

65. α - and β -Santalols.

By A. E. BRADFIELD, A. R. PENFOLD, and J. L. SIMONSEN.

It has been observed by one of us (Penfold, *J. Proc. Roy. Soc. New South Wales*, 1928, 52, 60; 1932, 66, 240) that the essential oil from the wood of *Santalum lanceolatum* contains a lævorotatory sesquiterpenic primary alcohol, $C_{15}H_{24}O$, yielding a crystalline allophanate, m. p. 114°. Since preliminary experiments showed that this alcohol gave acetylcarbinol on oxidation, it was clear that it was closely related to the α - and the β -santalol present in the wood oil from *Santalum album*. Prior to a study of this new alcohol it appeared desirable to elucidate the structure of the dicyclic alcohol, β -santalol, and to determine its relationship to the tricyclic alcohol, α -santalol, the constitution of which has been rigidly established (for references, see Simonsen, "The Terpenes," Vol. II, p. 544).

The separation of the two santalols from each other by fractional distillation is a matter of some difficulty, and Semmler, as the result of some twenty fractionations, records $\alpha_D + 1^\circ$ and -42° for α - and β -santalol respectively. Paolini and Divizia (*Atti R. Accad. Lincei*, 1914, 23, II, 226) after a preliminary fractionation purified the alcohols by fractional crystallisation of the strychnine salts of the hydrogen phthalates and confirmed Semmler's values. Our experience has shown that this method is of little value except for the final purification, since the strychnine salts form mixed crystals.

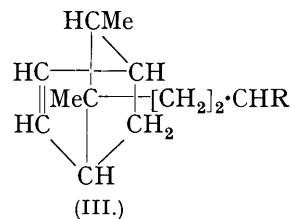
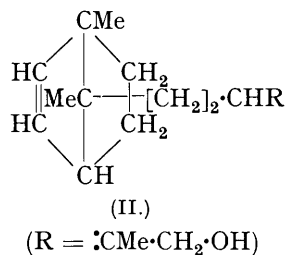
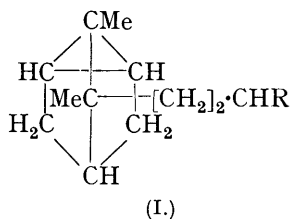
By repeated distillation of Mysore oil from *S. album* under diminished pressure in carbon dioxide through a still-head of special design (Bradfield, *J. Soc. Chem. Ind.*, 1935, 54, 6T), the progress of the separation being followed by observation of rotatory power and by oxidation with percamphoric acid (Milas and McAlevy, *J. Amer. Chem. Soc.*, 1933, 55, 352), we have obtained both α - and β -santalol in a state of purity. α -Santalol has b. p. 166—167°/14 mm., d_{25}^{25} 0.9770, n_D^{25} 1.5017, $\alpha_{5461} + 10.3^\circ$, $\alpha_{5780} + 9.0^\circ$, $[R_L]_D$ 66.4 (calc., 65.93). The observed exaltation agrees well with that anticipated for a substance containing a cyclopropane ring. Apart from the rotatory power, these values are in close accord with those recorded by Semmler and by Paolini and Divizia. We find, however, that the strychnine salt of the hydrogen phthalate has m. p. 144—145°, not 155° as stated by the latter authors. The purity of the alcohol was checked by titration with percamphoric acid, 1.02 mols. of oxygen per mol. being absorbed.*

From the higher-boiling distillate a fraction of β -santalol, b. p. 177—177.5°/17 mm.,

* Mr. B. Sanjiva Rao, Indian Institute of Science, Bangalore, informs us that he has obtained pure α -santalol having a similarly high rotatory power.

