[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Synthetic Estrogens. IV. Estrogenic Tetrahydrobiphenylcarboxylic Acids[1a,b,c]

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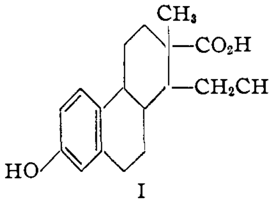
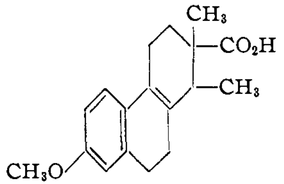
The synthesis of 2-methyl-3-ethyl-4-(*p*-anisyl)-3-cyclohexenecarboxylic acid (IXb) and its isomeric 3-olefin VIIIb is described. These substances have estrogenic activity as measured subcutaneously in rats approximately equal to that of subcutaneously administered estradiol.

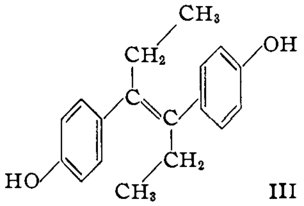
Miescher and co-workers have described[2a-c] the synthesis of "doisynolic acid" (I) and several structurally related, highly estrogenic acids. Previous work in our laboratories,[3] that had as its objective the total synthesis of estrone from 3-methyl-4-carbethoxy-2-cyclohexenone (IV, Hagemann's ester)[4a,b] led to an analog (II) of doisynolic acid that also exhibited a high order of estrogenic activity. We now wish to report the synthesis from Hagemann's ester of some partially saturated biphenylcarboxylic acids (VIIIb, IX, X) which bear a structural resemblance to II and also to diethylstilbestrol (III). These compounds were found to possess an unusually high degree of estrogenic activity (see Table I).



I



II



III

The method of synthesis is outlined in Chart I. 3-Methyl-4-carbethoxy-2-cyclohexenone (IV, Hagemann's ester) has been alkylated with ethyl bromide[4b] or ethyl iodide. In the present work the use of potassium *t*-butoxide in *t*-butyl alcohol, rather than sodium ethoxide in ethanol, raised the yield of V from 55 to 84%. The alkylated product V rapidly absorbed one molecular equivalent of hydrogen in the presence of palladium, yielding 2-ethyl-3-methyl-4-carbethoxycyclohexanone (VIa). Geometric isomers of the latter compound were not separated, although a moderate spread in boiling range indicated that such isomers might be present. The ester VIa was saponified to give the corresponding acid VIb.

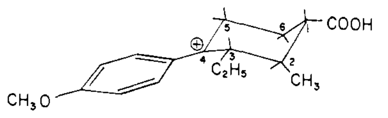
2-Methyl-3-ethyl-4-(*p*-anisyl)-4-hydroxycyclohexanecarboxylic acid (VIIb, m.p. 191–192°) was formed by the alkaline hydrolysis of the products of the reaction of *p*-anisylmagnesium bromide with VIa. By using two equivalents of the Grignard reagent, VIb was also converted to VIIb. The methyl ester VIIa (m.p. 118–120°) was prepared by the action of diazomethane on the free acid.

Dehydration of VIIa with thionyl chloride and pyridine gave methyl 2-methyl-3-ethyl-4-(*p*-anisyl)-4-cyclohexenecarboxylate (VIIIa, m.p. 78.5–79°). The corresponding acid VIIIb (m.p. 181–182°; λ_{max} 241, ϵ 10,480) was produced when the hydroxy acid VIIb was treated with boron trifluoride etherate in ether solution.

However, the isomeric olefin, 2-methyl-3-ethyl-4-(*p*-anisyl)-3-cyclohexenecarboxylic acid (IX, m.p. 158–159°; λ_{max} 230 mμ, ϵ 10,740) was obtained when the hydroxy acid VIIb was dehydrated either by dry hydrogen chloride in benzene solution or by refluxing with toluenesulfonic acid in acetic acid. The Δ^4-isomer VIIIb was converted to the Δ^3-isomer by the same treatment. The assignment of the double bond position in VIIIb and IX was made by inference from the products of ozonolysis of each isomer, which produced, in the case of VIIIb, a dicarboxylic acid XII and, in the case of IX, a monocarboxylic acid XIII.

