563. *The* Euphorbia *Resins. Part VI.* The Oxidative Degradation of the Side Chain of Euphol and Tirucallol.*

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The oxidation of euphadienyl acetate with potassium permanganate gives acetoxydiketotrisnoreuphenic acid (II), $C_{29}H_{42}O_6$, which is hydrolysed to the hydroxy-acid (III), $C_{27}H_{40}O_5$, identical with eupholic acid obtained directly by a similar oxidation by Dupont, Dulou, and Vilkas (*Bull. Soc. chim.*, 1949, **16**, 811). The two forms of the methyl ester of (III) reported by Dupont *et al.* are found to be the methyl esters of (II) and (III).

Oxidation of euphadienyl acetate with chromic acid proceeds similarly, to give (III) which is identical with the acid previously formulated by Krusi (*J.*, 1950, 2864) as $C_{25}H_{36}O_5$.

The " noreupholic acid " of Vilkas, Dupont, and Dulou (*Bull. Soc. chim.*, 1949, **16**, 813) is shown to be dehydroeupholic acid (triketotrisnoreuphenic acid), $C_{27}H_{38}O_5$.

The evidence for the existence of a hexenyl chain in euphol is accordingly not established.

Oxidation of tirucalladienyl acetate with potassium permanganate gives compounds isomeric with those obtained similarly from euphadienyl acetate.

The reducible ethylenic linkage in euphol (euphadienol), $C_{30}H_{50}O$, was shown by McDonald, Warren, and Williams (*J.*, 1949, S155) to exist as an *iso*propylidene grouping forming part of a longer chain. Krusi (*J.*, 1950, 2864) reported that the action of *N*-bromosuccinimide on euphadienyl acetate gave an "acetate mixture" containing euphatrienyl acetate in which the additional double bond was thought to be conjugated with the original *iso*propylidene group. Furthermore the oxidation of the " acetate mixture " with chromic acid was stated to yield an acetoxy-diketo-acid, isolated as its methyl ester (II′), $C_{28}H_{40}O_6$, m. p. 170—171°. This ester was hydrolysed to a hydroxy-diketo-acid (III′), $C_{25}H_{36}O_5$, m. p. 233—234°, which with diazomethane gave a methyl ester (IV′), $C_{26}H_{38}O_5$, m. p. 185—186°.

Dupont, Dulou, and Vilkas (*Bull. Soc. chim.*, 1949, **16**, 811) had previously oxidised euphadienyl acetate with potassium permanganate to eupholic acid, $C_{27}H_{40}O_5$, m. p. 231—231·5°, which with methyl sulphate gave a mixture of two forms of a methyl ester, m. p. 160·5—161° and m. p. 190—190·5°, from which methyl eupholate, $C_{28}H_{42}O_5$, m. p. 184° was isolated. The similarity in melting point of eupholic acid and Krusi's hydroxy-diketo-acid (III′), as well as of their methyl esters, seemed significant in that the French workers indicated the possibility of a C_{26}-formula, whilst Krusi's analytical figures did not exclude the formulation of his C_{25} acid as a C_{26} acid. On the other hand Vilkas, Dupont, and Dulou (*ibid.*, p. 813) reported that oxidation of euphone, as well as of eupholic acid, with chromic acid gave " noreupholic acid," $C_{26}H_{38}O_5$. Before applying similar oxidations to isomeric triterpenes from the *Euphorbia* species these degradations were re-investigated.

Oxidation of euphadienyl acetate with potassium permanganate under the conditions described by Dupont *et al.* (*loc. cit.*) gave a semi-solid acid from which a yellow acid, m. p. 230—230·5°, was obtained as reported by these workers. Recrystallisation from aqueous alcohol gave light yellow needles having the same melting point and analysing after being dried in a high vacuum, to the same formula, although the French workers reported the isolation of a colourless crystalline monohydrate, m. p. 245·5—246·5°. The oily residue from the mother-liquors was readily converted by boiling alcoholic potash into the same solid acid which was thus obtained in a larger yield. The methyl ester, prepared by the action of diazomethane, was carefully chromatographed over alumina to show the homogeneity of the compound. Our analytical figures, particularly those of the acid obtained by way of the methyl ester or after hydrolysis of the oxidation product, confirmed the C_{27} formulation of the hydroxy-acid. Thus the oxidation of euphadienyl acetate (I*b*) with potassium permanganate gives acetoxy-diketotrisnoreuphenic acid (V) which is partly hydrolysed during the process to hydroxy-diketotrisnoreuphenic (eupholic) acid (III), $C_{27}H_{40}O_5$, m. p. 231—232°, yielding a methyl ester

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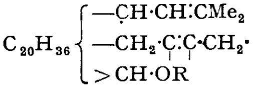
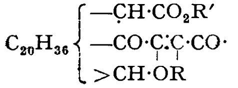
* Part V, *J.*, 1951, 2864.

