

PART -A

A BRIEF ACCOUNT OF FURANOEREMOPHILANES

INTRODUCTION

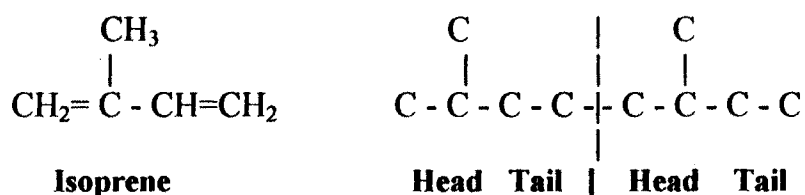
Amongst various compounds of natural occurrence, terpenoids * constitute the largest group having plant origin. Most of the natural terpene hydrocarbons have the molecular formula $(C_5H_8)_n$. Depending upon the value of 'n' terpenes are classified into mono ($C_{10}H_{16}$), sesquiterpenes ($C_{15}H_{24}$), diterpenes ($C_{20}H_{32}$), triterpenes ($C_{30}H_{48}$), tetraterpenes $C_{40}H_{64}$ (carotenoids) and polyterpenes.

Mono and sesquiterpenes are the main constituents of volatile essential oils, which are obtained from sap and tissues of plants while di and tri terpenes are not steam volatile and are obtained from gums and resins of plants. Besides terpene hydrocarbons, there occur their oxygenated derivatives such as alcohols, ketones and aldehydes; also found to occur naturally.

All the classes of terpenoids have one feature in common and that is, most of them obey a well known isoprene rule.

Isoprene rule :

On thermal decomposition almost all terpenes form isoprene as one of the products, which lead to the suggestion that the skeleton structures of all naturally occurring terpenes can be built up of isoprene units. This is known as 'isoprene rule' and was first of all pointed out by Wallach. Thus, divisibility into isoprene units may be regarded as an essential condition to be satisfied by the structure of any plant synthesized terpene.

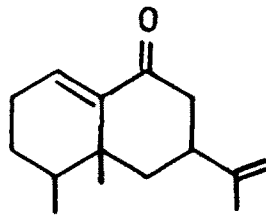


Ingold pointed out that the isoprene units in natural terpenes were joined 'head to tail'. This divisibility into isoprene units and their head to tail union may conveniently be referred to as special isoprene rule. However, this rule can only be used as a guiding principle and not as a fixed rule.

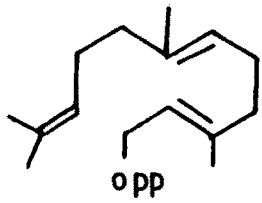
In short, carbon frameworks in isoprene units can be arrived at by assembling of isoprene units in head to tail fashion. As there exists exception to every rule, this special isoprene rule also has exceptions. There exists one class of sesquiterpenoids viz. eremophilanes which do not obey and conform structurally to isoprene rule. For this reason only, though the first member of this group was discovered in 1932¹, its structure (1.1) as a non-isoprenoid compound was not established till 1939, when Robinson² assigned the correct structure to it. Thus 'eremophilane' (1.1) is the first naturally occurring non-isoprenoid compound. The detailed investigation of this class of compounds has earlier been done by Pinder³ and Sorm⁴. In light of our work on the synthesis of pyrocurzerenone, which is structurally similar to other furanoeremophilanes isolated and synthesised earlier, it will be appropriate here to discuss those compounds as a group.

From biogenetic point of view, farnesyl pyrophosphate (1.2) on removal of pyrophosphate anion gives rise to a classical cation intermediate (1.4) through a non-classical cation (1.3). The double bond migration in cation (1.4) results in the formation of two more intermediates (1.5) and (1.6). The

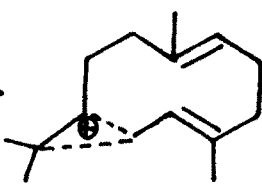
CHART - 1



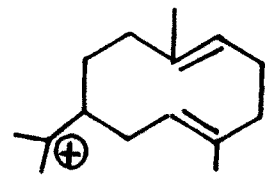
(1)



(2)

