735. *Triterpene Resinols and Related Acids. Part XXIII.** (a) *The Decarboxylation of Acetylketoursolic Acid.* (b) *The Oxidation of Methyl Acetylursolate with Hydrogen Peroxide.*

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Decarboxylation of acetylketoursolic acid in quinoline gives nor-α-amyrenonyl acetate in which the ketone group and the ethylenic linkage are not conjugated.

Oxidation of methyl acetylursolate with hydrogen peroxide yields a mixture from which two stereoisomeric keto-esters, $C_{33}H_{52}O_5$, have been isolated, each of which is converted into methyl acetylketo*iso*ursolate on treatment with bromine.

(*a*) THE investigation described in this part is a continuation of that described in Part XIV (Ewen and Spring, *J.*, 1943, 523), in which it was shown that acetylursolic acid resembles α-amyrin acetate in yielding an αβ-unsaturated ketone on oxidation with chromic anhydride. The product, acetylketoursolic acid, resembled acetylketo-oleanolic acid in that when heated with quinoline it loses the elements of formic acid to give a conjugated dienone showing a high-intensity absorption maximum at approximately 3000 Å. These facts were interpreted as

* Part XXII, *J.*, 1951, 3019.

indicating that the carboxyl group of ursolic acid, like that of oleanolic acid, is in the neighbourhood of the ethylenic linkage. Although nor-α-amyradienonyl acetate, obtained from ursolic acid, and the nor-β-isomer, obtained from oleanolic acid (Ruzicka, Cohen, Furter, and Sluys-Veer, *Helv. Chim. Acta*, 1938, **21**, 1735), both show absorption maxima at approximately 3000 Å, the molecular extinction coefficients of these maxima are markedly different, that of nor-β-amyradienonyl acetate being approximately 22,000 and that of nor-α-amyradienonyl acetate being 10,000. The decarboxylation of acetylketoursolic acid was therefore re-examined.

When heated in quinoline, the conditions described in Part XIV being used, acetylketoursolic acid gives a neutral product, m. p. 206—208°, $[\alpha]_D$ +45°, which in these respects is very similar to the nor-α-amyradienonyl acetate described by Ewen and Spring (m. p. 203—205°; $[\alpha]_D$ +41°). Like Ewen and Spring's nor-α-amyradienonyl acetate, the compound, m. p. 206—208°, showed an absorption maximum at approximately 3000 Å, the molecular extinction coefficient of which was, however, only 6000. The decarboxylation of acetylketoursolic acid in quinoline is accompanied by the formation of resinous material and in an attempt to avoid this, the reaction was carried out in a nitrogen atmosphere. In these conditions, the neutral reaction product gives a compound, $C_{31}H_{48}O_3$, m. p. 216—217°, $[\alpha]_D$ +37°, which gives a yellow coloration with tetranitromethane in chloroform and does not exhibit selective absorption in the ultra-violet. The presence in the compound, m. p. 216—217°, of one ethylenic linkage was established by its oxidation with perbenzoic acid to a monoxide, which gives no colour with the tetranitromethane reagent. The compound, $C_{31}H_{48}O_3$, is therefore a nor-α-amyrenonyl acetate produced by decarboxylation of acetylketoursolic acid with simultaneous migration of the ethylenic linkage. Hydrolysis of nor-α-amyrenonyl acetate gave nor-α-amyrenonol, m. p. 257—259°, $[\alpha]_D$ +34°, acetylation of which regenerated the parent acetate.

The properties of nor-α-amyrenonyl acetate, of Ewen and Spring's nor-α-amyradienonyl acetate, and of the compound, m. p. 206—208°, described above, apart from the selective light absorption, are very similar, and the possibility that the last two compounds are mixed crystals of nor-α-amyradienonyl acetate with variable proportions of nor-α-amyrenonyl acetate became apparent. A chromatographic examination of the compound, m. p. 206—208°, showing selective absorption at 3000 Å, $\varepsilon = 6000$, was undertaken in the hope that it would lead to a separation of nor-α-amyrenonyl acetate and nor-α-amyradienonyl acetate. This did not prove to be the case; nor-α-amyrenonyl acetate was readily isolated in relatively high yield from the least strongly adsorbed fractions of the chromatogram but subsequent fractions, which gave strong brown colorations with the tetranitromethane reagent and showed an absorption maximum at 2980 Å ($\varepsilon = 10{,}500$), could not be obtained crystalline.

