

253. *The Oxidation of Lupenyl Esters.*

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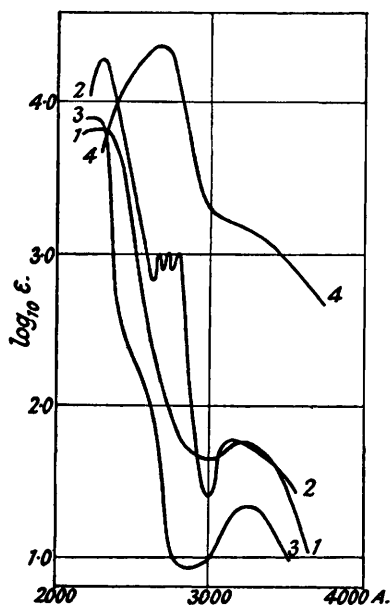
An examination of the absorption spectra of ketolupeol and its derivatives, originally prepared by Ruzicka and Rosenkranz (*Helv. Chim. Acta*, 1939, 22, 778) by selenium dioxide oxidation of lupenyl esters, has revealed that these ketones are $\alpha\beta$ -unsaturated, this decision being confirmed by the ultra-violet absorption of *ketolupenyl acetate semicarbazone*, which is typical for the semicarbazone of an $\alpha\beta$ -unsaturated ketone.

Ozonolysis of ketolupenyl acetate gives excellent yields of a crystalline acetate-acid, $C_{30}H_{50}O_4$, which has proved to be identical with an acid isolated by Duerden, Heilbron, McMeeking, and Spring (J., 1939, 322) from the acidic products of the ozonolysis of lupenyl acetate itself.

By the oxidation of lupenyl acetate and benzoate with selenium dioxide in benzene solution Ruzicka and Rosenkranz (*loc. cit.*) obtained products described as ketolupenyl acetate and ketolupenyl benzoate, but although the latter was hydrolysed to a ketolupeol, no evidence that the ketolupenyl acetate was derived from the same keto-alcohol was

given. We have confirmed the work of the Swiss authors in the preparation of these ketones, and in addition the ketolupeol produced by hydrolysis of ketolupenyl acetate has been converted into ketolupenyl benzoate, identical with that obtained by direct oxidation of lupenyl benzoate.

Ruzicka and Rosenkranz examined the absorption spectra of ketolupeol and its esters and concluded that the chromophore was a carbonyl group with no double bond in the $\alpha\beta$ -position. We have investigated the absorption spectra of these compounds and although the curves we obtain (see Figure) are similar to those given by Ruzicka and Rosenkranz we cannot agree with the conclusions drawn by these authors concerning the nature of the chromophoric group present. It is well known that isolated carbonyl groups exhibit either absorption maxima or inflexions of low intensity in the region of



Curve.

1. Ketolupeol.
2. Ketolupenyl benzoate.
3. Ketolupenyl acetate.
4. Ketolupenyl acetate semicarbazone.

Solvents.

1. Alcohol.
2. Alcohol-chloroform.
3. Alcohol.
4. Alcohol.

2800 A., and that $\alpha\beta$ -unsaturated ketones or aldehydes usually show a band of high intensity at 2200—2500 A., and the characteristic low-intensity carbonyl band is displaced to longer wave-lengths (3150—3300 A.). Ketolupeol and its two derivatives all exhibit secondary maxima at 3150—3300 A., and all three ketones show absorption of a high intensity at 2200—2300 A., although a well-defined maximum cannot be discerned except in the case of ketolupenyl benzoate. From these considerations it appears that ketolupeol is an $\alpha\beta$ -unsaturated ketone, and it is to be anticipated that in ketones in which the $\alpha\beta$ -ethenoid linkage is exocyclic the high-intensity maximum would be somewhat displaced towards the ultra-violet from the position normally observed with cyclic compounds.

