9. *Triterpene Resinols and Related Acids. Part XII. The Oxidation of β-Amyradienyl-I Acetate with Selenium Dioxide, a New Route to Jacobs' Keto-diol,* $C_{30}H_{44-46}O_3$.

By C. W. Picard and F. S. Spring.

The preparation of β-amyradienol-I (III, R = H) from β-amyrenonol (II) is accompanied by the formation of β-amyradienol-II (IV). Oxidation of β-amyradienyl-I acetate (III, R = COMe) with selenium dioxide gives the keto-acetate $C_{32}H_{48(46)}O_4$ previously described by Jacobs and Fleck and by Simpson. With a view to determining the structure of the last-mentioned compound, β-amyrenonyl esters have been oxidised by bromine to the corresponding esters of *β-amyradienonol*, to which is ascribed the provisional structure (V). Oxidation of *β-amyradienonyl acetate* with potassium permanganate yields an *acetate*, $C_{32}H_{48}O_4$, which differs from Jacobs' keto-acetate.

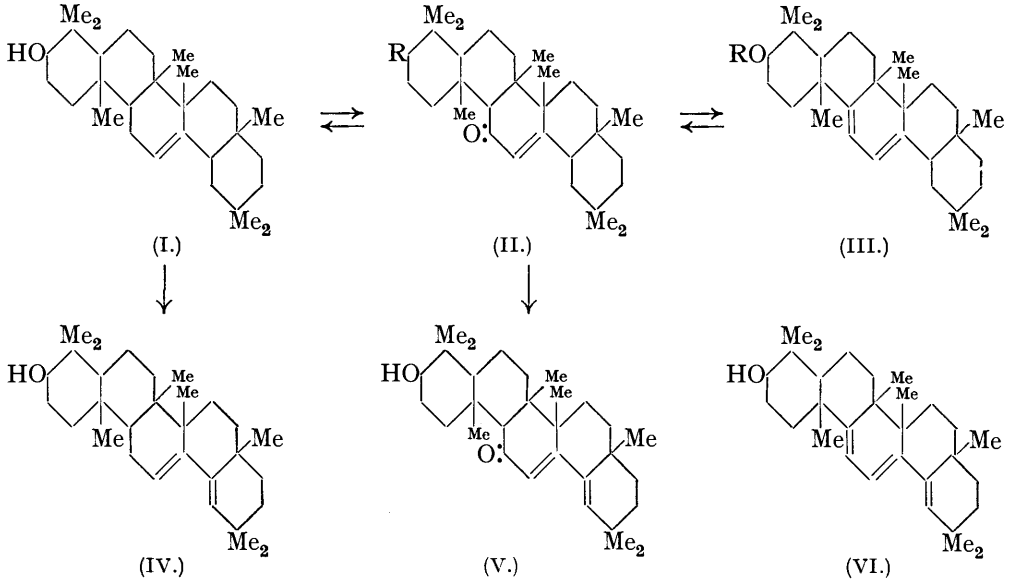
Reduction of β-amyrenonol with sodium and amyl or ethyl alcohol, followed by treatment of the intermediate addition-reduction compound with acetic anhydride, gives β-amyradienyl acetate, m. p. 216—217° (Picard and Spring, J., 1940, 1198). This compound and its derivatives are characterised by an absorption maximum at 2820 A., $\varepsilon_{max.} \simeq 10{,}000$, and by an extremely strong dextrorotation ($[\alpha]_D > 300°$). The parent alcohol we now designate β-amyradienol-I. From the mother-liquors of the product obtained by reduction of β-amyrenonol with sodium and amyl alcohol, we have now obtained an isomeric β-amyradienol, m. p. 227—228° (acetate, m. p. 226—227°), the absorption spectrum of which exhibits a major maximum at 2510 A. This compound is identical with the β-amyradienol obtained by oxidation of β-amyrenyl esters with selenium dioxide (Ruzicka, Müller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 767), which we now term β-amyradienol-II. β-Amyradienol-I contains its two ethylenic linkages as a conjugated system located in a single ring; the location of the absorption maximum of β-amyradienol-II indicates that the conjugated system is not contained in a single ring (cf. Ruzicka, Müller, and Schellenberg, *loc. cit.*).