The decarboxylation of triterpenoid keto-acids in the presence of quinoline does not appear to give uniformly reproducible results. Thus Ruzicka, Cohen, Further, and Sluys-Veer (*loc. cit.*) showed that treatment of acetylketo-oleanolic acid with boiling quinoline gave nor-β-amyradienonyl acetate, a result confirmed by Ewen and Spring (*loc. cit.*). Bilham, Kon, and Ross (*J.*, 1942, 535) were unable to repeat this result; using the conditions described by Ruzicka and his collaborators they obtained as sole product nor-β-amyrenonyl acetate, produced by decarboxylation and migration of the ethylenic linkage. Subsequently in a repetition of the original experiment, Ruzicka, Jeger, and Winter (*Helv. Chim. Acta*, 1943, **26**, 265) obtained a mixture of approximately equal amounts of nor-β-amyrenonyl acetate and nor-β-amyradienonyl acetate. In a recent repetition of this experiment using a purified quinoline we have obtained nor-β-amyrenonyl acetate as sole product.

(*b*) Oxidation of methyl acetylursolate with hydrogen peroxide gives a product, $C_{33}H_{52}O_5$, m. p. 250—253°, $[\alpha]_D$ +25°, which is either methyl acetylursolate oxide or methyl acetyldihydroketoursolate. Oxidation of acetylursolic acid with hydrogen peroxide gave a mixture of a neutral and an acidic product. The latter was not obtained crystalline but was esterified with diazomethane. Chromatographic purification of the ester fraction gave the compound, $C_{33}H_{52}O_5$, identical with that obtained by direct oxidation of methyl acetylursolate. The compound, $C_{33}H_{52}O_5$, m. p. 250—253°, is probably identical with the methyl acetyldihydroketoursolate described by Jeger, Borth, and Ruzicka (*Helv. Chim. Acta*, 1946, **29**, 1999). Since oxidation of α-amyrin esters with hydrogen peroxide yields the corresponding oxides, we at first inclined to the view that the compound, $C_{33}H_{52}O_5$, is methyl acetylursolate oxide. When treated with hydrochloric acid, the compound, $C_{33}H_{52}O_5$, gave an isomer, m. p. 254—256°, $[\alpha]_D$ +35°. In spite of the similarity in physical properties, the two compounds are distinct, a mixture showing a pronounced depression in melting point. There are substantial reasons for discarding the view that the isomers, m. p. 250—253° and m. p. 254—256°, are oxide and saturated ketone, respectively. Both exhibit low-intensity maxima in the region of 2900 Å,

indicating that each is a saturated ketone. α-Amyrin acetate oxide (+114°) and α-amyranonyl acetate (+11°) differ very considerably in their specific rotations, as do α-amyrin benzoate oxide (+132°) and α-amyranonyl benzoate (+25°), whereas the isomeric compounds, $C_{33}H_{52}O_5$, show no such striking difference in specific rotation. We conclude that the latter pair are stereoisomeric methyl acetyldihydroketoursolates.

The relationship between the isomeric keto-esters is further established by their behaviour on treatment with bromine in presence of hydrogen bromide when they each give the same αβ-unsaturated keto-ester, methyl acetylketo*iso*ursolate (Dreiding, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1325). Bromination of methyl acetyldihydroketoursolate under relatively mild conditions gave the intermediate methyl acetylbromodihydroketoursolate which when warmed with acetic acid loses hydrogen bromide, yielding methyl acetylketo-*iso*ursolate.

Experimental.

M.p.s are uncorrected; specific rotations were measured at room temperature (15—19°) in chloroform in a 10-cm. tube.