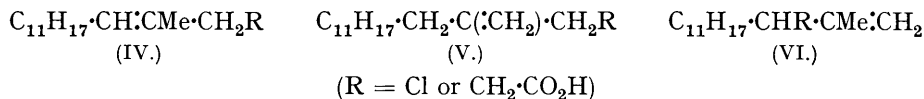
$\alpha_{5461} - 69.2^\circ$, was obtained, which was not appreciably altered by further distillation. Determination of unsaturation by percamphoric acid showed, however, only 1.86 ethylenic linkages. The oil was therefore further purified through the strychnine salt of the hydrogen phthalate and a specimen of the pure alcohol (percamphoric acid value, 1.97) having the following constants was obtained: b. p. 177—178°/17 mm., $d_{25}^{25} 0.9717$, $n_D^{25} 1.5100$, $\alpha_{5461} - 87.1$, $[R_L]_D 67.71$ (calc., 67.66). It is evident that previous specimens of this alcohol must have been highly contaminated with α -santalol.

It has been assumed, without direct experimental evidence, that β -santalol (II) or (III) is similar in structure to α -santalol (I).

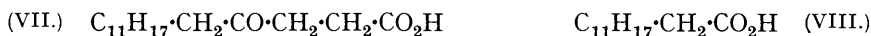


As is well known, the *cyclopropane* ring in α -santalol readily undergoes fission, and it appeared to us that if tetrahydro- α -santalol were prepared by hydrogenation of both the ethylenic linkage and the *cyclopropane* ring a direct comparison with tetrahydro- β -santalol would be possible. Attempts to reduce α -santalol catalytically resulted only in the formation of a saturated hydrocarbon, water being eliminated (compare Semmler and Risse, *Ber.*, 1913, **46**, 2306). A comparison of derivatives of the two alcohols was, however, successfully effected by an indirect method.

α -Santalol is converted by thionyl chloride in pyridine solution into *α -santalyl chloride*, which on oxidation with potassium permanganate in acetone solution yields mainly tricycloekasantalic acid together with a small quantity of a chloro-ketone, and with ozone it yields formaldehyde. The formation of tricycloekasantalic acid is to be expected from (IV; R = Cl), but the production of formaldehyde and a chloro-ketone suggests the presence of the isomeride (V; R = Cl) or of (VI; R = Cl) formed by an anionotropic change.

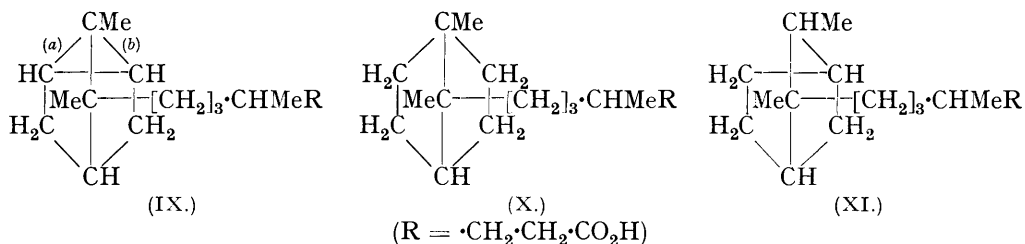


Condensation of the chloride with ethyl sodiomalonate and hydrolysis of the resulting *ester* gave *α -santalylmalonic acid*, m. p. 120—121°, the structure of which is discussed on p. 311. *α -Santalylacetic acid*, prepared by elimination of carbon dioxide at 160—180°, yields on oxidation with potassium permanganate in alkaline solution a liquid keto-acid, C₁₆H₂₄O₃, which does not react with sodium hypobromite at 0°, but at 28° it yields a monobasic acid, C₁₃H₂₀O₂, with the loss of three carbon atoms. This reaction excludes (VI; R = CH₂·CO₂H) as a representation of the acetic acid, since an acid of this structure would yield a substituted succinic acid on oxidation. It follows, therefore, that the keto-acid must be γ -keto- ϵ -teresantalylhexoic acid (VII), and its oxidation product β -teresantalylpropionic acid (VIII), α -santalylacetic acid being (V; R = CH₂·CO₂H) (compare p. 311).



