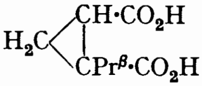
192. *The Synthesis of Umbellularic Acid; a Synthetic Proof of the Presence of the* cyclo*Propane Bridge in the Terpenes of the Thujane Series.*

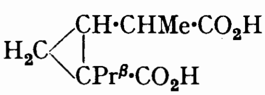
By H. N. RYDON.

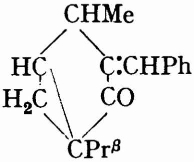
SEMMLER (*Ber.*, 1907, **40**, 5019; 1908, **41**, 3988) showed that umbellularic acid, obtained by Tutin (J., 1906, **89**, 1104) by the degradation of umbellulone, has the structure (I) and, further, established a connection between umbellulone and thujone (and thus all the other members of the thujane series) by showing that enantiomorphous homothujadicarboxylic acids (II) were obtained by the oxidation of benzylidene-β-dihydroumbellulone (III) and of benzylidenethujone (IV). The present work provides synthetic proof of the presence of the *iso*propyl*cyclo*propane system in umbellulone and the terpenes of the thujane series, for which the carbon skeleton (V) (Semmler, *Ber.*, 1900, **33**, 275) has been accepted for many years, although no synthetic evidence for this has previously been put forward.

(I.)

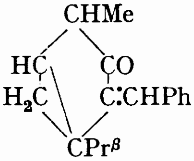


(II.)

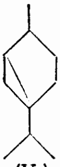




(III.)



(IV.)



(V.)

Ethyl *iso*propylfumarate readily underwent the Buchner–Curtius condensation (*Ber.*, 1885, **18**, 2371; 1890, **23**, 703; cf. v. Auwers and Ungemach, *Annalen*, 1934, **511**, 152) with diazomethane. The resulting pyrazoline lost nitrogen on distillation, yielding *ethyl*

1-iso*propyl*cyclo*propane*-1 : 2-*dicarboxylate.* Hydrolysis of this gave an easily separable mixture of the *dl-cis-* and *-trans*-acids.

dl-trans-1-iso*Propyl*cyclo*propane*-1 : 2-*dicarboxylic acid* (I) had m. p. 197°, and was readily resolved by means of its neutral *brucine* salt. The active acids melted at 155° and had $[\alpha]_{5461}$ $+232{\cdot}1°$ and $-236{\cdot}2°$; the crystalline form of the active acids was markedly different from that of the *dl*-acid and they were also considerably more soluble in water.

dl-cis-1-iso*Propyl*cyclo*propane*-1 : 2-*dicarboxylic acid* (I) crystallised from water as the *monohydrate*, m. p. 98—99°; the anhydrous acid crystallised from benzene–light petroleum had m. p. 126—127°. The resolution of this acid was considerably more troublesome than that of its stereoisomeride, but was eventually achieved by means of the acid brucine salt. The active *acids* crystallised from water as *monohydrates*, m. p. 78—79°, somewhat more soluble in water than the *dl-cis*-acid; these lost water at 100° or in a vacuum over phosphoric oxide and the resulting anhydrous acids, crystallised from benzene–light petroleum, had m. p. 119—120°, $[\alpha]_D$ $+86{\cdot}9°$ and $-88{\cdot}8°$; Tutin (*loc. cit.*) found $[\alpha]_D$ $-89{\cdot}7°$ for his acid.

Tutin (*loc. cit.*) records m. p. 85° for the monohydrate of umbellularic acid; his original specimen (for which I am indebted to Professor Simonsen), however, on examination melted at 78°, not depressed by synthetic *l-cis*-1-*iso*propyl*cyclo*propane-1 : 2-dicarboxylic acid monohydrate (confirmed by Professor Simonsen); on dehydration at 100° Tutin's specimen yielded the anhydrous acid, m. p. 119—120°, not depressed by the synthetic anhydrous *l-cis*-acid. It is thus evident that umbellularic acid has the structure (I) assigned to it by Semmler (*loc. cit.*).

Experiments are in progress to confirm the relationship between thujone and umbellulone by the degradation of thujadicarboxylic acid to umbellularic acid.

EXPERIMENTAL.

iso*Propylfumaric Acid.*—The following is a modification of Walden's method (*Ber.*, 1891, **24**, 2038; cf. Ssemenoff, *J. Russ. Phys. Chem. Soc.*, 1899, **30**, 1003). 110 G. of bromine were added dropwise during 40 minutes to 57 g. of ethyl *iso*propylacetoacetate in 100 c.c. of anhydrous ether. The hydrogen bromide and ether were then removed on the water-bath, and the cooled product added during 15 minutes with shaking to a mixture of 105 g. of powdered potassium hydroxide and 62 c.c. of absolute alcohol, the vigorous reaction being moderated by water-cooling (volatile products are formed which have an irritant action on the skin and eyes). The product was heated under reflux on the water-bath for 30 minutes and then steam-distilled, 300 c.c. of distillate being collected. The acidified residue deposited the crude acid, which was crystallised from water; yield, 22 g. (42%), m. p. 184—186°.

