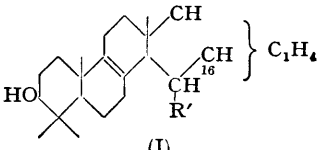
120. *The Chemistry of the Triterpenes. Part XVII.* Some Aspects of the Chemistry of Tetracyclic Triterpenes.*

By M. C. Dawson, T. G. Halsall, and R. E. H. Swayne.

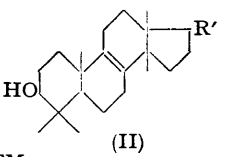
The action of chloroformic hydrogen chloride on euphenyl and euphadienyl acetates is described and the chemistry of the resulting isomerisation products is discussed.

The tetracyclic triterpenes are classified into two groups on the basis of both rotation and ultra-violet absorption data.

To determine whether the effect of chloroformic hydrogen chloride on butyrospermyl acetate (Dawson, Halsall, Jones, and Robins, preceding paper) and lanosteryl acetate (Dorée and Petrow, *J.*, 1936, 1562) was of a general nature, its action on euphyl (euphadienyl) acetate has been investigated. A chlorine-containing product was obtained which on dehydrochlorination gave *iso*euphadienyl acetate. The infra-red spectrum [band at 886 cm.$^{-1}$ (ms)] showed that a vinylidene group was present and this was confirmed by ozonolysis. Hydrogenation gave *iso*euphenyl acetate, identical with that obtained by Vilkas, Dupont, and Dulou (*Bull. Soc. chim.*, 1949, 813) by the action of hydrochloric acid in acetic acid on dihydroeuphyl acetate (euphenyl acetate). Hydrolysis of *iso*euphenyl acetate in the cold gave *iso*euphenol, isolated as a crystalline solid. Oxidation gave *iso*euphenone, characterised as its oxime. *iso*Euphenyl acetate was also obtained by the

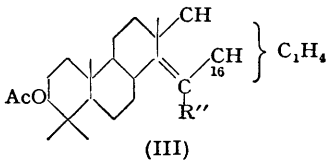


(I)



(II)

R′ = ·CHMe·[CH$_2$]$_2$·CH:CMe$_2$



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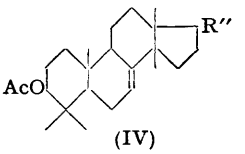

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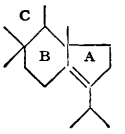


(V)

R″ = ·CHMe·[CH$_2$]$_3$·CHMe$_2$

action of chloroformic hydrogen chloride on dihydroeuphyl acetate. Hence the behaviour of euphyl acetate is similar to that of butyrospermyl and lanosteryl acetates, *i.e.*, isomerisation of the less reactive double bond, and addition of hydrogen chloride to the *iso*propylidene group. Further, as proved in the case of butyrospermol and suspected for lanosterol, dehydrochlorination yields an *iso*propenyl, rather than an *iso*propylidene group.

Since the above work was carried out, Christen, Dunnenberger, Roth, Heusser, and Jeger (*Helv. Chim. Acta*, 1952, **35**, 1756) have proposed structure (I) for euphol in which the double bond is situated in a somewhat different environment from that in lanosterol (II) (Curtis, Fridricksons, and Mathieson, *Nature*, 1952, **170**, 1321; Barnes, Barton, Cole, Fawcett, and Thomas, *Chem. and Ind.*, 1952, 426), and (III) for *iso*euphenyl acetate. The work of Vilkas (*Bull. Soc. chim.*, 1950, 582) on *iso*euphenyl acetate indicated that its double bond was differently situated from that in *iso*lanostenyl acetate (IV) (Barton, Fawcett, and Thomas, *J.*, 1951, 3147; Cavalla, McGhie, and Pradhan, *J.*, 1951, 3142); and this has been confirmed by an examination of the low wave-length ultra-violet absorption of *iso*euphenyl acetate (Table 1) (cf. Bladon, Henbest, and Wood, *J.*, 1952, 2737; Halsall, *Chem. and Ind.*, 1951, 867). Whilst the intensity values for dihydro*iso*butyrospermol and its acetate are a little lower than those of dihydrobutyrospermol and its acetate (preceding

* Part XVI, preceding paper.

