b. r. 85-86°, was 87% of the theoretical. Total yield including that containing traces of water was 88.7%.

The distillation residues consisted of a mixture of high-boiling by-products. Very little unreacted tetrahydrofurfuryl alcohol could be isolated. Small amounts of δ-hydroxyvaleraldehyde were present and the remaining components probably were reaction products of dihydropyran with 2-hydroxytetrahydropyran and with tetrahydrofurfuryl alcohol. Since these materials decompose on heating above 100°,[3] it was not possible to isolate them in pure form.

Various temperature and feed-rate conditions were investigated to establish the limitations and optimum conditions for this procedure. Although the dehydration of tetrahydrofurfuryl alcohol over activated alumina takes place to some extent at temperatures as low as 200°, the best yields and conversion efficiencies are obtained in the range of 350 to 375° at feed rates of 2.0–3.0 g. per minute per 100 cc. of catalyst. Feed rates above 3 g. per minute or temperatures of 400° or over gave lower yields. For example, yields of 88–90% of the theoretical were consistently obtained at 2.0–2.5 g. per minute at both 350 and 375° whereas 3.1 g. per minute gave 86% yields in both cases. The maximum yield at 400° was 85.3%.

Catalyst life under optimum operating conditions was found to be excellent. In at least one instance 60 moles of tetrahydrofurfuryl alcohol was dehydrated over a 100 cc. volume of catalyst before any noticeable decrease in activity occurred.

δ-Hydroxyvaleraldehyde.—Dihydropyran, 100 g. (1.19 moles), and 400 cc. of 0.2 *N* hydrochloric acid were mixed and heated to boiling. After refluxing for forty minutes the water-insoluble layer disappeared. Refluxing was continued for another twenty minutes after which the acid was neutralized by addition of 0.4 *N* sodium hydroxide to a faint phenolphthalein alkalinity. The reaction mixture was then distilled under reduced pressure. Eighty grams of δ-hydroxyvaleraldehyde, b. r. 54–55° (3 mm.); $n^{25}\text{D}$ 1.4514, d^{25}_{4} 1.0537, was obtained.

The water distillate contained an additional 15 g. increasing the total yield to 95 g. or 78.2%. Since this portion of the product was difficult to isolate, the aqueous distillates were usually used for subsequent hydrolyses in which cases the 95-g. yields were obtained directly on distillation. Absorption spectrum analysis ($E^{1\%}_{1\,\text{cm.}}$ 2900 Å. = 0.059) showed this material to exist as 95% 2-hydroxytetrahydropyran and 5% as δ-hydroxyvaleraldehyde. The product was completely miscible with water and the same equilibrium mixture was found to exist in the aqueous solutions.

1,5-Pentanediol.—δ-Hydroxyvaleraldehyde, 102 g. (1 mole), was dissolved in 400 cc. of ethyl alcohol and the solution mixed with 5 g. of copper chromite in a hydrogenation bomb. The hydrogenation was conducted at 150° under 2000 pounds per square inch pressure and was complete in ten to fifteen minutes. The catalyst was removed by centrifugation and the alcoholic solution of the product fractionated under reduced pressure. A yield of 100 g., 96.2% of the theoretical was obtained; b. r. 118–119 (3 mm.); $n^{26}\text{D}$ 1.4480; d^{26}_{4} 0.989. No by-products were formed in this operation. The over-all yield of 1,5-pentanediol from tetrahydrofurfuryl alcohol was 70%.

Attempts were also made to prepare 1,5-pentanediol without the intermediate isolation of the hydroxyvaleraldehyde. Dihydropyran, 100 g., was hydrolyzed with 0.02 *N* hydrochloric acid as described above and the neutralized reaction mixture was charged into the hydrogenation bomb with 10 g. of copper chromite. The hydrogenation was conducted at 200° under 2000 pounds per square inch pressure. The reaction mixture was centrifuged to remove the catalyst and the aqueous mixture distilled. Yields of 75 to 77 g., 60–62% of the theoretical, were obtained.

Summary

A three-step method for the conversion of tetrahydrofurfuryl alcohol to 1,5-pentanediol in 70% yield is described.