By the catalytic hydrogenation of α -santalylmalonic acid the dihydro-acid was prepared; this on elimination of carbon dioxide yielded *dihydro- α -santalylacetic acid* (IX), from which, by the action of hydrogen bromide in acetic acid at 100°, a *hydrobromide* was obtained. This by reduction with sodium and alcohol gave tetrahydrosantalylacetic acid, characterised by its crystalline *p-bromophenacyl* and *diphenacyl* derivatives. This acid must be

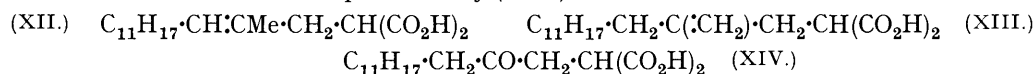
either (X) or (XI), since the fission of the bonds *a* and *b* in (IX) leads to products which are structurally identical but have enantiomorphous configurations (XI).



Since it has been shown synthetically by Hasselström (*J. Amer. Chem. Soc.*, 1931, **53**, 1097) that dihydroteresantalic acid, prepared by the fission of the *cyclopropane* ring in teresantalic acid with hydrogen chloride and subsequent reduction with sodium and alcohol, is identical with π -apocamphoric acid, it may reasonably be assumed that tetrahydro-santalylic acid is represented by (X).

In an analogous manner we have prepared from β -santalol β -santalylmalonic acid, m. p. 99—101°, which after catalytic hydrogenation and elimination of carbon dioxide, gives a tetrahydrosantalylic acid identical with that prepared from α -santalol as shown by the melting points of the *p*-bromophenacyl and diphenacyl derivatives. It follows that β -santalol, which yields acetylcarbinol on ozonolysis, must be represented by (II), since no other position for the second ethylenic linkage in the ring is possible without contravening the Bredt rule. The possibility of both ethylenic linkages being situated in the side chain is excluded by the facts that the alcohol cannot be reduced with sodium and alcohol and the molecular refraction is normal.

We must revert here to a consideration of the structure of α -santalylmalonic acid. This acid, which is highly crystalline and apparently homogeneous, provided results of considerable interest on oxidation. With ozone it yields exclusively *tricycloekasantalic* acid, no formaldehyde being formed. This result implies the presence of the ethylenic linkage in the 3 : 4-position (XII). If, however, the acid is oxidised with potassium permanganate in alkaline solution, the keto-acid (XIV) is obtained. *Tricycloekasantalic* acid, which is readily isolable owing to its volatility in steam, could not be detected; the malonic acid would then be represented by (XIII).



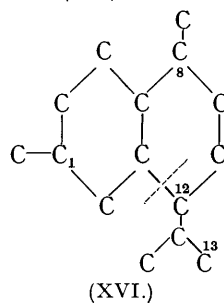
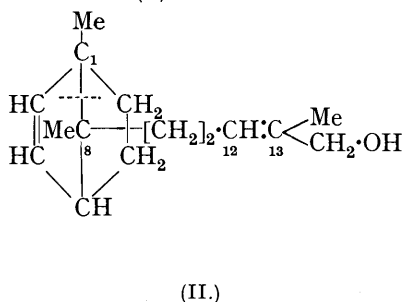
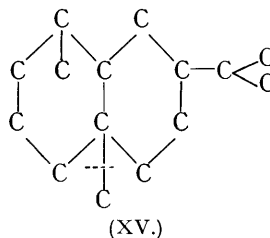
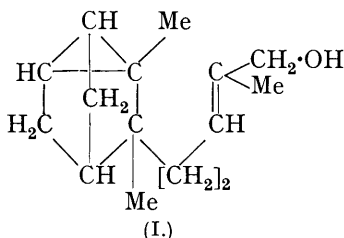
These results, apparently unequivocal, appear to be mutually contradictory. Here is provided a clear example of the difficulty, which has for some time been familiar in terpene chemistry, of interpreting oxidation experiments in cases where the groups $\text{—C} \begin{smallmatrix} \diagup \text{C} \\ \diagdown \text{C} \end{smallmatrix}$ and

