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

# Santonin and Related Compounds. VIII. 2-Bromo-*trans*-9-methyl-3-decalone[1]

MASAITI YANAGITA and KOJI YAMAKAWA

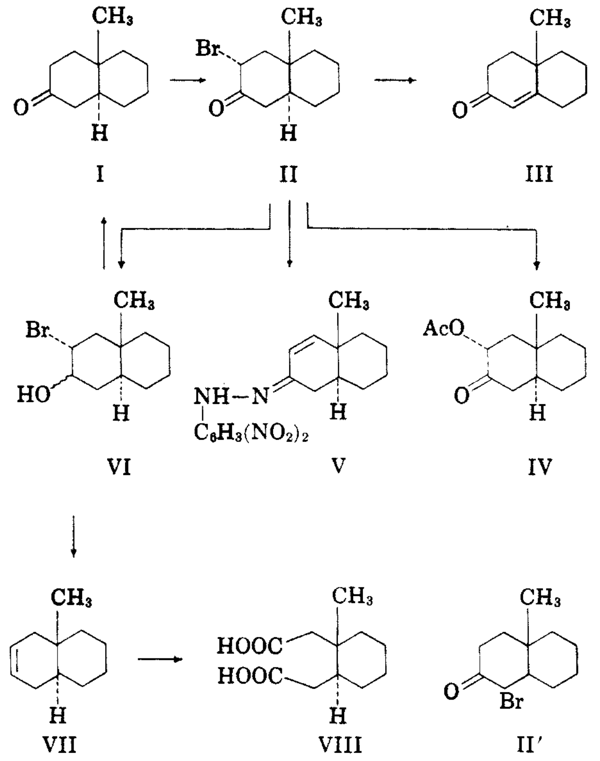
*Received November 28, 1955*

It was confirmed that monobromination in *trans*-9-methyl-3-decalone (I) takes place at the 2-position, but not at the 4-position as proposed previously.

In the previous papers from this Laboratory it was shown[2] that *trans*-9-methyl-3-decalone (I),[3] at the time regarded as *cis*, reacted with bromine in acetic acid to give the monobromo derivative, which with γ-collidine or sodium acetate yielded the $\Delta^4$-3-ketone (III) or the 2-acetoxy-3-ketone (IV), respectively.

It is known[4] that dehydrobromination of monobromoketosteroids with γ-collidine is seldom attended with rearrangements while the reaction with the acetate is accompanied rather frequently by rearrangements. In view of this, the 4-bromo structure (II′) was proposed for the monobromo derivative of I on the basis of the result of the collidine dehydrobromination.[5]

Recently, Riniker, *et al.*[6] stated in their Communication to the Editor that *d*-*trans*-9-methyl-3-decalone on treatment with bromine in acetic acid gave the 2-bromo-3-ketone, which in turn was converted to the $\Delta^1$-3-ketone 2,4-dinitrophenylhydrazone (V) and semicarbazone. The details of their finding, which we are awaiting with interest, have as yet not been published. Therefore, the monobromo ketone was subjected to the Mattox-Kendall procedure with 2,4-dinitrophenylhydrazine in hot acetic acid. As reported by Riniker, *et al.*, the hydrazone (V) of the $\Delta^1$-3-ketone was obtained in 64% yield from this reaction. The location of double bond in the known $\Delta^1$-3-ketone,[7] regenerated from the 2,4-dinitrophenylhydrazone (V) with pyruvic acid, was supported by the ultraviolet absorption spectrum, $\lambda_{\max}^{\text{MeOH}}$ 228 mμ (ε 10600), characteristic for an α,β-unsaturated ketone with no substituents.[8] Since, so far as we know, the saturated cyclic α-bromoketones were readily dehydrobrominated by the Mattox-Kendall procedure with no rearrangements, the above result apparently favored the 2-bromo structure (II).



Now, it is necessary to decide between these two possible structures II and II′ for the monobromo derivative of I. For this purpose, a modification of the method employed by Fieser, *et al.*[9] for the elucidation of the configuration of bromine atom in the α-bromo-3-keto steroids was applied to the present problem. The bromo ketone was reduced with sodium borohydride to a bromohydrin (VI), which was presumably a mixture of epimers of the 3-hydroxyl group, as in the cases of α-halo-3-keto steroids.[9] Without attempting to separate the possible epimers, the bromohydrin was reduced with zinc and acetic acid, by which the analogous bromohydrins of steroids are known to be converted into unsaturated compounds with the double bond between

---

[1] This work was supported in part by the Grant in Aid for Scientific Research from the Ministry of Education of Japan.

[2] Yanagita and Tahara, *J. Org. Chem.*, **18**, 792 (1953).

[3] Yanagita, Yamakawa, Tahara, and Ogura, *J. Org. Chem.*, to be published.

