73. *The Acidic Oxidation Products of Lupenyl Esters: The Addition of Hydrogen Chloride to Lupeol.*

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In addition to the neutral products previously described (J., 1938, 329) the oxidation of lupenyl acetate with ozone and with chromic anhydride gives rise respectively to what appear to be isomeric acetyl monocarboxylic acids $C_{30}H_{50}O_3$ (or $C_{29}H_{48}O_3$). Lupeol reacts with hydrogen chloride, giving lupeol hydrochloride, from which *iso*-lupenyl acetate is obtained by removal of hydrogen chloride with acetic anhydride.

WE recently described a neutral product formed by the oxidation of lupenyl acetate with both ozone and chromic anhydride and reported that the acidic products simultaneously obtained in each reaction were being investigated (Heilbron, Kennedy, and Spring, J., 1938, 329). Although this investigation has not as yet been completed, we record our results at this stage in view of the appearance of memoirs on the same subject by Dieterle and Biedebach (*Arch. Pharm.*, 1938, **276**, 312) and by Ruzicka, Schellenberg, and Rosenkranz (*Helv. Chim. Acta*, 1938, **21**, 1391).

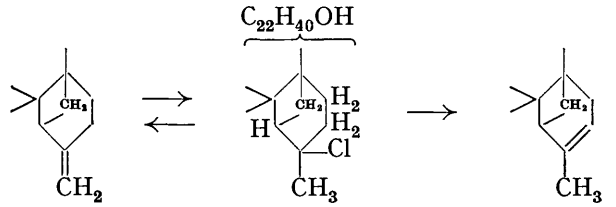
Ozonolysis of lupenyl acetate in chloroform solution gives a mixture of non-volatile products, from which potassium hydroxide extracts the soluble potassium salt of a crystalline acid, m. p. 272° (*acetate-acid A*). Neither the acetate-acid A nor its *methyl* ester gives a coloration with tetranitromethane in chloroform solution, and analyses of both indicate that the parent hydroxy-acid has the molecular formula $C_{30}H_{50}O_3$ (or $C_{29}H_{48}O_3$).

Ozonolysis of lupenyl benzoate yields an amorphous acidic product, which on hydrolysis gives the same hydroxy-acid A, m. p. 262—264°, as is obtained on hydrolysis of the acetate-acid A.

Oxidation of lupenyl acetate with chromic anhydride gives the acid (acetate-acid B) first prepared by Cohen (*Rec. Trav. chim.*, 1909, **28**, 368) and again described by Ruzicka, Schellenberg, and Rosenkranz (*loc. cit.*). In agreement with the latter authors we find

that this acid exhibits no selective absorption in the ultra-violet and gives no coloration with tetranitromethane. Treatment with acetic anhydride yields an *acetate-anhydride* [the " diacetate " of Cohen (*loc. cit.*)] which on recrystallisation from methyl alcohol readily regenerates the acetate-acid B, a behaviour comparable in all respects with that of oleanolic and ursolic acids on similar treatment. Oxidation of lupenyl benzoate with chromic anhydride gives a crystalline benzoate-acid, m. p. 320—322°. The relationship of this to the acetate-acid B has been established by its hydrolysis, followed by acetylation and esterification by diazomethane. The acetate-methyl ester so obtained was identical with that prepared directly from the acetate-acid B.

Treatment of lupeol with hydrogen chloride yields *lupeol hydrochloride*, m. p. 195—196° (decomp.). Removal of hydrogen chloride from this compound proved to be difficult, the hydrochloride being recovered unchanged after heating with an alcoholic solution of potassium acetate, with pyridine, or with alcoholic potassium hydroxide solution. The reaction was effected, however, by heating either with dimethylaniline or better with acetic anhydride; an iso*lupenyl acetate*, m. p. 269—270°, was then obtained. Removal of hydrogen chloride from lupeol hydrochloride was also accomplished by heating with silver acetate, but in this case lupenyl acetate was the product. This reaction shows that the formation of the hydrochloride has been achieved by simple addition without rearrangement; the relationship of lupeol and *iso*lupeol can be provisionally represented thus:



Lupeol. Lupeol hydrochloride. *iso*Lupeol.

