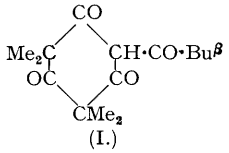
187. *Leptospermone. Part II.*

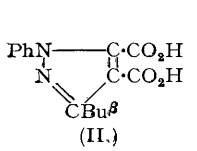
By L. H. Briggs, C. H. Hassall, and W. F. Short.

Further evidence for the structure of leptospermone has been obtained by oxidative disruption.

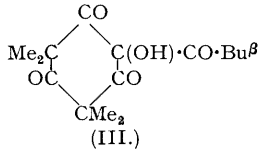
In Part I (Briggs, Penfold and Short, *J.*, **1938**, 1193) it was suggested that the naturally occurring β-diketone leptospermone may be represented by (I) and further evidence for this structure has now been obtained. Bromination of leptospermone in chloroform solution affords a *tribromo derivative*, $C_{15}H_{19}O_4Br_3$, and since the bromine atoms are removed by acidified potassium iodide, it is evident that they are all in α-position to a CO group. Reductive hydrolysis of leptospermone with zinc dust and aqueous sodium hydroxide affords dimethylmalonic acid, *iso*butyric acid, *iso*valeric acid and probably di*iso*propyl ketone, so that complete disruption of the ring occurs just as in the oxidation experiments described in Part I.



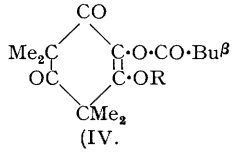
(I.)



(II.)



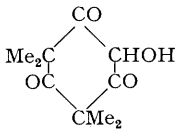
(III.)

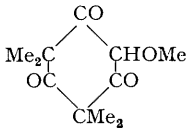


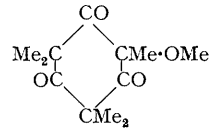
(IV.)

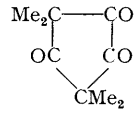
Oxidation of anhydroleptospermonephenylhydrazone (Part I) with potassium permanganate affords a *1-phenylpyrazoledicarboxylic acid*, $C_{15}H_{16}O_4N_2$ (*methyl* ester, m. p. 191°) which gives the fluorescein reaction and loses carbon dioxide on heating. This acid is probably 1-*phenyl*-3-iso*butylpyrazole*-4 : 5-*dicarboxylic acid* (II) or 1-*phenyl*-5-iso*butylpyrazole*-3 : 4-*dicarboxylic acid*, but attempts to confirm the structure by oxidation to 1-phenylpyrazole-3 : 4 : 5-tricarboxylic acid were unsuccessful, the compound either being unaffected or extensively degraded by a variety of oxidising agents.

Leptospermone and alcoholic semicarbazide at room temperature afford hydrazodicarbonamide and two isomeric *pyrazoles*, $C_{15}H_{22}O_2N_2$, m. p. 130° and 113°. A carbonamide group is lost during the reaction as in the case of other β-diketones (Wislicenus, *Annalen*, 1899, **308**, 255; Posner, *Ber.*, 1901, **34**, 3973; Wallach, *Annalen*, 1903, **329**, 109) and the same pyrazole derivatives are obtained from leptospermone and hydrazine. The production of a single anhydrophenylhydrazone is probably due to the steric effect of the phenyl group which inhibits the production of the isomer in which both potentially enolisable nuclear carbonyl groups participate in the formation of the pyrazole nucleus.


(V.)


(VI.)

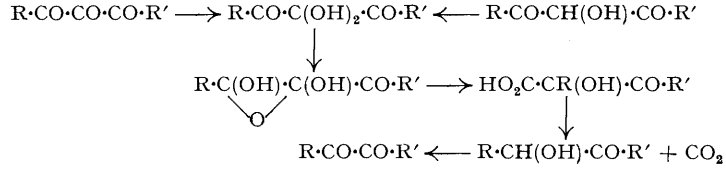

(VII.)


(VIII.)