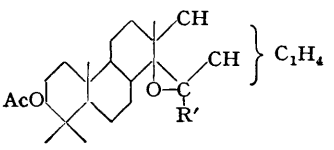
paper), those for *iso*euphenyl acetate are considerably higher than the corresponding values for euphenyl acetate. They definitely indicate that the double bond in *iso*euphenyl acetate is tetrasubstituted and, further, they strongly suggest that it is exocyclic to one ring, but not to two as with the double bond of δ-amyrenyl acetate. The correlation with the intensity values for the isomer (partial formula V) obtained from γ-lupene by Nowak, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1949, **32**, 323) is very striking. This isomer is an exact model for comparison purposes, the double bond being in a position corresponding

TABLE 1.

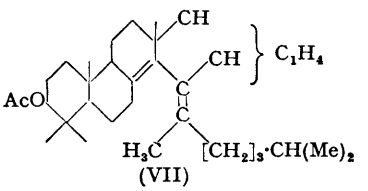
$\varepsilon_{obs.}$ in alcohol at :	2100 Å	2150 Å	2200 Å	2230 Å
Euphenyl acetate	5000	2700	1000	400
*iso*Euphenyl acetate	7200	4400	2000	900
Isomer from γ-lupene	6600	4500	2500	1300
δ-Amyrenyl acetate	7700	5300	4200	—

to that in structure (III) for *iso*euphenyl acetate. An interesting comparison may be drawn between the acidic isomerisation of euphenyl acetate and that of $\Delta^{8(9)}$-cholestenol to $\Delta^{14(15)}$-cholestenol (Wieland and Görnhardt, *Annalen*, 1947, **557**, 248).

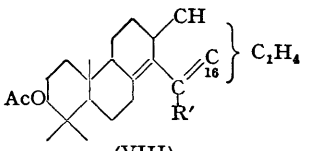
Oxidation of *iso*euphenyl acetate with chromic acid under mild conditions gave a compound, $C_{32}H_{54}O_3$, which showed no light absorption of appreciable intensity above 2100 Å, and is identical with the epoxide (VI) described by Vilkas and the Swiss workers. Treatment with ethanolic hydrogen chloride yielded the diene previously obtained from *iso*euphenyl acetate oxide by Christen *et al.* (*loc. cit.*), with maximal absorption at 2470, 2555, and 2650 Å (ε = 18,200, 21,400, and 13,200, respectively). The Swiss workers put forward two structures (VII) and (VIII) for their diene. The chromophores present in



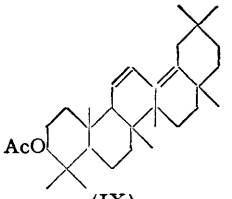
(VI)



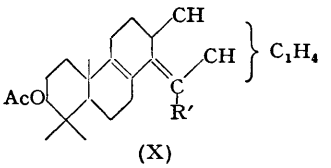
(VII)



(VIII)



(IX)



(X)

R′ = ·CH(Me)·[CH₂]₃·CH(Me)₂

these two formulations would be expected to have different, but characteristic ultra-violet absorption properties. The *cisoid* chromophore of (VII) should give rise to a relatively low maximum intensity of absorption corresponding to ε = *ca.* 10,000 at 2600—2650 Å, whilst for (VIII) with a *transoid* chromophore the corresponding value of ε would be *ca.* 25,000 at 2500—2550 Å (cf. the discussion of the absorption spectra of dehydro- and *iso*dehydro-oleanolic acids by Barton and Brooks, *J.*, 1951, 261). Inspection of the spectrum of the diene from *iso*euphenyl acetate epoxide, with its high ε of 22,000, shows that (VII) may be discounted. The chromophore of (VIII) is very similar to that of β-amyradienyl-II acetate (olea-11 : 13-dien-2″β″-yl acetate) (IX) [$\lambda_{max.}$ 2430, 2510 (ε = 31,000), 2600 Å; Green, Mower, Picard, and Spring, *J.*, 1944, 527], the only difference being the further substitution of the diene system of (VIII) by at least one more carbon substituent. The positions of the maxima in the spectrum of (VIII), assuming only one further substituent on the diene system than in (IX) and hence that a hydrogen atom is attached to $C_{(16)}$, should be 40—50 Å nearer to the visible than those of (IX). The spectrum of the diene from *iso*euphenyl acetate oxide does in fact show this shift. This confirms that (VIII) rather than (VII) is the probable structure of the diene, and indicates that one

hydrogen atom is attached to $C_{(16)}$ of the diene and that two are attached to $C_{(16)}$ of euphol. The ultra-violet data would be equally consistent with (X), but this structure provides a far less satisfactory basis for explaining the course of the hydrogenation of the diene (cf. Christen *et al.*, *loc. cit.*).