1. Dihydropyran was prepared in 85 to 90% yield by catalytic dehydration of tetrahydrofurfuryl alcohol over a preconditioned alumina catalyst.
2. Hydrolysis of dihydropyran to δ-hydroxyvaleraldehyde was accomplished in 78% yield.
3. Catalytic hydrogenation of δ-hydroxyvaleraldehyde to 1,5-pentanediol was practically quantitative.

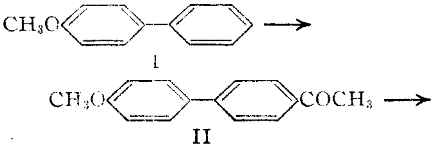
PEORIA, ILLINOIS
RECEIVED MARCH 29, 1946

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

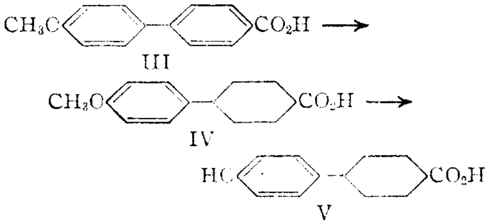
4-(*p*-Hydroxyphenyl)-cyclohexanecarboxylic Acid and Derivatives

BY WILLIAM S. JOHNSON, C. DAVID GUTSCHE AND ROBERT D. OFFENHAUER[1]

In a previous communication[2] we described a synthesis of 4-(*p*-hydroxyphenyl)-cyclohexanecarboxylic acid, V, and the preparation of several derivatives which may be considered structural models of estrone. In the present paper an improved synthesis of V is described, together with the preparation of four dialkylaminoalkyl esters (VI through IX) which are interesting as possible spasmolytic substances.



I
II



III
IV
V

The new synthesis of V is outlined in the accompanying flow sheet. 4-(*p*-Methoxyphenyl)-acetophenone, II, was prepared in 62% yield *via* the Friedel–Crafts acetylation of *p*-methoxybiphenyl, I, according to the method of Fieser and Bradsher.[3] Oxidation of II with sodium hypobromite gave 4-(*p*-methoxyphenyl)-benzoic acid, III in 91% yield. Successful selective reduction of

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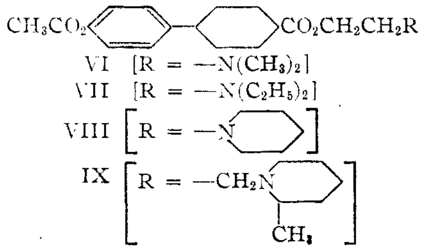
(1) Present address: Allied Chemical and Dye Corporation, Central Research Laboratory, Morristown, N. J.

(2) Johnson and Offenhauer, THIS JOURNAL, **67**, 1045 (1945).

(3) Fieser and Bradsher, *ibid.*, **58**, 1738 (1936).

the ring bearing the carboxyl group was realized with sodium and amyl alcohol. The yields, however, proved to be somewhat capricious. In most of the runs the product was contaminated with varying amounts of starting material which, being less soluble, was difficult to remove. Occasionally, however, almost pure 4-(*p*-methoxyphenyl)-cyclohexanecarboxylic acid, IV, was obtained in yields as high as 92%. Ultimately it was discovered that consistently good yields of IV could be realized by submitting the crude reduced product to a second reduction treatment. Demethylation of the methoxy acid IV afforded the desired 4-(*p*-hydroxyphenyl)-cyclohexanecarboxylic acid, V, in 86% yield.



The esters VI through IX were prepared by the interaction of the appropriate amino alcohol with the acid chloride of the acetyl derivative of V.[2] The yields of the ester hydrochlorides based on 4-(*p*-acetoxyphenyl)-cyclohexanecarboxylic acid were: VI, 81%; VII, 72%; VIII, 54%; IX, 48%. These products are being submitted to pharmacological examination by Ciba Pharmaceutical Products, Inc., through the kindness of Dr. C. R. Scholz.

Experimental Part[4]

4-(*p*-Methoxyphenyl)-acetophenone (II).—Fieser and Bradsher[3] reported the preparation of this ketone in 5-g. runs, but gave few experimental details. Their general procedure has been found quite adaptable to larger scale preparation.

