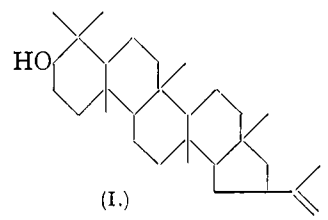
135. *The Constitution of Lupeol.*

By E. R. H. Jones and R. J. Meakins.

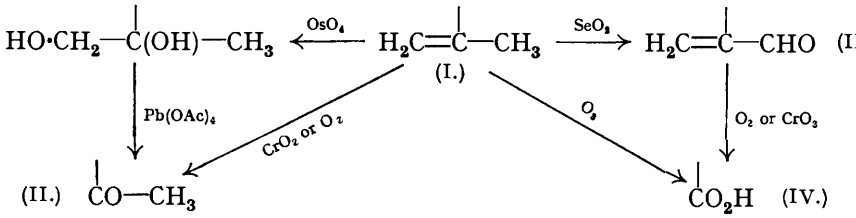
The non-reactivity of the carbonyl and the carboxyl group in norlupanonol and bisnorlupanolic acid respectively indicates that the *iso*propenyl group in lupeol is attached to a quaternary carbon atom of the polycyclic system, and a modification of the formula proposed by Ruzicka and Rosenkranz (*Helv. Chim. Acta*, 1940, **23**, 1311) is suggested. The preparation of a number of lupane derivatives required for surface-film measurements is described.

In a previous publication (Jones and Meakins, J., 1940, 1335) it was suggested that the behaviour on oxidation of lupenyl esters and their selenium dioxide oxidation products 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. At almost the same time Ruzicka and Rosenkranz (*loc. cit.*) published evidence which indicated that the unsaturated centre of lupeol is located in an *iso*propenyl group and that this triterpene alcohol could well be represented by the formula (I). On this basis norlupanonol, $C_{29}H_{48}O_3$, obtained by lead tetra-acetate oxidation of lupanetriol (Jones and Meakins J., 1940, 456), or in poor yield by oxidation of lupenyl esters with ozone or chromic acid (Heilbron, Kennedy, and Spring, J., 1938, 329), is represented by the partial formula (II), lupenalol (formerly ketolupeol), $C_{30}H_{48}O_2$, an $\alpha\beta$-unsaturated aldehyde produced on selenium dioxide oxidation of lupenyl esters (Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1939, **22**, 778; 1940, **23**, 1311; Jones and Meakins, J., 1940, 1335), is formulated as (III), and bisnorlupanolic acid, $C_{28}H_{46}O_3$, obtained by ozonolysis either of esters of lupeol or of lupenalol (Jones and



(I.)

Meakins, J., 1940, 1335), must be represented by (IV). The lupeol constitution (I), proposed by Ruzicka and Rosenkranz, is acceptable on the basis of the " isoprene " rule



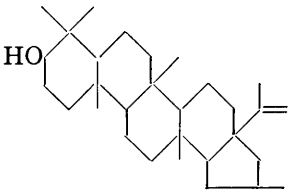
and also provides an explanation of the absence of 1 : 8-dimethylpicene and 1 : 2 : 7-trimethylnaphthalene, and the isolation of only 1 : 2 : 5-trimethylnaphthalene and 6-hydroxy-1 : 2 : 5-trimethylnaphthalene on selenium dehydrogenation (Ruzicka, Furter, Pieth, and Schellenberg, *Helv. Chim. Acta*, 1937, **20**, 1564; Heilbron, Kennedy, and Spring, *loc. cit.*).

