Hydrogen Peroxide Oxidation of Lupanone in Presence of Selenium Dioxide

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The oxidation of lupanone (Ia) with molar proportion of hydrogen peroxide and catalytic amount of selenium dioxide in *t*-butanol affords lup-1-ene-3-one (Ib), lupane dicarboxylic acid (Ic) and 2α-carboxyl-A-nor-lupane (Id); with excess of hydrogen peroxide, Ia furnishes 4,23, 24-tri-nor-lupane-3 → 5-olide, a δ-lactone (Ie) together with lupane dicarboxylic acid (Ic).

THE selenium dioxide catalysed reaction of hydrogen peroxide on stereoidal 3-ketones was studied by Caspi and Balasubrahmanyam[1]. A similar reaction of pentacyclic triterpene-3-ketone is lacking and hence the title investigation was undertaken.

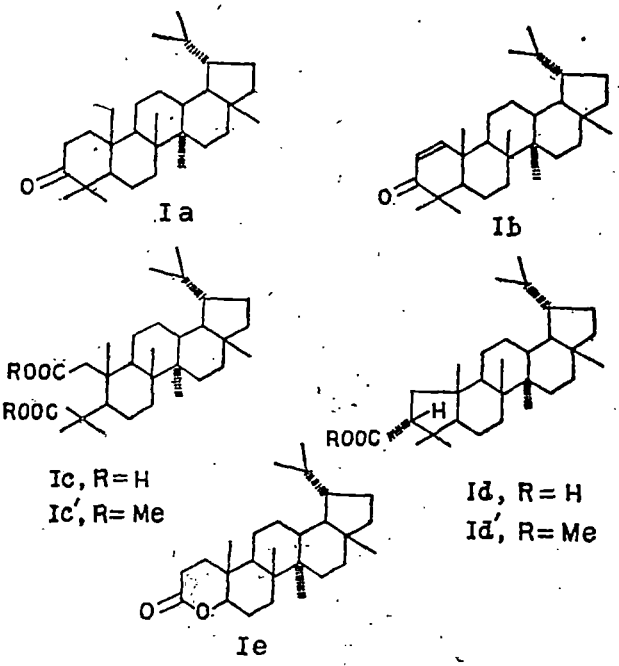
A solution of lupanone (Ia, 1.2 g) in *t*-butanol (60 ml) mixed with molar proportion of hydrogen peroxide (17%, 0.2 ml) and catalytic amount of selenium dioxide (0.008 g) was refluxed for 35 hr when black selenium metal precipitated out at the end of the reaction. The reaction mixture was then separated into acid and neutral fractions by usual method.

The neutral product on purification by chromatography and crystallisation from chloroform-methanol furnished a crystalline solid, $C_{30}H_{48}O$, m.p. 175-77°. That the product was an α, β-unsaturated ketone was indicated by characteristic UV absorption in methanol (λ_{max} 228 nm) and its IR spectrum in nujol (ν_{max} 1675 cm^{-1}). The PMR support for this product was forthcoming by the appearance of a pair of doublets each at δ 5.85 (J=10 Hz) and 7.19 (J = 10 Hz) assignable to the moiety —CO—CH=CH—C—. The compound was found to be identical (m.m.p and co-IR) with an authentic sample of lup-1-ene-3-one[2] (Ib).

The acidic part was esterified and then chromatographed. Elution with pet. ether (b.p. 60-80°) furnished a solid, which crystallised from chloroform-methanol and analysed for $C_{31}H_{52}O_2$ (M+ 456), m.p. 174-77°, IR (nujol) : 1740 cm^{-1} (carbomethoxy); PMR ($CDCl_3$, δ) : 0.8 (*s*, 3H, *t*-CH_3), 0.75 (*d*) + 0.85 (*d*) (J = 7 Hz, 6H, $HC(CH_3)_2$), 0.94-1.04 (5*s*, 15H, 5 × *t*-CH_3), 2.7 (*m*, J = 1 6Hz, 1H, *H*-C-$COOCH_3$) and 3.7 (*s*, 3*H*, —$COOCH_3$).

