SUMMARY

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PART I

INTRODUCTION

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The Flacourtiaceae family is well known for a long period for its characteristic medicinal oils. The oils from some of the plants belonging to this family are reported to have medicinal applications in skin diseases with some success. The selection of the family for the present work stemmed from the fact that no thorough chemical investigations has been carried out on this family.

Section A : Morphological features of the plants of Flacourtiaceae family

Flacourtiaceae is a family of seventy genera and about five hundred species which are chiefly found in tropical and subtropical regions. Leaves are simples, alternate, stipules. Flowers are herphrodite or unisexual. Fruits are indehiscent. Seeds are with fleshy endosperm and medium-sized embryo.

Gynocardia odorata (R Br) is a ever green tree; all parts are glabrous. It flowers April and May, and fruits November to January. Leaves are oval-shaped, about 20 cm by 6 cm. Flowers are pale yellow, almost 3.8 cm diametre. It is easily recognized by hard round fruits growing on the stem and main branches. The seeds are

poisonous. The oil from the seeds is externally used in leprosy and other form of skin diseases.

Flacourtia sepiaria (Roxb) is a thorny small rigid bush. Leaves on the young shoots are alternate, fascicled, 2-3.5 cm by 1.2 cm. Flowers are dioecious, small, axillary, greenish. Berry is globular, reddish turning dark -coloured when ripe; about 6-10 mm diametre. The bark triturated in sesamum oil, is used as a liniment in rheumatism.

Section B : Review of the investigated plants of Flacourtiaceaefamily

Literature survey showed that out of five hundred species, phytochemical investigation has been reported for ten species. Some of them yielded therapeutically effective oils from their seed kernels. Most of them yielded sitosterol and triterpenoids. Monosaccarides, glycosides, mangostins and flavonoids were also isolated.

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PART II

CHEMICAL INVESTIGATION ON GYNOCARDIA ODORATA (R BR)

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CHAPTER 1

REVIEW OF PENTACYCLIC TRITERPENOIDS IN BRIEF

All the reported pentacyclic triterpenoids may be classified according to twenty five different skeletons (Chart 1, p 13 in the text). A fairly good amount of review works on various aspects of triterpenoid has been published in the literature. In the present review, a list of naturally occurring pentacyclic triterpenoid lactones has been given (Chart 2, p 16 in the text).

CHAPTER 2

ISOLATION AND STRUCTURE ELUCIDATION OF ODOLACTONE, A NEW TRITERPENOID

Section A : Preliminary investigation on odolactone

From the benzene extract of the bark of Gynocardia odorata, an ether insoluble portion has been obtained which furnished a semi-amorphous solid on repeated crystallization from MeOH-$CHCl_3$, mp > 320°, $[\alpha]_D$ - 47.06° and it has been shown to be a new triterpenoid, named odolactone. It showed positive L-B test for triterpenoid and negative TNM test for double bond.

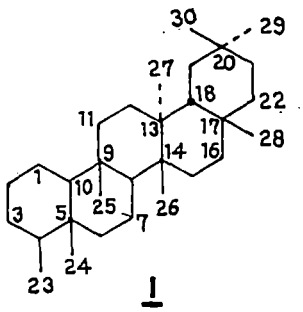
Section B : Spectroscopic analysis of odolactone

Odolactone exhibited the following spectral data. IR ν_{max}^{nujol} cm^{-1} : 1720 (ketone), 1755 (γ-lactone); CD (MeOH - $CHCl_3$) : $\Delta\epsilon$ - 2.30 at 289 nm; ^1H NMR ($CDCl_3$ with TMS, ppm) : 0.73, 0.88, 0.96, 0.98, 1.02, 1.16 (18H, each s, 6 tert Me), 0.87 (3H, d, J7 Hz, 1 sec Me), 2.25 (1H, ddd, J 13, 13 & 7 Hz, C2-Ha), 2.30 (1H, q, J 7 Hz, C4-Ha), 2.40 (1H, ddd, J 13, 5 & 3 Hz, C2-He), 4.38 (1H, t, J 3 Hz, He geminal to lactone oxygen); ^{13}C NMR ($CDCl_3$ with TMS, ppm) : 6.79 (q), 13.55 (q), 14.54 (q), 16.40 (q), 19.96 (t), 22.13 (t), 22.43 (t), 28.20 (s), 29.63 (q), 30.46 (s), 31.05 (q), 34.15 (t), 34.27 (2C, q & t), 35.58 (t), 35.79 (t), 36.55 (s), 39.96 (t), 40.30 (t), 41.30 (t), 41.91 (s), 44.23 (d), 47.85 (s), 48.01 (d), 51.01 (s), 57.73 (d), 58.20 (d), 80.73 (d), 180.07 (s), 212.53 (s).

