietenine

Both the naturally occuring 6-deoxy-3-destigloyl swietenine (6 mg.) and the synthetic epi isomer (3 mg.) were individually oxidized with chromic acid in acetone in micro test-tubes. The 6-deoxy-3-destigloyl-3-oxoswiestenine (LVIIg) (5 mg. m.p. 220-232°; 2 mg. m.p. 224-234° respectively) obtained from both of them was shown to be identical by i.r. and t.l.c. Recrystallisation raised

the m.p. to 233-235°. $\nu_{max.}$ 1736 (ester and lactone); 1709 sh. (ketone); 1502, 877 cm.$^{-1}$ (furan).

(III) Extractives from the Bark

Khaya senegalensis bark (50.5 kg.) gave by usual method of extraction a gum (including 18.5 g. solid) which was taken in benzene (300 ml.) and chromatographed over deactivated alumina (1 l.).

Elution products with various solvent ratios are as shown:

(i) 50% benzene-ethyl acetate gave 1.38 g. steroid.

(ii) ethyl acetate gave 1.34 g. methyl angolensate

(iii) ethyl acetate gave 14.0 g. methyl-6-hydroxy angolensate (LVIIIb)

(iv) methanol gave 80 mg. 7-deacetoxy-7-oxogedunin (LV).

The mother liquor of the fractions containing the steroid was concentrated and methanol added. Crystals of 6-deoxy-3β,12β-diacetoxyswietenolide (0.23 g.) m.p. 250-252°, $[\alpha]_D$ - 131° came down. $\lambda_{max.}$ 210 mμ, ε = 6,000. $\nu_{max.}$ 1727 (ester and lactone); 1233 (ester; 1497, 873 cm.$^{-1}$ (furan).

(IV) EXTRACTIVES FROM THE ROOT

Khaya senegalensis root was extracted in the usual way and the gum (ca. 10 g.) was taken up in benzene (50 ml.) and chromatographed over silica gel (Merk 0.05-0.20 mm.). Elution with 50% benzene-ethylacetate gave khayasin (2.4 g.). Later fractions gave a non-furanoid oil.

(V) EXTRACTIVES FROM THE ROOT-BARK

Khaya senegalensis root-bark was extracted with light petroleum in the normal way. A gum (ca. 20 g.) obtained was taken in benzene (40 ml.) and chromatographed over a long column of alumina (25" x 1¼").

Elution with ethylacetate brought down methyl 6-hydroxyangolensate (1.4 g.) identical in every respect with authentic sample.

KHAYA GRANDIFOLIOLA

(I) Extract from the Timber

Khaya grandifoliola wood collected from Ife and after extraction a gum (26 g.) was chromatographed over neutral alumina (Fluka). Elution with 75% benzene-ethyl acetate gave deoxyandirobin (2.1 g.); with 50% benzene ethyl acetate gave mexicanolide (0.41 g.); ethyl acetate gave methyl angolensate (1.05 g.).

Deoxyandirobin m.p. 182-184° $[\alpha]_D$ + 392° was easily recognized from the n.m.r. and infra red spectra. Comparison with authentic sample showed no difference (i.r., t.l.c., m.p.). $\lambda'_{max.}$ 217 mμ, ε = 17,500; $\lambda''_{max.}$ 234 mμ, ε = 17,000.

(II) Extract from the Seed

Khaya grandifoliola seed (300 g.) was extracted in the normal way. The crude solid (11.2 g.) and the gum from the methanol layer were chromatographed over silica gel M.N. The elution results are as follows:

75% benzene-ethyl acetate - sterol (probably β-sitosterol)

75% " " " - mexicanolide (0.50 g.)

50% " " " - Grandifoliolin (LXIa) (= fissinolide)[75] (4.59 g.), and 3β-dihydromexicanolide (see p. 134-b).

Grandifoliolin $[\alpha]_D$ - 165°, m.p. 169-171°, is identical in every respect with an authentic specimen previously reported as fissinolide[71] and obtained as a product of reaction by Overton et al.[21] ($\nu_{max.}$ 1740 (lactone and ester); 1712 (ketone); 1506, 877 cm.$^{-1}$ (furan).

25% benzene-ethyl acetate gave 6-deoxyswietenolide (gum). After extracting the seed with light petroleum, methanol was substituted and the resulting methanol extract chromatographed over silica gel M.N. whence elution with ethyl acetate brought 3-deoxy-3β-hydroxycarapin (50 mg.) m.p. 208-218°, $\nu_{max.}$ 3470 (OH); 1718 (ester); 1500, 888 cm.$^{-1}$ (furan).

Methanolic Sulphuric Acid Treatment of Grandifoliolin

Grandifoliolin (LXIa) (0.92 g.) was refluxed with sulphuric acid (1 ml.) in methanol (85 ml.) for 20 min. On working up in the usual way a crystalline compound (0.76 g.) m.p. 195-198° was obtained. This was the corresponding ring-opened compound, 3-deoxy-3β-acetoxy C.O.C. (LXXI). $\lambda_{max.}$ 212, ϵ = 13,200, $[\alpha]_D$ - 39°. $\nu_{max.}$ 1733 (lactone and ester): 1706 (ketone); 1495, 873 cm.$^{-1}$ (furan).

Hydrolysis of above

Compound (LXXI) (0.4 g.) was refluxed (2 hr.) with 2N-sodium hydroxide (45 ml.) in methanol (60 ml.). The product after working up in the usual way was taken in methanol to give crystals (0.19 g.) m.p. 229-232°. This was acidic and methylation with ethereal diazomethane and crystallisation from cyclohexane-ether mixture afforded crystals of (LIa and b) (0.15 g.) m.p. 189-192°, $\nu_{max.}$ 3509 (OH); 1745 (lactone); 1730 sh. (ester); 1715 (ketone; 1495, 877 $cm.^{-1}$ (furan).

Khaya grandifoliola bark

Khaya grandifoliola bark (35.75 kg.) was extracted with light petroleum and a gum (120 g.) obtained. Part of the gum (60 g.) was dissolved in benzene (60 ml.), and chromatographed over deactivated alumina.

Elution with benzene gave

(i) a compound (50 mg.) which may be a mixture of methyl angolensate and methyl 6-acetoxyangolensate

(ii) methyl angolensate (0.80 g.).

With 50% benzene ethyl acetate, a steroid (2.4 g.) m.p. 161-2° was obtained. This was characterised by hydrolysis and oxidation

as the methyl ester of 20-dihydroprogesterone. The compound was characterised as 20β-acetoxy-3-oxopregne-4-ene (LXVa). $\lambda_{max.}$ 240 mμ (ε = 11,500) with shoulder at 205 mμ $\nu_{max.}$ 1724, 1240 (ester); 1672 cm.$^{-1}$ (αβ-unsaturated ketone).

In addition elution with ethyl acetate gave methyl 6-hydroxy-angolensate (LVIIIb) from methanol (0.62 g.) m.p. 248-249°. Recrystallisation from methylene chloride/methanol raised m.p. to 252°, $\nu_{max.}$ 3497 (OH); 1721 (ester); 1502, 877 cm.$^{-1}$ (furan) $[\alpha]_D$ - 83°. (Found: C, 66.8; H, 6.7. $C_{27}H_{34}O_8$ requires C, 66.65; H, 7.0%). Acetylation with acetic anhydride in pyridine overnight gave methyl 6-acetoxy angolensate m.p. 173-174° from methanol. $\nu_{max.}$ 3546 (methanol of crystallisation); 1751 (lactone); 1736 (ester); 1706 (ketone); 1495, and 873 cm.$^{-1}$ (furan), $[\alpha]_D$ - 84°. (Found: C, 64.7; H, 6.7. $C_{29}H_{36}O_9 . CH_3OH$ requires C, 64.3; H, 7.2%).

Extract from the root-bark

Extraction of K. grandifoliola root-bark (11.5 kg.) gave a gum (55 g.) which was taken in benzene (100 ml.) and chromatographed over deactivated alumina (800 ml.).

Elution with

benzene gave	deacetylgedunin (3.6 g.)
benzene/ethylacetate (4:1) gave	methyl 6-hydroxyangolensate (1.2 g.), and a mixture of methyl angolensate and methyl 6-acetoxyangolensate
ethyl acetate gave	7-deacetoxy-7-oxokhivorin.

KHAYA NYASICA

K. nyasica seed (460 g.) from Mingoli Forest Reserve (Zomba) was extracted and the extract was chromatographed to give khivorin (0.5 g.); 3-deacetylkhivorin (0.23 g.), and 3-destigloyl-6-deoxy-3β,12β-diacetoxyswietenine (LVIc).

KHAYA IVORENSIS

Extract from the Wood

Extraction of K. ivorensis wood gives a large precipitate of khivorin. Chromatography of the mother-liquor of such an extract (34 g.) on alumina gave further khivorin (30 g.). The mother liquor of the resulting fractions was separated by preparative thin layer chromatography using Kieselgel $PF_{254 + 366}$ and detecting separation under a u.v. lamp to give 3-deacetylkhivorin (10 mg.), and methyl angolensate (4 mg.) which are easily recognised from their spectral properties. In addition there was another product which was shown to resemble deoxykhayanthone. I.r., n.m.r. and t.l.c. show them dissimilar see plates 15 and 15a.

