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A NEW CLASS OF TRITERPENOIDS FROM AILANTHUS MALABARICA DC
DERIVATIVES OF MALABARICANE

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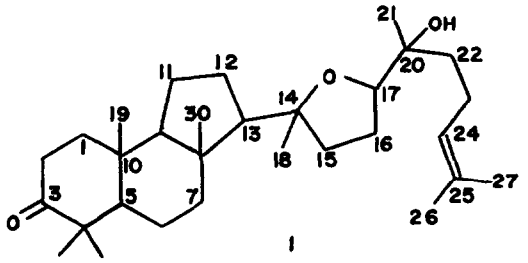
THE resinous exudate from the trunk of Ailanthus malabarica DC (Kannada, Hal-maddi; Malayalam, Mattipal) has been found to contain several triterpenoids belonging to a hitherto unknown (naturally occurring) skeletal type. Nine closely related compounds have been isolated from this source, so far. The major component (malabaricol) is shown to possess the gross structure I. Structures of two other compounds have been elucidated by correlation with I, and are reported in the sequel. As can be seen, I represents a new triterpene type and is the first example of a tricarbo-



I

cyclic triterpene from a plant source[1]. We propose the name malabaricane for the parent, fully saturated carbon-frame work.

Malabaricol, m.p. 68–69.5°, $[\alpha]_D$ +36.1° ($CHCl_3$), $C_{30}H_{50}O_3$ (M^+, m/e = 458) shows in the IR spectrum (Nujol) bands for C=O (1700 cm^{-1}) and OH (3550 cm^{-1}, sharp) and, in the UV, besides end-absorption (ε_{220} 263, ε_{225} 120), a low intensity maximum at 280 mμ (ε 46). The UV data require that the C=O group in malabaricol should be that of a ketone and its intensity is consistent[2] with the presence of only one such group. Thus, the third oxygen function of malabaricol must be located as an ether or another OH. The compound is not acetylated by Ac_2O-pyridine (20–25°, one week) and is not attacked by CrO_3-pyridine (20–25°, one week), hence the OH group(s) must be tertiary.

Its PMR spectrum[3] shows signals for six quaternary methyls (58.5, 58.5, 58.5, 61, 65 and 70 c/s; in C_6H_6: 46.5, 50, 58.5, 68, 68 and 76.5 c/s)

two vinylic methyls (95 and 98 c/s; in C_6H_6: 98 and 102 c/s), one olefinic proton (1H triplet centred at 298 c/s, J = 6 c/s) and a 2H multiplet centred at 138 c/s, the pattern and position of which are reminiscent[4] of the C_2-methylene of 3-ketotriterpenoids. The PMR spectrum also displays a 1H triplet (J = 7 c/s) centred at 212 c/s(in C_6H_6: 221 c/s), which is assigned to $-CH_2-\underset{C}{CH}-O-$, and since, it has been demonstrated earlier that there is no oxidisable (pyridine-CrO_3) hydroxyl function in malabaricol, this oxygen function must be located as an ether: $-CH_2-\underset{C}{CH}-O-C$.

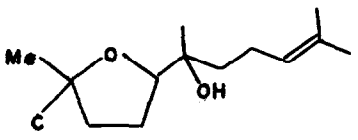
From the above, it is clear that malabaricol must be a triterpenoid with a keto, a tert-OH and an ether function, the keto group, in all probability, being located at C_3.

Malabaricol gives a blear yellow colour with tetranitromethane (TNM). On catalytic hydrogenation (PtO_2, AcOH) it took up 1.5 - 2 mole equiv. of H_2 to furnish a diol (II, m.p. 101-102.5°) and dihydromalabaricol (m.p. 98-99°). The diol was readily oxidised by CrO_3-pyridine to dihydromalabaricol. The PMR spectrum of dihydromalabaricol is consistent with the saturation of an isopropylidene group in malabaricol to isopropyl in its dihydroderivative. Both the diol and the dihydroketone give a negative TNM test. Thus, malabaricol is only mono-olefinic and from its molecular formula and functionality discussed earlier, must be either tetracarbocyclic with an acyclic ether linkage or tricarbocyclic with a cyclic ether function.