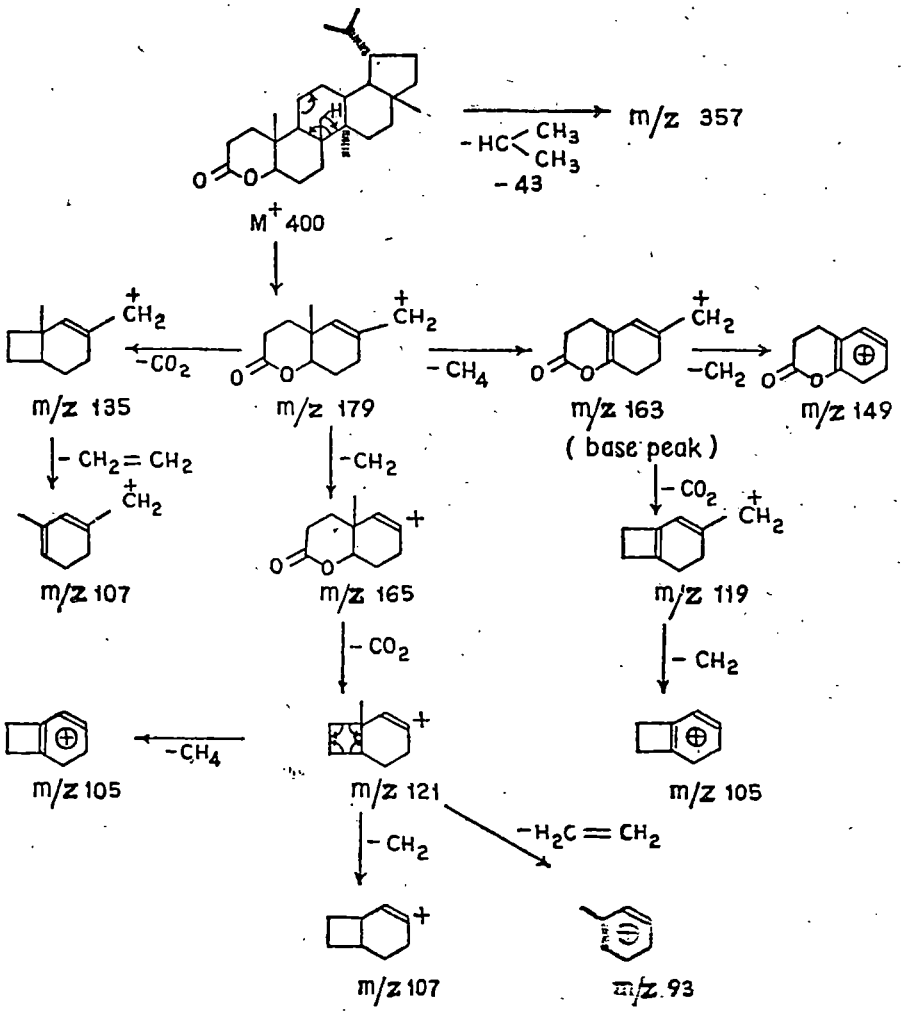
From the spectral data the ester has been identified as 2α-methoxycarbonyl-A-norlupane[3] (Id'), corresponding to the acid (Id).

Further elution of the column with pet. ether-benzene (4:1) gave a seco-diester, $C_{32}H_{54}O_4$, m.p. 116-18°; MS : *m/z* 502 (M^+), 443 (M^+—$COOCH_3$), 429 (M^+—CH_2COOCH_3), 400 [443-$CH(CH_3)_2$], 205, 189; IR (nujol) : 1740, 1730 cm^{-1} (2-carbomethoxyl groups); PMR ($CDCl_3$, δ) : 0.92 to 1.22 [24H, 6*t*-CH_3, 1 $HC(CH_2)_2$], 2.37 (*m*, 2H, CH_2-COOMe), 3.64 (*s*, 3H, $COOCH_3$), 3.68 (*s*, 3H; $COOCH_3$). Hydrolysis of the seco-diester (Ic') by methanalic KOH furnished a diacid, m.p. 270-71°, identical with lupane dicarboxylic acid[4] (Ic).

