[Contribution from the Pharmaceutical Research Institute, Medical School, Keio-Gijuku University]

SANTONIN AND RELATED COMPOUNDS. VI. "*cis*-9-METHYL-3-DECALONE" FROM 3-KETO-9-DICHLOROMETHYL-$\Delta^{1,4}$-HEXAHYDRONAPHTHALENE[1]

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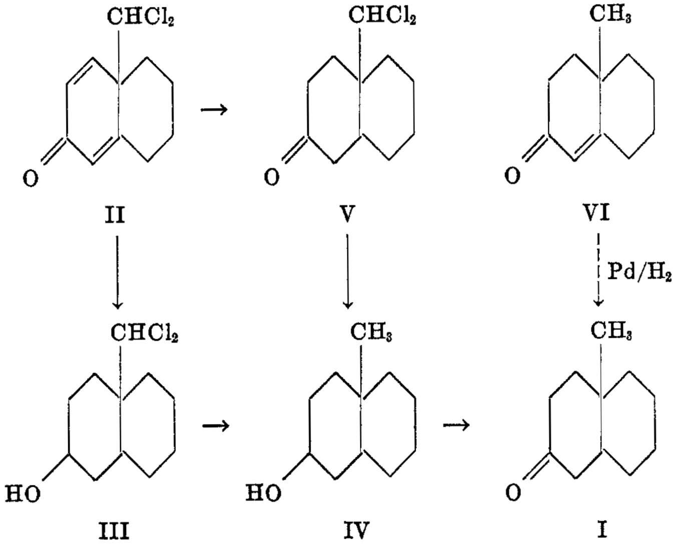
Received July 13, 1955

Woodward (1) reported the preparation of a 9-methyl-3-decalone (I) from 3-keto-9-dichloromethyl-$\Delta^{1,4}$-hexahydronaphthalene (II) through III and IV, and claimed the identification of the ketone (I) with the compound prepared by the catalytic hydrogenation of 3-keto-9-methyl-Δ^4-octahydronaphthalene (VI) (2). Later, it was definitely established by Woodward, *et al.* (3) that the 9-methyl-3-decalone, prepared from VI, was *cis*-locked, and further these authors (4) assigned a *cis*-configuration to the ketone from II. Independently Yanagita and Tahara (5) also gave, from the mode of formation, the *cis*-structure to the same ketone (I), produced from II through V and IV by a slight modification of the method of Woodward (1).



Recent work in this laboratory on the reaction of 9-methyl-3-decalone created the need for a sample of the *trans*-isomer. *trans*-3-Keto-9-methyl-$\Delta^{1,6}$-hexahydronaphthalene, which was prepared from *trans*-1-keto-3-methoxy-9-methyl-$\Delta^{2,6}$-hexahydronaphthalene[2] following the procedure of Speziale, Stephens, and Thompson (6), was readily hydrogenated with palladium-charcoal to *trans*-9-methyl-3-decalone (3). Unexpectedly, it was found that the *trans*-compound so

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[1] This work was supported in part by grants in aid for Scientific Research from the Ministry of Education of Japan and from the Keio-Gijuku University.

[2] The authors are deeply indebted to Dr. Knowles, the Organic Chemicals Division of the Monsanto Chemical Company, for generously supplying this material.

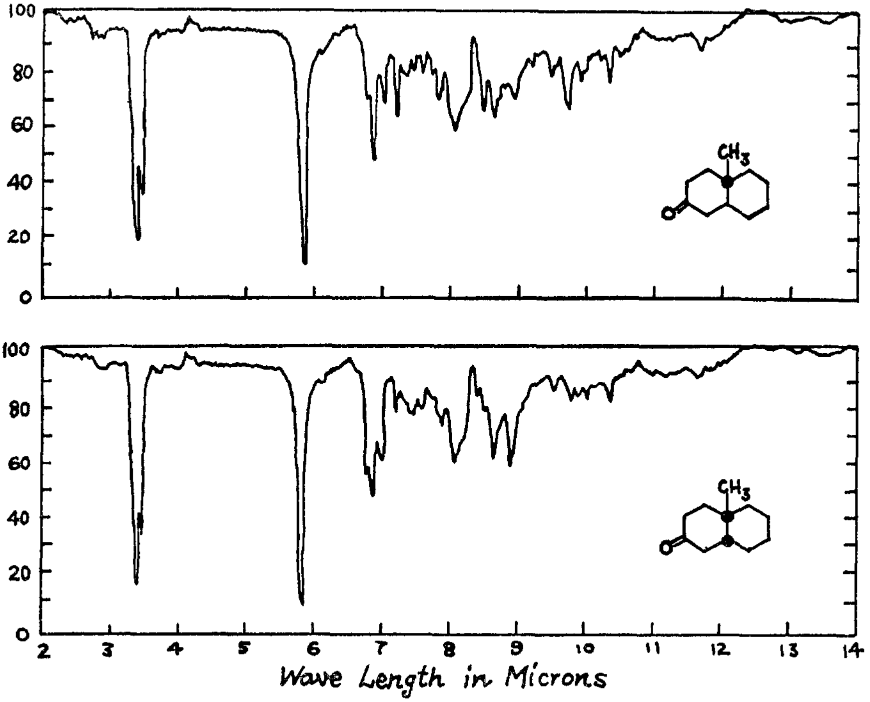

FIG. 1. INFRARED ABSORPTION SPECTRA. Upper curve: *trans*-9-Methyl-3-decalone (I); Lower curve: *cis*-9-Methyl-3-decalone.