The facile rearrangement of VIII to IX by acid established the latter as the thermodynamically more stable isomer. It is probable that the stabilizing effect of hyperconjugation resonance involving five hydrogens in the Δ^3-isomer IX, even though opposed by the steric interaction of the ethyl and anisyl groups, is still a greater factor in conferring stability of the molecule than would be the case in the Δ^4-isomer where only three hydrogen atoms are involved.

The Δ^4-isomer VIII must be the product of kinetic control and is probably the isomer first formed irrespective of the reagent used for the dehydration. The carbonium ion XIV is very likely the common intermediate in all of the above described methods of dehydration.



XIV

Since there would be maximum steric interaction between the ethyl and anisyl groups in the planar transition state required for the formation of the Δ^3-isomer the tendency to expel a proton at C-3 would be suppressed. In addition, the presence of two hydrogen atoms at C-5 statistically favors the

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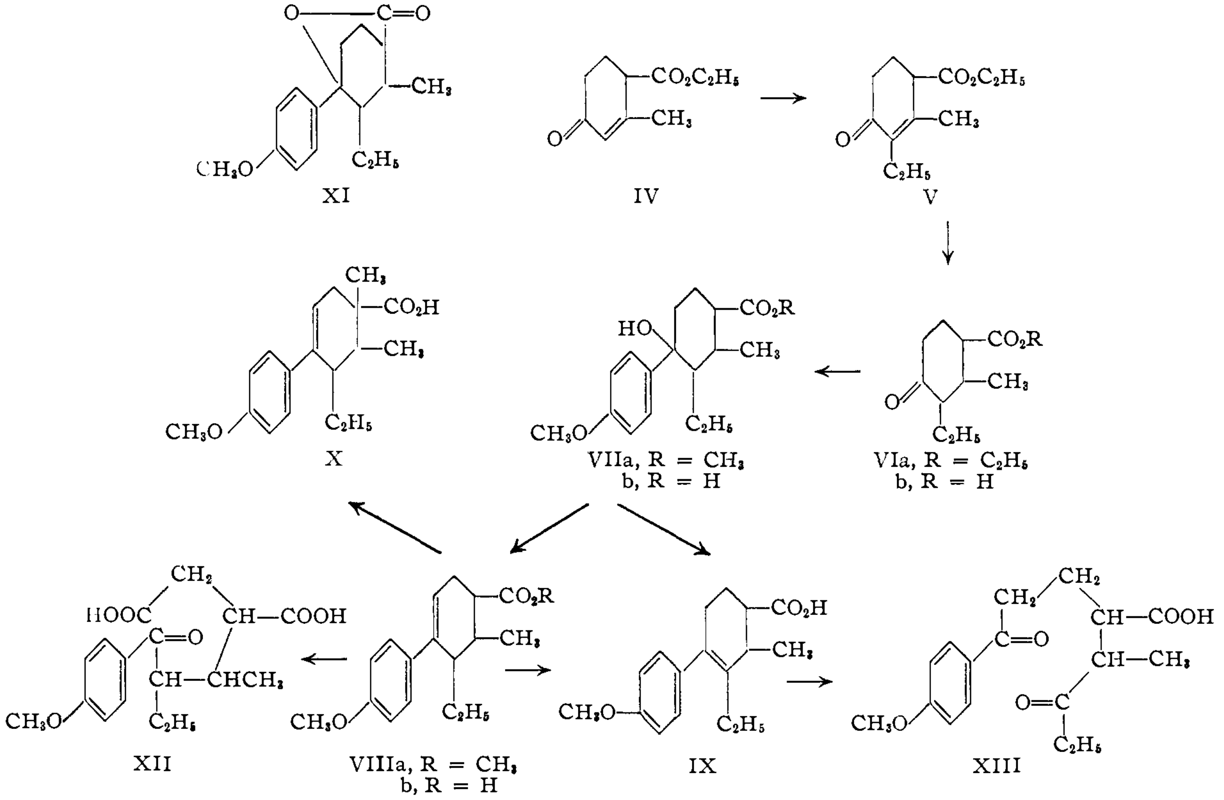
(1) (a) Presented at the Dallas Meeting of the American Chemical Society, April 8-13, 1956; (b) previous paper in this series, J. H. Hunter and J. A. Hogg, THIS JOURNAL, **71**, 1922 (1949); (c) U. S. Patent 2,582,253, Jan. 15, 1952.