$\text{C} \begin{smallmatrix} \diagup \text{C} \\ \diagdown \text{C} \end{smallmatrix}$ are involved, since products arising from both $\Delta^{\alpha\beta}$ - and $\Delta^{\beta\gamma}$ -forms are frequently obtained. Of particular interest is the recent work of Kuhn and Roth (*Ber.*, 1932, **65**, 1285), who have estimated quantitatively, by means of ozone, followed by potassium permanganate, the acetone formed on oxidation of a number of substances considered to contain the *isopropylidene* group. They find in general that it amounts to only 60—90% of the calculated quantity, and oxidation with potassium permanganate alone yields still less. These authors discuss in particular the two forms of dehydrogeranic acid, which, like α -santalylmalonic acid and unlike the majority of substances examined, is crystalline. Cahn, Penfold, and Simonsen (*J.*, 1931, 3134) have reported that permanganate oxidation of dehydrogeranic acid yields both acetone and formic acid. Kuhn and Roth on the basis of optical properties consider this acid to be homogeneous and with regard to the oxidation state : “Dann lässt sich die Annahme nicht vermeiden, dass beim oxydativen Abbau durch Ozon und durch Kaliumpermanganat β -Formen [*isopropylidene*] teilweise die Spaltungsprodukte von α -Formen [*isopropenyl*] liefern können.”

This view, equally with its opposite that substances behaving in this manner are in actuality inseparable mixtures (compare Simonsen, "The Terpenes," Vol. I, pp. 59 *et seq.*), seems now to be scarcely sufficient. It must be conceded that in α -santalylmalonic acid, and presumably therefore in other cases, the ethylene link is mobile, either under the action of reagents or even merely on solution, and in the present state of knowledge the phenomenon is best classified as tautomerism, and the two forms are to be regarded as tautomerides.

This tautomerism is observed also in the two santalols themselves, since they yield on ozonolysis both formaldehyde and acetylcarbinol; the formulæ (I) and (II) adopted for α - and β -santalol respectively are to be interpreted therefore in this sense.

It has been pointed out by Ruzicka and Stoll (*Helv. Chim. Acta*, 1922, 5, 928) that α -santalol (I) may be regarded as a derivative of eudalene (XV). The structure now advanced for β -santalol (II) derives it from cadalene (XVI) by fission at the dotted line and



ring closure. α -Santalol (and α -santalene) can therefore equally well be considered to be a derivative of cadalene and hence occupies an intermediate position between the two parent hydrocarbons. Ruzicka and Stoll (*ibid.*, 1924, 7, 260) have shown that the sesquiterpene alcohols in camphor oil yield on dehydrogenation a mixture of cadalene and eudalene.

EXPERIMENTAL.

α -Santalol.

The allophanate crystallised from methyl alcohol in fine needles, m. p. 162—163°. The strychnine salt of the hydrogen phthalate separated from ethyl acetate or acetone in rosettes of well-formed prisms, m. p. 144—145°, $[\alpha]_{5461} - 5.62^\circ$ (in benzene, c 4.68).*

Oxidation with Ozone.—Ozone was passed through a solution of α -santalol in ethyl acetate cooled in ice, and the issuing gases were led through water. No formaldehyde was detected in the wash water in this experiment, but in other experiments carried out under apparently identical conditions formaldehyde was formed in considerable quantity. The ethyl acetate was removed under diminished pressure, and the product decomposed by boiling with water. After extraction with ether, acetylcarbinol was identified in the aqueous solution by preparation of the 2 : 4-dinitrophenylosazone, decomp. 300° after recrystallisation from nitrobenzene (compare Ingold, Pritchard, and Smith, J., 1934, 83), which gave a deep violet colour on warming with sodium hydroxide, and by the phenylosazone, m. p. 143—144°. The residue from evaporation of the ethereal extract was suspended in water, neutralised with potassium carbonate,

* Rotations were observed in a 1 dm. tube, except those followed by "(mic.)", for which a $\frac{1}{2}$ dm. micro-tube was used.

and extracted with ether. On acidification of the aqueous solution, *tricycloekasantalic acid*, m. p. 74—75°, was obtained. Evaporation of the ethereal extract yielded an oil, from which *tricycloekasantal semicarbazone* was prepared, m. p. 163—164° (Semmler and Bode, *Ber.*, 1907, 40, 1136, give ca. 156°) (Found: C, 66.4; H, 8.6. Calc.: C, 66.4; H, 8.9%).