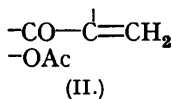
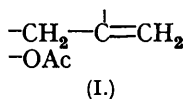
In view of the conclusions of Ruzicka and Rosenkranz we felt that further evidence of the conjugation in ketolupeol might be considered necessary and consequently we have prepared *ketolupenyl acetate semicarbazone*, m. p. 251° (decomp.), and determined that it has a maximum absorption at 2650 A. (Figure). Ruzicka, Huber, Plattner, Deshapande, and Studer (*Helv. Chim. Acta*, 1939, 22, 716) have demonstrated quite clearly that the semicarbazones of saturated ketones exhibit absorption of high intensity at 2200—2300 A., and the same authors quote the observation of Menschick, Page, and Bossert (*Annalen*, 1932, 495, 225) that the semicarbazones of $\alpha\beta$ -unsaturated ketones have maxima of high intensity at about 2650 A.

Although ketolupeol and its derivatives give no colorations with tetranitromethane, ketolupenyl acetate reacts slowly with perbenzoic acid, taking up the equivalent of one atom of oxygen during a week, and both ketolupeol and its acetate react with osmium tetroxide in ethereal solution. That the exocyclic methylene group of lupeol is also to be found in ketolupeol was readily proved by ozonolysis of ketolupenyl acetate in acetic acid solution, formaldehyde being produced in 33% yield. In addition, it was possible to isolate a crystalline acetate-acid, m. p. 260—261° (decomp.), in extremely good yield. This acid has been further characterised by the preparation of several derivatives and analyses indicate the formula $C_{28}H_{48}O_3$ for the parent hydroxy-acid. Duerden, Heilbron, McMeeking, and Spring (*loc. cit.*) describe the isolation of a hydroxy-acid A, $C_{30}H_{50}O_3$ or $C_{29}H_{48}O_3$, from the acidic products of the oxidation of lupenyl acetate with ozone. As is shown in the accompanying table, there is agreement between the m. p.'s of their acid and its derivatives and of our product obtained from ketolupenyl acetate. No rotations of this acid-A had been described in the previous work and hence it was considered necessary, in order to confirm the identity of the two materials, to reinvestigate the ozonolysis

	Acetate-acid.		Acetate-methyl ester.		Hydroxy-acid.	
	M. p.	$[\alpha]_D^{20}$.	M. p.	$[\alpha]_D^{20}$.	M. p.	$[\alpha]_D^{20}$.
Ozonolysis of lupenyl acetate (Duerden, Heilbron, McMeeking, and Spring)	272°	—	232—234°	—	262—264°	—
Ozonolysis of ketolupenyl acetate (Jones and Meakins)	260—261 (decomp.)	+10°	233	-4.0°	260—261	-25°
(a) <i>In chloroform.</i>						
Ozonolysis of lupenyl acetate (Jones and Meakins)	258—260 (decomp.)	+ 8.3			260—261	-22
(b) <i>In acetic acid.</i>						
	261—262 (decomp.)	—			260	-23

of lupenyl acetate. Repetition of the oxidation in chloroform solution gave a product identical with that from the ozonolysis of ketolupenyl acetate (Table). The same acid was obtained by using acetic acid as the solvent, but in addition an *acetate-acid*, m. p. 285—286° (decomp.), $[\alpha]_D^{20} = 9.7^\circ$ [methyl ester, m. p. 242—245° (decomp.)], was isolated in poor yield. From a comparison of the optical rotations it is obvious that this acetate-acid is not identical with either of the acids isolated by chromic acid oxidation of lupenyl acetate (Duerden, Heilbron, McMeeking, and Spring, *loc. cit.*; Ruzicka, Schellenberg, and Rosenkranz, *Helv. Chim. Acta*, 1938, 21, 1391) or of lupenyl acetate oxide (Ruzicka and Rosenkranz, *loc. cit.*). The presence of traces of this new acid might possibly explain the discrepancy between the m. p.'s of the acetate-acid obtained in this and in the previous work.