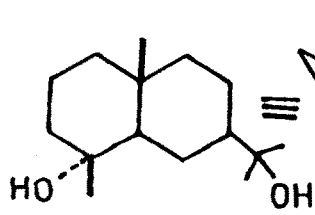


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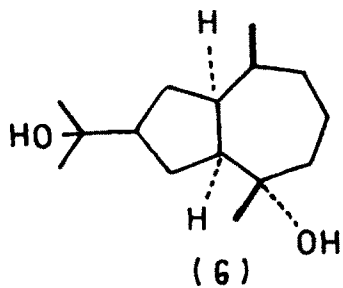
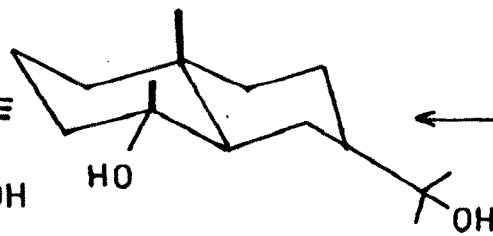


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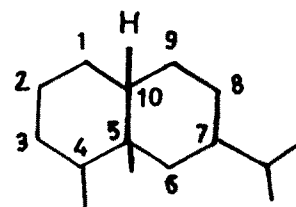
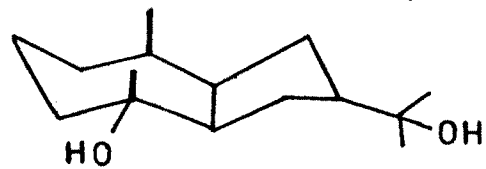
↓ Bond
migration



(5)



(6)



(7)

intermediate (1.5) has been postulated to be an ideal precursor for eremophilane class. Rearrangement of (1.5) involving migration of methyl group is expected to give eremophilane.

More than 300 compounds of this class have been isolated and they have become now a major group of sesquiterpenoids.

Eremophilanes can broadly be divided into two sub classes

- 1) Bicyclic eremophilanes
- 2) Furanoeremophilanes

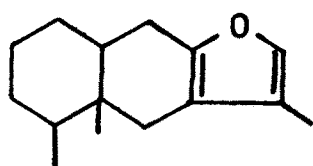
Owing to the limitations of the thesis, a brief account of furanoeremophilanes only has been taken here.

Furanoeremophilanes

? — ¹⁹⁷⁸ Recent investigations ^{ref. 21} by Bohlmann and co-workers have resulted in the *
isolation of several eremophilanes having furan ring fused to the original bicyclic framework. This new class is conveniently known as furanoeremophilanes or furanosesquiterpenoids. In this, there exists one more group of compounds in which instead of a furan ring, a butenolactone type of ring system exists. The two groups are related by the fact that, mild oxidation of furanoeremophilane (2.1) leads to corresponding butenolactone (2.2)

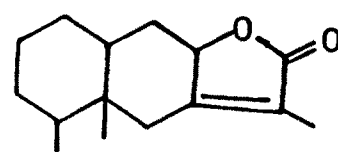
All compounds of furanoeremophilane class are ^{designed} desired from the same *
parent substance furanoeremophilane (2.1) ^{and} the functional groups present in *
them.

CHART-2

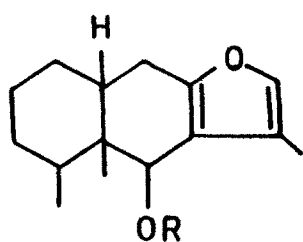


(1)

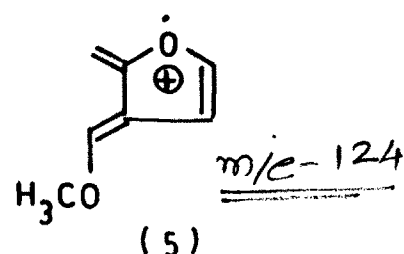
Mild Oxidation →



(2)



OR

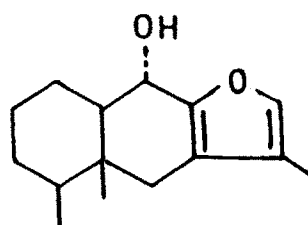


(5)

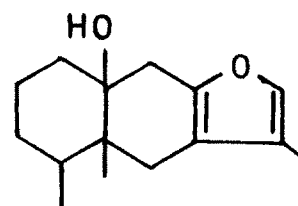
m/e-124

(3) R = H , (4) R = CH₃ ,

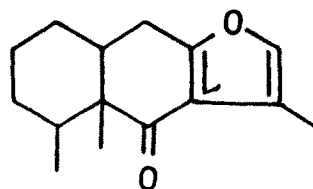
(6) R = Senecieryl , (7) R = Angelyl



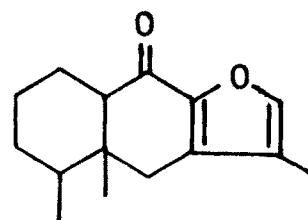
(8)



