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Synthesis of 2-Methoxycarbonyl-5-methyl-7-methoxy-8-isopropyl-tetrahydronaphthalen-1-one and Rearrangement of Isopropyl Group of γ-(5-Isopropyl-4-methoxy-2-methylphenyl)-butyric Acid in Polyphosphoric Acid Cyclization

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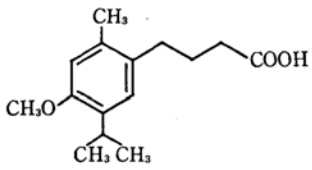
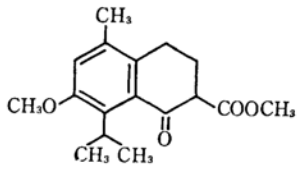
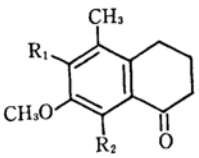
This paper describes the synthesis of the title compound, a tetralone derivative (II) which is regarded as an important intermediate in our synthetic project of sesquiterpenes. Rearrangement of the isopropyl group in γ-(5-isopropyl-4-methoxy-2-methylphenyl)-butyric acid (I) occurred during the cyclization by polyphosphoric acid (PPA). In the course of the preparation of II, a tetralone (III) was required. It was previously reported that tetralone (III) was prepared by a Friedel-Crafts reaction of the acid chloride of I, employing stannic chloride.[1] We attempted to prepare tetralone (III) in a single step by cyclizing butyric acid (I) with PPA.



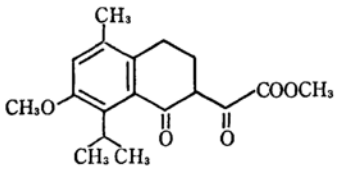
I



II



III: R_1=H, R_2=*i*-C_3H_7
IV: R_1=R_2=H
V: R_1=*i*-C_3H_7, R_2=H



VI

When acid (I) was treated with PPA (77% as P_2O_5), a mixture of three compounds, A, B, and C was obtained in the ratio of 3 : 68 : 29 (determined by gas chromatography). The minor product A, obtained in a crystalline form was found to be the expected tetralone (III) by comparison with authentic III prepared by the unambiguous route.[1] The major product B was a desisopropyl tetralone (IV), which was identified with the authentic specimen[2] prepared from *m*-cresol methylether. Though elimination of alkyl groups (usually *t*-butyl group) on a benzene ring is a recognized feature in certain Friedel-Crafts reactions, very few cases of dealkylations have been recorded for the intramolecular ring closure reactions.[3,4]

The third product C was isomeric with tetralone (III). The NMR spectral patterns of C were similar to those of tetralone (III) except for two signals. The signal (7.31 ppm) due to an aromatic proton in product C appeared at a significantly lower field than the corresponding signal (6.71 ppm) in tetralone (III), and the reverse relationship was observed with the signal due to a methine proton of the isopropyl group (3.40 ppm in C and 3.82 ppm in III) (Fig. 1 and Fig. 2). These differences were ascribed to the anisotropic effect of the carbonyl group and structure V was assigned to product C. Formation of tetralone (V) evidently indicated that a rearrangement of the isopropyl group occurred during cyclization of I. In order to determine whether or not the rearrangement took place after cyclization, tetralone (III) was

1) P. B. Talukdar, *J. Org. Chem.*, **21**, 506 (1956).
2) L. Ruzicka and L. Sternbach, *Helv. Chim. Acta*, **23**, 355 (1940); R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950); A. S. Dreiding and W. J. Pummer, *ibid.*, **75**, 3162 (1953); P. Cagniant and Mme. P. Cagniant, *Bull. soc. chim. France*, **1956**, 1152.
3) N. P. Buu-Hoi and P. Cagniant, *Bull. soc. chim. France*, **11**, 349 (1944).
4) B. A. Nagasampagi, S. Dev, C. Rai and K. L. Murthy, *Tetrahedron*, **22**, 1949 (1966).