obtained was identical with the supposed "*cis*-9-methyl-3-decalone" (I), derived from II, as shown by the mixture melting point determination of their 2,4-dinitrophenylhydrazones. Moreover, it was found, contrary to the result of Woodward (1), that the "*cis*-material" was obviously different from the above *cis*-isomer (3) prepared from the Δ^4-ketone (VI) (2), as shown by the mixture melting point depression of the above derivative. These *cis*- and *trans*-compounds were definitely characterized by comparisons of the infrared absorption spectra (Fig. 1) with those given for the same materials by Woodward, *et al.* (4). It is, therefore, concluded that the supposed "cis-9-methyl-3-decalone" (I) and all the intermediates for preparing I from II, including IV, possess the *trans*-configuration at the ring juncture. Another route (4, 8) to the *cis*-isomer, involving the catalytic hydrogenation of 3-keto-9-methyl-$\Delta^{1,4}$-hexahydronapththalene, was confirmed in the present work.

The foregoing different results on the steric configuration obtained with a dichloromethyl and a methyl group at the 9-position are quite similar to the analogous results reported by Dauben, *et al.* (7) with a carbethoxyl and a methyl substituent in the same octalone system. As pointed out by these authors, the

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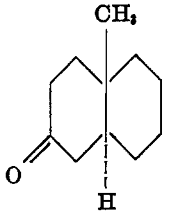
[3] The nomenclature is employed in conformity with that suggested by Hussey, *et al.* (9), and the numbering system is in conformity with that conventionally used for santonin and related natural products.

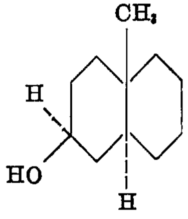
above situation may possibly attribute to an increase in catalyst hindrance due to the larger grouping at the ring juncture.

Recently the alcohol (IV) was assigned the configurational structure of *cis*-9-methyl-*cis*-3-decalone[3] by Hussey, Liao, and Baker (9), but subsequently this formulation was refuted by Dreiding and Tomasewski (10). The latter authors reported that on treatment with lithium aluminium hydride, *trans*-9-methyl-3-decalone (I) gave, in a low yield, *cis*-9-methyl-*trans*-3-decalol, in which the hydroxyl group at the 3-position must be equatorial oriented. As published previously (1, 5), the hydroxyl group in the alcohol (IV) was formed from the keto group in II or V by hydrogenation with platinic oxide in a neutral medium or with sodium metal in wet ether, respectively. It is generally accepted (7) that on hydrogenation under such conditions, an unhindered ketone normally yields an alcohol with the hydroxyl group in an equatorial conformation. From this consideration and the identical melting points, it may be deduced that the present alcohol (IV) is probably identical with the *cis*-9-methyl-trans-3-decalol of Dreiding and Tomasewski (10). In support of this deduction it was found that sodium and boiling ethanol, which seems to control the asymmetry at the ketone group more strongly, effected reduction of the *trans*-ketone (I) to the alcohol (IV) in a much better yield than that reported by lithium aluminium hydride (10).

It is well known that on lithium-liquid ammonia reduction of α,β-unsaturated ketone in a simpler compound (11) and steroids (12), where the double bond terminates at the juncture of the two six-membered rings, the more stable *trans*-ring junction is usually favored. When the 3-keto-9-methyl-Δ^4-octahydronaphthalene (VI) was subjected to lithium-liquid ammonia reduction, the *trans*-ketone (I) was isolated as its 2,4-dinitrophenylhydrazone, in 60% yield. This reaction may constitute a useful method for the preparation of the *trans*-ketone (I). In the above reduction, in addition to I, a small amount of the alcohol (IV) was isolated as its *p*-nitrobenzoate.



I



IV

EXPERIMENTAL

All temperatures are uncorrected. Infrared absorption spectra[4] were determined with a Perkin-Elmer model 21 double beam spectrophotometer in chloroform solution.

cis-9-Methyl-trans-3-decalol (IV). (*a*). According to the procedure of Woodward (1), this compound was prepared by dechlorination of *cis*-9-dichloromethyl-*trans*-3-decalol (III), which was produced in catalytic hydrogenation of 3-keto-9-dichloromethyl-$\Delta^{1,4}$-hexahydro-

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[4] The authors are greatly indebted to Mr. Shindo, the Takamine Research Laboratory of the Sankyo Company, Tokyo, for this spectra.

naphthalene (II) with platinic oxide in ethanol. It had m.p. 69–70°. Reported, m.p. 69–70° (5).