(9)



(10)



(11)

1) ~~a)~~ Mohohydric alcohols, their ethers and esters : *

Petasalbin (2.3) and its methyl ether (2.4) occur in the roots of several *Petasites* and *Ligularia* species. ^{ref.} *

The catalytic hydrogenation of petasalbin gave tetrahydrofuranoremorphilane which confirmed its carbon skeleton. The position '6' for the hydroxyl function was assigned on the basis of following evidences.

i) Autooxidation of petasalbin gave 6 β -hydroxyeremophilanolide of known structure and geometry.

ii) The mass spectrum of petasalbin methyl ether show a peak at m/e = 108, [?] * which is characteristic of furan ring with an allylic methoxyl group i.e. fragment (2.5). This confirms position '6' for methoxyl and ultimately for hydroxyl group in petasalbin. *

Petasalbin senecioate (2.6) is an ester of senecioic acid with petasalbin and it has been isolated from *furfugium japonicum*⁵. There also exists an angelate of petasalbin (2.7) known as alpopetasin and occur in various *Petasites* species.

From *P. hybridus* and *Tetradymia glabrata* two more alcohols of this class have been isolated and they are 9 α -hydroxyfuranoremorphilane (2.8) and 10 β -hydroxyfuranoremorphilane⁶ (2.9) respectively.

2) ~~b)~~ Monoketones : *

Ligularone (2.10) occurs in the roots of *Ligularia fischeris*⁷ and *P. japonicus*⁸. From the spectral data, this was found to be a

furanoeremophilane with a ketone moiety in it either at position 6 or position 9. The calculated dipole moments of these two compounds were 2.35 and 3.66 D respectively while the observed one 2.55 D was in close agreement with former. This indicated that, ketone function must be at position 6 and not at 9. The structure was further confirmed through its synthesis⁹.

The furanoeremophilane with keto group at position 9 is also known i.e. 9-oxofuranoeremophilane (2.11). This occurs in *P. hybridus*¹⁰ and *P. officinalis*. Its structure was confirmed by the fact that, it can be obtained by oxidation of 9 α -hydroxyfuranoeremophilane (2.8) with manganese dioxide.

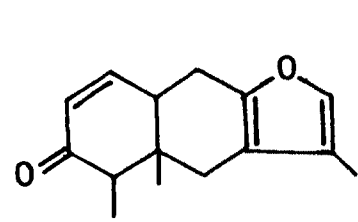
Furanoligularone (3.1) is found in the roots of *Ligularia fischeri*¹¹ and *L. stenocephala*¹². Two possible structures were considered for it viz. (3.1) and (3.2) but the mass spectrum showed the peaks at m/e 108 and 122, characteristic for fragments (3.3) and (3.4) which can arise only from (3.1) and not from (3.2). *why not from (3.2)* *

3) Epoxydes :

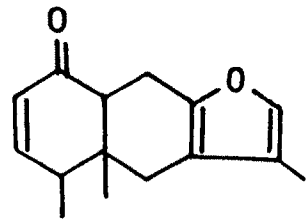
8,8 α -Epoxyfuranoligularone (3.5) is present in *Senecio silvaticus*.^{ref} Its structure was proved through series of reactions [chart-3A]. *

Senemorin (3.7) occurs in the rhizomes of *Senecio nemorensis*. It is 6 β -angeloxy-1 β -10 β -epoxyfuranoeremophilane. Senemorin on complete reduction with LAH gave diol (3.8) which on successive oxidation, dehydration and catalytic hydrogenation gave ligularone, which proved position 6 for angelyl moiety in Senemorin.

