

Antibiotic Substances from the Heart Wood of *Thuja plicata***D. Don. VII *. A Partial Synthesis of Thujic Acid**

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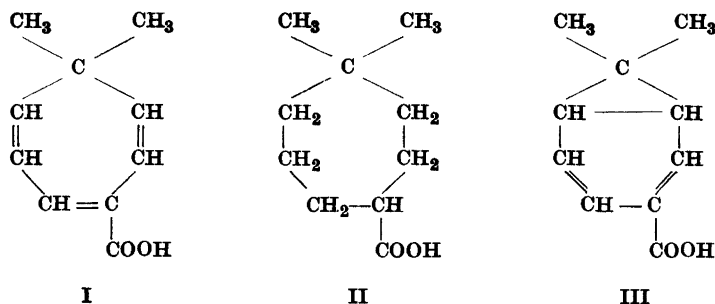
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In a previous paper in this series the structure (I) was proposed for thujic acid¹. This suggestion was based on the hydrogenation of thujic acid to hexahydrothujic acid and degradation of the latter to known compounds. While the formulation of hexahydrothujic acid as 4,4-dimethylcycloheptane carboxylic acid (II) appears to be well founded, the deduction of structure (I) for thujic acid was based on the fact that this was the only way in which three double bonds could be placed in the ring skeleton of hexahydrothujic acid. The presence of three double bonds in the molecule of thujic acid was inferred from the ready uptake of three molecules of hydrogen on catalytic hydrogenation^{1,2}.

Later experiments on the hydrogenation of thujic acid, however, led to evidence, which appeared to throw some doubts on the validity of this assumption. When a less active platinum catalyst was used, a marked decrease in the hydrogenation rate was observed after an initial uptake of two molecules of hydrogen. This effect was even more marked when a palladium-charcoal catalyst was used, the uptake of hydrogen ceasing altogether when two molecules had been absorbed. These observations could be interpreted on the assumption that thujic acid contains a cyclopropane ring as in (III); the slower uptake of the third molecule of hydrogen would then correspond to the rupture of this ring.

Although from a biogenetic point of view this formulation appears very attractive, being closely related to the carenes, there are several objections to it. The most serious of these are: 1) The cyclopropane ring in the carenes cannot be hydrogenated under conditions similar to those used in the hydro-