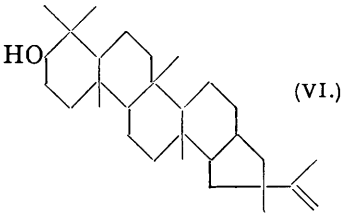
It was mentioned (J., 1940, 1335) that certain of the experimental results obtained in the lupeol field are opposed to the assumption that this triterpene alcohol contains a side chain of at least three carbon atoms and in view of the publication of such a suggestion by Ruzicka and Rosenkranz (*loc. cit.*) it becomes necessary to consider these objections in the light of this recent work. Heilbron, Kennedy, and Spring (*loc. cit.*) and Biedebach (*Arch. Pharm.*, 1939, **277**, 163) were unable to prepare ketonic derivatives of norlupanonyl acetate (II) and Jones and Meakins (J., 1940, 456) recovered unchanged norlupanonol on attempted oximation, a behaviour which could not readily be interpreted on formula (I) for lupeol, since it is well known that progesterone easily forms a dioxime (Butenandt and Schmidt, *Ber.*, 1934, **67**, 1901). Ruzicka and Rosenkranz (*Helv. Chim. Acta*, 1940, **23**, 1311), however, succeeded in isolating an oxime of norlupanonol under the usual conditions. In spite of a number of attempts under these and other conditions we have been unable to confirm this result, intractable resins or unchanged material invariably being obtained. Neither was success achieved on attempted oximation in pyridine solution and norlupanone (*q.v.*) was also recovered unchanged under the oximation conditions described by Ruzicka and Rosenkranz. It should also be noted that closely analogous products in the betulin series, diacetoxynorlupanone (Ruzicka and Brenner, *Helv. Chim. Acta*, 1940, **23**, 1325) and the methyl ester of norlupanonolic acid (Ruzicka and Lamberton, *ibid.*, p. 1338) also failed to yield crystalline ketonic derivatives. Heilbron, Kennedy, and Spring (*loc. cit.*) observed that norlupanonyl acetate is extremely resistant to oxidation, being unaffected by prolonged treatment with chromic anhydride in boiling acetic acid. We have confirmed this observation and it has also been found that this keto-acetate is not oxidised either with alkaline hypobromite at 20° for 72 hours or with selenium dioxide in boiling benzene for 7 hours. Further, the reduction of norlupanonyl acetate with sodium and alcohol gives norlupanediol in poor yield, and reduction of norlupanone to norlupanol (*q.v.*) by the latter method or with aluminium *iso*propoxide in *iso*propyl alcohol is also difficult. The methyl ester-acetate of bisnorlupanolic acid is practically unaffected by heating under reflux with 10% methyl-alcoholic potassium hydroxide for 16 hours (Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1940, **23**, 1311; see also Jones and Meakins, J., 1940, 1335). In an attempt to carry out a Wieland degradation on bisnorlupanolic acid methyl ester (m. p. 189°; $[\alpha]_D^{20°}$ — 18·7° in chloroform) this substance was recovered quantitatively after treatment with phenylmagnesium bromide, a result which was somewhat unexpected in view of the success obtained by Wieland, Schlichting, and Jacobi (*Z. physiol. Chem.*, 1926, **161**, 80) in the degradation of ætiocholanic acid.

This general lack of reactivity of the methyl ketone group of norlupanonol (II) and of the carboxyl group of bisnorlupanolic acid (IV) would hardly be expected if these were located on a tertiary carbon atom as in the formulation (I). A possible explanation of the inert nature of these substances is afforded if the *iso*propenyl group of lupeol is considered to be attached to the quaternary carbon atom between two rings as in formula (V) or to a carbon atom which also carries a methyl group as in formula (VI). These two formulations are both in accordance with the " isoprene rule " and as a result of surface-film experiments on lupane derivatives containing water-attracting groups introduced into or in place of the

*iso*propenyl group of α-lupene (see following paper), formula (VI) may be preferred. The small limiting area values obtained with these compounds make it improbable that the

(V.)





(VI.)

*iso*propenyl group could be located elsewhere than at an extremity of the polycyclic system, suggesting that lupeol is better represented by structure (VI). The fact that the hydrolysis of bisnorlupanolic esters is more facile than that of esters in the oleanolic acid series can also be regarded as evidence for constitution (VI) rather than (V). This argument is based on the accepted formula for oleanolic acid; a modification of this, however, has recently been suggested by Bilham and Kon (this vol., p. 552).

A number of lupane derivatives were prepared for the surface-film experiments described in the following paper. A considerably improved yield (95%) in the conversion of lupenone into α-lupene has been obtained by carrying out a modified Kishner–Wolff reduction involving the treatment of lupenone with hydrazine hydrate and sodium ethoxide in an autoclave at 190° (cf. Kon and Soper, J., 1940, 1335). *Lupanediol*, m. p. 242—245°, was obtained by the action of osmium tetroxide on α-lupene, and the diol was oxidised to *norlupanone*, m. p. 172—173°, with lead tetra-acetate. Reduction of this ketone with sodium and alcohol or by the Ponndorf method yielded *norlupanol*, m. p. 160—161° (*acetate*, m. p. 166—167°). Lupenal was obtained by prolonged oxidation of α-lupene with selenium dioxide in benzene before we learned of the more rapid method in acetic acid (Ruzicka and Rosenkranz, *loc. cit.*). This aldehyde on reduction by the Ponndorf method gave *ψ-lupenol*, m. p. 166—167° (*acetate*, m. p. 107·5°). We have found that bisnorlupanic acid, prepared by Ruzicka and Rosenkranz (*loc. cit.*) by the oxidation of lupenal with chromic anhydride, is obtained more readily from the aldehyde by ozonolysis. Reduction of lupenalyl acetate by the Ponndorf method yielded *lupenediol*, m. p. 231—232° (*diacetate*, m. p. 163—164°) and some *lupenediol monoacetate*, m. p. 240—241°. Treatment of lupenyl acetate with osmium tetroxide gave *lupanetriol monoacetate*, m. p. 259—262°.

Experimental.