Acetylketoursolic Acid.—A boiling solution of acetylursolic acid (5 g.), m. p. 286—289°, $[\alpha]_D$ +62° (*c*, 1·3), in glacial acetic acid (125 c.c.) was oxidised with chromic anhydride, the conditions described by Ewen and Spring (*loc. cit.*) being used with the difference that the period of reflux was 2 hours. Acetylketoursolic acid (2·7 g.) was obtained as stout prismatic needles, m. p. 323—325° (decomp.), $[\alpha]_D$ +89° (*c*, 1·4) (the value +41° given by Ewen and Spring is incorrect) (Found: C, 74·9; H, 9·3. Calc. for $C_{32}H_{48}O_5$: C, 75·0; H, 9·4%). Light absorption in ethanol: Maximum at 2500 Å, ε = 12,500.

Ethyl acetylketoursolate separates from aqueous methanol as stout prismatic needles, m. p. 215—216°, $[\alpha]_D$ +85° (*c*, 1·0) (Found: C, 75·4; H, 9·5. Calc. for $C_{34}H_{52}O_5$: C, 75·6; H, 9·7%). Light absorption in ethanol: Maximum at 2500 Å, ε = 10,500.

Methyl acetylketoursolate was prepared by esterification of acetylketoursolic acid by use of diazomethane. It separates from aqueous ethanol as stout needles, m. p. 243—245°, $[\alpha]_D$ +86° (*c*, 0·91) (Found: C, 75·1; H, 9·8. $C_{33}H_{50}O_5$ requires C, 75·3; H, 9·5%). Light absorption in ethanol: Maximum at 2500 Å, ε = 10,500.

Nor-α-amyrenonyl Acetate.—A solution of acetylketoursolic acid (0·69 g.) in dry, freshly distilled quinoline (30 c.c.) was gently refluxed for 18 hours. Throughout the reaction, a slow stream of nitrogen was passed through the solution. The issuing gas stream was cooled at −10°, and passed through a standard solution of barium hydroxide. After 8 hours the carbon dioxide absorption corresponded to 0·3 mol. and after 16 hours to 0·8 mol. The cooled reaction mixture was poured into excess of dilute hydrochloric acid and extracted with ether. The extract was washed with dilute hydrochloric acid, water, and finally with dilute sodium hydroxide solution which precipitated an insoluble sodium salt (0·12 g.). The sodium salt was dissolved in hot aqueous ethanol, and the solution acidified (Congo-red) with dilute hydrochloric acid. On cooling, acetylketoursolic acid separated as prismatic needles, m. p. 310—313° undepressed when mixed with the starting material. After removal of the sodium salt, the ethereal solution was washed with water and dried (Na_2SO_4). Removal of the ether gave a crystalline solid (0·46 g.) after which four recrystallisations from aqueous ethanol gave *nor-α-amyrenonyl acetate* (0·30 g.) as plates, m. p. 216—217°, $[\alpha]_D$ +37° (*c*, 0·94), which gave a yellow coloration with tetranitromethane in chloroform (Found: C, 79·1; H, 10·2. $C_{31}H_{48}O_3$ requires C, 79·4; H, 10·3%).

Nor-α-amyrenonol.—Nor-α-amyrenonyl acetate (0·07 g.) was refluxed for 3 hours with ethanolic potassium hydroxide (5%; 10 c.c.). The cooled reaction product was poured into water, and the flocculent precipitate collected and thrice crystallised from ethanol, giving *nor-α-amyrenonol* as silky needles, m. p. 257—259°, $[\alpha]_D$ +34° (*c*, 0·89), which give a yellow coloration with tetranitromethane in chloroform (Found: C, 81·9; H, 11·0. $C_{29}H_{46}O_2$ requires C, 81·6; H, 10·8%). Acetylation of nor-α-amyrenonol with acetic anhydride in pyridine gave nor-α-amyrenonyl acetate as plates, m. p. 210—212° undepressed when mixed with the specimen described above.