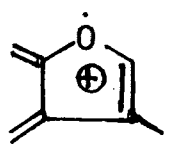
CHART-3



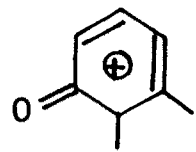
(1)



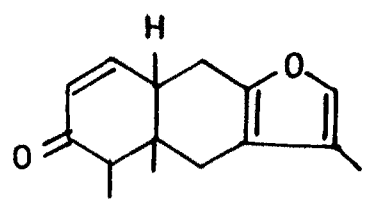
(2)



(3)

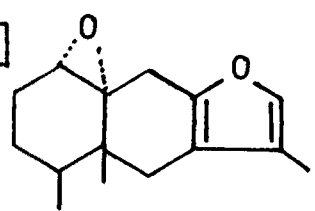


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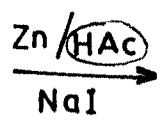


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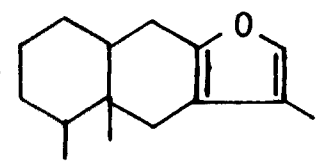
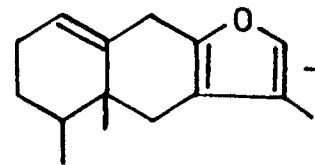
A]



(5)

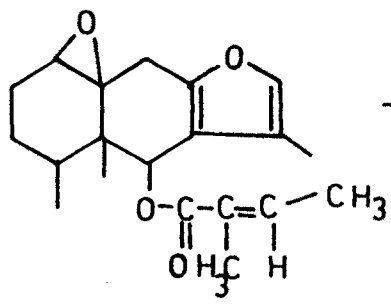


HAc - Acetic acid

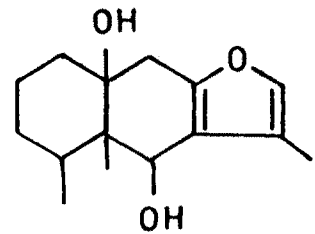


(1) H_2
 (2) w.k. reduction

*



(7)



(8)

4) Dihydric and Trihydric alcohols, their ethers and epoxides :

Furanoeremophilane 6 β , 10 β - diol (4.1) and 10 β -hydroxy-6 β -methoxyfuranoeremophilane (4.2) occur in the roots of *Ligularia japonicus*^{ref.} *
less. The former diol (4.1) on selective methylation with methyl iodide and silver oxide gave corresponding methoxy compound (4.2). The third substance (4.3) isolated from the same source was a monoester of diol (4.1) with 2-methyl butanoic acid. *

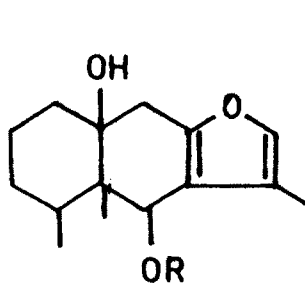
Furanopetasin (4.4) occurs in several *Petasites*¹³ species. On mild alkaline hydrolysis it gave angelic acid and a diol, furanopetasol (4.5) of known structure and geometry. Furanofukinol (4.6) is another diol having *Petasites japonicus* origin¹⁴. This was converted into 6-oxofuranoeremophilane (4.7). Thus one hydroxyl group must be at position 6. On oxidation it gave a diketone, which showed a quartet- (1H) at 2.8 for CH - CH₃, in its PMR spectrum, proving that the other hydroxyl is at position 3. Thus furanofukinol is 3,6-dihydroxy-furanoeremophilane.

Euryopsol (4.8) has been isolated from resin of *Euryops floribundas* while kablicin (4.9) has been isolated from *Petasites kablikanus*¹⁵

5) Ketoalcohols and Ketoesters :

Euryopsonol (5.1) occurs in unsaponifiable fraction of the resin of *Euryops floribundas*¹⁶. Through a series of reactions [chart-5A] it gave 9-oxofuranoeremophilane hence the ketone must be at position-9. Euryopsonol on oxidation gave a ^{di-}ketone (5.2). This was not a β -diketone and was shown to be different from 2,9-dioxofuranoeremophilane hence second keto function *

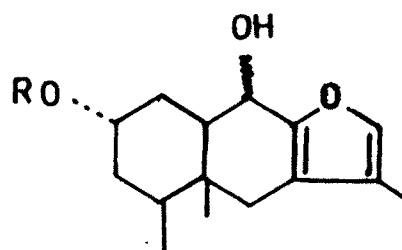
CHART-4



(1) R = H

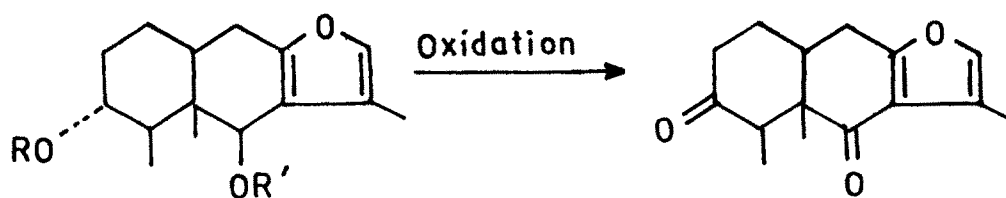
(2) R = CH₃

(3) R = $\begin{array}{c} \text{---C---CH---CH}_2\text{---CH}_3 \\ \parallel \quad | \\ \text{O} \quad \text{CH}_3 \end{array}$



