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4-(*p*-Hydroxyphenyl)-hexahydroacetophenone and Homologs

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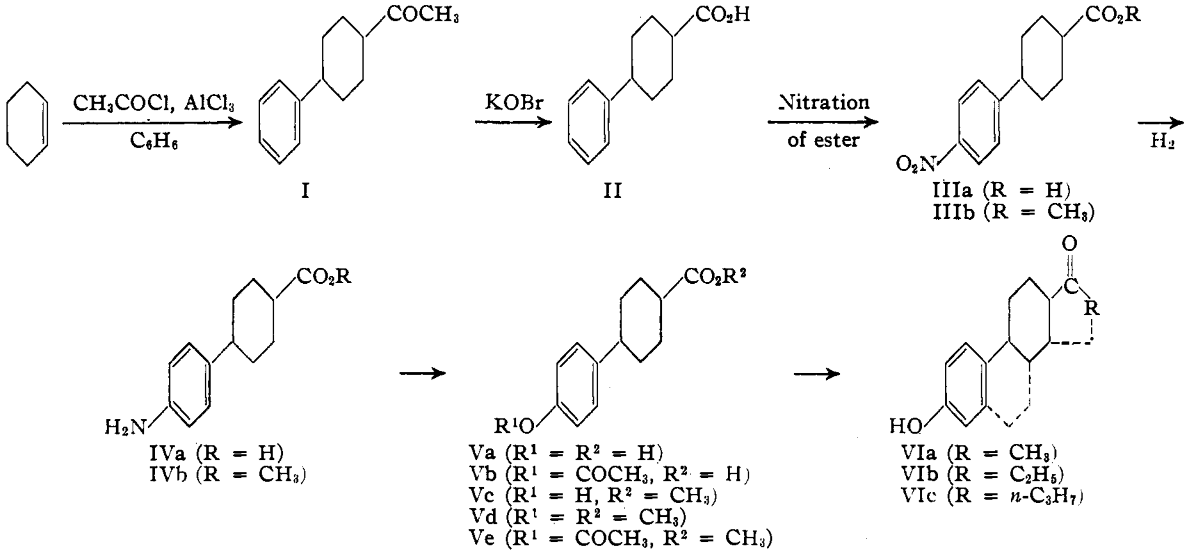
This communication deals with the synthesis of 4-(*p*-hydroxyphenyl)-hexahydroacetophenone, VIa, and the two higher homologs VIb and VIc. These substances are of particular interest in that they represent "open-models" of estrone, as suggested by the dotted lines in formula VI. The reactions which were employed are indicated in the accompanying flow sheet.



Nenitzescu and Gavat[2] have reported the preparation of 4-phenylhexahydroacetophenone, I, in 34% yield by the remarkable reaction between benzene and 2-chlorohexahydroacetophenone (from cyclohexene and acetyl chloride) in the presence of aluminum chloride. It was hoped that the benzene could be replaced by anisole in this reaction to produce the methyl ether of the ketone VIa directly, but preliminary experiments were not promising. The reaction with benzene, therefore, was employed. By slight modification of the reported procedure a liquid ketone fraction, apparently corresponding with that described by the Rumanian workers, was obtained in about 60% yield from cyclohexene. This material, however, was not homogeneous, and by crystallization from petroleum ether we have been able to separate one of the two possible stereoisomers of I as a crystalline substance melting at 55–55.5°. The separation was tedious and usually not more than one-half of the crude product could be rendered crystalline. The pure ketone gave in practically quantitative yield a semicarbazone melting at 191°. Hypobromite oxidation afforded an excellent yield of an acid (II) melting at 203–204°. These same derivatives, which evidently correspond with those described (without

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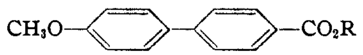
[2] Nenitzescu and Gavat, *Ann.*, **519**, 260 (1935).

yields) by Nenitzescu and Gavat, could be obtained directly from the crude ketone, but only in fair yield. Since there was some doubt as to the homogeneity of the material which was used by the Rumanian workers to prove the structure, it seemed advisable to obtain conclusive evidence. The 204° acid was, therefore, converted to the methyl ester and dehydrogenated over palladium–charcoal. Methyl 4-phenylbenzoate was thus obtained in good yield, and was identified by comparison with an authentic specimen.