To a boiling mixture of 46 g. of *p*-methoxybiphenyl and 38 g. of aluminum chloride in 300 cc. of carbon bisulfide was added dropwise with mechanical stirring, 20 g. of acetyl chloride. After the addition was complete (fifteen minutes) the mixture was allowed to stir and reflux for forty-five minutes. The total organic material obtained after decomposition with ice and hydrochloric acid and removal of the carbon bisulfide amounted to 56.1 g. After trituration twice with ether the desired product was isolated; yield 41.2 g. (73%); m. p. 148–151°. A single recrystallization from isopropyl alcohol gave pure 4-(*p*-methoxyphenyl)-acetophenone, m. p. 153–154° (reported 153–154°)[3]; yield, 35.2 g. (62%). No attempt was made to isolate the isomeric ketone previously reported.[3]

4-(*p*-Methoxyphenyl)-benzoic acid (III) has been previously obtained in unspecified yield by potassium permanganate oxidation of the ketone II.[3] In the present investigation this method proved to be unsatisfactory for preparative purposes.

A solution of sodium hypobromite, prepared at 0° by dissolving 42 g. of sodium hydroxide and 15 cc. of bromine in 200 cc. of water, was added slowly during thirty minutes to a stirred solution of 15.0 g. of 4-(*p*-methoxyphenyl)-acetophenone in 150 cc. of dioxane. During the addition the temperature was allowed to rise to 35–40°. After stirring for an additional fifteen minutes, the suspension of the sparingly soluble sodium salt was treated with enough sodium bisulfite to destroy the excess hypobromite. One liter of water was added, and about 200 cc. of the liquid was boiled off to remove the bromoform and some of the dioxane. Acidification of the hot solution gave after cooling 13.8 g. (91% yield) of 4-(*p*-methoxyphenyl)-benzoic acid, m. p. 247–248°, of sufficient purity for the reduction step. A sample recrystallized from acetic acid had the m. p. of 248–249° (reported 248–249°)[3].

4-(*p*-Methoxyphenyl)-cyclohexanecarboxylic Acid (IV).—The experiment described below represents one of the successful runs in which essentially complete reduction was realized.

To 50 cc. of isoamyl alcohol in a 1-liter flask equipped with a mechanical stirrer, reflux condenser and dropping funnel, was added 20 g. of metallic sodium (cut in slices) while the temperature was maintained at about 125° (oil bath). A solution of 5.00 g. of 4-(*p*-methoxyphenyl)-benzoic acid, m. p. 246–248°, in 500 cc. of isoamyl alcohol heated almost to boiling was poured into the separatory funnel, the stirrer was started and the solution was added over a period of about three minutes, the oil-bath temperature being maintained at 130–131°. After fifteen minutes another 20 g. of sodium was added and about three minutes thereafter the heavy white precipitate of the sodium salt which had formed at the beginning of the reaction, had completely dissolved. After fifteen minutes an additional 30 g. of sodium and 150 cc. of isoamyl alcohol were added, and the refluxing and stirring continued for forty minutes. The oil-bath (final temperature 145°) was then removed and the mixture carefully treated with 1000 cc. of water. After steam distillation to remove the alcohol, the solution was acidified with dilute sulfuric acid, and again steam distilled to remove a volatile acidic substance, probably isovaleric acid.[5] On cooling 4.75 g. (92% yield) of 4-(*p*-methoxyphenyl)-cyclohexanecarboxylic acid separated; m. p. 205–215° with previous softening. This material was entirely satisfactory for the succeeding step of the synthesis. Recrystallization from benzene gave in 77% recovery material melting at 216–219° with previous softening. A sample after sublimation at 210° (1 mm.) and recrystallization from methanol melted at 220.5–222°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.71; H, 7.75.

As mentioned in the discussion, the above procedure did not always give complete reduction. When this was the case the melting point range of the product was usually considerably lower and some starting material could be isolated on recrystallization. When such products were again submitted to reduction by the procedure described above they were always converted into material of sufficient purity for the demethylation step, the over-all yields for two reduction steps being 87–91% (in five runs). Surprisingly the use of additional sodium in a single reduction did not give comparable results.

