

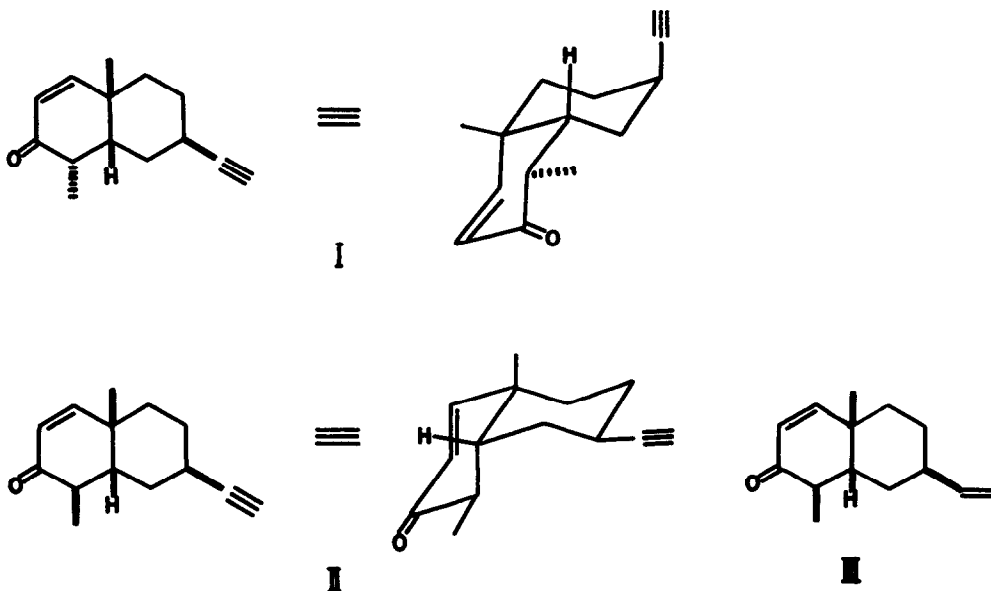
THE TOTAL SYNTHESIS OF CHAMAECYNONE

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Chamaecynone (I), one of the nor-sesquiterpenoids isolated from the essential oil of the Benihi tree (*Chamaecyparis formosensis* Matsum., Cupressaceae), has recently been shown to have the novel non-steroid cis-decalin conformation, and to be one of the first examples of a natural acetylenic compound of terpenoid origin (1); the isolation and the structure of freelingyne, acetylenic sesquiterpene, were reported at about the same time (2).

We now wish to describe the total synthesis of chamaecynone (I) and the related natural products, isochamaecynone (II) and dihydroisochamaecynone (III).



Santonin (IV) (3) was transformed to the dienone carboxylic acid (VI), m.p. 96.5-97.5°C, via santonin 6-epimer (V), according to the method reported (4,5). Reduction of VI using 5% Pd-C in ethanol containing 1% potassium hydroxide (1,6) gave the cis-decalone (VII), m.p. 129°C; ORD, negative Cotton effect ( $[\Phi]_{304}$ , -300,  $[\Phi]_{260}$ , +1020 in MeOH).

Chlorodecarboxylation (7) of the acid (VII) with 7.5 molar equivalents of lithium chloride and 8.5 molar equivalents of lead tetraacetate in refluxing anhydrous benzene under nitrogen atmosphere afforded an oily chloroketone (VIII) in 80% yield. Sodium borohydride reduction of the ketone (VIII) in methanol-ether gave an oily mixture of epimeric chloroalcohol (IX).

Dehydrochlorination of IX with potassium t-butoxide in t-butanol at 90°C under nitrogen atmosphere afforded a mixture of olefinic alcohol, which after being separated by silicic acid chromatography, afforded a 53% yield of an oily compound (X) and 7.5% of a crystalline compound (XI), m.p. 49-51°C. The hydroxy group was shown to have an  $\alpha$ -configuration (equatorial) in X and a  $\beta$ -configuration (axial) in XI by their NMR spectra (8). The NMR of X in  $\text{CCl}_4$  shows a broad sextet (d, d, d) centered at 3.00 ppm due to an axial C-3 hydrogen with coupling constants of 9, 9 and 5 cps. On the other hand, the NMR of XI in  $\text{CCl}_4$  shows a multiplet (half-band width = 7 cps) at 3.69 ppm due to an equatorial hydrogen.

These compounds could be prepared by an alternate route. Thus, treatment of the ethylene ketal (XII), from the chloroketone (VIII), with potassium t-butoxide gave the olefinic ketal (XIII), which was hydrolyzed with dilute hydrochloric acid to afford an oily olefinic ketone (XIV) in a good yield. Sodium borohydride reduction of the ketone in ether-methanol afforded a 80% yield of the olefinic alcohol (X) and (XI) in a ratio of 5 : 3.