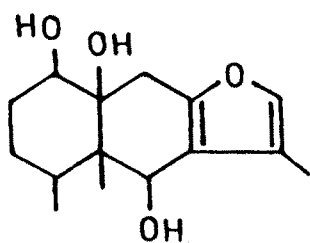
(4) R = Angelyl

(5) R = H

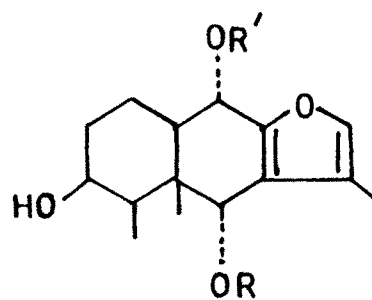


(6) R = R' = H

(7)



(8)



(9)

R = Angelyl

R' = Senecieryl

must be at position 3. Thus Euryopsonol must be 3-hydroxy-9-oxo-furanoeremophilane.

Warburgin (5.3) is a yellow ketoester occurring in the heart wood of *Warburgia ugandensis*.^{ref.} Hydrogenation of Warburgin gave tetrahydro-warburgin which after a series of reactions [Chart 5B] gave furanoligularone of known structure. This confirmed position-3 for ketofunction. *

Four esters derived from 6 β -hydroxy-9-oxofuranoeremophilane (6.1) are found in nature which are : adenostylone (6.2) , neoadenostylone (6.3) , isoadenostylone (6.4) and decompostin (6.5). Decompostin occurs in the roots of *Cacalia decomposita*¹⁷. The structure was assigned through chemical and spectral evidences and confirmed by total synthesis¹⁸. The other two compounds from *C. decomposita* are cacalol and cacalone. The aerial parts of *Senecio filaginoides* yielded¹⁹ two new furanoeremophilanes (6.6) and (6.7).

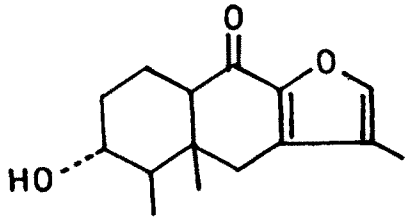
6) Miscellaneous furanoeremophilanes:

8,12-Dimethoxydihydrofuranoeremophilane (6.8) is a constituent of *Petasites hybridus* rhizomes. Furanoeremophilane-14 β -6 α -olide (6.9) occurs in the roots of *Ligularia hodgsoni* hook²⁰, from South African *Senecio* species a dimeric furanoeremophilane (6.10) has been isolated²¹. The structures of these compounds have been proved by spectroscopic studies only.

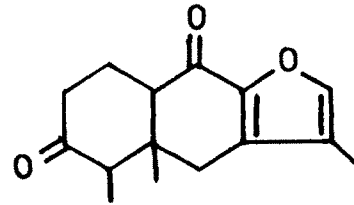
7) Aromatic furanoeremophilanes :

There are several examples of isolation of non-aromatic compounds from natural sources initially and later on the existence and isolation of corresponding analogs was proved e.g. Atlantone and *ar*-atlantone, juvabione

CHART-5



(1)



(2)