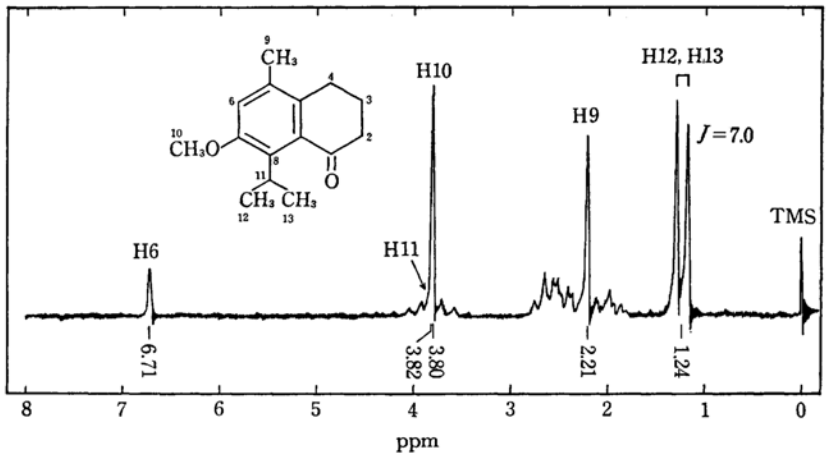


Fig. 1. NMR spectrum of III (CCl_4).

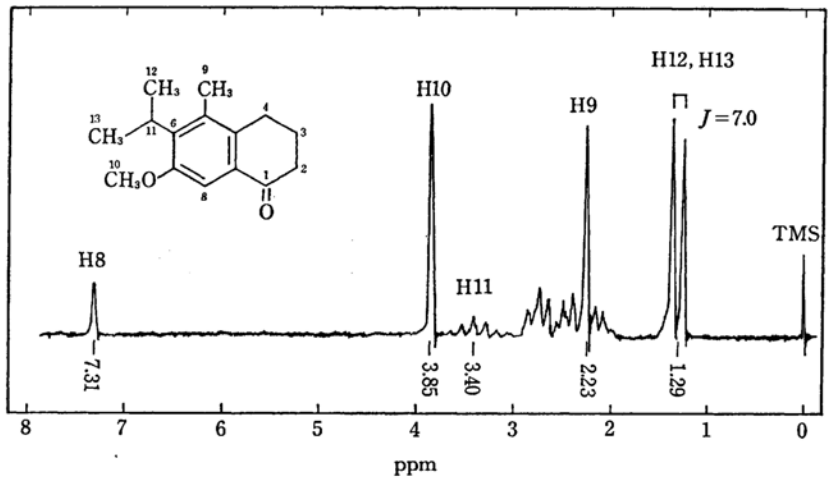


Fig. 2. NMR spectrum of V (CCl_4).

treated with PPA under the same conditions as employed for cyclization of I, affording IV and V. The result indicated that elimination and rearrangement of the isopropyl group occurred after cyclization.

It is of interest that on treatment of tetralone (IV) with PPA in the presence of isopropyl alcohol tetralones (III) and (V) were formed in an almost equal amount after a short period of time, while tetralone (V) was a sole product after a long reaction time. From the findings described above it was deduced that the rearrangement of isopropyl group observed in PPA cyclization of butyric acid (I) was an intermolecular one, the process of which would be as follows. Butyric acid (I) was initially transformed into a normal product, tetralone (III), which underwent elimination of the isopropyl group to give tetralone (IV); some IV further reacted with isopropyl carboium ion which resulted from the reaction, III→IV, at the C-6 position to afford tetralone (V).

Attempts were made to introduce a carboxyl function in the C-2 position of III for the preparation of tetralone (II) having a cadalene skeleton. Among the reactions examined the following sequence of reactions was found to be satisfactory.

