41. **Masahisa Yoshida**: Ring Cleavage of 7-Hydroxysantenone. I.*

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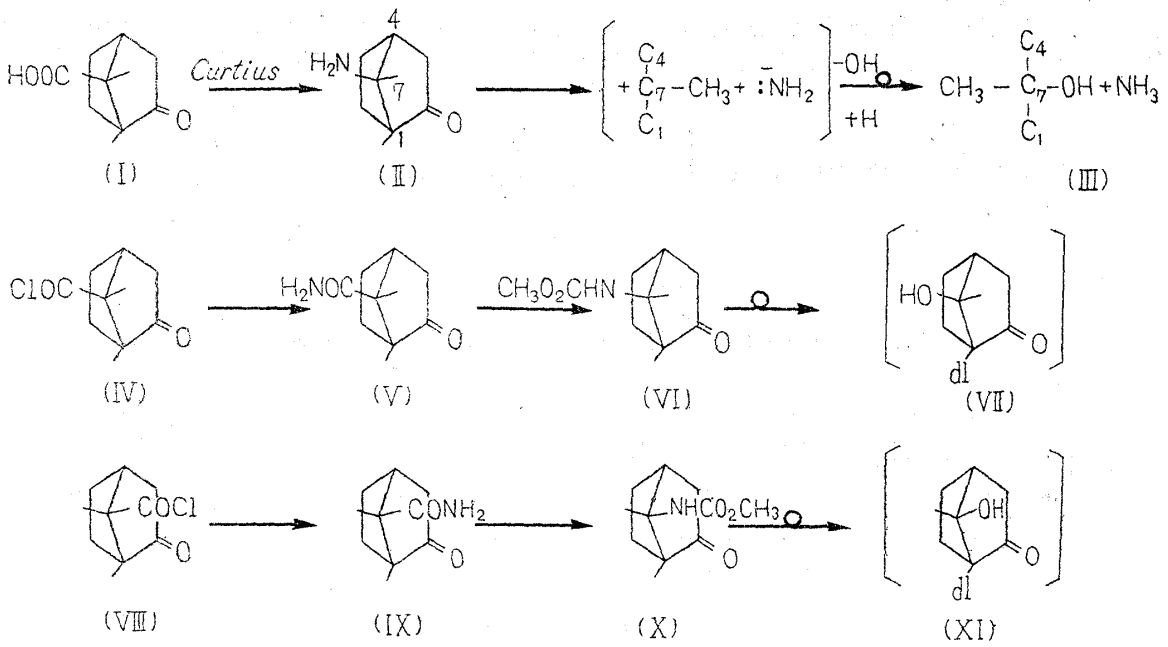
The author previously reported that in view of the fact that *trans*-π-oxocamphor changes into the corresponding peracid[1] by autoxidation and that it is decomposed by alkali into sodium formate and santenone,[2] the aldehyde group of this compound resembles an α,β-unsaturated aldehyde group.[3] In other words, the bridged bond of camphor seems to behave like a double bond.

This time, the author attempted the Hofmann reaction on *d*-isoketopinic acid, a compound obtainable by replacing the aldehyde group of *trans*-π-oxocamphor with a carboxyl group, and clarified the mechanism of ring cleavage of the resulting 7-hydroxysantenone ascribable to the resemblance of its aldehyde group to an α,β-unsaturate aldehyde group and that of the racemization of the product caused by the cleavage. The result is reported herein.

Formerly, Ishidate and Tani[4] attempted the Curtius reaction of *d*-isoketopinic acid (I) and reported the formation of *rac*-7-hydroxysantenone (III) by hydrolyzing the resulting *d*-7-amino-α-santenone (II).

Since this racemization is a peculiar phenomenon, the author studied it from the viewpoint of the formation of antipodes (*d*- and *l*-compounds) and of the isomerization at C_7. If the racemization is caused merely by the formation of antipodes, the products, (VII) and (XI), must be different from each other. To make certain of this point, (I) and its isomer at C_7, *d*-oxodihydroteresantalic acid, were respectively subjected to the Hofmann reaction and the resulting *d*-methoxycarbonylamino-α-santenone (VI) and *d*-methoxycarbonylamino-β-santenone (X) were hydrolyzed to obtain (VII) and (XI).



