565. *The* Euphorbia *Resins. Part VIII.** *Epoxides from, and Oxidations at the Inert Double Bond of, Euphol, Euphorbol, and Tirucallol.*

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The action of perbenzoic acid on euphadienyl, euphorbadienyl, and tirucalladienyl acetates and their dihydro-compounds has given solid epoxides; and per-acid titration may be used to measure unsaturation in these compounds. Euphatriene forms triepoxyeuphane.

The epoxy-derivatives of euphenyl, euphorbenyl, and tirucallenyl acetates gave with concentrated sulphuric acid in acetic acid the dehydro-compounds which contain two conjugated double bonds and which react with only one mole of perbenzoic acid.

Diketoeuphenyl and diketoeuphorbenyl acetates with selenium dioxide give triketoeuphadienyl and triketoeuphorbadienyl acetates.

Euphol (euphadienol) and tirucallol (tirucalladienol) (cf. Haines and Warren, *J.*, 1950, 1562), as well as euphorbol (euphorbadienol) (cf. Barbour, Warren, and Wood, preceding paper) contain an inert double bond situated between two methylene groups, *e.g.*, $\cdot CH_2\cdot C{:}C\cdot CH_2$. The reducible double bond in euphadienol (cf. Macdonald, Warren, and Williams, *J.*, 1949, S 155; Dupont, Dulou, and Vilkas, *Bull. Soc. chim.*, 1949, **16**, 811) and in tirucalladienol (Haines *et al.*, *loc. cit.*) exists as an *iso*but-1-enyl group, $\cdot CH{:}CMe_2$, whilst euphorbadienol contains a methylene linkage (Barbour *et al.*, *loc. cit.*).

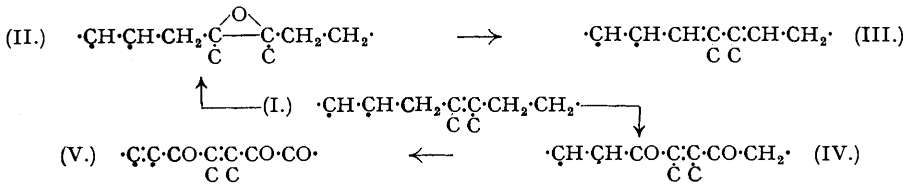
Oxidative degradation of euphadienyl and tirucalladienyl acetates (cf. Bennett, Krusi, and Warren, *J.*, 1951, 2534) with potassium permanganate and chromic acid had resulted in an attack in the neighbourhood of both double bonds. It was felt that the failure after ozonolysis to isolate in reasonable yields the C_{27} compound from euphadienyl acetate (cf. Macdonald *et al.*, *loc. cit.*) and the C_{29} ketone from euphorbadienyl acetate (cf. Barbour *et al.*, *loc. cit.*) was due in part to some oxidation at the inert double bond. A study was therefore made of the action of perbenzoic acid on these three isomeric triterpene acetates with a view to the determination of the relative reactivity of the ethylenic linkages to oxidation and the possible preparation of epoxides which could be used as starting materials for further studies.

It was found that the *iso*butenyl groups in both euphadienyl and tirucalladienyl acetates were very reactive whilst the inert ethylenic bonds in all three triterpenes were slowly attacked. In every case it was possible to isolate the corresponding epoxide, and in this series of triterpenes perbenzoic acid may be used to determine unsaturation. Euphadienyl acetate gave on all occasions a crystalline compound, $C_{32}H_{52}O_3$, m. p. 126—127°, $[\alpha]^{20}_{D}$ +32·7°, whereas Vilkas, Dupont, and Dulou (*Bull. Soc. chim.*, 1949, **16**, 831) give m. p. 126—127°, $[\alpha]_D$ +35·4°. Euphatriene, prepared by the dehydration of euphadienol (cf. Bennett and Warren, *J.*, 1950, 697), gave triepoxyeuphane. The stability of the epoxide grouping attached to the inert double bond in these three triterpene alcohols is in contrast with that found by Birchenough and McGhie (*J.*, 1949, 2038) for the epoxide of dihydrolanosteryl acetate which Ruzicka, Rey, and Muhr (*Helv. Chim. Acta*, 1944, **27**, 472) showed contained a similar inert ethylenic grouping. The stability of the epoxide grouping was revealed in another experiment. In an attempt to open the ring at the position of the original hydroxyl group, euphenone was treated with perbenzoic acid. No lactone formation could be detected and the product was epoxyeuphanone, identical with the oxidation product of epoxyeuphanol, which was obtained by the hydrolysis of, and which could be reacetylated into, its acetate.