Since the same acetate-monocarboxylic acid (III) is obtained by ozonolysis either of lupenyl acetate (I) or of ketolupenyl acetate (II), where in the latter a methylene group adjacent to the ethenoid linkage is replaced by a carbonyl group, it would be expected



that the parent hydroxy-acid could contain no more than 28 carbon atoms, a conclusion which is in complete agreement with the analytical data. Although it is realised that the results described in this paper could be interpreted more easily by assuming that the ethenoid linkage of lupeol is present in a side chain of at least three carbon atoms, much of the previous work in this field would be directly opposed to such an assumption.

EXPERIMENTAL.

All m. p.'s are uncorrected. Analytical specimens were dried at 110° in a high vacuum for 3 hours. Rotations, except where otherwise stated, were done in chloroform solution in a 1 dcm. tube.

Ketolupenyl Benzoate.—Lupenyl benzoate (5 g.) was oxidised as described by Ruzicka and Rosenkranz (*loc. cit.*) and after being purified twice by adsorption on alumina the product was crystallised from chloroform-methyl alcohol and then twice from acetone, ketolupenyl benzoate (2.2 g.) separating from the latter solvent in flat needles, m. p. 265—267° (slight decomp.) [Ruzicka and Rosenkranz give m. p. 268.5° (corr.)], $[\alpha]_D^{20} + 37.5^\circ$ ($c = 1.15$) (Found: C, 81.6; H, 9.8. Calc. for $\text{C}_{27}\text{H}_{52}\text{O}_3$: C, 81.6; H, 9.6%). *Light absorption* (Figure): Maxima, 2290 and 3150 Å.; $\log \epsilon = 4.3$ and 1.9 respectively. Inflexion, 2730 Å.; $\log \epsilon = 2.9$. Either unchanged material or intractable resins were obtained in numerous attempts to hydrolyse the benzoate, although Ruzicka and Rosenkranz successfully prepared ketolupenyl in this manner.

Ketolupenyl Acetate.—Lupenyl acetate (12.4 g.) was oxidised as described by Ruzicka and Rosenkranz for 66 hours only, and after two purifications by adsorption, the product was crystallised from chloroform-methyl alcohol and alcohol, yielding ketolupenyl acetate (7 g.) in short rods, m. p. 221—222° [lit., m. p. 224—226° (corr.)], $[\alpha]_D^{20} + 17^\circ$ ($c = 1.4$) (Found: C, 79.25; H, 10.5. Calc. for $\text{C}_{22}\text{H}_{50}\text{O}_3$: C, 79.6; H, 10.45%). *Light absorption* (Figure): Maxima, 2250 and 3250 Å.; $\log \epsilon = 3.8$ and 1.3 respectively. A solution of ketolupenyl acetate (99 mg.) in chloroform (40 c.c.) was treated with a solution of perbenzoic acid in chloro-

form (2 c.c., 0.7N), and the mixture set aside at 0°. From time to time 2 c.c. samples of the solution were treated with potassium iodide and titrated with standard thiosulphate, the titres being compared with a blank containing no ketolupenyl acetate.

Time (hours)	24	48	112	168
Atoms of oxygen	0.4	0.7	0.8	0.93

Semicarbazone. A solution of ketolupenyl acetate (200 mg.) and semicarbazide acetate (200 mg.) in aqueous alcohol was heated under reflux for 2 hours. The residue obtained on removal of the solvent under reduced pressure was thoroughly washed with hot water and after two crystallisations from benzene, *ketolupenyl acetate semicarbazone* was obtained in microscopic plates, m. p. 251° (decomp.) (Found: C, 73.0; H, 10.0. $C_{33}H_{53}O_3N_3$ requires C, 73.5; H, 9.9%). *Light absorption* (Figure): Maxima, 2650 Å.; $\log \epsilon = 4.4$.

Prepared in the usual manner with 2:4-dinitrophenylhydrazine sulphate in alcohol, the 2:4-dinitrophenylhydrazone separated from benzene-alcohol in yellow plates, m. p. 252° (decomp.). The m. p. varies with rate of heating (Found: N, 8.6. $C_{35}H_{54}O_6N_4$ requires N, 8.4%).

