an additional 30 hours. The oil which separated on cooling slowly crystallized when seeded with 9-ethylphenanthrene. The crude product thus obtained was recrystallized from methanol (Norite) as feathery white needles, m.p. 59–61°; yield 50 mg. (12%). This gave no depression of melting point when mixed with an authentic sample.

Dilution of the cyclizing medium yielded 300 mg. of pink material, m.p. 153–189°. Recrystallized from benzene, this yielded 120 mg. (24%) of white needles, m.p. 199–202°.

The analytical sample which gave a positive test for nitrogen, consisted of feathery white needles, m.p. 202.5–203.5°.

Anal. Calcd. for $C_{17}H_{15}ON$: C, 81.90; H, 6.06. Found: C, 81.88; H, 5.96.

9-Ethylphenanthrene from (2-Biphenylyl)-propionylacetonitrile.—When 0.5 g. of the ketonitrile was refluxed in 15 ml. of the usual cyclizing mixture for one week, an oil was obtained which crystallized on seeding with 9-ethylphenanthrene. The product was collected and washed with water; yield 0.30 g. (73%), m.p. 58–61°. This was shown to be 9-ethylphenanthrene.

The acidic mother liquor was diluted and extracted with methylene chloride. From the washed extract, a white powder was obtained by evaporation. Recrystallization yielded 100 mg. (20%) of white crystals, m.p. 203–204°. This did not depress the melting point of the 9-ethyl-10-phenanthramide described above.

DURHAM, N. C.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, SHARP AND DOHME DIVISION, MERCK AND CO., INC.]

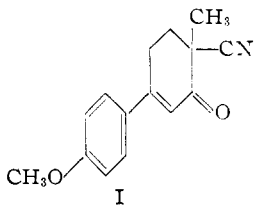
2-Keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile and Related Compounds. Analogs of Doisynolic Acid[1]

BY FREDERICK C. NOVELLO, MARCIA E. CHRISTY AND JAMES M. SPRAGUE

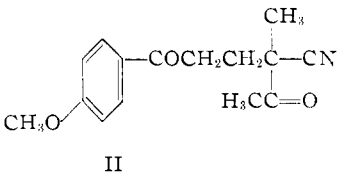
RECEIVED SEPTEMBER 8, 1953

2-Keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile (I) was synthesized by a Michael-type condensation between β-dimethylamino-*p*-methoxypropiophenone hydrochloride and α-methylacetoacetonitrile. This intermediate was utilized to prepare 2-ethyl-4-(*p*-hydroxyphenyl)-1-methylcyclohexanecarboxylic acid, 1,2-dimethyl-4-(*p*-hydroxyphenyl)-cyclohexanecarboxylic acid and 1,2-dimethyl-4-(*p*-hydroxyphenyl)-3-cyclohexenecarboxylic acid. These compounds are analogs of doisynolic acid and possess estrogenic activity.

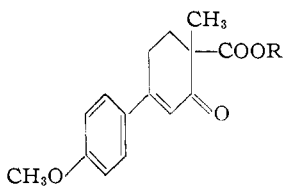
In a previous paper[2] a method was described for the synthesis of 3-substituted-2-cyclohexenones based on a Michael reaction between β-dialkylaminoalkyl ketone hydrochlorides and β-ketoesters. During our studies on further ramifications of this reaction, α-methylacetoacetonitrile was investigated as an active methylene component. Unlike the reactions with β-ketoesters where considerable cleavage of the carboalkoxy group occurs, with α-methylacetoacetonitrile no loss of the nitrile group was observed and the reaction with β-dimethylamino-*p*-methoxypropiophenone hydrochloride afforded the cyclic β-ketonitrile (I).



I



II



III, R = CH_3, C_2H_5

Formation of this compound was promoted by the use of potassium *t*-butoxide as condensing agent, which was selected for this study, since previous work[2] on the Michael reaction with β-ketoesters had demonstrated that alcoholysis was minimized under these conditions. Although cleavage of the nitrile group proved to be a negligible factor in this reaction, potassium *t*-butoxide was effective, however, in controlling the rate of the reaction to an extent that permitted isolation of the intermediate acyclic addition product II. When the condensation reaction was carried out in dioxane with potassium *t*-butoxide which contained a trace of *t*-butyl alcohol, the product was the cyclic compound I; however, when the potassium *t*-butoxide was freed completely of all traces of *t*-butyl alcohol, the product was a mixture of I and II which was separated readily by fractional crystallization. Subsequent treatment of the uncyclized product with alcoholic potassium hydroxide gave the β-ketonitrile I. As a consequence of these observations, further improvement in the synthesis of I was realized when the condensation reaction was carried out with alcoholic potassium hydroxide. Under these conditions I was obtained in 88.5% yield. Conversion of I to the carboalkoxy compounds III was accomplished by treatment with alcoholic hydrogen chloride.[3]

In the light of these observations, some conclusions about the course of the reaction may be drawn It is quite probable that the formation of I proceeds by two steps: (1) the formation of the acyclic intermediate II and (2) the aldol cyclization of II to I. Although the mechanism by which the acylic intermediate II arises from the Mannich ketone has not been investigated, two possible routes are presented: (1) by a Michael reaction involving a 1,4-addition of the active methylene component to the aryl vinyl ketone that arises by decomposition of the Mannich base[4]; (2) by a direct

(1) Presented before the Division of Medicinal Chemistry, XIIth International Congress, New York, N. Y., Sept. 10–13, 1951.