The other stereoisomeric form of I was isolated as the semicarbazone from the oily ketonic material which remained after separation of the 55° ketone. Fractional crystallization of the semicarbazone mixture afforded some of the 191° derivative, and a small amount of a new isomeric semicarbazone melting at 231–232°. That this was stereoisomeric with the 191° compound was proved by hydrolysis to an oily ketone which on hypobromite oxidation was converted in 50% yield into the 204° acid. At some stage during the degradation an isomerization evidently occurred to give the more stable of the two stereoisomeric forms of II.[3]

For the preparation of 4-phenylcyclohexanecarboxylic acid, II, it was found expedient to oxidize the crude ketone I directly, even though the yield of the 204° acid was only about 35%. Rassow has prepared this acid in good yield by the reduction of 4-phenylbenzoic acid with sodium and amyl alcohol. Using this reaction we have prepared the pure 204° acid in 48% over-all yield from biphenyl. Considering the relative amounts of manipulation involved, the two approaches to II are about equally satisfactory. Nenitzescu and Gavat have reported that the interaction of benzene and 1-cyclohexenecarboxylic acid in the presence of aluminum chloride also gives the 204° acid.[2] Using methyl 1-cyclohexenecarboxylate instead of the free acid we have obtained II in 30% yield. The relative inaccessibility of starting materials, however, renders this method less practicable than those considered above.

Attempts to obtain homogeneous products upon nitration of the 55° ketone (I) or of the 204° acid (II) were unsuccessful. The methyl ester of II, however, afforded a mono-nitro derivative IIIb in 71% yield, which on hydrolysis gave the nitro acid IIIa. The nitro groups in both IIIa and IIIb were reduced readily over platinum oxide to produce the amino acid IVa and the amino ester IVb, respectively. The former substance was tested for bacteriostatic properties by Eli Lilly and Company, and was found to be inactive. Conversion of the amino acid IVa or the ester IVb to 4-(*p*-hydroxyphenyl)-cyclohexanecarboxylic acid, Va, was effected particularly readily by a procedure involving the use of 85% phosphoric acid and nitrosylsulfuric acid for the diazotization.[4] The structure of the hydroxy acid Va was confirmed by conversion to the methoxy ester Vd followed by dehydrogenation over palladium–charcoal. Methyl 4-(*p*-methoxyphenyl)-benzoate VIIb was thus produced and identified by comparison of it and the free acid VIIa with authentic specimens prepared by the synthesis of Fieser and Bradsher.[5]



VIIa (R = H)
VIIb (R = CH_3)

4-(*p*-Hydroxyphenyl)-hexahydroacetophenone, VIa, was prepared from the hydroxy acid Va by the following sequence of reactions. The hydroxy acid Va was converted with acetic anhydride into the crystalline acetate Vb which with thionyl chloride afforded the acid chloride of Vb. Without isolation this was allowed to react with sodiomalonic ester, and the resulting keto ester was submitted directly to acid hydrolysis affording the desired methyl ketone VIa in 91% over-all yield from the acetate Vb. The transformation is summarized as follows:

$$\mathrm{Va} \xrightarrow{\mathrm{Ac_2O}} \mathrm{Vb} \xrightarrow{\mathrm{SOCl_2}}$$

$$\mathrm{CH_3CO_2C_6H_4C_6H_{10}COCl} \xrightarrow{\mathrm{Na[CH(CO_2C_2H_5)_2]}}$$

$$\mathrm{CH_3CO_2C_6H_4C_6H_{10}COCH(CO_2C_2H_5)_2} \xrightarrow[\mathrm{H_2O}]{\mathrm{Acid}} \mathrm{VIa}$$

When methylmalonic ester was employed in the sequence of reactions described above, the crystalline ethyl ketone VIb was obtained in only 37% crude yield. A better (63%) yield was obtained by alkylation of the acid chloride of Vb with diethylcadmium, and purification of the ketone through the semicarbazone.

The *n*-propyl ketone VIc could not be prepared by the malonic ester synthesis. The keto ester apparently formed, but hydrolysis gave only "acid cleavage" as evidenced by the isolation of the hydroxy acid Va. Alkylation with di-*n*-propylcadmium, however, afforded the crystalline *n*-propyl ketone VIc in 74% yield. It will be of interest to test the ketones VIa, VIb and VIc for possible estrogenic activity.

