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PREPARATION AND CIRCULAR DICHROISM STUDIES OF TRITERPENE LACTONES OF LUPANE SERIES

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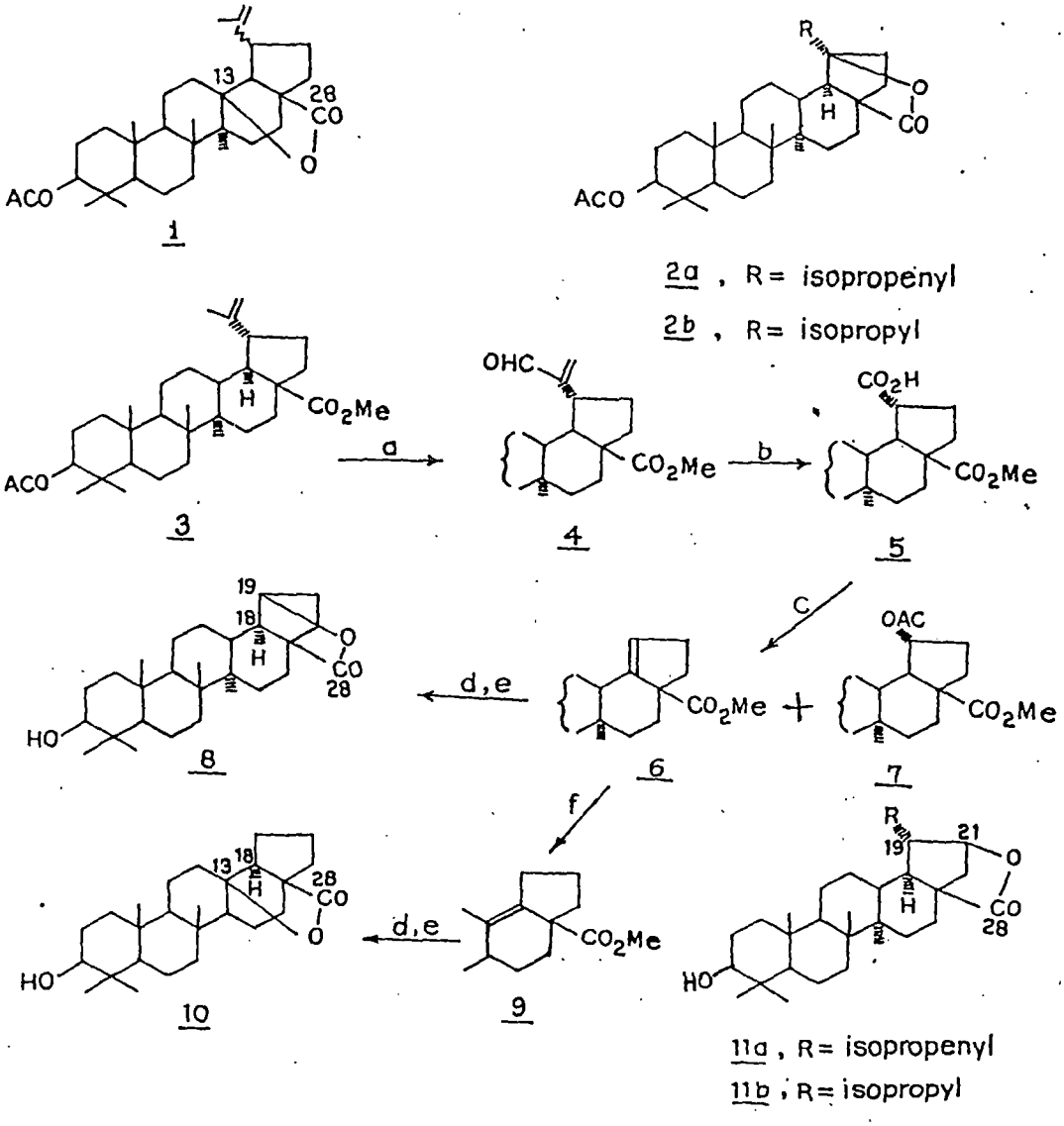
Summary : The authentic triterpene lactones 3 and 10 of the lupane series were obtained by a chemical degradative sequence from betulinic acid. Comparison of CD spectra of 3 and 10 with those of the lactones 2a and 11a provided additional evidence for their revised formulation.