Section C : The structure of odolactone

Elemental analysis and MS (M^+ , 454) established the molecular formula $C_{30}H_{46}O_2$. IR showed the presence of six membered ketone (1710 cm^{-1}) and γ-lactone moiety (1755 cm^{-1}). APT showed the presence of 7 CH_3, 10 CH_2,

5 CH and 8 quarternary carbons. One of the seven methyl groups is a secondary methyl (from ^{1}H NMR). These functionalities could be well fitted with the skeleton of friedelane (1). In friedelane, there are 8 CH_3 (C-23 methyl is secondary), 12 CH_2, 4 CH and 6 quarternary carbons. In odolactone one of the tertiary methyl groups has been converted to the lactone carbonyl carbon, one of the CH_2 groups is attached to the lactone oxygen making it a methine group and another CH_2 has been converted to the ketone carbonyl carbon; thus accounting for the 8-1 = 7 CH_3, 12-2 = 10 CH_2, 4+1 = 5 CH and 6+2 = 8 quarternary carbons in the molecule.



1

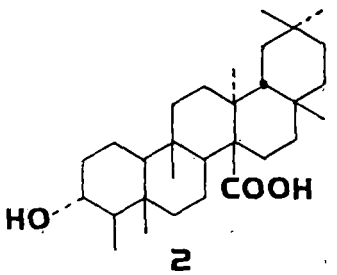
Friedelane

The keto group is placed at C-3, because only this assignment could explain the multiplicity of the protons at 2.25 (ddd), 2.30 (q) and 2.40 (ddd) ppm for C2-Ha, C4-Ha and C2-He respectively. Moreover, the negative effect, $\Delta\epsilon^{MeOH}_{289}$ - 2.30 (cf $\Delta\epsilon^{Dioxan}_{290}$ - 2.69 for friedelan-3-one) is strongly supporting the position of the 3-keto group at C-3.

The methyl chemical shifts in ^{1}H NMR are assigned as shown in the adjacent table by comparison of the reported values of friedelane derivatives. Thus it is inferred that the C-26 methyl of friedelane is converted to the lactone carbonyl carbon. This was supported by transforming odolactone to trichadenic acid A which was reported to have the structure 2.

Me resonances (ppm)	Assignment
0.73(s)	C-24
0.87(d)	C-23
0.88(s)	C-25
0.96(s)	C-29
0.98(s)	C-30
1.02(s)	C-27
1.16(s)	C-28

The termination point of lactone oxygen has been deduced from the following argument. The signal at 4.38 ppm (t, J 3 Hz) is attributed to the proton geminal to lactone oxygen. The low coupling constant suggests that the oxygen is axially oriented. Each of the protons centred at 1.76 and 1.85 ppm is a double doublets with J_{gem} 13 Hz and J 3 Hz. Obviously, the protons are vicinal to the proton geminal to the lactone oxygen. These are slightly broadened. Such a situation is found if lactone oxygen is attached to C-12. Now the signals at 1.76 and 1.85 ppm could be attributed to C-11-H_2, the broadening of which are due to the four bond distance coupling with the nearby axial C-25 methyl. Thus structure 3 was proposed for odolactone and was reported in the Tetrahedron Letters. A xerox copy of the reprint has been enclosed (Appendix 1).



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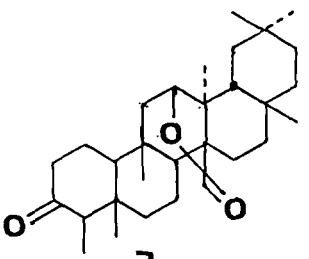
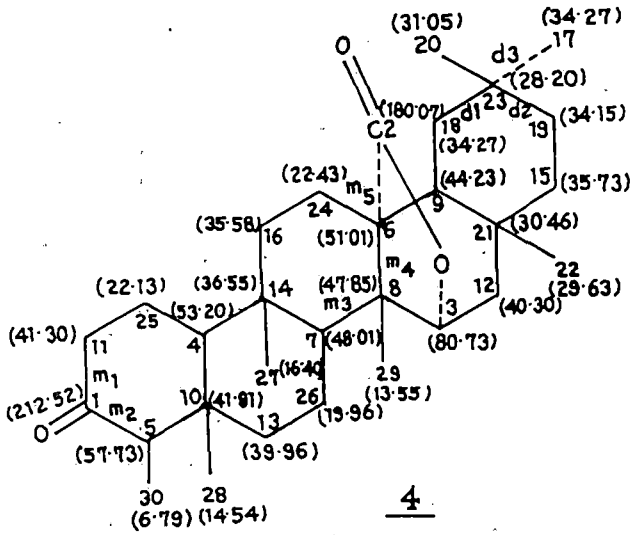