(2) F. C. Novello, M. E. Christy and J. M. Sprague, THIS JOURNAL, **75**, 1330 (1953).

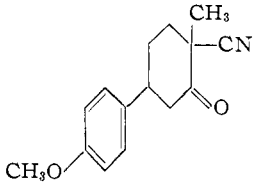
(3) V. Migrdichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold Publ. Corp., New York, N. Y., 1947, p. 84.

(4) F. F. Blicke in "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 320.

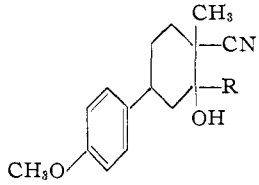
alkylation process in which the dimethylamino moiety undergoes a nucleophilic displacement by the anion of the active methylene component.[5]

The availability of I provides a useful intermediate for syntheses of compounds related to the steroid hormones and the doisynolic acids.[6] The material presented in this paper is concerned with that phase of synthetic work directed toward analogs of the latter class of compounds and transformations of compound I involving reactions of the carbonyl and nitrile groups have led to the preparation of analogs[7] XVI–XIX.

Introduction of the alkyl substituent at the carbonyl group *via* the Grignard reaction was studied with both I and its partially reduced product, 2-keto-4-(*p*-methoxyphenyl)-1-methylcyclohexanecarbonitrile (IV).



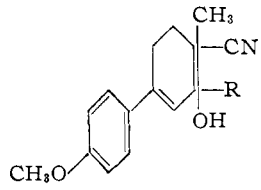
IV



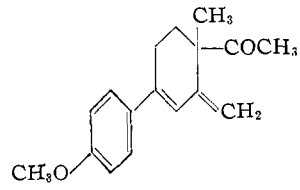
V, R = CH_3
VI, R = C_2H_5

Reactions of IV with methyl- or with ethylmagnesium halides proceeded smoothly to give the carbinols V and VI, respectively. Dehydration of these carbinols, however, proved unsuccessful despite the variety of conditions investigated and further study was abandoned in favor of the alternate approach, starting with I. The ketonitrile I exhibited a marked difference in reactivity toward methyl- and ethylmagnesium halides. In both cases, the reaction was particularly sensitive to traces of magnesium. This effect was investigated with methylmagnesium iodide and it was found that magnesium promoted dehydration of the carbinol VII to the diene X. Preparation of the methylcarbinol VII was best accomplished by inverse addition of excess methylmagnesium iodide followed by a brief reflux period. Preparation of the ethylcarbinol VIII proceeded less favorably and required milder conditions due to reaction at the nitrile group as shown by the formation of acid-soluble ketimine. Simultaneous reaction of methylmagnesium iodide at both the nitrile and carbonyl groups also could occur, but only under vigorous conditions, to yield the ketodiene IX. When the intermediate ketimine in this reaction was subjected to prolonged acid hydrolysis, aromatization with loss of the acetyl group occurred which resulted in the formation of 3,4-dimethyl-4′-methoxydiphenyl.

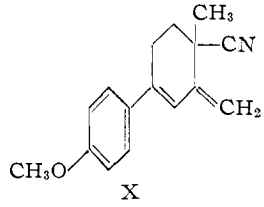
Unlike the saturated carbinols V and VI, dehydration of VII and VIII was accomplished readily by treatment with oxalic acid, formic acid or potassium acid sulfate and afforded the dienes X and XI, respectively. Successful dehydration in these



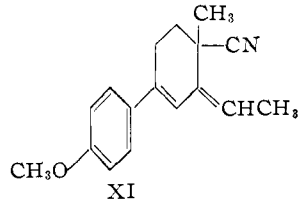
VII, R = CH_3
VIII, R = C_2H_5



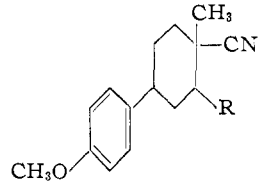
IX



X



XI



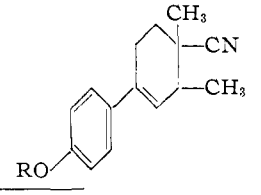
XII, R = C_2H_5
XIII, R = CH_3

instances may be due in part to a more labile hydroxyl group since it is present in an allylic system.