Bromination of X in carbon tetrachloride gave the dibromide (XV), m.p. 127-128°C, in quantitative yield, which was subsequently treated with potassium t-butoxide in a mixture of benzene-butanol overnight at room temperature under nitrogen atmosphere, and then was heated at boiling temperature for 6.5 hr. to give an oily acetylenic alcohol (XVI) in 97% yield. Oxidation of XVI with pyridine-chromic acid complex afforded the acetylenic ketone (XVII), m.p. 49°C, in 62% yield, NMR (in  $\text{CCl}_4$ ), 1.08 ppm ( $-\overset{|}{\text{C}}-\text{CH}_3$ , s), 1.00 ppm ( $-\overset{|}{\text{C}}\text{H}-\text{CH}_3$ , d, J = 6.2

cps), 1.91 ppm ( $-\overset{|}{\text{C}}\text{H}-\overset{|}{\text{C}}\equiv\text{C}\text{H}$ , d,  $J \approx 2$  cps); IR (KBr disk), 3290, 2110, 1710  $\text{cm}^{-1}$ ; ORD, negative Cotton effect ( $[\Phi]_{304}$ , -440,  $[\Phi]_{265}$ , +880 in MeOH).

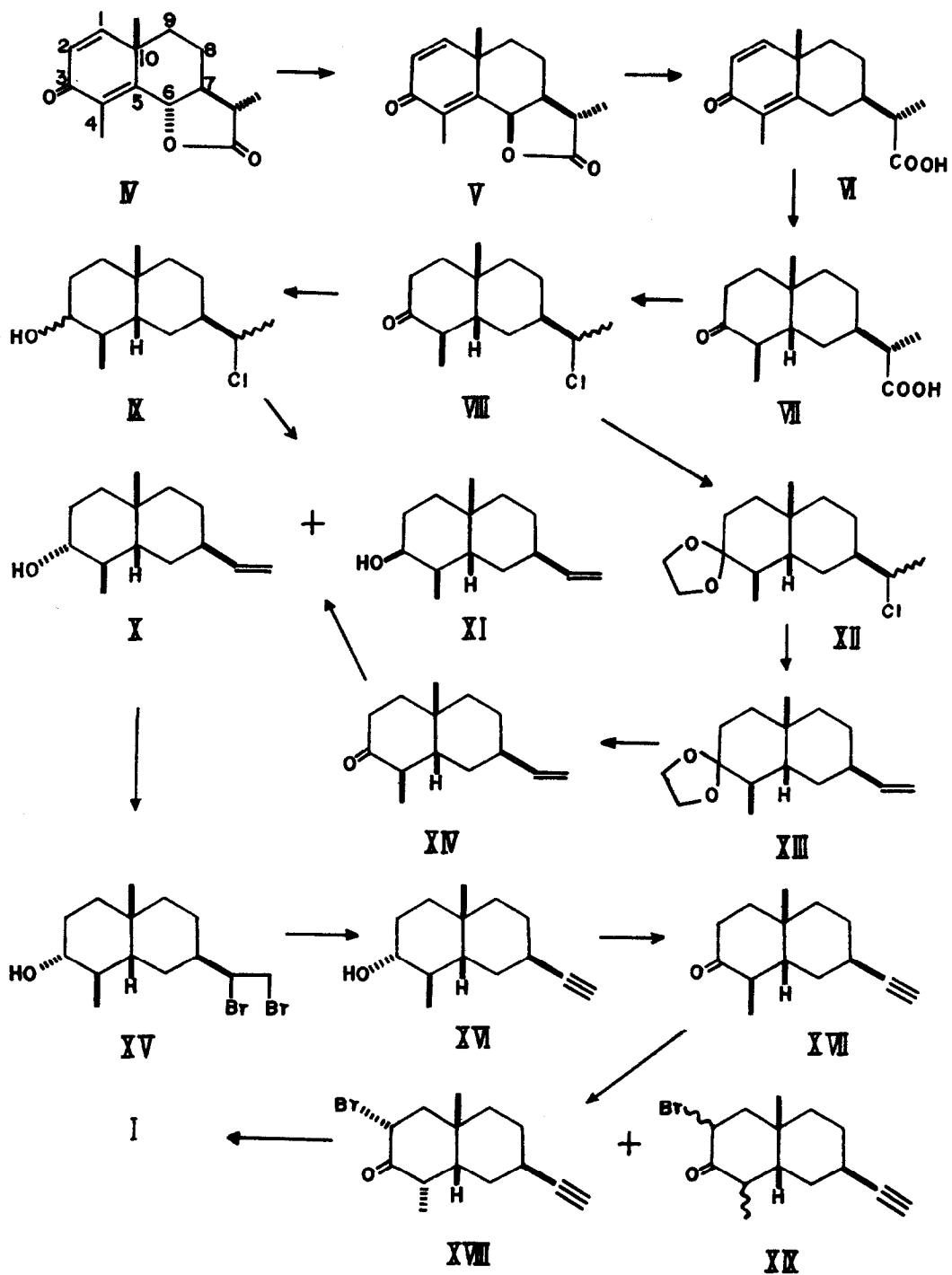
Bromination of the compound (XVII) with bromine in acetic acid in the presence of hydrobromic acid at 5°C afforded two kinds of monobromide, an oil (XVIII) and crystals (XIX) m.p. 129°C, in 56% yield in the approximate ratio of 1 : 1 after separation on a column of silicic acid.