[4] Fieser, Romero, and Fieser, *J. Am. Chem. Soc.*, **77**, 3305 (1955).

[5] Yanagita and Tahara, *J. Org. Chem.*, **20**, 963 (1955), footnote 3.

[6] Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward, *J. Am. Chem. Soc.*, **76**, 313 (1954).

[7] Woodward, Sondheimer, Taub, Heusler, and MacLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

[8] Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 190.

[9] Fieser and Ettorre, *J. Am. Chem. Soc.*, **75**, 1700 (1953); Fieser and Dominguez, *J. Am. Chem. Soc.*, **75**, 1704 (1953); Beereboom, Djerassi, Ginsburg, and Fieser, *J. Am. Chem. Soc.*, **75**, 3500 (1953).

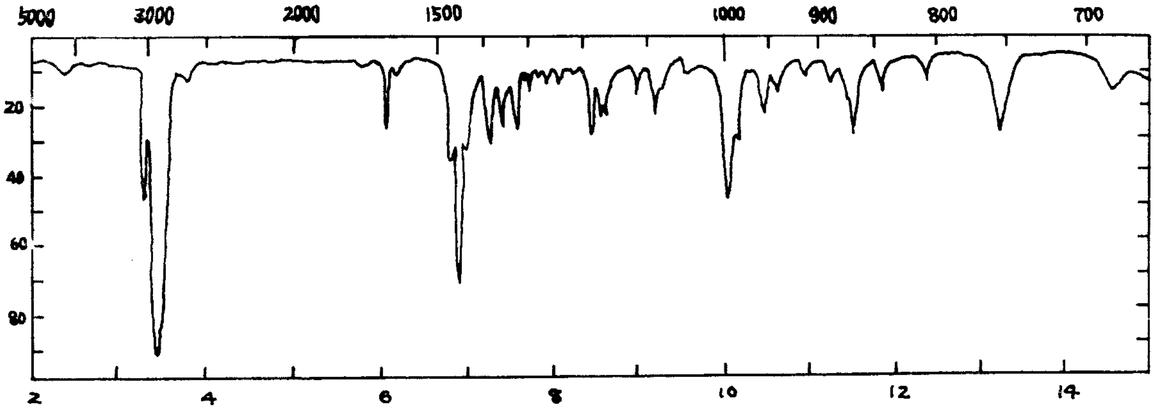


FIG. 1

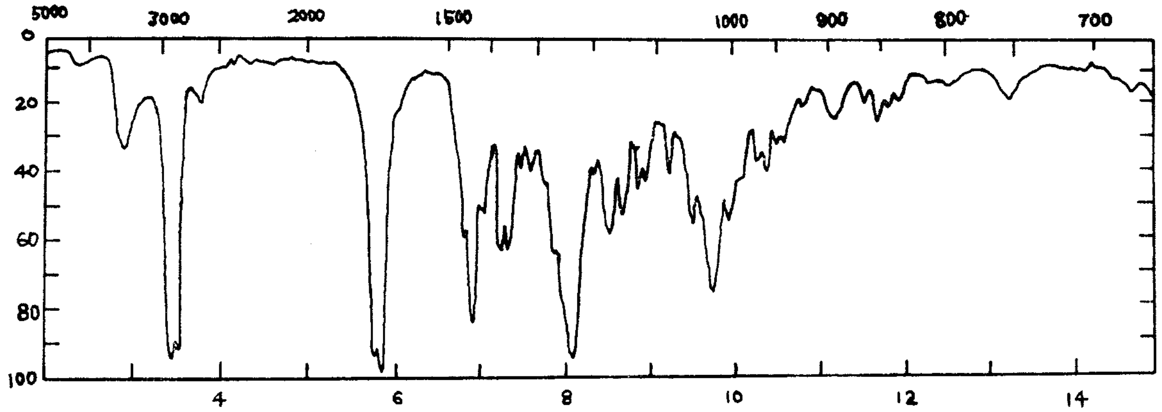


FIG. 2

the carbon atoms initially bearing the bromine atom and the hydroxyl group.[9] The zinc reduction product of VI gave two fractions on distillation. A fraction of the lower boiling point, obtained in 27% yield, showed a weak but sharp absorption band at 1655 cm.$^{-1}$ (Fig. 1), possibly attributed to the *cis*-sym-disubstituted ethylene.[10] Oxidation of this fraction with permanganate afforded the known *trans* - 1 - methylcyclohexane - 1,2 - diacetic acid (VIII),[2,11] indicating that the unsaturated compound has the structure of *trans*-9-methyl-$\Delta^2$-octalin (VII). Consequently the possibility of the formulation of II′ for the monobromo derivative, of I was completely excluded. It is notable that, as described above, the 2-bromo ketone (II) with collidine was converted exclusively to the $\Delta^4$-3-ketone (III) under simultaneous rearrangement, and on reaction with the acetate, gave the normal acetoxy ketone (IV) with its transformation product. These behaviors of II are markedly different from those cited above for the $\alpha$-bromo-3-keto steroids.[4]

