338. *Lanceol, a Sesquiterpene Alcohol from the Oil of* Santalum lanceolatum. *Part II. Some Observations on the Degradation Product.*

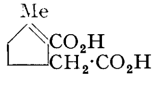
By L. N. Owen.

Syntheses of 3-*methyl*cyclo*pent*-2-*ene*-1-*carboxylic*-1-*acetic acid* (IV) and of 4-*methyl*cyclo*hex*-3-*ene*-1 : 3-*dicarboxylic acid* (III) are described. A compound synthesised by Bradfield, Francis, Penfold, and Simonsen (*J.*, 1936, 1619), originally thought to be the acid (III), is probably the $\beta\gamma$-unsaturated isomer. The acid obtained by ozonolysis of lanceol is shown to be a keto-acid, $C_{11}H_{14}O_5$ (compare Bradfield *et al.*, *loc. cit.*), six possible structures for which are discussed, the most probable being (XV).

The sesquiterpene alcohol, lanceol, $C_{15}H_{24}O$, was shown by Bradfield, Francis, Penfold, and Simonsen (*J.*, 1936, 1619) to give on oxidation an unsaturated acid (*A*), m. p. 174°, to which the formula $C_9H_{12}O_4$ was allocated, and it was further observed that ozonolysis of this acid yielded hexan-5-one-1 : 2-dicarboxylic acid (I). On this basis there are eight possible structures, (II)—

(IX), for the C_9-acid, and these authors described the synthesis of two of these, viz. (II) and (III), neither of which was identical with (*A*); they considered that, of the remaining possible *cyclo*pentene structures, (IV) was the most likely. At the suggestion of Sir John Simonsen, a study of the synthesis of this acid was begun several years ago but had to be temporarily abandoned; more recently, it has been resumed, and the results have led to a re-examination of the whole problem.

$Me{\cdot}CO{\cdot}[CH_2]_2{\cdot}CH(CO_2H){\cdot}CH_2{\cdot}CO_2H$
(I.)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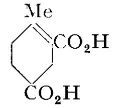
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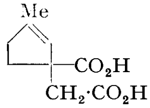
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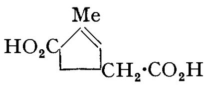
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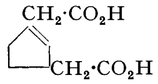
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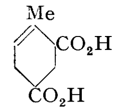
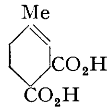
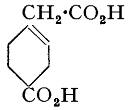
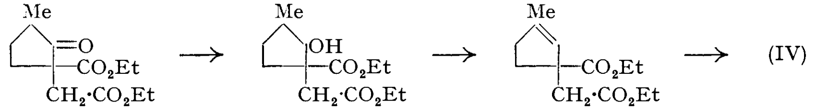

(VII.)


(VIII.)


(IX.)

Ethyl 2-carbethoxy-5-methyl*cyclo*pentan-1-one-2-acetate (X) (Bradfield *et al., loc. cit.*) is not affected by treatment with aluminium amalgam in ether (private communication from Sir John Simonsen) and, although it appeared to be reduced under the Ponndorf conditions with aluminium *iso*propoxide, the product was not homogeneous, probably owing to the occurrence of simultaneous alcoholysis. Catalytic hydrogenation in the presence of Raney nickel, however, gave *ethyl 2-carbethoxy-5-methyl*cyclo*pentan-1-ol-2-acetate* (XI) in good yield. Considerable difficulty was experienced in the subsequent dehydration, and after unsuccessful trials with thionyl chloride and pyridine, with which only sulphur-containing products were obtained, recourse was had to the use of phosphoric oxide in a benzene solution of the hydroxy-ester; this effected partial dehydration and gave a mixture of the required unsaturated ester (XII) with some unchanged (XI). Attempts to carry the dehydration to completion by prolonging the reaction led only to considerable decomposition, and the mixed esters, which could not be satisfactorily separated by distillation, were therefore hydrolysed, and the resulting acids fractionated under high vacuum. A small quantity of *3-methyl*cyclo*pent-2-ene-1-carboxylic-1-acetic acid* (IV), m. p. 158—159°, was thus obtained, the main product being an oily lactone (the formation of isomeric lactonic acids is an obvious side-reaction). The overall yield of (IV) was extremely poor, but its structure was confirmed by ozonolysis to (I); it was clearly not identical with the acid (*A*).