4-(*p*-Hydroxyphenyl)-cyclohexanecarboxylic Acid (V).—A solution of 18.2 g. of the crude reduced methoxy acid IV in 210 cc. of acetic acid and 63 cc. of 48% hydrobromic acid was boiled under reflux for five hours, at the end of which the solution was homogeneous. The acetic acid was largely removed by steam distillation, and the hydroxy acid precipitated as the solution cooled; yield, 14.8 g. (86%); m. p. 230–240° (dec.). Recrystallization from ethanol gave a colorless product melting at 247–249° (dec.); yield 12.4 g. (72%). The melting point was not depressed on admixture with the sample of 4-(*p*-hydroxyphenyl)-cyclohexanecarboxylic acid (m. p. 249–250.5°, dec.) prepared by independent synthesis.[2]

Since the acetate of V was much easier to purify than the hydroxy acid, it was advantageous to prepare this derivative from the crude acid. Thus from 5.00 g. of the crude hydroxy acid, m. p. 230–240° (dec.), there was obtained by the previously described procedure,[2] 5.39 g. (90% yield) of the acetate, m. p. 223–226° (dec.) pure enough for the preparation of the esters described below.

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(4) All melting points are corrected.

(5) *Cf.* Rassow, *Ann.*, **282**, 147 (1894).

It should be noted that the acetate is very sensitive to hydrolysis, and during the preparation it is important to decompose the excess acetic anhydride in the cold otherwise the product will be contaminated with the hydroxy acid.

β-Dimethylaminoethyl 4-(*p*-Acetoxyphenyl)-cyclohexanecarboxylate Hydrochloride.—To a refluxing solution of 1.23 g. of β-dimethylaminoethanol in 175 cc. of benzene was added a solution of the acid chloride, prepared[2] from 3.60 g. of the above acetate, in 180 cc. of benzene. The addition was carried out dropwise, with stirring, over a period of three hours. The mixture was then allowed to reflux for fifteen hours longer. Upon cooling, 4.30 g. of the crude hydrochloride crystallized, and an additional 0.14 g. was obtained by concentrating the mother liquor making the total yield 88% of colorless material melting at 164–168° (dec.). One gram of this product was purified by treating an aqueous solution with sodium bicarbonate to liberate the free base which was taken up in ether and washed well with water. After removal of the solvent, the residue was heated at 60° at the water pump to remove any remaining water and amino alcohol. The base was then dissolved in dry ether and treated with dry hydrogen chloride. In this way 0.92 g. of hydrochloride was obtained, m. p. 168–171° (dec.). Recrystallization from benzene raised the m. p. to 170.5–171.5° (dec.) with previous softening.

Anal. Calcd. for $C_{19}H_{28}O_4ClN$: C, 61.71; H, 7.63. Found: C, 61.81; H, 7.44.

β-Diethylaminoethyl 4-(*p*-Acetoxyphenyl)-cyclohexanecarboxylate Hydrochloride.—This ester was prepared by the procedure described above. From 1.95 g. of β-diethylaminoethanol in 200 cc. of benzene and the acid chloride (from 4.76 g. of the acetate) in 200 cc. of benzene, there was obtained a total of 5.76 g. (80% yield) of hydrochloride melting at 205–209° (dec.).

One gram of material purified *via* the free base afforded 0.90 g. of hydrochloride melting at 211–213° (dec.). After recrystallization from benzene the m. p. was 212–213.5° (dec.).

Anal. Calcd. for $C_{21}H_{32}O_4ClN$: C, 63.38; H, 8.11. Found: C, 63.55; H, 7.96.

β-Piperidinoethyl 4-(*p*-acetoxyphenyl)-cyclohexanecarboxylate hydrochloride was prepared by a slight modification of the above procedure, using 1.26 g. of β-piperidinoethanol, b. p. 86–87° (16 mm.), in 125 cc. of benzene, and the acid chloride (from 2.50 g. of the acetate) in 125 cc. of benzene. After the slow mixing of the reagents was complete the solution was allowed to reflux for one hour longer and then to stand overnight at room temperature. The yield of crude hydrochloride was 3.00 g. (77%); m. p. 168–181° (dec.). After purification *via* the free base, the product melted at 182–187° (dec.); yield 2.10 g. (54%). A sample further purified by two recrystallizations from benzene had the m. p. 192.5–195° (dec.).