Dehydrobromination of the bromide (XVIII) with lithium bromide and lithium carbonate in dimethylformamide at 140°C produced chamaecynone, in a 38% yield, identical with natural material (I) in mixed melting point, thin-layer and gas chromatographic behavior and infrared, NMR, mass spectra and ORD curve.

From the above result and the spectral properties of the bromide (XVIII) (1, 9), IR (in  $\text{CCl}_4$ ), 3330, 2110, 1736  $\text{cm}^{-1}$ ; NMR (in  $\text{CCl}_4$ ), 1.32 ppm ( $-\overset{|}{\text{C}}-\text{CH}_3$ , s), 0.98 ppm ( $-\overset{|}{\text{C}}\text{H}-\text{CH}_3$ , d,  $J = 6.3$  cps), 1.85 ppm ( $-\overset{|}{\text{C}}\text{H}-\overset{|}{\text{C}}\equiv\text{C}\text{H}$ , d,  $J = 2.3$  cps), 4.56 ppm ( $-\overset{\text{O}}{\underset{\text{Br}}{\text{C}}}-\overset{|}{\text{C}}\text{H}-\text{CH}_2-\text{C}$ , q,  $J = 12.5$  and 7.3 cps); (in benzene), 0.80 ppm ( $-\overset{|}{\text{C}}-\text{CH}_3$ , s), 0.88 ppm ( $-\overset{|}{\text{C}}\text{H}-\text{CH}_3$ , d); ORD (in MeOH or  $\text{CCl}_4$ ), positive Cotton effect, the bromide (XVIII) could be assumed to have the non-steroidal conformation with 2- $\alpha$ (equatorial)-bromo and 4- $\alpha$ (equatorial)-methyl groups as shown in the Figure.

The spectral properties of the other bromide (XIX), IR (in  $\text{CCl}_4$ ), 3330, 2120, 1736  $\text{cm}^{-1}$ ; NMR (in  $\text{CCl}_4$ ), 1.20 ppm ( $-\overset{|}{\text{C}}-\text{CH}_3$ , s), 1.05 ppm ( $-\overset{|}{\text{C}}\text{H}-\text{CH}_3$ , d,  $J = 6.5$  cps), 1.90 ppm ( $-\overset{|}{\text{C}}\text{H}-\overset{|}{\text{C}}\equiv\text{C}\text{H}$ , d, 1.7 cps), 4.67 ppm ( $-\overset{\text{O}}{\underset{\text{Br}}{\text{C}}}-\overset{|}{\text{C}}\text{H}-\text{CH}_2-\text{C}$ , q,  $J = 13.0$  and 6.7 cps); ORD (in MeOH or  $\text{CCl}_4$ ), positive Cotton effect, show that the bromine atom is attached at C-2 in the same plane with carbonyl group, however, the configurations of the bromine and the C-4 methyl group, and the conformation of the ring system could not be established, and the investigations are still continued.

The formation of XVIII from XVII indicates that the configuration of C-4 methyl group and the conformation has inverted during the bromination. Epimerization of an unstable  $\beta$ -methyl group to the stable  $\alpha$ -configuration at C-4 during bromination at C-2 has been observed in trans decalone system (6, 10). However, the above result is the first example for a cis-decalone and this indicates that the stabilities of the steroidal and the non-steroidal conformations are compara-



ble. Ketones XIV or XVII are equilibrated to a mixture of the steroidal and non-steroidal conformations when the C-4 methyl group is epimerized by treatment with base or acid, the results will be reported elsewhere. Since naturally occurring chamaecynone has already been converted (1) to isochamaecynone (II) and dihydroisochamaecynone (III), the total synthesis of these natural products (I-III) are now completed.

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