Experimental Part[6]

4-Phenylhexahydroacetophenone (I).—The most important change which was made in the reported procedure[2] involved conducting the first phase of the reaction at lower temperature. This appeared to prevent polymerization, and thus to effect a corresponding increase in yield.

To a mixture of 60 g. of aluminum chloride, 30.0 g. of acetyl chloride and 120 cc. of carbon bisulfide which was cooled to −50° in a Dry Ice-bath, was added with vigorous mechanical stirring 30.0 g. of cyclohexene (b. p. 82–84°) which had been pre-cooled to −50°. The addition was complete in fifteen minutes and the temperature of the reaction mixture did not rise above −20°. Stirring was continued for an additional fifteen minutes in the Dry Ice-bath. The solvent was immediately decanted from the yellow, pasty complex, and 300 cc. of thiophene-free benzene was added. After heating for three hours at 40–

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(3) Rassow, *Ann.*, **282**, 139 (1894).

(4) *Cf.* Hodgson and Walker, *J. Chem. Soc.*, 530 (1935).

(5) Fieser and Bradsher, THIS JOURNAL, **58**, 1738 (1936).

(6) All melting points are corrected.

45° the mixture was poured onto a mixture of ice and hydrochloric acid. The organic layer was washed well with dilute hydrochloric acid followed by dilute sodium hydroxide, and dried over calcium chloride. Distillation at reduced pressure first through a short Vigreux column, then carefully through a modified Widmer column, afforded 44.3 g. of a yellow oil, b. p. 116–121° (1–2 mm.). This material had a mercaptan-like odor and darkened on exposure to air.

In the reaction between benzene and ethyl 2-methyl-Δ^1-cyclohexeneacetate Chuang, Chu and Kao[7] discovered that better yields were obtained when additional aluminum chloride was employed. No increase in yield was observed when an extra mole of catalyst was used in the present reaction.

From a solution of the crude ketone in an equal volume of 40–60° petroleum ether at −6° the crystalline form of I separated. The filtrate which had darkened somewhat was redistilled through a short Vigreux column, and the distillate crystallized again from petroleum ether. After repetition of this treatment until no more crystals could be obtained, a total of from 15 to 33 g. (depending on the run) of slightly yellow material, m. p. 51–54°, was obtained. Recrystallization gave colorless rods, m. p. 55.1–55.6°, which did not darken on exposure to air.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.01; H, 8.96.

The semicarbazone formed quantitatively in methanol with excess semicarbazide hydrochloride and pyridine. The m. p. was 190–191° (reported[2] 190–191°).

An alcoholic solution of 37.0 g. of the oil (combined from several runs) remaining after removal of the crystalline ketone described above, was treated with excess semicarbazide hydrochloride and pyridine. After several days at room temperature the dark mixture was diluted. The crude semicarbazone amounted to 45.0 g., m. p. 125–140°. On exposure to air this material, at first almost colorless, gradually turned brown. Fractional crystallization from methanol afforded 14.1 g. of the semicarbazone described above, melting at 190–191°, and 1.1 g. of the stereoisomeric substance melting at 231.3–232.1° (dec.); colorless flat rods from methanol.

Anal. Calcd. for $C_{15}H_{21}ON_3$: C, 69.46; H, 8.16. Found: C, 69.27; H, 8.31.

Steam distillation of a suspension of 0.509 g. of the 232° semicarbazone in a 10% solution of oxalic acid gave 0.372 g. of oily ketone which after evaporative distillation at 125° (1 mm.) had the $n^{25}D$ 1.5300. It did not crystallize on seeding with the 55° ketone. To a solution of 0.301 g. of this oil in 5 cc. of dioxane was added at room temperature a solution of 0.7 cc. of bromine in 10 cc. of water containing 3 g. of potassium hydroxide. After about an hour 35 cc. of water was added followed by sodium bisulfite to destroy the excess hypobromite. The neutral material was removed by ether extraction, and the aqueous solution was acidified. The crude acid amounted to 0.185 g., m. p. 185–195°. Recrystallization from dilute acetic acid raised the m. p. to 203–204°; yield 0.152 g. (50%). A mixture of this material with authentic 4-phenylcyclohexanecarboxylic acid (see below) had the same m. p. 203–204°. The m. p., 29–30°, of the methyl ester, prepared with diazomethane, likewise was undepressed by an authentic sample.

