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Studies on Camphor Derivatives. II.[1] An Oxidized Product of Dihydrocampholenolactone

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The structure of ketodihydrocampholenolactone (II), which had been obtained by oxidation of dihydrocampholenolactone (I) (1,8,8-trimethyl-2-oxabicyclo[3,3,0]octan-3-one) and called by Fujita,[1] was established to be the formula of 1,8,8-trimethyl-2-oxabicyclo[3,3,0]octan-3,6-dione (III).

Keywords——1,8,8-trimethyl-2-oxabicyclo[3,3,0]octan-3,6-dione; 1,8,8-trimethyl-2-oxabicyclo[3,3,0]octan-3-one; anthelmintic; NMR; lactone formation from oxime; catalysis of $HgSO_4$

In the preceding paper Fujita,[1] one of the authors, reported that on treatment with chromium trioxide dihydrocampholenolactone (I)[3] was converted to an oxidized product which was called ketodihydrocampholenolactone (II) whose structure was assumed to be either of the two formulae, that is, 1,8,8-trimethyl-2-oxabicyclo[3,3,0]octan-3,6-dione (III) or 1,8,8-trimethyl-2-oxabicyclo[3,3,0]octan-3,7-dione (IV) shown in Chart 1. The structure of I described by Fujita[1] was based on the formula of 1,8,8-trimethyl-2-oxabicyclo[3,3,0]-octan-3-one.[3]

It is therefore the purpose on this paper to elucidate the structure of II obtained from I.

It was found that treatment of *d*-campohr (V) with hydroxylamine hydrochloride and sodium hydroxide did not afford completely camphor oxime (VI) for an hour stated by Auwers[4] but for ten hours. Treatment of VI with acetic acid and 30% sulfuric acid using mercuric sulfate[5] as a catalyst afforded directly I, though Tiemann[3] had prepared I through three steps from VI. The structure of I was confirmed as being identical with I prepared from *l*-1,2-campholide (VII) (1,8,8-trimethyl-2-oxabicyclo[3,2,1]octan-3-one) according to the method of Sauers.[3]

Oxidation of I with chromium trioxide in acetic acid and acetic anhydride afforded II in 10% yield stated by Fujita.[5] At this juncture yield of II rose to 30% by adding a few drops of conc. sulfuric acid in the reaction mixture. The infrared (IR) spectrum of II showed bands at 1750 cm^{-1} indicative of the presence of a five membered lactone, at 1392, 1374 and 1178 cm^{-1} indicative of geminal dimethyl group. The nuclear magnetic resonance (NMR) spectrum of II showed signals at δ (ppm) 1.17, 1.32 and 1.51, together along with singlet coupling constant, indicative of the presence of three methyl groups, at 2.23 (doublet) and 2.55 (doublet), together along with $J=18$ Hz, indicative of sole methylene protons of AB type, at 2.81 (quartet, $J=18$, 3.6 Hz) and 2.94 (doublet, $J=18$ Hz) indicative of methylene protons nearby the lactone, and at 2.86 (doublet, $J=3.6$ Hz) indicative of a methine protone which held coupling constant of 3.6 Hz due to one of neighboring methylene protons. From these

1) Part I: A. Fujita and M. Akatsuka, *Yakugaku Zasshi*, **62**, 224 (1947).
2) Location: *5-1, Oe-hon-machi, Kumamoto, 862, Japan.*
3) *a*) F. Tiemann, *Ber.*, **28**, 2166 (1895); *b*) *Idem, ibid.*, **30**, 594 (1897); *c*) J. Bredt, *Ann.*, **314**, 369 (1901); *d*) R.R. Sauers, *J. Am. Chem. Soc.*, **81**, 925 (1959); *e*) T. Hirata, T. Suga, and T. Matsuura, *Bull. Chem. Soc. Japan.* **43**, 2588 (1970); *f*) *Idem, J. Chem. Soc. Perkin I*, **1972**, 258.
4) K. Auwers, *Ber.*, **22**, 605 (1889).
5) Reported as an unpublished method in experimental of the preceding paper.[1]

evidences the position of carbonyl group of II would be more rational in C-6 position of the formula of III than in C-7 of IV.

Consequently, the structure of II has been represented by the formula of III.