Ketolupeol.—A solution of ketolupenyl acetate (200 mg.) and potassium hydroxide (200 mg.) in methyl alcohol (7 c.c.) was heated under reflux for 2 hours. The solid obtained on dilution with water was well washed and crystallised successively from methyl alcohol, acetone, and alcohol, yielding ketolupeol (130 mg.), m. p. 225–226°, in fine needles [lit., m. p. 232–233° (corr.)], $[\alpha]_D^{20} + 1.1^\circ$ ($c = 1.7$) (Found: C, 81.4; H, 11.1. Calc. for $C_{30}H_{48}O_2$: C, 81.7; H, 11.0%). *Light absorption* (Figure): Maxima, 2250 and 3180 Å.; $\log \epsilon = 3.8$ and 1.8 respectively. Both ketolupeol and its acetate react with osmium tetroxide in anhydrous ether, but as yet no homogeneous hydroxylation products have been isolated.

Acetate. Treatment with acetic anhydride and pyridine at 100° yielded ketolupenyl acetate, m. p. 221–222°, undepressed on admixture with an authentic specimen.

Benzoate. A solution of ketolupeol (380 mg.) in dry pyridine (5 c.c.) and benzene (30 c.c.) was treated dropwise with benzoyl chloride (1 c.c.), and the mixture heated on the steam-bath for 4 hours. Isolation by means of ether and crystallisation of the product from chloroform-methyl alcohol and then thrice from acetone yielded ketolupenyl benzoate, m. p. 263–265° (decomp.), undepressed on admixture with a specimen prepared by the oxidation of lupenyl benzoate. $[\alpha]_D^{20} + 36^\circ$ ($c = 1.3$).

Ozonolysis of Ketolupenyl Acetate.—A stream of ozonised oxygen was passed into a solution of ketolupenyl acetate (2 g.) in purified acetic acid (120 c.c.) for 4 hours, the issuing gases being led through water. The aqueous washings were then combined with the acetic acid solution, and the mixture distilled in steam until about 800 c.c. of distillate had been collected. The distillate was treated with dimedon solution; on standing, the formaldehyde derivative crystallised, 390 mg. of dried product, m. p. 186–187°, being obtained. It gave no depression in m. p. on admixture with an authentic specimen and corresponds to a 33% yield of formaldehyde.

The residual resinous solid was taken up in ether and on shaking with 2N-sodium hydroxide a crystalline sodium salt separated at the interface. This was filtered off and acidified, and the acid isolated by means of ether; after successive crystallisations from ethyl acetate, methyl alcohol, and acetone, the acetate-acid (1 g.) was obtained in rods, m. p. 260–261° (decomp.). A further quantity (300 mg.) of the acid was isolated after acidification of the alkaline washings. $[\alpha]_D^{20} + 10^\circ$ ($c = 1.5$) (Found: C, 75.7, 75.7; H, 10.35, 10.3. Calc. for $C_{30}H_{50}O_4$: C, 75.9; H, 10.6%). The acid was recovered unchanged after refluxing for 3 hours with semicarbazide acetate in alcohol, and showed no absorption of appreciable intensity in the ultra-violet. The acetate-methyl ester, obtained by means of diazomethane, crystallised from methyl alcohol in plates, m. p. 233°, undepressed on admixture with a specimen obtained by Duerden, Heilbron, McMeeking, and Spring (*loc. cit.*) by the ozonolysis of lupenyl acetate. $[\alpha]_D^{20} - 4.0^\circ$ ($c = 1.5$) (Found: C, 76.0; H, 10.6. Calc. for $C_{31}H_{52}O_4$: C, 76.2; H, 10.7%). The ester was hydrolysed to acid to the extent of only 20% on heating under reflux with alcoholic potassium hydroxide (5%) for 3 hours.