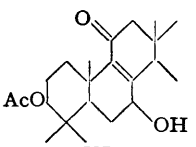
TABLE 2. *Tetracyclic triterpenes.*

	A	B	C	D Main max., Å		
Euphenol	+116° [1]	−479° [2]	−595°	2325	2400	— [2]
Euphenyl acetate	+165 [1]	−429 [2] *	−594	2330	2400	2475 [2]
Euphorbenol	− 9 [3]	−579 [2]	−570	2320	2390	— [2]
Euphorbenyl acetate	± 0 [3]	−650 [2]	−650	2320	2390	— [2]
Tirucallenol	+ 13 [4]	−697 [2]	−710	2325	2400	— [2]
Tirucallenyl acetate	− 54 [4]	−634 [2]	−580	2325	2375	— [2]
Methyl acetyldihydro-α-elemolate	−169 [5]	−590 [6]	−421	2320	2390	2470 [6]
Lanosterol	+258 [9]	+326 [7]	+ 68	—	—	—
Lanosteryl acetate	+306 [9]	+410 [7]	+104	—	—	—
Dihydrolanosterol	+260 [9]	+286 [10]	+ 26	—	—	—
Dihydrolanosteryl acetate	+275 [9]	+411 [10]	+136	2360 2380	2430 2450	2510 2500 } [8]
Methyl acetyldihydroburicoate	+288 [11]	+302 [11]	+ 14	—	2430	2510 [11]

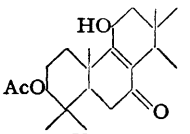
Column headings: A, $[M]_D$ of the triterpene; B, $[M]_D$ of the corresponding dehydro-derivative; C, $\Delta[M]_D$ for the conversion of the triterpene into its dehydro-derivative; D, $\lambda_{max.}$ of the corresponding dehydro-derivative. [1] Jeger and Krüsi, *Helv. Chim. Acta*, 1947, **30**, 2047. [2] Barbour, Bennett, and Warren, *J.*, 1951, 2540. [3] Vogel, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 510. [4] Haines and Warren, *J.*, 1949, 2554. [5] Ruzicka, Rey, and Spillman, *Helv. Chim. Acta*, 1942, 1375. [6] Halsall, Jones, and Swayne (unpublished results). [7] Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472. [8] Dorée, McGhie, and Kurzer, *J.*, 1949, 570. [9] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1945, **28**, 759. [10] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 204. [11] Lahey and Strasser, *J.*, 1951, 873.

* Barbour, Bennett, and Warren (*loc. cit.*) quote a rotation $[\alpha]_D$ −9·16°. This is almost certainly a misprint for −91·6°; our calculations are based on this latter figure.

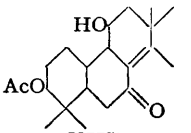
For some time evidence has been accumulating which permits a classification of the tetracyclic triterpenes into two groups, one typified by lanosterol and the other by euphol. With the first, dehydrogenation at two of the carbon atoms at positions α to the unreactive double bond and the formation of a diene results in a positive change of rotation, whilst the main absorption maximum of the diene is at 2430—2450 Å, with subsidiary maxima at 2380 and 2510 Å. With the second group a very large negative change of rotation occurs whilst the main maximum is found at *ca.* 2390 and the subsidiary maxima at 2320 and *ca.* 2470 Å (Table 2). Into the first group fall lanosterol, eburicoic acid, and (from data which



(XI)



(XII)



(XIII)

are not yet complete) possibly polyporenic acids A and C. Into the second fall euphol, euphorbol, tirucallol, and α-elemolic acid.