(X.) (XI.) (XII.)

Before proceeding to a consideration of the syntheses of any of the remaining possibilities, the acid (*A*) was subjected to a routine spectrographic examination, and, quite unexpectedly, it showed an absorption band at $\lambda_{max.}$ 2390 A. ($E^{1\%}_{1\,cm.}$ 560). Of the eight structures, only (II) and (III) would be expected to show selective high-intensity absorption above 2000 A.* and, as mentioned above, syntheses of both of these acids had been described by Bradfield *et al.* When, however, the original specimens were examined, it was found that although the acid (II), m. p. 200—202°, showed the expected absorption ($\lambda_{max.}$ 2290 A.; ε 13,800 in alcohol), the acid of m. p. 193—195°, to which the structure (III) had been assigned, showed no selective absorption in this region and consequently could not possess that formula; it nevertheless had given (I) on ozonolysis and must therefore be formulated as the $\beta\gamma$-unsaturated isomer (VII). Support for this conclusion is afforded by the observation that on heating with concentrated aqueous alkali it was partly isomerised into the $\alpha\beta$-form (III), since the product then showed $\lambda_{max.}$ 2280 A. (ε 5000). Bradfield *et al.* (*loc. cit.*, p. 1622) mentioned that the yield of the *cyclo*hexene acid was extremely low, most of the product appearing in the aromatised form, and it is clear that under the vigorous conditions necessary to effect hydrolysis of their cyanide the position of the double

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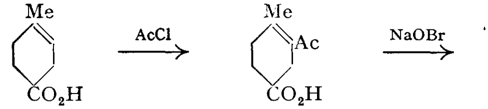
* The wave-length of maximum absorption is somewhat higher than that normally found for $\alpha\beta$-unsaturated acids; an explanation of this anomaly is given later.

bond cannot be regarded as fixed ; by an unusual coincidence the αβ- and βγ-unsaturated isomers give the same products on ozonisation.

Unfortunately, the amount of the original *cyclo*hexene acid, m. p. 193—195°, was insufficient to enable the αβ-unsaturated isomer (III) to be isolated from the alkaline-equilibration mixture, and it was necessary to devise a new synthesis. This was readily achieved by the following route : 4-methyl*cyclo*hex-3-ene-1-carboxylic acid (XIII) (Lehmann and Paasche, *Ber.*, 1935, **68**, 1068), on reaction with acetyl chloride in the presence of stannic chloride and subsequent dehydrochlorination by heating with diethylaniline (compare Ruzicka, Koolhaas, and Wind, *Helv. Chim. Acta*, 1931, **14**, 1151) was converted into 3-*acetyl*-4-*methyl*cyclo*hex*-3-*ene*-1-*carboxylic acid* (XIV), m. p. 78°. Wichterle (*Chem. Abs.*, 1945, **39**, 1841⁹) claimed to have synthesised this keto-acid, and gave m. p. 97°, but his compound was prepared under somewhat vigorous conditions and its structure was not proved. The structure of (XIV) was confirmed by its absorption spectrum and by ozonolysis to (I). It was smoothly oxidised with sodium hypobromite to give 4-*methyl*-cyclo*hex*-3-*ene*-1 : 3-*dicarboxylic acid* (III), m. p. 230°, which showed the expected absorption maximum at 2240 A., the structure being also confirmed by ozonolysis.

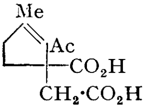


(III)

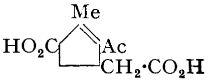
(XIII.) (XIV.)

It is thus established that the acid (*A*) is not identical with either of the two possible αβ-unsaturated acids (II) and (III), and it is necessary to consider more closely the evidence on which the C_9-formula of Bradfield *et al.* is based. The analytical figures given by these authors (Found : C, 58·9; H, 6·3) are in fair agreement with a formula $C_{11}H_{14}O_5$ (requires C, 58·4; H, 6·2%), although the analysis quoted for the *p*-phenylphenacyl ester supports the original C_9-formulation. Only a trace of the original ester was available, but a new preparation, which had the same m. p. (106°), analysed correctly for a derivative of a C_{11} acid; furthermore, a fresh analysis and determination of the equivalent of the acid (*A*) also gave figures in excellent agreement with the formula $C_{11}H_{14}O_5$, whilst on hydrogenation it gave a *dihydro-acid*, $C_{11}H_{16}O_5$. Conclusive evidence is provided by the observation that (*A*) reacts slowly with aqueous 2 : 4-dinitrophenylhydrazine sulphate and also gives a *semicarbazone*; it is therefore a keto-acid, and the position of the wave-length of maximum absorption (anomalous for an αβ-unsaturated acid) indicates that the double bond is conjugated with the carbonyl group.