* This constitutes a part of series entitled "Studies on the Cleavage of Camphor Ring" by M. Ishidate.

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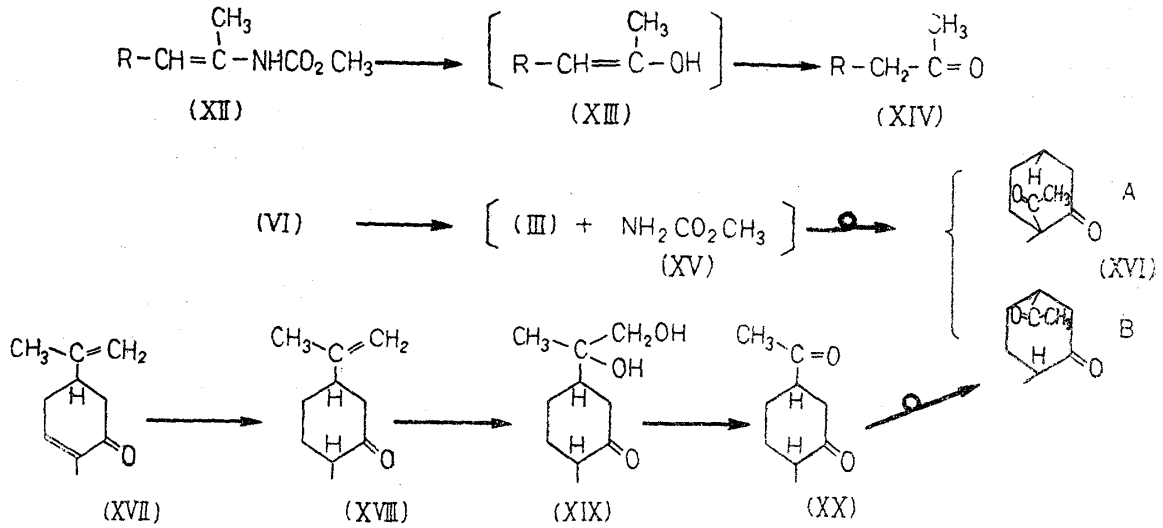
1) M. Yoshida: J. Pharm. Soc. Japan, **73**, 748(1953).
2) M. Ishidate, T. Sano: *Ibid.*, **61**, 350(1941).
3) M. Yoshida: Paper read before the Monthly Meeting of the Pharmaceutical Society of Japan, February 12, 1955.
4) M. Ishidate, T. Tani: J. Pharm. Soc. Japan, **62**, 12(1942).

Contrary to anticipation, however, both products and that of Ishidate and Tani all possessed the same boiling point (b.p_{13} 130°) and their semicarbazones as well as their oximes showed no depression in m.p. on admixture.

The compounds which were thought to be (III), (VII), and (XI) were found to be the same. Incidentally, the attempt to obtain the corresponding amino compounds of (VI) and (X) by hydrolyzing the latter resulted in the liberation of the amino group as methylurethane, which was identified after isolating in crystalline form in the case of (VI).

From the above facts, it may be thought that the racemization was caused by the simultaneous occurrence of the formation of antipodes and isomerization at C_7 to give the isomers (VII, XI), at the time of the introduction of the hydroxyl group into the sextet at C_7. However, although isomerization at C_7 can be explained by the electron theory, it is difficult to explain the simultaneous occurrence of the formation of antipodes and isomerization at C_7 by this theory. The racemization can be elucidated only when the bridged bond is presumed to have the property of a double bond. That is, when (I), which has a carboxyl group at the carbon of the bridged bond, is supposed to have the structure $R-CH=\overset{R'}{\underset{|}{C}}-COOH$, the α,β-unsaturated methoxycarbonylamino compound produced from $R-CH=\overset{R'}{\underset{|}{C}}-COOH$ by the Hofmann reaction is converted by hydrolysis not only into the amino compound, but also into the corresponding aldehyde compound if R′ is a hydrogen,[5] and into the ketone compound if R′ is a methyl. Since in the case of (XII) it is considered to be converted first into (XIII) and then into (XIV) by prototropy, the hydrolysis of (VI) also seems to produce (III) first, which is then converted into (XVI) by the cleavage of the bridged bond when transformed into the keto-form. This explanation well applies also to the formation of the same methyl ketone compound from (X) derived from *d*-oxodihydroteresantalic acid.