(2) (a) K. Miescher, *Helv. Chim. Acta*, **27**, 1726 (1944); (b) J. Herr and K. Miescher, *ibid.*, **28**, 156 (1945); (c) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Third Ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 346.

(3) J. A. Hogg, THIS JOURNAL, **70**, 161 (1948).

(4) (a) C. Th. L. Hagemann, *Ber.*, **26**, 876 (1893); (b) L. I. Smith and G. F. Rouault, THIS JOURNAL, **65**, 631 (1943).

CHART I



loss of proton at this position and, hence, the formation of the Δ^4-isomer VIII.

The hypsochromic shift, with slightly lower extinction coefficient, exhibited in the ultraviolet absorption spectrum of the Δ^3-isomer IX as compared with the Δ^4-isomer is in line with other recorded cases involving steric inhibition of resonance.[5]

In one experiment a non-acidic compound (m.p. 102–102.5) was isolated after the Grignard reaction. On the basis of an absorption band at 1762 $cm.^{-1}$ in the infrared, together with its analysis, the lactone structure XI was assigned to this compound.

In another experiment, the crude product of the reaction between *p*-anisylmagnesium bromide and the keto acid VIb was esterified with ethanol in benzene, using as catalyst a small amount of sulfuric acid. After refluxing for 6 hours a small amount of an unsaturated acid was found still unesterified. Although, like IX, it melted at 157–158°, it proved to be a different isomer from either VIIIb or IX; analysis indicated the same empirical formula, but its absorption in the ultraviolet was at 254 mμ. The fact that this acid was not formed from the hydroxy acid VIIb was shown when a similarly conducted esterification of pure VIIb gave solely the ethyl ester of VIIIb.

Methyl 1,2-dimethyl-3-ethyl-4-(*p*-anisyl)-4-cyclohexenecarboxylate was prepared by the action of triphenylmethylsodium and methyl iodide[3] upon the ester VIIIa. Saponification gave the acid X, which, like VIIIb, showed an absorption maximum at 241 mμ.

It is interesting to note, from the results given in Table I, that X is less active than the parent compound VIIIb. Both VIIIb and IX are several times more active estrogenically in rats than doisynolic acid (I).

TABLE I

ESTROGENIC ACTIVITY IN RATS[6]

Compound	Activity, micrograms per rat
VIIb	36.1
IX	0.048
VIIIb	.045
X	.10
II[3]	.24
Doisynolic acid (I)	.7-1
Estradiol	.04

Experimental[7]

2-Ethyl-3-methyl-4-carbethoxy-2-cyclohexenone (V).—To a solution of 7.8 g. (0.2 gram-atom) of potassium in 160 ml. of sodium-dried *t*-butyl alcohol were added 36.4 g. (0.2 mole) of 3-methyl-4-carbethoxy-2-cyclohexen-1-one and 22 g. (0.2 mole) of ethyl bromide. The mixture was boiled gently under reflux for three hours. Most of the solvents were removed by distillation, and the residue was worked up as described by Smith and Rouault.[4b] The product was collected at 149–154° (13 mm.), $n^{26}\text{D}$ 1.4854, yield 35.0 g. (83.5%). Ethyl iodide was used for the alkylation with equally satisfactory results.

