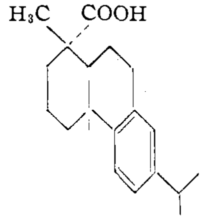
[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

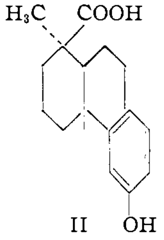
Synthesis of 2,6-Dimethyl-2-*p*-isopropylphenyl-6-carbomethoxycyclohexanone

BY E. C. HORNING, M. G. HORNING AND E. J. PLATT[1]

The generally accepted structures for dehydroabietic acid and podocarpic acid are represented by I and II, respectively. A possible synthetic route to these compounds involved application of the Reformatsky reaction to 2,6-dimethyl-2-*p*-isopropylphenyl-6-carbomethoxycyclohexanone or the corresponding *m*-methoxyphenyl ketone. This proposed reaction sequence is one which is frequently useful for the synthesis of partially hydrogenated phenanthrene derivatives, but many possible applications have never been explored because of the inaccessibility of appropriately substituted cyclohexanones.



I



II

We have investigated a method for the synthesis of 2,6-dimethyl-2-*p*-isopropylphenyl-6-carbomethoxycyclohexanone (VI); the steps involved are shown in Fig. 1. No difficulties were encountered in these reactions, and the final ketone was obtained as a viscous oil which presumably was a mixture of stereoisomers. The fact that the dinitrile II undergoes alkylation rather than cyclization under the usual sodamide alkylation conditions was expected, in view of previous work.[2] This behavior is very likely a general one for dinitriles of this kind.

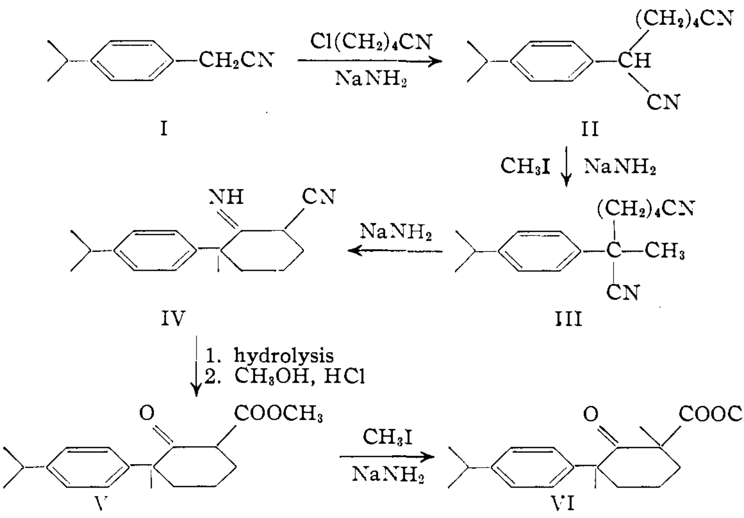


Fig. 1.

The application of the Reformatsky reaction to the ketone VI has not yielded satisfactory results. A yield of about 25% of material, presumably derived from the usual Reformatsky product, has been obtained, but it has not been possible to isolate a pure compound from this material, either before or after the dehydration and hydrolysis steps. The chief difficulty in the proposed synthetic method, therefore, appears to lie in the application of the Reformatsky reaction, rather than in the synthesis of the required ketone or ketones. It is known that highly hindered cyclohexanones give poor yields in the Reformatsky reaction, and we are presently engaged in a study of the behavior of several substituted hindered arylcyclohexanones in this reaction.

Acknowledgment.—We are indebted to Mrs. Sarah M. Woods for the analyses reported here.

Experimental

All melting points are corrected.

***p*-Isopropylbenzyl Chloride.**—A mixture[3] of 750 g. of acetic acid, 720 g. of isopropylbenzene, 850 ml. of concentrated hydrochloric acid, 400 ml. of 85% phosphoric acid, and 325 g. of paraformaldehyde was heated under reflux with stirring for four and one-half hours. The organic layer was separated, washed well with water, and distilled through a 24-inch Vigreux column under reduced pressure. There was obtained 214 g. (21%) of *p*-isopropylbenzyl chloride, b. p. 120–124° (26 mm.). A considerable forerun contained much unchanged isopropylbenzene.