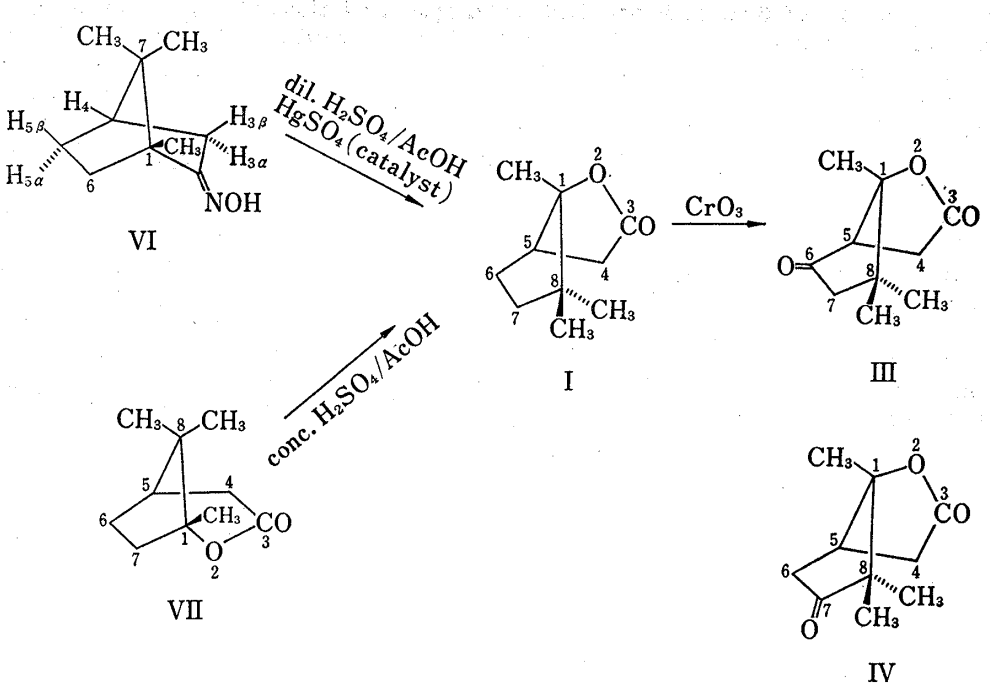

Chart 1

Experimental[6]

Camphor Oxime (VI)——To a solution of $NH_2OH \cdot HCl$ (15 g) in H_2O (60 ml) combined with a solution of NaOH (22.5 g) in H_2O (90 ml) was added a solution of V (15 g) in EtOH (225 ml). The reaction mixture was refluxed for 10 hr, poured into water and acidified with AcOH. The deposited precipitate was recrystallized from 70% EtOH to give VI of quantitative yield, mp 115—117° (lit.[4] mp 117°). IR (KBr) cm^{-1}: 3288 (νO–H), 1690 (νC–N–OH), 1392 and 1376 (δgem. $(-CH_3)_2$). NMR (C_5D_5N) ppm: 0.8 (3H, s, $-CH_3$), 1.15 (3H, s, $-CH_3$), 2.25 (1H, d, 3α-H, $J_{3\alpha\text{-H},\ 3\beta\text{-H}}=18$ Hz), 2.75 (1H, octet, 3β-H, $J_{3\beta\text{-H},\ 3\alpha\text{-H}}=18$ Hz, $J_{3\beta\text{-H},\ 4\beta\text{-H}}=3$ Hz, $J_{3\beta\text{-H},\ 5\beta\text{-H}}=2$ Hz[7]).