Extract from the Seed

K. ivorensis seed (130 g.) was minced and extracted in the usual way. A white solid precipitate and the chloroform extract of the aqueous methanol layer from the light petroleum mixture was chromatographed over alumina. The compounds obtained include the known mexicanolide (0.2 g.), methyl angolensate (0.3 g.) and in addition 3β-dihydromexicanolide. The latter came as a gum and although it was difficult to crystallise, t.l.c. showed it was homogeneous. Confirmation of structure came from oxidation to give mexicanolide and acetylation (pyridine and acetic anhydride) to give grandifoliolin. The gum in ether gave a non-crystalline solid m.p. 116-119°.

KHAYA IVORENSIS ROOT BARK

Light petroleum extraction of khaya ivorensis root bark gave a gum (ca. 38 g.). The gum was dissolved in benzene (80 ml.) and chromatographed over deactivated alumina (500 ml.).

Elution with benzene-ethylacetate (3:1) gave methyl angolensate (1.7 g.). The fractions from eluting with ethyl acetate was combined and rechromatographed over deactivated alumina. Elution with ether subsequently gave a new compound substance A (LXIII) which came out in ether as crystals (1.2 g.) m.p. 195-200°. Recrystallisation from methanol afforded crystals m.p. 196-198° $[\alpha]_D$ - 123°; $\lambda_{max.}$ 219 mμ, ε = 9,000 $\nu_{max.}$ 3560 (OH); 1745 (ester and lactone) 1709 (ketone); 1497, 876 $cm.^{-1}$ (furan). Substance A was formulated as 2-hydroxygrandifoliolin.

About 50 mg. of this was oxidised with chromic acid in acetone, but the reaction did not go. With a little heating the reaction product, a gum showed no -OH and has $\lambda_{max.}$ 221 and 284 mμ.

Acetylation of Substance A (LXIII)

Substance A (0.2 g.) in acetic acid (15 ml.) was treated with acetic anhydride (5 ml.) and p-toluene sulphonic acid (0.25 g.) for about 48 hr. with an additional 15 minutes boiling. On working up the usual way a semi-solid

crystalline substance was obtained (60 mg.) m.p. 250 - 256° $\epsilon = 7{,}500$ (285mμ, $\epsilon \simeq 700$ with a drop of NaOH, shifting to 265mμ with HCl) $[\alpha]_D$ - 140°; $\lambda_{max.}$ 215mμ/ $\nu_{max.}$ 1762 (lactone!); 1727, 1241 (ester); 1497, 876 $cm.^{-1}$ (furan).

Treatment of Substance A with Methanolic H_2SO_4

Substance A (0.2 g.) in methanol (50 ml.) was refluxed (20 min.) with conc. sulphuric acid (0.5 ml.). Working up the usual way a crude solid was obtained, difficult to crystallise though homogeneous (t.l.c.) and pure (n.m.r.). On long standing flat plates of crystals were obtained, m.p. 187-190°.

Another lot of K. ivorensis root bark from Omo Forest Reserve was extracted with a view of getting more of substance A. 25 gm. of gum was chromatographed. Substance A was not obtained, but at least three new substances were isolated in low yield: (i) a mixture of mexicanolide and an unknown substance (70 mg.) came down with ethyl acetate/methanol (1:1) m.p. 230-233°; (ii) a substance (210 mg.) identical in every respect with the strong-acetylation product of substance A came down in the benzene fraction of a second chromatography of the ethyl acetate fraction in the first chromatography; (iii) Substance B (LXIV) (300 mg.) came down with ethyl acetate/benzene (1:1). It is very soluble in methanol and

crystallises out reluctantly in benzene. M.p. 150-160 melting sharply at 172°, $\nu_{max.}$ 3509, 3322 (-OH); 1792; 1742 (ester/lactone); 1653; 1242 (ester); 1504 and 888 $cm.^{-1}$ (furan). $\lambda_{max.}$ 213 mμ, ε = 10,700; $[\alpha]_D$ - 22°. (Found: C, 60.15; H, 6.5. $C_{29}H_{36}O_{11}$ requires C, 62.1; H, 6.4%).

Hydrolysis of Substance B

Substance B (0.1 g.) in methanol (25 ml.) was refluxed with sodium hydroxide (2N., 15 ml.) for 1 hr. and worked up as usual. The residual gum showed only one strong methyl signal.

Cold Hydrolysis of Substance B

Substance B (0.1 g.) was allowed to stand in cold 10% methanolic potassium hydroxide (3 ml.) for 10 min. The reaction was worked up to give a gum whose n.m.r. signals are at δ 7.40, 6.35 (furan: 2α-H, 1β-H resp.); 5.57 (H-17); 4.20 (H-15) 3.66 (-CO.OMe); and 3.47 (methanol solvent). The methyl region is not well resolved.

Treatment with methanolic H_2SO_4

Substance B (90 mg.) in methanol (12 ml.) was refluxed for 26 min. with sulphuric acid (0.1 ml.). On working the product up, the starting material was obtained.

Khaya ivorensis root

Khaya ivorensis root was extracted in the usual way. The crude solid (12.0 g.) obtained was chromatographed to give the known khivorin (1.5 g.) and methyl angolensate (3.1 g.). These were readily identified by their spectral properties. There were spots showing the presence of smaller quantities of other substances (t.l.c.) and attempts at isolating and characterising these are continuing.

KHAYA ANTHOTECA (Welw) C.DC.

Khaya anthotheca seed (210 g.) was extracted with light petroleum for 6 hr. in the usual way.

The solid that separated and the gum from the methanol layer were combined and chromatographed over alumina.

Elution with ethyl acetate gave khivorin (0.53 g.) and 50% ethyl acetate-methanol gave 3-deacetylkhivorin. Both were shown to be identical with authentic samples (i.r., t.l.c., m.p.).

In addition elution with 50% benzene-ethyl acetate gave khayanthone (LXVIII) (0.29 g.) m.p. 190-210°. A second recrystallisation from methanol raised the m.p. 215-217° $[\alpha]_D$ - 57° $\lambda_{max.}$ 210 mμ (ε = 8,000); $\nu_{max.}$ 1730, 1250 (ester); 1493, 876 $cm.^{-1}$ (furan). (Found: C, 67.4; H, 7.4. $C_{32}H_{42}O_9$ requires C, 67.35; H, 7.4%).

Chromous chloride reduction[76] of khayanthone

Aqueous chromous chloride solution (25 ml.) was slowly run into a flask containing khayanthone (40 mg.) in acetic acid (25 ml.) in such a way that virtually all the air was displaced. The reaction was allowed to take place overnight.

Excess water was added and the product extracted in chloroform. After washing and evaporation of the extract, a gum (LXIX) with a clean spot on t.l.c. (not the same as khayanthone) was obtained but could not be crystallised. Its infra-red and u.v. showed αβ-unsaturated ketone. The u.v. of the solid gum was determined: $\lambda_{max.}$ 209 mμ (ε = 18,000); 237 mμ, (ε = 17,000).

MEXICANOLIDE

Treatment of Mexicanolide with Alkali

Mexicanolide (XLV) (0.5 g.) was boiled under reflux with methanol (50 ml.), and 2N-sodium hydroxide (5 ml.) for 10 min. Water (100 ml.) was added to the cooled solution and this was subsequently acidified with dilute sulphuric acid. The product was extracted with chloroform (3 x 25 ml.). The chloroform extract was washed thoroughly and evaporated to give a gum which was crystallised from benzene-light petroleum. This gave needle-like crystals (sometimes amorphous solid) of C.O.D. (XLVa) (0.4 g.) m.p. 173-175°. (Found: C, 69.1; H, 6.7; O, 24.15. $C_{27}H_{32}O_7$ requires C, 69.2; H, 6.9; O, 23.9%). $\lambda_{max.}$ 209 ε = 12,000; 288 mμ ε = 26,000 $\nu_{max.}$ (CH_2Cl_2): 1730 (ester); 1712 (unsaturated lactone); 1670 sh. (unsaturated ketone); 875 $cm.^{-1}$ (furan).

Acetylation of C.O.D.

Acetylation of C.O.D. (1 g.) with acetic anhydride in pyridine yielded a gum, which was chromatographed on deactivated alumina (25 ml.). Elution with benzene-ethyl acetate (1:1) yielded the acetate (XLVc) (0.4 g.) partially melting 165-167° and finally at 180°. (Found: C, 68.3; H, 6.7; O, 24.8; OMe, 6.2; OAc, 8.7. $C_{26}H_{28}O_5$, OMe, OAc requires, C, 68.2; H, 6.7; O, 25.1; OMe, 6.1; OAc, 8.4%). $\lambda_{max.}$ 220 (ϵ = 12,000); 240 (ϵ = 14,000); and 277 mμ (ϵ = 14,000). $\nu_{max.}$ (CH_2Cl_2) 1760 (enol acetate); 1733 (ester); 1712 (unsaturated lactone); 1675 (unsaturated ketone); 875 cm.$^{-1}$ (furan).