4-Phenylcyclohexanecarboxylic Acid (II).—(*a*) *From Pure I.*—A solution of sodium hypobromite was prepared by adding 27 cc. of bromine to a solution of 60 g. of sodium hydroxide in 400 cc. of water at 0°. This reagent was added with stirring to a solution of 25.4 g. of 4-phenylhexahydroacetophenone, m. p. 51–54°, in 125 cc. of dioxane. The temperature was maintained below 20°, the addition requiring about one hour. After stirring for an additional ten minutes, the solution was treated with sodium bisulfite to destroy the excess hypobromite, and then acidified. The colorless acid amounted to 25.0 g. (97% yield), m. p. 190–196°. Recrystallization from dilute acetic acid gave colorless plates, m. p. 203–204° (reported, 202°[3] and 204°[3]).

(*b*) *From Crude I.*—A solution of sodium hypobromite (from 120 cc. of bromine, 300 g. of sodium hydroxide and 2 liters of water) was added slowly with stirring to a solution of 99.0 g. of the crude ketone I in 400 cc. of dioxane. The reaction was noticeably slower than with the pure ketone. The addition required two hours, and the stirring was continued for another hour. The temperature was never allowed to exceed 25°. After the addition of sodium bisulfite the mixture was extracted with ether to remove neutral material. Acidification of the aqueous layer gave an oily solid which after trituration with 100 cc. of isopropyl ether melted at 180–185°; yield 42.7 g. Recrystallization from dilute acetic acid gave a total of 35.0 g. (35% yield) of colorless plates, m. p. 203–204°.

(*c*) *By the Reduction of 4-Phenylbenzoic Acid.*—4-Phenylbenzoic acid was prepared in 70% over-all yield from biphenyl by Friedel–Crafts acetylation followed by hypobromite oxidation. The reduction was carried out by a procedure similar to that described by Müller[8] for the reduction of salicylic acid. From 5.0 g. of the crude acid, m. p. 219–222°, obtained directly from the oxidation there was obtained 3.54 g. (69% yield) of recrystallized 4-phenylcyclohexanecarboxylic acid, m. p. 203–204°. A total of 25 g. of sodium and 370 cc. of isoamyl alcohol was employed. As described by Rassow[3] it was found expedient to steam distill the acidified reaction mixture before filtration of the crude acid. This operation removed some volatile acidic material and gave a somewhat purer product. The crude acid thus obtained amounted to 4.87 g., m. p. 175–185°. No effort was made to isolate the lower-melting isomer of II described by Rassow.

(*d*) *From Methyl 1-Cyclohexenecarboxylate.*—Methyl 1-cyclohexenecarboxylate was prepared in 57% over-all yield from cyclohexanone by a modification of the procedure of Chatterjee.[9] The crude 1-hydroxycyclohexanecarboxylic acid, obtained from 100 g. of cyclohexanone amounted to 108 g., m. p. 95–101°. One hundred grams of this material was heated with 280 g. of phosphorus pentachloride on the steam-bath for twelve hours. After cooling the mixture was poured into 400 cc. of methanol at 0° and allowed to stand overnight. Dehydrohalogenation apparently occurred during the treatment with phosphorus pentachloride, for on working up the neutral organic material by distillation through a modified Widmer column methyl 1-cyclohexenecarboxylate was obtained directly, b. p. 70–75° (9 mm.); yield 75.1 g. This material contained no chlorine, and the treatment with alcoholic alkali advocated by Chatterjee, therefore, was unnecessary.

A cooled solution of 35.40 g. of the above ester in 90 cc. of thiophene-free benzene was saturated with dry hydrogen chloride. Seventy grams of aluminum chloride was then added slowly with stirring and cooling (ice-bath). The addition required one hour. The mixture was allowed to stir for an additional two hours, and then to stand at room temperature overnight. The product was worked up in the customary manner. The fraction boiling at 80–90° (0.2–0.3 mm.) (28.0 g.) contained methyl 4-phenylcyclohexanecarboxylate, but could not be crystallized. Saponification of 2.00 g. of this material afforded a total of 1.18 g. of recrystallized 4-phenylcyclohexanecarboxylic acid, m. p. 203–204°.