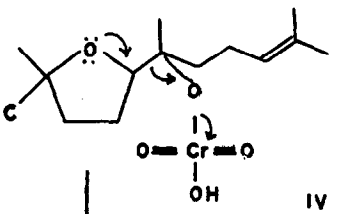
The key reaction in the structure determination of malabaricol turned out to be its oxidation with Jones reagent[5], which readily furnished, in good yield, a compound (m.p. 145-146°, $[\alpha]_D$ +29.4°) characterised as an octa-nor-γ-lactone, $C_{22}H_{34}O_3$ (M^+, m/e = 346; $\nu^{C=O}$ 1702, 1775 cm^{-1}). Its PMR spectrum shows the presence of only five methyls (all quaternary): 59, 61, 62, 63.5 and 83 c/s (in C_6H_6: 44, 46, 58, 63 and 66 c/s), the 83 c/s signal clearly arising due to a quaternary methyl on a carbon atom linked to oxygen; the $-\underline{CH_2}-C=O$ signal, which occurs centred at 138 c/s in the PMR spectrum of malabaricol, is still present (now centred at 142 c/s), while the other two down-field signals of malabaricol have now disappeared in the lactone. The same lactone is produced in essentially the same yield by Jones oxidation or RuO_4[6] oxidation of dihydromalabaricol (or the diol II). All the above results can be rationalised in terms of the part structure III for malabaricol, the cleavage proceeding through IV → VI. A close analogy is provided by the CrO_3 acid cleavage of ocotillol (VIII) to the lactone IX[7]. The part structure III is further supported by the isolation and identification of methylheptenone (VII) as the other cleavage product of malabaricol.

The above work clearly formulates the ether linkage of malabaricol

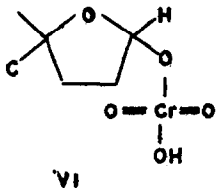
in a ring, hence this compound can only be tricarbocyclic. While examining theoretically the possible modes of cyclisation of squalene, the well-established[8] precursor of triterpenoids and steroids, to arrive at a tricyclic system suitable for incorporation in malabaricol structure, it was noted that if ring C is closed Markownikoff-wise (X), rather than the usual anti-Markownikoff-wise so far observed for all naturally occurring triterpenes, the resulting species (XI) is eminently suited for incorporating the part structure III (cf.XII)[9] to finally give I, as the possible structure of malabaricol.



III

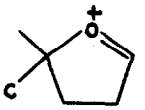


IV



VI

$HCrO_4^-$



V

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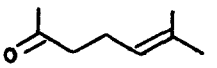
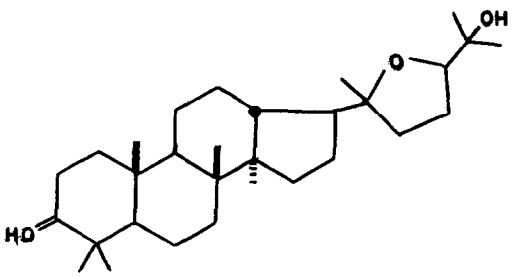
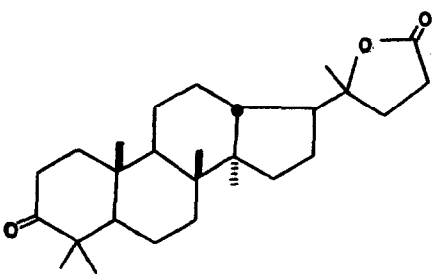