Hydrogenation of Mexicanolide in presence of platinum oxide

Mexicanolide (0.6 g.) in acetic acid (40 ml.) was hydrogenated at atmospheric pressure in the presence of Adam's catalyst (0.1 g.). The intake of hydrogen (4.0 moles) ceased after 3 hr. Water (200 ml.) was added after the catalyst was removed by filtering over thick folds of filter paper. The product was extracted into chloroform (3 x 50 ml.), washed and evaporated. A gum obtained could not be induced to crystallise and was methylated with diazomethane. Still the product did not crystallise. It was chromatographed on deactivated alumina and crystals were obtained (90 mg.) m.p. 87-119°.

Recrystallisation from benzene-light petroleum raised the m.p. 120-125°. (Found: C, 68.3; H, 8.2. $C_{27}H_{40}O_7$ requires C, 68.0; H, 8.5, O, 23.5%).

Reduction of Mexicanolide with Sodium Borohydride

Mexicanolide (2.7 g.) was dissolved in a mixture of chloroform (60 ml.) and methanol (60 ml.). Sodium borohydride (0.7 g.) in water (5 ml.) was added and the mixture was allowed to stand with occasional shaking for 2 hr. (shorter reaction times were tried with same result). Excess sodium borohydride was destroyed with acetone (ca. 10 ml.) and water (150 ml.) added. Extraction with chloroform, and evaporation gave a gum. (The gum has six spots on t.l.c. but the gum gave mexicanolide on oxidation with Jones reagent).

The gum was chromatographed on deactivated alumina and two compounds "A" and "B" were obtained crystalline.

Compound A (LXXII) (1.03 g.) m.p. 200-202° crystallised from benzene. Recrystallisation raised m.p. to 203-204°. (Found: C, 68.31; H, 7.68. $C_{27}H_{36}O_7$ requires C, 68.62; H, 7.68%). Compound "B" (LXXVa) 0.29 g.) m.p. 247-249° came down in methanol. It is in fact insoluble in common solvents. (Found: C, 67.42, H, 8.09.

$C_{27}H_{38}O_7$ requires C, 68.33, H, 8.07%). $\nu_{max.}$ 3356 (OH); 1724 (ester); 1672, 1497, 876 cm.$^{-1}$ (furan). Compound A was characterised as 3,16-dihydromexicanolide and compound B as a 3-dihydro-δ-hydroxyacid derivative of C.O.C.

Mild Methanolic Sulphuric Acid Treatment of Compound A

Compound A (0.43 g.) was heated under reflux with sulphuric acid (0.3 ml.) in methanol (75 ml.) for 24 min. The mixture was poured into water (ca. 100 ml.) and extracted into chloroform (3 x 50 ml.). Evaporation yielded a gum which crystallised from methanol to give an acetal (LXXIII) (0.30 g.) m.p. 186-197°. Recrystallisation from methanol raised the melting point to 191-194°. (Found: C, 69.8; H, 8.0. $C_{28}H_{38}O_7$ requires C, 69.1; H, 7.9%). $\lambda_{max.}$ 208 mμ (ε = 9,000); $\nu_{max.}$ 3484 (OH); 1733 (ester); 1712 (ketone), 3125, 1502, 876 cm.$^{-1}$ (furan).

Jones oxidation on the product of mild sulphuric acid on mexicanolide reduction product

Mexicanolide reduction product with its ring D-lactone opened (2 g.) was oxidised with chromic acid, and worked up in the normal way. The reaction did not go. A repetition with longer time than

usual and more of the acid afforded a gum which crystallised from methanol (0.54 g.). $\nu_{max.}$ 1733 (ester) 1701 (ketone); 1500, 876 cm.$^{-1}$ (furan). δ 7.53, 7.42 (α-furan); 6.52 (β-furan); 5.20 (H-17); 4.88 (H-C-OMe); 3.75 (CO.OMe); 3.65 (OMe); 1.25, 1.08, 1.06, 0.87 (methyls).

Treatment of compound A with stronger methanolic sulphuric acid

Compound A (0.25 g.) and 50% concentrated sulphuric acid (2 ml.) in methanol (40 ml.) were refluxed for 21 min. Working up the usual way afforded crystals of the $\Delta^{14,15}$-compound (LXXIV) (0.13 g.) from methanol m.p. 195-197°. (Found: C, 70.6, 70.5; H, 7.5, 7.4. $C_{27}H_{34}O_6$ requires C, 71.3; H, 7.5%) $\lambda_{max.}$ 211 (ϵ = 9,200); 263 mμ (ϵ = 15,400). $\nu_{max.}$ 3534 (OH); 1715, 1245 (ester); 1692 (ketone); 1603 (unsaturation); 1497, 873 cm.$^{-1}$ (furan).

C. O. C.

Mexicanolide (1.0 g.) in methanol (100 ml.) and conc. sulphuric acid (1.0 ml.) was heated under reflux (30 min.). Water (ca. 100 ml.) was added to the hot solution and crystals of C.O.C. (LII) (0.85 g., m.p. 165-170°) were deposited on cooling. Recrystallisation from methanol raised the m.p. to 171-173°. (Found: C, 67.9; H, 7.6;

O, 24.8; OMe 18.2. $C_{26}H_{29}O_5$ $(OMe)_3$ requires C, 67.7; H, 7.4; O.24.9; OMe 18.1%). $[\alpha]_D^{25}$ + 42.5°; $\lambda_{max.}$ 212 mμ, ε = 12,000 $\nu_{max.}$ (CH_2Cl_2) 1735 (esters); 1705 (ketone); 1500 and 876 $cm.^{-1}$ (furan).

Reduction of C.O.C.

Sodium borohydride (1.5 g.) in water (ca. 5 ml.) was added to C.O.C. (10 g.) in ethanol (450 ml.) and chloroform (50 ml.). The mixture was stirred for 2 hr. at 25°. Water (ca. 250 ml.) was added and the product extracted with chloroform (5 x 50 ml.). The extract was washed with water (2 x 100 ml.) and evaporated. The resulting gum was taken up in hot ethyl acetate-benzene, and chromatographed on deactivated alumina (250 ml.). Elution with 10% ethyl acetate-benzene yielded mainly the 3β-ol (LIa) (5.45 g.). (Found: C, 67.8; H, 7.5. $C_{29}H_{40}O_8$ requires C, 67.4; H, 7.8%. $[\alpha]_D^{26}$ - 6°; m.p. complex but ending sharply at 179°. Elution with ethylacetate gave some 3α-ol (LIb) (700 mg., $[\alpha]_D^{25}$ + 93°; m.p. 188-196° after recrystallisation from methanol). Other fractions, and mother-liquors from these fractions gave mixed products.

Attempted Acetylation of the 3β-ol from Mexicanolide Reduction Product

The 3β-ol (5 g.) and toluene-p-sulphonic acid (5 g.) in acetic anhydride (50 ml.) and acetic acid (200 ml.) were left to stand for 16 hr. The product was poured into water (650 ml.), and extracted with chloroform (4 x 50 ml.). After washing and evaporation, the gum was crystallised from benzene, yielding C.O.E. (LXXVII) (2.45 g., m.p. 178-186°), as brownish crystals. Recrystallisation from benzene-light petroleum afforded cream crystals m.p. 196-199° [Found: C, 68.3; H, 7.4; O, 24.5; OMe 11.6%. $C_{28}H_{32}O_6$ $(OMe)_2$ requires C, 68.4; H, 7.3; O, 24.3; OMe 11.8%]. $\lambda_{max.}$ 208 (ε = 12,000) $\nu_{max.}$ 1735 (ester); 1715 (ketone); 1674 (conjugated ketone); 1570 $cm.^{-1}$.

Treatment of C.O.C. with Ozone

C.O.C. (2.16 g.) in ethyl acetate (100 ml.) was treated with a stream of ozonised oxygen (15%) for 5 hr. Hydrogen peroxide (30 ml., 100 vols) in water (100 ml.) was added and the mixture refluxed for 1 hr. Saturated sodium bicarbonate solution was added to the solution then it was acidified with dil. hydrochloric acid. The product (probably LXXIX) was extracted with chloroform,

evaporated, washed and the resulting gum treated with diazomethane. The product was chromatographed over deactivated alumina. Only one fraction after standing for many days gave crystals (80 mg. m.p. 190-202°). (Found: C, 61.9, H, 9.85%).

Hydrogenation of C.O.C.

C.O.C. (0.57 g.) in acetic acid (40 ml.) was hydrogenated at atmospheric pressure in the presence of Adam's catalyst (100 mg.). Hydrogen uptake ceased after 2 hr. The product after working up the usual way yielded a gum which could not be crystallised. The gum was chromatographed on deactivated alumina from which a fraction gave solid (0.30 g.) which on crystallisation from methanol gave crystals of tetrahydro C.O.C. (LXXX) (0.27 g.) m.p. 131-134°. (Found: C, 67.6; H, 8.25; $C_{29}H_{42}O_8$ requires C, 67.2; H, 8.2%).