X formed a maleic anhydride adduct but XI failed to do so. Upon catalytic reduction, XI was readily reduced to 2-ethyl-4-(*p*-methoxyphenyl)-1-methylcyclohexanecarbonitrile (XII).

The dienic structures assigned to compounds IX, X and XI are tentative and may be subject to further elucidation since an alternate cyclohexadiene structure is possible. However, in support of the exocyclic system, the infrared spectrum[8] of X contains bands of medium intensity at 900 and 1625 cm.$^{-1}$. In the ultraviolet, compound X has an absorption maximum at 288 mμ and compound XI at 292 mμ. These maxima are in accord with Woodward's rule[9] which predicts the latter compound should have a maximum at 5 mμ longer wave length than X and therefore supports the proposed structures.

Upon hydrogenation in glacial acetic acid or alcohol in the presence of palladium catalyst, X gave the cyclohexane compound XIII. In ethyl acetate with platinum oxide catalyst, partial hydrogenation of the diene afforded a cyclohexene to which structure XIV has been assigned. Demethylation of XIV by means of pyridine hydrochloride yielded the phenol XV.



XIV, R = CH_3
XV, R = H

(5) Compare the work of H. R. Snyder and co-workers on carbon alkylations with 1-methylgramine and its methiodide: H. R. Snyder and E. L. Eliel, THIS JOURNAL, **71**, 663 (1949).

(6) J. Heer, J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, **28**, 1342 (1945); K. Miescher, *Chem. Revs.*, **43**, 367 (1948).

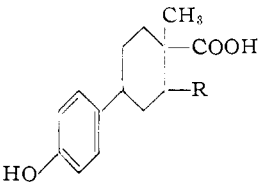
(7) The stereochemical aspects of this problem have not been studied in detail; however, some stereoisomers have been separated and these are reported.

(8) The infrared data for compound X are interpreted with reservation and are considered merely supporting evidence for the proposed structure since an exocyclic methylene group is characterized in the infrared by bands of medium strength at 1645 cm.$^{-1}$ and very strong bands at 890 cm.$^{-1}$. H. Günthard and L. Ruzicka, *Helv. Chim. Acta*, **31**, 642 (1948); *ibid.*, **32**, 2125 (1949). D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard and G. B. B. M. Sutherland, *J. Chem. Soc.*, 915 (1950).

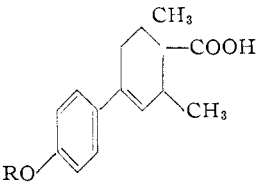
(9) R. B. Woodward, THIS JOURNAL, **64**, 72 (1942).

Hydrolysis of XII, XIII and XIV to the carboxylic acids was accomplished with simultaneous demethylation of the methoxy substituent by treatment with alcoholic potassium hydroxide at elevated temperature. XII afforded 2-ethyl-4-(*p*-hydroxyphenyl)-1-methylcyclohexanecarboxylic acid (XVI) as a glass which failed to crystallize presumably due to the fact that the product was a mixture of diastereoisomers.

1,2-Dimethyl-4-(*p*-hydroxyphenyl)-cyclohexanecarboxylic acid (XVII) was obtained from XIII as a crystalline solid from which one racemic modification was isolated by fractional crystallization. 1,2-Dimethyl-4-(*p*-hydroxyphenyl)-3-cyclohexenecarboxylic acid (XVIII) was isolated as an amorphous solid and upon purification through its crystalline benzoate XIX afforded a crystalline racemic modification.



XVI, R = C_2H_5
XVII, R = CH_3



XVIII, R = H
XIX, R = C_6H_5CO

Both XVII and XVIII on catalytic dehydrogenation with palladium-on-charcoal gave 3,4-dimethyl-4′-hydroxydiphenyl. This compound was identical with a sample prepared by an independent synthesis.

Compounds XVI, XVII, XVIII and XIX were assayed for biologic activity and found to possess estrogenic activity. Bioassay of these compounds was performed by Drs. Roland K. and Elva S. Meyer, University of Wisconsin, who will report their results in a future publication.

Acknowledgment.—The infrared determination was carried out by the microanalytical staff at Massachusetts Institute of Technology and the authors wish to express their thanks to Dr. Arthur C. Cope for his coöperation. The authors are also indebted to the following members of the research staff of Sharp and Dohme: Mr. Kermit B. Streeter and his associates, Mrs. T. P. Buchanan, Mr. J. P. Laux and Miss J. L. Pyett for many of the microanalyses and Mr. W. Riley McGaughran for the ultraviolet determinations.