There are six possible structures (XV)—(XX) [derived by introducing an acetyl group at one end of the double bond in each of the C_9-acids (IV)—(IX)], which agree with these facts and also allow of the formation of (I) on ozonolysis. Bradfield *et al.* pointed out that the acid (*A*) might be a secondary product of the ozonisation of lanceol. On the new formulation this would appear to be even more probable, since the acids (XV)—(XX) could be derived by an intra-molecular aldol condensation from the appropriate diketones, *e.g.*, (XXI). On this basis, formulæ (XVI), (XVII), (XVIII), and (XX), the precursors of which would be β-keto-acids, are perhaps less likely that the other two. The evidence from the absorption spectra supports (XV) rather than (XIX), since the latter, containing the 2-acetyl-1-methyl*cyclo*hexene system, would be expected to show a much lower intensity of maximum absorption than that actually observed (ε 13,000) ; furthermore, the semicarbazone shows maximum absorption at 2680 A., thus differing



(XV.)



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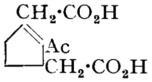
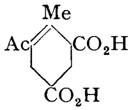


(XVII.



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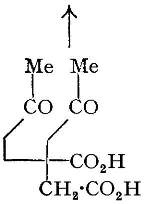
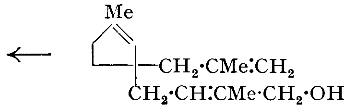
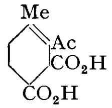


(XXI.)



(XXII.)



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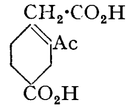

(XX.)

considerably from the semicarbazone of 2-acetyl-1-methyl*cyclo*hexene ($\lambda_{\text{max.}}$ 2350 and 2450 A.) (compare Braude, Jones, Sondheimer, and Toogood, this vol., p. 607; Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *ibid.*, in the press). Formula (XV) is also in agreement with the stability of the acid towards sulphuric acid (Bradfield *et al.*, *loc. cit.*) and accounts for the low reactivity towards 2 : 4-dinitrophenylhydrazine, since the carbonyl group is sterically hindered. It is of interest that Bradfield *et al.* postulated a keto-acid of structure (XV) as a possible intermediate in their scheme of degradation to the supposed C_9 acid, and the structure (XXII) which they advanced as a working basis may indeed be correct for the sesquiterpene alcohol; until further evidence is available, however, the other five formulæ for the keto-acid cannot be disregarded, and the structure of lanceol consequently remains uncertain.

EXPERIMENTAL.

(Absorption spectra were determined in alcohol unless stated otherwise).

Reduction of Ethyl 2-*Carbethoxy*-5-*methyl*cyclo*pentan*-1-*one*-2-*acetate*.—(*a*) The keto-ester (2·8 g.) (Bradfield *et al.*, *loc. cit.*) and aluminium *iso*propoxide (3 g.) in *iso*propanol (30 c.c.) were heated under almost total reflux, the temperature of the oil-bath being adjusted so that the distillation rate was *ca.* 2 c.c. per hour. After 30 hours (during which time more *iso*propanol was added when necessary) no more acetone appeared to be distilling, and the remaining solvent was then removed under reduced pressure. The residue was dissolved in dilute hydrochloric acid, the oil removed in ether, and the aqueous portion extracted twice with ether. The combined ethereal solutions were evaporated to an oil, which on distillation gave a main fraction (3·3 g.), b. p. 195°/17 mm., $n_{\text{D}}^{22^\circ}$ 1·4340 (Found : C, 62·2; H, 8·9%), probably consisting mainly of the di*iso*propyl ester of the hydroxy-acid ($C_{15}H_{26}O_5$ requires C, 62·9; H, 9·2%); the high yield also indicates the occurrence of alkoxy-interchange.