Ozonolysis of *iso*lupenyl acetate gave formaldehyde in 6% yield, and a parallel experiment with lupenyl acetate gave an 18% yield, pointing to a possible degree of mobility between the endocyclic bond of *iso*lupeol and the exocyclic bond of lupeol. The mixture from the mother-liquors obtained in the preparation of lupeol hydrochloride, on heating with acetic anhydride, gave, in addition to *iso*lupenyl acetate, an isomeric acetate, m. p. 230—232°, which, although having the same m. p. as β-amyrenyl acetate, showed a large depression on admixture with this substance.

Experimental.

All m. p.'s are uncorrected.

Ozonolysis of Lupenyl Acetate.—The aqueous potassium hydroxide extract obtained from the non-volatile product of the ozonolysis of lupenyl acetate (see J., 1938, 333) was acidified and extracted with ether. Removal of solvent from the dried solution yielded a slightly resinous solid (5·5 g. from 10 g. of lupenyl acetate), which was crystallised successively from alcohol (charcoal), ethyl acetate, and aqueous alcohol, from which the *acetate-acid A* separated in flat needles, m. p. 272° (Found: C, 76·3; H, 10·3. $C_{32}H_{52}O_4$ requires C, 76·7; H, 10·5. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·6%). The *methyl* ester, obtained by means of diazomethane, formed prisms (alcohol), m. p. 232—234° (Found: C, 76·8; H, 10·5. $C_{33}H_{54}O_4$ requires C, 77·0; H, 10·6. $C_{32}H_{52}O_4$ requires C, 76·7; H, 10·5%).

Hydroxy-acid A.—The acetate-acid A was heated under reflux with a large excess of alcoholic potassium hydroxide (5%) for 4 hours. The product was crystallised from glacial acetic acid and finally from alcohol, from which it separated in long needles, m. p. 262—264° (Found: C, 76·4; H, 10·7. $C_{30}H_{50}O_3,C_2H_5{\cdot}OH$ requires C, 76·0; H, 11·2%).

Ozonolysis of Lupenyl Benzoate.—The ozonolysis was effected exactly as in the case of lupenyl acetate. The acid fraction could not be obtained crystalline; it was therefore hydrolysed, and the product repeatedly crystallised from alcohol, the hydroxy-acid A, m. p. 262—264°, then obtained being identical with that from lupenyl acetate.

Oxidation of Lupenyl Esters with Chromic Anhydride.—(a) *Lupenyl acetate.* The insoluble potassium salt (J., 1938, 333) was treated with dilute mineral acid, and the solid collected and

washed. Attempts to obtain the acetate-acid B in crystalline form from alcohol, acetic acid, acetone, ethyl acetate and benzene–alcohol were unsuccessful. From alcohol it was obtained as a powder, m. p. 296° [Cohen (*loc. cit.*) gives m. p. 295°; Ruzicka, Schellenberg, and Rosenkranz (*loc. cit.*) give m. p. 295—297° (corr.)] (Found: C, 76·1, 76·3; H, 10·1, 10·2. Calc. for $C_{32}H_{54}O_4$: C, 76·7; H, 10·5%. Calc. for $C_{31}H_{50}O_4$: C, 76·5; H, 10·6%). The methyl ester, prepared by means of diazomethane, separated from alcohol in plates, m. p. 268—272° [Ruzicka *et al.* (*loc. cit.*) give m. p. 260—262° (corr.)] (Found: C, 76·5, 76·7; H, 10·1, 10·3. Calc. for $C_{33}H_{54}O_4$: C, 77·0; H, 10·6%. Calc. for $C_{32}H_{52}O_4$: C, 76·7; H, 10·5%). The *acetate-anhydride* was prepared by heating the acetate-acid (1 g.) with acetic anhydride (40 c.c.) for 4 hours; the solid deposited on cooling crystallised from dry light petroleum in plates, m. p. 195—197°, resolidifying and melting again at 277—284° (Cohen, *loc. cit.*, gives 198° and " over 260° ") (Found: C, 75·7; H, 10·35. $C_{34}H_{54}O_5$ requires C, 75·2; H, 10·5%). Crystallisation of the acetate-anhydride from methyl alcohol regenerated the acetate-acid, B, m. p. 296°.