Experimental

2-Keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile (I).—A mixture of 69 g. (0.29 mole) of β-dimethylamino-*p*-methoxypropiophenone hydrochloride and 132.3 g. (0.33 mole) of α-methylacetoacetonitrile[10] in 600 ml. of *t*-butyl alcohol and a solution of 20 g. (0.36 mole) of potassium hydroxide in 100 ml. of methanol was heated under reflux for 24 hours. After acidification in the cold with acetic acid, the solution was concentrated to dryness *in vacuo* and the residual oil taken up in ether. The ethereal solution was washed with water, 2% sodium hydroxide, water and dried over sodium sulfate. Crystallization from ethanol yielded 47 g. of glistening, pale-yellow prisms, m.p. 77–80°. Further processing of the residue from the mother liquor by distillation *in vacuo* and crystallization yielded an additional 13.8 g., m.p. 72–75° (total yield 88.5%).

This compound exhibited dimorphism upon recrystallization from different solvents. From benzene–hexane, pale-yellow prismatic plates were obtained, m.p. 65.5–66.8°, and from acetone–petroleum ether or alcohol, pale-yellow prisms, m.p. 85.6–86.2°. Both forms were interconvertible.

Anal. Calcd. for $C_{15}H_{15}O_2N$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.73; H, 6.37; N, 5.77.

A 2,4-dinitrophenylhydrazone was obtained as small, orange needles from alcohol, m.p. 216.3–216.6°.

Anal. Calcd. for $C_{21}H_{19}O_5N_5$: C, 59.85; H, 4.54. Found: C, 59.88; H, 4.56.

When the condensation was conducted on a larger scale, some of the **2-keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarboxamide** was obtained as by-product which was readily separated by virtue of its ether insolubility. Recrystallization of a sample from alcohol gave colorless flakes, m.p. 171.2–172.2°.

Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.47; H, 6.61; N, 5.40. Found: C, 69.54; H, 6.46; N, 5.40.

4-Cyano-1-(*p*-methoxyphenyl)-4-methylhexane-1,5-dione (II).—A mixture of 25 g. (0.10 mole) of β-dimethylamino-*p*-methoxypropiophenone hydrochloride, 14.2 g. (0.13 mole) of potassium *t*-butoxide (dried for 8 hours in high vacuum at 90° and several days in a vacuum desiccator over phosphorus pentoxide) and 10.0 g. (0.13 mole) of α-methylacetoacetonitrile in 250 ml. of purified dioxane[11] was heated under reflux for 24 hours. After removal of solvent *in vacuo*, the cooled residue was treated with 100 ml. of cold dilute hydrochloric acid and the product taken up in ether and washed and dried. Distillation *in vacuo* gave 20.7 g. of viscous, cloudy, yellow oil, b.p. 210° (0.25 mm.), which upon crystallization from ethanol gave a mixture of I and II; yield 18.1 g., m.p. 56–71°. Purification was accomplished by repeated fractional crystallizations from ethanol and afforded II as colorless, glistening prisms, m.p. 78.8–80.5°.

Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.47; H, 6.61; N, 5.40. Found: C, 69.46; H, 6.56; N, 5.39.

A 5-g. sample of the above mixture was heated under reflux for 30 minutes in 50 ml. of a solution of 2% potassium hydroxide in methanol and yielded 3.8 g., m.p. 71.5–75°, of 2-keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile (I). A mixed m.p. with an authentic specimen showed no depression.

Ethyl 2-Keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarboxylate (III).—A suspension of 2.4 g. (0.01 mole) of 2-keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile in 25 ml. of absolute ethanol was treated in the cold with dry hydrogen chloride for 15 minutes. After 3 days in a stoppered flask at 0°, the clear red solution was poured into 75 ml. of water and allowed to stand in the cold for 5 hours. The partially crystalline product was taken up in ether and washed and dried. Crystallization from ether–petroleum ether gave 2.0 g. (70%) of colorless crystals, m.p. 74.0–76.5°. Recrystallization from alcohol–hexane yielded glistening, rhombic needles, m.p. 78.5–79.5°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.83; H, 7.00.

The methyl ester was prepared in a similar fashion; yield 80%; colorless, prismatic plates, m.p. 84.2–85.2°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.19; H, 6.69.

2-Keto-4-(*p*-Methoxyphenyl)-1-methylcyclohexanecarbonitrile (IV).—A solution of 2.4 g. (0.01 mole) of 2-keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile in 50 ml. of methanol containing 0.5 g. of dissolved potassium hydroxide was hydrogenated at atmospheric pressure in the presence of 0.5 g. of 5% palladium-on-calcium carbonate. Reduction ceased upon absorption of 1 mole of hydrogen (1 hour). The solution was filtered, acidified with acetic acid and concentrated *in vacuo*. The residue was taken up in ether, washed with water, and dried over sodium sulfate. Crystallization from ether–petroleum ether gave 2.1 g. (86.4%) of colorless needles, m.p. 60–64°. A sample upon fractional crystallization from ether–petroleum ether afforded one racemic modification as clusters of small needles, m.p. 130.7–131.9°; a second racemic form was obtained upon further fractionation of the mother liquor as flakes, m.p. 66.3–69°.