(*b*) The keto-ester (5·5 g.) and Raney nickel (*ca.* 2 g.) in ethanol (100 c.c.) were stirred under hydrogen at 100°/50 atm. for 6 hours. The filtered solution was evaporated to an oil, which on distillation furnished *ethyl* 2-*carbethoxy*-5-*methyl*cyclo*pentan*-1-*ol*-2-*acetate* (XI) (5·0 g.), b. p. 166—168°/15 mm., $n_{\text{D}}^{20^\circ}$ 1·4610 (Found : C, 60·5; H, 8·4. $C_{13}H_{22}O_5$ requires C, 60·4; H, 8·6%).

Dehydration of the Hydroxy-ester (XI).—The ester (4·75 g.) was gradually added to a stirred suspension of phosphoric oxide (5 g.) in benzene (30 c.c.). After being stirred at room temperature for 2 hours and heated under reflux for a further 20 minutes, the solution was filtered and evaporated to an oil. Distillation gave 2·5 g., b. p. 162°/16 mm., $n_{\text{D}}^{18^\circ}$ 1·4580, which was unsaturated towards alkaline permanganate but evidently still contained some hydroxy-ester (Found : C, 63·7; H, 8·2. Calc. for $C_{13}H_{20}O_4$: C, 65·0; H, 8·4%).

3-*Methyl*cyclo*pent*-2-*ene*-1-*carboxylic*-1-*acetic Acid* (IV).—The above unsaturated ester (2·5 g.) was heated under reflux with methanolic potassium hydroxide (50 c.c.; 0·7 N.) for 7 hours. The cooled solution was then treated with a slight deficiency of aqueous sulphuric acid (49·5 c.c.; 0·7 N.) and evaporated to dryness under reduced pressure. Extraction of the residue with boiling dry acetone furnished an oil, which distilled at 100—120° (bath temp.)/10^{-5} mm. (1·8 g.), and partly crystallised after a year. The solid *acid* was drained on porous tile and recrystallised from water; it formed needles (0·1 g.), m. p. 158—159° (Found : C, 59·0; H, 6·8. $C_9H_{12}O_4$ requires C, 58·7; H, 6·6%); it rapidly reduced alkaline permanganate, and on ozonolysis in aqueous sodium carbonate solution gave hexan-5-one-1 : 2-dicarboxylic acid, m. p. 118°. The liquid portion appeared to consist mainly of an isomeric lactonic acid [Found : equiv. (by direct titration with aqueous alkali), 149, (by heating with excess alkali), 93. $C_9H_{12}O_4$ requires equiv. (as lactonic acid), 184, (as dibasic acid), 92].

Action of Alkali on 4-*Methyl*cyclo*hex*-4-*ene*-1 : 3-*dicarboxylic Acid* (VII).—The acid (30 mg.), m. p. 193—195°, in 25% aqueous potassium hydroxide (0·3 c.c.) was heated in a sealed tube for 10 hours at 100°. The cooled solution was acidified with excess of hydrochloric acid and evaporated to dryness. Extraction of the residue with dry acetone gave a solid acid (25 mg.), m. p. 160—180°, which crystallised from water in nodules, m. p. 175—180°. Light absorption : $\lambda_{\text{max.}}$ 2280 A.; ε, 5000.

3-*Acetyl*-4-*methyl*cyclo*hex*-3-*ene*-1-*carboxylic Acid* (XIV).—Finely powdered 4-methyl*cyclo*hex-3-ene-1-carboxylic acid, m. p. 98—99° (16·5 g.) (Lehmann and Paasche, *loc. cit.*), was added in small portions to a stirred solution of stannic chloride (30 g.) and acetyl chloride (10 g.) in carbon disulphide (100 c.c.) at −15°, a viscous lower layer gradually separating. Stirring was continued while the mixture was allowed to warm to room temperature, and next morning the complex was decomposed by the addition of crushed ice. Chloroform (100 c.c.) was added, the lower organic layer separated, and the aqueous portion extracted twice with more chloroform. The combined chloroform extracts were washed with water, dried ($CaCl_2$), and evaporated to a brown oil (17 g.), which was heated with diethylaniline (20 g.) at 180° for 3 hours; the mixture was then cooled, dissolved in excess of dilute hydrochloric acid, and extracted four times with ether. The ethereal extracts were washed with dilute hydrochloric acid and then with water, dried ($CaCl_2$), and evaporated to an oil, distillation of which gave (i) 6·6 g. of unchanged starting material, b. p. 110—112°/0·5 mm., which solidified, and (ii) 2·5 g., b. p. 140—145°/0·1 mm., which slowly crystallised when kept and on recrystallisation from benzene–light petroleum (b. p. 40—60°) formed needles of 3-*acetyl*-4-*methyl*cyclo*hex*-3-*ene*-1-*carboxylic acid*, m. p. 78°, unchanged on further recrystallisation (Found : C, 66·1; H, 8·0. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·75%). Light absorption : $\lambda_{\text{max.}}$ 2440 A.; ε, 7500. The comparatively low intensity is characteristic of a 2-substituted acetyl*cyclo*hexene (cf. Braude *et al.*, *loc. cit.*). Ozonisation of the keto-acid in aqueous sodium carbonate solution gave hexan-5-one-1 : 2-dicarboxylic acid, which crystallised from ethyl acetate in prisms, m. p. and mixed m. p. 118—119°.