In connection with this classification it is of interest that the catalytic reduction of diketoeuphenyl acetate, diketoeuphorbenyl acetate (Barbour and Warren, *Chem. and Ind.*, 1952, 295), and methyl acetyl*iso*elemenadionolate (Ruzicka, Rey, Spillman, and Baumgartner, *Helv. Chim. Acta*, 1943, **26**, 1659) leads in each case to the formation of an αβ-unsaturated ketone with maximal absorption of only moderate intensity (ε <10,000) at about 2580—2600 Å. The chromophoric systems are probably identical in each case, but the structures of these unsaturated ketones are not clear. In the case of euphol the two partial structures (XI) and (XII) are the most obvious, but these should give rise to a maximum at about 2500 Å (*cf.* 7-ketoergost-8-en-3-yl acetate with $\lambda_{max.}$ 2520 Å, ε 10,000). A more likely alternative structure is (XIII) for which the calculated maximum would be 2590 Å [*cf.* also 3 : 7-diketoergost-8(14)-en-5-ol, $\lambda_{max.}$ 2540 Å (in ether) corresponding to

$\lambda_{max.}$ 2610 Å (in alcohol), log ε 4·0, and 15-ketoergost-8(14)-en-3-yl acetate, $\lambda_{max.}$ 2590 Å, log ε 4·1] which agrees much better with the observed value of 2580—2600 Å. Further the low intensity values would be compatible with the *cisoid* chromophore of (XIII). Its formation during the hydrogenation process would involve a migration of the double bond, but this is analogous to the behaviour of the 8 : 9-double bond in zymosterol on hydrogenation with platinum–acetic acid, resulting in the formation of $\Delta^{8(14)}$-cholestenol (cf. Fieser and Fieser, " Natural Products Related to Phenanthrene," 3rd Edn., Reinhold Publ. Corp., pp. 289, 290). If (XIII) is the correct structure for these hydroxy-ketones then a reversed double bond shift occurs on chromic oxidation in the euphol series, for diketoeuphenyl acetate is produced.

Experimental

M.p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform. The alumina used for chromatography had an activity of I—II.

iso*Euphadienyl Acetate*.—Euphadienyl acetate (400 mg.) was dissolved in chloroform (40 c.c.), and a slow stream of dry hydrogen chloride was passed through for 5 days at 20°, the reaction being followed by measurement of the optical activity of the solution. Evaporation under reduced pressure then yielded a viscous oil which gave a positive test for halogen. Diethylaniline (6 c.c.) was added and the mixture heated under reflux for 1½ hours. The product was isolated with light petroleum (b. p. 60—80°) and the solution, after it had been washed and dried, was adsorbed on a column of alumina (35 g.). Elution with benzene–light petroleum (b. p. 60—80°) (1 : 9) gave a fraction which yielded iso*euphadienyl acetate* as platelets (from methanol) (275 mg.), m. p. 96—98°, $[\alpha]_D^{20}$ −10° (*c*, 1·3) (Found: C, 81·75; H, 11·3. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%).

iso*Euphenyl Acetate*.—(*a*) Euphenyl acetate (310 mg.) was dissolved in chloroform (35 c.c.) and a slow stream of dry hydrogen chloride was passed through for 4 days, the reaction being followed by the change in the optical activity of the solution. The chloroform was then evaporated under reduced pressure and the residue was crystallised from methanol–ethyl acetate to give *iso*euphenyl acetate, m. p. 112—113°, $[\alpha]_D^{20}$ −9° (*c*, 1·4). Christen *et al.* (*loc. cit.*) give m. p. 113°, $[\alpha]_D$ −10°.

(*b*) *iso*Euphadienyl acetate (380 mg.) in acetic acid (60 c.c.) was shaken with hydrogen at 20° in the presence of Adams's catalyst (30 mg.) until absorption was complete. After filtration and evaporation of the filtrate under reduced pressure, the residue was crystallised from methanol to give *iso*euphenyl acetate, m. p. 113—114°, $[\alpha]_D^{20}$ −7° (*c*, 1·0), identical with that prepared by method (*a*). Hydrolysis of the acetate (260 mg.) with methanolic potassium hydroxide (1%; 50 c.c.) at 20° for 100 hours gave *iso*euphenol which crystallised with difficulty from nitromethane; it had m. p. 98—101°, $[\alpha]_D^{20}$ −20° (*c*, 1·15) (Found: C, 83·5; H, 12·05. Calc. for $C_{30}H_{52}O$: C, 84·05; H, 12·2%. Chromic acid in acetone (8N) was added to *iso*euphenol (≡ 380 mg. of *iso*euphenyl acetate) until a faint brown colour remained. The product, isolated with ether, was a gum, $[\alpha]_D^{20}$ +24° (*c*, 1·5). Oximation of the gum gave iso*euphenone oxime* as needles (ethanol–water), m. p. 142—143° (Found: N, 3·0, 3·3. $C_{30}H_{51}ON$ requires N, 3·15%).

