

ORGANIC PHOTOCHEMISTRY - PART II¹, PHOTOCHEMICAL SYNTHESIS OF THE NATURALLY
OCCURRING TRITERPENE LACTONE, 3 β -HYDROXY LUPAN-28, 13 β -OLIDE

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Summary : The photochemical synthesis of the title lactone was achieved by irradiation in the presence of Pb(IV) acetate alone or Pb(IV) acetate + calcium carbonate + iodine or mercuric oxide + iodine. Chiroptical measurements (CD) of this and other related lactones provided convincing evidence in support of the lactone ring structure.

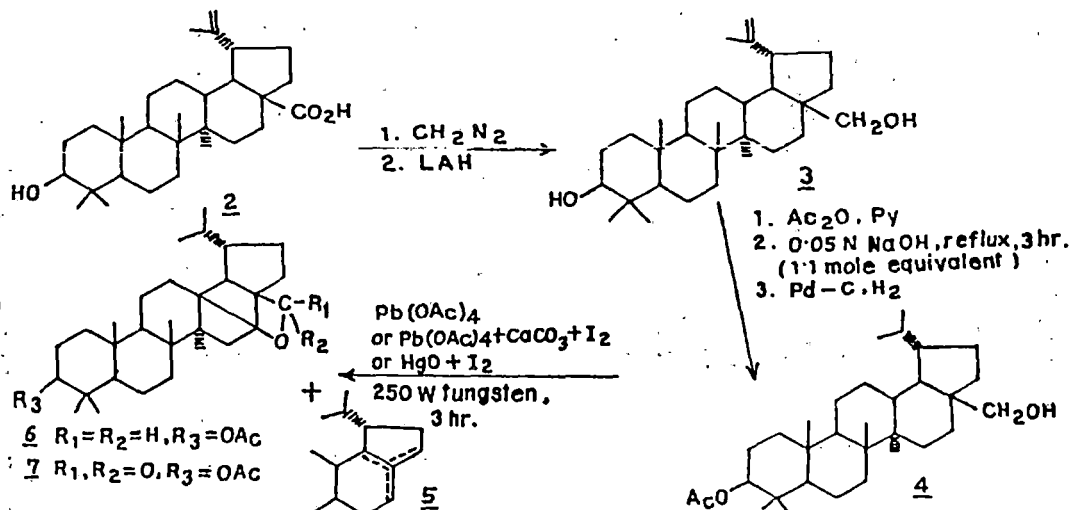
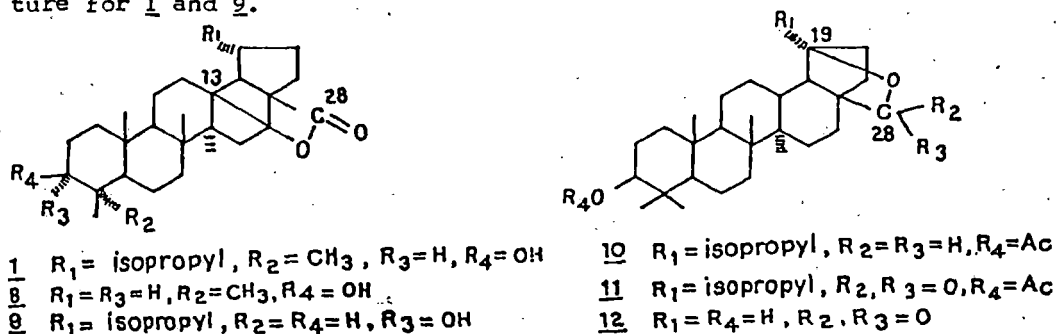
The photochemical synthesis of organic compounds, in many cases, is a convenient technique especially when conventional chemical procedures are difficult to manipulate. Here, we report on the photochemical synthesis of the naturally occurring lactone, 3 β -hydroxy lupan-28, 13 β -olide **1**. The structure of this lactone **1** obtained from *Dilena indica*², was deduced earlier; but neither synthesis nor stereochemistry has been elaborated. This photochemical synthesis provided an unequivocal proof of its structure and stereochemistry. Also we present here chiroptical measurements (CD) of this and other related lactones of the lupane series.