* Part VI. Gripenberg, J. *Acta Chem. Scand.* 3 (1949) 1137

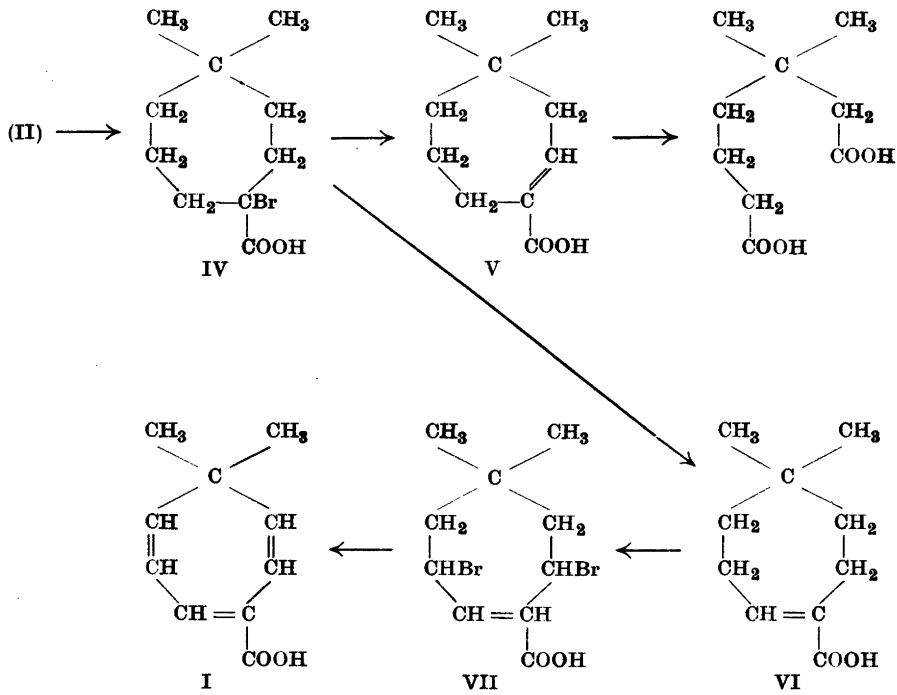


genation of thujic acid ³, and even if such a ring fission were to occur in the latter case, it would be expected to give rise to either 3- or 4-*isopropylcyclohexane* carboxylic acid rather than 4,4-dimethyl*cycloheptane* carboxylic acid, or at least to a mixture of these compounds ⁴. The hydrogenation product is, however, definitely quite homogeneous. 2) Permanganate oxidation of thujic acid gives only dimethylmalonic acid ¹; no caronic acid, the product which would be expected from a substance of structure (III), is formed. The possibility that caronic acid can be further oxidised to dimethylmalonic acid can be ruled out since Baeyer ⁵ has observed that caronic acid is definitely stable towards permanganate.

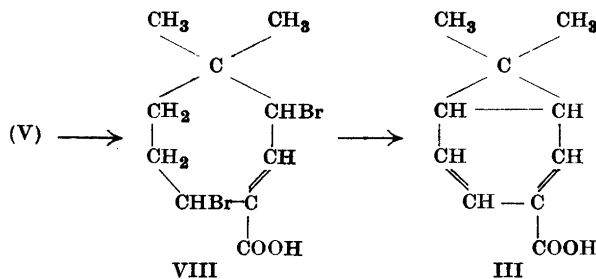
In view of this conflicting evidence, some confirmation of the structure of thujic acid appeared to be highly necessary, and a logical way to achieve this seemed to be to synthesise the acid itself. A natural intermediate in such a synthesis is hexahydrothujic acid (II). While the synthesis of this acid was expected to present little difficulty, its conversion into thujic acid was more uncertain owing to its low stability and the ease with which it rearranges into cumic acid. The second part of the synthesis was therefore carried out first and will be described in this paper. Experiments on the synthesis of hexahydrothujic acid are in progress, and it is hoped to report the completion of the total synthesis of thujic acid in the near future.

The synthesis of thujic acid from hexhydrothujic acid was carried out according to the following scheme.

Hexahydrothujic acid (II) was converted into α -bromohexahydrothujic acid (IV) by the Hell-Volhard-Zelinsky-method. Hydrogen bromide was removed from (IV) by heating with diethylaniline, which was expected to give a mixture of the two unsaturated acids 4,4-dimethyl*cyclohepta-1-ene* carboxylic acid (V) and 4,4-dimethyl*cyclohepta-6-ene* carboxylic acid (VI). The acid (VI), after bromination with N-bromosuccinimide to give (VII) and subsequent removal of two molecules of hydrogen bromide, should give the compound (I).



From the acid (V) it should, on the other hand, be possible to obtain a substance of formula (III) in the following way:



This formation of a *cyclopropane* ring on removal of hydrogen bromide would be analogous to the formation of carone from dihydrocarvone hydrobromide ⁶.

It must however be borne in mind that the bromination with N-bromo-succinimide can be accompanied by an allylic rearrangement ⁷, whereby the dibromo-acid (VII) could be formed from (V) and the dibromo-acid (VIII) from (VI).

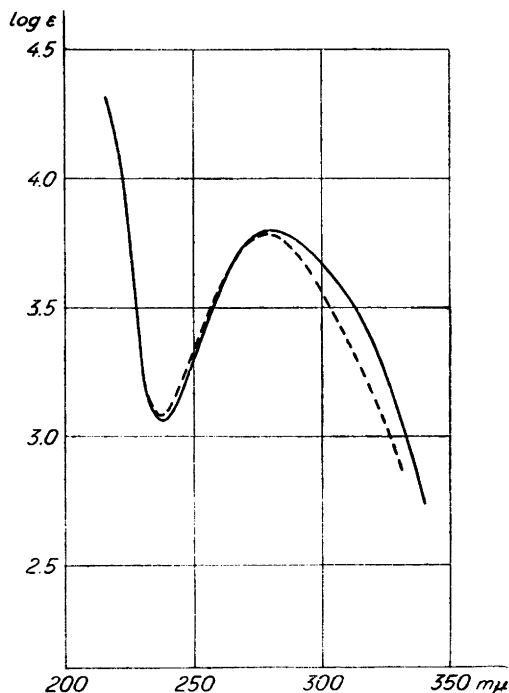


Fig. 1. U. V.-absorption spectra of natural thujic acid (—) and synthetic thujic acid (---) both in ethanol.