(IV), $C_{28}H_{42}O_5$, m. p. 188—188·5°. The second form of the methyl ester, m. p. 160·5—161°, reported but not analysed by Dupont *et al.* (*loc. cit.*), is almost certainly the methyl ester of the unhydrolysed acetoxy-acid (V). The oxidation of euphadienyl acetate with potassium permanganate in neutral solution and esterification of the product gave the methyl ester (II), $C_{30}H_{44}O_6$, m. p. 163—164°. The ester (II) and its hydrolysis product (III), m. p. 229—231°, showed no depression of their melting points when mixed with compounds (II′) and (III′) above respectively.



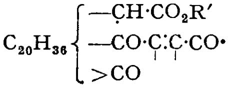
$$\mathrm{C_{20}H_{36}}\left\{\begin{array}{l}\mathrm{-\underset{|}{C}H\cdot CH{:}CMe_2}\\ \mathrm{-CH_2\cdot\underset{|}{C}{:}\underset{|}{C}\cdot CH_2\cdot}\\ \mathrm{>CH\cdot OR}\end{array}\right.$$

(I*a*; R = H.)
(I*b*; R = Ac.)



$$\mathrm{C_{20}H_{36}}\left\{\begin{array}{l}\mathrm{-\underset{|}{C}H\cdot CO_2R'}\\ \mathrm{-CO\cdot\underset{|}{C}{:}\underset{|}{C}\cdot CO\cdot}\\ \mathrm{>CH\cdot OR}\end{array}\right.$$

(II; R = Ac, R′ = Me.)
(III; R = H, R′ = H.)
(IV; R = H, R′ = Me.)
(V; R = Ac, R′ = H.)



$$\mathrm{C_{20}H_{36}}\left\{\begin{array}{l}\mathrm{-\underset{|}{C}H\cdot CO_2R'}\\ \mathrm{-CO\cdot\underset{|}{C}{:}\underset{|}{C}\cdot CO\cdot}\\ \mathrm{>CO}\end{array}\right.$$

(VI; R′ = H.)
(VII; R′ = Me.)

These experiments indicated that the acid (III′) was identical with (III) for which the C_{27} formula seems now established. The compound (III′), obtained in over 50% yield (Krusi, *loc. cit.*), was almost certainly the oxidation product of euphadienyl acetate and not of euphatrienyl acetate, which, according to the value given for the extinction coefficient, probably comprises much less than 50% of the " acetate mixture." To confirm this, euphadienyl acetate was oxidised with chromic acid under exactly the same conditions as described for the oxidation of the " acetate mixture." There resulted an acetoxy-diketo-acid, m. p. 146—147°, giving a methyl ester, m. p. 168—169°, which was hydrolysed to an acid, m. p. 230—232°. The melting point of this acetoxy-diketo-acid methyl ester and of its hydrolysis product showed no depression when these compounds were mixed with (II′) and (III′) above respectively. The low values for carbon, approximating to the C_{25} formula, cannot be accounted for by hydration as the hydrate is unstable under the conditions of drying, and they remain unexplained.

Direct oxidation of euphadienol with chromium trioxide gave an acid which was esterified to methyl triketotrisnoreuphenate (VII), $C_{28}H_{40}O_5$, m. p. 142—143°, whilst Vilkas *et al.* (*loc. cit.*) give for methyl noreupholate, m. p. 140·5—141·5°. The supposed " noreupholic acid " (see above) is really dehydroeupholic acid (VI) formed from eupholic acid (III) by oxidation of the secondary hydroxyl group.

The C_{27} formulations given above were further confirmed by the oxidation of tirucallyl (tirucalladienyl) acetate (I*b*) which Haines and Warren (*J.*, 1949, 2554; 1950, 1562) showed was isomeric with euphadienyl acetate. Oxidation with potassium permanganate and complete hydrolysis of the product gave hydroxydiketotrisnortirucallenic acid (III), $C_{27}H_{40}O_5$, m. p. 211—212°, yielding a methyl ester (IV), $C_{28}H_{42}O_5$, m. p. 183—184°. The extinction curves of these oxidation products show a maximum similar to that found for the corresponding compounds from euphol, and the chromophoric group is certainly $\cdot\mathrm{CO\cdot\underset{|}{C}{:}\underset{|}{C}\cdot CO}\cdot$. The above tirucallenic acid (III) and its methyl ester (IV) showed pronounced depression of their melting points when they were mixed with the isomeric eupholic acid (III) and methyl eupholate (IV) respectively.