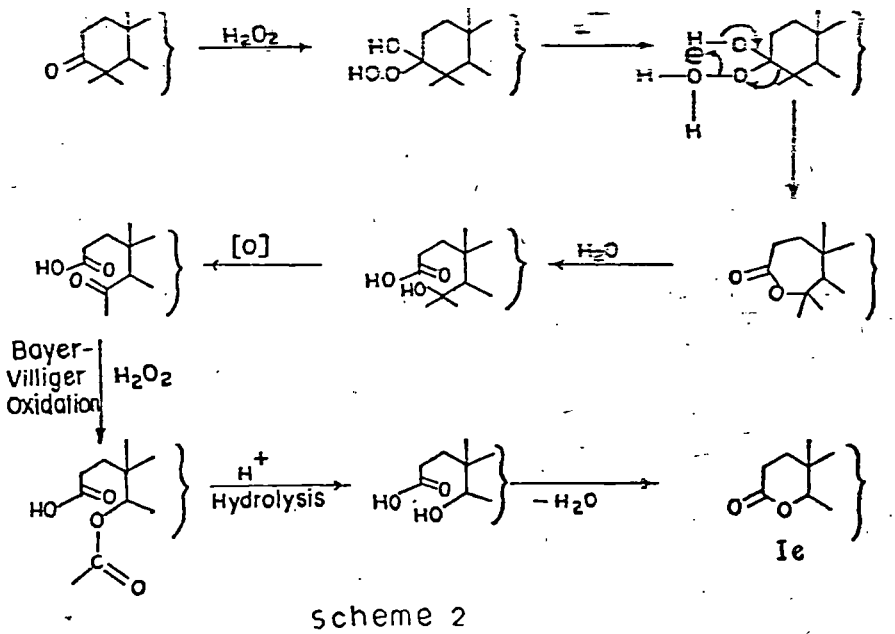


When lupanone (2g) was oxidised with excess amount of hydrogen peroxide (17%, 30 ml) by refluxing for 30 hr in the presence of selenium dioxide (0.5 g) in *t*-butanol (150 ml), it yielded in acidic fraction a compound characterised as Ic[4]. The neutral part on chromatography followed by elution with benzene afforded a solid, which recrystallised from chloroform-methanol and analysed for $C_{27}H_{44}O_2$ (M+ 400), m.p. 252°. The band at 1740 cm^{-1} in its IR spectrum indicated the presence of a δ-lactone, which was corroborated by the appearance of a lactonic proton (CO-O-C*H*-CH_2) at δ 3.9 as a triplet[5] (J=18Hz), in its PMR spectrum. The high J value showed the lactonic proton to be axially oriented with one axial and another equatorial neighbours. Besides, the compound gave a pair of peaks centred at δ 2.6 (2*H*) indicating the presence of methylene protons alpha to the carboxyl group (—CH_2—CH_2—COO). The structure of this compound as Ie was further supported by its mass spectral fragmentation pattern shown in Scheme 1. This is the first report of formation of a δ-lactone (Ie) by the loss of three carbon atoms of ring -A from a 3-keto-triterpene by the action of hydrogen peroxide in the presence of selenium dioxide.

The mechanism of formation of δ-lactone (Ie) is



Scheme 1



Scheme 2

suggested in Scheme 2, based on similar reaction by Pettit *et al.*[6] on steroidal systems.

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Oxidation of Friedelin with Hydrogen Peroxide in Presence of Selenium Dioxide

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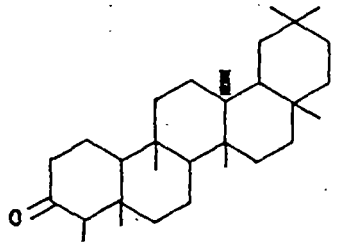
Friedelin (I) on oxidation with molar proportion of hydrogen peroxide and catalytic amount of selenium dioxide in *t*-butanol affords a δ-lactone (II), friedelin dicarboxylic acid (IIIa) and 2α-carboxyl-A-nor-friedelin (IVa). The compounds have been fully characterised by spectral data (IR, PMR).

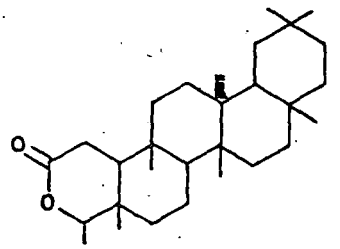
In our previous communication[1], hydrogen peroxide-selenium dioxide oxidation of lupanone was reported to afford 4, 23, 24-trinor-lupane-3→5-lide (A). Friedelin (I) on similar reaction gave a δ-lactone different from (B), obtained by Corey *et al.*[2] by the oxidation of I with peracetic acid. The preparation and characterisation of the different products obtained in the reaction of I with $H_2O_2-SeO_2$ are reported in this note.

A solution of friedelin (I, 0.9 g) in *t*-butanol (80 ml) mixed with hydrogen peroxide (15 ml, 22%) and selenium dioxide (0.225 g) was refluxed on a water-bath for 60 hr. Precipitation of black selenium metal in the reaction mixture indicated the completion of the reaction. The reaction mixture was then separated into neutral and acid parts by usual method.