Treatment of C.O.C. with Hydrochloric Acid

C.O.C. (500 mg.) in chloroform (25 ml.) was heated under reflux (3 hr.) with conc. hydrochloric acid (2 ml.). The resulting solution was washed with water, evaporated and crystallised from methanol/chloroform (4:1) yielding mexicanolide (200 mg., m.p. 216-220°), shown to be identical with the authentic material by

infra red, t.l.c. and mixed m.p.

The same result was obtained when hydrogen chloride gas was used although this was found to be less efficient. The gas was generated by adding conc. sulphuric acid from a funnel into sodium chloride in a flask fitted with a pressure equaliser tube. The gas generated was passed through conc. sulphuric acid before being let in to the C.O.C. solution..

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Grandifoliolin, a New Limonoid from *Khaya grandifoliola* C. DC.

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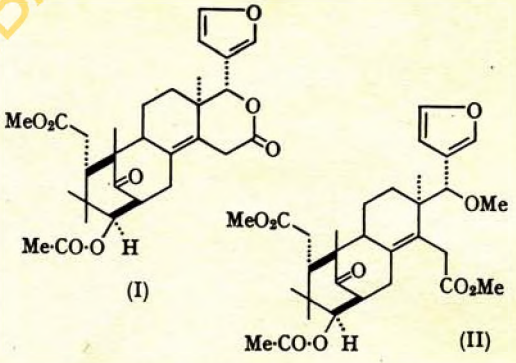
FROM a sample (F.H.I. No. 4278) of the timber of *Khaya grandifoliola* collected in Aponmu forest reserve, we obtained khivorin;[1] from another sample (F.H.I. No. 54740) from Balogun village near Ibadan, we obtained a mixture of mexicanolide and methyl angolensate.[2,3] We have subsequently examined six more specimens, and find them similar to the second of these samples. In view of this discrepancy the herbarium specimen of F.H.I. 4278 has been re-examined. It is now considered to be of doubtful authenticity, and may be *Khaya ivorensis*, which would agree with the chemical evidence. The sample has been referred to Kew for a further opinion.

Recently Conolly, Handa, McCrindle, and Overton[4] have described the examination of timber said to be *Khaya grandifoliola*, of unspecified origin, and the isolation of the interesting 16-keto-compound, grandifolione, together with methyl angolensate, 7-deacetylkhivorin, methyl 6-hydroxy-angolensate, and 7-oxo-7-deacetoxykhivorin.

We now report the investigation of the seed of *Khaya grandifoliola*. Seed from a single tree at Balogun village near Ibadan (Herbarium specimens are retained as D.A.H.T. 157 and will be deposited in the Forest Herbarium at Oxford) was extracted with light petroleum and gave, in unusually high yield (*ca.* 1%), a crystalline solid, m.p. 169—170°, $[\alpha]_D$ −165°, which we name grandifoliolin. The n.m.r. spectrum suggested that grandifoliolin was the acetate (I) of the 3β-alcohol corresponding to the ketone, mexicanolide. This was confirmed by treatment with methanolic hydrochloric acid, which gave the acetate (II), m.p. 195—198°, hydrolysed by alkali to the equilibrium mixture of the previously known α- and β-alcohols.[3] This acetate (I) has been obtained by Conolly, McCrindle, and Overton by partial synthesis from mexicanolide,[5] but has not been described before as a natural product, although we have isolated the corresponding isobutyrate, khayasin, from the timber of *Khaya senegalensis*.[3]



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[4] J. D. Conolly, K. L. Handa, R. McCrindle, and K. H. Overton, *Chem. Comm.*, 1966, 867.
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West African Timbers. Part XVIII.[1] Some Reactions of *Cedrela odorata* substance " B " and Khayasin

By E. K. Adesogan, C. W. L. Bevan, J. W. Powell, and D. A. H. Taylor

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West African Timbers. Part XVIII.[1] Some Reactions of *Cedrela odorata* substance "B" and Khayasin

By E. K. Adesogan, C. W. L. Bevan, J. W. Powell, and D. A. H. Taylor

Two closely related compounds, the diketone *Cedrela odorata* B (Ia) and khayasin (Ib), the isobutyrate of the corresponding hydroxyketone, have been obtained from the heartwood of trees belonging to the family Meliaceae. Some derivatives in which the lactone has been opened are described; one (IVa) is shown to arise by an interesting rearrangement, in which a cyclopropane ring is formed. The preparation of deoxyandirobin (X) from methyl angolensate (IV) is also described, and the n.m.r. spectra of all new compounds are recorded.

Cedrela odorata substance "B" (C.O.B.)[2,3] (Ia), is present in varying amounts in the light petroleum extract from the heartwood of *Cedrela odorata* L. (family Meliaceae), often with 7-deacetyl-7-oxogedunin [2] (VIIa) in varying proportions. C.O.B. can be isolated from the mixture by careful fractional crystallisation from methanol or by treatment of the mixture with hydroxylamine, when it remains unaffected, whilst 7-deacetyl-7-oxogedunin is converted to a non-crystalline oxime.

More recently, C.O.B. (Ia) has been obtained from the light petroleum extract from *Khaya grandifoliola* C.D.C.; it occurs in this extract with varying amounts of methyl angolensate (IX).[4] Separation is possible by careful crystallisation from methanol, when the methyl angolensate comes down as very large prisms which can be manually separated from the smaller C.O.B. crystals.

[1] Part XVII, D. E. U. Ekong and E. O. Olagbemi, *J. Chem. Soc.* (*C*), 1966, 944.

[2] C. W. L. Bevan, J. W. Powell, and D. A. H. Taylor, *J. Chem. Soc.*, 1963, 980.

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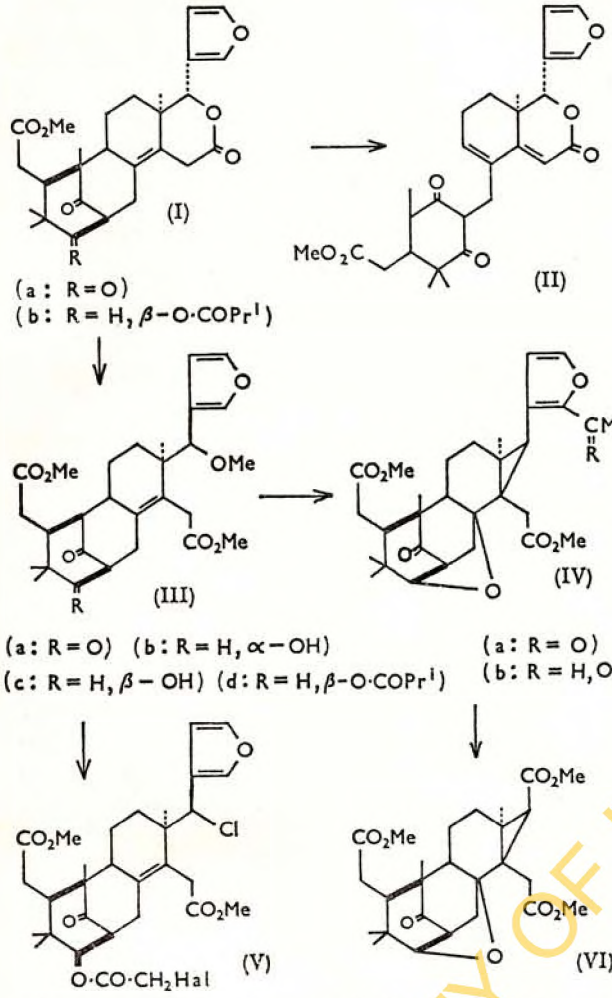
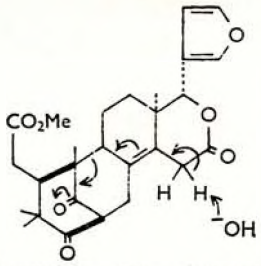


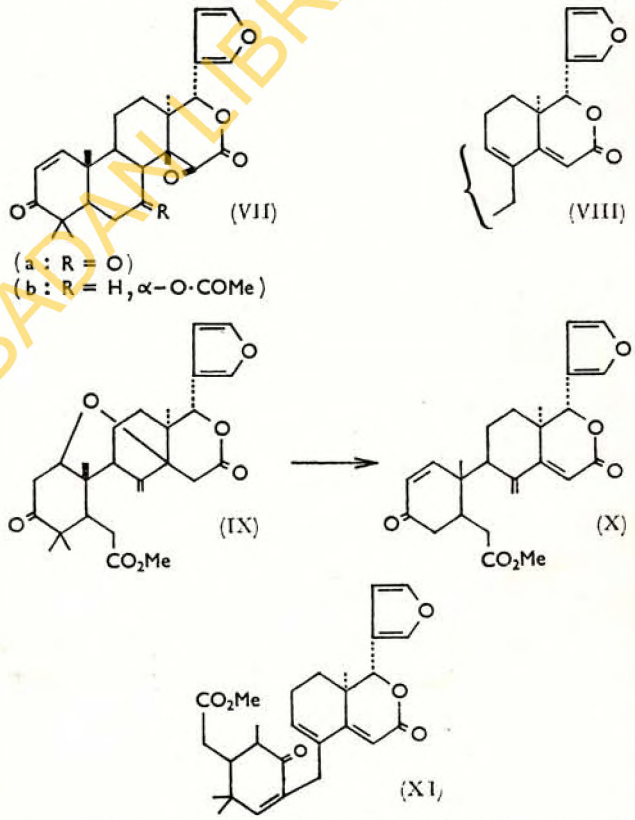
Structure (Ia) has been ascribed to C.O.B.[3] (= mexicanolide[5]). C.O.B. shows the ultraviolet absorption of a furan derivative ($\lambda_{max.}$ 212 mμ, ε = 14,000), although the intensity is considerably stronger than usual [c.f., dihydrogedunin[6] (1,2-dihydro-VIIb), $\lambda_{max.}$ 212 mμ, ε = 4,000]. On treatment with very mild methanolic alkali, a profound change takes place, leading to C.O.D. (II), which shows, in addition to the furanoid absorption ($\lambda_{max.}$ 209 mμ, ε = 12,000), a very intense new band at 288 mμ, ε = 26,000. The new band is the result of two almost coincident chromophores, corresponding to an enolised β-diketone and a transoid diene lactone. The latter corresponds to the chromophore in the transoid diene lactone[7] (VIII) derived from limonin, which shows $\lambda_{max.}$ 284 mμ, ε = 16,400.