An unsuccessful attempt was made to isomerise β-amyradienyl-I acetate to the isomeric dienyl-II acetate by treatment with mineral acids; the stability of the dienyl-I acetate was further demonstrated by its failure to react with bromine under a variety of experimental conditions. A satisfactory structural formulation of the two dienols is obtained in terms of the variant of the hydropicene triterpene formula suggested by Haworth (*Ann. Reports*, 1937, 338) [β-amyrenol = (I)] according to which β-amyrenonol will be (II, R = OH), the dienol-I (III, R = H), and the dienol-II (IV). Although these hypothetical formulæ represent the production of β-amyradienol-II (IV) from β-amyrenol (I) (by selenium dioxide oxidation) as the simple introduction of a conjugated ethylenic linkage, the formation of this dienol as a minor product of the reduction of β-amyrenonol (II, R = OH) requires a migration of ethylenic linkages.

In order to test these formulæ and at the same time accumulate further information about the immediate environment of the unsaturated centre in β-amyrenol, the oxidation of β-amyradienyl-I acetate (III, R = COMe) with selenium dioxide was examined; this reaction might be expected to yield a trienol (VI). The more soluble product of the oxidation is an acetate, $C_{32}H_{48}O_4$ (or $C_{32}H_{46}O_4$), m. p. 233—235°, hydrolysis of which gives the corresponding alcohol $C_{30}H_{46}O_3$ (or $C_{30}H_{44}O_3$), m. p. 286—287°. By direct comparison we find that this alcohol is identical with the keto-diol obtained by Jacobs and Fleck (*J. Biol. Chem.*, 1930, **88**, 137) by the oxidation of the thio-derivative of β-amyrenol, $C_{30}H_{44}OS$ (as benzoate) with potassium permanganate. The method of preparation of the keto-diol has been improved by Simpson (J., 1938, 1313; 1939, 755) and an examination of its reactions led this author to the view that it contains an isolated benzenoid ring; Ruzicka, Müller, and Schellenberg (*loc. cit.*) have shown this view to be untenable.

The less soluble product of the oxidation of the dienyl-I acetate is β-amyrenonyl acetate, m. p. 262—264° (II, R = O·COMe). We have previously shown that oxidation

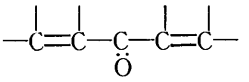
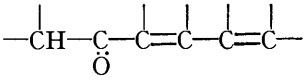
of β-amyradienol-I with chromic anhydride gives β-amyrenedione (Picard and Spring, *loc. cit.*), the conjugated system suffering 1 : 2-oxidation with formation of an αβ-un-

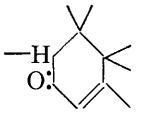


saturated ketonic system. This observation, together with the simultaneous formation of β-amyrenonyl acetate during the conversion of the dienyl-I acetate into Jacobs' ketodiol monoacetate, strongly suggested that the ketone group in the latter may originate in one of the ethylenic linkages of β-amyradienol-I. With this in mind, attempts have been made to introduce a second ethylenic linkage into β-amyrenonol and into *iso*-β-amyrenonol (Picard, Sharples, and Spring, J., 1939, 1045). In the first place it was observed that β-amyrenonyl and *iso*-β-amyrenonyl esters are not oxidised by selenium dioxide under conditions more drastic than those employed in the preparation of β-amyradienol-II. The desired oxidation, however, was readily effected when β-amyrenonyl benzoate was treated with bromine, reaction proceeding smoothly and giving *β-amyradienonyl benzoate*, m. p. 251—252°, in good yield. Hydrolysis of this ester gave *β-amyradienonol*, m. p. 239—240°, acetylation of which yielded *β-amyradienonyl acetate*, m. p. 255°. The latter ester is also obtained directly from β-amyrenonyl acetate by treatment with bromine.