Acetyl betulinic acid on mercuric acetate oxidation gave a tertiary γ-lactone which, initially assigned C-29, 13-lactone structure[1] 1, has been revised[2] more recently to C-29, 19-lactone 2a. Subsequently, the naturally occurring lactone thurberogenin, originally allocated[3] a C-28, 19-lactone structure, has been modified[4] to C-29, 21-lactone 11a. The physical techniques IR, NMR and mass are not of much use in distinguishing the two tertiary γ-lactones 1 and 2a. Since the powerful physical tool CD is increasingly being applied at present to solve structure and stereochemical aspects of the asymmetric environment of the lactone chromophore, we intend in this communication to provide physical evidence from CD measurements for the structure of the lactones 2a and 11a. For this purpose, we prepared authentic C-28, 19-lactone 3 and C-29, 13-lactone 10 from betulinic acid and measured CD curves of these two lactones and the lactones 2a and 11a.

Preparation of the lactones 8 and 10 : They have been prepared by a chemical degradative sequence starting from acetylmethylbetulinate 3 as illustrated in the scheme I. The structure of the key intermediate 6 m.p. 205-7° was ascertained by ^{1}H NMR peak at δ 5.4 (1H, m) attributable to a vinyl proton of a trisubstituted double bond. The lactone 8 m.p. 261-2° exhibited IR band at 1775 cm^{-1} (γ-lactone) and ^{1}H NMR resonence at δ 4.2 (1H, m) due to the C-19 proton on the lactone ring. The absence of a vinyl proton resonance in the acid-induced isomerisation product 9 m.p. 153-70° showed the tetrasubstituted nature of the double bond. The lactone 10 m.p. 241-2° showed IR band at 1770 cm^{-1} (γ-lactone). The absence of a signal in the region δ 4 in the ^{1}H NMR of 10 showed the tertiary nature of the γ-lactone and confirmed C-29, 13-lactone formulation in 10.

Inspection of a Dreiding model shows that the lactone 10 with C19α-H can be easily constructed as the two five membered E ring and the lactone ring

being cis-fused are reasonably strain free while C18 β-H would have these two five membered rings trans-fused and would be very strained. Thus, on stereochemical grounds, α-orientation of C-19H in 10 has been assigned. For the lactone 9 only C-19H α stereochemistry is possible.



Reagents and Conditions : (a) SeO_2, AcOH, reflux, 3h, 70%, Ref.14 (b) CrO_3, 90% Aq AcOH, 30°, 15h, 60%, Ref.15 (c) 5(3g), $Pb(OAc)_4$(5g), $Cu(OAc)_2$(0.3g), Pyridine (0.2g) dry C_6H_5 (300 ml), reflux, 4h, N_2, 80%, Ref.16 (d) KO^tBu, DMSO, 100°, 3h, 70%, (e) HCl, dry $CHCl_3$, 0°, 50h, 40%, (f) 2(N)H_2SO_4, AcOH, reflux, 2h, 75%

Scheme I : Synthesis of model triterpene lactones of lupane series.

CD studies of lactones : Considerable work has been reported in the literature on CD studies of lactones. Various rules, of course, on emperical ground have been formulated to develop the theoretical aspect of the lactone Cotton effect and to provide a satisfactory explanation of the experimental data.

The sector rule has been advanced by Klyne[5] in the light of octant rule for ketones and considerations have been given for planarity of the lactone ring. Though it was quite successful in explaining observed CE for a large number of lactones, was not of much use in complex lactones. Snatzke[5] propounded modified sector rule considering lactones having curved nodal surfaces. Both the sector rules are applicable for lactones containing no chiral second sphere. Since bridged ring lactones are not coplanar, the chirality of the second sphere i.e. the chirality or helicity of the lactone ring is to be taken into consideration. According to the ring chirality rules published by Wolf[7] as well as Bucourt and Legrand[8] the torsion angle around the $-C(=O)-C_{\alpha}$ - bond determines the sign of the CD. If it is positive the CD is negative and vice-versa. Becham[9] also applied these rules successfully in some bridged ring lactones. Application to our compounds is complecated by the fact that the -COO- grouping is incorporated at the same time into two second spheres which have different ring sizes, making emperical proposition difficult.[10]