The rapid formation of C.O.D. from C.O.B. (addition of one drop of 2N-sodium hydroxide to a methanolic solution of C.O.B. in a spectroscopic cell transforms it to C.O.D. with a half-life of approximately one minute), proceeds, we suggest,[8] by a concerted mechanism, subject to frangomeric acceleration:[9]

[5] J. D. Connolly, R. McCrindle, and K. H. Overton, *Chem. Comm.*, 1965, 162.
[6] A. Akisanya, C. W. L. Bevan, J. Hirst, T. G. Halsall, and D. A. H. Taylor, *J. Chem. Soc.*, 1960, 3827.



Acetylation of C.O.D. with acetic anhydride–pyridine readily gives an enol acetate, which shows three maxima in the ultraviolet spectrum at 220sh (ε = 12,000), 240 (ε = 14,000), and 277 mμ (ε = 14,000). The band at 240 mμ is due to the enol acetate, whilst the remaining absorption at 277 mμ is due to the diene lactone.



Treatment of C.O.B. with 1% methanolic sulphuric acid readily converts[3] it to C.O.C. (IIIa), in which two new methoxyl groups appear in the n.m.r. spectrum at δ 3·6 and 3·2. C.O.C. arises by the acid-induced opening of the lactone ring, the allylic C-17 oxygen being replaced by methoxyl and the carboxylic acid being subsequently methylated under the reaction conditions. We suggest that the reason why gedunin[6] (VIIb) and its 14,15-deoxy-derivative do not undergo this lactone-opening reaction is that the rigid stereochemistry in the C-14,

[7] D. H. R. Barton, S. K. Pradhan, S. Sternhell, and J. F. Templeton, *J. Chem. Soc.*, 1961, 255.
[8] E. O. Arene, C. W. L. Bevan, J. W. Powell, and D. A. H. Taylor, *Chem. Comm.*, 1965, 302.
[9] C. A. Grob and W. Schwarz, *Helv. Chim. Acta*, 1964, **47**, 1870.

C-15 region means that when the lactone is protonated by the acid, ring opening is sterically unfavourable Although methyl angolensate [4] (IX) has the possibility of free rotation about the single 14,15 bond, on treatment with methanolic sulphuric acid an alternative reaction involving cleavage of the C-1, C-14 ether linkage and dehydration of the resulting 14-ol, leading to deoxyandirobin [10] (X), predominates. This experiment was carried out by Mr. A. K. Fasina in this laboratory.

hydroxyl group, the methoxyl group on C-17 suffers replacement by chlorine, yielding the compound (V). Ready replacement is a common feature of allylic and benzylic ethers. Treatment of the resulting 3-chloroacetyl-17-chloro-derivative with sodium iodide in acetone [7] leads to replacement of the chlorine of the chloroacetate by iodine; but the C-17 chlorine is not affected. An *X*-ray structural analysis was carried out on this derivative by Adeoye and Bekoe,[11] and from

N.m.r. spectra of C.O.B. and khayasin derivatives (δ values)

(All spectra were recorded for deuterochloroform solutions)

	H-3	H-15	H-17	CO_2Me	−OMe	α-Furan	β-Furan		Methyl groups
C.O.B. (Ia)	—	3·5m	5·27s	3·73s	—	7·38m 7·57m	6·48m		0·88, 1·02 (2), 1·27
C.O.C. (IIIa)	—	N.A.	4·45s	3·57s 3·68s	3·22s	7·30m 7·42m	6·37m		0·89, 0·93, 1·08, 1·23
3α-ol (IIIb)	N.A.	N.A.	4·65s	3·58s 3·67s	3·22s	7·47m	6·48m		0·67, 0·97, 1·03, 1·10
3β-ol (IIIc)	N.A.	N.A.	4·62s	3·58s 3·65s	3·23s	7·45m	6·53m		0·77, 0·93, 1·00, 1·13
Chloroacetate (V)	5·0d J = 10 c./sec.	N.A.	5·67s	3·57s 3·70s	—	7·47m 7·67m	6·66m	$OCOCH_2Cl$ 4·07s	0·85 (2); 1·15, 1·23
Iodoacetate (V)	4·98d J = 10 c./sec.	N.A.	5·70s	3·57s 3·70s	—	7·50m 7·70m	6·70m	$OCOCH_2I$ 3·70s	0·83, 0·92, 1·17, 1·23
Khayasin (Ib)	4·95d J = 10 c./sec.	N.A.	5·67s	3·70s	—	7·38m 7·53m	6·47m		N.A.
Khayasin C (IIId)	4·83d J = 10 c./sec.	N.A.	4·67s	3·53s 3·65s	3·17s	7·45m 7·62m	6·55m		N.A.
17-Demethoxy-17-chloro-khayasin C	4·86d J = 10 c./sec.	N.A.	5·69s	3·57s 3·70s	—	7·45m 7·69m	6·70m		N.A.
C.O.E. (IVa)	3·97d J = 5·5 c./sec.	N.A.	2·78s	3·62s 3·68s	—	7·43d J = 2 c./sec.	6·38d	$COCH_3$ 2·48s	0·62, 0·90, 0·92, 1·08
C.O.E. Ozonolysis ester (VI)	3·98d J = 6 c./sec.	N.A.	2·40s	3·65s (9 H)	—	—	—		0·61, 0·88, 1·13, 1·25
C.O.E. Reduction product (IVb)	N.A.	N.A.	N.A.	3·62s 3·66s	—	7·15m	6·25m	*CH*OH 4·8bm	0·97, 1·05 (2), 1·13, and 1·24 (d, J = 5 c./sec.)

Abbreviations: s = singlet; d = doublet; m = multiplet; b = broad; N.A. = not assigned.

Unlike C.O.B., C.O.C. is stable to mild attack by alkali, stronger conditions leading to hydrolysis of the two methyl ester groups. We attribute [3] the relative stability of C.O.C. towards alkali to the observation of Grob [9] that synchronous fragmentation of the type leading to C.O.D. occurs in rigid cyclic systems, but far less readily in open-chain systems.

Reduction of C.O.C. with sodium borohydride in ethanol leads mainly to two mono-hydroxy-reduction products, to which we attribute the structures (IIIb) and (IIIc), *i.e.*, the 3α- and 3β-ols, respectively. The 3β-hydroxy compound is the major one (*ca.* 60—80%); it is readily crystallisable from methanol or benzene. The 3α-hydroxy compound is generally the minor product (10—20% yield), and does not readily crystallise. The two products can be separated by absorption chromatography, the 3β-ol being eluted first. The 3β-ol can crystallise in either of two forms, and these interconvert during melting point determination, leading to complex behaviour, though the final m. p. is sharp.

On treatment of the 3β-ol with chloroacetyl chloride in chloroform,[7] in addition to chloroacetylation of the it, the structure of the C.O.C. reduction product, and thence C.O.C., was derived.

Hydrolysis of the iodoacetate with alkali in aqueous methanol, followed by remethylation of the carboxyl groups with diazomethane, resulted in a mixture of the 3α- and 3β-alcohols as shown by thin-layer chromatography, from which the 3β-isomer could be isolated by crystallisation from methanol. The 17-chlorine substituent had been replaced by a methoxyl group under these conditions. The presence of the 3α-hydroxy-derivative in the hydrolysis product will be discussed later.

Khayasin [previously described as the low-melting compound from *Khaya senegalensis* (Desr.) A. Juss [2,12]], (Ib), on treatment with methanolic sulphuric acid, undergoes a ring-opening reaction parallel to that in the formation of C.O.C. from C.O.B., giving khayasin C (IIId), which has a second methoxycarbonyl group and a new ether-type methoxyl group (bands at δ 3·6 and 3·2, respectively, in the n.m.r. spectrum). The molar rotation change for the reaction khayasin to khayasin C, $\Delta M = +660°$, is closely similar to that for the change

[10] W. D. Ollis, A. D. Ward, and R. Zelnik, *Tetrahedron Letters*, 1964, **37**, 2607.