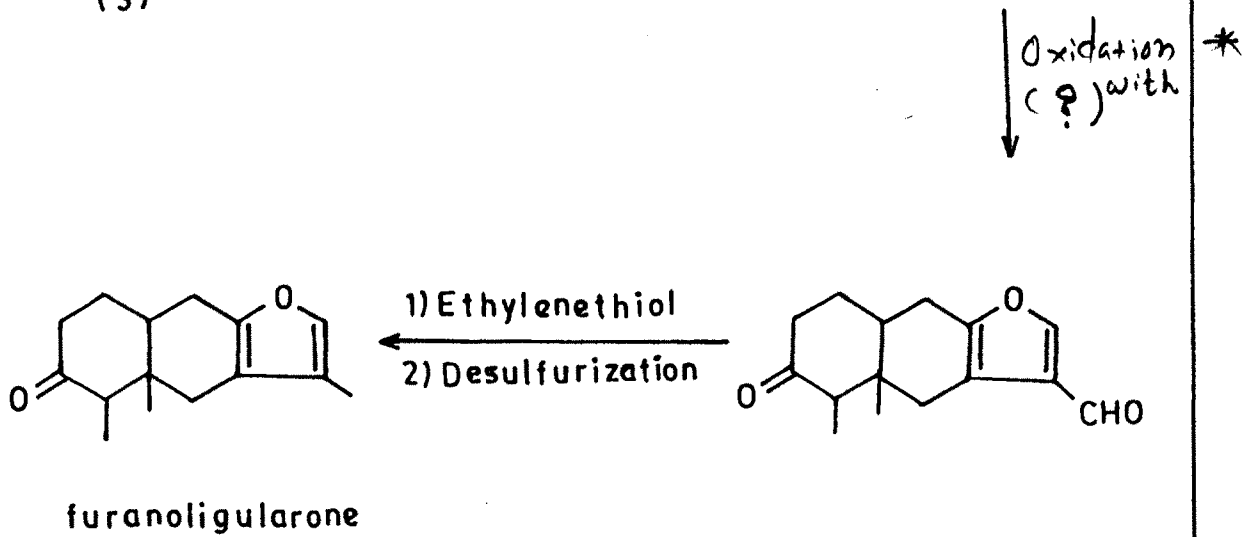
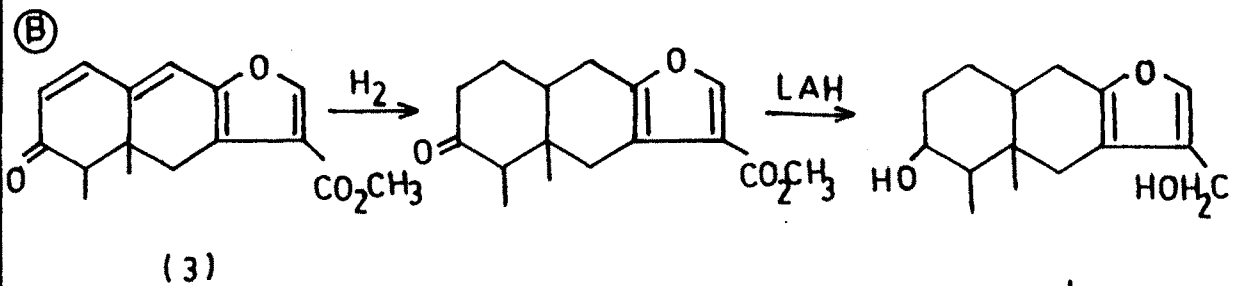
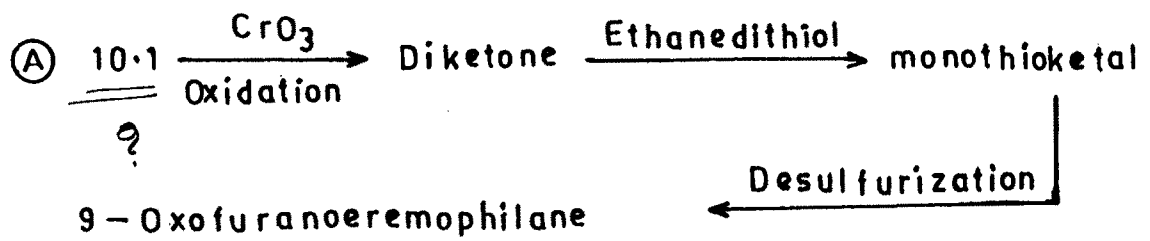
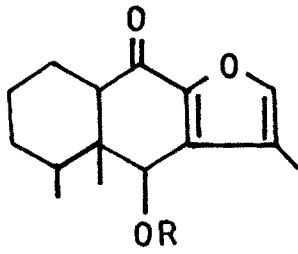
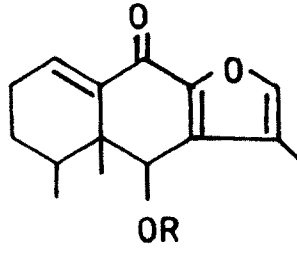