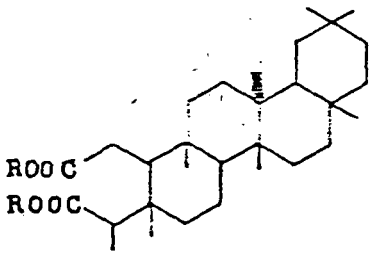
The acidic part on esterification with diazomethane followed by chromatography yielded two products. The less polar solid was crystallised from chloroform-methanol, m.p. 263-65°. It analysed for $C_{31}H_{52}O_2$;



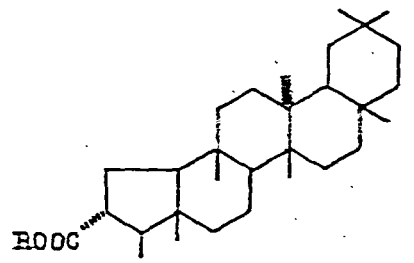
I



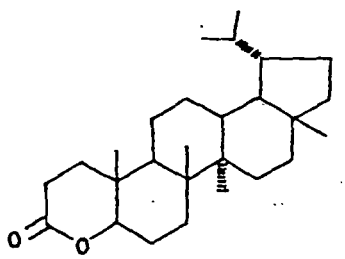
II



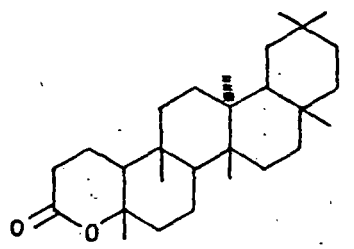
III a, R = H
III b, R = Me



IV a, R = H
IV b, R = Me



A

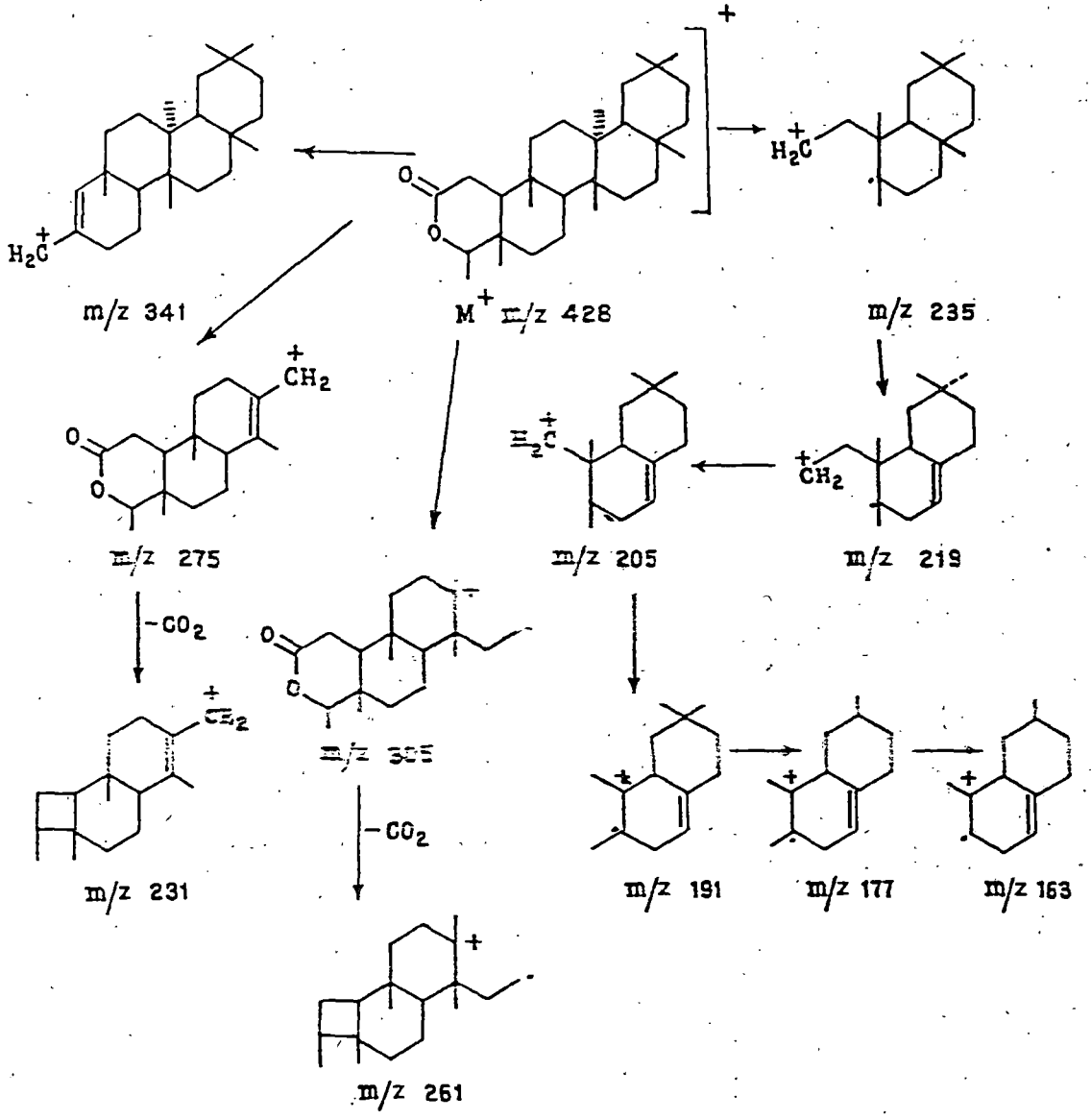


B

