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Antibiotic Substances from the Heart Wood of *Thuja plicata* D. Don

III.* The Constitution of α-Thujaplicin

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As briefly mentioned in the preceding paper[1] a compound, m. p. 34° has been isolated from the heart wood of Western red cedar *(Thuja plicata* D. Don) grown in Sweden (Böda, Öland) in addition to »dehydroperillic acid» and γ-thujaplicin. This substance is an isomeride of the latter compounds possessing the formula $C_{10}H_{12}O_2$. For reasons given below it has been termed α-thujaplicin.

The well crystalline substance is less acidic than γ-thujaplicin. It exhibits exactly the same green ferric colour reaction and similar green chloroform soluble copper complex as does γ-thujaplicin. Their ultra violet absorption curves are also very similar (Fig. 1 in the previous paper).

It seemed justifiable, therefore, to assume a closely analogous structure for α-thujaplicin and consequently the degradation experiments were carried out correspondingly.

Depending upon the quality of the platinum oxide catalyst α-thujaplicin on catalytic hydrogenation absorbs three or four moles of hydrogen in alcoholic solution. In the first case the resulting hydrogenation product is an oil which yields a yellow crystalline precipitate with 2,4-dinitrophenylhydrazine. It reacts with periodic acid and hence probably contains the grouping —CO—CHOH—. On oxidation with potassium permanganate an acid $C_{10}H_{18}O_4$ was obtained, which did not crystallise but was characterised as the well crystalline diamide. Attempts to characterise the acid as its benzylthiuronium salt failed since, probable due to hydrolysis, the salt could not be obtained with a constant melting point. When four moles of hydrogen are consumed

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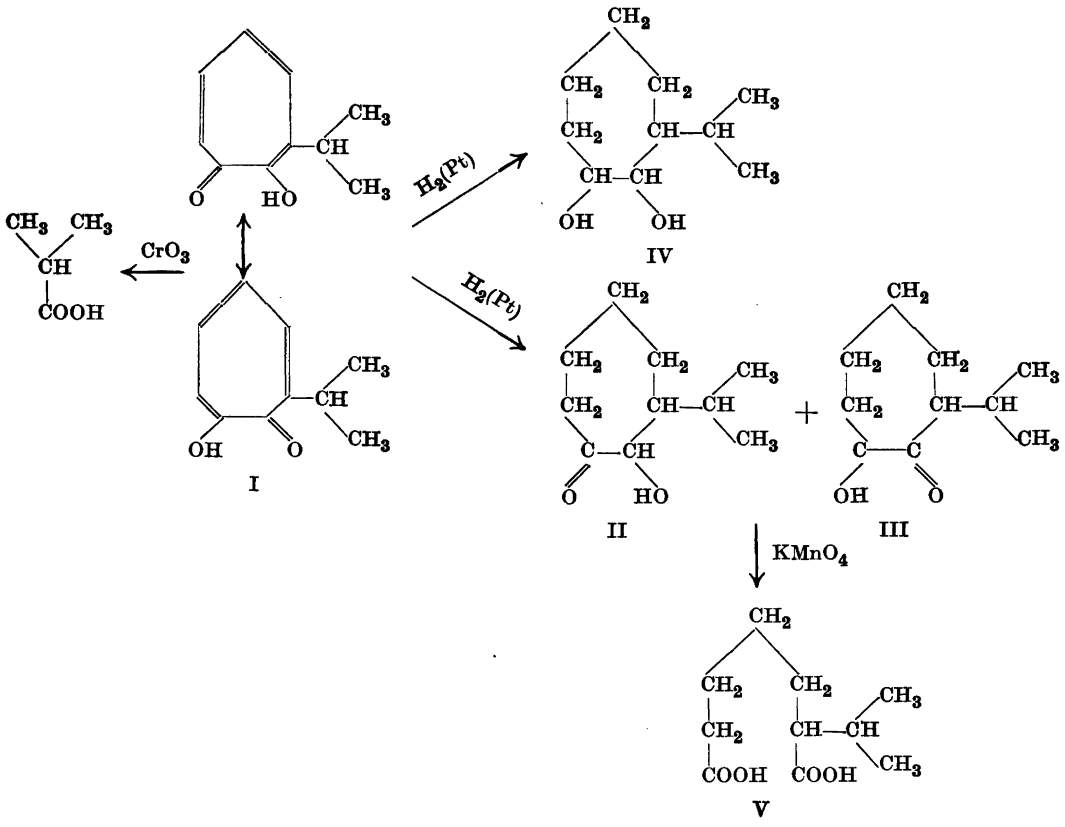
during the hydrogenation of α-thujaplicin an oily diol is formed. Like γ-thujaplicin, α-thujaplicin on carefully conducted oxidation with chromic acid yields *iso*butyric acid. Hence, by analogy with the degradation of γ-thujaplicin to γ-*iso*propylpimelic acid one would expect the acid $C_{10}H_{18}O_4$ to be α- or β-*iso*propylpimelic acid. The former was synthesised and found to be identical with the acid obtained by degradation of α-thujaplicin.