Unfortunately it proved to be impossible to separate completely the two acids obtained upon dehydrobromination of bromohexahydrothujic acid. When the mixture of acids was fractionally crystallised a small amount of an apparently pure compound of m.p. 83—85° was obtained as the least soluble fraction, which on ozonisation gave β,β -dimethylpimelic acid, thus proving that it was the acid (V). From the more soluble fractions only preparations with very indefinite melting-points between 30° and 50° could be obtained; analysis of one of these preparations agreed well with the theoretical values for (V) and (VI) thus showing that it was a mixture of these acids. In view of this failure to obtain the acid (VI) in a pure state, the following reaction was carried out on the crude product, in spite of the uncertainty this introduces into the synthesis.

Treatment with two molecules of N-bromosuccinimide gave a very viscous oil, which without further purification was heated with diethylaniline. The product obtained consisted of a steam-volatile component accompanied by relatively large amounts of non-volatile products. The steam-volatile product was a colourless oil, which rapidly solidified. After several recrystallisations from light petroleum a small amount of a substance with m.p. 83—85° was

obtained, and a mixture of this with thujic acid of m.p. 86—88° melted at 84—86°. The difficulty encountered in its purification was not unexpected, since thujic acid obtained from *Thuja plicata* has to be recrystallised very many times before it can be obtained in a pure state. The absorption spectrum of the synthetic product was very similar to, although not quite identical with, the spectrum of authentic thujic acid, as is seen from Fig 1.

Definite evidence of the identity of the synthetic product with thujic acid was obtained by the preparation of its *p*-bromophenacyl ester, which was easy to purify and had the same m.p. as the *p*-bromophenacyl ester prepared from authentic thujic acid and did not depress the melting point of the latter on admixture.

Although the transformation of hexahydrothujic acid into thujic acid has thus been realised it does not differentiate between the structure (I) and (III) for thujic acid, for reasons given above.

A definite proof that thujic acid has the structure (I) was however obtained by a study of the product of the hydrogenation of thujic acid using a palladium-charcoal catalyst. As already mentioned, this led to the uptake of two molecules of hydrogen. From the reaction product there could be isolated a tetrahydrothujic acid which proved to be identical with the acid (V) described above. This fact was established by a mixed melting point determination and by the identity of their absorption spectra with a maximum at 223 $m\mu$ ($\log \epsilon = 4.0$). It would actually have been expected to obtain in this hydrogenation the acid (VI) formed by addition of two molecules of hydrogen to the double bonds more remote from the carboxyl group. The formation of the acid (V) must be assumed to proceed by addition of one molecule of hydrogen to the double bond in 5,6-position followed by addition of a second molecule of hydrogen to the ends of the remaining conjugated doublebond system. In view of the difficulty earlier encountered in obtaining the acid (VI) in a pure state, no search for it was made, but it is quite possible that small amounts of it can occur in the mother liquors of (V). The amount of (VI) produced in the hydrogenation must, however, be very small as judged from the ease with which the acid (V) was obtained in a pure state.

The structure of the acid (V) is established by its mode of formation, its behaviour on ozonisation and its u.v.-absorption spectrum, which definitely show the presence of a double bond in conjugation to the carboxyl group. Thus the failure of thujic acid to take up more than two molecules of hydrogen upon hydrogenation with a palladium-charcoal catalyst is due to the resistance of the α , β -unsaturated linkage under the conditions employed, and not to the presence of a cyclopropane ring in the molecule.

EXPERIMENTAL

 α -Bromohexahydrothujic acid

Hexahydrothujic acid (7 g), obtained by catalytic hydrogenation of thujic acid, was treated with bromine (13 g) in the presence of red phosphorus (0.45 g). After all the bromine had been added, the mixture was heated on a water-bath for one hour, then poured into water and allowed to stand for two days. The solid precipitate was collected and recrystallised from dilute acetic acid. Yield 8.9 g (87 %). For analysis it was further recrystallised from dilute acetic acid and finally sublimed *in vacuo*. M. p. 106°.