The fraction of the higher boiling point, obtained in 14% yield by the zinc reduction of VI, has a strong carbonyl band at 1713 cm.$^{-1}$ (Fig. 2).[12] After treatment with chromium trioxide to remove the impurities, this fraction formed the 2,4-dinitrophenylhydrazone of the starting ketone (I) in a relatively pure state. This result is somewhat unexpected, since the analogous bromohydrins of the steroids, in which the bromine atom is equatorial, gave only the corresponding olefinic compounds on such a reduction, irrespective of the configuration of the hydroxyl group.[9] The equatorial orientation of the bromine atom in the 2-bromo-3-ketone (II) is indicated by the position of the infrared carbonyl band at 1738 cm.$^{-1}$, representing a shift of 20 cm.$^{-1}$ over that (1718 cm.$^{-1}$) of the carbonyl band of the parent ketone (I).[13] This situation is further supported by the ultraviolet spectrum, $\lambda_{\max}^{\text{MeOH}}$ 283 m$\mu$ ($\epsilon$ 22.3), almost identical with that of the parent ketone (I).[14] It is likely that the formation of I from the bromohydrin (VI) may involve *trans* elimination of hydrogen bromide from a part of the possible *cis*-epimer of VI by the acetate ion.

---

(10) Bellamy, *the Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954, p. 33; Henbest, Meakins, and Wood, *J. Chem. Soc.*, 800 (1954).

(11) Yanagita and Yamakawa, *J. Org. Chem.*, 20, 1473 (1955).

(12) Reference 10, p. 127.

(13) Jones, Ramsay, Herling, and Dobriner, *J. Am. Chem. Soc.*, 74, 2828 (1952).

(14) Cookson, *J. Chem. Soc.*, 282 (1954).

## EXPERIMENTAL[15]

All temperatures are uncorrected. Infrared absorption spectra were determined with a Perkin-Elmer model 21 double-beam spectrophotometer.[16]

*trans-9-Methyl-3-decalone* (I). This compound was prepared from *trans*-1-keto-3-methoxy-9-methyl-$\Delta^{2,6}$-hexahydronaphthalene[17] by the procedure reported previously.[7,18] It showed b.p. 130–133° at 21 mm., $\lambda_{max}^{EtOH}$ 283 mμ (ε 20.0), infrared spectrum (C═O) 1715 cm.$^{-1}$ (liquid film), 1718 cm.$^{-1}$ ($CCl_4$).

*trans-2-Bromo-trans-9-methyl-3-decalone* (II). This was prepared from *trans*-9-methyl-3-decalone (I) with bromine by the procedure reported previously.[2] The product (98%) was recrystallized from petroleum ether-benzene (10:1) to colorless needles, m.p. 101–102.5°; $\lambda_{max}^{MeOH}$ 222 mμ (ε 186) and 283 mμ (ε 22.8); infrared spectrum (C═O) 1738 cm.$^{-1}$ ($CCl_4$). Reported,[2] m.p. 99–100°.

*Anal.* Calc'd for $C_{11}H_{17}BrO$: C, 53.87; H, 6.97. Found: C, 53.50; H, 6.93.

*3-Keto-9-methyl-$\Delta^4$-octahydronaphthalene* (III). This substance was prepared from the above 2-bromo-3-ketone (II) with hot collidine by the procedure reported previously.[2] The use of a slow stream of nitrogen did not improve the result. It showed b.p. 115–123° at 8 mm.; $\lambda_{max}^{MeOH}$ 236 mμ (ε 11800); infrared spectrum 1685 cm.$^{-1}$ ($CCl_4$, α,β-unsaturated C═O).[19] Reported,[2] b.p. 140–170° at 2 mm. (bath temperature). It formed the *2,4-dinitrophenylhydrazone*, m.p. 169°.[2]

*trans-3-Keto-9-methyl-$\Delta^1$-octahydronaphthalene 2,4-dinitrophenylhydrazone* (V). A mixture of 220 mg. of the 2-bromo-3-ketone (II) and 200 mg. of 2,4-dinitrophenylhydrazine in 5 cc. of glacial acetic acid was heated on a water-bath in a stream of nitrogen. The red reaction mixture was poured into water, and there was obtained 280 mg. (64%) of an orange-red solid, m.p. 155–160°. Two recrystallizations from ethanol-chloroform (10:1) gave red plates (V), m.p. 161–162°; $\lambda_{max}^{CHCl_3}$ 256.5 mμ (ε 17,350) and 383 mμ (ε 28,830). Reported, m.p. 161–162°[7]; $\lambda_{max}$ 256.5 mμ (ε 17,000) and 383 mμ (ε 29,000).[6] It showed an obvious depression of the m.p. on admixture with the same derivative of the $\Delta^4$-3-ketone (III).