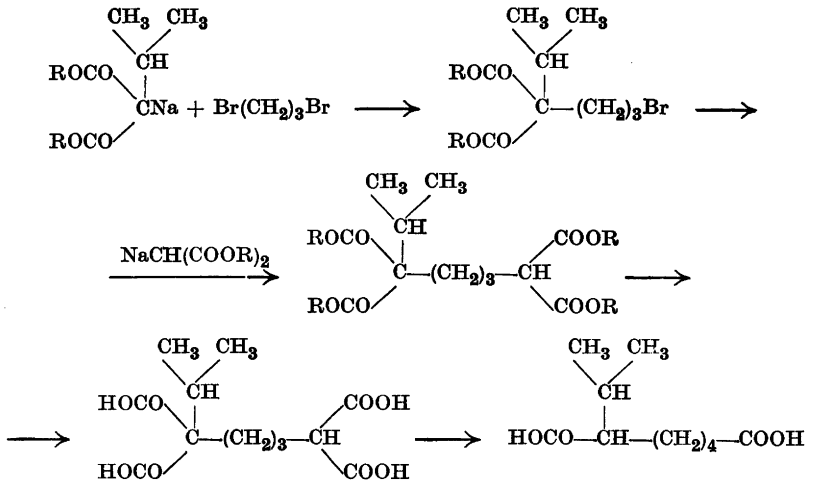
It follows that α-thujaplicin possesses structure I and the hydrogenation and oxidative fission of the hydrogenation product may be outlined in the scheme:



The name α-thujaplicin defines the position of the *iso*propyl group as being α relative to the oxygen atoms.

The oily hydrogenation product of α-thujaplicin most probably is a mixture of the keto alcohols II and III and the glycol IV. On oxidation they are oxidised to α-*iso*propylpimelic acid.

The synthesis of *α-iso*propylpimelic acid was accomplished by a method closely analogous to that of Francke and Kroupa [2] for the synthesis of *α-n*-propylpimelic acid.



V

The acid V was only obtained as an oil but furnished a diamide, the m. p. of which was undepressed when mixed with the diamide of the acid obtained by degradation.

Regarding the physico-chemical aspects of the α-thujaplicin molecule, so similar to those of γ-thujaplicin, it is sufficient to refer to the previous paper [1].

Like γ-thujaplicin, α-thujaplicin is a potent antibiotic. It appears, however, to be somewhat less active than γ- and β-thujaplicin. A full account of these properties will be published shortly by Docent E. Rennerfelt.

EXPERIMENTAL

The extraction of the heart wood and the separation of α-thujaplicin from the accompanying γ-thujaplicin has been described in the previous paper. The α-thujaplicin thus obtained was distilled in a vacuum and recrystallised from light petroleum, m. p. 34°.