Oxidation of leptospermone with hydrogen peroxide in pyridine or ethyl alcohol yields di-*iso*propyl ketone, *iso*valeric acid and an acidic compound, $C_{15}H_{22}O_5$, which cannot be an α-ketol (III) since it does not reduce ammoniacal silver nitrate or Schiff's reagent. Hydrolysis with water at 120° affords *iso*valeric acid and a compound, $C_{10}H_{14}O_4$ which behaves as a strongly acidic β-diketone and exhibits the reducing properties of an α-ketol. Such an α-ketol could be produced from (III) by hydrolysis, but decisive evidence against this formula is provided by the observation that the initial oxidation product, $C_{15}H_{22}O_5$, and $C_{10}H_{14}O_4$ formed by its hydrolysis yield the same di-*iso*valeryl ester, $C_{20}H_{30}O_6$ (IV; R = $CO{\cdot}Bu^{\beta}$) with *iso*valeryl chloride in pyridine. The α-ketol, $C_{10}H_{14}O_4$, is therefore regarded as 2 : 4 : 6-*triketo*-3 : 3 : 5 : 5-*tetramethyl*cyclo*hexanol* (V). The strong acidity of the compound indicates that it must be highly enolised and this probably accounts for our unsuccessful attempts to convert it by methylation into tetramethyliretol (VI) and its methyl derivative (VII) which were obtained by de Laire and Tiemann (*Ber.*, 1893, **26**, 2033) by the progressive methylation of iretol (2-methoxyphloroglucinol).*

The initial oxidation product of leptospermone is therefore formulated as (IV; R = H). Its formation is reminiscent of the production of enol-acetates in the oxidation of αβ-unsaturated ketones with peracids (Boeseken and Kremer, *Rec. trav. chim.*, 1931, **50**, 827) and a number of similar oxidations are recorded in the literature (Burckhardt and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 1434). Leptospermone, however, is not attacked by perbenzoic acid.

Oxidation of the triketoalcohol (V) with selenious acid in alcoholic solution affords a yellow *triketone*, $C_9H_{12}O_3$, and a small quantity of a colourless *compound*, $C_{10}H_{14}O_4$ or $C_9H_{12}O_4$; the latter was not examined further. The triketone affords a *quinoxaline* and, on oxidation with hydrogen peroxide, yields a dibasic acid which must be *tetramethylacetonedicarboxylic acid*, $HO_2C{\cdot}CMe_2{\cdot}CO{\cdot}CMe_2{\cdot}CO_2H$, since on heating to 200° it is converted into di-*iso*propyl ketone. The triketone is therefore 1 : 2 : 4-*triketo*-3 : 3 : 5 : 5-*tetramethyl*cyclo*pentane* (VIII) and its production from (V) may involve the formation of a ketone hydrate which then undergoes ring contraction by the following mechanism which is applicable generally to similar transformations (de Neufville and Pechmann, *Ber.*, 1890, **23**, 3375; Schönberg and Azzam, *J.*, 1939, 1428) and exemplified by many α-ketols (Chaletzki, *J. Gen. Chem. Russ.*, 1938, **8**, 164, 225) :



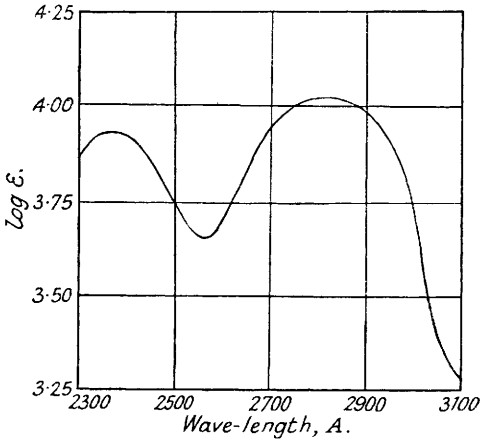
The high value of ε in the absorption spectrum of leptospermone in *cyclo*hexane (see figure) requires the presence of a conjugated chromophore in the molecule and indicates that (I) exists in enolic forms. The band at 2730 A. (log ε = 3·93) indicates the conjugation of the ethylene linkage with a carbonyl group (Menschick, Page, and Bossert, *Annalen*, 1932, **495**, 225; Woodward, *J. Amer. Chem. Soc.*, 1940, **62**, 1208; Evans and Gillam, *J.*, 1941, 815). On analogy with salicylaldehyde, *o*-hydroxyacetophenone and acetylacetone (Pfeiffer *et al.*, *Annalen*, 1913, **398**, 137; Hilbert, Wulf, Hendriks, and Liddel, *Nature*, 1935, **135**, 147) strong hydrogen bond formation should occur in the enolised form of structure (I) but not in (IV; R = H) and would account for the fact that leptospermone is insoluble in aqueous sodium bicarbonate whereas the ester (IV; R = H) is soluble.