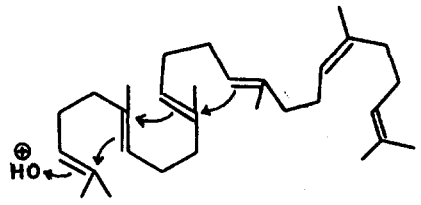
VII



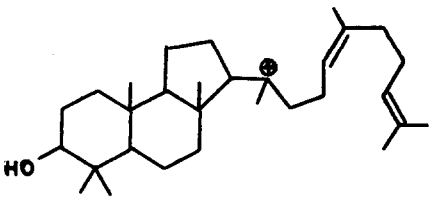
VIII



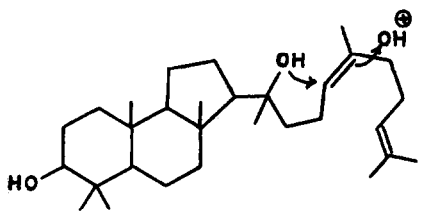
IX



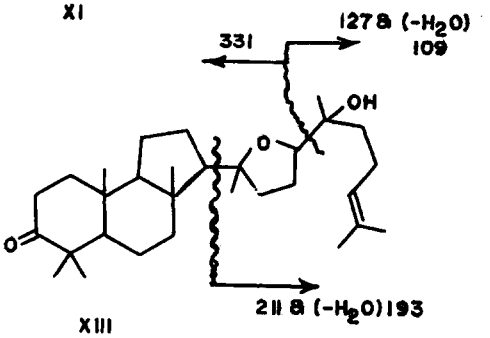
X



XI



XII



XIII

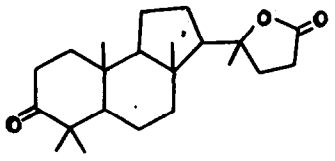
Malabaricol, if correctly represented by I, should show, on electron impact, the fragmentation depicted in XIII, the characteristic α-fission of α-substituted tetrahydrofurans[10]. As can be seen from Table 1, all these are important fragments in the mass spectrum of malabaricol.

Finally, systematic degradation of the octa-nor-γ-lactone, which may now be represented by XIV, gives clear further support. $LiAlH_4$ reduction of the γ-lactone gave a triol ($C_{22}H_{40}O_3$, m.p. 190-191°), which on acetylation (Ac_2O-pyridine) gave in good yield an hydroxydiacetate ($C_{26}H_{44}O_5$, m.p.61-64°, $[\alpha]_D$ +7.34. IR: OH 3500, 1045 cm^{-1}; OAc 1750, 1730, 1250 cm^{-1}), formulated as XV (PMR: 5 quaternary methyls, 9H signal at 52.5 c/s, and 3H signals at 57, 71 c/s; CH_3COO, 6H signal at 120 c/s; $-CH_2OAc$, 2H triplet centred at 241 c/s, J = 6 c/s; CHOAc, 1H quartet centred at 268 c/s). The hydroxydiacetate on dehydration ($SOCl_2$-pyridine) furnished essentially a mixture of two olefins (TLC), one of them predominating considerably. The mixture was separated on SiO_2-gel and the major component recognised (IR,PMR) as XVI, while the minor product (m.p. 110-112°) was shown from its PMR spectrum (four quaternary methyls, 51, 51, 53.5 and 59 c/s; one vinylic methyl, 98.5 c/s; two CH_3COO, 120, 120 c/s; CH_2OAc, 2H triplet centred at 244 c/s; CHOAc, 1H quartet centred at 266 c/s; one olefinic proton, 1H triplet centred at 300 c/s) to be the desired isomer XVII. The required compound XVII was

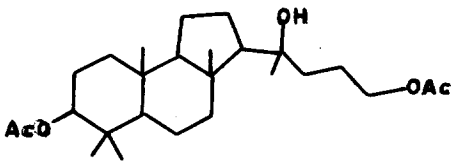
TABLE 1 - IMPORTANT PEAKS IN THE MASS SPECTRUM OF MALABARICOL

m/e	458	443	331	289	245	211	193	135	127	109	95	85	81	69	55
%base peak	8	2	36	33	44	67	22	41	47	74	43	75	57	100	71
% Σ_{40}	0.3	0.1	1.8	1.6	2.2	3.3	1.1	2.0	2.3	3.6	2.1	3.7	2.8	4.9	3.5

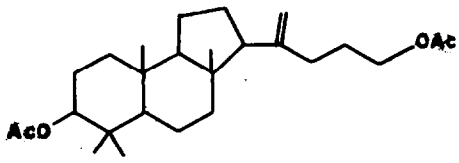
expeditiously obtained by isomerising the total olefin mixture with Li in ethylene diamine[11], when this isomer predominated. Osmylation of XVII gave the corresponding α-glycol (m.p. 175-177°) with the expected spectral data (IR,PMR). The glycol was cleaved with $Pb(OAc)_4$ and the resulting crude methyl ketone (m.p. 122-127°) oxidised with perbenzoic acid and the product hydrolysed with 10% alc. KOH to give a solid, m.p. 208-210°. The last