Hydroxy-acid, m. p. 260–261°.—A solution of the acetate-acid (250 mg.) in methyl alcohol (10 c.c.) was heated under reflux for 4 hours with potassium hydroxide (300 mg.). After acidification with dilute acid, the product, isolated with ether, was thrice crystallised from methyl alcohol, the hydroxy-acid separating in a felt of fine needles, m. p. 260–261°, $[\alpha]_D^{20} - 25^\circ$ ($c = 1.3$ in pyridine). Satisfactory analytical data for the acid could not be obtained, even after crystallisation from benzene, probably owing to retention of solvent. Duerden, Heilbron,

McMeeking, and Spring were similarly unable to obtain satisfactory analytical data for their hydroxy-acid-A [Found : C, 76.4, 76.6; H, 11.0, 10.6; *M* (titration), 431, 435, 432. Calc. for $C_{28}H_{48}O_3$: C, 77.7; H, 11.2%; *M*, 432.5]. The *methyl* ester, prepared with diazomethane in ether, was crystallised thrice from methyl alcohol and finally from light petroleum (b. p. 40—60°), from which solvents it separated in fine needles, m. p. 220—221°, $[\alpha]_D^{20} - 22^\circ$ ($c = 1.65$). Unsatisfactory analyses were obtained with specimens crystallised from methyl alcohol alone (Found : C, 78.3; H, 11.2. $C_{29}H_{50}O_3$ requires C, 78.0; H, 11.3%). The ester was hydrolysed to the acid to the extent of 60% on heating under reflux with alcoholic potassium hydroxide (10%) for 3 hours.

Ozonolysis of Lupenyl Acetate.—(a) *In chloroform.* Ozonised oxygen was passed into a solution of lupenyl acetate (4.3 g.) in purified chloroform (40 c.c.) for 6 hours at 20°. The reaction mixture was distilled with steam, and the residual resinous solid taken up in ether. The ethereal solution was washed with potassium hydroxide solution (10%), the combined washings and gummy potassium salts acidified with hydrochloric acid, and the product isolated with ether. The solid acid (1.4 g.) was repeatedly crystallised from ethyl acetate and then from methyl alcohol, yielding the acetate-acid, m. p. 258—260° (decomp.), not depressed on admixture with the acetate-acid obtained by ozonolysis of ketolupenyl acetate. $[\alpha]_D^{20} + 8.3^\circ$ ($c = 1.5$). Hydrolysis of the acetate-acid (160 mg.) under reflux for 3½ hours yielded the hydroxy-acid, which after three crystallisations from alcohol had m. p. 260—261°, undepressed on admixture with a specimen obtained from the ozonolysis product of ketolupenyl acetate. $[\alpha]_D^{20} - 22^\circ$ ($c = 1.6$ in pyridine).

(b) *In acetic acid.* Ozonised oxygen was passed into a suspension of lupenyl acetate (5.3 g.) in purified acetic acid (200 c.c.) at 20° for 4 hours, solution being complete after 2 hours. The reaction mixture was distilled in steam, and the distillate (1 l.) treated with dimedon; the formaldehyde-dimedon derivative (950 mg., 30%), m. p. 186—187°, undepressed on admixture with an authentic specimen, was obtained.

An ethereal solution of the residual solid was washed with sodium hydroxide solution (10%) and after acidification of the alkaline washings the acid product (1.5 g.) was isolated by means of ether. Repeated crystallisation from alcohol gave an *acetate-acid* (50 mg.) as a microcrystalline powder, m. p. 285—286° (decomp.), $[\alpha]_D^{20} - 9.7^\circ$ ($c = 1.5$) (Found : C, 76.3; H, 10.35. $C_{31}H_{50}O_4$ requires C, 76.5; H, 10.4%). The methyl ester, prepared with diazomethane, could not be readily purified and after numerous recrystallisations had m. p. 242—245° (decomp.). Shortage of material precluded further examination of this acid.

The combined mother-liquors obtained from the purification of the acetate-acid, m. p. 285—286°, were evaporated, and the residue (1.4 g.) was hydrolysed, yielding, after three crystallisations of the product from alcohol, the hydroxy-acid, m. p. 260°, undepressed on admixture with the hydroxy-acid obtained either by method (a) or by the ozonolysis of ketolupenyl acetate. $[\alpha]_D^{20} - 23^\circ$ ($c = 1.8$ in pyridine). Acetylation gave the acetate-acid, m. p. 261—262° (decomp.), indistinguishable from an authentic specimen.

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