***p*-Isopropylphenylacetonitrile.**—The "Organic Syntheses" procedure[4] for the preparation of phenylacetonitrile was followed; from 203 g. of *p*-isopropylbenzyl chloride there was obtained 149 g. (78%) of *p*-isopropylphenylacetonitrile, b. p. 104–110° (1.5 mm.).

α-(*p*-Isopropylphenyl)-pimelonitrile (II).—Sodamide was prepared from 12.7 g. (0.55 mole) of sodium by the usual procedure,[5] using approximately 600 ml. of liquid ammonia. To the stirred ammonia–sodamide mixture was added 80.0 g. (0.50 mole) of *p*-isopropylphenylacetonitrile, over about fifteen minutes. Approximately 20 ml. of dry ether was used to aid in transfer of the sample. The mixture was stirred for twenty minutes, and 200 ml. of dry toluene was added. The ammonia was removed, and then 67.0 g. (0.56 mole) of δ-chlorovaleronitrile was added as rapidly as possible, with cooling and stirring. Heating and stirring under reflux were continued for two hours; the mixture was then cooled and treated with 15 ml. of methanol and 100 ml. of water. The toluene layer was

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[1] Rohn and Haas Research Assistant, 1947.

[2] Horning, Horning and Platt, THIS JOURNAL, **70**, 2072 (1948).

[3] This method follows the general procedure of Cambron, *Can. J. Research*, **17B**, 10 (1939).

[4] "Organic Syntheses," Coll. Vol. I, 107 (1941).

[5] "Organic Syntheses," **25**, 25 (1945).

separated, and the aqueous layer was extracted with 100 ml. of benzene. The combined benzene–toluene solution was washed with 100-ml. portions of 5% sodium hydroxide solution, water, 5% hydrochloric acid, and saturated sodium bicarbonate solution. After drying the solvents were removed by distillation at atmospheric pressure, and the residue distilled under reduced pressure. The fore-run (17.2 g.) contained both δ-chlorovaleronitrile and *p*-isopropylphenylacetonitrile; the product was collected at 180–200° (0.5–0.7 mm.) as a light yellow viscous oil; yield 70.0 g. (58%).

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39. Found: C, 79.94; H, 8.16.

α-Methyl-α-(*p*-isopropylphenyl)-pimelonitrile (III).—Sodamide was prepared as usual from 7.4 g. (0.32 mole) of sodium. To the stirred sodamide–ammonia mixture was added 70.0 g. (0.29 mole) of α-(*p*-isopropylphenyl)-pimelonitrile, and 100 ml. of dry ether. The mixture was stirred for twenty minutes. An additional 100 ml. of dry ether was added, a nitrogen atmosphere was provided, and the ammonia was allowed to evaporate. There was added 57 g. (0.40 mole) of methyl iodide in 60 ml. of dry ether. After the initial reaction subsided, the mixture was stirred under reflux for one hour. Methanol (25 ml.) and water (200 ml.) were added, and the ether layer was separated. The ether solution was washed with 100-ml. portions of water, 5% hydrochloric acid, water and saturated sodium bicarbonate solution. After drying, the ether was removed and the residue distilled under reduced pressure to yield 63.2 g. (85%) of light yellow viscous oil, b. p. 178–183° (0.6 mm.).

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.26; H, 8.72; N, 11.02. Found: C, 80.18; H, 8.51; N, 11.10.

2-Methyl-2-(*p*-isopropylphenyl)-6-cyanocyclohexanone-imine (IV).—Sodamide was prepared from 6.3 g. (0.27 mole) of sodium. There was then added, in the usual way, 63.2 g. (0.25 mole) of α-methyl-α-(*p*-isopropylphenyl)-pimelonitrile, 30 ml. of dry ether, and 150 ml. of dry benzene. The mixture was allowed to stand under a nitrogen atmosphere until the ammonia had evaporated, and it was then heated to reflux and stirred (under nitrogen) for two hours. Methanol (15 ml.) and water (200 ml.) were added to the cooled solution, the benzene layer was separated, and the aqueous layer was extracted with 100 ml. of benzene and three 50-ml. portions of ethyl acetate. The combined extracts were washed with 100-ml. portions of water, 5% hydrochloric acid, water and saturated sodium bicarbonate solution, and dried. The solvents were removed by distillation, and the residue distilled under reduced pressure to yield 44.5 g. (70%) of very viscous oil, b. p. 182–185° (0.6 mm.).

