[CONTRIBUTION FROM THE INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

Synthesis of 1-Methyl- and 1,6-Dimethyl-3-methoxy-4-isopropylnaphthalene[1]

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Condensation of succinic and methylsuccinic anhydrides with thymoyl methyl ether was investigated and the resultant ketoacids through usual series of reactions furnished 1-methyl- and 1,6-dimethyl-3-methoxy-4-isopropylnaphthalene.

The present paper describes the synthesis of two naphthalene derivatives (VIII, R = H, CH_3) by the method of Haworth.[2]

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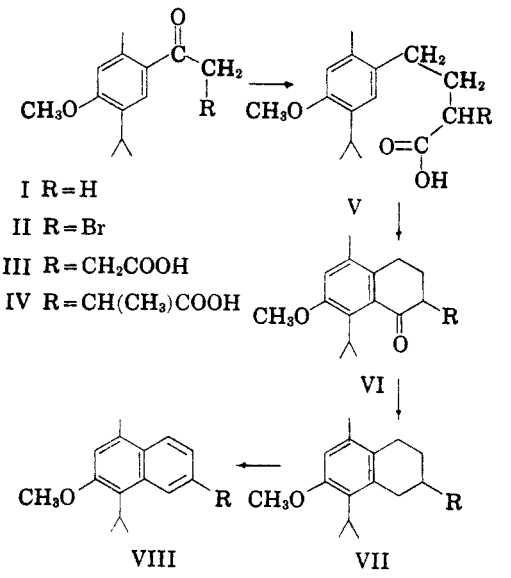

A Friedel-Crafts reaction between thymol methyl ether and succinic anhydride using nitrobenzene as a solvent gave β-(2-methyl-4-methoxy-5-isopropylbenzoyl)propionic acid (III) in quite good yield. This substance was obtained previously by a similar method by Solov'eva and Preobrazhenskii[3] who, however, did not provide any proof of its structure. We now have established its structure by an alternative synthesis in which 2-methyl-4-methoxy-5-isopropylphenyl bromomethyl ketone (II), prepared by bromination[4] of I, was condensed with diethyl sodiomalonate followed by hydrolysis and decarboxylation. The bromo ketone (II) gave 2-methyl-4-methoxy-5-isopropylbenzoic acid when its pyridinium compound was boiled with alkali.[5] Formation of this acid from I conclusively proves that during Friedel-Crafts reaction the acyl groups entered in the position *para* to the methoxy group.[6]

Condensation of methyl succinic anhydride with thymoyl methyl ether under similar conditions furnished a keto acid of m.p. 125–126° as the sole product. It is to be observed that the product might have two possible structures. But it is well known[2,6–8] that the product in which the methyl group is away from the point of attachment to the aromatic ring generally is formed, especially, in solvents with high dielectric constant, such as nitrobenzene. Its structure (IV) was settled unequivocally by its synthesis through condensation of the bromo ketone (II) with diethyl sodiomethylmalonate as described in case of the lower homolog.

The ketoacids (III and IV) were reduced to the corresponding butyric acids (V, R = H, CH_3) using Martin's modification of the Clemmensen reduction[9] in high yields. Usually, small quantities of high-boiling fractions were obtained which might be the pinacol dilactone type of product,[10] but these were not investigated in the present case. The acid (V, R = H) easily solidified, but the other acid (V, R = CH_3) failed to solidify even on long standing.

The butyric acids (V, R = H, CH_3) were converted to the corresponding tetralones (VI, R = H, CH_3) following the intramolecular acylation technique of Johnson and Glenn[11] but it was found that aluminum chloride partially demethylated the product, consequently, the ketones on standing developed a color. Moreover, persistent attempts under different conditions resulted in only moderately improved yields. This result is not surprising in view of the presence of a methoxy group in the *meta*[12] and the bulky isopropyl group in the *ortho*

(1) A preliminary communication appeared in *Science and Culture, (India)*, **17**, 225 (1951).