The ethyl ester was prepared by refluxing the acid (50 g.) for 24 hours with absolute alcohol (145 c.c.), benzene (225 c.c.), and sulphuric acid (33 c.c.). The product was poured into water, extracted with benzene, washed with sodium carbonate solution and water, dried, and distilled; yield, 47 g. (69%), b. p. 117—118°/21 mm., 91—92°/1·5 mm.

Condensation of Ethyl iso*Propylfumarate and Diazomethane.*—16 G. of the ester, dissolved in 50 c.c. of ether, were added to an ethereal solution (200 c.c.) of diazomethane prepared from 10 g. of methylurea (Arndt, " Organic Syntheses," 1935, **15**, 3). The mixture was kept (at first in ice) until the yellow colour had faded (14 days). The ether was removed in a vacuum, and the viscous residue distilled; vigorous decomposition set in at 160° (bath temperature) and the product (16 g.) distilled at 126—130°/18 mm. Redistillation afforded 14 g. (82%) of *ethyl* 1-iso*propyl*cyclo*propane*-1 : 2-*dicarboxylate* as a colourless liquid with a faint pleasant smell, b. p. 121—122°/13 mm., 94—96°/0·6 mm. (Found : C, 63·3; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%). The ester was practically unchanged after refluxing for 24 hours with concentrated hydrochloric acid (3 vols.).

14 G. of the ester were refluxed on the water-bath for 3 hours with a solution of potassium hydroxide (14 g.) in ethyl alcohol (56 c.c.). The product was poured into water and, after removal of neutral products with ether, acidified and thoroughly extracted with ether. Evaporation of the ether left the crude acid (8 g.; 75%) as a semi-solid mass. This was triturated with 10 c.c. of acetyl chloride; the insoluble portion was filtered off and proved to be the crude *trans*-acid, m. p. 192—195°; crystallisation from water afforded dl-trans-1-iso*propyl*cyclo*propane*-1 : 2-*dicarboxylic acid* in magnificent flattened prisms, m. p. 197° [Found : C, 55·6; H, 6·9; equiv. (by titration), 86·0. $C_8H_{12}O_4$ (dibasic) requires C, 55·8; H, 7·0%; equiv.,

86·0]. The acetyl chloride filtrate was poured into water and evaporated several times on the water-bath, water being added when necessary. Crystallisation of the product from water yielded dl-cis-1-iso*propyl*cyclo*propane*-1 : 2-*dicarboxylic acid monohydrate* in massive prisms, m. p. 98—99° (Found : C, 50·6; H, 7·5; H_2O, 9·3. $C_8H_{12}O_4,H_2O$ requires C, 50·5; H, 7·4; H_2O, 9·5%). The water of crystallisation was lost in a vacuum over phosphoric oxide; the *anhydrous acid* obtained crystallised (in a phosphoric oxide desiccator) from benzene–light petroleum (both dried over phosphoric oxide *) in rosettes of fine needles, m. p. 126—127° (Found : C, 56·1; H, 6·9%).

In another experiment, the hydrolysis product from 38 g. of the ester was poured into 200 c.c. of water, and the alcohol evaporated on the water-bath. Acidification gave 14·3 g. (50%) of crude *trans*-acid, m. p. 191—193°, and extraction of the filtrate afforded 8 g. (28%) of crude *cis*-acid, which was crystallised from water.

The *cis*-acid was also prepared by heating the *trans*-acid (14·5 g.) with acetyl chloride (5 vols.) in a sealed tube for 6 hours at 220°; the product was poured into water. After several evaporations with water the *cis*-acid obtained was crystallised from water (charcoal); yield, 13·0 g., m. p. 98—99°.

Resolution of the trans-*Acid.*—8 G. of the acid were dissolved in 1700 c.c. of hot water, and 40 g. (2 mols.) of powdered brucine added in small portions, with stirring. After 12 hours, the neutral *brucine* salt of the *l*-acid (19·8 g.) was deposited in feathery aggregates of prisms, m. p. 149—151° (decomp.), $[\alpha]^{25°}_{5461}$ $-$ 98·8° (l = 2, c = 2·060 in chloroform), unchanged on recrystallisation (Found : C, 60·9; H, 7·1. $C_{54}H_{64}O_{12}N_4,6H_2O$ requires C, 60·7; H, 7·1%). This salt was decomposed with ammonia, the brucine removed by filtration, and the residual solution acidified and extracted with ether. The dried extract, on evaporation, yielded 3·27 g. (41%) of crude *l*-acid; on crystallisation from water, this yielded interlacing clusters of fine needles consisting of l-trans-1-iso*propyl*cyclo*propane*-1 : 2-*dicarboxylic acid*, m. p. 155°, $[\alpha]^{21°}_{5461}$ $-$ 236·2° (l = 2, c = 1·317 in acetone) (Found : C, 56·0; H, 6·9%).