Vilkas *et al.* (*loc. cit.*) and Krusi (*loc. cit.*) had deduced by different reasoning that the side chain of euphol contained the grouping $\mathrm{-CH_2\cdot CH_2\cdot CH{:}CMe_2}$. The experimental evidence, however, as now represented only permits the conclusion that a five-carbon chain is present as in (I). The ease of hydrolysis of methyl eupholate (IV) as well as of methyl dehydroeupholate (VII) (cf. Vilkas *et al.*, *loc. cit.*) necessitates that the carboxyl group is not tertiary. The parallel experiments with tirucalladienol (I*a*) establish the existence of a similar side chain.

EXPERIMENTAL.

Microanalyses are by Weiler and Strauss, Oxford. All m. p.s are uncorrected. Light absorptions were determined in alcohol.

Oxidation of Euphadienyl Acetate with Alkaline Potassium Permanganate.—Euphadienyl acetate (10 g.) was added to a solution of potassium permanganate (20 g.) in acetone (2 l.), and the whole stirred for 24 hours. The excess of permanganate was destroyed with sulphur dioxide, the solution filtered, and the manganese mud extracted (Soxhlet) with methanol. The combined methanol and acetone solutions were evaporated under reduced pressure, the residue was poured into water, and the solution, acidified with hydrochloric acid, was extracted with ether. The ethereal extract was shaken with sodium carbonate solution, and the acid precipitated from the carbonate extract with hydrochloric acid and re-extracted with ether. This ethereal extract gave a yellow-orange oil (6 g.) which, lixiviated with ether, left a solid which crystallised from ethanol in yellow rhombohedra, m. p. 230—230·5°

(Found : C, 73·4; H, 9·1%; equiv., 431·3, 441·6). The m. p. of this acid was not depressed when it was mixed with the hydroxy-diketo-acid obtained by the oxidation of euphadienyl acetate with chromic acid (see below). Crystallisation from aqueous ethanol (1 : 1) gave the acid as light yellow needles, m. p. 231—232° (Found : C, 73·4; H, 9·1%). The combined oily and solid crude acid product was hydrolysed with 5% alcoholic potassium hydroxide and then all the acid was obtained as a solid which, crystallised from ethanol, gave hydroxydiketotrisnoreuphenic (eupholic) acid as rhombohedra, m. p. 231—232°, showing $\lambda_{max.}$ 272·5 mμ. (log ϵ 3·93) (Found : C, 72·85; H, 8·85%; equiv., 454, 455. Calc. for $C_{27}H_{40}O_5$: C, 72·9; H, 9·1%; equiv., 444·6). The crude hydrolysed acid oxidation product was treated with diazomethane in ether, and the resulting neutral ester (4 g.) in light petroleum–benzene (5 : 1) was chromatographed through alumina (100 g.; activity I—II), and the column developed with light petroleum–benzene (1 : 1). No apparent separation occurred and the solid product, crystallised three times from methanol, gave methyl hydroxydiketotrisnoreuphenate (eupholate) as fine greenish-yellow needles, m. p. 186°, $[\alpha]_D^{20}$ +18·7° in chloroform (c = 1), showing $\lambda_{max.}$ 272·5 mμ. (log ϵ 3·95) (Found : C, 72·8, 73·05; H, 9·0, 8·9. Calc. for $C_{28}H_{42}O_5$: C, 73·3; H, 9·2%). The methyl ester sublimed at 170° in a high vacuum, giving stout yellow needles, m. p. 188—188·5° (Found : C, 73·2; H, 9·4%). Hydrolysis of the methyl ester with 10% alcoholic potassium hydroxide and two crystallisations of the product from absolute ethanol gave the acid as light greenish-yellow rhombohedra, m. p. 230—231° (Found : C, 72·7, 73·1; H, 9·1, 9·2%; equiv., 439, 442).