[11] S. A. Adeoye and D. A. Bekoe, *Chem. Comm.*, 1965, 301.

[12] E. K. Adesogan, C. W. L. Bevan, J. W. Powell, and D. A. H. Taylor, *Chem. Comm.*, 1966, 27.

of C.O.B. to C.O.C. ($\Delta M = +690°$). Mild treatment of khayasin (Ia) with alkali yielded a gum which failed to crystallise; its ultraviolet spectrum showed bands attributable to furan (214); to αβ-unsaturated ketone (230sh); and to an αβ,γδ-unsaturated lactone (276 mμ). This is consistent with the structure (XI), proposed by Connolly, McCrindle, and Overton [5] for the hydrolysis product from the acetylated reduction product (III, R = H β-OAc) of mexicanolide. Unlike khayasin itself, khayasin C simply undergoes ester hydrolysis on treatment with aqueous methanolic alkali, and remethylation of the two carboxyl groups with diazomethane yields a mixture of the two reduction products from C.O.C., (IIIb) and (IIIc) in which the 3α-isomer predominates. Alkaline hydrolysis of khayasin (Ib), gave a volatile acid fraction, which was neutralised and evaporated to dryness. The resulting sodium salts were taken up in deuterium oxide; the n.m.r. spectrum showed a six proton doublet ($J = 7$ c./sec.) at δ 1·1 and a one proton septet at δ 2·4, corresponding to sodium isobutyrate; there was also a minor band at δ 1·8, corresponding to sodium acetate. The isobutyric acid was also identified by preparation of the *p*-phenylphenacyl derivative, which was shown to be identical with the authentic material.

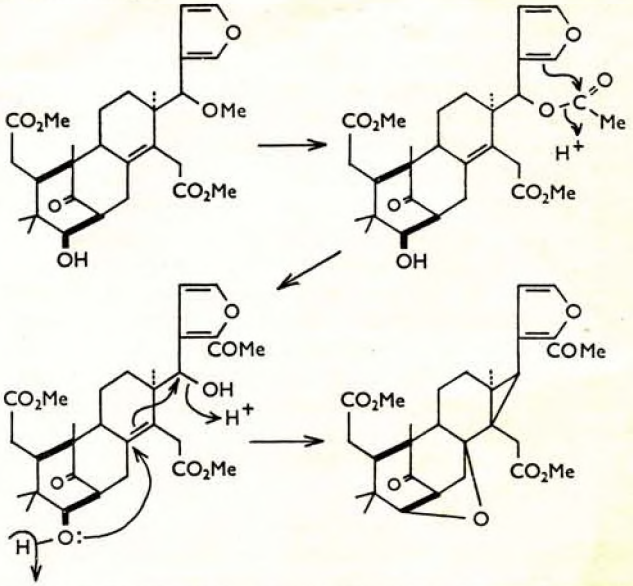
It is known from the *X*-ray work [11] that the iodoacetate group in compound (V) has the β-configuration; and the n.m.r. spectra of both khayasin (Ib) and khayasin C (IIId) show the proton at C-3 as a doublet, $J = 10$ c./sec.; this splitting is the same as that observed for the iodoacetate, indicating the β-configuration for the isobutyrate ester in khayasin. A 3α-ester should give a much smaller value of the coupling constant. This configuration was confirmed by synthesis of khayasin C by isobutyrylation of the 3β-alcohol (IIIc).

The production of the 3α-ol as the main product from the hydrolysis of khayasin C is probably not due to an unusual mechanism of hydrolysis, involving the $-CH_2{\cdot}CO_2H$ group, as suggested earlier.[12] Subsequent experiments have shown that treatment of either reduction product of C.O.C. with alkali, under conditions used in the hydrolysis of both iodoacetate and isobutyrate, followed by remethylation with diazomethane, leads to an equilibrium mixture of the two isomers, in which the 3α-isomer predominates. It seems most probable that this equilibration involves a reversible aldol reaction of the β-hydroxy-ketone, as suggested by Overton and his colleagues [13] to explain the chemistry of closely related swietenine derivatives.

On treatment of C.O.C., (IIIa), with hydrochloric acid in chloroform, the main reaction is the reclosure of ring D, giving C.O.B. (Ia). When the same reaction is carried out on khayasin C, (IIId), the product isolated is that in which the 17-methoxyl group has been replaced by a 17-chloro-atom, as occurred in the preparation of the chloroacetate. This replacement is indicated by the loss of the ether methoxyl band in the n.m.r. spectra, and by the down-field shift of the H-17 absorption to 5·69 p.p.m.

One of the most interesting rearrangements in this series results from attempted acetylation of the 3β-hydroxy reduction product of C.O.C. Attempted acetylation with acetic anhydride in pyridine leads to quantitative recovery of starting material; but treatment with acetic anhydride in acetic acid solution, with toluene-*p*-sulphonic acid as catalyst,[14] leads to the formation in good yield of a new compound that we name C.O.E.

The infrared spectrum of C.O.E. shows the absence of hydroxyl absorption at 3300 cm.$^{-1}$; but shows the presence of a new unsaturated carbonyl group (1675 cm.$^{-1}$). The ultraviolet spectrum shows an intense new absorption (280 mμ, $\varepsilon = 12{,}000$), together with a weaker band at shorter wavelength (206 mμ, $\varepsilon = 4800$). Chemical analysis shows no *O*-acetyl; but the n.m.r. spectrum shows a new three proton singlet at δ 2·48. The methoxyl peak at δ 3·2 has disappeared, and the singlet due to H-17 at δ 4·6 has moved to δ 2·78, showing that the C-17 methoxyl has not been replaced by another electronegative substituent. Furthermore, in the furan region, there are now only two protons; these appear as well-defined doublets, $J = 2$ c./sec. A doublet at δ 3·97 suggests a proton at the end of an ether linkage (not an −OH, from the infrared evidence); the other end of the ether bridge must be tertiary, from the absence of second proton in the appropriate range in the n.m.r. spectrum. On the basis of this evidence, we put forward (IVa) as the structure of C.O.E. As the furan acetylation does not occur under these conditions with C.O.B. (Ia), it would seem that the mechanism of the acetylation must be included in the mechanism of the rearrangement. Therefore, we suggest, firstly, substitution of *O*-acetyl for the C-17 *O*-methyl; then intramolecular *C*-acetylation by the acetate, involving a five-membered transition state; then elimination of the remaining C-17 hydroxyl, the resulting carbonium ion rearranging to the final product:



[13] J. D. Connolly, R. Henderson, R. McCrindle, K. H. Overton, and N. S. Bhacca, *J. Chem. Soc.*, 1965, 6935.
[14] R. B. Turner, *J. Amer. Chem. Soc.*, 1953, **75**, 3489.

Further support for the structure assigned to C.O.E. comes from ozonolysis, followed by methylation of the carboxyl group produced from the furan substituent Although this ester (VI) could not be obtained crystalline, it gave a very sharp n.m.r. spectrum. The three $-CO_2Me$ groups gave a single sharp resonance at δ 3·65; a doublet ($J = 6$ c./sec.) at δ 3·98 was observed for the proton at C-3; a singlet at δ 2·40 corresponded to H-17 (this compares with 2·78 before ozonolysis; the methoxycarbonyl would be expected to exert less deshielding influence than the substituted furan it replaces); there was no absorption corresponding to furanoid protons. In the ultraviolet, the ozonolysis ester showed only weak absorption at short wavelength ($\lambda_{max.}$ 205 mμ, $\varepsilon = 1100$). This compares with $\lambda_{max.}$ 208 mμ, $\varepsilon = 76$ for ethyl cyclopropylcarboxylate.[15]

Reduction of C.O.E. with sodium borohydride gave a non-crystalline product (IVb) but like the ozonolysis ester, this gave a clean n.m.r. spectrum, with a new secondary methyl absorption (δ 1·24, $J = 5$ c./sec.) in place of the former acetyl singlet at δ 2·48. The reduction product gave an absorption maximum in the ultraviolet at 222 mμ, which is intermediate between that observed for a simple furan [*e.g.*, dihydrogedunin [6] (VIIa), at 212 mμ] and a vinyl furan (*e.g.*, α-vinyl furan [16] at 266 mμ). This is in accordance with the formulation as a cyclopropylfuran.

EXPERIMENTAL

All melting points were taken on a hot-stage microscope, and are uncorrected. Infrared spectra quoted are for Nujol mull unless otherwise noted, and were taken on a Perkin-Elmer model 137, or 221, instrument. Ultraviolet spectra were taken, in methanol solution, on a Perkin-Elmer model 137 UV, or Unicam S.P. 700, instrument. "Deactivated alumina" refers to Peter Spence type H, shaken with 5% by volume of 10% acetic acid. Light petroleum refers to the fraction b. p. 60—80°. Optical rotations were taken in chloroform solution.