3

Section D : Application of 2D NMR techniques on odolactone. Revision of the previous structure of odolactone and some other naturally occurring triterpenoids of the friedelane group

Doubt about the validity of structure 3 for odolactone remained because in the structure elucidation of trichadenic acids, Sultanbawa et al located the carboxylic acid function at C-26 in the friedelane skeleton without any valid scientific ground. Moreover, the termination point of the lactone oxygen of odolactone at C-12 in 3, was established by some of its selective ^1H peaks of interest.

To solve this structural problem, 2D NMR techniques, namely, $^{1}H-^{1}H$ 2D COSY and CCC2D were employed. 2D COSY spectrum of odolactone assigned the C-23, C-24, C-25 methyls and gem-dimethyls (C-29 & C-30), but failed to assign the remaining two methyls. However, the CCC2D spectrum unambiguously established the structure of odolactone as 4. Out of 34 carbon-carbon bonds, 26 bonds show distinct connectivities in the CCC2D plot, three bonds (marked with 'd' letters) are deduced to arise from superimposed ^{13}C doublets and five bonds (marked with 'm' letters) are missing. The assignments of the missing bonds are obvious from the multiplicities of the respective carbon centres and other general spectral features found in odolactone.



4

Correct structure of odolactone. The numbering of carbons corresponds to a numbering of the signals as they appear in the BBD ^{13}C spectrum. Data in parentheses are ^{13}C chemical shifts.

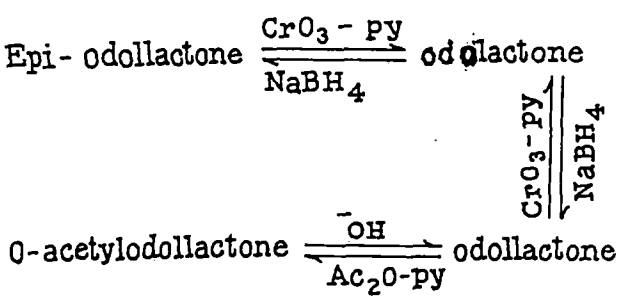
This revision of the structure of odolactone also leads to the revision of the structures of some previous reported naturally occurring triterpenoids of the friedelane group; namely, O-acetylodollactone, odollactone, trichadenic acid A, O-acetyltrichadenic acid A, trichadenic acid B, O-acetyltrichadenic acid B, trichadonic acid, trichadonal, O-acetyltrichadenal, 3-oxofriedelan-21α,26-diol, kokoonol, kokoondiol, kokoononol, kokzeylanol and kokzeylanonol as 3α-acetoxyfriedelan-27→15α-olide, 3α-hydroxyfriedelan-27→15α-olide, 3α-hydroxyfriedelan-27-oic acid, 3α-acetoxyfriedelan-27-oic acid,

3β-hydroxyfriedelan-27-oic acid, 3β-acetoxyfriedelan-27-oic acid, 3-oxofriedelan-27-oic acid, 3-oxofriedelan-27-al, 3β-acetoxyfriedelan-27-al, 3-oxofriedelan-21α, 27-diol, 3-oxofriedelan-26-ol, 3-oxofriedelan-21α, 26-diol, 26-hydroxyfriedelan-3, 21-dione, 3-oxofriedelan-6β, 26-diol, 6β,26-dihydroxyfriedelan-3,21-dione respectively.

The results of the CCC2D spectrum of odolactone have been communicated in Tetrahedron Letters recently. A xerox copy of the manuscript is attached towards the end of the dissertation (Appendix 2).

CHAPTER 3
SYSTEMATIC INVESTIGATION ON THE NEUTRAL PART OF GYNOCARDIA ODORATA

Chromatography of the neutral part of benzene extract of G odorata afforded β-sitosterol, mp 136-7°, $[\alpha]_D$ - 34°, trichadenic acid A (revised structure is 3α-hydroxyfriedelan-27-oic acid), mp 292-3°, $[\alpha]_D$ + 25° and three new triterpenoids, O-acetylodollactone (3α-acetoxyfriedelan-27→15α-olide), mp > 320°, $[\alpha]_D$ (MeOH) - 19°, epi-odollactone (3β-hydroxyfriedelan-27→15α-olide), mp > 320°, $[\alpha]_D$ - 12.14°. The structures of these new lactones have been determined from spectral data and chemical correlations with odolactone.