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

α-Lupene.—A mixture of lupenone (12 g.), sodium (15 g.) in alcohol (300 c.c.), and hydrazine hydrate (80 c.c.; 50%) was stirred and heated in an autoclave at 190° for 6 hours. The crystalline deposit obtained on cooling, together with a further quantity of material from the alcoholic solution, on crystallisation from alcohol (850 c.c.) yielded α-lupene (11·5 g.; 96% yield) in tufts of needles, m. p. 162—163°, undepressed on admixture with an authentic specimen.

Lupanediol (α-Lupene Glycol).—Solutions of α-lupene (1·7 g.) in dry ether (600 c.c.) and osmium tetroxide (1 g.) in dry ether (100 c.c.) were mixed and set aside at 20° for 16 days. The black residue obtained on removal of the ether was heated under reflux with a solution of sodium sulphite (20 g.) in water (200 c.c.) and alcohol (100 c.c.), the liquid filtered, and the residue repeatedly extracted with boiling alcohol. The combined filtrates were evaporated under diminished pressure and an ethereal solution of the residual solid was washed, dried, and evaporated, leaving a residue which was further purified by percolation of an alcoholic solution through a column of activated alumina. Three crystallisations from benzene yielded *lupanediol* (1·1 g.) in tufts of fine needles, m. p. 242—245°, $[\alpha]_D^{20°}$ + 5·1° (c = 1·86 in pyridine) (Found: C, 81·2; H, 11·5. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%). The diol gave no coloration with tetranitromethane in chloroform solution.

Norlupanone.—A solution of lupanediol (1·0 g.) and lead tetra-acetate (1·25 g.) in purified acetic acid (160 c.c.) was set aside at 20° for 18 hours. The solid precipitated from the reaction mixture with water was isolated by means of ether and two crystallisations from alcohol gave *norlupanone* (710 mg.) in flakes, m. p. 172—173°, $[\alpha]_D^{20°}$ − 18·4° (c = 1·72) (Found: C, 84·85;

H, 11·8. $C_{29}H_{48}O$ requires C, 84·4; H, 11·7%). *Light absorption in alcohol:* Maximum 2800 A., log ε = 1·56. The ketone was recovered unchanged on heating under reflux for 4 hours with hydroxylamine acetate in methyl alcohol.

Norlupanol.—(*a*) Norlupanone (190 mg.) was heated under reflux for 24 hours with aluminium *iso*propoxide (300 mg.) in dry *iso*propyl alcohol (15 c.c.), the solvent removed, and the residue treated with dilute hydrochloric acid and ether. The gummy ethereal extract was dissolved in benzene and adsorbed on alumina (15 g.); elution with ether then gave a residue which solidified on trituration with methyl alcohol. After three recrystallisations from the latter solvent *norlupanol* (30 mg.) was obtained in needles, m. p. 160—161°. Owing probably to extensive solvation good analytical data could not be obtained for the free alcohol (Found: C, 84·8; H, 12·2. $C_{29}H_{50}O$ requires, C 84·0; H, 12·15%).

(*b*) To a solution of norlupanone (420 mg.) in boiling alcohol (25 c.c.), sodium (1·6 g.) was added as rapidly as possible. After addition of a further quantity of alcohol (20 c.c.) and sodium (0·8 g.) the mixture was heated under reflux for 2 hours; it was then decomposed with water, and the product isolated with ether. The resinous product was adsorbed on a column of alumina (30 g.) from light petroleum solution (b. p. 40—60°); elution with light petroleum–benzene (1 : 1) yielded a small quantity of starting material, but with ether–benzene (1 : 9) norlupanol was obtained, which after two crystallisations from methyl alcohol had m. p. 160—161° (60 mg.), giving no depression on admixture with the product prepared by method (*a*).

Norlupanyl Acetate.—Prepared in the usual manner in pyridine solution with acetic anhydride, the *acetate* was crystallised first from alcohol and then from acetone, forming needles, m. p. 166—167°, $[\alpha]_D^{20°}$ − 22·4° (*c* = 0·41) (Found: C, 81·5, 81·5; H, 11·5, 11·5. $C_{31}H_{52}O_2$ requires C, 81·6; H, 11·5%).

Lupenal.—α-Lupene (8·5 g.) was heated under reflux for 66 hours in benzene (200 c.c.) with selenium dioxide (2·5 g.; freshly sublimed). The cooled mixture was submitted to filtration, the filtrate evaporated to dryness, and the residue adsorbed from light petroleum (b. p. 40—60°)–benzene (2 : 1) on a column of alumina (500 g.); elution with the same solvent mixture then gave a crystalline product, which on crystallisation first from chloroform–methyl alcohol and then from alcohol yielded lupenal (4 g.) in glistening flakes, m. p. 200°, $[\alpha]_D^{20°}$ + 3·4° (*c* = 2·32) (Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1940, **23**, 1311, give for lupenal prepared in acetic acid solution, m. p. 203° corr., $[\alpha]_D^{20°}$ + 4·3°).