Euphenyl, euphorbenyl, and tirucallenyl acetates gave stable isomeric epoxy-compounds, $C_{32}H_{54}O_3$, which were readily converted by concentrated sulphuric acid in acetic acid into isomeric dehydro-compounds, $C_{32}H_{52}O_2$, formulated as euphadienyl, euphorbadienyl, and tirucalladienyl acetates respectively, which were readily hydrolysed to the corresponding alcohols. These dehydro-derivatives, which were isomeric with euphyl, euphorbyl, and tirucallyl acetates respectively, showed, however, absorption in the ultra-violet indicative of a conjugated system of double bonds. Dehydroeuphenyl acetate in alcohol showed three distinct maxima, at λ 233 (log ε 4·26), 240 (log ε 4·3), and 247·5 mμ. (log ε 4·1) whilst dehydroeuphorbenyl and dehydrotirucallenyl acetates as well as the corresponding alcohols revealed pronounced maxima at the first two wave-lengths. The mode of formation of the dehydro-compounds is

* Part VII, preceding paper.

assumed to be the opening of the epoxy-group (II) to give a ditertiary glycol which then is dehydrated to give (III).



(II.) $\cdot\underset{\cdot}{C}H\cdot\underset{\cdot}{C}H\cdot CH_2\cdot\underset{\dot{C}}{C}\overset{O}{\frown}\underset{\dot{C}}{C}\cdot CH_2\cdot CH_2\cdot \longrightarrow \cdot\underset{\cdot}{C}H\cdot\underset{\cdot}{C}H\cdot CH{:}\underset{C}{C}\cdot\underset{C}{C}{:}CH\cdot CH_2\cdot$ (III.)

(I.) $\cdot\underset{\cdot}{C}H\cdot\underset{\cdot}{C}H\cdot CH_2\cdot\underset{C}{C}{:}\underset{C}{C}\cdot CH_2\cdot CH_2\cdot$

(V.) $\cdot\underset{\cdot}{C}{:}\underset{\cdot}{C}\cdot CO\cdot\underset{C}{C}{:}\underset{C}{C}\cdot CO\cdot CO\cdot \longleftarrow \cdot\underset{\cdot}{C}H\cdot\underset{\cdot}{C}H\cdot CO\cdot\underset{\dot{C}}{C}{:}\underset{\dot{C}}{C}\cdot CO\cdot CH_2\cdot$ (IV.)

The action of perbenzoic acid on dehydroeuphenyl acetate showed that only one atom of oxygen was absorbed, in which respect it resembles dihydroagnosteryl acetate (cf. Birchenough and McGhie, *loc. cit.*).

Except for the stability of the epoxides, the inert ethylenic linkage in the three triterpenes under discussion is seemingly similarly placed to that in lanosterol. Dorée, McGhie, and Kurzer (*J.*, **1949**, **560**) were able to effect further oxidation in the neighbourhood of the inert double bond by the action of selenium dioxide on dihydrodiketolanosteryl acetate. This reaction has been reinvestigated by Voser, Montavon, Gunthard, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1950, **33**, 1893) and interpreted in the light of infra-red spectra of the product. The action of selenium dioxide on both diketoeuphenyl and diketoeuphorbenyl acetates, containing the grouping (IV), has given respectively triketoeuphadienyl and triketoeuphorbadienyl acetates, containing the grouping (V), which showed strong absorption in alcohol at $\lambda_{max.}$ 285 mμ. (log ε 4·0 and 3·9 respectively). The properties of these triketones resemble those of triketolanostadienyl acetate and it seems that the carbon atoms in the neighbourhood of the inert double bond are similarly placed. This concept is also in agreement with the hypothesis previously advanced by Haines and Warren (*J.*, 1950, 1562) that the two polar groups in diketoeuphenyl acetate acted in opposite directions.