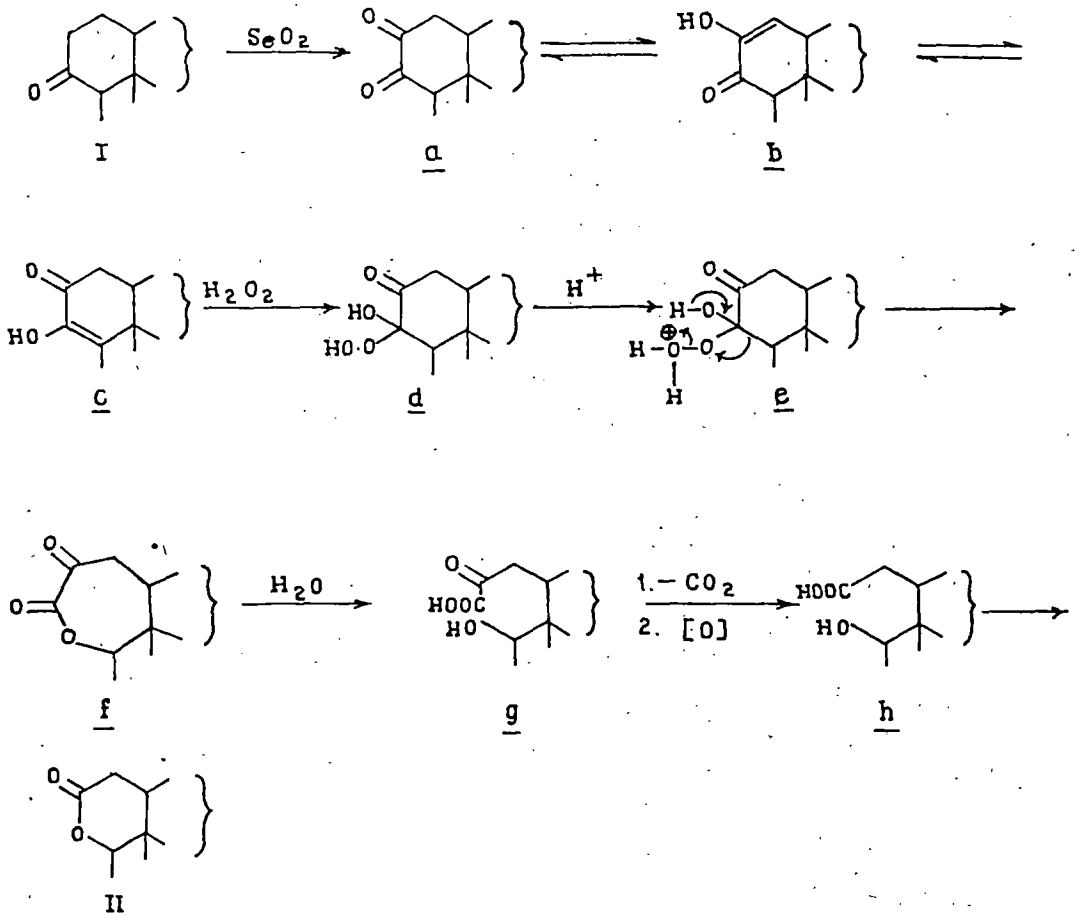
MS: m/z456(M^+), 332, 303, 276, 262, 248, 234, 223, 205(base), 191, 179, 121, 109 and 107; IR (nujol): 1720 cm^{-1} (one carbomethoxyl group); PMR ($CDCl_3$): δ 3.53 (*s*, 3H, $COOCH_3$), 2.8 (*m*, 1H, $H-\underset{|}{C}-COO$), 0.9 to 1.2 (7*s*, 21H, 7 × *t*-CH_3), 0.87 (*d*, 3H, $H-\underset{|}{C}-CH_3$, $J=7$ Hz) These spectral data led to the establishment of structure (IVb) for this compound and the corresponding acid presumably corresponded to structure (IVa).