CHAPTER 4

INVESTIGATION OF THE ACID PART OF GYNOCARDIA ODORATA

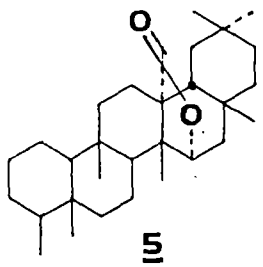
Chromatography of the acid part of benzene extract of G odorata afforded trichadenic acid A, mp 292-3°, $[\alpha]_D$ + 25°.

CHAPTER 5

SOME NOVEL TRANSFORMATION OF FUNCTIONAL GROUPS OF ODOLACTONE

Section A : Isomerization of γ-lactone moiety to δ-lactone

The modified Wolff-Kishner reduction of odolactone (4) yielded two products — one is the normal 3-deoxy compound (5), mp 314-5°, $[\alpha]_D$ - 14.25°, IR 1760 cm^{-1} (γ-lactone moiety) and other is the isomerized 3-deoxy lactone (6) mp > 320°, $[\alpha]_D$ + 23°, IR 1725 cm^{-1} (δ-lactone moiety). The structures of 5 and 6 were confirmed by ^1H and ^{13}C spectra.



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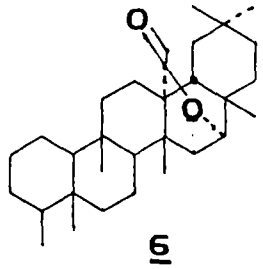

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It was observed that the lactone 5 isomerized to the lactone 6 when refluxed with diethylene glycolic potassium hydroxide. In order to make this novel rearrangement of friedelan-27→15α-olide system as generalized one, the action of KOH-diethylene glycol was studied on two more systems, the results are shown in the following table.

	Substrate lactones	Products	Yield
1	Friedelan-27→15α-olide (5)	Friedelan-27→16α-olide (6)	80%
2	3α-Hydroxyfriedelan-27→15α-olide	3α-Hydroxyfriedelan-27→16α-olide	80%
3	Odolactone (4)	99	75%

The keto group of odolactone has been found to be reduced to the hydroxy group (Entry 3 of the above table) by the action of KOH-diethylene glycol. This led to a series of reaction on some ketones in order to test the general applicability of the reagent in furnishing alcohols from ketones. These results have been published in Tetrahedron. A xerox copy of the reprint has been enclosed in Appendix 3. This report had projected the conversion of keto groups to alcohols originated from the observation that methyltrichadonate is converted to its corresponding epimeric alcohols during its hydrolysis with KOH-diethylene glycol. Actually, the reaction of odolactone with KOH-diethylene glycol had been the fountainhead for these and allied series of reactions. Initially, as the CCC2D spectral data had not been available there had been slight confusion over the structure of odolactone.

Section B : Reductive cleavage of lactone rings with lithium-ethylenediamine

Attempts to open lactone rings of odolactone by conventional methods (eg by the action of acids, alkali and lithium aluminium hydride) were unsuccessful. Barton et al reported deoxygenation of hydroxy groups of alcohols by alkali metal-amine reduction of their derived esters

with carboxylic acids. Since lactones are cyclic esters, it was anticipated that lactone oxygen might be deoxygenated from its point of attachment by the action of Li-ethylenediamine, which came out to be true. The results are given in the following table.

	Substrate lactones	Products	Yield
1	3α-Hydroxyfriedelan-27→15α-olide (odollactone)	3α-Hydroxyfriedelan-27-oic acid	80%
2	3α-Acetoxyfriedelan-27→15α-olide	a) Friedelan-27-oic acid	40%
		b) 3α-Hydroxyfriedelan-27-oic acid	40%
3	Odolactone (4)	3α-Hydroxyfriedelan-27-oic acid	80%
4	Friedelan-27→15α-olide (5)	Friedelan-27-oic acid	80%
5	Friedelan-27→16α-olide (6)	a) Friedelan-27-oic acid	20%
		b) Friedelan-16α, 27-diol	60%
6	3β-Acetoxyoleanan-18αH 28→13β-olide	a) Oleanan-18αH-28-oic acid	40%
		b) 3β-Hydroxyoleanan 18αH-28-oic acid	40%
7	3-Oxofriedelan-18αH-28→13β-olide	3β-Hydroxyoleanan-18αH-28-oic acid	85%

(continued from previous page)

	Substrate lactones	Products	Yield
8	3β-Acetoxyleanan-18αH -28→19β-olide	a) Oleanan-18αH-28 -oic acid	30%
		b) 3β-Hydroxyoleanan -18αH-28-oic acid	30%
		c) Oleanan-18αH-3β, 19β,28-triol	15%

From the above study, it has been concluded that tertiary lactones (entry 6,7) and sterically constrained lactones (entry 1-4) are exclusively converted to acids whereas the stable lactones (entry 5) yield diols in substantial amount. This novel method, unlike the conventional methods, obviates the introduction of hydroxy group at the position where the lactone oxygen is attached.