Dupont *et al.* (*loc. cit.*) drew attention to the seeming identity of bassenyl and euphenyl acetates indicated by mixed melting points. Since basseol has been cyclised by Heilbron, Moffatt, and Spring (*J.*, 1934, 1583) to β-amyrin the disposition of the carbon atoms was assumed to be similar. It is not easy, however, to see how to accommodate the grouping (I) in a structure of euphol based on the accepted formulation of β-amyrin.

EXPERIMENTAL.

Microanalyses are by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.

Formation of Epoxides.—An approximately 5% solution of perbenzoic acid in chloroform was added to the substance at 0° and the mixture set aside. Aliquot portions were withdrawn at intervals and the excess of perbenzoic acid was determined iodometrically. When the theoretical amount of oxygen had been absorbed (see Table) the chloroform solution was shaken three times with 5% sodium carbonate solution, then three times with water and dried (Na_2SO_4). Evaporation of the solvent usually gave an oil which slowly solidified. Unless otherwise stated below, not more than two crystallisations from ethanol sufficed to give the following epoxy-compounds colourless and pure.

Starting material.	Perbenzoic acid (mols.).	Temp.	Reaction time.	Oxygen uptake (mols.).	Product.
Euphadienyl acetate	1·1	0°	4 hours	1	(VIII)
Euphadienyl acetate	2·2	0	—	2	(IX)
Euphenyl acetate	1·1	20	3 days	1	(X)
Euphorbenyl acetate	1·1	0	4 ,,	1	(XI)
Tirucallenyl acetate	1·1	0	8 ,,	1	(XII)
Euphatriene	3·4	20	17 ,,	3	(XIII)
Euphenone	1·0	0	3 ,,	1	(XIV)

Epoxyeuphenyl acetate (VIII), needles, m. p. 126—127°, $[\alpha]_D^{20}$ +32·7° in chloroform (*c*, 1) (Found: C, 79·3; H, 10·9. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

Diepoxyeuphanyl acetate (IX), felted needles, m. p. 180—181°, $[\alpha]_D^{20}$ +57·7° in chloroform (*c*, 1·2) (Found: C, 76·45; H, 10·5. $C_{32}H_{52}O_4$ requires C, 76·7; H, 10·5%).

Epoxyeuphanyl acetate (X), needles, m. p. 176—177°, $[\alpha]_D^{20}$ +59°, giving no colour with tetranitro) methane (Found: C, 78·9; H, 11·3. Calc. for $C_{32}H_{54}O_3$: C, 78·9; H, 11·2%). Vilkas *et al.* (*loc. cit.*- give m. p. 178—178·5°, $[\alpha]_D$ +63°. Hydrolysis of the acetate and crystallisation of the product three times from methanol gave fine white felted needles of *epoxyeuphanol*, m. p. 140—141°, $[\alpha]_D^{20}$ +51·1° in chloroform (*c*, 1) (Found : C, 80·4; H, 11·7. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8).

Epoxyeuphorbanyl acetate (XI) was obtained after five crystallisations from ethanol as colourless plates, m. p. 195—196° (Found : C, 79·8, 79·4; H, 11·2, 10·0. $C_{32}H_{54}O_3$ requires C, 78·9; H, 11·2%). The crystals gave no colour with tetranitromethane.

Epoxytirucallanyl acetate (XII), after two crystallisations from acetone, had m. p. 161—162°, $[\alpha]_D^{20}$ +17·9° in chloroform (*c*, 1·1) (Found : C, 79·1; H, 11·1. $C_{32}H_{54}O_3$ requires C, 78·9; H, 11·2%). The crystals gave no colour with tetranitromethane.