C.O.B. (*Ia*) *from* Cedrela odorata *Extract*.—Crystalline *Cedrela odorata* extract ("A" & "B," 20 g.) in methanol (250 ml.) and chloroform (250 ml.) was treated with hydroxylamine hydrochloride (50 g.) and sodium acetate (50 g.) in water (100 ml.). After refluxing the mixture (15 min.), water (500 ml.) was added, and the organic material extracted into chloroform. The extract was washed and evaporated; crystallisation of the resulting gum from methanol–chloroform yielded C.O.B. (Ia) as crystals, m. p. 226—230° (17 g.). Recrystallisation from methanol did not raise the m. p. (Found: C, 69·1; H, 6·8; O, 24·25; OMe, 6·1; OAc, 0·0. Calc. for $C_{27}H_{32}O_7$: C, 69·2; H, 6·9; O, 23·9; 1 OMe 6·6%) $\lambda_{max.}$ 212 mμ, $\varepsilon = 14{,}000$. $[\alpha]_D^{25} = -100°$, $\nu_{max.}$ (CH_2Cl_2): 1733 (ester and lactone); 1704 (cyclohexanone); 1505 and 875 cm.$^{-1}$ (furan).

Extraction of Khaya grandifoliola.—The ground heartwood (210 kg.) was extracted with hot light petroleum by percolation for 24 hr. Evaporation of the solvent, and addition of ether, gave a solid. Fractional crystallisation from methanol yielded methyl angolensate (IX) (39 g., m. p. 197°), and C.O.B. (Ia) (11·5 g., m. p. 225—230°).

[15] G. W. Cannon, A. A. Santilli, and P. Shenian, *J. Amer. Chem. Soc.*, 1959, **81**, 1660.

Treatment of C.O.B. with Alkali.—C.O.B. (Ia) (0·5 g.) was dissolved in boiling methanol (50 ml.), and 2N-sodium hydroxide (5 ml.) was added. After refluxing for 10 min., the solution was cooled; water (100 ml.) was added, and the solution acidified with dil. sulphuric acid. The product was extracted with chloroform (3 × 25 ml.), the extract washed, and evaporated to dryness. Crystallisation from benzene–light petroleum gave *C.O.D.* (II) (0·4 g.) as a solid, m. p. 173—175° (Found: C, 69·1; H, 6·7; O, 24·15; $C_{27}H_{32}O_7$ requires: C, 69·2; H, 6·9; O, 23·9%) $\lambda_{max.}$ 209 ($\varepsilon = 12{,}000$); 288 mμ ($\varepsilon = 26{,}000$); $\nu_{max.}$ (CH_2Cl_2): 1730 (ester); 1712 (unsaturated lactone); 1670sh (unsaturated ketone); 875 cm.$^{-1}$ (furan).

Acetylation of C.O.D. (II).—Acetylation of C.O.D. (II) (1 g.) with acetic anhydride–pyridine yielded a gum, which was chromatographed on deactivated alumina (25 ml.). Elution with benzene–ethyl acetate (1 : 1) yielded the *acetate* (0·4 g.), m. p. 165—167°, but partially recrystallising, and melting finally at 180° (Found: C, 68·3; H, 6·7; O, 24·8; OMe, 6·2; OAc, 8·7. $C_{26}H_{28}O_5$,OMe,OAc requires: C, 68·2; H, 6·7; O, 25·1; OMe, 6·1; OAc, 8·4%) $\lambda_{max.}$ 220 ($\varepsilon = 12{,}000$); 240 ($\varepsilon = 14{,}000$); and 277 mμ ($\varepsilon = 14{,}000$). $\nu_{max.}$ (CH_2Cl_2) 1760 (enol acetate); 1733 (ester); 1712 (unsaturated lactone); 1675 (unsaturated ketone); 875 cm.$^{-1}$ (furan).

C.O.C. (IIIa).—C.O.B. (Ia) (1·0 g.) in methanol (100 ml.) and conc. sulphuric acid (1·0 ml.) was heated under reflux (30 min.). Water (*ca.* 100 ml.) was added to the hot solution. On cooling, crystals of *C.O.C.* (IIIa) were deposited (0·85 g., m. p. 165—170°). Recrystallisation from methanol raised the m. p. to 171—173° (Found: C, 67·9; H, 7·6; O, 24·8; OMe, 18·2. $C_{26}H_{29}O_5(OMe)_3$ requires: C, 67·7; H, 7·4; O, 24·9; OMe, 18·1%) $\alpha_D^{25} = +42·5°$; $\lambda_{max.}$ 212 mμ, $\varepsilon = 12{,}000$. $\nu_{max.}$ (CH_2Cl_2) 1735 (esters); 1705 (cyclohexanone); 1500 and 876 cm.$^{-1}$ (furan).

C.O.C. (IIIa) *from* Cedrela odorata *Extract*.—(i) Crystalline *Cedrela odorata* extract ("A" + "B", 6·5 g., m. p. 222—228°) in methanol (400 ml.) and conc. sulphuric acid (6·5 ml.) was refluxed on the water-bath (30 min.). Water (*ca.* 100 ml.) was added to the hot solution. On cooling, crystals (6·0 g., m. p. 115—155°) were deposited. Recrystallisation from methanol yielded C.O.C. (IIIa) (4·9 g., m. p. 169—172°).

(ii) Crystalline *Cedrela odorata* extract (13·5 g., m. p. 220—226°) in methanol (1 l.) and conc. sulphuric acid (13·5 ml.) was slowly distilled on the water-bath (60 min.). Addition of water to the hot solution gave crystals (12·0 g.). This mixed product was dissolved in methanol (*ca.* 750 ml.); hydroxylamine hydrochloride (12 g.) and sodium acetate (12 g.) in water (*ca.* 50 ml.) was added, and the mixture refluxed (15 min.). Addition of water to the hot solution yielded, on cooling, crystalline C.O.C. (IIIa) (11·5 g., m. p. 168—170°).

Action of Methanolic Sulphuric Acid on Methyl Angolensate (IX).—Methyl angolensate (IX) (0·5 g.) in methanol (30 ml.) and conc. sulphuric acid (3 ml.) was heated under reflux (2 hr.). Water (10 ml.) was added to the hot solution. On cooling, deoxyandirobin (X) was precipitated (0·31 g., m. p. 170—172°). This was shown to be identical to an authentic sample.

Reduction of C.O.C. (IIIa).—To a solution of C.O.C. (IIIa) (10 g.) in ethanol (450 ml.) and chloroform (50 ml.), sodium borohydride (1·5 g.) was added, and the mixture was

[16] H. A. Laitinen, F. A. Miller, and T. D. Parks, *J. Amer. Chem. Soc.*, 1947, **69**, 2707.

stirred for 2 hr. at 25°. Water (250 ml.) was then added, and the product extracted with chloroform (5 × 50 ml.). The extract was washed with water (2 × 100 ml.), and evaporated to dryness. The resulting gum was taken up in hot ethyl acetate–benzene, and chromatographed on alumina (250 ml.). Elution with 10% ethyl acetate–benzene yielded mainly the 3β-ol (IIIc) (5·45 g.) (Found: C, 67·8; H, 7·5. $C_{29}H_{40}O_8$ requires C, 67·4; H, 7·8%) $[\alpha]_D^{25} = -6°$; m. p. complex, but ending sharply at 179°. Elution with ethyl acetate gave some 3α-ol (IIIb) (700 mg., $[\alpha]_D^{25} = +93°$; m. p. 188—196° after recrystallisation from methanol). Other fractions, and mother-liquors from these fractions, gave mixed products.

Chloracetylation of the 3β-*ol* (IIIc).—The 3β-ol (IIIc) (1·0 g.) in chloroform (65 ml.) was heated under reflux with chloracetyl chloride (25 ml.) and pyridine (2 drops) for 6 hr. After cooling, the solution was poured into water (250 ml.), shaken, and separated. The organic layer was washed with aqueous sodium carbonate and water, and evaporated. The resulting brown gum was chromatographed on deactivated alumina (25 ml.). Elution with benzene gave the 17-*demethoxy*-17-*chloro*-3β-*chloroacetate* (V) 198 mg., m. p. 225—237°. Recrystallisation from benzene did not significantly alter the melting point (Found: Cl, 11·8%. $C_{31}H_{40}O_9Cl_2$ requires Cl, 11·3%).

The Iodoacetate (V).—The chloroacetate (V) (1·5 g.) and sodium iodide (10 g.) were refluxed in acetone (250 ml.) for 5 hr. Water (500 ml.) was added, and the product extracted with chloroform. The extract was washed (water, dilute sodium thiosulphate solution, and water) and evaporated. Crystallisation from benzene yielded the *iodoacetate* (V) 0·90 g., m. p. (decomp.) 220—230° (Found: I, 16·5. $C_{31}H_{40}O_9ClI$ requires I, 16·1%).

Hydrolysis of the 3β-*Iodoacetate* (V).—The iodoacetate (V) (0·23 g.) in methanol (45 ml.) and chloroform (10 ml.) was treated with 2N-sodium hydroxide (25 ml.) under reflux (2 hr.). After acidification, the product was extracted into chloroform (4 × 20 ml.), and the extract washed and evaporated. Treatment with diazomethane, followed by crystallisation from methanol, yielded a microcrystalline solid (0·13 g.). T.l.c. of this showed two spots, corresponding to the 3α- and 3β-ols (IIIb and IIIc), respectively; the latter spot predominated. The i.r. and n.m.r. spectra also showed the product to be mainly the 3β-compound (IIIc).