Nor-α-amyrenonyl Acetate Oxide.—Nor-α-amyrenonyl acetate (75 mg.) in chloroform (10 c.c.) was treated with a solution of perbenzoic acid in chloroform (0·4N; 4·25 c.c.) and kept at 0° for 120 hours. After 5 days, absorption corresponding to 1·2 atoms of oxygen had occurred. The reaction mixture was washed with 2% sodium hydroxide and then with water. After the solution had been dried (Na_2SO_4), the solvent was removed under reduced pressure and the solid residue crystallised from ethanol, giving *nor-α-amyrenonyl acetate oxide* (30 mg.) as plates, m. p. 219—220° (Found: C, 76·3; H, 10·0. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%). Nor-α-amyrenonyl acetate oxide does not give a coloration with the tetranitromethane reagent nor does it exhibit high-intensity selective absorption in the ultra-violet.

Nor-β-amyrenonyl Acetate (with A. G. McInnes).—Acetylketo-oleanolic acid (1 g.) was refluxed for 8 hours in quinoline (50 c.c.). On cooling, the solution was poured into excess of hydrochloric acid (3%; 200 c.c.), and the mixture extracted with ether. The ethereal extract was washed with aqueous sodium hydroxide (5%; 400 c.c.), and water, and, after being dried ($MgSO_4$), was evaporated to dryness. The residue (0·75 g.) was dissolved in light petroleum, and the solution filtered through a column of activated alumina (Grade II; 25 g.). The column was then washed and fractions collected: fractions 1—10, with light petroleum (b. p. 60—80°; 1000 c.c.), giving 0·324 g. of eluate; fractions 11—13, with light petroleum–benzene (1 : 1; 300 c.c.), giving 0·335 g. of eluate; and fractions 14—16, with benzene (225 c.c.), giving 0·046 g. of eluate.

Fractions 1—10, 11—13, and 14—16 were crystallised separately from methanol giving long needles, m. p. 228—231°, 228—231°, and 226—230°, respectively, undepressed when intermixed. The three fractions were combined and crystallised from methanol, giving nor-β-amyrenonyl acetate as needles, m. p. 238—239°, $[\alpha]_D$ +50° (*c*, 0·53) (Found: C, 79·3; H, 10·5. Calc. for $C_{31}H_{48}O_3$: C, 79·4; H, 10·3%). It gives a yellow coloration with tetranitromethane in chloroform, and displays no high-intensity light absorption in the ultra-violet.

Methyl Acetyldihydroketoursolate.—(*a*) A solution of acetylursolic acid (5 g.) in glacial acetic acid (200 c.c.) was treated during 15 minutes with hydrogen peroxide (30%; 20 c.c.) in glacial acetic acid (20 c.c.), the mixture being stirred and heated on the steam-bath during the addition and for a further 2 hours. A second treatment with hydrogen peroxide (30%; 20 c.c.) in glacial acetic acid (20 c.c.) was made, and the mixture stirred at steam-bath temperature for 2 hours. The mixture was concentrated under reduced pressure to 50 c.c., cooled, and poured into water. The mixture was extracted with ether (3 × 40 c.c.), and the extract washed with sodium hydroxide solution (5%; 5 × 20 c.c.) and with water. The alkaline extract was acidified with dilute hydrochloric acid, and the precipitated solid (0·95 g.) collected, dissolved in ether, and esterified with an ethereal solution of diazomethane. The neutral fraction (0·75 g.), obtained in the usual manner, was dissolved in light petroleum (b. p. 60—80°; 200 c.c.) and filtered through a column of activated alumina (25 × 1·75 cm.). The column was washed, first with light petroleum (b. p. 60—80°)–benzene (1 : 1; 500 c.c.), giving 0·410 g. of eluate. A further 300 c.c. of the same solvent eluted material (0·120 g.) differing from the first and subsequent eluates (the latter obtained by washing the column with benzene and with methanol) by crystallising readily from ethanol. After three crystallisations from this solvent, methyl acetyldihydroketoursolate was obtained as fine needles, m. p. 246—249°, $[\alpha]_D$ +27° (*c*, 0·42) (Found: C, 75·1; H, 9·7. Calc. for $C_{33}H_{52}O_5$: C, 75·0; H, 9·9%) {Jeger, Borth, and Ruzicka, *loc. cit.*, give m. p. 248—250° (corr.), $[\alpha]_D$ +35°, and m. p. 246—248° (corr.), $[\alpha]_D$ +29°, for two specimens of methyl acetyldihydroketoursolate, the first of which was prepared by peroxide oxidation of acetylursolic acid followed by esterification, and the second by treatment of methyl acetylursolate with ozonised oxygen}.