Triepoxyeuphane (VIII), feathery needles, m. p. 161—162°, $[\alpha]_D^{20}$ +46° in chloroform (*c*, 1) (Found : C, 78·5; H, 10·6. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

Epoxyeuphanone.—(*a*) Epoxyeuphanol (2·2 g.) in benzene (65 ml.) was added to a solution of chromium trioxide (2·2 g.) in acetic acid (65 ml.) and water (30 ml.), and the whole stirred for 24 hours at room temperature. Methanol was then added, the benzene layer separated, and the aqueous layer run into water and extracted with ether. The benzene and ether solutions were washed with 3% sodium carbonate solution and water and then evaporated under reduced pressure. The product in light petroleum was chromatographed through alumina, to give epoxyeuphanone as a colourless oil (2 g.). *Epoxyeuphanone oxime* crystallised from ethanol in pearly white laminæ, m. p. 188—189°, $[\alpha]_D^{20}$ +56·4° in chloroform (*c*, 1·1) (Found : C, 79·1; H, 11·3; N, 3·2. $C_{30}H_{51}O_2N$ requires C, 78·7; H, 11·2; N, 3·1%).

(*b*) Euphenone was treated with perbenzoic acid (see table above), and the product in light petroleum was filtered through alumina. The colourless oil (XIV), which gave no colour with tetranitromethane, gave an oxime, m. p. 189—190°, undepressed when mixed with epoxyeuphanone oxime (Found : C, 80·3; H, 11·3. Calc. for $C_{30}H_{51}O_2N$: C, 78·7; H, 11·2%)

Dehydroeuphenol (*Euphadienol*).—Epoxyeuphanyl acetate (1·5 g.) in acetic acid (75 ml.) was treated with concentrated sulphuric acid (6 drops) and set aside at room temperature for 24 hours. The product was poured into water and extracted with ether. The ethereal solution, washed successively with dilute sodium carbonate solution and water, was dried (Na_2SO_4) and filtered through activated alumina (10 g.). The solid (1·4 g.) obtained by the evaporation of the ether crystallised from ethanol, to give *dehydroeuphenyl acetate*, m. p. 111—112°, $[\alpha]_D^{20}$ −9·16° in chloroform (*c*, 1), showing λ_{max} 233, 240, 247·5 mμ. (log ε 4·26, 4·3, 4·1 respectively) in alcohol (Found : C, 81·9; H, 10·95. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). The crystals were coloured reddish-brown with tetranitromethane. Hydrolysis of the acetate with alcoholic potassium hydroxide and crystallisation of the product from methanol gave *dehydroeuphenol*, m. p. 116—117°, $[\alpha]_D^{20}$ −119° in chloroform (*c*, 1), showing $\lambda_{max.}$ 232·5, 240 mμ. (log ε 4·17, 4·21 respectively) in alcohol (Found : C, 84·35; H, 11·75. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). Treatment of dehydroeuphenyl acetate with perbenzoic acid as previously described led to absorption of 1·2 mols. after 7 days at 0°, to give an oil. A solution of the oil in light petroleum was filtered through alumina and the product crystallised from aqueous acetone as fine colourless felted needles, m. p. 234—236°. This was probably epoxydehydroeuphanyl acetate. There was not sufficient for analysis.

Dehydroeuphorbenol (*Euphorbadienol*).—Epoxyeuphorbanyl acetate (400 mg.) in acetic acid (30 ml.) was treated at the b. p. with concentrated sulphuric acid (2 drops) and allowed to cool. The yellow crystalline solid (350 mg.) which separated was filtered off and dissolved in ether. The ethereal solution, washed with sodium carbonate solution, then water and dried, was percolated through activated alumina (20 g.). Ether (50 ml.) eluted a colourless solid which, crystallised six times from methanol, gave *dehydroeuphorbenyl acetate* as colourless plates (38 mg.), m. p. 144—144·5°, $[\alpha]_D^{20}$ —139° in chloroform (c, 0·8), showing light absorption at $\lambda_{max.}$ 232, 239 mμ. (log $\varepsilon_{max.}$ 4·15, 4·19 respectively) in alcohol (Found C, 81·8; H, 11·1. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). Hydrolysis with 8% alcoholic potassium hydroxide and crystallisation of the product from acetone–methanol gave *dehydroeuphorbenol* as fine needles, m. p. 104°, $[\alpha]_D^{20}$ −136° in chloroform (*c*, 0·9), showing light absorption at $\lambda_{max.}$ 232, 239 mμ. (log $\varepsilon_{max.}$ 4·02, 4·06 respectively) in alcohol (Found : C, 83·2; H, 11·7. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). Both the alcohol and the acetate gave a deep brown colour with tetranitromethane.