The more polar product was purified by crystallisation from $CHCl_3$-MeOH. It analysed for $C_{32}H_{54}O_4$ (M^+ 502); m.p. 167-69°; IR (nujol): 1735 cm^{-1}; PMR ($CDCl_3$, δ): 3.53 (*s*, 3H, $COOCH_3$), 3.57 (*s*, 3H, $COOCH_3$), 0.9 to 1.2 (21H, 7 × *t*-CH_3), 1.32 (*d*, 3H, $H-\underset{|}{C}-CH_3$, $J=7$ Hz). Based on these data, this compound was assigned structure (IIIb). Hydrolysis of the seco-diester (IIIb) by methanolic KOH furnished the diacid (IIIa), m.p. 280° (d), identical with 3, 4-seco-friedelonic acid (IIIa)[2].

The neutral part was chromatographed over deactivated alumina column. Elution with petroleum-benzene (2 : 3) afforded a white solid (≈10 mg), which analysed for $C_{29}H_{48}O_2$ (M^+ 428), m.p. 262°; CD (hexane): 230 nm (ε − 0.56). In the IR spectrum, a band at 1740 cm^{-1} was characteristic of δ-lactone moiety, the presence of which was supported by its PMR spectrum (multiplet at δ 4.05 due to lactonic proton[3], $-CO-O-\underset{|}{C}H-CH_3$). The appearance of a pair of doublet at δ 2.48 (2H, $J_{aa}=7.5$ Hz, $J_{ae}=2.5$ Hz) indicated the presence of methylene protons adjacent



Scheme 1



Scheme – 2

to the carbonyl group ($-O-\underset{\underset{O}{\|}}{C}-\underset{\underset{OH}{|}}{CH}-CH_2-$). A three-proton doublet at δ 1.18 (J = 6.5 Hz) was assignable to methyl protons ($HC-CH_3$). The peaks between δ 0.88 and 1.10 represented seven tertiary methyl groups (21H). These observations led to the establishment of structure (II) for the lactone, further supported by its mass fragmentation pattern shown in Scheme 1. This is perhaps the first report of the formation of δ-lactone from friedelin.

The mechanism of formation of II is shown in Scheme 2. It is well known that SeO_2 oxidises α-methylene ketones to 1, 2-diketones[4,5]. The formation of II probably proceeds via the formation of the diketone (a) [$\rightleftharpoons$diosphenol b$\rightleftharpoons$c]. One mol of hydrogen peroxide may attack (c) to give the intermediate α-keto-ε-lactone (f), which may undergo hydrolysis to furnish the α-keto acid (g). The acid (g) on decarboxylation furnishes 3, 4-seco-C-3-nor-4-hydroxy-friedelin-2-carboxylic acid (h) which undergoes lactonization to form the δ-lactone (II). All the above intermediates are formed during the reaction conditions *in situ*. The formation of a similar lactone in the oxidation of lupanone by H_2O_2-SeO_2 is not possible due to the presence of *gem*-dimethyl group at C-4, which hinders the formation of a diosphenol, similar to c, from lupanone. Thus the oxidation of lupanone gave compound (A) only, different from II.

The authors are thankful to Dr P M Scopes, University of London, UK for recording the CD and PMR spectra. One of the authors (S D) is grateful to CSIR, New Delhi for the award of a junior research fellowship.

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Oxidation of Taraxerone with Hydrogen Peroxide in Presence of Selenium Dioxide

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Taraxerone (I) on oxidation with hydrogen peroxide in the presence of selenium dioxide in *t*-butanol affords 1α,2α-epoxide (II), 4,23,24-tri-nor-taraxerene-3→5-olide, a δ-lactone (III) and taraxerene-ε-lactone(IV) from neutral part and 2α-carboxy-A-nor-taraxerene(V) together with taraxerene-3,4-seco-dicarboxylic acid (VI) from the acid part.

We reported in our previous communications[1,2] the results of selenium dioxide oxidation of saturated triterpenoids. We have now extended the reaction to taraxerone, a 3-keto triterpenoid having a trisubstituted double bond, and the products obtained have been characterised.