ψ-Lupenol.—A solution of lupenal (1 g.) and aluminium *iso*propoxide (1 g.) in dry *iso*propyl alcohol (100 c.c.) was heated under reflux for 22 hours. Isolated as described above for norlupanol, *ψ-lupenol* after three crystallisations from methyl alcohol was obtained in plates (0·55 g.), m. p. 167—168°, $[\alpha]_D^{20°}$ − 6·50 (*c* = 1·84). With tetranitromethane in chloroform solution it gave a bright yellow colour (Found: C, 84·5; H, 11·7. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). The *acetate*, prepared with acetic anhydride and pyridine, was crystallised twice from methyl alcohol and then twice from alcohol, being obtained in needles, m. p. 107·5°, $[\alpha]_D^{20°}$ − 2·9° (*c* = 1·84) (Found: C, 82·6; H, 11·2. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). Hydrolysis of the acetate with methyl-alcoholic potassium hydroxide gave ψ-lupenol, m. p. 166—167°, undepressed on admixture with the original specimen.

Ozonolysis of Lupenal.—A suspension of lupenal (1·8 g.) in purified acetic acid (150 c.c.) was treated with ozonised oxygen for 5 hours; all the material had then passed into solution. The reaction mixture was distilled with steam, and the solid residue taken up in ether. The acidic product, separated by washing the ethereal solution with aqueous potassium hydroxide (10%), crystallised on trituration with methyl alcohol. Recrystallisation from chloroform–methyl alcohol and thrice from alcohol gave bisnorlupanic acid (350 mg.) in long fine needles, m. p. 237—238°, $[\alpha]_D^{20°}$ −9·2° (*c* = 1·85) [Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1940, **23**, 1311, for a specimen prepared by chromic acid oxidation, give m. p. 238—240° (vac.) corr.; $[\alpha]_D^{20°}$ − 8·8°].

Lupenediol.—A mixture of lupenalyl acetate (1 g.) and aluminium *iso*propoxide (1 g.) in dry *iso*propyl alcohol (75 c.c.) was heated under reflux for 20 hours. The product was isolated in the usual manner and five recrystallisations from benzene gave *lupenediol* (300 mg.) in tufts of needles, m. p. 231—232°, $[\alpha]_D^{20°}$ − 3·5° (*c* = 1·56 in pyridine) (Found: C, 81·6; H, 11·5. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%). Evaporation of the first benzene mother-liquors and repeated crystallisation of the residual solid from alcohol gave some *lupenediol monoacetate* (40 mg.) in short needles, m. p. 240—241°, $[\alpha]_D^{20°}$ + 7·2° (*c* = 2·17) (Found: C, 78·8, 78·8; H, 11·2, 11·0. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). Hydrolysis of this acetyl derivative with alcoholic potassium hydroxide under reflux gave lupenediol, m. p. 228—231°, undepressed on admixture with the specimen described above.

Lupenediol Diacetate.—Prepared with acetic anhydride and pyridine in the cold, the *diacetate*

crystallised from methyl alcohol in glistening prisms, m. p. 163—164°, $[\alpha]_D^{20°}$ + 9·7° (c = 1·89) (Found: C, 77·5; H, 10·6. $C_{34}H_{54}O_4$ requires C, 77·5; H, 10·3%). The diacetate gave a marked yellow colour with tetranitromethane in chloroform solution. No crystalline products, acidic or neutral, could be isolated from the product obtained on ozonolysis of this diacetate in acetic acid solution.

Lupanetriol Monoacetate.—To a solution of lupenyl acetate (1·05 g.) in dry ether, a solution of osmium tetroxide in dry ether (70 c.c.; 1%) was added, and the mixture set aside at 20° for 18 days. The residue obtained on removal of the solvent was heated under reflux for 2 hours with a solution of sodium sulphite (16 g.) in water (120 c.c.) and alcohol (100 c.c.), the solution filtered, and the black precipitate repeatedly extracted with boiling alcohol. The combined filtrates were evaporated, and the residual solid taken up in ethyl acetate, the solution being dried and evaporated. Crystallisation of the residue from acetone gave *lupanetriol monoacetate* (500 mg.) in rosettes of needles, m. p. 259—262°, $[\alpha]_D^{20°}$ + 12·4° (c = 1·76) (Found: C, 76·3; H, 10·95. $C_{32}H_{54}O_4$ requires C, 76·4; H, 10·8%). Hydrolysis of the acetyl derivative with alcoholic potassium hydroxide under reflux for 4 hours gave lupanetriol, m. p. 278—284° (decomp.), undepressed on admixture with an authentic specimen.

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