(*b*) A solution of methyl acetylursolate (7·5 g.) in boiling glacial acetic acid (150 c.c.) was treated during 10 minutes with hydrogen peroxide (30%; 75 c.c.) in glacial acetic acid (75 c.c.). The mixture was refluxed for 2 hours, diluted to turbidity with water, and cooled. The fine needles which separated, after five recrystallisations from ethanol, gave methyl acetyldihydroketoursolate (4·4 g.) as needles, m. p. 250—253° (decomp.), $[\alpha]_D$ +25° (*c*, 0·92) (Found: C, 75·0; H, 9·8. Calc. for $C_{33}H_{52}O_5$: C, 75·0; H, 9·9%). The compound gave no coloration with tetranitromethane in chloroform, and was undepressed in m. p. when mixed with a specimen prepared by method (*a*).

Methyl Acetyldihydroketoisoursolate.—(*a*) A solution of methyl acetyldihydroketoursolate (0·75 g.) in chloroform (10 c.c.) and glacial acetic acid (40 c.c.) was treated with concentrated hydrochloric acid (2 c.c.), and kept at 40° for 30 minutes. The mixture was concentrated under reduced pressure, diluted with water, and extracted with ether. The extract was washed with dilute sodium carbonate solution and then with water, and dried (Na_2SO_4). A solution of the residue (0·52 g.), which crystallised from methanol, in light petroleum (b. p. 60—70°; 150 c.c.) was filtered through a column of activated alumina (13 × 1·75 cm.) which was then washed, first with light petroleum–benzene (1 : 1; 350 c.c.); the eluate was discarded. More of this solvent (400 c.c.) gave an eluate (80 mg.), m. p. 242—248°. Benzene (300 c.c.) then gave material (100 mg.), m. p. 246—253°, which was combined with the previous fraction and repeatedly crystallised from ethanol to yield *methyl acetyldihydroketoisoursolate* (70 mg.) as small prismatic needles, m. p. 253—256°, $[\alpha]_D$ +32° (*c*, 0·86) (Found: C, 75·3; H, 9·8. $C_{33}H_{52}O_5$ requires C, 75·0; H, 9·9%). A mixture of methyl acetyldihydroketo*iso*ursolate and methyl acetyldihydroketoursolate (m. p. 250—253°) had m. p. 230—234°. Methyl acetyldihydroketo*iso*ursolate does not give a coloration with tetranitromethane in chloroform, and exhibits an absorption maximum at 2890 Å (ε = 84).

The column was washed with more benzene (100 c.c.) (the small eluate was discarded), then with benzene–ether (1 : 1; 200 c.c.), and then with ether alone (100 c.c.). The eluates obtained by means of these solvents were combined and crystallised from ethanol, giving needles, m. p. 249—252° undepressed when mixed with methyl acetyldihydroketoursolate.

(*b*) A solution of methyl acetyldihydroketoursolate (0·50 g.) in glacial acetic acid (18 c.c.) was heated on a steam-bath for 6 hours with concentrated hydrochloric acid (10%; 0·5 c.c.). The mixture was kept at room temperature for 24 hours, and then diluted with water. The precipitate was collected and crystallised repeatedly from methanol and then from ethanol from which methyl acetyldihydroketo-*iso*ursolate separated as prismatic needles (0·085 g.), m. p. 254—256°, $[\alpha]_D$ +35° (*c*, 1·03), not depressed in m. p. when mixed with the specimen described under (*a*) (Found: C, 74·9; H, 10·2. Calc. for $C_{33}H_{52}O_5$: C, 75·0; H, 9·9%). Methyl acetyldihydroketo*iso*ursolate was recovered unchanged after being refluxed for 10 hours with ethanolic hydroxylamine acetate.