Tetralone (III), when treated with dimethyl oxalate in the presence of sodium methoxide, afforded a product (VI), which was decarbonylated by heating with powdered glass to give a crystalline product (II). The spectral data obtained for this compound were in complete agreement with the assigned structure.

Experimental

Melting points and boiling points were uncorrected. The IR spectra were measured on a JASCO IR-S spectrophotometer and the UV spectra (ethanol as solvent) on a Beckman DK-2 spectrophotometer. The NMR spectra (carbon tetrachloride as solvent) were

recorded on a Varian A-60 spectrometer: only prominent peaks are cited; chemical shifts are given in ppm relative to internal tetramethylsilane (TMS); s, singlet; d, doublet; m, multiplet; coupling constants are given in cps. Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer equipped with an all glass inlet system. The gas chromatographic analysis was performed on a Hitachi K-52 instrument. Thin layer chromatography (TLC) was carried out on silica gel G, (E. Merck, A. G., Germany) and column chromatography on silicic acid (100 mesh, Mallinckrodt, U. S. A.).

Polyphosphoric Acid Cyclization of Butyric Acid (I). A solution of acid (I) (3 g) in PPA (70 g: 77% as P_2O_5) was kept at 70°C for 7 hr and left at room temperature overnight. The resulting reddish solution was poured into ice-water. The mixture was extracted with three 30 m*l* portions of ether. The ethereal extract was washed with water, a 5% sodium hydroxide solution (20 m*l*), water (twice) and a saturated sodium chloride solution, and dried over sodium sulfate. On acidification of the sodium hydroxide solution (I) (240 mg) was obtained. The ethereal solution was concentrated to afford a neutral oil (2.2 g), GLC analysis (2 m column, SE-30 on Chromosorb W, 210°) of which showed three peaks, III, IV, and V in the ratio of 3 : 68 : 29. The oily mixture was distilled under reduced pressure (bp 141—144°C/ 2 mmHg) to give an almost colorless liquid, which solidified on standing. The solid mixture was dissolved in hot ethanol and after cooling a crystalline precipitate of IV appeared, which was filtered (0.5 g). The filtrate was concentrated and the residue was chromatographed on silicic acid with ethyl acetate - *n*-hexane (v/v 1 : 25): early fractions afforded crystalline III (40 mg), which was recrystalized from *n*-hexane, and from later fractions a colorless liquid (*ca.* 0.7 g) was obtained, which was distilled to give pure V (*ca.* 330 mg; analytical sample was obtained by preparative GLC); elution with ethyl acetate - *n*-hexane (v/v 1 : 10) gave IV (430 mg), which was recrystallized from *n*-hexane. Spectral and analytical data of III, IV, and V were as follows.

III: mp 88—89°C (lit[1] 88°C); IR (CCl_4), 1685, 1590 (weak) cm^{-1}; UV, 325 mμ (ε, 2400), 259 (6100), 220 (19000); NMR (see Fig. 1).

Found: C, 77.87; H, 8.62%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%.

IV: mp 57—58°C (lit[2] 57—57.5°C); IR (KBr), 1680, 1605 (medium), 1580 (shoulder) cm^{-1}; UV, 321 mμ (ε, 3200), 257 (8400), 218 (20000); NMR, 2.23 (3H, s, aromatic CH_3), 3.77 (3H, s, OCH_3), 6.79 (1H, d, J=3.0, meta coupling, aromatic H), 7.24 (1H, d, J=3.0, meta coupling, aromatic H).

Found: C, 75.73; H, 7.37%. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42%.

V: bp 156—157°C / 2 mmHg; IR (CCl_4), 1685, 1590 (weak) cm^{-1}; UV, 323 mμ (ε, 4000), 269 (12000), 224 (20000); NMR (see Fig. 2); Mass, M^+ 232.

Found: C, 77.20; H, 8.55%. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68%.