The key intermediate 3 β -acetoxy dihydrobetulin **4** was prepared from betulinic acid³ **2** as illustrated in the scheme I. **4** in cyclohexane was irradiated with Pb(IV) acetate alone and also separately with Pb(IV) acetate + calcium carbonate + iodine using 250W tungsten lamp for 3 hr, giving same type of products distribution in both cases. Chromatography first eluted **5** (35%) m.p. 158-54°. Its GLC behaviour and spectral characteristics indicated it to be a mixture of 'olefins' resulting from the oxidative removal of -CH₂OH at C-17. **5** was also formed from Pb(IV) acetate oxidation of betulinic acid⁴. The second component eluted was **6** (18%) m.p. 192-4° (α)_D + 17°. A clean photoreaction occurred when **4** was irradiated with HgO + iodine in cyclohexane and **6** was obtained as the sole, isolable product (28%). ¹H NMR revealed tetrasubstituted ether linkage (-O-CH₂-) in **6** which must be either C-28, 19 β or C-28, 13 β . **6** on chromium trioxide-AcOH oxidation yielded **7** m.p. 315°. IR band at 1762 cm⁻¹ and absence of ¹H NMR peak around δ 4 established tertiary γ -lactone structure of **7**. **6** and **7** are not identical with Hg(II) acetate oxidation products⁵ dihydro C-28, 19 β -ether **10** and dihydro C-28, 19 β -lactone **11** respectively. Thus, **6** was assigned 3 β -acetoxy-28, 13 β -epoxy lupane and **7** 3 β -acetoxy lupan-28, 13 β -olide which on alkaline hydrolysis afforded **1**, m.p. 321°, (α)_D + 60° [lit.² m.p. 325°(d), (α)_D + 53.4°].

Since in no step of the sequence α -orientation of the C-19 isopropenyl group (isopropyl in dihydro derivative) of betulinic acid **2** was affected, this synthesis proved unequivocally the α -stereochemistry of isopropyl substituent at C-19 in **1**.

The tertiary γ -lactones of the types **1** and **11** are difficult to distinguish by physical techniques such as IR, ¹H NMR, ¹³C NMR and mass spectral analysis. We obtained CD measurements to distinguish them. Very recently we synthesised⁷ the authentic C-28, 19 β -lactone **12** and C-28, 13 β -lactone

9 and measured their CD spectra. Both the synthetic⁷ lactone **12** and the lactone **11** obtained by Hg(II) acetate oxidation⁵, exhibited negative CD⁷ with maxima at 215 nm ($\Delta\epsilon = -3.6$) and at 217 nm ($\Delta\epsilon = -5.05$) respectively. On the other hand, the synthetic lactone⁷ **8** and the lactone **1** obtained photochemically both showed positive CD having maxima at 219 nm ($\Delta\epsilon = 3.19$) and at 220 nm ($\Delta\epsilon = 1.04$) respectively. We also recorded CD spectrum of epicaltholide **9**, another naturally occurring lupane triterpene⁸ having C-28, 13 β -lactone which also exhibited a positive CD band ($\Delta\epsilon = 2.32$ at 217 nm). Thus, CD data provided convincing physical evidence in support of C-28, 13 β -lactone structure for **1** and **9**.



Scheme I: Photochemical synthesis of 3 β -hydroxylupan-28, 13 β -olide.

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Lead(IV) acetate oxidation of triterpenoid 3-ketohydrazones

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Lead(IV) acetate oxidation of triterpenoid 3-ketohydrazones yields olefins and acetates. Based on mercury(II) oxide oxidation of hydrazones and Bamford-Stevens reaction of the corresponding tosylhydrazones carbocation has been postulated as the precursor of the olefin formation. (1)

Debono and Molloy¹ reported that steroid 3-ketohydrazones on lead(IV) acetate oxidation furnished olefins (25%) and epimeric acetate mixture (52%; 3 α and 3 β in about 2:1 ratio). The predominance of 3 α -acetate although indicated some measure of stereospecificity, the product ratio remained unchanged by varying the concentration of acetic acid or by using pyridine. Barton and coworkers² carried out oxidation of steroid 7-ketohydrazones and noted the formation of single acetate (7 α , 68%) and olefins (20%). Since no such similar studies have been carried out on triterpenoid 3-ketohydrazones, we have presently carried out the title investigation on 3-ketohydrazones(I) and (IV) of 4,4-dimethylupan-3-one and 4-methylfriedelin respectively. Lead(IV) acetate oxidation of I and IV was carried out in dichloromethane according to the procedure of Barton². For efficient and smooth separation, the reaction mixture was saponified with 5% methanolic KOH for 2 hr. Chromatography over silica gel furnished hydrocarbons and alcohols, which are described in Table 1.