The CD measurement[11] of the lactone 10 exhibited a positive CE ($\Delta\epsilon$ = 3.19 at 219 nm) which was very similar to the CE curve of C-28, 13-lactones of 19 αoleanane derivatives.[12] The lactones 9 and 2a both showed negative CE with maxima at 215 nm ($\Delta\epsilon$ = -3.5) and 217 nm ($\Delta\epsilon$ = -7.02) respectively. Since olefins[13] show CE below 220 nm corresponding to the absorption of the olefin chromophore and therefore CD curve observed for the lactone 2a will contain overlapping CE due to both the lactone and the olefin groups. So the CD of dihydrolactone 2b was also measured, which too recorded a negative CE ($\Delta\epsilon$ = -5.05 at 215 nm). Both thurberogenin 11a and its dihydro derivative 11b showed positive CD band at 215 nm ($\Delta\epsilon$ = 1.46) and 219 nm ($\Delta\epsilon$ = 1.44) respectively.

The negative CE curve of the model lactone 9 is similar to the CE curve of 2a, the revised formulation of mercuric acetate oxidation product. Had the structure been 1, as was proposed initially, a positive CD band would have been obtained by comparison with structurally analogous synthetic lactone 10. Thurberogenin 11a exhibited a positive CD. If its structure were of the type 2a, as advanced originally, a negative CE would have been expected by analogy with the model lactone 9. Thus, the comparabilities of CD data in the two types of lactones provided convincing physical evidence in support of the revised formulation of mercuric acetate oxidation product as well as thurberogenin.

Acknowledgements : The authors are greatly indebted to Late Professor W. Klyne and Dr. P.M.Scopes both in Westfield College, University of London and professor G.Snatzke, Ruhr University, Bochum, Germany for helpful discussion and the CD spectra. They also thank Professor C.Djerassi, Stanford university for samples of thurberogenin and dihydro thurberogenin and the Director, CDRI, Lucknow for mass and ^{1}H NMR spectra.

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Acetoxylation of friedelin by lead (IV) acetate and anti-octant behaviour of 2-acetoxyketones

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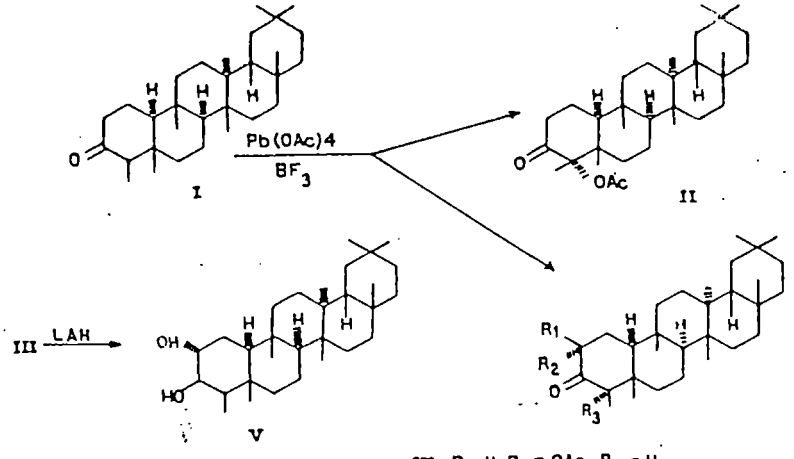
Four products have been isolated by boron trifluoride-catalysed lead (IV) acetate acetoxylation of friedelin. Three of them have been characterised as 2α-acetoxyfriedelin, 4α-acetoxyfriedelin and 2β, 4α-diacetoxyfriedelin. The former has been efficiently converted into pachysandiol-A. Chiroptical measurements (CD) of these 2-acetoxyketones show considerable anti-octant behaviour.