To a solution of taraxerone (I) (0.9 g) in *t*-butanol (80 ml) was added hydrogen peroxide (15 ml, 17%) and selenium dioxide (0.225 g) and the mixture refluxed for 20 hr. The deposition of the precipitates of black selenium metal indicated the completion of the reaction. The reaction mixture was filtered and separated into neutral and acid parts.

Chromatography of the neutral part over deactivated alumina column and elution with benzene-pet. ether (1:4) gave a solid which crystallised from chloroform-methanol, m.p. 188°. It analysed for $C_{30}H_{46}O_2$; MS: *m/z* (re. int.) 438 (M^+, 39.9), 423 (23.2), 314 (70), 299 (28), 205 (75), 204 (100), 189 (10); IR(Nujol): 1705 (>C=O), 1255 (epoxide), and 820 cm^{-1} (trisubstituted double bond); no UV absorption above 220 nm; PMR($CDCl_3$, δ): 0.837 to 1.132 (s, 24H, $8\times t-CH_3$), 5.56 (*m*, 1H, >C=C*H*); a pair of doublets each at 3.52 (J=4 Hz) and 3.35 (J=4.5 Hz) assignable to two protons[3] of oxirane ring of each carbon. That this compound is a 1,2-epoxide of taraxerone is supported by presence of the fragments IIa, IIb, and IIc in its mass spectrum[4]. Thus from the above spectral data structure (II) has been assigned for the epoxide.

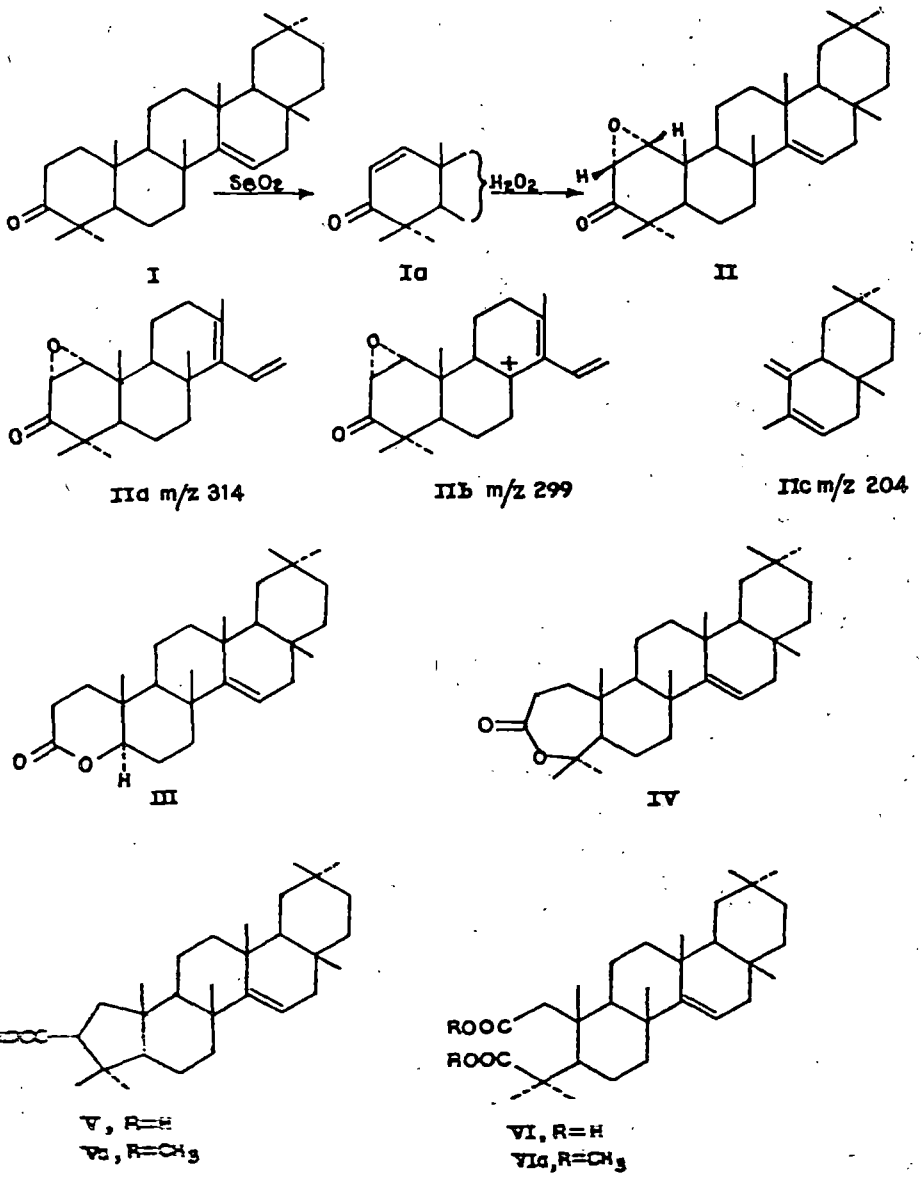
Further elution of the column with pet. ether-benzene (2:3) afforded a solid which on fractional crystallisations from chloroform-methanol afforded two solid compounds (A) and (B): A, m.p. 228-30°, $C_{27}H_{42}O_2$ (M^+ 398); and B, m.p. 218°, $C_{30}H_{48}O_2$ (M^+ 440). The IR spectrum of A exhibited bands at 1750 (δ-lactone) and 810 cm^{-1} (trisubstituted double bond); MS: *m/z* (rel. int.) 398 (M^+ 32.91), 383 (18.45), 274 (100), 259, 204 (75); PMR($CDCl_3$, δ): 0.83 to 1.12 (6*s*, 18H, $6\times t-CH_3$), 5.57 (*m*, 1H, >C=C*H*), 2.26 (*m*, 2H, $-CH_2-CH_2-CO-O-$), 3.92 (*q*, J_{ae}=5 Hz, J_{aa}=12 Hz, lactonic proton, $CO-O-CH-CH_2-$)[5]. The high J-value showed the lactonic proton to be axially oriented with one axial and another equatorial neighbours. On the basis of these data compound (A) is assigned structure (III). The IR spectrum of B exhibited bands at 1720 (ε-lactone) and 810 cm^{-1} (>C=C<H); MS: *m/z* 440 (M^+), 425, 316, 301, 204, 189. The mass spectrum of B confirmed its structure as IV.