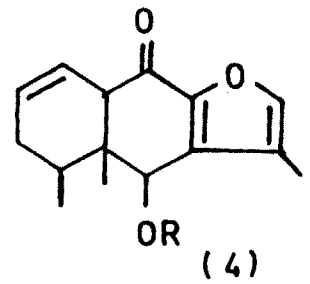
CHART-6



(1) R = H



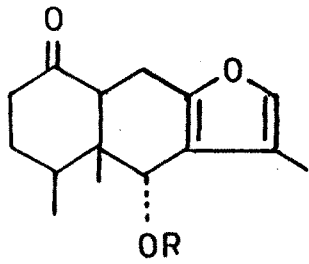
(2) R = $-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}(\text{CH}_3)_2$



R = $-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}(\text{CH}_3)_2$

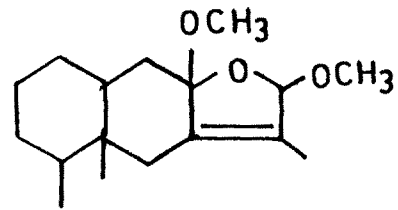
(3) R = $-\overset{\text{O}}{\parallel}{\text{C}}-\text{C}(\text{CH}_3)=\text{C}\begin{matrix} \text{H} \\ \text{CH}_3 \end{matrix}$

(5) R = $-\overset{\text{O}}{\parallel}{\text{C}}-\text{CH}_3$

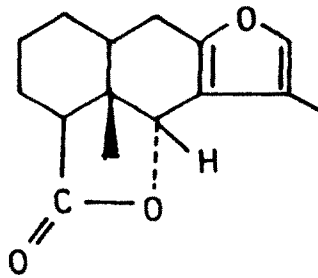


(6) R = Acetyl

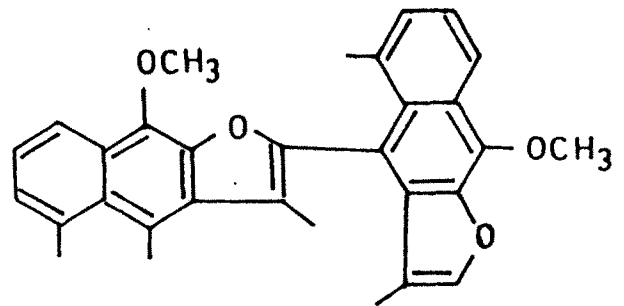
(7) R = Tiglyl



(8)



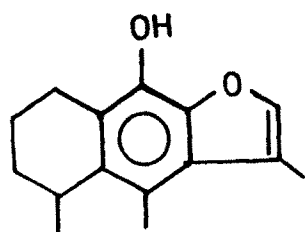
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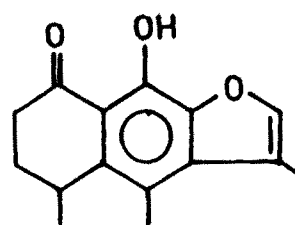
(10)

and *ar*-juvabione, turmerone and *ar*-turmerone etc. Similarly, several furanoeremophilanes, in which ring B is aromatised, have been isolated from plant sources e.g. cacalol (7.1) and cacalone (7.2) are isolated from Mexican shrub *Cacalia decomposita*,²¹ 1-oxo-9-desoxycacalol (7.3) from the leaf extract of Bolivian *Senecio serratifolius*²², e (7.4) from rhizomes of *Curcuma zedoaria*²³ Roscoe. The structures of all these compounds were suggested on the basis of spectral evidence and proved by their synthesis.²⁴⁻²⁷

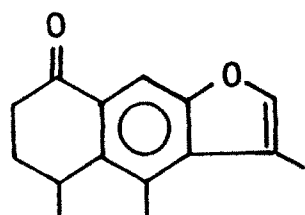
In part-B of this thesis, we report our contribution to the synthesis of pyrocurzerenone.

CHART-7

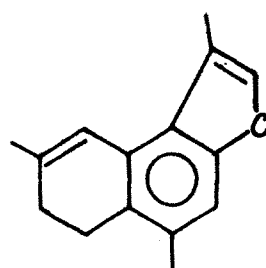
(1)



(2)



(3)



(4)

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J. Chem. Soc., 2744 (1932).

- 2) A. R. Penfold and J.L. Simmonsens

J. Chem. Soc., 87 (1939).

- 3) A. R. Pinder

'Recent developments in the eremophilane sesquiterpene Group I -
Bicyclic structures and Group II -Tricyclic structures' PeRf. Ess,
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