(10) E. Mohr, *J. prakt. Chem.*, [2] **90**, 195 (1914); H. Adkins and G. M. Whitman, THIS JOURNAL, **64**, 152 (1942).

(11) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Edition, D. C. Heath and Company, Boston, Mass., 1941, p. 368.

Anal. Calcd. for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.05; N, 5.76. Found (high-melting isomer)[12]: C, 73.93; H, 6.96, N, 5.72; (low-melting isomer[13]): C, 74.08; H, 7.30; N, 5.83.

1,2-Dimethyl-2-hydroxy-4-(*p*-methoxyphenyl)-cyclohexanecarbonitrile (V).—A solution of 9.7 g. (0.04 mole) of 2-keto-4-(*p*-methoxyphenyl)-1-methylcyclohexanecarbonitrile in a mixture of 20 ml. of dry benzene and 80 ml. of absolute ether was added at room temperature over a 10-minute period to a stirred solution of methylmagnesium iodide prepared from 4.86 g. (0.2 mole) of magnesium and 28.4 g. (0.2 mole) of methyl iodide in 200 ml. of absolute ether. The mixture was heated under reflux with stirring for 1.5 hours, cooled and poured onto ice and dilute hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ether. The combined ethereal fraction was washed with water, dilute sodium thiosulfate solution, water and dried over sodium sulfate. The product was obtained upon crystallization from ether–petroleum ether as colorless needles; yield 7.0 g. (67.5%); m.p. 82–90°. One racemic modification was isolated by crystallization from ether–petroleum ether as glistening, rhombic needles, m.p. 90.7–92.5°.

Anal. Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found[14]: C, 74.25; H, 8.17; N, 5.39.

2-Ethyl-2-hydroxy-4-(*p*-methoxyphenyl)-1-methylcyclohexanecarbonitrile (VI) was prepared in the same manner as described for V with ethylmagnesium bromide as the preferred Grignard reagent; yield 50%, m.p. 92–95°.

One racemic modification was obtained by recrystallization from ether–petroleum ether as colorless, glistening needles, m.p. 97.0–98.2°.

Anal. Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found[15]: C, 74.75; H, 8.53; N, 5.12.

1,2-Dimethyl-2-hydroxy-4-(*p*-methoxyphenyl)-3-cyclohexenecarbonitrile (VII).—A filtered solution of methylmagnesium iodide prepared from 2.43 g. (0.1 mole) of magnesium and 14.2 g. (0.1 mole) of methyl iodide in 120 ml. of ether was added over a 10-minute period to a stirred solution of 4.8 g. (0.02 mole) of 2-keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile in a mixture of 20 ml. of benzene and 60 ml. of ether at room temperature. After refluxing for 1.5 hours, the mixture was cooled, poured onto ice and dilute hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ether. The combined ethereal fraction was washed with water, dilute sodium thiosulfate solution, water and dried over sodium sulfate. Crystallization from ether–petroleum ether gave 3.4 g. (66%) of colorless needles, m.p. 79–86°. Fractional crystallization from ether–petroleum ether gave one racemic modification as clusters of glistening needles, m.p. 90–91.8°. A second racemic modification was obtained by chromatography and crystallization from ether–petroleum ether as needles, m.p. 113.0–114.3°; λ_{max}^{EtOH} 258 mμ, ε 17,000.

Anal. Calcd. for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found (low-melting isomer): C, 74.69; H, 7.34; N, 5.43; (high-melting isomer[13]): C, 75.19; H, 7.56.

When the reaction was conducted with normal addition to unfiltered Grignard reagent, the product obtained melted at 60–68°, clear at 80°. Upon refluxing a sample in benzene with maleic anhydride, an adduct was obtained identical with that prepared from 4-(*p*-methoxyphenyl)-1-methyl-2-methylene-3-cyclohexenecarbonitrile (X).

2-Ethyl-2-hydroxy-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile (VIII).—To a stirred cold (0°) solution of ethylmagnesium bromide prepared from 2.43 g. (0.1 mole) of magnesium and 11.4 g. (0.105 mole) of ethyl bromide in 120 ml. of absolute ether, a solution of 4.8 g. (0.2 mole) of 2-keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile in 15 ml. of dry benzene and 35 ml. of absolute ether was added over a 5-minute period. After stirring at 0° for 3 hours, the reaction was processed in the usual fashion. Fractional crystallization from ether–petroleum ether gave two crystalline fractions; yield 1.5 g., m.p. 100–112° and 1.1 g., m.p. 71–83°. Further purification of each fraction by recrystallization from alcohol–hexane yielded two racemic modifications as colorless, glistening needles, m.p. 122.6–125.4° and m.p. 91.8–94.2°, respectively.