Dehydrotirucallenol (*Tirucalladienol*).—Epoxytirucallanyl acetate (600 mg.) was dehydrated as above and the dried yellow ethereal solution percolated through alumina (6 g.). Three crystallisations from acetone–methanol gave colourless hexagonal laminæ of *dehydrotirucallenyl acetate*, m. p. 132—133°, $[\alpha]_D^{20}$—135·5° in chloroform (*c*, 1·06) (Found : C, 82·0; H, 11·2. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). The crystals showed in alcohol absorption of light at $\lambda_{max.}$ 232·5, 237·5 mμ. (log ε 4·32, 4·31 respectively) and were coloured reddish-brown with tetranitromethane. Similar dehydration of the mother-liquor residues from the purification of epoxytirucallanyl acetate and crystallisation of the resulting product from chloroform–methanol gave flat crystals of dehydrotirucallenyl acetate, m. p. 134—134·5° (Found : C, 82·2; H, 11·1%). The acetate (90 mg.) was refluxed with 5% alcoholic potassium hydroxide (8 ml.) for 2 hours. Two crystallisations of the product from methanol gave regular plates of *dehydrotirucallenol*, m. p. 85—86°, $[\alpha]_D^{20}$ −163·6° in chloroform (*c*, 1·08) (Found : C, 83·6; H, 11·5. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). The crystals showed in alcohol absorption of light at $\lambda_{max.}$ 232·5, 240 mμ. (log $\varepsilon_{max.}$ 4·13, 41·7 respectively), and gave a reddish-brown colour with tetranitromethane.

Triketoeuphorbadienyl Acetate.—Diketoeuphorbenyl acetate (1 g., 1 mol.) in acetic acid–acetic anhydride (1 : 1; 25 ml.) was treated with selenium dioxide (1 g., 4·5 mols.) dissolved in a minimum quantity of water (*ca.* 1 ml.). After the initial ebullition the solution was refluxed for 4 hours, and the cooled solution filtered to remove selenium, poured into water and extracted with ether. The ethereal extract was washed with aqueous sodium hydroxide until no further selenium separated at the ether–water interface, then with water, and dried. The removal of the solvent under reduced pressure left an orange-yellow solid which was chomatographed on activated alumina (40 g.). Light petroleum (1500 ml.) eluted a yellow solid (350 mg.), m. p. 218°, which was crystallised four times from chloroform–methanol, to give *triketoeuphorbadienyl acetate* as light yellow plates, m. p. 228—229°, which fell to 199—200° on drying at 100° in a high vacuum (Found : C, 74·8; H, 9·1. $C_{32}H_{46}O_5$ requires C, 75·25; H, 9·1%). A further quantity of light petroleum (750 ml.) eluted only a trace of solid. Ether (200 ml.) eluted a dark yellow solid (100 mg.), m. p. 218°, which was crystallised twice from ether to give a further small quantity of impure triketoeuphorbadienyl acetate as stout orange-yellow needles, m. p. 228—229°, which fell to 197—198° on drying at 100° in a high vacuum (Found : C, 74·2; H, 10·9%). Admixture of the two different samples, m. p. 228—229°, showed a m. p. 195—205°, whilst a mixture of the two different samples, m. p. 197—198°, showed no depression.

Triketoeuphadienyl Acetate.—Diketoeuphenyl acetate (3 g.), now obtained with m. p. 110—111° (cf. Macdonald *et al.*, *loc. cit.*; Haines and Warren, *loc. cit.*), was oxidised and worked up as described above. Greater difficulty was experienced in the removal of the selenium. Filtration through alumina (60 g.) with light petroleum as solvent gave deep yellow crystals, m. p. 175—180°, which after two crystallisations from methanol gave *triketoeuphadienyl acetate* as deep yellow needles, m. p. 186°, $[\alpha]_D^{20}$ −16·4° in chloroform (*c*, 1·06) (Found, after drying at 100° and 25° respectively : C, 75·2, 75·0; H, 9·0, 9·0. $C_{32}H_{46}O_5$ requires C, 75·2; H, 9·1%). The crystals on exposure to air or heat at 100° in a high vacuum darkened, but assumed the original yellow colour on storage.

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