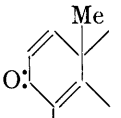
The αβ-unsaturated ketone β-amyrenonyl acetate (II, R = O·COMe) exhibits an intense absorption maximum at 2450 A. β-Amyradienonyl acetate, on the other hand, exhibits an equally intense absorption maximum at 2815 A. The introduction of a second ethylenic linkage into β-amyrenonol by means of bromine could give rise to two different types of chromophoric group represented by (VII) and (VIII). The presence of the chromophore of type (VII) in a single six-membered ring produces an absorption maximum in the region 2300—2500 A.; thus 3-keto-$\Delta^{1:4}$-cholestadiene (Inhoffen and Huang-Minlon, *Ber.*, 1938, **71**, 1721) and santonin (Ruzicka, Cohen, Furter, and Sluys-Veer, *Helv. Chim. Acta*, 1938, **21**, 1735), each of which is represented by the partial structure (X), exhibit absorption maxima at approximately 2400 A. No data are available concerning the optical properties produced by this chromophoric type when it is distributed over two rings as in (XI). Turning now to the case of the chromophoric group (VIII), we have established that the saturated carbon atom adjacent to the carbonyl group in β-amyrenonol (II, R = OH) carries a hydrogen atom, since this αβ-unsaturated ketone can be converted into the conjugated β-amyradienol-I (III, R = H) and the latter is oxidised by chromic acid with re-formation of the αβ-unsaturated ketone group and simultaneous oxidation of the secondary alcohol group with the production of β-amyrenedione (II, R = O) (Picard and Spring, *loc. cit.*), thus proving that the formation of (III, R = H) from (II, R = OH) has been effected without the intervention of a retropinacolinic rearrangement.

Without making an assumption regarding the position of the extra-nuclear methyl group attachments in the β-amyrenol molecule, the unsaturated ring of β-amyrenonol is represented by (IX); the introduction of a second ethylenic linkage into (IX) to complete the chromophoric group (VIII) would produce a phenol. The presence in β-amyradienonol of the chromophoric group (VIII) located in a single ring system is excluded, since this dienonol does not exhibit phenolic properties either chemically or optically.

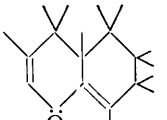
(VII.)   (VIII.)



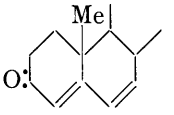
(IX.)



(X.)



(XI.)

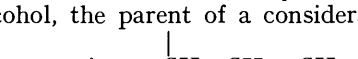


(XII.)

Polycyclic compounds containing the chromophoric group (VIII) distributed over two rings are well known; 3-keto-$\Delta^{4:6}$-cholestadiene (Dane, Wang, and Schulte, *Z. physiol. Chem.*, 1936, **245**, 80), 3 : 17-diketo-$\Delta^{4:6}$-androstadiene (Ruzicka and Bosshard, *Helv. Chim. Acta*, 1937, **20**, 328), 6-dehydrotestosterone, 6-dehydroprogesterone and 6-dehydrodeoxycorticosterone (Wettstein, *Helv. Chim. Acta*, 1940, **23**, 388), each of which contains the major chromophore (XII), all exhibit well-defined absorption maxima at approximately 2800 A. The influence of environment upon the chromophoric group (VIII) is emphasised in the case of the dienone prepared by pyrolysis of ketoacetyloleanolic acid (Ruzicka, Cohen, Furter, and Sluys-Veer, *loc. cit.*), which exhibits a maximum at 2975 A.

The absorption spectra of β-amyradienonyl esters strongly suggest that these contain the chromophoric group (VIII) but that this is not located in a single ring; the formula (I) for β-amyrenol being used, a satisfactory formulation (V) is obtained for β-amyradienonol.