* (*Note added, July 30th*, 1945.) Hydrolysis of leptospermone with 2N-hydrochloric acid at 120—130° affords tetramethylphloroglucinol, m. p. and mixed m. p. 189°, and other products.

Tetra- and penta-methylphloroglucinol, in which intramolecular hydrogen bonding cannot occur, are soluble in sodium bicarbonate solution (Spitzer, *Monatsh.*, 1890, **11**, 104).

Leptospermone has some anthelmintic activity, as would be expected from its structural relation to the constituents of male fern root.

Synthetic experiments are in progress.



Experimental.

p-*Toluidinoleptospermone*.—A mixture of leptospermone (1 g.) and *p*-toluidine (1 g.) was heated at 100° for ½ hour, then boiled for 5 minutes and poured into water. After washing with dilute acid, alkali, and water the product (1·21 g.) was crystallised from 60% aqueous alcohol (charcoal) from which it separated in needles, m. p. 101° (Found: C, 74·55; H, 8·3; N, 3·95. $C_{22}H_{29}O_3N$ requires C, 74·4; H, 8·2; N, 3·9%).

Bromination of Leptospermone.—A solution of leptospermone (2·66 g.) and bromine (1·6 g.; 2 mols.) in chloroform (10 c.c.) evolved hydrogen bromide at once but decolorisation was complete only after 6 weeks. The oily crystals obtained by removing the solvent were washed with ligroin (b. p. 80—100°) and recrystallised from the same solvent giving *tribromoleptospermone* (0·6 g.) which separated in fine needles, m. p. 95° (Found: C, 35·75; H, 3·9; Br, 47·0. $C_{15}H_{19}O_4Br_3$ requires C, 35·8; H, 3·8; Br, 47·5%). The bromo-compound was readily soluble in ether, chloroform, benzene, and dioxan and gave a slightly yellow solution in water. The bromine was estimated with potassium iodide and sodium thiosulphate.

The experiment was repeated on twice the scale and after keeping for 3 months an attempt was made to distil the product at 3 mm. Decomposition occurred and crystallisation of the residue from boiling ligroin (b. p. 80—100°) afforded needles (1·5 g.) which sintered at 130° and melted at 138° after repeated crystallisation from ligroin–alcohol. The *compound*, which was insoluble in water and readily soluble in alcohol and in ethyl acetate, contained no bromine [Found: C, 67·25; H, 7·3; *M* (Rast), 234. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%; *M*, 250]. Concentration of the mother liquor gave a tarry solid (3·13 g.) separated by fractional crystallisation from ligroin into the compound, m. p. 138°, and a more soluble *compound* separating in needles, m. p. 113° [Found: C, 68·2; H, 7·7; *M* (Rast), 252. $C_{15}H_{20}O_4$ requires C, 68·2; H, 7·6%; *M*, 264]. This compound contained no bromine and did not give colour reactions with tetranitromethane or in the pine-shaving test.