The acidic part was esterified and subjected to chromatography over a deactivated alumina column. Elution with pet. ether (b.p. 60-80°) furnished compound (C) which crystallised from chloroform-methanol, analysed for $C_{31}H_{50}O_2$, m.p. 161-63°; MS: *m/z* (rel. int.) 454 (M^+, 32), 439 (13), 330 (14), 315 (10), 287 (20), 204 (75); IR(nujol): 1735 (carbomethoxy), 815 cm^{-1} (trisubstituted double bond); PMR($CDCl_3$, δ): 3.6 (*s*, 3H, $-COOCH_3$), 2.75 (*q*, 1H, J_{ae}=5 Hz, J_{aa}=11 Hz, $-CH_2-C-CO-O-$), 0.82 to 1.13 (24H, $8\times t-CH_3$), 5.54 (*m*, 1H, C=C*H*). The PMR data and the mass fragmentation pattern proved the ester as 2α-methoxycarbonyl-A-nor-taraxerone (Va).

Further elution of the column with pet. ether-benzene (1:1) gave a solid ester (D) which analysed for $C_{32}H_{52}O_4$, m.p. 151°; MS: *m/z* (rel. int.) 500 (M^+, 17), 485 (6), 470 (7), 468 (9), 440 (6), 395 (7), 376 (7), 361 (2), 344 (20), 316 (12), 287 (17), 204 (100); IR (Nujol): 1725 and 1730 (two carbomethoxy), 810 cm^{-1} (trisubstituted double bond); PMR($CDCl_3$, δ): 5.54 (*m*, 1H, >C=C*H*), 3.65 (*s*, 3H, $-COOCH_3$), 3.60 (*s*, 3H, $-COOCH_3$), 2.3 (*m*, 2H, $-CH_2-CH_2-COOCH_3$), 0.81 to 1.25 (24H, $8\times t-CH_3$). On the basis of the spectral data structure (VIa) has been assigned for D. This compound is reported in literature as taraxadioic acid[6].

The formation of the products II, III, IV, V and VI shows that in the SeO_2 oxidation of I no migration of 14-15 double bond has occurred. Compounds II, III, IV and V are probably being reported for the first time.

It may be concluded from the results of previous studies[1,2] and those obtained presently that the δ-lactones are formed irrespective of the presence of methyl groups at C-4 position. Further, isolation of ε-lactone (IV), though in a very small amount (2%), supports the mechanism of formation of the δ-lactone



via the δ-lactone. Efforts to confirm the reaction path for the formation of the δ-lactone as suggested previously[1] are in progress. The epoxide II is most probably formed via the unsaturated ketone (Ia).

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