*Anal.* Calc'd for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 58.85; H, 5.64; N, 15.98.

A mixture of 150 mg. of the hydrazone (V), 0.5 cc. of pyruvic acid, and 10 cc. of 50% acetic acid was heated on a water-bath for 1 hour. The reaction mixture was worked up in the usual manner. The parent $\Delta^1$-3-ketone (35 mg., 45%) was obtained as a colorless oil, b.p. 115° at 4 mm.; $\lambda_{max}^{MeOH}$ 228 mμ (ε 10,600). Reported,[7] b.p. 69° at 0.1 mm.

*Sodium borohydride reduction of trans-2-bromo-trans-9-methyl-3-decalone* (II). To a solution of 120 mg. of sodium borohydride in 45 cc. of methanol was added, dropwise, a solution of 750 mg. of the 2-bromo-3-ketone (II) with stirring. After the stirring was continued for 6 hours, the solution was allowed to stand overnight at room temperature. Most of the methanol was distilled under reduced pressure, and the oily residue was acidified with 10% acetic acid, and extracted with ether. After washing with aqueous sodium carbonate and then with water, the ether extract was dried and evaporated to leave 520 mg. (70%) of an oil. which showed no ketonic character and presumably consisted mainly of an epimeric mixture of the bromohydrin (VI).

*Reaction of the bromohydrin* (VI) *with zinc and acetic acid.* To a solution of 520 mg. of the above bromohydrin (VI) in 10 cc. of glacial acetic acid was added 1 g. of acid-washed zinc dust, and the mixture was refluxed in an oil-bath for 2 hours. After cooling the zinc was filtered off, and the filtrate was diluted with water, neutralized with sodium carbonate, and extracted with ether. The ether extract was washed with water, dried, and evaporated to leave an oil, which was fractionally distilled to give two fractions, b.p. 77–83° at 11 mm. (85 mg., 27%) and b.p. 110–120° at 7 mm. (50 mg., 14%). The fraction of the lower boiling point showed an absorption band at 1655 cm.$^{-1}$ (probably *cis*-disubstituted ethylene),[10] but not the hydroxyl and carbonyl band in the infrared spectrum (Fig. 1).

This fraction, containing chiefly the $\Delta^2$-methyloctalin (VII), was oxidized with permanganate. To an ice-cooled solution of 30 mg. of the fraction in 2 cc. of acetone was added, dropwise, a solution of 120 mg. of potassium permanganate in 2 cc. of the same solvent, with stirring. After the stirring was continued for 2 hours, the ice-bath was taken away, and the stirring was maintained for an additional 2 hours at room temperature. A small amount of methanol was added to the reaction mixture and the separated manganese dioxide was filtered off. Evaporation and acidification of the filtrate gave about 10 mg. of a solid, which was washed with petroleum ether and recrystallized from ethyl acetate. *trans*-1-Methylcyclohexane-1,2-diacetic acid (VIII) was obtained as prisms, m.p. 190–193°. It showed no depression of the m.p. on admixture with a sample of VIII obtained directly from I by nitric acid oxidation.[2]

The fraction of the higher boiling point showed the carbonyl band at 1713 cm.$^{-1}$ [12] and a weak band at 3470 cm.$^{-1}$ (presumably due to OH)[20] (Fig. 2). This fraction (8.5 mg.) was oxidized with a mixture of chromium trioxide (10 mg.) and pyridine (0.1 cc.) at room temperature. The oily product formed the 2,4-dinitrophenylhydrazone (4.4 mg., 23%), m.p. 150–163°, of I. Recrystallization from ethanol gave yellow plates, m.p. and mixture m.p. 173–174°.[3,7]

SHINJUKU-KU
TOKYO, JAPAN

---

(15) Microanalyses were carried out by Miss Shibuya of this Laboratory; ultraviolet measurements were by Miss Suzuki in this School.

(16) The authors are greatly indebted to Mr. Shindo, the Sankyo Company, Tokyo, for the determination and interpretation of the infrared spectra.

(17) The authors are deeply indebted to Dr. Knowles, the Organic Chemicals Division of the Monsanto Chemical Company, for the generous supply of this material.

(18) Speziale, Stephens, and Thompson, *J. Am. Chem. Soc.*, **76**, 5011 (1954).

(19) Jones, Humphries, and Dobriner, *J. Am. Chem. Soc.*, **72**, 956 (1950).

(20) Reference 10, p. 84.