Acetoxylation of carbonyl compounds by lead (IV) acetate is a well-documented process having a great synthetic potential[1]. It has been extensively studied in steroidal 3-ketones and tetracyclic and pentacyclic triterpenoids bearing a 4,4-dimethyl-3-ketone moiety. The reaction is believed to proceed through the enol form and markedly catalyzed by boron trifluoride[2]. The pentacyclic triterpene ketone, friedelin (I) would serve as an interesting candidate for this acetoxylation reaction because the ketone group is flanked by α-methylene on one side and α'-methine on the other giving rise to two different enols. Recently, in connection with the structure elucidation of 2α-hydroxy-3-oxo-D:A-friedooleanan-28-oic acid Kumar and coworkers[3] reported briefly the lead tetraacetate reaction of 3-oxocanophylate, a friedelin derivative, and isolated two products 2α-acetoxy and 4α-acetoxy compounds from this reaction. Herein, we wish to report the isolation of four products from the lead (IV) acetate reaction of friedelin, and use of one of them for a short convenient synthesis of pachysandiol-A. We also report the CD measurements of these 2-acetoxyketones, which showed considerable anti-octant behaviour.

Friedelin (I), obtained from petroleum extract of cork waste, was treated with Pb(IV) acetate in acetic acid solution in the presence of boron trifluoride etherate at room temperature for 3 hr. The crude product was subjected to chromatography on silica gel. The least polar product (24%) eluted in petroleum-benzene (5:1) was crystallised from chloroform-methanol to furnish II as needles, m.p. 290°, $[\alpha]_D$ +15.0° (c 1, chloroform), $C_{32}H_{52}O_3$ (M⁺ 484). Its IR spectrum (nujal) showed bands at 1740 and 1260 ($OCOCH_3$) and 1725 cm^{-1} (CO). PMR spectrum (100 MHz, $CDCl_3$, TMS) exhibited signals at δ 2.15 (3H, s, $OCOCH_3$), 2.35 (2H, m, $-CH_2CO-$), 1.6 (3H, s, 23-CH_3) and six saturated tertiary methyl groups between 1.25 and 0.82. The mass spectrum (70 eV, direct) showed a strong molecular ion peak at m/z 484 (M^+, 65%) and other prominent peaks at 442(92), 424 ($M^+ - ACOH$, 100), 398(10), 341(12), 205(65) and 176(14). The absence of acetate methine proton established the structure of this



III, R_1=H, R_2 = OAc, R_3 = H
IV, R_1= OAc, R_2=H, R_3 = H
VI, R_1=H, R_2 =OH, R_3 = H
VII, R_1= OAc, R_2 = H, R_3=OAc

product as 4-acetoxyfriedelin (II). Based on the known preference of attack of the acetate ion on the intermediate organolead salt from the less hindered α-face[4] of the molecule the stereochemistry of the acetate group was assigned α.

The second product (22%) eluted in petroleum-benzene (5:2) was crystallised from chloroform-methanol to afford fine needles, $C_{32}H_{52}O_3$ (M^+, 484), m.p. 256-8°, $[\alpha]_D$ −29°. The structure of this product was established as 2α-acetoxyfriedelin (III; cerin acetate) by direct comparison with acetylation product of cerin. The formation of this product is also consistent with the preferred attack of the acetate ion from the less hindered α-face[3].

The third product (28%) isolated from petroleum-benzene (1:1) eluate was crystallised from chloroform-methanol as needles m.p. 290°, $C_{34}H_{54}O_5$. Its IR spectrum showed bands at 1750, 1730, 1242 ($OCOCH_3$) and 1720 cm^{-1} (CO). The PMR spectrum gave signals for two acetoxy groups at δ 2.16 (3H, s, $OCOCH_3$) and 2.06 (3H, s, $OCOCH_3$). The protons of one methyl group appeared at δ 1.69 (3H, s, C-23 CH_3) and those of six saturated tertiary methyl groups between 1.25 and 0.88. The acetate methine proton appeared at δ 3.72 (1H, dd, −COCHOAc−). The considerable upfield shift of the acetate methine proton could be attributed to the shielding by the carbonyl group in the distorted 2,4-diacetoxy-3-keto ring-A of this product. An inspection of the molecular model supports this view. The mass spectrum registered the highest peak at m/z 482 (M^+ − AcOH, 26%). Assignment of the configuration of the acetoxy groups at C-2 and C-4 was based on chemical conversions. This diacetoxy compound could be prepared either from 2β-acetoxyfriedelin (IV) (epicerin acetate) or from 4-α-acetoxyfriedelin (II), but not from 2α-acetoxyfriedelin (III) (cerin acetate) under the same conditions of boron trifluoride-catalysed Pb(IV) acetate reaction. Thus, the stereostructure of this compound was established as 2β,4α-diacetoxyfriedelin (VII). Besides monoacetoxylation, α,α′-diacetoxylation where such positions are available is also reported to occur in many cases[1a]. α-Acetoxyketones may react to furnish α, α′-diacetoxy compounds[5].