Separation of Khayasin (Ib) *from* Khaya senegalensis *Extract.*—The crude light petroleum extract (50 g.) was chromatographed on deactivated alumina (1 l.). Elution with 25% benzene–light petroleum yielded khayasin (Ib) (*ca.* 5% of the total extract); recrystallisation from benzene gave crystals, 2·48 g., m. p. 114—116°, $[\alpha]_D^{25}$ −165°; $\lambda_{max.}$ 209 mμ, ε = 12,500. $\nu_{max.}$ 1730 (ester and lactone); 1705 (ketone); 1505 and 875 cm.$^{-1}$ (furan) (Found: C, 72·0; H, 7·6%. $C_{31}H_{40}O_8,C_6H_6$ requires C, 71·8; H, 7·5%). The presence of benzene of crystallisation was confirmed by spectral evidence (infrared and n.m.r.).

Mild Hydrolysis of Khayasin (Ib).—Khayasin (Ib) (0·36 g.) in methanol (40 ml.) was treated with 2N-sodium hydroxide (3 ml.) under reflux, for 10 min. After cooling, water (40 ml.) was added, the solution acidified (dil. sulphuric acid), and the product extracted with chloroform (3 × 20 ml.). Washing and evaporation yielded a gum, which would not crystallise. $\lambda_{max.}$ 214 (furan); 230sh (αβ-unsaturated carbonyl); and 276 mμ (αβ,γδ-unsaturated lactone).

Khayasin C (IIId).—Khayasin (Ib) (0·58 g.) was heated with methanolic sulphuric acid (1%, 100 ml.) for 20 min. Water (100 ml.) was added, and the product extracted with chloroform (3 × 20 ml.). Evaporation yielded a gum; crystallisation from methanol yielded *khayasin C* (IIId) as crystals (0·39 g., m. p. 146—156°). Recrystallisation raised the m. p. to 154—157°. $[\alpha]_D^{25}$ −39° (Found: C, 67·8; H, 7·9. $C_{33}H_{46}O_9$ requires C, 67·55; H, 7·9%). $\lambda_{max.}$ 209 mμ, ε = 10,000. $\nu_{max.}$ 1740 (esters); 1710 (ketone); 1505 and 875 cm.$^{-1}$ (furan).

Hydrolysis of Khayasin C (IIId).—Khayasin *C* (IIId, 0·45 g.) in methanol (50 ml.) and 2N-sodium hydroxide (50 ml.) was refluxed for 2 hr. After acidification, the hydrolysis product was extracted into chloroform; evaporation yielded a gum, which was treated with diazomethane to give the alcohols (IIIb and IIIc) (0·31 g., m. p. 179—181°) as a solid from ether–methanol. T.l.c. and i.r. spectra showed the product to be mainly the 3α-ol (IIIb); this was confirmed by the observed rotation $[\alpha]_D^{25}$ +69° {cf. α-ol (IIIb), $[\alpha]_D^{25} = +93°$; β-ol (IIIc), $[\alpha]_D^{25} = -6°$}.

Vigorous Hydrolysis of Khayasin (Ib).—Khayasin (Ib) (1·1 g.) in methanol (80 ml.) was heated under reflux with 2N-sodium hydroxide solution (50 ml.) for 2 hr. The solution was then just neutralised with sulphuric acid, and the mixture distilled to dryness; water (10 ml.) was added to the residue, and the solution distilled to dryness. The combined distillate was titrated with 2N-caustic soda (2·01 ml) (phenolphthalein). The resulting sodium salt solution was evaporated to dryness, the residue was taken up in deuterium oxide, and the n.m.r. spectrum taken. This revealed a mixture of sodium isobutyrate (*ca.* 85%) and sodium acetate (*ca.* 15%). The *p*-phenylphenacyl derivative of the acid was prepared, m. p. 74—77°, and shown to be identical with that from authentic isobutyric acid.

Oxidation of Hydrolysis Product from Khayasin C.—The methylated hydrolysis product (IIIb + IIIc) from khayasin C, (0·31 g.) in acetone (25 ml.) was treated dropwise with chromic acid solution (8N) until a yellow colour persisted for five min. Saturated aqueous potassium carbonate (25 ml.) was then added, and the product extracted into ether (3 × 30 ml.). The organic product, recrystallised (methanol), had m. p. 169—170°, and was shown by infrared and n.m.r. spectra to be identical with authentic C.O.C. (IIIa).

Isobutyrylation of the 3β-*ol* (IIIc).—The 3β-ol (IIIc) (0·67 g.) was heated under reflux (6 hr.) with isobutyryl chloride (20 ml.) and pyridine (3 drops) in chloroform (50 ml.). After cooling, the solution was thoroughly washed [water, 2N-sodium carbonate, and water]; then dried and evaporated, yielding a solid which gave the isobutyrate (IIId) (0·61 g., m. p. 153—155°, $[\alpha]_D^{25}$ −40°). This product was shown to be identical to khayasin C (IIId) by infrared and n.m.r. spectra.

The Action of Alkali on the 3β-*ol* (IIIc).—The 3β-ol (IIIc) (0·15 g.) in methanol (50 ml.) was treated with 2N-sodium hydroxide (35 ml.) under reflux for 2 hr. The chloroform extract from the neutralised solution was washed and evaporated, and the resultant gum treated with excess diazomethane. Crystallisation from methanol gave a microcrystalline product (0·073 g.), which was shown by t.l.c. to be predominantly the 3α-ol (IIIb). This was confirmed by both i.r. and n.m.r. spectroscopy.

Treatment of C.O.C. (IIIa) *with Conc. Hydrochloric Acid.*—C.O.C. (IIIa) (500 mg.) in chloroform (25 ml.) was heated under reflux (3 hr.) with conc. hydrochloric acid (2 ml.).

The resulting solution was washed with water, then evaporated, and the residual gum crystallised from methanol/chloroform (4 : 1), yielding C.O.B. (Ia) (200 mg., m. p. 216—220°), shown to be identical with the authentic material by infrared, t.l.c., and mixed m. p.

Treatment of Khayasin C (IIId) *with Conc. Hydrochloric Acid.*—Khayasin C (IIId) (100 mg.) in chloroform (15 ml.) and conc. hydrochloric acid (2 ml.) was heated under reflux for 10 hr. Water (25 ml.) was added, and the organic layer separated. After evaporation and crystallisation from ethanol, crystals of 17-*demethoxy*-17-*chlorokhayasin C* (50 mg., m. p. 188—192°) were obtained (Found: Cl, 6·4%. $C_{32}H_{43}O_8Cl$ requires Cl, 6·0%).

Attempted Acetylation of the 3β-*ol* (IIIc).—The 3β-ol (IIIc) (5 g.), toluene-*p*-sulphonic acid (5 g.), acetic anhydride (50 ml.) and acetic acid (200 ml.) were stored at room temperature (22°) overnight (16 hr.). The product was poured into water (650 ml.), and extracted with chloroform (4 × 50 ml.). After washing and evaporation, the gum was crystallised from benzene, yielding *C.O.E.* (IVa) (2·45 g., m. p. 195—200°), as brownish crystals. Recrystallisation from benzene–light petroleum afforded *cream crystals*, m. p. 196—199° [Found: C, 68·3; H, 7·4; O, 24·5; OMe, 11·6%. $C_{28}H_{32}O_6\cdot(OMe)_2$, requires: C, 68·4; H, 7·3; O, 24·3; OMe, 11·8%. $\lambda_{max.}$ (methanol) 206 (ε = 4,800); 280 mμ (ε = 12,000). $\nu_{max.}$ (Nujol) 1735 (ester), 1715 (ketone), and 1674 cm.$^{-1}$ (conjugated ketone)].

Ozonolysis of C.O.E. (IVa).—C.O.E. (IVa) (1·0 g.) in ethyl acetate (150 ml.) was treated with ozone at −80°. When the solution became blue (1·5 hr.), the ozone supply was stopped; hydrogen peroxide (20 vol., 50 ml.) was added, and the mixture refluxed for 3 hr. Water (150 ml.) was added, and the product extracted into chloroform. The acidic fraction was isolated with sodium carbonate and esterified with diazomethane. Attempts to crystallise the resulting *ester* (VI) failed, even after chromatography on alumina (25 ml.). [$\lambda_{max.}$ (ethanol) 205 mμ, ε = 1,100.]

Reduction of C.O.E.—C.O.E. (IVa) (0·5 g.) in ethanol (125 ml.) was treated with sodium borohydride (0·5 g.) in water (*ca.* 10 ml.), and the mixture stirred for 24 hr. (*ca.* 25°). After addition of acetone (*ca.* 5 ml.), and water (125 ml.), the *product* (IVb) was extracted with chloroform (50 ml. + 4 × 25 ml.), washed, and evaporated to give a solid foam, which could not be induced to crystallise ($\lambda_{max.}$ 222 mμ, ε = 6,400).

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