Mixtures of the specimens of 4-phenylcyclohexanecarboxylic acid prepared by the above procedures (a) through (d) showed no depression of the m. p.

Methyl 4-phenylcyclohexanecarboxylate was prepared from the acid obtained by procedure (a) above. The sulfuric acid method was used, and from 10.0 g. of II there was obtained 10.0 g. of distilled ester, b. p. 180–185° (20 mm.); m. p. 29–30° (reported, 28–30°[3]).

Dehydrogenation of Methyl 4-Phenylcyclohexanecarboxylate.—One gram of the above ester was dehydrogen-

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[7] Chuang, Chu and Kao, *Ber.*, **73**, 1347 (1940).

[8] Müller, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 535.

[9] Chatterjee, *J. Ind. Chem. Soc.*, **14**, 417 (1937).

ated with 0.10 g. of 30% palladium–charcoal catalyst.[10] After one and one-half hours at 260–280° the calculated amount of hydrogen was evolved. The residue was separated with ether and amounted to 0.94 g., m. p. 104–107°. Recrystallization from petroleum ether (b. p. 40–60°) gave colorless crystals, m. p. 115–117°; yield 0.80 g. The reported m. p. for methyl 4-phenylbenzoate is 117.5°.[11] Saponification of a sample of the dehydrogenated material gave an acid, m. p. 222–223° (reported for 4-phenylbenzoic acid, 223°[11]). A mixture with authentic 4-phenylbenzoic acid, m. p. 222–223°, had the same m. p.

Methyl 4-(*p*-Nitrophenyl)-cyclohexanecarboxylate (IIIb).—To a solution of 5.32 g. of methyl 4-phenylcyclohexanecarboxylate in 1 cc. of nitrobenzene, cooled by the direct addition of small pieces of Dry Ice, 10 cc. of concentrated sulfuric acid was added with stirring, care being taken not to allow the mixture to become warm. To this solution which was maintained between 0 and −10° by addition of Dry Ice, 1.25 cc. of fuming nitric acid (sp. gr. 1.49–1.50) was added slowly with stirring. After the addition was complete, stirring was continued for fifteen minutes; then the mixture was poured onto ice and extracted with ether. The ether solution was washed with dilute ammonium hydroxide which on acidification gave practically no precipitate. The material obtained on evaporation of the ether was recrystallized from methanol giving a total of 4.56 g. (71% yield) of the nitro ester IIIb, m. p. 125–125.5°. A sample purified for analysis by further recrystallization was obtained as almost colorless blades, m. p. 125.8–126°.

Anal. Calcd. for $C_{14}H_{17}O_4N$: C, 63.86; H, 6.51. Found: C, 63.88; H, 6.62.

No other crystalline product could be isolated from the mother liquor.

4-(*p*-Nitrophenyl)-cyclohexanecarboxylic acid (IIIa) was prepared by saponification of the above ester. It crystallized from methanol in the form of colorless prisms, m. p. 206.6–207.4°.

Anal. Calcd. for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07. Found: C, 62.66; H, 6.19.

Methyl 4-(*p*-Aminophenyl)-cyclohexanecarboxylate (IVb).—The pure nitro ester IIIb (0.50 g.) in 20 cc. of ethyl acetate was hydrogenated at atmospheric pressure and room temperature in the presence of 0.05 g. of Adams platinum oxide catalyst. The calculated volume of hydrogen was absorbed in seven minutes. After filtration and removal of the solvent the amino ester remained as a colorless crystalline solid, m. p. 70–71°; yield, 0.45 g. (quantitative). After evaporative distillation at 100–105° (1 mm.) the m. p. was 70.8–71.6° (varying somewhat with the rate of heating).

Anal. Calcd. for $C_{14}H_{19}O_2N$: C, 72.07; H, 8.21. Found: C, 71.75; H, 8.28.