The most polar material (4% yield) eluted in petroleum-benzene (1:4) was crystallised from chloroform-methanol as fine microcrystals, m.p. 250°. Its IR spectrum exhibited bands at 1750, 1250 (acetate) and 1700 cm^{-1} (CO). Studies are underway for the complete characterization of this minor product.

Partial synthesis of pachysandiol-A(V)

Pachysandiol-A(V) (friedelane-2α,3β-diol) was isolated from *Pachysandra terminalis*[6]. Later on it was partially synthesised[7] from friedelin (I) by a sequence of reactions involving LAH reduction, benzoylation, pyrolytic elimination, epoxidation, followed by acid-catalysed epoxide cleavage. We have now carried out a short and convenient synthesis of this compound. 2α-Acetoxyfriedelin (III), one of the major products of lead (IV) acetate acetoxylation of friedelin (I), on lithium aluminium hydride reduction furnished V in high yield (76%).

Chiroptical measurement

Circular dichroism (CD) measurement of friedelin (I) in dioxane showed a negative cotton effect (CE) at 290 nm ($\Delta\varepsilon = -2.68$) and cerin acetate, 2α-acetoxyfriedelin (III), in the same solvent also showed negative CE $\Delta\varepsilon = -1.47$ at 300 nm. An examinatiion of the octant diagram revealed that 2α-acetoxy substituent (axial) lies in the back lower-left octant and hence should make more negative contribution than that of the parent ketone (I), but actually it makes less negative contribution. This anti-octant behaviour of 2-acetoxyketones has been studied in steroids and other types of compounds[8,9]. In 2β-acetoxyfriedelin (epicerin acetate; IV), obtained by acid-catalysed epimerization of III, the substituent 2β-acetoxy group (equatorial) lies almost in the nodal plane and has practically little contribution. This has been reflected in its CD spectrum, $\Delta\varepsilon = -2.36$ at 298 nm (dioxane), almost the same as that of friedelin mentioned above. ORD spectra of III and IV were recorded by Kikuchi and Toyoda[6], but their anti-octant behaviour was not studied. The anti-octant behaviour was also observed in II which showed a negative CE [$\Delta\varepsilon = -3.17$ at 300 nm (dioxane)]. In II, 4β-methyl group lies in the nodal plane making no contribution but 4α-acetoxy group which lies in back lower-right octant should make positive contribution but actually it makes negative contribution thereby making CE more negative in comparison to the parent ketone (I). In short, 2-acetoxy-3-keto derivatives of friedelane show significant anti-octant behaviour as reflected in CD measurements.

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252. Phytochemical Investigation of two Euphorbiaceae Plants- *Mallotus albus* and *Bischofia javanica.*

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Phytochemical investigation of benzene extract of *Mallotus albus* yielded taraxerone, epitaraxerol, stigmastan 3,6 dione and β-sitosterol. Reinvestigation of the plant, *Bischofia javanica* afforded epi-friedelanol acetate, friedelin, β-sitosterol, betulinic acid, fridelanol and a triterpene dihydroxy ketone m.p. 295°, diacetate m.p. 228°.

253. Sterols and Triterpenoids of two Euphorbiaceae Plants- *Antidesma acuminatum* and *Bridelia retusa.*

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Benzene extract of the bark of *Antidesma acuminatum* afforded α-spinosterol and that of *Bridelia retusa* gave friedelin, epifriedelanol and stigmasterol.

254. A Search for Anticancer Constituents of Natural Origin— Chemical Examination of Latex of *E. nerifolia* Linn.

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and
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The petroleum ether (60-80°) extract of the fresh latex the plant *Euphorbia nerifolia* yielded the following compounds :