CHAPTER 6
EXPERIMENTAL

The experimental works undertaken in Part II are discussed in the text.

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PART III
CHEMICAL INVESTIGATION ON FLACOURTIA SEPIARIA (ROXB)

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EXTRACTION

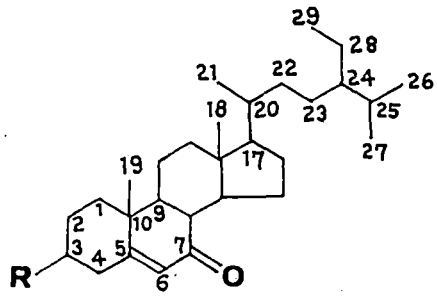
The benzene extract of trunk, bark and stem of F sepiaria separated into the neutral and acid parts.

CHAPTER 1

INVESTIGATION ON THE NEUTRAL PART OF FLACOURTIA SEPIARIA (ROXB)

Chromatography of the neutral part of F sepiaria furnished 1-hexacosanol, mp 78-9°, β-sitosterol, mp 136-7°, $[\alpha]_D$ - 34°, 20-hydroxylupan-3-one, mp 213-4°, 3β,20-dihydroxylupane, mp 243-4°, $[\alpha]_D$ + 26.7° and a a new sterol, named sepesteonol (7), $C_{29}H_{48}O_2$, mp 132-3°, $[\alpha]_D$ - 98°, λ_{max} 235 nm, ν_{max} cm^{-1}, 3520 (OH), 1655 and 1620 (enone system). It gave sepesteonol acetate, mp 169-70°, $[\alpha]_D$ - 92°, ν_{max} 1724, 1655, 1260, 1245 cm^{-1}, with Ac_2O-py. The homonuclear 2D spectroscopy in conjunction with ^{13}C data have correctly established the structure (7) of the sterol.

The ^1H NMR of the acetate 8 showed the presence of two singlet methyls at 0.67 and 1.19 ppm and the remaining four methyls appeared in the region 0.78-0.92 ppm which were splitted. The HOM2DJ spectrum distinguished the C-26 and C-27 methyl groups as two doublets at 0.78 and 0.80 ppm (J 7.5 Hz), and the C-29 methyl at 0.81 ppm as triplets (J 7.5 Hz). The C-21 methyl appears at 0.89 ppm as a doublet (J 7.5 Hz). The 3β-acetoxy-5-en-7-one disposition for 8 has been confirmed from the 2D COSY spectrum. It exhibited the correlation of the proton on C-6 (5.7 ppm) with the protons on C-4 (2.5 ppm). On the other hand, the protons on C-4 couple with the proton on C-3 (4.7 ppm) and the latter also couples with the axial and equatorial C-2 protons. The ^{13}C chemical shifts of C-22 to C-29 are agreed well with those of the model compound,



7 R=OH

8 R=OAc

2-methyl, 3-ethyl pentane in accordance with Lindeman -Adam's additivity rules. The ^{13}C chemical shifts of rest of the carbons (C-22 to C-29) of 8 are very close to those of 3β-acetoxy-cholest-5-en-7-one.

Finally the structure 8 for sepesteonyl acetate was confirmed by preparing it from β-sitosterol acetate by $Na_2Cr_2O_7$ oxidation, and transforming it to tremulone (stigmast-3,5-dien-7-one) by the action with both alkali and acid.

The structure 7 for sepesteonol, a new sterol, has been published in the Indian Journal of Chemistry, a xerox copy of which is enclosed (Appendix 4).

CHAPTER 2

INVESTIGATION ON THE ACID PART OF FLACOURTIA SEPIARIA (ROXB)

From the acid part of benzene extract of F sepiaria, tetracosanoic acid, mp 86-7° and benzoic acid, mp 121° have been isolated. Benzoic acid was identified by direct comparison with the authentic sample. Tetracosanoic acid was identified from the study of ^1H and ^{13}C spectra of its methyl ester (mp 60-1°). It was finally confirmed by checking the mps of the acid and its ester (lit mp of tetracosanoic acid is 87-8° and 59-60° of its ester).

CHAPTER 3

EXPERIMENTAL

The experimental works undertaken in Part III are discussed in the text.