4-(*p*-Aminophenyl)-cyclohexanecarboxylic Acid (IVa).—A suspension of 4.32 g. of the nitro acid IIIa (m. p. 206.6–207.4°) in 50 cc. of ethanol was hydrogenated with 0.1 g. of Adams catalyst as described above for the methyl ester. As the hydrogenation proceeded (one hour) the nitro acid went into solution rapidly and the amino acid later precipitated in a powdery form. This was disadvantageous in larger runs for the precipitate repeatedly clogged the hydrogen inlet tube. The suspension of the amino acid was heated to boiling, enough methanol (about 75 cc.) was added to effect solution, and the hot mixture was filtered. Evaporation afforded 3.78 g. (quantitative yield) of colorless crystalline amino acid, m. p. 190–192°. Sublimation at 185° (1 mm.) followed by crystallization from methanol gave colorless crystals, m. p. 193–194° (varying somewhat with the rate of heating).

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82. Found: C, 71.35; H, 8.15.

4-(*p*-Hydroxyphenyl)-cyclohexanecarboxylic Acid (Va).—(*a*) *From the Amino Acid* (*IVa*).—A solution of nitrosylsulfuric acid, prepared by dissolving 1 g. of sodium nitrite in 10 cc. of concentrated sulfuric acid at −5°, was added with stirring to a chilled (to −5°) solution of 1.00 g. of the amino acid in 25 cc. of 85% phosphoric acid. The temperature was not allowed to rise above 0° during the addition, after completion of which stirring was continued for one-half hour. Urea was then added until a drop of the solution diluted with water gave a negative test with starch-iodide paper. The mixture was added to 100 cc. of water and heated for a short while until a drop failed to give a red color with an alkaline solution of β-naphthol. The hydroxy acid which precipitated as a gray solid from the cooled solution amounted to 1.00 g., m. p. 247–249° (dec.). A sample was purified for analysis by conversion to the methyl ester (see below), sublimation of the ester at 130° (1 mm.), saponification of the ester, and finally recrystallization from methanol. The colorless crystals thus obtained melted at 249.2–250.6° (dec.).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.92; H, 7.44.

(*b*) *From the Amino Ester* (*IVb*).—A solution of 19.0 g. of the amino ester in 500 cc. of 85% phosphoric acid was treated with a solution of nitrosylsulfuric acid (from 20 g. of sodium nitrite and 200 cc. of concentrated sulfuric acid) as described above under (a). The hydrolysis was carried out with 1500 cc. of water. The precipitate consisted of a mixture of the hydroxy acid and the methyl ester, which was filtered and dissolved in dilute sodium hydroxide solution. The solution was heated to boiling and acidified. The hydroxy acid which precipitated amounted to 15.54 g. (87% yield), m. p. 247–249° (dec.). This material was satisfactory for the succeeding steps of the synthesis.

Methyl 4-(*p*-hydroxyphenyl)-cyclohexanecarboxylate (Vc) was prepared by the direct esterification of 5.23 g. of the crude hydroxy acid (m. p. 247–249°) with 150 cc. of methanol and 2 cc. of sulfuric acid. After heating for six hours the mixture was worked up in the usual way to give 5.06 g. of colorless ester, m. p. 123–134°. Sublimation of this material at 130° (1 mm.) gave long colorless needles, m. p. 140.9–141.8°; yield 4.90 g. (88%).

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.67; H, 7.79.

Methyl 4-(*p*-acetoxyphenyl)-cyclohexanecarboxylate (Ve) was prepared by acetylation of the ester Vc with acetyl chloride and pyridine. After evaporative distillation at 80° (1 mm.) and recrystallization from 40–60° petroleum ether the acetate was obtained as clusters of colorless rods, m. p. 56.8–57.8°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.47; H, 7.49.

Methyl 4-(*p*-methoxyphenyl)-cyclohexanecarboxylate (Vd) was obtained by methylation of the hydroxy acid in alkaline solution with dimethyl sulfate, followed by esterification with methyl alcohol. The methoxy ester was purified by evaporative distillation at 80° (1 mm.) and recrystallization from 40–60° petroleum ether; colorless plates and needles, m. p. 69.8–72.4°.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.75; H, 8.04.