Methyl Acetylbromodihydroketoursolate.—A solution of methyl acetyldihydroketoursolate (0·5 g.) in glacial acetic acid (60 c.c.) containing hydrogen bromide (0·2 c.c.; 47% solution in water), was treated dropwise with a solution of bromine in glacial acetic acid (3%; 5·5 c.c.) at room temperature with stirring. After 3 hours the mixture was poured into water. The precipitated solid was collected and crystallised thrice from aqueous acetone yielding *methyl acetylbromodihydroketoursolate* as needles, m. p. 126—128°; after being heated in a high vacuum for 1 hour at 55°, the bromo-ketone had m. p. 196—198°. Crystallisation of this high-melting form from acetone again gave needles, m. p. 126—128°, $[\alpha]_D$ +106° (*c*, 0·76). The bromo-ketone does not give a coloration with tetranitromethane in chloroform (Found: C, 64·9; H, 8·6. $C_{33}H_{51}O_5Br$ requires C, 65·2; H, 8·4%). Similar bromination of methyl acetyldihydroketo-*iso*ursolate gave the bromo-ketone as needles (from acetone), m. p. 118—122° not depressed when mixed with the specimen, m. p. 126—128°.

Methyl Acetylketoisoursolate.—(*a*) Methyl acetyldihydroketoursolate (0·5 g.) in glacial acetic acid (60 c.c.) was treated with an aqueous solution of hydrogen bromide (47%; 0·2 c.c.), and then at 60° with a solution of bromine in glacial acetic acid (3%; 5 c.c.) added dropwise, and with stirring. After the addition was complete, the solution was kept for 1 hour at 70°, and then poured into water. The solid was collected, washed with water, and crystallised four times from aqueous ethanol, giving methyl acetylketo*iso*ursolate (0·28 g.) as needles, m. p. 186—188°, $[\alpha]_D$ +87° (*c*. 0·81). Light absorption in ethanol: Maximum at 2490 Å, $\varepsilon = 15{,}500$. Methyl acetylketo*iso*ursolate does not give a coloration with tetranitromethane in chloroform.

(*b*) A solution of methyl acetylbromodihydroketoursolate (0·3 g.) in glacial acetic acid (15 c.c.) containing a trace of aqueous hydrogen bromide, was heated on a steam-bath for 3 hours. The solution was kept at room temperature for 12 hours and then poured into water, and the mixture extracted with ether. The extract was washed with dilute sodium carbonate solution and then with water, and dried (Na_2SO_4). After removal of the ether the residue was thrice crystallised from acetone, giving methyl acetylketo*iso*ursolate (0·2 g.) as needles, m. p. 186—188° undepressed when mixed with the specimen prepared by method (*a*); $[\alpha]_D$ +85° (*c*, 0·93) (Found: C, 74·9; H, 9·6. Calc. for $C_{33}H_{50}O_5$: C, 75·2; H, 9·6%). Light absorption in ethanol: Maximum at 2490 Å, $\varepsilon = 15{,}000$. Dreiding, Jeger, and Ruzicka (*loc. cit.*) report m. p. 193° (corr.), $[\alpha]_D$ +85°, for methyl acetylketo*iso*ursolate.

Hydrolysis of methyl acetylketo*iso*ursolate with 0·5% ethanolic potassium hydroxide gave methyl keto*iso*ursolate as plates, m. p. 236—238°, $[\alpha]_D$ +82° (*c*, 0·61) (Found: C, 76·5; H, 9·7. Calc. for $C_{31}H_{48}O_4$: C, 76·8; H, 9·9%). Light absorption in ethanol: Maximum at 2500 Å, $\varepsilon = 15{,}500$. Dreiding, Jeger, and Ruzicka (*loc. cit.*) give m. p. 240° (corr.), $[\alpha]_D$ +71°, for methyl keto*iso*ursolate.

The authors acknowledge assistance in various phases of this work from Mr. R. Bhuvanendram, B.Sc., and from Mr. J. T. Farquhar, B.Sc.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, July 13th*, 1951.]