The data in Table 1 reveal that in the oxidation of I there is not much stereospecificity as regards the formation of epimeric acetates (IIIb and IIIa) (3 α :3 β ::5:6). In contrast, the steroid substrate lacking 4,4-dimethyl functionality demonstrated considerable stereospecificity¹ (3 α :3 β ::2:1). In the oxidation of IV exclusive formation of 3 α -acetate (VI) may be ascribed to the presence of 5 β -methyl group which imposes a strong 1,3-diaxial interaction for the attack by the acetate ion from the more hindered β -face of IV at C-3 position.

Barton *et al.*² demonstrated that the olefins formed by the mercury(II) oxide oxidation of steroid 7-ketohydrazone was not identical with that obtained by lead(IV) acetate path. This led them to postulate carbonium ion path in the latter case. When I was subjected to mercury(II) oxide oxidation³ the hydrocarbon obtained was not identical with that obtained by lead(IV) acetate oxidation product(II), but identical with lup-2-ene, a phosphorus oxychloride-pyridine dehydration product of lupanol. The lead tetraacetate product was identical with the product(II) obtained from the

retropinacol dehydration of lupanol with phosphorus pentachloride in petroleum, which is believed to proceed via a carbonium ion⁴. This led us also to propose that carbonium ion is the precursor of olefin formation. Similarly lead(IV) acetate oxidation of IV yielded friedel-3-ene(V), which was different from the mercury(II) oxide reaction product, i.e. friedel-2-ene.

It is well documented⁵ that the base-catalysed thermal decomposition of tosylhydrazones (Bamford-Stevens reaction) in protic solvents leads to products arising via a carbonium ion intermediate while the product in aprotic solvent results via a carbene intermediate. Lupanone tosylhydrazone on decomposition with sodium in ethylene glycol gave A-norisopropylidene(II) while aprotic decomposition with NaOMe in diglyme afforded lup-2-ene. Protic decomposition of friedelin tosylhydrazone also furnished the same product(V) as obtained from the lead tetraacetate oxidation of friedelin hydrazone.

Thus, the experiments devised here adduce further evidence in support of the intermediacy of carbocation in the formation of olefins by lead(IV) acetate reaction of the hydrazones.

Experimental

Melting points are uncorrected. IR spectra were recorded in Beckman IR-20 infracord spectrophotometer, PMR spectra in CDCl₃ on a Perkin-Elmer R-32 (90 MHz) instrument using TMS as an internal standard and mass spectra or Jeol D-300 mass spectrometer (70 eV, direct inlet). Hydrazones and tosylhydrazones were prepared according to the procedures of Barton *et al.*² and Bamford and Stevens⁶ respectively. The characterization data of compounds II, IIIa, IIIb, V and VI are given in Table 1. Pet. ether used throughout the experiments had the boiling range 60-80°.

Lead(IV) acetate oxidation of lupanone hydrazone(I)

I (1 g) in dry dichloromethane (100 ml) was treated with lead(IV) acetate (2.2 g) at 20°. There was immediate evolution of nitrogen and precipitation of lead diacetate. When nitrogen evolution was complete the mixture was filtered. Ethane diol (10 ml) was added to destroy the excess oxidant and then poured into water. The organic layer was separated and the aqueous layer extracted with ether (3 \times 50 ml). The combined solution was washed with aqueous sodium bicarbonate (2 \times 50 ml) until neutral and water (2 \times 50 ml), dried (Na₂SO₄) and evaporated. The solid (0.94 g) thus obtained was dissolved in benzene (20 ml). Methanolic KOH (5%, 20 ml) was added to it and refluxed for 2 hr. The mixture was poured into water and extracted with ether in the usual way. The crude gummy material (0.83 g) was chromatographed on silica gel (25 g) column. Separation and yields of the products II, IIIa and IIIb are given in Table 1.

Lead(IV) acetate oxidation of friedelin hydrazone(IV)

Similar treatment of IV (1.5 g) in dichloromethane (160 ml) with lead(IV) acetate (3.4 g) afforded products V and VI as shown in the Table 1.