Proof of Structure.—A sample (0.187 g.) of the pure methoxy ester Vd, described above, was dehydrogenated with 0.020 g. of 30% palladium–charcoal catalyst.[10] After one and one-half hours at 270–300°, 95% of the calculated amount of hydrogen was evolved. The crude product amounted to 0.172 g., m. p. 140–154°. After recrystallization from methanol the m. p. was 172–173° (reported for methyl 4-(*p*-methoxyphenyl)-benzoate, 172–173° (cor.)[5]). The acid obtained upon saponification of the ester melted at 248–249° after recrystallization from acetic acid. 4-(*p*-Methoxyphenyl)-benzoic acid is reported to melt at 248–249° (cor.).[5] Authentic specimens of the aforementioned ester and acid were prepared by the procedure of Fieser and Bradsher,[5] and mixtures of these samples with the corresponding substances from the dehydrogenation experiment showed no m. p. depression.

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(10) Linstead and Thomas, *J. Chem. Soc.*, 1127 (1940).

(11) Schlenk, *Ann.*, **368**, 304 (1909).

4-(*p*-Acetoxyphenyl)-cyclohexanecarboxylic Acid (Vb).—A suspension of 0.92 g. of the pure hydroxy acid described above (m. p. 249.2–250.6° (dec.)) in 6 cc. of acetic anhydride was treated with three drops of concentrated sulfuric acid. The mixture became warm and the acid dissolved. After standing for three hours the solution was treated with water in the cold. The acetate which precipitated after the anhydride was hydrolyzed amounted to 1.10 g., m. p. 222–224° (dec.). Recrystallization from benzene gave small colorless plates, m. p. 225.1–227.1° (dec.).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.63; H, 6.66.

The crude hydroxy acid (obtained directly from the amino acid) upon acetylation by the above procedure could be converted into the acetate, m. p. 224–226° (dec.), in over 90% yields. This material was satisfactory for the preparation of the ketones described below.

4-(*p*-Hydroxyphenyl)-hexahydroacetophenone (VIa).—The following procedure was modeled after the excellent method of Wilds and Beck[12] for the preparation of 1-keto-2-methyl-1,2,3,4-tetrahydrophenanthrene-2-acetone. The acid chloride was prepared from 0.477 g. of the acetate Vb (m. p. 224–226° (dec.)) and 1.75 cc. each of benzene and of purified[13] thionyl chloride. After refluxing for thirty minutes the solution was concentrated under reduced pressure. The last traces of thionyl chloride were removed by adding 2–3 cc. of benzene and removing it under reduced pressure, and then repeating the process. The colorless solid acid chloride was dissolved in 25 cc. of dry ether and added to a cooled suspension of sodiomalonic ester prepared from 1.80 cc. of malonic ester added to 0.2 g. of fine sodium wire in 30 cc. of dry ether. The mixture was stirred for five minutes in the cold, for five minutes at room temperature, and finally for one hour at reflux. The suspension was treated with cold dilute hydrochloric acid, and the organic material separated by ether extraction. The residue obtained on evaporation was treated with a mixture of 15 cc. each of acetic and concentrated hydrochloric acid, and 8 cc. of water. After refluxing for two hours the solution was steam-distilled to remove the acetic acid. The ketone solidified in the aqueous residue; yield 0.402 g.; m. p. 150–153°. Recrystallization from dilute methanol gave 0.362 g. (91% yield) of colorless needles, m. p. 154.7–156.1°.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.89; H, 8.36.

The **semicarbazone of VIa** crystallized from methanol in the form of colorless rectangular plates, m. p. 235.5–236.5° (dec.).

Anal. Calcd. for $C_{16}H_{21}O_2N_3$: C, 65.43; H, 7.69. Found: C, 65.43; H, 7.68.

4-(*p*-Hydroxyphenyl)-hexahydropropiophenone (VIb).—(*a*) *By the Malonic Ester Synthesis.*—A solution of the acid chloride (prepared from 2.00 g. of the acetate Vb according to the procedure described above) in 25 cc. of dry ether was added to a suspension of sodiomethylmalonic ester (from 4 g. of methylmalonic ester and 0.35 g. of sodium in 100 cc. of dry ether). The procedure described above for the methyl ketone was followed. For the hydrolysis 30 cc. each of acetic and concentrated hydrochloric acid and 15 cc. of water were used. The final product was not homogeneous and was treated with dilute ammonium hydroxide which removed 0.62 g. of the hydroxy acid Va, m. p. 248–250° (dec.). The neutral material amounted to 0.65 g. (37% yield) of the crude ethyl ketone, m. p. 110–125°. For purification the product was converted to the **semicarbazone.** The yield of this derivative after recrystallization from methanol was 0.61 g., m. p. 228.5–229.5° (dec.).