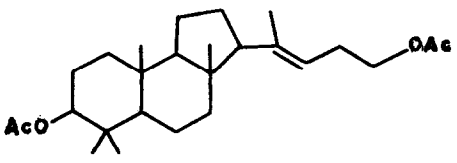
XIV



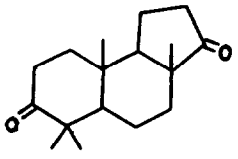
XV



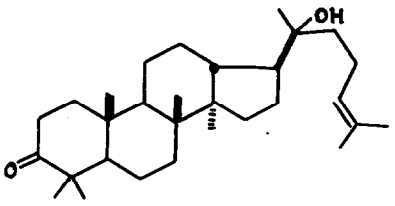
XVI



XVII



XVIII



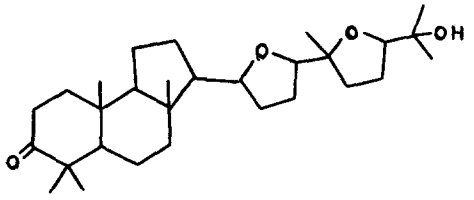
XIX

product was oxidised with Jones reagent to give a diketone, m.p. 64-66°, and having all the spectral requirements of XVIII: M^+, m/e = 262; IR(CCl_4): C=O 1703, 1738 cm^{-1}, both bands of almost same intensity. PMR: four quaternary methyls: 58, 61, 63 and 63 c/s; $-C\underline{H}_2CO$, one 2H multiplet centred at 144 c/s (cf. PMR of malabaricol) and another 2H multiplet centred at 120 c/s. This degradation provides unequivocal evidence for the size of ring C and its mode of linking to the tetrahydrofuran moiety. Since ring A must be 6-membered (IR, PMR), the size of ring B follows, which also must be six-membered.

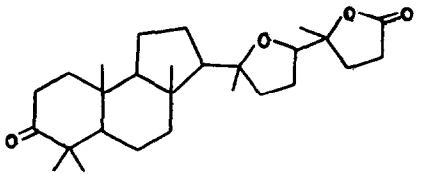
Malabaricol and the lactone XIV, both show a positive Cotton-effect, just like dipterocarpol (XIX) (or the trinor-lactone IX)[12] and hence A/B ring junction in I may be expected to be <u>trans</u> and with the same absolute stereochemistry. Further work is in progress.

It should be mentioned here that van Tamelen and co-workers[13] have recently demonstrated that one of the products of nonenzymic cyclisation of squalene-2,3-epoxide has the same gross carbon framework as I.

<u>Epoxymalabaricol</u>, m.p. 143-144°, $[\alpha]_D$+24.6° ($CHCl_3$), analyses for $C_{30}H_{50}O_4$ and displays bands for OH (3500, 1082 cm^{-1}) and C=O (1703 cm^{-1}) in the IR spectrum. Its PMR spectrum shows signals for: eight-quaternary methyls (56, 59, 59, 59, 62, 65, 68 and 74 c/s) and $C\underline{H}_2$-C=O (a 2H multiplet centred at 142 c/s); a 2H multiplet located between 212-240 c/s is considered to arise from two overlapping triplets due to two protons of type $-CH_2-\underset{C}{\underline{C}}H-O-$. A comparison of this data with that of malabaricol, suggested that the new compound is clearly closely related to it and could have possibly arisen from I by additional oxygenation involving the side-chain olefinic linkage. In clear support of this, percamphoric acid oxidation of I, furnished a product indistinguishable (m.p., mixed m.p., IR) from the new compound, which was then named epoxy-malabaricol. This compound is assigned the structure XX, rather than an oxirane structure, because the newly generated proton of type $-CH_2-\underset{C}{\underline{C}}H-O-C$, shows its PMR signal, well outside the range of a secondary



XX



XXI

proton located on an oxirane ring[14]. There are several analogies[9] for such an epoxidation with a per acid, the closest being the conversion of dipterocarpol (XIX) into ocotillone (C_3-ketone of VIII) by percamphoric acid[15].

Oxidation of epoxymalabaricol with Jones reagent, furnished a γ-lactone, m.p. 155-156°, $C_{27}H_{42}O_4$ (IR: C=O 1705, 1776 cm^{-1}). Its PMR spectrum is in complete accord with XXI. The same tri-nor-lactone is produced, when I is oxidised with RuO_4.

Malabaricanediol, this compound, $[\alpha]_D$ +23.03 ($CHCl_3$), which could not be obtained crystalline, was considered from its spectral data to be the C_3-alcohol corresponding to I. $NaBH_4$ reduction of I gave a product indistinguishable from the naturally occurring material.

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