Dihydrocampholenolactone (I)=α 1,8,8-Trimethyl-2-oxabicyclo[3,3,0]octan-3-one——To a solution of VI (10 g) in AcOH (50 ml) and 30% H_2SO_4 (100 ml) was added powdered $HgSO_4$ (0.5 g). The reaction mixture was heated at 100—105° for 10 hr and steamdistilled subsequently. The steamdistillate was extracted with ether. The ether layer was taken up and evaporated. To the residue was added 1 N NaOH solution (150 ml). The whole was heated on a boiling water bath for an hour and after cooling, shaken with ether. To the NaOH solution layer was added excess conc. HCl (100 ml) and successively heated on a boiling water bath for an hour. The whole was extracted with ether. The ether layer was taken up, shaken with 5% Na_2CO_3 solution, washed with H_2O, dried and evaporated. The residue was distilled under 20 mmHg to give the main fraction of 140—141° (lit.[3d] bp 126°/13 mmHg) which became colorless plate crystals of I, mp 32° (lit.[3e,f] mp 30—31°, mp 32—33°), 6 g of 60% yield. *Anal.* Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.68; H, 9.50. MS *m/e*: 168 (M^+). IR (KBr) cm^{-1}: 1775 (νC=O, γ-lactone), 1392 and 1374 (δgem. $(-CH_3)_2$). NMR ($CDCl_3$) ppm: 0.94 (3H, s, 8α-CH_3), 1.11 (3H, s, 8β-CH_3), 1.34 (3H, s, 1-CH_3), 2.4 (1H, d, 4β-H, $J_{4\beta\text{-H},\ 4\alpha\text{-H}}=19$ Hz), 2.67 (1H, *ca.* triplet pair of doublet, 5-H, $J_{5\text{-H},\ 6\alpha\text{-H}}=2$ Hz, $J_{5\text{-H},\ 4\alpha\text{-H}}=8$ Hz, $J_{5\text{-H},\ 6\beta\text{-H}}=9$ Hz), 2.97 (1H, quartet pair of doublet, 4α-H, $J_{4\alpha\text{-H},\ 4\beta\text{-H}}=19$ Hz, $J_{4\alpha\text{-H},\ 5\text{-H}}=8$ Hz, $J_{4\alpha\text{-H},\ 6\beta\text{-H}}=2$ Hz). The IR spectrum

6) Melting points were measured with a micromelting point apparatus of Yanagimoto Co. without correction, IR spectra with a 701-G of Japan Spectroscopic Co. (Jasco) Ltd., NMR spectra with a JEOL C-6H (60 MHz) of Japan Electron Optics Lab. (JEOL) Co. using tetramethylsilane (TMS) as an internal standard, mass spectra (MS) with a JEOL-JMS-01 SG of JEOL Co. and optical rotations with a Spectropolarimeter of Jasco Ltd.

7) T. Kamikawa, "The Experimental Chemistry Course, second series," Vol. 5 ed by the Chemical Society of Japan, Maruzen Co. Tokyo, 1965, p. 95.

of I was superimposable on that of the authentic sample of I prepared from VII according to the method of Sauers.[3d] Melting point of I showed no depression on admixture with the authentic sample of I[3d] mentioned above.

Ketodihydrocampholenolactone (II)=1,8,8-Trimethyl-2-oxabicyclo[3,3,0]octan-3,6-dione (III)——To a solution of I (2 g) in AcOH (10 ml) and conc. H_2SO_4 (3 drops), a solution of CrO_3 (3 g) in AcOH (7.5 ml) and Ac_2O (7.5 ml) was added dropwise while stirring at 60°, then kept stirring at 60° for 4 hr. The mixture was allowed to stand overnight at a room temperature and poured into water. The whole was extracted with ether. The ether layer was taken up, washed in order with H_2O, 3% $NaHCO_3$ and H_2O, dried with Na_2SO_4 and evaporated. The left solid became gradually colorless crystalline mass which was recrystallized from petroleum ether to give colorless fine needles of II III, mp 123—124° (lit.[1] mp 122.5°), 0.63 g of 30% yield. *Anal.* Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.94. Found: C, 65.84; H, 7.72. IR (KBr) cm^{-1}: 1765 (νC=O, γ-lactone), 1745 (νC=O, cyclopentanone), 1392 and 1374 δ gem. $(-CH_3)_2$). MS *m/e*: 182 (M^+). NMR ($CDCl_3$) ppm: 1.17 (3H, s, 8α-CH_3), 1.32 (3H, s, 8β-CH_3), 1.51 (3H, s, 1-CH_3), 2.23 (1H, d, 7α-H, $J_{7\alpha\text{-H},\ 7\beta\text{-H}}$=18 Hz), 2.55 (1H, d, 7$\beta$-H, $J_{7\beta\text{-H},\ 7\alpha\text{-H}}$=18 Hz), 2.81 (1H, q, 4$\alpha$-H, $J_{4\alpha\text{-H},\ 4\beta\text{-H}}$=18 Hz, $J_{4\alpha\text{-H},\ 5\text{-H}}$=3.6 Hz), 2.86 (1H, d, 5-H, $J_{5\text{-H},\ 4\alpha\text{-H}}$=3.6 Hz), 2.94 (1H, d, 4$\beta$-H, $J_{4\beta\text{-H},\ 4\alpha\text{-H}}$=18 Hz).

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