If the methyl ketone compound was really produced by the cleavage of the bridged bond, it must contain two keto groups and this was confirmed by its ability to form a dioxime and a disemicarbazone. Presence of a methyl ketone group was also proved by the Legal reaction. Although two formulae, A and B, can be assumed for the methyl ketone compound (XVI), preference is given to the B, on the fact that when

5) Rinkes: Rec. trav. chim., **39**, 200(1920); **45**, 319(1926).

camphor is heated with sulfuric acid for a long time, carvenone[6] is produced by the cleavage of the bond between C_1 and C_7. When the formula B is adopted, formation of the racemic product is well explained because the asymmetric centers at C_1 and C_4 would be broken by the enolation of the adjacent keto groups. The compound corresponding to the formula B is a known compound, *rac*-1-methyl-4-acetylcyclohexanone-2.[7,8] Therefore, the product was compared with the same compound synthesized from *l*-carvone (XVII) in the foregoing manner.

(XX) was derived from (XVII) by a series of reactions shown by the foregoing formulae and racemized with alkali to produce (XVI-B).

The disemicabazone, m.p. 220~222°(decomp.), as well as the dioxime, m.p. 191~195° of the product showed no depression in m.p. when fused with the corresponding compounds of the methyl ketone compound obtained from (VI) and (X).

From the results mentioned above it has been made clear that the hydrolysis of (II), (VI), and (X) probably produces 7-hydroxy compound (III), which however, is soon converted by ring cleavage into the diketo compound (XVI B), simultaneously undergoing racemization.

The author is grateful to Mr. Daijiro Ohata and Mr. Eisaku Kimura for the elementary analyses.

Experimental***

Hofmann Reaction of Isoketopinic Acid :

Isoketopinyl Chloride (IV)[4]—The starting material, isoketopinic acid (I),[9] is a by-product obtained in the preparation of *trans*-π-oxoycamphor by oxidizing *d*-*trans*-π-hydroxycamphor with chromosulfuric acid. To purify the acid it is dissolved in 10% Na_2CO_3 solution, the solution is treated with decolorizing carbon, the acid precipitated with sulfuric acid, and recrystallized from water to colorless needles, m.p. 250~251°, $[\alpha]_D^{23}$: +0.98°(5% solution in EtOH).

Fifty grams of (I) is heated with 100 cc. of $SOCl_2$ for about 2 hrs., the reaction mixture is evaporated to dryness under a reduced presure, and the residue is dissolved in 500 cc. of ether. The ethereal solution is washed successively with water and 20% Na_2CO_3 solution, dried, and concentrated to give colorless needles, m.p. 126~128°, $[\alpha]_D^{23}$: +50.5°(10% solution in $CHCl_3$). Yield, 46.6 g.

Isoketopinyl Amide (V)—To a solution of 40 g. of (IV) in 400 cc. of ether is added conc. NH_3, when the mixture becomes warm and crystals separate, which are recrystallized from dil. EtOH to colorless plates, m.p. 240~242°, $[\alpha]_D^{24}$: +43.9°(10% solution in EtOH). Yield, 34.7 g. *Anal.* Calcd. for $C_{10}H_{15}O_2N$: C, 66.25; H, 8.34, N, 7.74. Found: C, 66.48; H, 8.44; N, 7.78.

***d*-7-Methoxycarbonylamino-α-santenone (VI)**—Twenty grams of (V) is dissolved in MeONa solution prepared from 5 g. Na and 200 cc. MeOH, and 5.5 cc. of bromine is gradually dropped therein under cooling. The mixture is heated at 50° for 4 hrs., allowed to stand overnight and, after diluting with water, extracted with ether. The ethereal solution is dried, evaporated, and the residue is recrystallized from MeOH to colorless prisms, m.p. 109~110°, $[\alpha]_D^{23}$: −8.0°(2.5% solution in EtOH). *Anal.* Calcd. for $C_{11}H_{17}O_3N$: C, 65.62; H, 8.52; N, 6.64. Found: C, 65.75; H, 8.58; N, 6.71.