Although the absorption spectrum of β-amyradienonyl acetate, $C_{32}H_{48}O_3$, is very similar to that of Jacobs' keto-diol monoacetate, $C_{32}H_{48(46)}O_4$, a very marked difference is to be observed in their reactions with tetranitromethane, the former giving a pronounced yellow coloration, whereas the latter (Simpson, *loc. cit.*), like β-amyrenonyl esters, fails to give a colour with this reagent. With a view to determining whether β-amyradienonol is related to Jacobs' keto-diol, the oxidation of the acetate of the former has been examined. β-Amyradienonyl acetate is resistant to oxidation by selenium dioxide, but is very readily oxidised by potassium permanganate to give an *acetate*, $C_{32}H_{48}O_4$, m. p. 233—235°. Although this acetate fails to give a coloration with tetranitromethane, it is different from Jacobs' keto-diol monoacetate, which has the same melting point.

A consideration of the series of step-wise oxidations of β-amyrenol represented at (I) ⟶ (V) shows that this triterpene alcohol, the parent of a considerable number of naturally occurring products, contains the grouping  , a fragment which finds expression in the hypothetical formula (I). The behaviour of *iso*-β-amyrenonyl acetate on treatment with bromine will be reported upon later.

Experimental.

β-Amyradienol-II.—The acetone mother-liquors obtained from the crystallisation of the addition-reduction compound $C_{35}H_{62}O_3$ (Picard and Spring, *loc. cit.*, p. 1201) (from 15 g. of β-amyrenonol) were combined, and the solvent removed; the solid (5·5 g.) in boiling alcohol (275 c.c.) was treated with sodium (15 g.), added during 30 minutes with vigorous stirring. The product was precipitated by the addition of water, collected, thoroughly washed with hot water, and dried. It was then heated with acetic anhydride (100 c.c.) and sodium acetate (1 g.) for 2 hours; the acetylated mixture was isolated by means of water and ether and fractionally crystallised from acetone. The top crop was repeatedly crystallised from the same solvent to yield β-amyradienyl-I acetate in needles, m. p. 213—214°; when mixed with an authentic specimen of the dienyl-I acetate, m. p. 216°, it melted at 214—216°. Hydrolysis

was effected by heating the acetate with 1% alcoholic potassium hydroxide solution for 5 hours. The product, isolated in the usual manner, after two crystallisations from methanol gave β-amyradienol-I in needles, m. p. 212—214°, undepressed by an authentic specimen. Concentration of the original acetone mother-liquor of the top crop gave a second crop of heavy plates, m. p. 218—220°; the remarkably sharp separation is to be ascribed to the fact that the minor component of the original mixture has a higher m. p. than the major component. After repeated crystallisation from acetone this crop gave β-amyradienyl-II acetate in plates, m. p. 226—227° (const.) either alone or when mixed with a specimen prepared by the selenium dioxide method (Ruzicka, Müller, and Schellenberg, *loc. cit.*). The dienyl-II acetate (0·1 g.) was heated under reflux with alcoholic potassium hydroxide (4%; 10 c.c.) for 2 hours. The mixture was diluted with water and extracted with ether, and the product crystallised from alcohol. Recrystallisation from the same solvent gave β-amyradienol-II in plates, m. p. 227—228°, undepressed by a specimen prepared by the method of Ruzicka, Müller, and Schellenberg (*loc. cit.*) but depressed to 200—210° by the parent acetate (Found: C, 84·7; H, 11·5. Calc. for $C_{30}H_{48}O$: C, 84·8; H, 11·4%). *Light absorption in alcohol:* Principal maximum, 2515 A., $\varepsilon_{max.}$ = 29,000; secondary maximum 2600 A., $\varepsilon_{max.}$ = 18,000. Both β-amyradienol-II and its acetate give a deep brown coloration with the tetranitromethane reagent.