Anal. Calcd. for $C_{17}H_{21}O_2N$: C, 75.24; H, 7.80; N, 5.16. Found (high-melting isomer): C, 75.14; H, 7.74; N, 5.20; (low-melting isomer): C, 75.32; H, 7.70; N, 5.13.

1-Acetyl-4-(*p*-methoxyphenyl)-1-methyl-2-methylene-3-cyclohexene (IX).—A solution of methylmagnesium iodide (0.1 mole) in 100 ml. of dry toluene was heated to reflux and treated with stirring under nitrogen with a solution of 4.8 g. (0.02 mole) of 2-keto-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile in 50 ml. of dry toluene over a 10-minute period. The mixture was heated under reflux for 1 hour, cooled and poured onto ice and dilute hydrochloric acid. The acid solution was washed with ether and warmed on the steam-bath for 1.5 hours. Upon cooling, the solid product was collected on the filter and crystallized from ether–petroleum ether; yield 1.65 g. of a mixture of yellow needles and amorphous solid, m.p. 66–70°. Further purification by distillation *in vacuo* and crystallization from ether–petroleum ether gave pale-yellow needles, m.p. 80–82°.

Anal. Calcd. for $C_{17}H_{20}O_2$: C, 79.65; H, 7.87; OCH_3, 12.11. Found[13]: C, 79.03; H, 7.74; OCH_3, 12.23.

When the acid solution was heated on the steam-bath for 18 hours, the product obtained was 3,4-dimethyl-4'-methoxybiphenyl; pale-yellow plates from ether–petroleum ether, m.p. 68.6–70.0°.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60; OCH_3, 14.62. Found: C, 84.81; H, 7.55; OCH_3, 14.64.

4-(*p*-Methoxyphenyl)-1-methyl-2-methylene-3-cyclohexenecarbonitrile (X).—A melt prepared from 5 g. of 1,2-dimethyl-2-hydroxy-4-(*p*-methoxyphenyl)-3-cyclohexenecarbonitrile and 1.0 g. of potassium acid sulfate was distilled at 0.5 mm. and the distillate crystallized from methanol; yield 2.4 g. (51.7%) of colorless, glistening needles, m.p. 87.0–89.8°, λ_{max}^{EtOH} 288 mμ, ε 13,600.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.33; H, 7.15; N, 5.89.

A solution of 1.9 g. (0.008 mole) of diene and 0.8 g. (0.008 mole) of maleic anhydride in 20 ml. of benzene was heated under reflux on the steam-bath for 3 hours and yielded 1.25 g. of adduct as pale yellow needles, m.p. 165–171°. Recrystallizations from acetone–ether–petroleum ether gave colorless, glistening flakes, m.p. 183–184.2°.

Anal. Calcd. for $C_{20}H_{19}O_4N$: C, 71.20; H, 5.68; N, 4.15. Found[12]: C, 71.30; H, 5.92; N, 4.16.

2-Ethylidene-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile (XI).—A solution of 1.0 g. of 2-ethyl-2-hydroxy-4-(*p*-methoxyphenyl)-1-methyl-3-cyclohexenecarbonitrile in 5 ml. of 98–100% formic acid was heated under reflux for 1 hour, cooled, poured into water and extracted with ether. The ethereal solution was washed with water, 2% aqueous sodium hydroxide, water, and dried over sodium sulfate. Crystallization from ether–petroleum ether gave 750 mg. (80.5%) of pale-yellow needles, m.p. 66–77°. An analytical sample was obtained as colorless, prismatic plates, m.p. 78.8–80.2°, λ_{max}^{EtOH} 292 mμ, ε 26,100. Both racemic modifications upon dehydration gave the same product.

Anal. Calcd. for $C_{17}H_{19}ON$: C, 80.59; H, 7.56; N, 5.53. Found[12]: C, 80.35; H, 7.66; N, 5.55.

2-Ethyl-4-(*p*-methoxyphenyl)-1-methylcyclohexanecarbonitrile (XII).—A solution of 3.7 g. (0.015 mole) of XI in 25 ml. of glacial acetic acid was shaken with hydrogen in the presence of 150 mg. of palladium black until reduction ceased (1 hour). The filtered solution was concentrated to dryness at the water pump and the residue taken up and washed in ether with 5% aqueous sodium hydroxide, water, and dried over sodium sulfate. Upon distillation, the product was obtained as a colorless oil; yield 3.15 g. (81.7%), b.p. 167–168° (0.5 mm.).

Anal. Calcd. for $C_{17}H_{23}ON$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.41; H, 8.90; N, 5.43.