Action of Polyphosphoric Acid on III. A stirred solution of III (50 mg) in PPA (2 m*l*) was kept at 70°C for 8 hr and at room temperature for 2 days. The solution was carefully diluted with ice-water and extracted with ether. The ethereal extract was washed with water, a saturated sodium bicarbonate solution, water and a saturated sodium chloride solution, and dried over sodium sulfate. On removal of ether there remained an oil, GLC analysis of which showed formation of IV and V in the ratio of 88 : 12.

Action of Polyphosphoric Acid on V. A stirred solution of V (50 mg) in PPA (2 m*l*) was kept at 70°C for 7 hr and at room temperature overnight. After usual work-up the liquid product (47 mg) was obtained, which was shown to be V.

Action of Polyphosphoric Acid on IV in the Presence of Isopropyl Alcohol. a) A solution of IV (50 mg) in PPA (5 m*l* : 77% as P_2O_5) containing isopropyl alcohol (0.4 m*l*) was heated at 70 for 1 hr. The mixture was diluted with ice-water and extracted with three 10 m*l* portions of ether. The ethereal extract was washed with a 5% sodium hydroxide solution (5 m*l*), water and a saturated sodium chloride solution and dried over sodium sulfate. On removal of ether there remained a colorless oily mixture (*ca.* 50 mg), which consisted of V, III and IV in the ratio of 13 : 17 : 70 (GLC analysis).

b) The experiment in a) was repeated except that the reaction time was extended to 10 hr. GLC analysis of the resulting mixture showed the presence of V and IV in the ratio of 48 : 52.

Tetralone (VI). To a stirred solution of dimethyl oxalate (472 mg) and sodium methoxide (220 mg) in benzene (3 m*l*) was added dropwise a solution of III (455 mg) in benzene (3 m*l*) under ice-bath cooling. The operation was carried out under nitrogen. On standing at room temperature overnight the gray mixture partly solidified, to which 2 N hydrochloric acid was gradually added under cooling. The resulting mixture was extracted with ether repeatedly and the reddish ethereal extract was washed with water and a saturated sodium chloride solution, and dried over sodium sulfate. On removal of ether and excess dimethyl oxalate there remained a crystalline solid (*ca.* 500 mg), which was recrystallized from benzene to give pale yellow needles, VI; mp 133—134°C; IR (KBr), 1735, 1610, 1585 cm^{-1}; UV, 330 mμ (ε, 12000); NMR, 1.30 (6H, d, J=7.0, $\underline{CH_3}$–CH–$\underline{CH_3}$), 2.25 (3H, s, aromatic CH_3), *ca.* 2.7 (4H, m, $-CH_2-CH_2-$), 3.77 (1H, m, $CH_3-\underline{CH}-CH_3$), 3.82 (3H, s, OCH_3 or $COOCH_3$), 3.85 (3H, s, OCH_3 or $COOCH_3$), 6.77 (1H, s, aromatic H), 15.50 (1H, s, enolic OH due to β-diketone).

Found: C, 67.98; H, 7.11%. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97%.

Tetralone (II). Powdered glass was added to melted tetralone (VI) (100 mg) in a flask kept at 160°C. Gas was evolved for several minutes. After cooling the residue was extracted with benzene and the benzene extract was concentrated to give a solid. Recrystallization from methanol and from *n*-hexane afforded pure II (60 mg); mp 77—78°C; IR (KBr), 1745, 1685, 1595 (weak) cm^{-1}; UV, 328 mμ (ε, 2900), 262 (7000); NMR, 1.24 (3H, d, J=7.0, $\underline{CH_3}$–CH–CH_3), 1.27 (3H, d, J=7.0, $CH_3-\underline{CH}-\underline{CH_3}$), 2.21 (3H, s, aromatic CH_3), 3.65 (1H, m, $CH_3-\underline{CH}-CH_3$), 3.68 (3H, s, OCH_3 or $COOCH_3$), 3.80 (3H, s, OCH_3 or $COOCH_3$), 6.73 (1H, s, aromatic H); Mass, M^+ 290.

Found: C, 70.46; H, 7.95%. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64%.