Hydrolysis of *d*-7-Methoxycarbonylamino-α-santenone (VI)—Twenty grams of (VI) is heated with 150 cc. of 30% HCl for 6 hrs., cooled, and the reaction mixture is neutralized with K_2CO_3. The separated resinous substance is removed. Additional K_2CO_3 is added to the mixture, the separated oil is taken up in ether, and the ethereal solution is concentrated. Although the concentrated solution is left standing in an ice-box, the expected amino-α-santenone does not separate out. So the solution is evaporated and the residue is subjected to fractional distillation. From the forerun, $b.p_{13}$ 120~130°, separate colorless plates, m.p. 54°, $[\alpha]_D^{23}$: 0°(5% solution in EtOH), which are in accored with methylurethane (XI). *Anal.* Calcd. for $C_2H_5O_2N$: N, 18.6. Found: N, 18.6.

The main product, $b.p_{13}$ 130°, $[\alpha]_D^{23}$: 0°(5% solution in EtOH), corresponds to *rac*-1-methyl-4-acetylcyclohexanone(2) (XVI). *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.13; H, 9.09. Found: C, 69.62; H, H, 8.93.

*** All melting points are uncorrected.

6) Armstrong, Kipping: J. Chem. Soc., **63**, 75(1893); Bredt, Roehuvsen, Mohnhein: Ann., **314**, 376 (1900).
7) Tiemann, Semmler: Ber., **28**, 2147(1895).
8) Wallach: *Ibid.*, **28**, 2704(1895).
9) The author is indebted to Yoshitomi Pharmaceutical Industries, Ltd. for the gift of isoketopinic acid.

Disemicarbazone of *rac*-1-Methyl-4-acetylcyclohexanone-2 (XVI)—A mixture of 1 g. of (XVI), 1 g. of semicarbazide hydrochloride, 0.5 g. of AcOK, 5 cc. MeOH, and 2 cc. water is left standing, and the separated product is recrystallized first from MeOH (m.p. 212~214°) and then from dil. EtOH to colorless prisms, m.p. 222°(reported m.p. 213~215°[8]). *Anal.* Calcd. for $C_{11}H_{20}O_3N_6$: C, 49.22; H, 7.52; N, 31.34. Found: C, 48.96; H, 7.34; N, 30.95.

Dioxime of *rac*-1-Methyl-4-acetylcyclohexanone-2 (XVI)—To a solution of 1.5 g. of (XVI) in 15 cc. EtOH is added an aqueous solution of 1.5 g. of $H_2NOH \cdot HCl$ and 3 g. Na_2CO_3. The mixture is heated and the separated crystals, m.p. 110~180°, are recrystallized first from a mixture of ether and EtOH (m.p. 184~188°) and then from a dil. EtOH in colorless needles, m.p. 191~195°, $[\alpha]_D^{20.5}$: 0°(4% solution in 10% NaOH solution). *Anal.* Calcd. for $C_9H_{16}O_2N_2$: C, 58.65; H, 8.76; N, 15.21. Found: C, 58.30; H, 8.81; N, 15.40.

Hofmann Reaction of *d*-Oxodihydroteresantalic Acid

***d*-Oxodihydroteresantalinyl Chloride (VIII)**—The starting material, *d*-oxodihydroteresantalic acid,[10] is a by-product obtained by mild oxidation with chromosulfuric acid of campherol, which is an intermediate in the oxidation of camphor in the living body. Thirty grams of the acid (m.p. 274°, $[\alpha]$: +61.5°) is dissolved in 100 cc. of $SOCl_2$ and processed as usual to obtain the chloride (VIII) as colorless crystals, m.p. 96~100°, $[\alpha]_D^{16}$: +69.0°. Yield, 21 g.

***d*-Oxodihydroteresantalinyl Amide (IX)**—To a solution of 10 g. of (VIII) in ether is added conc. NH_3, and the resulting amide is purified by recrystallization from dil. EtOH as colorless needles, m.p. 236~237°, $[\alpha]_D^{15.5}$: +73.1°. Yield, 8 g. *Anal.* Calcd. for $C_{10}H_{15}O_2N$: C, 66.25; H, 8.34. Found: C, 66.00; H, 8.47.