α -Santalyl Chloride.—To a solution of the alcohol (33.3 g.) in pyridine (12 g.) cooled in ice and stirred mechanically, thionyl chloride (18.5 g.) was added gradually. The mixture was kept in ice for 15 minutes and then heated at 100° for 30 minutes. The brown reaction mixture was poured on ice, the oil extracted with ether, and the extract washed successively with dilute sulphuric acid, sodium carbonate solution, and water. Removal of the solvent from the dried solution (calcium chloride) gave an oil (32 g.), b. p. 155—158°/14 mm., $n_D^{20.5}$ 1.5042, $\alpha_{5461} + 7.6^\circ$ (mic.) (Found: Cl, 15.3. $C_{15}H_{23}Cl$ requires Cl, 14.9%).

Oxidation of α -Santalyl Chloride.—(i) *With potassium permanganate.* To the chloride (5.5 g.) in acetone (50 c.c.), potassium permanganate (7.5 g.) was added gradually, the solution being cooled by ice and mechanically stirred. The oxidation was complete in 3 hours. The acetone solution was filtered, the manganese dioxide sludge well washed with acetone, and the filtrate (A) reserved. The manganese dioxide was suspended in water, and sulphur dioxide passed until the dioxide was dissolved; a gummy acid remained in suspension. This was collected, dissolved in aqueous sodium hydroxide, a trace of insoluble oil removed by extraction with ligroin, the alkaline filtrate acidified, and the semi-solid acid which separated dissolved in ether. Removal of the solvent left an acid (3.3 g.), which crystallised from acetic acid (50%) and then had m. p. 76—77° both alone and after admixture with authentic *tricycloekasantalic acid*. The filtrate (A) left on evaporation of the acetone a lachrymatory oil (0.7 g.), b. p. 150—160°/17 mm., which contained chlorine and reacted with carbonyl-group reagents. No crystalline derivatives could, however, be prepared.

(ii) *With ozone.* Oxidation with ozone in ethyl acetate gave a considerable quantity of formaldehyde (dimedone test). The other products of the oxidation were not investigated.

Ethyl α -Santalylmalonate.—To ethyl sodiomalonate (ethyl malonate, 16.4 g.; sodium, 2.3 g.) in alcohol (50 c.c.), α -santalyl chloride (24 g.) was added gradually with cooling. Sodium chloride rapidly separated and after 1 hour the mixture was heated on the water-bath for a further hour. The cooled neutral solution was poured into water, the oil which separated dissolved in ether, the solution dried, and the solvent evaporated. After a small quantity of unchanged ethyl malonate had passed over, the condensation product distilled at 180—220°/13 mm. and on redistillation *ethyl α -santalylmalonate* was obtained as a colourless oil, b. p. 212—213°/13 mm. (Found: C, 74.5; H, 9.6. $C_{22}H_{34}O_4$ requires C, 72.9; H, 9.4%). For the preparation of the acid, the oil (16 g.) was mixed with methyl-alcoholic potassium hydroxide (KOH, 10 g.); on warming on the water-bath, a sparingly soluble potassium salt crystallised in needles. After 1 hour water was added, the alcohol evaporated, and the solution made acid; a viscid oil then separated. This was dissolved in ether, and the solution dried and evaporated. The oil, which remained, crystallised on scratching and after trituration with ligroin (b. p. 40—60°), which removed a gummy impurity, *α -santalylmalonic acid* was recrystallised from ligroin-benzene and obtained in fine needles, m. p. 120—121°, not altered by further crystallisation, $[\alpha]_{5461} + 4.7^\circ$ (in methyl alcohol, $c = 5.25$) (Found: C, 70.8; H, 8.7. $C_{18}H_{26}O_4$ requires C, 70.6; H, 8.5%). When the acid was heated at 160—180°, elimination of carbon dioxide occurred with formation of *α -santalylacetic acid*, b. p. 188°/2 mm. (Found: C, 78.0; H, 10.2. $C_{17}H_{26}O_3$ requires C, 77.9; H, 9.9%).