Hydrolysis of Leptospermone.—When a solution of leptospermone (3 g.) in 15% aqueous sodium hydroxide (40 c.c.) was boiled for a few minutes the *sodium* salt of leptospermone separated as a white solid. After repeated crystallisation from ethyl acetate–ligroin the m. p. was not sharp but the sintering point remained constant at 217° (Found: Na, 8·0. $C_{15}H_{21}O_4Na$ requires Na, 8·0%). The solid was soluble in water and acidification of the solution liberated leptospermone. A solution of leptospermone (15 g.) in 10% aqueous sodium hydroxide (800 c.c.) was boiled for 36 hours with zinc dust (30 g.) and then diluted to 1·2 litres with water and filtered. The alkaline filtrate was exhaustively extracted with ether and the dried ethereal solution evaporated. The residue consisted of the sodium salt of leptospermone (1·4 g.) and a neutral oil (80 mg.), b. p. ca. 98°, having a camphoraceous odour. The latter afforded a semicarbazone, m. p. 156·5—157°, which is the m. p. of di*iso*propyl ketone semicarbazone, but there was insufficient material for a mixed m. p. determination. The alkaline liquid was saturated with carbon dioxide, and, after removing zinc carbonate, was extracted exhaustively with ether. In this way unchanged leptospermone (3·9 g.) was recovered and identified by conversion into its anilino-derivative, m. p. and mixed m. p. 91° (Part I, *loc. cit.*). The aqueous solution was then acidified with hydrochloric acid and extracted exhaustively with ether. The crystalline part of the extract (1·4 g.) consisted of dimethylmalonic acid, m. p. 192°, identified by the preparation of dimethylmalonamide, m. p. and mixed m. p. 270°. The oily portion (2·7 g.) of the extract was distilled giving *iso*butyric acid, b. p. 150—160° (2·2 g.), and *iso*valeric acid (0·3 g.), identified by preparing their anilides, m p.'s and mixed m. p.'s 97° and 105° respectively.

Anhydroleptospermonehydrazones.—When a solution of leptospermone (5·32 g.), semicarbazide hydrochloride (8·88 g.), and crystalline sodium acetate (6·56 g.) in aqueous alcohol was kept for 28 days two solids had separated, one, m. p. 105°, on the surface of the liquid and the other, m. p. 245°, at the bottom of the vessel. Repeated crystallisation from water raised the m. p. of the higher melting product to 267° (decomp.) and it was identified as hydrazodicarbonamide (Found: C, 20·7; H, 5·4; N, 47·6. Calc. for $C_2H_6O_2N_4$: C, 20·3; H, 5·1; N, 47·5%). The solid isolated from the mother liquors was added to the product of lower m. p., the mixture was extracted with boiling alcohol and filtered from hydrazodicarbonamide. The alcoholic extract was fractionally crystallised from ligroin (b. p. 40—50°) and separated into two isomeric *pyrazoles*, (1) m. p. 130° (Found: C, 68·6; H, 8·25; N, 10·5, 10·9. $C_{15}H_{22}O_2N_2$ requires C, 68·7; H, 8·4; N, 10·7%), and (2) m. p. 113° (Found: C, 68·4; H, 8·4; N, 10·6%) which is more soluble. The same two compounds were produced when an aqueous alcoholic solution of leptospermone (1·3 g.), hydrazine sulphate (0·7 g.) and excess of crystalline sodium acetate was kept for a week at room temperature.

Oxidation of Anhydroleptospermonephenylhydrazone.—Anhydroleptospermonephenylhydrazone (Part I, *loc. cit.*; 1·8 g.) was boiled with a solution of potassium hydroxide (1 g.) in water (150 c.c.) and potassium permanganate (20 g.) was added in portions to the boiling solution during 30 hours. The product was saturated with sulphur dioxide, cooled and filtered. The solid so obtained was extracted with warm dilute aqueous sodium hydroxide which left a residue of the unchanged anhydrophenylhydrazone (0·1 g.). When the alkaline solution was acidified no solid separated after keeping for many hours but precipitation occurred at once when the walls of the vessel were scratched with a glass rod. The *acid* (0·5 g.) so obtained was a hydrate melting indefinitely at 175—180° but, after drying over phosphoric oxide, the m. p. rose to 210—212°. Recrystallisation from anhydrous ether raised the m. p. to 216—216·5° decomp. [Found: C, 62·5; H, 5·4; equiv. (by titration), 150. $C_{15}H_{16}O_4N_2$ requires C, 62·5; H, 5·6%; equiv., 144]. The acid responded to the fluorescein test but did not give a coloration with alcoholic ferric chloride. Esterification of the acid was achieved (1) with excess of diazomethane; (2) by the catalytic method with sulphuric acid; (3) by heating the silver salt with methyl iodide in benzene solution; (4) by the action of methyl sulpha e on an aqueous solution of the sodium salt, or (5) by the successive action of thionyl chloride and methyl alcohol. The same neutral *methyl* ester was obtained in all cases and separated from methyl alcohol in glistening rods, m. p. 191° (Found: C, 64·7; H, 5·8; N, 8·4, 8·5. $C_{17}H_{20}O_4N_2$ requires C, 64·6; H, 6·3; N, 8·8%).