(*b*). To a refluxed solution of 300 mg. of the *trans*-9-methyl-3-decalone (I), described below, in 300 cc. of ethanol was rapidly added, in small portions, 1 g. of sodium metal. After the completion of the reaction, the mixture was diluted with water, concentrated under reduced pressure, and extracted with ether. The ether solution was washed with water, dried, and evaporated, leaving 250 mg. (83%) of a viscous oil, which crystallized, m.p. 60–65°. Washing with petroleum ether and recrystallization from dilute ethanol gave colorless platelets, m.p. 69°, undepressed with the sample prepared by the preceding method (a).

trans-9-Methyl-3-decalone (I). (*a*). This compound was prepared by the chromic oxidation of the above alcohol (IV) according to the procedure of Woodward (1). The product, b.p. 95–112° at 7 mm., formed the 2,4-dinitrophenylhydrazone, yellow platelets, m.p. 175–178°. Reported, m.p. 151–152° (1), and m.p. 171–173° (5).

(*b*). *trans*-3-Keto-9-methyl-$\Delta^{1,6}$-hexahydronaphthalene, prepared from *trans*-1-keto-3-methoxy-9-methyl-$\Delta^{2,6}$-hexahydronaphthalene[2] as described by Speziale, Stephens, and Thompson (6), was readily hydrogenated over palladium-charcoal. The product, b.p. 130–133° at 21 mm., quantitatively gave the 2,4-dinitrophenylhydrazone, m.p. 140–145°, which, after being refluxed in ethanol for 4 hours, was recrystallized from ethanol to yellow platelets, m.p. 175°. It showed no depression of the melting point on admixture with the material prepared from IV. Woodward, *et al.* (4) reported that the same $\Delta^{1,6}$-ketone was hydrogenated over palladium-strontium carbonate to the *trans*-ketone (I), b.p. 130° at 20 mm., giving the 2,4-dinitrophenylhydrazone, m.p. 177–178° (4).

(*c*). A solution of 1.0 g. of 3-keto-9-methyl-Δ^4-octahydronaphthalene (VI) in 5 cc. of absolute ether was cautiously added to 50 cc. of liquid ammonia, and under rapid stirring, 3 g. of lithium was added in small portions at −40°. After the stirring was continued for additional 30 minutes, excess lithium was decomposed with ammonium chloride and the ammonia was allowed to evaporate. The residue was mixed with water, extracted with benzene, and the benzene solution was washed with acid, then with water, and dried. Evaporation of the benzene left 0.9 g. of a brown oil, which (40 mg.) was reacted with *p*-nitrobenzoyl chloride in pyridine. The product was chromatographed on alumina; petroleum ether eluted only an oil, and benzene eluted a small amount of *cis*-9-methyl-*trans*-3-decalol (IV) *p*-nitrobenzoate, m.p. 66°, undepressed with the same derivative of IV prepared from II. The original reduction product gave, in 60% yield, the 2,4-dinitrophenylhydrazone, m.p. 174° (after two crystallizations from ethanol), undepressed with the same derivative of I, prepared from II.

cis-9-Methyl-3-decalone. (*a*). This was prepared by the catalytic hydrogenation of 3-keto-9-methyl-Δ^4-octahydronaphthalene (VI) as described by DuFeu, McQuillin, and Robinson (2). The product (90%), b.p. 101–105° at 5 mm., was converted to the 2,4-dinitrophenylhydrazone, m.p. 124–132°, which on three crystallizations from ethanol gave orange needles, m.p. 170–173°. Reported, m.p. 174–175° (4). It showed an obvious depression (15–20°) of the melting point on admixture with the same derivative of the *trans*-isomer (I) derived from II.

(*b*). A mixture of stereoisomeric ketones, produced by the catalytic hydrogenation of 3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene as described by Woodward and Singh (8), was converted to 2,4-dinitrophenylhydrazone, m.p. 110–113°. The hydrazone mixture was absorbed on alumina in petroleum ether, and eluted with petroleum ether-benzene (1:1), and then with benzene. The more readily eluted fraction gave the predominant hydrazone of the *cis*-ketone, m.p. and mixture m.p. 173–174° (after crystallization from ethanol). The hydrazone of the *trans*-isomer (I) was isolated, as less soluble crystals, mainly from the less readily eluted fraction.

SUMMARY

1. The supposed "*cis*-9-methyl-3-decalone" (I), derived from 3-keto-9-dichloromethyl-$\Delta^{1,4}$-hexahydronaphthalene (II) was proved to be *trans*.

2. The stereochemistry of 9-methyl-3-decalol (IV), prepared from II, was described.

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