$C_{10}H_{12}O_2$ (164.1)	Calc.	C 73.13	H 7.37
	Found.	» 73.27	» 7.41

Oxidation of α-thujaplicin

α-Thujaplicin was oxidised in the same manner as γ-thujaplicin, 0.2 g α-thujaplicin yielding 0.615 millimole of volatile acid (50 % of theoretical amount). The salt solution

was evaporated to dryness and the acid converted to its *p*-bromophenacyl ester. After recrystallisation from dilute alcohol this had m.p. 76—77° alone or admixed with an authentic sample of *iso*butyric acid *p*-bromophenacyl ester.

Hydrogenation of α-thujaplicin

a) α-Thujaplicin (1 g) was dissolved in alcohol and hydrogenated with Adams' PtO_2-catalyst. The hydrogen uptake amounted to 430 ml (the consumption of three moles of hydrogen requires 410 ml). The alcohol was removed in a vacuum and the product distilled. B.p. 100—110°/17 mm. With 2,4-dinitrophenylhydrazine a yellow precipitate appeared immediately.

$C_{10}H_{18}O_2$ (170.2)	Calc.	C 70.51	H 10.68
	Found.	» 69.67	» 10.92

b) α-Thujaplicin (0.2 g) was hydrogenated with Adams' PtO_2-ctalyst [of better quality than in a)] in alcohol. 110 ml of hydrogen were absorbed (calculated for 4 moles 110 ml). The alcohol was removed in a vacuum. The remaining very viscous oil was distilled in a high vacuum.

$C_{10}H_{20}O_2$ (172.2)	Calc.	C 69.69	H 11.73
	Found.	» 69.30	» 11.55

Oxidation of the hydrogenation product

The hydrogenation product from a) (0.35 g) was suspended in water, and a small amount of sodium carbonate added followed by potassium permanganate (0.4 g) in small portions. The reaction mixture was acidified and the manganese dioxide dissolved with sulphur dioxide. The acid was extracted with ether and the ether shaken with sodium hydrogen carbonate solution. The acid was regenerated with mineral acid and recovered by ether extraction. After evaporation of the ether 0.22 g of an oil was obtained, which did not crystallise.

The acid was converted into its diamide through the acid chloride in the usual manner. The diamide was recrystallised from ethyl acetate m.p. 167—168°.

$C_{10}H_{20}O_2N_2$ (200.2)	Calc.	N 13.99
	Found.	» 14.02

Synthesis of α-*iso*propylpimelic acid

α-*Iso*propyl-α,α'-dicarboxypimelic acid was prepared following the directions of Francke and Kroupa [2] for the preparation of α-*n*-propyl-α,α'-dicarboxypimelic acid, using *iso*propyl bromide instead of *n*-propyl bromide. The acid was recrystallised from light petroleum—ether, decomposition point 180—185°. It can also be recrystallised from conc. hydrochloric acid. Prolonged heating with the mineral acid, however, causes decarboxylation.

$C_{12}H_{18}O_8$ (290.2)	Calc.	C 49.62	H 6.27
	Found.	» 49.93	» 6.47

*α-Iso*propylpimelic acid was obtained by heating the tetracarboxy compound (0.5 g) to 190° in an oil bath until carbon dioxide evolution ceased. The product was distilled in a vacuum and obtained as an oil which could not be induced to crystallise. It was converted into its amide which on recrystallisation from ethyl acetate, had m. p. 166—167°, undepressed on admixture with the amide of the acid obtained by degradation of α-thujaplicin.

$C_{10}H_{20}O_2N_2$ (200.2)	Calc.	N 13.99
	Found.	» 13.97

SUMMARY

The structure of α-thujaplicin, one of the toxic principles of the heart wood of *Thuja plicata* D. Don, grown in Sweden, has been elucidated. It is 1-*iso*propyl*cyclo*heptatrien-(1,4,6)-ol-(2)-one-(3) *viz.* 1-*iso*propyl*cyclo*heptatrien-(3,5,7)-ol-(3)-one-(2), or *α-iso*propyltropolone.

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REFERENCES

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2. Francke, A., and Kroupa, A. *Monatsh.* **69** (1936) 167.

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