Anal. Calcd. for $C_{22}H_{32}O_4ClN$: C, 64.46; H, 7.87. Found: C, 64.79; H, 7.99.

γ-(2-Methylpiperidino)-propyl 4-(*p*-acetoxyphenyl)-cyclohexanecarboxylate hydrochloride was prepared by the procedure described in the preceding experiment; 1.51 g. of γ-(2-methylpiperidino)-propyl alcohol (supplied by the Eli Lilly Co.; b. p. after redistillation, 116–119° at 19 mm.) was used. Since the ester hydrochloride proved to be soluble in benzene the product was worked up by conversion to the free base and reconversion to the hydrochloride in dry ether solution. The material thus obtained melted at 159–165° (dec.); yield 2.00 g. (48%). Further purification was effected by treating a solution of the hydrochloride in benzene with ether. After three such precipitations it melted at 165–167.5° (dec.) with previous softening.

Anal. Calcd. for $C_{24}H_{36}O_4ClN$: C, 65.80; H, 8.29. Found: C, 65.93; H, 8.04.

Summary

A synthesis of 4-(*p*-hydroxyphenyl)-cyclohexanecarboxylic acid from *p*-methoxybiphenyl is described. Acetylation of the ether followed by hypobromite oxidation gives 4-(*p*-methoxyphenyl)-benzoic acid which is selectively reduced with sodium and amyl alcohol and then demethylated. The preparation of four dialkylaminoalkyl esters of this acid also is described.

MADISON, WISCONSIN RECEIVED MAY 8, 1946

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, UNIVERSAL OIL PRODUCTS COMPANY]

Condensation of Saturated Halides with Unsaturated Compounds. II. The Condensation of Alkyl Halides with Monohaloölefins[1]

BY LOUIS SCHMERLING

It has long been known that polychloroalkanes (particularly chloroform and carbon tetrachloride) can be condensed with chloroölefins (such as vinyl chloride and dichloroethylene) in the presence of aluminum chloride to yield polychloroalkanes of higher molecular weight. The reaction, which is usually referred to as the Prins reaction, was studied quite extensively by Prins[2] and has been the subject of several United States and foreign patents.[3] The condensation of monohaloalkanes (*i. e.*, alkyl halides) with haloölefins was, however, not described; in fact, Prins has stated[2c] that the reaction does not occur, his conclusion being based on experiments with methyl and ethyl chlorides. On the other hand, the present investigation has shown that propyl and alkyl halides of higher molecular weight can be condensed with olefins and haloölefins in the presence of metal halide catalysts to yield halides of higher molecular weight. The reaction with ethylene was described in the first paper of this series.[4] The reaction with monochloro- and monobromoölefins will be discussed in the present paper.

The condensation of the alkyl halide with the haloölefins proceeds *via* the addition of the alkyl group and the halogen atom to the double bond

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[1] Presented before the Division of Organic Chemistry of the American Chemical Society, Atlantic City, April, 1946.

[2] (a) J. Böeseken and H. J. Prins, *K. Akad. Wetenschappen*, **19**, 776 (1910); *C. A.*, **5**, 2845 (1911); (b) H. J. Prins, *J. prakt. Chem.*, **89**, 414, 425 (1914); (c) H. J. Prins, *Rec. trav. chim.*, **51**, 1065 (1932); (d) **54**, 249 (1935); (e) **56**, 779 (1937); (f) **57**, 659 (1938).

[3] (a) H. J. Prins, German Patent 261,689 (1912); (b) J. Sixt (to Consortium fuer elektrochemische Industrie G. m. b. H.) U. S. Patent 2,068,772 (Jan. 26, 1937); (c) F. W. Kirkbride (to Imperial Chemical Industries, Ltd.) U. S. Patent 2,297,564 (Sept. 29, 1942).

[4] L. Schmerling, THIS JOURNAL, **67**, 1152 (1945).