***d*-7-Methoxycarbonylamino-β-santenone** (X)—Five grams of (IX) is dissolved in MeONa solution prepared from 1.2 g. Na and 50 cc. MeOH, 1.5 cc. Br_2 is dropped therein under cooling, and the mixture is processed as for (VI) to obtain colorless needles, m.p. 120~122, $[\alpha]_D^{15.5}$: +97.7°. Yield, 2.5 g. *Anal.* Calcd. for $C_{10}H_{17}O_3N$: C, 65.62; H, 8.52. Found: C, 65.45; H, 8.31.

Hydrolysis of *d*-7-Methoxycarbonylamino-β-santenone (X)—Ten grams of (X) is heated with 100 cc. of 30% HCl for 6 hrs. After cooling, the reaction mixture is neutralized with K_2CO_3 and the separated resinous substance is removed. The mixture is then made alkaline with NaOH solution, extracted with ether, and the ethereal solution is subjected to fractional distillation. The disemicarbazone and dioxime of the product, $b.p_{13}$ 130°, $[\alpha]_D^{16}$: 0°, well agree with those of (XVI).

***rac*-1-Methyl-4-acetylcyclohexanone-2 from *l*-carvone (XVII)**[11]: i) ***l*-Carvone (XVII)**—10% H_2SO_4 is added to *l*-carvoxime[12] and the mixture is subjected to steam distillation. The distilate is extracted with ether, the ethereal solution is evaporated, and the residue is distilled *in vacuo*. The crude product, $b.p_{18}$ 130°, is redistilled and the portion distilling at 102°/8 mm. is collected; $[\alpha]_D^{11}$: −49.2°(15% solution in EtOH). Oxime, m.p. 71°(reported, m.p. 72°[13]). Semicarbazone (a new compound), m.p. 140~141°. *Anal.* Calcd. for $C_{11}H_{17}ON_3$: C, 63.80; H, 8.20; N, 20.30. Found: C, 63.67; H, 8.36; N, 20.44.

ii) ***d*-Dihydrocarvone (XVIII)**[14]—A mixture of 20 g. of (XVII), Zn dust, 25 g. NaOH, 100 cc. water, and 250 cc. EtOH is heated for 5 hrs. with vigorous stirring, and then EtOH is distilled off. The residue is subjected to steam distillation, the distillate is extracted with ether, and the ethereal residue is left standing overnight with $NaHSO_3$ solution. The resulting crystals are washed with EtOH and ether, and decomposed with NaOH solution. The product is extracted with ether, the ethereal solution is evaporated, and the residue is subjected to fractional distillation. The main product, $b.p_{17}$ 100~104°, $[\alpha]_D^{17.8}$: +14.25°(15% solution in EtOH). Oxime, m.p. 86~88° (Wallach reported m.p. 88~89°). Semicarbazone, m.p. 185~187°(Wallach reported m.p. 189~191°).

iii) ***d*-*p*-Methanone-2-diol-8,9(XIX)**[15]—Ten grams of (XVIII) is added to a solution of 20 g. $KMnO_4$ in 400 cc. of water and the mixture is shaken. After the reaction has been completed, the mixture is filtered, the filtrate is evaporated, and the residue (4.5 g.) is distilled under vacuum, $b.p_{12}$ 204°, $[\alpha]_D^{16.8}$: +28.5°. Yield, 4 g. Oxime, m.p. 198~200°(Wallach reported m.p. 202°). Semicarbazone, m.p. 204°(Wallach reported m.p. 187°).

iv) ***d*-1-Methyl-4-acetylcyclohexanone-2** (XX)—3.6 g. of (XIX) is added to a solution of 2 g. Cr_2O_3 and 3 g. H_2SO_4 in 200 cc. of water, and the mixture is heated on a water bath until it turns green. The reaction mixture is extracted with ether, and the ether residue (3.0 g.) is distilled under vacuum, $b.p_{14}$ 139~141°, $[\alpha]_D^{16.1}$: +30.6°(7% solution in EtOH). Yield, 2.3 g.