Oxidation of Tirucalladienyl Acetate with Potassium Permanganate.—Tirucalladienyl acetate (3 g.) was oxidised with potassium permanganate (6 g.) in acetone (900 ml.) as above, and the acid product hydrolysed by boiling alcoholic potassium hydroxide. The hydroxy-acid was isolated as a yellow solid which was difficult to crystallise and was esterified with diazomethane. An ethereal solution of the product was shaken with sodium carbonate solution to remove unesterified acid, and the solvent removed. The crystalline solid, dissolved in light petroleum–benzene (2 : 1), was filtered through alumina (20 g.; activity I—II). Two crystallisations from methanol gave *methyl hydroxydiketotrisnortirucallenate*, m. p. 183—184°, showing $\lambda_{max.}$ 272·5 mμ. (log ϵ 3·95) (Found : C, 73·1, 73·2; H, 8·9, 9·1. $C_{28}H_{42}O_5$ requires C, 73·3; H, 9·2%). Hydrolysis of the methyl ester with alcoholic potassium hydroxide and crystallisation of the product from methanol gave the *acid* as light greenish-yellow needles, m. p. 211—212°, $\lambda_{max.}$ 272·5 mμ. (log ϵ 3·94) (Found : C, 72·9, 72·9; H, 9·05, 8·9; equiv., 445, 435. $C_{27}H_{40}O_5$ requires C, 72·9; H, 9·1%; equiv., 444·6). The acid left unesterified in the formation of the methyl ester crystallised from aqueous ethanol in matted yellow needles, m. p. 190—198°, and from methanol in yellow needles, m. p. 212—213°, showing $\lambda_{max.}$ 272·5 mμ. (log ϵ 3·94) (Found : C, 72·6, 72·7; H, 9·0, 9·0%; equiv., 441, 445).

Oxidation of Euphadienyl Acetate with Potassium Permanganate in Neutral Solution.—Euphadienyl acetate (2·1 g.) in acetone (200 ml.) was stirred with aluminium sulphate (3 g.) whilst potassium permanganate (4·2 g.) in acetone (100 ml.) was added at room temperature, and the mixture was then refluxed for 4 hours. The excess of permanganate was destroyed with formaldehyde, and the acid product, isolated as described above, was treated with diazomethane. The neutral ester was chromatographed over alumina and crystallised from methanol, to give a methyl acetoxy-diketo-ester, m. p. 163—164° after sintering at 160°, undepressed on being mixed with the compound, m. p. 168—169° (see below) from the chromic acid oxidation (Found : C, 71·7; H, 8·5. Calc. for $C_{30}H_{44}O_6$: C, 71·9; H, 8·9. Calc. for $C_{29}H_{42}O_6$: C, 71·6; H, 8·7%). Hydrolysis with alcoholic potassium hydroxide and crystallisation of the product from acetone–water gave the hydroxy-diketo-acid, m. p. 229—231° after sintering at 225°, which showed no depression when the compound was mixed with the hydroxy-diketo-acid (see below) obtained from the oxidation of euphadienyl acetate with chromic acid.

Oxidation of Euphadienyl Acetate with Chromium Trioxide.—Euphadienyl acetate was oxidised and the product worked up as described previously for the " acetate mixture " by Krusi (*loc. cit.*). The potassium hydrogen carbonate extract gave an acid which, crystallised from acetone–water, yielded an *acetoxy-diketo-acid*, m. p. 146—147°, which was dried at 100° in a high vacuum for analysis (Found : C, 69·8; H, 8·9. $C_{29}H_{42}O_6$ requires C, 71·6; H, 8·7. $C_{27}H_{38}O_6$ requires C, 70·7; H, 8·35%). This acid gave the methyl acetoxy-diketo-ester, m. p. 168—169°, and the hydroxy-diketo-acid, m. p. 230—232° (Found, after drying at 100° in a high vacuum : C, 72·2; H, 8·95. Calc. for $C_{27}H_{40}O_5$: C, 72·9; H, 9·1. Calc. for $C_{25}H_{36}O_5$: C, 72·15; H, 8·7%). This methyl ester and its hydrolysis product showed no depression of their melting points when mixed with compounds (II′) and III′) from the " acetate mixture " respectively.

Oxidation of Euphol with Chromium Trioxide.—Euphol (1·3 g.) was treated with chromic acid and the product worked up as above. The methyl ester in light petroleum–benzene (10 : 1; 50 ml.) was filtered through alumina (12 g.), and the column developed wlth the same mixture (5 : 1; 70 ml.). The product was crystallised from methanol, to give *methyl triketotrisnoreuphenate*, m. p. 142—143°, sintering at 138°, which was sublimed at 140° in a high vacuum for analysis (Found : C, 73·6; H, 8·8. $C_{28}H_{40}O_5$ requires C, 73·6; H, 8·8%).

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