1,2-Dimethyl-4-(*p*-methoxyphenyl)-cyclohexanecarbonitrile (XIII).—A solution of 2.9 g. (0.012 mole) of 4-(*p*-methoxyphenyl)-1-methyl-2-methylene-3-cyclohexenecarbonitrile in 25 ml. of glacial acetic acid was hydrogenated at atmospheric pressure in the presence of 150 mg. of palla-

(12) Carbon, hydrogen analyses by S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Mass.

(13) Carbon, hydrogen analyses by C. Tiedcke, New York, N. Y.

(14) Carbon, hydrogen analyses by E. W. D. Huffman, Denver, Colo.

(15) Carbon, hydrogen analyses by H. S. Clarke, Urbana, Ill.

dium black. Reduction was complete in 1.5 hours. The filtered solution was concentrated to dryness *in vacuo* and the residue taken up and washed and dried in ether. On distillation, the product was obtained as a colorless, mobile oil; yield 2.25 g. (77%), b.p. 163–164° (0.5 mm.).

Anal. Calcd. for $C_{16}H_{21}ON$: C, 78.97; H, 8.70; N, 5.75. Found: C, 79.19; H, 8.78; N, 5.63.

1,2-Dimethyl-4-(*p*-methoxyphenyl)-3-cyclohexenecarbonitrile (XIV).—A solution of 4.8 g. (0.02 mole) of 4-(*p*-methoxyphenyl)-1-methyl-2-methylene-3-cyclohexenecarbonitrile in 100 ml. of ethyl acetate was hydrogenated at atmospheric pressure in the presence of 500 mg. of Adams catalyst. Reduction was complete in 3 hours. The filtered solution was concentrated to dryness and the residue distilled *in vacuo;* yield 4.05 g. (84%) of pale-yellow oil which gradually crystallized on standing. Fractional crystallization from ether–petroleum ether yielded one racemic modification as colorless flakes, m.p. 128.5–130°, λ_{max}^{EtOH} 257 mμ, ε 15,800. A second racemic form was obtained, although not completely homogeneous as colorless flakes, m.p. 66.5–68°, cloudy melt clear at 95°.

Anal. Calcd. for $C_{16}H_{19}ON$: C, 79.63; H, 7.94. Found (high-melting isomer): C, 79.89; H, 7.94; (low-melting isomer): C, 79.78; H, 8.04.

1,2-Dimethyl-4-(*p*-hydroxyphenyl)-3-cyclohexenecarbonitrile (XV).—A mixture of 1 g. of 1,2-dimethyl-4-(*p*-methoxyphenyl)-3-cyclohexenecarbonitrile (mixture of isomers) and 8 g. of pyridine hydrochloride was heated in an oil-bath at 200–210° for 2 hours, cooled, diluted with water and extracted with ether. The product was extracted from the ethereal solution with 10% aqueous sodium hydroxide and after acidification was taken up and washed and dried in ether. Crystallization from ether–petroleum ether gave 300 mg. (30%) of colorless flakes, m.p. 154–158°. A sample after repeated crystallizations from acetone–petroleum ether was obtained as glistening flakes, m.p. 169.2–170.2°.

Anal. Calcd. for $C_{15}H_{17}ON$: C, 79.26; H, 7.54; N, 6.16. Found[12]: C, 79.56; H, 7.72; N, 6.09.

2-Ethyl-4-(*p*-hydroxyphenyl)-1-methylcyclohexanecarboxylic Acid (XVI).—A mixture of 2.75 g. of 2-ethyl-4-(*p*-methoxyphenyl)-1-methylcyclohexanecarbonitrile, 13 g. of potassium hydroxide and 40 ml. of methanol was heated in a steel bomb with shaking at 210° for 36 hours. When cool, the pale yellow solution was decanted and evaporated to dryness on the steam-bath. The residue was dissolved in water, cooled in an ice-bath, and acidified. The resulting product was taken up in ether and extracted with 5% aqueous sodium hydroxide. Acidification of the alkaline extract yielded a gum which was taken up and washed and dried in ether. Upon evaporation of solvent, the product was obtained as an amber-colored glass; yield 2.5 g. (89%). Further purification by evaporative distillation in a molecular still at 135–145° (1 μ) gave a pale yellow glass.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.33; H, 8.49.

1,2-Dimethyl-4-(*p*-hydroxyphenyl)-cyclohexanecarboxylic Acid (XVII).—A mixture of 4.4 g. of 1,2-dimethyl-4-(*p*-methoxyphenyl)-cyclohexanecarbonitrile, 20 g. of potassium hydroxide and 50 ml. of methanol was heated in a steel bomb with shaking at 210° for 36 hours and the reaction processed according to the foredescribed procedure. Upon acidification of the sodium hydroxide extract, a solid was obtained which was crystallized from benzene–hexane; yield 2.0 g. of colorless needles, m.p. 179–186°. From the mother liquor an additional 950 mg. was obtained; m.p. 110–120°, clear melt at 145° (combined yield 65.5%). A sample of the higher-melting fraction after repeated crystallizations from benzene–hexane was obtained as colorless flakes which retained solvent of crystallization very tenaciously, m.p. 192.0–193.3° (dried over phosphorus pentoxide *in vacuo* at 100° for 10 hours).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.42; H, 8.09.