$C_{10}H_{17}O_2Br$	Calc.	C	48.2	H	6.9
	Found	»	48.2	»	7.0

Dehydrobromination of α -bromohexahydrothujic acid

α -Bromohexahydrothujic acid (8 g) and diethylaniline (20 g) were heated on an oil bath for one hour at 180°. On cooling diethylaniline hydrobromide crystallised out. The reaction mixture was poured into water, ether was added and the solution made alkaline with sodium carbonate. The ether layer was then separated and extracted with additional portions of sodium carbonate. Acidification of the combined sodium carbonate extracts gave a somewhat sticky precipitate, which was recrystallised from 85 % formic acid. Yield 4.2 g (77 %). On further recrystallisation of this product from formic acid a small amount (0.04 g) of 4,4-dimethylcyclohepta-1-ene carboxylic acid, m. p. 83–85°, was obtained.

$C_{10}H_{16}O_2$	Calc.	C	71.4	H	9.6
	Found	»	71.3	»	9.7

Fractional crystallisation of the mother liquors failed to give any pure substance, except some additional amounts of the same acid. All the more soluble fractions showed very indefinite melting points between 40–50°. A fraction of m. p. 35–40° gave the following analysis:

$C_{10}H_{16}O_2$	Calc.	C	71.4	H	9.6
	Found	»	71.0	»	9.7

Ozonisation of 4,4-dimethylcyclohepta-1-ene carboxylic acid

The acid (0.1 g) was dissolved in chloroform and ozonised at 0°. The chloroform was then evaporated *in vacuo* and the ozonide warmed with water on a water-bath until a clear solution was obtained. Steam was passed in, in order to remove any volatile products, and the solution was then evaporated to dryness giving an oil which subsequently crystallised. Recrystallisation from light petroleum-ether furnished crystals of m. p. 101–102°. No depression was observed on admixture with authentic β,β -dimethylpimelic acid of m. p. 103–104°.

Thujic acid

The acid obtained by dehydrobromination of bromohexahydrothujic acid (m. p. $40-50^\circ$) (1.5 g) was dissolved in carbon tetrachloride (100 ml); N-bromosuccinimide (3.2 g) was added and the mixture refluxed for 8 hours. During the heating a yellow colour developed, which, however, had nearly disappeared when heating was discontinued. The solvent was then distilled off on a boiling water bath, the last traces being removed *in vacuo*. The very viscous oil thus obtained was dissolved in diethylaniline (10 ml) and heated at 180° for one hour. The mixture was then treated in the same way as described above for the dehydrobromination of bromohexahydrothujic acid. The acid liberated upon acidification was taken up in ether and steam distilled; the distillate contained an oil which rapidly solidified and was collected by filtration. Yield 0.31 g (20%). The crude product was purified by recrystallisation from light petroleum, giving crystals of m. p. $82-84^\circ$.

$C_{10}H_{12}O_2$	Calc.	C	73.1	H	7.4
	Found	»	72.0	»	7.3

The p-bromophenacyl ester was prepared from the crude acid and recrystallised from methanol. Glistening leaflets of m. p. $105-106^\circ$ were obtained.

$C_{18}H_{17}O_3Br$	Calc.	C	59.8	H	4.8
	Found	»	59.0	»	4.7

The p-bromophenacyl ester prepared from authentic thujic acid had m. p. 106° .

$C_{18}H_{17}O_3Br$	Calc.	C	59.8	H	4.8	Br	22.1
	Found	»	60.0	»	5.2	»	22.2

Admixture of these two bromophenacyl esters showed m. p. $105-106^\circ$.

Hydrogenation of thujic acid with palladium catalyst

Thujic acid (1 g) was hydrogenated in alcoholic solution with a palladium-charcoal catalyst. The total uptake of hydrogen was 280 ml (calc. for two molecules, 274 ml). The catalyst was then filtered off, the alcohol removed *in vacuo*, and the residue taken up in ether and extracted with sodium carbonate. Acidification of the extract gave an oil that solidified. After recrystallisation, first from dilute methanol and then from light petroleum, it had m. p. $82-84^\circ$, not depressed on admixture with 4,4-dimethylcyclohepta-1-ene carboxylic acid.

SUMMARY

A partial synthesis of thujic acid has been achieved by conversion of hexahydrothujic acid into thujic acid. Definite evidence has been obtained that thujic acid is 4,4-dimethylcyclohepta-2,5,7-triene carboxylic acid.

The analyses were carried out by J. Hukki and K. Salo.

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