(2) Haworth and co-workers, *J. Chem. Soc.*, 1125, 1784, 2284, 2717, 2720 (1932); 454 (1934).

(3) Solov'eva and Preobrazhenskii, *J. Gen. Chem. (USSR)*, **15**, 60 (1945); [*Chem. Abstract*, **48**, 1820 (1946)].

(4) Haworth and Woodcock, *J. Chem. Soc.*, 811 (1938).

(5) Wagner and Moore, *J. Am. Chem. Soc.*, **72**, 2884 (1950).

(6) Berlinger, *Org. Reactions*, **5**, 229 (1949).

(7) Ali, Desai, Hunter, and Muhammad, *J. Chem. Soc.*, 1013 (1937).

(8) Desai and Wali, *Proc. Indian Acad. Sci.*, **6A**, 135 (1937).

(9) Martin, *J. Am. Chem. Soc.*, **58**, 1438 (1936).

(10) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(11) Johnson and Glenn, *J. Am. Chem. Soc.*, **71**, 1092 (1949).

(12) Johnson, *Org. Reactions*, **2**, 114 (1948).

position to the site of cyclization. But it was found that use of anhydrous stannic chloride gave a purer product in a slightly improved yield. Moreover, use of stannic chloride simplified the experimental procedure since removal of phosphorus oxychloride from the acid chloride was not essential. The tetralone (VI, R = H) easily crystallized out after distillation whereas the other tetralone (VI, R = CH_3) showed no such tendency.

Reduction of the tetralones (VI, R = H, CH_3) to the corresponding tetralins were carried out by Martin's modification of the Clemmensen reduction[9] or by the Huang-Minlon modification[10] of the Wolf-Kishner reduction. Either process of reduction gave good yields of the tetralins (VII, R = H, CH_3). Dehydrogenation of VII (R = H, CH_3) with the calculated quantity of sulfur furnished the corresponding naphthalene derivatives, 1-methyl-3-methoxy-4-isopropylnaphthalene (VIII, R = H) and 1,6-dimethyl-3-methoxy-4-isopropylnaphthalene (VIII, R = CH_3) as colorless oils which were characterized through their picrates.

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EXPERIMENTAL[13]

2-Methyl-4-methoxy-5-isopropylacetophenone (I) was prepared by the aluminum chloride (17 g.) catalyzed reaction of acetyl chloride (10 g.) with thymoyl methyl ether (20 g.) at −5 to 0°, using nitrobenzene (60 ml.) as a solvent. Yield, 21.3 g., b.p. 120–121°/4 mm., $n_D^{30.5}$ 1.5309; the literature[14] gives b.p. 155°/20 mm.; $n_\alpha^{14.1}$ 1.52477.[15]

The *2,4-dinitrophenylhydrazone* was crystallized in red microneedles from a benzene-ethyl acetate mixture, m.p. 186–187°.

Anal. Calc'd for $C_{19}H_{22}N_4O_5$: C, 59.05; H, 5.70. Found: C, 58.95; H, 6.01.

2-Methyl-4-methoxy-5-isopropylbenzoic acid. To a cold suspension of the ketone (I, 10.0 g.) in chloroform (50 ml.), a solution of bromine (3 ml.) in chloroform (10 ml.) was added dropwise. After an initial lag, bromine was rapidly consumed. After completion of addition the mixture was left at room temperature for three hours at which time hydrobromic acid was removed by drawing a thin current of dry air through the solution for one hour. The mixture was treated with water, washed successively with a dilute sodium bicarbonate solution and with water, dried over sodium sulphate, and chloroform was evaporated off under suction. The residual thick oil then was distilled to give 10.5 g. of the bromo ketone (II), b.p. 165–167°/5 mm.; n_D^{31} 1.5550. The bromo ketone (II, 2.0 g.) was dissolved in dry pyridine (2 ml.); the mixture warmed up rapidly and turned deep brown in color. It was cooled to room temperature and after 20 minutes the crude pyridinium salt was refluxed with sodium hydroxide solution (20 ml., 10%) for one hour. The reddish solution was extracted twice with ether and the cold alkaline solution, after acidification, gave a tan-colored acid, m.p. 136°. Recrystallization from methanol gave practically colorless needles, m.p. 140–141° (the literature[16] gives m.p. 139°).