1,2-Dimethyl-4-(*p*-hydroxyphenyl)-3-cyclohexenecarboxylic Acid (XVIII).—Hydrolysis of a 3.0-g. sample of 1,2-dimethyl-4-(*p*-methoxyphenyl)-3-cyclohexenecarbonitrile was carried out according to the foredescribed procedure. The crude product was obtained as a colorless, granular solid; yield 2.2 g. (72%), m.p. 88–97°. A sample purified through its benzoate was obtained from acetone–petroleum ether as glistening, colorless plates, m.p. 168–169.5°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found[14]: C, 73.14; H, 7.39.

4-(*p*-Benzoxyphenyl)-1,2-dimethyl-3-cyclohexenecarboxylic Acid (XIX).—A solution of 4.0 g. of crude 1,2-dimethyl-4-(*p*-hydroxyphenyl)-3-cyclohexenecarboxylic acid in 30 ml. of pyridine was cooled in an ice-bath and treated with 4 ml. of benzoyl chloride. After 48 hours at room temperature, the mixture was diluted with water and extracted with ether. The washed and dried ethereal solution was evaporated to dryness and the product crystallized from acetone–petroleum ether; yield 2.6 g. of colorless needles, m.p. 197–202°. Further processing of the mother liquor gave an additional 600 mg. of product, m.p. 182–192° (total yield 56.2%).

An analytical sample was obtained as glistening needles from benzene–hexane, m.p. 215.6–216.5°.

Anal. Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found[14]: C, 75.47; H, 6.35.

Dehydrogenation of 1,2-Dimethyl-4-(*p*-hydroxyphenyl)-3-cyclohexenecarboxylic Acid (XVIII) and 1,2-Dimethyl-4-(*p*-hydroxyphenyl)-cyclohexanecarboxylic Acid (XVII).—A mixture of 250 mg. of XVIII and 100 mg. of 10% palladium-on-charcoal was heated at 340–350° for 1.5 hours, cooled and extracted with ether. The filtered ethereal solution was evaporated to dryness and the residue crystallized from methanol–water; yield 100 mg. (50%) of glistening, colorless needles, m.p. 81.5–84°. After further purification by crystallization and sublimation, a sample melted at 98.5–99.5° and showed no depression in m.p. on admixture with a sample of 3,4-dimethyl-4′-hydroxydiphenyl prepared by the method described below.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.78; H, 7.04.

Dehydrogenation of XVII was accomplished in a similar manner and gave the identical product.

3,4-Dimethyl-4′-methoxybiphenyl.—A solution of 3,4-dimethylcyclohexanone, 8.5 g. (0.07 mole), which was prepared by chromic acid oxidation of 3,4-dimethylcyclohexanol,[16] in 50 ml. of benzene was added over a 5-minute period to a cold solution of *p*-methoxyphenylmagnesium bromide (0.09 mole) in 150 ml. of anhydrous ether and 50 ml. of benzene. The clear solution was heated under reflux for three hours, cooled and processed in the usual fashion. The product was obtained by distillation as a pale-yellow liquid; yield 7.9 g., b.p. 128–130° (0.8 mm.).

Aromatization was accomplished by heating 6.5 g. of the carbinol with 2.5 g. of 10% palladium-on-charcoal at 240–245° for 3 hours. Crystallization of the product from alcohol–water yielded 3.2 g. of glistening flakes, m.p. 62–66°. An analytical sample melted at 68.2–69.5°.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.86; H, 7.60. Found: C, 84.65; H, 7.66.

3,4-Dimethyl-4′-hydroxybiphenyl.—A solution of 3.2 g. of 3,4-dimethyl-4′-methoxybiphenyl in 40 ml. of glacial acetic acid and 15 ml. of 48% hydrobromic acid was heated under reflux for 10 hours and concentrated to dryness *in vacuo.* The residue was taken up in ether, washed with water and extracted with 5% sodium hydroxide. After acidification of the alkaline fraction, the product was taken up and washed and dried in ether and crystallized from alcohol–water; yield 1.75 g. of colorless needles, m.p. 83–86°.

An analytical sample prepared by sublimation and crystallization was obtained as fine, glistening needles, m.p. 100.5–101.6°.

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.71; H, 7.06.

WEST POINT, PENNSYLVANIA

(16) H. E. Ungnade and D. V. Nightingale, THIS JOURNAL, **66**, 1218 (1944).