4-*Methyl*cyclo*hex*-3-*ene*-1 : 3-*dicarboxylic Acid* (III).—A solution of sodium hypobromite, prepared by the addition of bromine (1·35 g.) to sodium hydroxide (1 g.) in water (8 c.c.) at −5° was added to the keto-acid (0·5 g.) in a solution of sodium hydroxide (0·15 g.) in water (3 c.c.) at −5°, the temperature being kept below 0° during the addition. The solution was then set aside at room temperature for 2 hours, and the slight excess of hypobromite was removed by the addition of a trace of sodium hydrogen sulphite. The lower layer of bromoform was diluted with several volumes of light petroleum to facilitate its removal, and the aqueous portion was then acidified with concentrated hydrochloric acid. A white solid separated, which was collected and recrystallised from boiling water (25 c.c.) to give fine needles (0·46 g.) of 4-*methyl*cyclo*hex*-3-*ene*-1 : 3-*dicarboxylic acid,* m. p. 230° (Found : C, 58·9; H, 6·8. $C_9H_{12}O_4$ requires C, 58·7; H, 6·6%). Light absorption : $\lambda_{max.}$ 2240 A. ; ε, 10,700. It was practically insoluble in cold, but soluble in about 50 parts of boiling water. On ozonolysis in sodium carbonate solution it gave hexan-5-one-1 : 2-dicarboxylic acid, m. p. and mixed m. p. 118—119°.

Structure of the Acid (A).—The acid recrystallised from water in plates, m. p. 174° (Found : C, 58·45; H, 6·4; equiv., 113·5. $C_{11}H_{14}O_5$ requires C, 58·4; H, 6·2%; equiv., 113). Light absorption : $\lambda_{max.}$ 2390 A. ; ε, 13,000. The di-*p*-phenylphenacyl ester, crystallised from methanol, had m. p. 105—106° (Found : C, 76·05; H, 5·8. Calc. for $C_{39}H_{34}O_7$: C, 76·2; H, 5·6%). The *semicarbazone* was prepared by keeping the acid (50 mg.), semicarbazide hydrochloride (35 mg.), and a slight excess of sodium acetate in water (1 c.c.), at room temperature during 10 days; after acidification with concentrated hydrochloric acid (0·1 c.c.) it slowly separated as a crystalline powder which crystallised from hot water in prisms (30 mg.), m. p. 154° (Found : C, 49·4; H, 6·4; N, 14·3. $C_{12}H_{17}O_5N_3,\frac{1}{2}H_2O$ requires C, 49·3; H, 6·2; N, 14·4%). Light absorption : $\lambda_{max.}$ 2680 A. ; ε, 24,000 (in dioxan).

Hydrogenation.—The acid (*A*) (0·2 g.) in 50% acetic acid (3 c.c.) was shaken with hydrogen in the presence of a 10% palladium–charcoal catalyst (50 mg.). Absorption (20 c.c.) was complete in ½ hour. The solution was evaporated, to give a solid residue of the *dihydro-acid,* which crystallised from ethyl acetate–light petroleum in prisms, m. p. 138° (Found : C, 58·0; H, 7·1. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·1%).

The author is indebted to Sir John Simonsen, F.R.S., at whose suggestion the investigation was taken up, and who has kindly made available the original specimens. Thanks are also due to Dr. E. A. Braude for the valuable evidence afforded by the absorption spectra.

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