Oxidation of β-Amyradienyl-I Acetate with Selenium Dioxide.—A boiling solution of the dienyl-I acetate (1·6 g.) in glacial acetic acid (50 c.c.) was treated during 1 hour with a solution of selenium dioxide (1·0 g.) in water (1 c.c.) and glacial acetic acid (50 c.c.). Sodium acetate (8 g.) was added, and the heating continued for 30 minutes. The selenium was removed, and the hot filtrate diluted with water and extracted with ether. The extract was washed with water and dried, removal of the solvent yielding a red resin. A solution of this in methanol deposited a top crop (A) (0·4 g.) of ill-defined crystals; concentration of the mother-liquor gave a second crop (B) (0·6 g.) of heavy plates. Each crop was contaminated with selenium and was difficult to crystallise.

β-Amyrenonyl Acetate.—The top crop (A) was refluxed with methyl-alcoholic potassium hydroxide solution (30 c.c.; 3%) for 2 hours; the solution was concentrated to 10 c.c., diluted with water, and extracted with ether. The ethereal solution was washed with water containing a trace of acetic acid, then with potassium carbonate solution, and dried. Removal of the solvent gave the hydrolysis product as a colourless solid, free from selenium. Crystallisation of the alcohol from the usual organic solvents was difficult because of its great solubility and the small amount of material available; it was therefore acetylated by heating on the steam-bath with pyridine (2 c.c.) and acetic anhydride (2 c.c.) for 1 hour. The acetylated product, isolated by means of ether, was thrice crystallised from acetone to give β-amyrenonyl acetate in prismatic needles, m. p. 262—264°, undepressed by the specimen described by Beynon, Sharples, and Spring (J., 1938, 1233); it did not give a coloration with tetranitromethane in chloroform and exhibited the typical light absorption properties of an αβ-unsaturated ketone (Found: C, 80·1; H, 10·8. Calc. for $C_{32}H_{50}O_3$: C, 79·6; H, 10·4%).

Jacobs' Keto-diol, $C_{30}H_{44(46)}O_3$.—Crop (B) was refluxed with methyl-alcoholic potassium hydroxide (40 c.c.; 3%) for 90 minutes. The solution was concentrated to approximately 10 c.c., diluted with water, and extracted with ether. On concentration of the dried extract the product separated in fine needles. Recrystallisation from light petroleum (b. p. 60—80°)–ether gave the keto-diol in needles, m. p. 286—287°, unchanged by subsequent recrystallisation from the same solvent. (From the first light petroleum mother-liquor, a second crop, m. p. 284—287°, was obtained.) A mixture of the keto-diol, m. p. 286—287°, with a specimen (m. p. 282—284°) prepared as described by Simpson (*loc. cit.*) had m. p. 285—286° (Found: C, 79·2; H, 10·1. Calc. for $C_{30}H_{46}O_3$: C, 79·25; H, 10·1. Calc. for $C_{30}H_{44}O_3$: C, 79·6; H, 9·8%). *Light absorption in alcohol:* Maximum at 2780 A., $\varepsilon_{max.}$ = 11,700. The keto-diol (0·1 g.), m. p. 286—287°, was heated on the water-bath for 2½ hours with pyridine (2 c.c.) and acetic anhydride (2 c.c.). The product, isolated in the usual manner, was crystallised twice from methanol, from which the keto-diol monoacetate separated in heavy plates, m. p. 233—235°, undepressed by a specimen prepared by Simpson's method (*loc. cit.*) (Found: C, 77·1; H, 9·8. Calc. for $C_{32}H_{48}O_4$: C, 77·4; H, 9·7. Calc. for $C_{32}H_{46}O_4$: C, 77·7; H, 9·4%). The keto-diol prepared by this method is more easily purified than that prepared from the thio-derivative of β-amyrenol.