Oxidation of α -Santalylmalonic Acid.—(i) *With potassium permanganate.* The acid (3.4 g.) was dissolved in aqueous sodium carbonate and to the cooled (ice) and stirred solution potassium permanganate (3%; 150 c.c.) was added, carbon dioxide being passed during the addition. The filtered solution was concentrated to a small bulk and acidified and the liquid acid which separated was extracted with ether. Evaporation of the ether left a gum, which did not solidify and was not volatile in steam. The *semicarbazone* of *β -keto- δ -teresantalylbutylmalonic acid*, after crystallisation from methyl alcohol, decomposed at 172—173° (Found: C, 58.9; H, 7.3. $C_{18}H_{27}O_5N_3$ requires C, 59.2; H, 7.4%).

(ii) *With ozone.* The acid (1 g.), in ethyl acetate (10 c.c.) cooled in ice, was ozonised. The wash water through which the issuing gases were led gave no precipitate with dimedone. After removal of the solvent, decomposition of the ozonide by boiling water yielded *tricycloekasantalic acid*. No keto-acid was detected.

Oxidation of α -Santalylacetic Acid.—When the acid (7 g.) was oxidised with potassium permanganate under conditions similar to those used for the malonic acid, a small quantity (0.2 g.) of a neutral oil volatile in steam was formed. The acid obtained by the acidification of

the concentrated alkaline solution was an oil, which did not yield crystalline derivatives with the usual carbonyl reagents. When it was distilled under diminished pressure (13 mm.), water was eliminated and a neutral oil, b. p. 200—210°, was obtained which was insoluble in cold alkali but dissolved on warming. It was probably the unsaturated lactone but was not further examined. *Methyl γ -keto- ϵ -teresantalylhexoate*, prepared from the silver salt, was an oil, b. p. 211°/17 mm. (Found: C, 73.2; H, 9.6. $C_{17}H_{26}O_3$ requires C, 73.4; H, 9.3%). The *semicarbazone* crystallised from benzene in needles, m. p. 176—177° (Found: C, 65.1; H, 9.2. $C_{18}H_{29}O_3N_3$ requires C, 64.5; H, 8.7%). The *phenylsemicarbazone* separated from methyl alcohol in fine needles, m. p. 192—193° (Found: C, 70.5; H, 8.1. $C_{24}H_{33}O_3N_3$ requires C, 70.1; H, 8.0%). The keto-acid (5 g.) was stable to sodium hypobromite at 0°, but at 28° oxidation proceeded rapidly with deposition of a bromo-derivative, the heat of the reaction being sufficient to maintain the temperature without further warming. Acidification of the filtered alkaline solution gave an oil, which after isolation by ether was found to contain bromine. It was dissolved in aqueous sodium hydroxide and, after the addition of zinc dust (3 g.), heated on the water-bath for 3 hours. The filtered solution was acidified and the acid, now free from bromine, was a viscid oil, from which no crystalline derivatives could be prepared. The *silver* salt was an amorphous powder readily soluble in alcohol (Found: Ag, 34.5. $C_{13}H_{19}O_2Ag$ requires Ag, 34.3%). *Methyl β -teresantalylpropionate* had b. p. 140—145°/19 mm. (Found: C, 75.4; H, 10.1. $C_{14}H_{22}O_2$ requires C, 75.6; H, 10.0%).