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10) The author is indebted to Takeda Phamaceutical Industries, Ltd. for the gift of *d*-oxodihydroteresantalic acid.
11) Royals, Horne: J. Am. Chem. Soc., **73**, 5856(1951).
12) The author's thanks are due Dr. Moroe, Takasago Perfumery Co., Ltd., for the gift of *l*-carvoxime.
13) Wallach: Ann., **275**, 116(1893).
14) Wallach: *Ibid.*, **279**, 377(1894).
15) Wallach: Ber., **28**, 2704(1895).

d-1-Methyl-4-acetylcyclohexanone-2 Dioxime: The crude dioxime, m.p. 194~178°, prepared from 0.14 g. of (XX), 2 cc. EtOH, 0.15 g. $NH_2OH \cdot HCl$, and 0.1 g. Na_2CO_3 is recrystallized from dil. EtOH to colorless needles, m.p. 200~202°, $[\alpha]_D^{20.5}$: +40.0°(4% solution in 10% NaOH solution). *Anal.* Calcd. for $C_9H_{16}O_2N_2$: C, 58.65; H, 8.69; N, 15.21. Found: C, 58.86; H, 8.78; N, 15.41.

d-1-Methyl-4-acetylcyclohexanone-2 Disemicarbazone: The crude disemicarbazone, m.p. 210~212°, prepared from 0.15 g. of (XX), 0.15 g. semicarbazide hydrochloride, 0.8 g. AcOK, 2 cc. MeOH, and 0.5 cc. of water is recrystallized from dil. EtOH to coloress needles, m.p. 220~222°. *Anal.* Calcd. for $C_{11}H_{10}O_2N_6$: C, 49.22; H, 7.52. Found: C, 49.49; H, 7.35.

v) ***rac*-1-Methyl-4-acetylcyclohexanone-2 (XVI-B)**—A solution of 1.5 g. of (XX) in 15 cc. of 12% NaOH solution is heated for 2 hrs., the reaction mixture is extracted with ether, and the ethereal residue is distilled under vacuum, b.p_{12} 119°, $[\alpha]_D^{14.9}$: 0°(3% solution in EtOH). Yield, 1.2 g. Admixture of the dioxime, m.p. 190~194°, (Tiemann,[7] m.p. 197~198°; Wallach,[8] m.p. 195°) with the dioxime, m.p. 191~195°, prepared from (XVI) shows no depression. The melting point 220°(decomp). (Wallach[8], m.p. 203~204°) of the disemicarbazone also agrees well with that (222°(decomp.)) of the disemicarbazone of (XVI).

Summary

It has previously been shown that in view of its ability to form peracid and its behaviour to alkali, *trans*-π-oxocamphor resembles an α,β-unsaturated aldehyde compound and that the bridged bond of camphor acts like a double bond. In the present study, *d*-isoketopinic acid (I) was subjected to Hofmann reaction, and the resulting *d*-methoxycarbonylamino-α-santenone (VI) was hydrolyzed on the assumption that if the bridged bond of camphor acts like a double bond, the resulting 7-hydroxysantenone (III) should be converted into the methyl ketone compound (XVI) by ring cleavage, and this assumption was confirmed. At the same time, the racemization in this reaction was clarified.

(Received March 26, 1955)

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42. **Masahisa Yoshida**: Ring Cleavage of 7-Hydroxysantenone. II.*

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Previously Ishidate and Tani[1] reported that *d*-7-amino-α-santenone (III) was not diazotized by the conventional method and that if the same reaction is conducted in a sealed tube, it was converted into a colored substance probably by the introduction of a nitroso group into the carbon atom adjacent to the carbonyl group, whereas when the compound was warmed a little with caustic alkali, it was readily changed into *rac*-7-hydroxy-α-santenone, evolving ammonia quantitatively.

The author[2] thereafter confirmed by synthetic method that the compound which had been considered as *rac*-7-hydroxy-α-santenone was nothing but *rac*-1-methyl-4-acetylcyclohexanone-2 (IX) produced by the ring cleavage of the 7-hydroxy compound.

However, the fact that (III) is stable to hydrochloric acid and is hardly diazotized and that it is readily hydrolyzed by caustic alkali to (IX) aroused the doubt that (III) might already be an imino compound produced by the ring cleavage. The author, therefore, investigated this point in the present study and found that it is an amino compound possessing a bridged bond. That is, the fact that (III) is positive to both dimethylaminobenzaldehyde and nitroprusside-acetaldehyde color reactions shows that

* This work is a part of series entitled "Studies on the Cleavage of Camphor Ring" by M. Ishidate.

** Hongo, Tokyo (吉田正久).

1) M. Ishidate, T. Tani: J. Pharm. Soc. Japan, **62**, 12(1932).

2) M. Yoshida: This Bulletin, **3**, 215(1955).