β-Amyradienonyl Benzoate.—β-Amyrenonyl benzoate (Beynon, Sharples, and Spring, *loc. cit.*) (1 g.) in glacial acetic acid (30 c.c.) was treated with a solution of bromine in glacial acetic acid (3%; 11 c.c.) added dropwise at 85—95°. The bromine was rapidly absorbed and after the addition of approximately three-quarters of the bromine solution, crystals began to

separate from the hot solution. When the addition was complete, the solution was cooled, and the crystalline solid collected, washed with acetic acid, and thrice crystallised from the same solvent to give β-*amyradienonyl benzoate* in heavy lustrous plates, m. p. 251—252°. By combining and concentrating the acetic acid mother-liquors, a further quantity of the dienonyl benzoate was obtained (yield, 85%). It gave a yellow coloration with tetranitromethane in chloroform solution (Found: C, 81·6; H, 9·4. $C_{37}H_{50}O_3$ requires C, 81·9; H, 9·3%). *Light absorption in alcohol:* Maximum at 2835 A., $\varepsilon_{max.}$ = 12,000. β-Amyradienonyl benzoate was recovered unchanged after heating with alcoholic hydroxylamine acetate for 5 hours.

β-*Amyradienonol.*—The benzoate (0·15 g.) was refluxed with alcoholic potassium hydroxide solution (7·5%; 15 c.c.) for 2 hours. After dilution with water, the solid was collected, washed with water, and thrice crystallised from methanol (in which it is moderately soluble), yielding β-*amyradienonol* in prismatic needles, m. p. 239—240° (Found: C, 81·6; H, 10·85. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%).

β-*Amyradienonyl Acetate.*—(a) β-Amyradienonol (0·25 g.) was heated on the steam-bath for 2 hours with pyridine (10 c.c.) and acetic anhydride (10 c.c.). After standing overnight, the solution was diluted with water, and the product collected and washed with water. After four crystallisations from methyl alcohol, β-*amyradienonyl acetate* separated in felted needles, m. p. 255° (Found: C, 79·7; H, 10·0. $C_{32}H_{48}O_3$ requires C, 80·0; H, 10·1%). *Light absorption in alcohol:* Maximum at 2815 A., $\varepsilon_{max.}$ = 14,000.

(b) A solution of β-amyrenonyl acetate (Beynon, Sharples, and Spring, *loc. cit.*) (3 g.) in glacial acetic acid (120 c.c.) was treated at 70—75° with a solution of bromine in acetic acid (3%; 38·5 c.c.) added dropwise during 10 minutes. The bromine was rapidly absorbed with evolution of hydrogen bromide. After heating for a further 10 minutes, the solution was diluted with water, and the solid collected and washed with water. After four crystallisations from methyl alcohol containing a small amount of acetone, this gave β-amyradienonyl acetate in needles, m. p. 254—255°, unchanged by the specimen prepared by method (a).

Oxidation of β-*Amyradienonyl Acetate.*—A solution of potassium permanganate (1·1 g.) in water (22 c.c.) was added dropwise during 90 minutes to a solution of β-amyradienonyl acetate (1 g.) in stabilised glacial acetic acid (90 c.c.), the mixture being stirred throughout and the temperature maintained at 20°. After standing for 1 hour at the same temperature, the mixture was acidified with dilute sulphuric acid and clarified with sulphur dioxide. The precipitated solid was collected, washed with water, and crystallised from methanol and then from aqueous acetone, from which the *acetate* separated in plates, m. p. 234—235° (slight decomp.). When it was mixed with Jacobs' keto-diol monoacetate, m. p. 234—235°, the m. p. was depressed to 195—205°. The new acetate does not give a coloration with tetranitromethane in chloroform (Found: C, 76·8; H, 9·9. $C_{32}H_{48}O_4$ requires C, 77·4; H, 9·8%). *Light absorption in alcohol:* Maximum at 2470 A., $\varepsilon_{max.}$ = 10,000.

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