Dihydro- α -santalylacetic Acid.— α -Santalylmalonic acid was hydrogenated in ethyl-alcoholic solution in the presence of palladium-norit. The dihydro-acid, obtained as a viscid oil, was converted into the acetic acid by heating at 160—180°, and the latter purified by distillation, *dihydro- α -santalylacetic acid* being obtained as a viscid colourless oil, b. p. 208—210°/15 mm. (Found: C, 77.4; H, 11.0. $C_{17}H_{28}O_2$ requires C, 77.3; H, 10.6%). The *α -aminoanthraquinonyl* derivative crystallised from methyl alcohol in terra-cotta nodules, seen under the microscope to consist of thin irregular prisms, m. p. 105—106° (sint. 94°) (Found: C, 79.4; H, 7.3. $C_{31}H_{35}O_3N$ requires C, 79.3; H, 7.5%). By the action of hydrogen bromide in acetic acid (HBr, 50%) at 100° in a sealed tube, *bromotetrahydrosantalylacetic acid* was obtained as a viscid oil (Found: Br, 20.5. $C_{17}H_{29}O_2Br$ requires Br, 23.0%). This, on reduction with sodium in ethyl-alcoholic solution, gave tetrahydrosantalylacetic acid, which was characterised by the preparation of the *p*-bromophenacyl derivative, m. p. 52—53°, and the diphenacyl derivative, m. p. 61—62°, both alone and in admixture with specimens of these derivatives prepared from the tetrahydro-acid derived from β -santalol (see p. 315).

β -Santalol.

The *allophanate* crystallised from methyl alcohol in fine needles, m. p. 159—160°, which was slightly raised on admixture with α -santalyl allophanate (Found: C, 66.6; H, 8.9. $C_{17}H_{26}O_3N_2$ requires C, 66.7; H, 8.5%). The strychnine salt of the hydrogen phthalate crystallised from ethyl acetate in prisms, m. p. 134—135°, $[\alpha]_{5461} - 37.5^\circ$ (in benzene; $c = 2.68$); it was indistinguishable in appearance from that of α -santalol and the m. p. of the mixture lay between that of the two constituents.

Oxidation with Ozone.— β -Santalol (1.1 g.), in ethyl acetate (10 c.c.) cooled in ice, was ozonised. The issuing gases were led through water, which at the end of the experiment contained formaldehyde (dimedone compound, m. p. 188°). The ozonide was decomposed by boiling water, and the aqueous liquid, after extraction with ether, shown to contain acetylcarbinol by preparation of the 2:4-dinitrophenylosazone. The ethereal extract was not further examined.

The following derivatives of β -santalol were prepared in a similar manner to those of the α -alcohol.

β -Santalyl chloride had b. p. 161°/20 mm., $n_D^{16} 1.5126$, $\alpha_{5461} - 66.6^\circ$ (Found: Cl, 15.2%). On oxidation with ozone it gave much formaldehyde.

Ethyl β -santalylmalonate was a colourless oil, b. p. 219—220°/15 mm. (Found: C, 74.0; H, 9.6%). *β -Santalylmalonic acid* crystallised from ligroin (b. p. 60—80°) in needles, m. p. 99—101°, $[\alpha]_{5461} - 60.0^\circ$ (in methyl alcohol, $c = 2.528$) and was somewhat more soluble than the α -acid. In admixture with the α -acid it had m. p. 107—110°. On oxidation with ozone, formaldehyde was formed.

Reduction of β -Santalylmalonic Acid.—Agitation of a solution of β -santalylmalonic acid in ethyl alcohol in the presence of a palladium-norit catalyst, with hydrogen at room temperature and atmospheric pressure, led to the absorption of rather more than one molecular proportion of

hydrogen only. The reduction was therefore completed at 3 atmospheres' pressure and at 50—60°. After filtration from the catalyst, the solution was made alkaline with sodium carbonate, and the ethyl alcohol removed. The residue was dissolved in water, extracted once with ether, acidified, and the reduced acid extracted with ether. After removal of the solvent and elimination of carbon dioxide, tetrahydro- β -santalylacetic acid had b. p. 210—213°/16 mm. The *p*-bromophenacyl derivative separated as an oil which slowly solidified when kept in the ice-box and then crystallised from methyl alcohol in thin plates, m. p. 52—53° (Found: Br, 17.0. $C_{25}H_{33}O_3Br$ requires Br, 17.4%). The *diphenacyl* derivative crystallised from methyl alcohol in leaflets, m. p. 61—62° (Found: C, 81.0; H, 8.6. $C_{31}H_{40}O_3$ requires C, 80.9; H, 8.7%).

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