Anal. Calcd. for $C_{16}H_{23}O_2N_3$: C, 66.41; H, 8.01. Found: C, 66.83; H, 8.18.

Hydrolysis of 0.41 g. of the semicarbazone was effected with a boiling solution of 10% oxalic acid. The ketone thus obtained melted at 130–131°; yield 0.33 g. (27% over-all). Sublimation at 125° (1 mm.) followed by recrystallization from benzene–petroleum ether (60–68°) gave colorless blades, m. p. 131.8–132.8°.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.51; H, 8.58.

(*b*) *By the Alkylcadmium Method.*—The following procedure is based on the excellent method worked out by Cason and Prout.[14] Powdered anhydrous cadmium chloride (1.34 g.) was added to a chilled solution of the Grignard reagent from 1.05 cc. of ethyl bromide and 0.334 g. of magnesium in 25 cc. of ether under an atmosphere of nitrogen. After stirring for five minutes at room temperature the solution was concentrated. The last traces of ether were removed from the gray residue by adding 50 cc. of benzene and distilling to dryness. Another 50 cc. of benzene was added, and the mixture was allowed to stir and to reflux until the solid was finely dispersed. The acid chloride from 1.20 g. of the acetate Vb (m. p. 224–226° (dec.)) in 25 cc. of benzene was then added to the refluxing mixture. The heating was continued for one hour after which the solution was treated with ice and sulfuric acid, and extracted with ether. The residue obtained on evaporation was saponified with 25 cc. of methanol and 100 cc. of 5% potassium hydroxide in an atmosphere of nitrogen. After refluxing for one hour, the solution was acidified and extracted with ether. The hydroxy acid obtained on washing the ether solution with sodium bicarbonate solution amounted to 0.20 g., m. p. 247–249° (dec.). The crude ketone remaining in the ether solution was purified through the semicarbazone as described under part (a) above. In this way 0.67 g. (63% yield) of the pure ethyl ketone VIb was obtained, m. p. 131.8–132.8°.

4-(*p*-Hydroxyphenyl)-hexahydro-*n*-butyrophenone (VIc).—By the procedure described directly above di-*n*-propylcadmium was prepared from 3.04 g. of cadmium chloride and *n*-propylmagnesium bromide (from 3 cc. of *n*-propyl bromide and 0.76 g. of magnesium), and this reagent was allowed to react with the acid chloride from 2.70 g. of the acetate Vb. The hydroxy acid Va which was separated with bicarbonate amounted to 0.10 g., m. p. 247–249° (dec.). The ketone was purified by conversion to the semicarbazone which amounted to 2.66 g., m. p. 175–194°; after recrystallization, 2.36 g. (75% yield), m. p. 200–202° (dec.). The ketone, m. p. 124–125.5°, was obtained in 99% yield by hydrolysis of the semicarbazone. Recrystallization from benzene–petroleum ether (60–68°) gave colorless needles, m. p. 124.4–125.8°.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.62; H, 9.05.

The **semicarbazone** of **VIc** was obtained in the form of small colorless crystals from methanol; m. p. 200–202° (dec.).

Anal. Calcd. for $C_{17}H_{25}O_2N_3$: C, 67.29; H, 8.31. Found: C, 67.40; H, 8.42.

Summary

4-(*p*-Hydroxyphenyl)-hexahydroacetophenone, VIa, and the two higher homologs VIb and VIc have been synthesized by the scheme which is outlined in the accompanying flow sheet. In the course of this work, the preparation of 4-phenylhexahydroacetophenone, I, by the Nenitzescu reaction[2] has been studied.

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[12] Wilds and Beck, This Journal, 66, 1688 (1944).

[13] Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, p. 381.

[14] Cason and Prout, This Journal, 66, 46 (1944).