β-(2-Methyl-4-methoxy-5-isopropylbenzoyl)propionic acid (III). (*a*) *Through the Friedel-Crafts reaction.* To a mixture of thymol methyl ether (32.0 g., 0.20 mole), succinic anhydride (22.0 g., 0.21 mole), and freshly distilled nitrobenzene (200 ml.), cooled to 0°, powdered aluminum chloride (59.0 g., 0.42 mole) was added in several portions with good stirring. During the addition (1.50 hours) the temperature was always maintained at 0 ± 2° and after completion of the addition the ice-bath was maintained for two hours more; then the reddish-violet mixture was slowly allowed to attain room temperature (30°). The mixture was left overnight and then was decomposed with crushed ice and concentrated hydrochloric acid (55 ml.). The nitrobenzene was removed by steam-distillation and a grey viscous liquid remained. On cooling this liquid solidified to a hard cake. It was dissolved in sodium carbonate solution and the alkaline solution was boiled with Norit, filtered, and the filtrate was extracted with ether. The cold alkaline solution was acidified with hydrochloric acid (Congo Red) when a light tan-colored keto acid was liberated which immediately solidified. This acid was filtered off, dried in air, and then in a vacuum desiccator. Yield, 49.3 g. (93.3%); m.p. 91–93°; literature[3] m.p. 92–93°. It was sufficiently pure for the next operation.

(*b*) *Through the bromo ketone* (II). To a cold suspension of sodium dust (0.33 g.) in dry benzene (25 ml.), diethyl malonate (5 ml.) was added and the mixture was refluxed on a water-bath for 4 hours. It was cooled and the bromo ketone (II) (4 g.) in benzene solution (25 ml.) was added; the mixture was refluxed again for 3.5 hours. Benzene was removed under suction and the residual thick reddish oil was refluxed with methanolic caustic potash solution (50 ml.; 10%) for 3 hours. The major portion of alcohol was removed and the residue was cooled and acidified with cold hydrochloric acid. The liberated acid was taken up in ether, dried over sodium sulphate, and solvent was evaporated. The residue then was decarboxylated at 180° for a half hour and the mixture was taken up in sodium bicarbonate solution. The alkaline solution was extracted with ether and then was acidified; an acid was obtained which, after evaporative distillation, melted at 88–90°. Recrystallization from methanol raised the m.p. 93–94° and the acid showed no depression in m.p. when mixed with the keto acid described under (*a*).

β-(2-Methyl-4-methoxy-5-isopropylbenzoyl)-α-methylpropionic acid (IV). (*a*) *Through the Friedel-Crafts reaction.* Following the procedure described above, methyl succinic anhydride (25 g., 0.21 mole), thymoyl methyl ether (32.8 g., 0.20 mole), nitrobenzene (200 ml.), and aluminum chloride (59 g., 0.42 mole) gave 51.5 g. (92%) of a keto acid of m.p. 118–120°; after two crystallizations from alcohol the m.p. was raised to 125–126°.

Anal. Calc'd for $C_{16}H_{22}O_4$: C, 69.06; H, 7.91. Found: C, 69.13; H, 7.68.

(*b*) *Through the bromo ketone* (II). Following the procedure described before, diethyl methylmalonate was condensed with the bromoketone (II) and the ketoacid after evaporative distillation melted at 117–120°. After crystallization from methanol, it melted at 126° and showed no depression in m.p. when mixed with the ketoacid described under (*a*).