(b) *Lupenyl benzoate.* The oxidation was effected as in the case of the acetate. The benzoate-acid separated from alcohol in fine needles, m. p. 320—322° [Ruzicka *et al.* (*loc. cit.*) give m. p. 328—329° (corr.) in a high vacuum] (Found: C, 78·7; H, 9·1. Calc. for $C_{37}H_{54}O_4$: C, 79·0; H, 9·7%. Calc. for $C_{36}H_{52}O_4$: C, 78·8; H, 9·55%). The methyl ester separated from alcohol in flat needles, m. p. 266—268° [Ruzicka *et al.* give m. p. 273° (corr.)] (Found: C, 79·0; H, 9·9. Calc. for $C_{38}H_{56}O_4$: C, 79·1; H, 9·8%. Calc. for $C_{37}H_{54}O_4$: C, 79·0; H, 9·7%).

Hydroxy-acid B.—The acetate-acid B (1 g.) was heated under reflux with 5% alcoholic potash for 12 hours. The solution was poured into water and acidified with dilute hydrochloric acid. The hydroxy-acid B was extracted with ether and after removal of solvent from the washed and dried solution the residue was repeatedly crystallised from acetone, from which it separated in microscopic needles, m. p. 278—280° (Cohen, *loc. cit.*, gives 282°; Ruzicka, Schellenberg, and Rosenkranz, *loc. cit.*, give 291—292° in an evacuated m. p. tube) (Found: C, 78·6; H, 10·95. Calc. for $C_{30}H_{50}O_3$: C, 78·5; H, 11·0%. Calc. for $C_{29}H_{48}O_3$: C, 78·3; H, 10·9%).

Lupeol Hydrochloride.—A solution of lupeol (10 g.) in alcohol (270 c.c.) was treated with a saturated solution of hydrogen chloride in alcohol (300 c.c.). After 2 days the separated solid (5 g.) was collected and repeatedly crystallised from alcohol, from which the *hydrochloride* separated in rosettes of fine needles, m. p. 195—196°, $[\alpha]_D^{20}$ — 10·3° ($l = 1$, $c = 0·9$ in chloroform) (Found: C, 77·6; H, 10·8; Cl, 7·5. $C_{30}H_{51}OCl$ requires C, 77·8; H, 11·0; Cl, 7·7%).

Lupenyl Acetate from Lupeol Hydrochloride.—The hydrochloride (0·75 g.) and silver acetate (1·0 g.) were heated under reflux with alcohol (20 c.c.) for 3 days. After the addition of water the product was isolated by means of ether and heated under reflux with acetic anhydride (5 c.c.) for 2 hours. Crystallisation from alcohol gave lupenyl acetate, m. p. 212—213° alone and in admixture with an authentic specimen.

iso*Lupenyl Acetate.*—(a) A solution of lupeol hydrochloride in dimethylaniline (10 c.c.) was heated under reflux for 24 hours. After dilution with water the mixture was extracted with ether, and the extract washed successively with dilute hydrochloric acid and water. The solid obtained after removal of the solvent was free from halogen but proved difficult to crystallise. It was therefore acetylated by heating with acetic anhydride; the product crystallised from alcohol in plates of iso*lupenyl acetate*, m. p. 269—270°, $[\alpha]_D^{20}$ + 25·26° ($l = 1$, $c = 0·95$ in chloroform) (Found: C, 81·7; H, 11·0. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). *iso*Lupenyl acetate gives a yellow coloration with tetranitromethane in chloroform solution.

(b) Lupeol hydrochloride (0·5 g.) was heated under reflux with acetic anhydride for 20 hours. The crystalline mass separating on cooling was recrystallised from alcohol, giving *iso*lupenyl acetate in plates, m. p. 269—270°, identical with that described under (a).

Acetate, m. p. 231—232°.—The alcoholic hydrogen chloride mother-liquors obtained in the preparation of lupeol hydrochloride were diluted with water and the solid was collected, dried, and heated under reflux with acetic anhydride (20 c.c.) for 2 hours; the product was fractionally crystallised from alcohol. The less soluble fraction was repeatedly crystallised from methyl alcohol, giving a further small quantity of *iso*lupenyl acetate. The more soluble fraction was crystallised six times from alcohol and six times from ethyl alcohol–methyl alcohol; the *acetate* was then obtained in needles with the constant m. p. 231—232° (Found: C, 81·8; H, 10·8. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%).

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