Oxidation of Leptospermone with Hydrogen Peroxide.—Addition of hydrogen peroxide (10 c.c. of 100 vol.; 2 mols.)

to a solution of leptospermone (10 g.) in pyridine (50 c.c.) produced a strongly exothermic reaction which was moderated by occasional cooling in water. After keeping for 16 hours at room temperature, the solution was poured into a mixture of conc. hydrochloric acid (53 c.c.) and ice. A pasty solid separated and the products were collected by repeated extraction with ether. The ethereal solution was concentrated to 50 c.c. and extracted successively with saturated aqueous sodium bicarbonate and sodium carbonate. Evaporation of the extracted ethereal solution afforded a trace of an oil with a camphoraceous odour, b. p. 120°, which was identified as di-*iso*propyl ketone by preparing the semicarbazone, m. p. and mixed m. p. 156°. Acidification of the sodium carbonate extract afforded unchanged leptospermone (4·5 g.). A crystalline solid (1·3 g.) separated when the sodium bicarbonate extract was acidified and crystallisation from ligroin (b. p. 40—60°) containing a little ethyl acetate furnished prisms of an *ester*, m. p. 115° [Found : C, 63·6; H, 7·7; *M* (Rast), 292, 301; equiv., 276. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·8%; *M*, 282]. When the aqueous layer was extracted with ether it afforded a volatile acid, b. p. 170—177°, identified as *iso*valeric acid by conversion into the anilide, m. p. and mixed m. p. 110°. The same ester was produced when the oxidation was carried out in presence of sodium hydroxide or in neutral alcoholic solution. Increase in the proportion of hydrogen peroxide reduced the quantity of unchanged leptospermone and increased the yield of neutral and acidic products without affecting that of the ester.

The ester, $C_{15}H_{22}O_5$, is readily soluble in alcohol, ethyl acetate and pyridine, moderately soluble in alcohol and almost insoluble in ligroin and in water. It gives a faint reddish-brown coloration with alcoholic ferric chloride. By the action of the appropriate acid chloride in pyridine solution it was converted into an *acetate*, m. p. 93° [Found : C, 63·0; H, 7·5; *M* (Rast), 324. $C_{17}H_{24}O_6$ requires C, 62·9; H, 7·4%; *M*, 324], and an iso*valerate*, m. p. 81° (Found : C, 65·6; H, 8·4. $C_{20}H_{30}O_6$ requires C, 65·5; H, 8·2%). Hydrolysis of the original ester or the acetate (1·7 g.) by heating with water (40 c.c.) under pressure at 120° for 24 hours afforded 2 : 4 : 6-*triketo*-3 : 3 : 5 : 5-*tetramethyl*cyclo*hexanol* (1·0 g.) which separated from ligroin–ethyl acetate in prisms, m. p. 170° (Found : C, 60·4; H, 7·1. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%). When the aqueous solution resulting from the hydrolysis of the ester, $C_{15}H_{22}O_5$, was extracted with ether it afforded *iso*valeric acid (0·2 g.), identified by conversion into the anilide, m. p. and mixed m. p. 110°. The triketo-alcohol must be highly enolised since it dissolved in aqueous sodium bicarbonate to a yellow solution, gave a violet-blue coloration with ferric chloride in neutral solution and formed a light brown chelate copper salt. It behaved as an α-ketol in reducing ammoniacal silver nitrate and Fehling's solution. The acetate and *iso*valerate are insoluble in aqueous alkali. When the triketo-alcohol (0·1 g.), phenylhydrazine hydrochloride (0·2 g.), anhydrous sodium acetate (0·3 g.) and water (4 c.c.) were heated at 100° for an hour, the product consisted of a red tar which deposited crystals on cooling. Recrystallisation from ligroin containing a trace of ethyl acetate gave colourless needles, m. p. 115—117° (decomp.) (Found : C, 62·6; H, 7·5. $C_{10}H_{14}O_4$,$C_8H_8N_2$ requires C, 62·7; H, 7·2%). This *compound* was unstable and was decomposed by boiling conc. hydrochloric acid with regeneration of the triketo-alcohol; it is probably a phenylhydrazine salt rather than a hydrated phenylhydrazone.