γ-(2-Methyl-4-methoxy-5-isopropylphenyl)butyric acid (V, R = H). A mixture of the ketoacid (III, 39.6 g.), amalgamated zinc (from 65 g. of zinc), water (40 ml.), hydrochloric acid (94 ml.), and toluene (55 ml.) was refluxed vigorously for 33 hours with additions of hydrochloric acid (27 ml.) and a few drops of glacial acetic acid at intervals of 6 hours. Then it was cooled and the toluene layer was separated and washed with water. Removal of the toluene left a viscous oil which was dissolved in excess caustic soda solution and was treated with sufficient dimethyl sulphate at 80° and left overnight. The alkaline solution was extracted once with ether and was acidified when a gummy acid was liberated. On evaporative distillation 30 g. (80%) of the butyric acid (V, R = H), b.p. 192–193°/2.5 mm.,

(13) All melting points and boiling points are uncorrected.
(14) Verley, *Bull. soc. chim.*, **19**, 137 (1898 iii).
(15) Eijkman, *Chem. Zentr.*, **78** II, 1209 (1907).
(16) Gattermann and Hess, *Ann.*, **244**, 68 (1888).

was obtained which was crystallized, m.p. 64–65°; literature[3] m.p. 63–65°.

γ-(2-Methyl-4-methoxy-5-isopropylphenyl)-α-methylbutyric acid (V, R = CH_3). Following the above procedure the keto acid (IV, 41.7 g.) was reduced with zinc amalgam (from 65 g. of zinc), water (40 ml.), hydrochloric acid (94 ml.), and toluene (55 ml.), to the corresponding butyric acid. Yield, 33.5 g. (84.4%) of a faintly yellow viscous oil, b.p. 190–192°/2–3 mm. which did not crystallize.

Anal. Calc'd for $C_{16}H_{24}O_3$: C, 72.72; H, 9.09. Found: C, 72.27; H, 8.96.

5-Methyl-7-methoxy-8-isopropyltetralin-1-one (VI, R = H). To a stirred suspension of phosphorus pentachloride (15.20 g.) in benzene (50 ml.), a solution of the butyric acid (V, R = H, 15 g.) in benzene (25 ml.) was added dropwise. When the vigour of the reaction subsided a little more benzene (15 ml.) was added and the mixture was warmed to 50–60° for 15 minutes to complete the reaction. The clear solution was chilled in an ice-bath and a solution of stannic chloride (40 g.) in benzene (20 ml.) was added dropwise with stirring while keeping the temperature below 5°. After being maintained for 1 hour more at 5–7°, the dark solution was decomposed by the slow addition of 1:1 hydrochloric acid (100 ml.) while avoiding a rise in temperature beyond 15°. The clear red solution was separated and thoroughly washed with dilute hydrochloric acid, water, and then with caustic potash (5%) and finally with water. Removal of benzene left a clear mobile oil which after distillation gave 9.0 g. (64.7%) of ketone (VI, R = H), b.p. 164°/4 mm., which solidified in thin needles, m.p. 80–82°; crystallization from alcohol raised the m.p. to 88°.

Anal. Calc'd for $C_{15}H_{20}O_2$: C, 76.92; H, 9.40. Found: C, 76.60; H, 9.49.

The *2,4-dinitrophenylhydrazone* crystallized in red cubes from benzene, m.p. 215–216°.

Anal. Calc'd for $C_{21}H_{24}N_4O_5$: C, 61.16; H, 5.82. Found: C, 61.53; H, 6.19.

2,5-Dimethyl-7-methoxy-8-isopropyltetralin-1-one (VI, R = CH_3). Following the above procedure the butyric acid (V, R = CH_3; 19 g.) was converted to acid chloride with phosphorus pentachloride (20 g.) in benzene (100 ml.). Contrary to previous observations, the mixture gradually turned dark with a bluish fluorescence. Then it was cyclized with a solution of stannic chloride (50 g.) in benzene (25 ml.) in the usual way and yielded 8.8 g. of the ketone (VI, R = CH_3), b.p. 163–165°/2–3 mm., as a light yellow viscous oil.

Anal. Calc'd for $C_{16}H_{22}O_2$: C, 78.04; H, 9.35. Found: C, 77.71; H, 9.12.