On evaporation of the mother-liquor from the brucine salt of the *l*-acid, a crop of needles (13·7 g.) was obtained. On recrystallisation this afforded the neutral brucine salt of the *d*-acid in prismatic needles (12·3 g.), $[\alpha]^{22°}_{5461}$ $-$ 15·39° (l = 2, c = 2·047 in chloroform), unchanged by further crystallisation. This was decomposed with ammonia in the usual manner; the recovered acid was crystallised from water, yielding d-trans-1-iso*propyl*cyclo*propane*-1 : 2-*dicarboxylic acid* in radiating clusters of fine needles, m. p. 155°, $[\alpha]^{17°}_{5461}$ + 232·1° (l = 2, c = 0·983 in acetone) (Found : C, 55·9; H, 7·15%). A mixture of this acid and the *l-trans*-acid melted at 194—195°.

Resolution of the cis-*Acid.*—6·6 G. of the monohydrate of the *dl-cis*-acid were dissolved in 200 c.c. of hot water, and 16·5 g. (1 mol.) of brucine stirred in. After 12 hours, a mixture (15·08 g.) of plates and needles was deposited. Six crystallisations from water afforded the pure acid brucine salt (5·61 g.) of the *d*-acid in transparent plates, m. p. 110—120° (decomp.), $[\alpha]^{20°}_{5461}$ + 6·2° (l = 2, c = 2·020 in acetone). On decomposition with ammonia in the usual manner, these yielded 1·49 g. of the *d-cis*-acid. d-cis-1-iso*Propyl*cyclo*propane*-1 : 2-*dicarboxylic acid monohydrate* crystallised from water in interlacing, stout, prismatic needles, m. p. 78—79° (Found : C, 50·4; H, 7·3; H_2O, 9·5%). The *anhydrous acid* crystallised from benzene–light petroleum (b. p. 60—80°) in rosettes of stout elongated prisms, m. p. 119—120°, $[\alpha]^{16°}_{D}$ + 86·9° (l = 2, c = 1·221 in chloroform) (Found : C, 55·6, 55·8; H, 7·2, 7·1%).

A long series of systematic fractional crystallisations of the mother-liquors failed to yield the *l*-acid in a state approaching purity. A similar lack of success attended conversion into the neutral brucine salt and attempts to use cinchonine, cinchonidine, and strychnine for the resolution. After many trials the pure *l*-acid was obtained by the following procedure. 13·0 G. of the monohydrate of the *dl-cis*-acid were dissolved in 500 c.c. of hot water, and 31·9 g. (1 mol.) of powdered recrystallised brucine (tetrahydrate) stirred in. The solution deposited over-night 32·6 g. of a mixture of plates and needles, the former much more rapidly than the latter. The mixture was accordingly crystallised from 600 c.c. of water and the resulting first crop of plates (brucine salt of the *d*-acid) was filtered off after 3 hours while the solution was still slightly warm. The filtrate was heated to boiling and kept over-night; the resulting crop of needles, after one recrystallisation, yielded the pure acid brucine salt of the *l*-acid (6·9 g.) in prismatic needles, $[\alpha]^{16°}_{5461}$ $-$ 29·5° (l = 2, c = 1·982 in acetone), unchanged by further crystallisation. This was decomposed with ammonia in the usual manner; crystallisation of the product (2·0 g.) from water yielded l-cis-1-iso*propyl*cyclo*propane*-1 : 2-*dicarboxylic acid monohydrate* in interlacing,

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* It is essential to observe these precautions, since the ordinary solvents contain sufficient water for the acid to crystallise as the monohydrate, m. p. 99°.

stout, prismatic needles, m. p. 78—79° (Found : C, 50·4; H, 7·4; H_2O, 9·8%). The *anhydrous acid* crystallised from benzene–light petroleum (b. p. 60—80°) in rosettes of prisms, m. p. 119—120°, $[\alpha]_D^{16°}$ − 88·8° ($l = 2$, $c = 2{\cdot}020$ in chloroform) (Found : C, 56·2; H, 7·1%).

A mixture of approximately equal amounts of the anhydrous *d*- and *l*-*cis*-acids melted at 106°, and a similar mixture of the monohydrates at 99° after softening at 76°.

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