Anal. Calcd. for $C_{17}H_{22}N_2$: C, 80.26; H, 8.72. Found: C, 80.18; H, 8.56.

2-Methyl-2-(*p*-isopropylphenyl)-6-cyanocyclohexanone.—A mixture of 7.5 g. of iminonitrile (IV), 110 ml. of methanol, 22 ml. of water, and 22 ml. of concentrated hydrochloric acid was heated under reflux for thirty-five minutes. The mixture was poured into 700 ml. of water and the product was extracted with four 100-ml. portions of ether. The combined extracts were washed with three 50-ml. portions of saturated sodium bicarbonate solution, with water, and dried. Evaporation of the ether at room temperature left a slightly discolored crystalline residue of crude ketonitrile in quantitative yield. Recrystallization of a small sample of this material from ether–pentane gave the colorless ketonitrile, m. p. 137–137.5°.

Anal. Calcd. for $C_{17}H_{21}ON$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.83; H, 8.25; N, 5.68.

2-Methyl-2-(*p*-isopropylphenyl)-6-carbomethoxycyclohexanone (V).—A solution of 6.50 g. of crude 2-methyl-2-(*p*-isopropylphenyl)-6-cyanocyclohexanone in 60 ml. of methanol was saturated with hydrogen chloride. After standing for twelve hours, the mixture was poured into 700 ml. of water, and the product extracted with five 100-ml. portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution, with water, and dried. The ether was removed, and the crude ketoester was evaporatively distilled at 110–112° (0.1 mm.); yield 4.62 g. of the methyl ester as a nearly colorless viscous oil.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.98; H, 8.39. Found: C, 74.71, H, 8.32.

2,6-Dimethyl-2-(*p*-isopropylphenyl)-6-carbomethoxycyclohexanone (VI).—2-Methyl-2-(*p*-isopropylphenyl)-6-carbomethoxycyclohexanone was alkylated with methyl iodide by the usual sodamide procedure, using 4.27 g. of the ketoester, 0.40 g. of sodium, 4.30 g. of methyl iodide, and 150 ml. of dry ether as the solvent. A nitrogen atmosphere was employed. The crude ethereal solution of the product was washed with water, 5% hydrochloric acid, water, and saturated sodium bicarbonate solution, and dried. Evaporative distillation at 100–130° (0.07–0.1 mm.) yielded 3.00 g. of keto-ester as a viscous oil.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.28; H, 8.77.

Summary

The synthesis of 2,6-dimethyl-2-*p*-isopropylphenyl-6-carbomethoxycyclohexanone is described.

PHILADELPHIA 4, PENNA. RECEIVED NOVEMBER 17, 1949

[CONTRIBUTION FROM THE WHITMORE LABORATORY OF THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

The Ketonic Decarboxylation Reaction[1]: The Ketonic Decarboxylation of Trimethylacetic Acid[2] and Isobutyric Acid

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Introduction

In 1944, Cook, Miller and Whitmore[2] reported that the ketonic decarboxylation of trimethylacetic acid yielded *t*-butyl isobutyl ketone. This was the first report of a ketonic decarboxylation of an acid with no alpha hydrogens and also the first successful application of this reaction that did not yield a symmetrical ketone. The study of these data has led to a clearer understanding of the nature of the ketonic decarboxylation reaction. This work has been extended to isobutyric acid, and in addition to the already reported diisopropyl ketone, *n*-propyl isopropyl ketone has been isolated.

In 1913, Senderens[5] formulated a general equation for ketonic decarboxylation

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(1) Presented before the Organic Section, American Chemical Society; Atlantic City, 1947.

(2) Presented before the Organic Section, American Chemical Society: New York, N. Y., 1944.

(3) (a) Celanese Corporation of America, Summit, N. J.; (b) General Electric Co., Schenectady, N. Y.

(4) Deceased June 1947.

(5) Senderens, *Ann. chim. phys.*, [8] **28**, 243 (1913).