The *2,4-dinitrophenylhydrazone* was crystallized from a benzene-ethyl acetate mixture as red needles, m.p. 222–223°.

Anal. Calc'd for $C_{22}H_{26}N_4O_5$: C, 61.97; H, 6.10. Found: C, 62.23; H, 6.35.

5-Methyl-7-methoxy-8-isopropyl-1,2,3,4-tetrahydronaphthalene (VII, R = H). A mixture of the ketone (VI, R = H; 8 g.), zinc amalgam (from 15 g. of zinc), water (9.40 ml.), hydrochloric acid (22 ml.), and toluene (12.5 ml.) was refluxed for 30 hours with the addition of hydrochloric acid (19 ml.) at approximate intervals of 6 hours. It was cooled, and the toluene layer was separated and washed with water. Removal of the toluene left an oil which was treated with excess caustic soda solution (10%) and dimethyl sulphate (2 ml.) at 80°. After 0.5 hour the mixture was cooled to room temperature and was extracted twice with benzene; The benzene solution was washed with water, and then was worked up in the usual way giving 6 g. (80.3%) of a colorless oil, b.p. 122–125°/2 mm., $n_D^{30.6}$ 1.5345.

Anal. Calc'd for $C_{15}H_{22}O$: C, 82.45; H, 10.09. Found: C, 82.20; H, 10.03.

2,5-Dimethyl-7-methoxy-8-isopropyl-1,2,3,4-tetrahydronaphthalene (VII, R = CH_3). The ketone (VI, R = CH_3; 9 g.) was reduced to VII (R = CH_3) by a similar procedure using zinc-amalgam (prepared from 10.7 g. of zinc), water (6.7 ml.), hydrochloric acid (16 ml.), and toluene (9 ml.) and additional amounts of hydrochloric acid (5 ml.) which were added at 6 hour intervals. On working up and distillation there was obtained 6.0 g. (70.7%) of a colorless mobile oil, b.p. 135–136°/3 mm.

Anal. Calc'd for $C_{16}H_{24}O$: C, 82.75; H, 10.34. Found: C, 83.19; H, 10.29.

1-Methyl-3-methoxy-4-isopropylnaphthalene (VIII, R = H). A mixture of the tetrahydronaphthalene (VII, R = H. 1.4 g.) and sulfur (0.5 g.) was heated in a metal bath at 180° for one hour and finally 3 hours more at 210–220°. It was cooled and extracted with benzene several times. The extract was dried over sodium sulphate, evaporated, and the residual oil was refluxed with freshly precipitated copper (0.5 g.) in dry thiophene-free benzene (10 ml.) for one hour. It was filtered and distilled to give 1.10 g. of colorless oil, b.p. 135–137°/1 mm.; n_D^{33} 1.5818. The analytical sample was collected by distillation over metallic sodium.

Anal. Calc'd for $C_{15}H_{18}O$: C, 84.11; H, 8.41. Found: C, 84.06; H, 8.28.

The *picrate* was crystallized from ethanol in golden-yellow needles, m.p. 116–117°.

Anal. Calc'd for $C_{21}H_{21}N_3O_8$: N, 10.21. Found: N, 9.94.

1,6-Dimethyl-3-methoxy-4-isopropylnaphthalene (VIII, R = CH_3). The hydrocarbon (VII, R = CH_3; 1.5 g.) was dehydrogenated with sulfur (0.5 g.) at 230–240°. Essentially the above procedure was adopted for purification and there was obtained 1.10 g. of a colorless oil, b.p. 150–152°/8 mm., 140–143°/4 mm.; n_D^{33} 1.5860. The analytical sample was distilled over metallic sodium.

Anal. Calc'd for $C_{16}H_{20}O$: C, 84.21; H, 8.79. Found: C, 84.08; H, 8.40.

The *picrate* was crystallized in orange-yellow needles from methanol, m.p. 174–175°.

Anal. Calc'd for $C_{22}H_{23}N_3O_8$: N, 9.19. Found: N, 9.21.

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