Oxidation of 2 : 4 : 6-*Triketo*-3 : 3 : 5 : 5-*tetramethyl*cyclo*hexanol*.—Selenium separated immediately when a solution of selenium dioxide (2·08 g.) in water (5 c.c.) was added to the triketo-alcohol (3·65 g.) in absolute alcohol (40 c.c.), and after heating at 100° for 7 hours the mixture was filtered and evaporated to dryness. The oily residue was unstable in moist air and could not be purified by crystallisation. Micro-sublimation at 40—50° at 3 mm. left a residue (see below) and gave 1 : 2 : 4-*triketo*-3 : 3 : 5 : 5-*tetramethyl*cyclo*pentane* which sublimed in golden yellow needles, m. p. 70—73° (Found : C, 63·7, 63·7; H, 7·4, 7·4. $C_9H_{12}O_3$ requires C, 64·3; H, 7·1%). The triketone (0·1 g.) and *o*-phenylenediamine (0·06 g.), dissolved in acetic acid–alcohol and heated at 100° for 15 minutes, afforded a *quinoxaline*, m. p. 146° (Found : C, 74·5, 74·5; H, 6·8, 6·7; N, 11·2. $C_{15}H_{16}ON_2$ requires C, 75·0; H, 6·7; N, 11·7%). A filtered benzene solution of the residue from the sublimation was evaporated and the residue sublimed at 60—70° at 3—5 mm. In this way a small amount of the triketone was obtained, but the main product consisted of colourless dome-like crystals (0·4 g.), m. p. 59° [Found : C, 59·7, 59·8; H, 7·6, 7·7; *M* (Rast), 214. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%; *M*, 198. $C_9H_{12}O_4$ requires C, 58·7; H, 6·5%; *M*, 184]. This *compound* is insoluble in dilute aqueous sodium carbonate but soluble in 20% aqueous sodium hydroxide to a yellow solution and does not give a coloration with ferric chloride solution.

Oxidation of 1 : 2 : 4-*Triketo*-3 : 3 : 5 : 5-*tetramethyl*cyclo*pentane*.—When the triketone (0·8 g.) was added to a mixture of 90—100 vol. hydrogen peroxide (1 c.c.) and water (6 c.c.) the crystals dissolved in 5 minutes. Evaporation of the solution in a vacuum gave a quantitative yield of *tetramethylacetonedicarboxylic acid* which separated from ligroin–ethyl acetate in prisms, m. p. 130° decomp. (Found : C, 53·6; H, 7·0. $C_9H_{14}O_5$ requires C, 53·5; H, 6·9%). When the acid (0·47 g.) was heated at 150—200° in a micro-distilling flask carbon dioxide was evolved and a liquid (0·22 g.) with a camphoraceous odour distilled at ca. 100° and afforded a semicarbazone, m. p. 156°, either alone or mixed with an authentic specimen of di-*iso*propyl ketone semicarbazone.

We are indebted to Messrs. E. J. Batham and D. A. Medley, Hydatid Department, Otago Medical School, for experiments on the anthelmintic properties of leptospermone against the hydatid worm (*Echinococcus granulosus*) in dogs. The optimum dose, 0·08 g. per kg. body-weight, caused the removal by vomiting of 60 terminal segments from 68 worms. This effect, however, is of little practical value since unless the whole worm is removed further segments are readily regenerated.

The analyses are by Dr. Burger, Messrs. J. A. Mills, and C. Carter.

We are indebted to the Chemical Society for continued grants.

Auckland University College, New Zealand.
Otago University, Dunedin, New Zealand.
The College of Technology, Manchester.

[*Received, April 7th,* 1945.]