Ozonolysis of iso*Euphadienyl Acetate*.—A solution of *iso*euphadienyl acetate (650 mg.) in ethyl acetate (20 c.c.) was cooled to −78° and to it was added a saturated solution of ozone in ethyl acetate at −78° until a faint blue coloration remained. The mixture was allowed to warm to 20° and was then refluxed for 2 hours with Raney nickel, nitrogen being passed through the solution. The issuing gases were passed through an aqueous solution of dimedone which was kept for 16 hours at 0°. The dimedone derivative was collected, dried (75 mg.), and crystallised from aqueous ethanol. The m. p., 188°, was undepressed on admixture of the sample with an authentic specimen of formaldehyde dimedone.

Oxidation of Hydroxyketoeuphenyl Acetate.—To a solution of hydroxyketoeuphenyl acetate (140 mg.) (m. p. 184—189°) in acetone (12 c.c.) a solution of chromic acid in acetone (0·8N) was added dropwise until a faint brown coloration remained. After 2 minutes, dilution with water and extraction with ether yielded a product (130 mg.), crystallisation of which from methanol gave diketoeuphenyl acetate as needles, m. p. 109—113° undepressed on admixture with an authentic specimen of m. p. 111—114°. $\lambda_{max.}$ 2735 Å; ε = 8,500.

iso*Euphenyl Acetate Epoxide*.—To a solution of *iso*euphenyl acetate (1·5 g.) in acetic acid (90 c.c.) at 20°, a solution of chromic acid (2·7 g.) in acetic acid (90%; 30 c.c.) was added. After 10 minutes, dilution with water and extraction with ether yielded a product (1·5 g.)

which was adsorbed from light petroleum (b. p. 60—80°)–benzene (1 : 1) on alumina (150 g.). Elution with benzene gave *iso*euphenyl acetate epoxide (740 mg.) which crystallised from methanol as plates, m. p. 119·5—121°, $[\alpha]_D^{21}$ +7° (*c*, 1·2) (Found: C, 78·75; H, 11·5. Calc. for $C_{32}H_{54}O_3$: C, 79·0; H, 11·2%). A further preparation gave *iso*euphenyl acetate epoxide as plates, which melted at 109—111°, followed by crystallisation of the melt and remelting at 137—139°. The melting point (138—140°) of an authentic specimen of *iso*euphenyl acetate epoxide prepared by the action of perbenzoic acid on *iso*euphenyl acetate was not depressed on admixture of the authentic specimen with either of the samples prepared by chromic acid oxidation. Christen *et al.* (*loc. cit.*) give m. p. 134°, $[\alpha]_D$ +6°.

Action of Ethanolic Hydrogen Chloride on iso*Euphenyl Acetate Epoxide.*—A solution of the epoxide (145 mg.) in ethanol (12 c.c.) and concentrated hydrochloric acid (1 c.c.) was heated under reflux for 2 hours. Dilution with water and extraction with ether yielded a gummy residue which was acetylated at 20° for 16 hours with pyridine (2 c.c.) and acetic anhydride (2 c.c.). The acetylated product was dissolved in benzene and adsorbed on alumina (20 g.). Elution with benzene gave the diene (110 mg.), plates (from methanol), m. p. 91—93°, $[\alpha]_D^{19}$ +18° (*c*, 0·25), $\lambda_{max.}$ 2470, 2555, and 2650 Å; ε 18,300, 21,500, and 13,000, respectively. Christen *et al.* (*loc. cit.*) give m. p. 91—92°, $[\alpha]_D$ +17°.

The authors thank Professor E. R. H. Jones, F.R.S., for his interest and advice. One of them (M. C. D.) is indebted to the Department of Scientific and Industrial Research for a maintenance grant and another (R. E. H. S.) to the Ministry of Education for a F.E.T.S. grant. Thanks are also due to Mr. E. S. Morton and Mr. H. Swift for the microanalyses, and to Dr. G. D. Meakins for advice on the interpretation of the infra-red spectra.

THE UNIVERSITY, MANCHESTER, 13. [*Received, October 13th,* 1952.]