2-Ethyl-3-methyl-4-carbethoxycyclohexanone (VIa).—Hydrogenation of the unsaturated ester V in two volumes of 95% alcohol with 5% of its weight of palladinized charcoal

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(5) See, for example, R. A. Friedel, M. Orchin and L. Reggel, THIS JOURNAL, **70**, 199 (1948).

(6) Assay by the Kahnt-Doisy method. We are indebted to Mr. S. C. Lyster and Dr. W. W. Byrnes, Department of Endocrinology, The Upjohn Co., for these tests. Their studies will be reported in more detail elsewhere.

(7) Melting points were taken on a Fisher-Johns block and are reported uncorrected.

at 2.5 atmospheres resulted in rapid, exothermic absorption of one molecular equivalent of hydrogen. The catalyst was removed, the product distilled, giving a 96% yield of 2-ethyl-3-methyl-4-carbethoxycyclohexanone (VIa) boiling at 140–150° (13 mm.), n^{26}D 1.462. A semicarbazone prepared from this compound in the usual way melted at 188–188.5° after one recrystallization from alcohol and was analyzed.

Anal. Calcd. for $C_{13}H_{23}N_3O_3$: C, 58.0; H, 8.62; N, 15.62. Found: C, 58.4; H, 8.84; N, 15.75.

2-Ethyl-3-methyl-4-carboxycyclohexanone (VIb).—The above ester was saponified by refluxing for one hour in a solution composed of four equivalents of potassium hydroxide in a mixture of 7 ml. of water and 7 ml. of 95% alcohol per gram of ester. The alcohol was removed under reduced pressure and the alkaline solution extracted with ether, about 5% of unsaponified ester being recovered. The solution was then acidified, extracted with ether, and the ether extracts dried and distilled. The acid boiled at 122° (0.12 mm.), and the yield was 76.5% based on ester actually used.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.3; H, 8.75. Found: C, 64.9; H, 8.76.

The crude ester VIa resulting from the hydrogenation was saponified in a similar manner without first distilling it, in which case the yield of acid, boiling at 131–135° (0.2 mm.), was 83.5%, based on the starting unsaturated ester.

The Grignard Reaction. (a) With 2-Ethyl-3-methyl-4-carbethoxycyclohexanone (VIa).—An ethereal solution of *p*-anisylmagnesium bromide, prepared in the usual way from 19.65 g. (0.105 mole) of *p*-bromoanisole, was added slowly, with continual stirring, to an ice-cold solution of 21.2 g. (0.1 mole) of the keto-ester VIa in 100 ml. of ether. Heat was evolved and a yellow complex separated. The mixture was warmed under reflux for 0.5 hour and then hydrolyzed with cold dilute sulfuric acid. The products were taken up in ether, washed with water, dried over potassium carbonate, and subjected to vacuum distillation. The distillate consisted of 2.30 g. of anisole, b.p. 46° (12 mm.), n^{22}D 1.5123 (reported $n^{20.6}$D 1.5173), and 10.50 g. of unchanged keto ester VIa, b.p. 89–91° (0.4 mm.), which furnished a semicarbazone melting at 188–189°. The residue, 13.1 g., was a viscous oil which after dissolving in alcohol deposited a small amount of white crystalline material melting at 172–173°. The latter, because of its small quantity (*ca.* 0.085 g.), was not further investigated but was probably bi-*p*-anisyl. The material in the alcoholic filtrate (150 ml.) was saponified by refluxing for 1.5 hours with 40 ml. of 5 *N* aqueous potassium hydroxide. The acidic fraction resulting from the saponification crystallized slowly upon long standing in alcohol solution. The yield was 1.94 g. (6.6%) of crystalline 2-methyl-3-ethyl-4-(*p*-anisyl)-4-hydroxycyclohexanecarboxylic acid (VIIb), m.p. 175.5–177.5°. Recrystallization from dilute methanol, ethyl acetate or acetone and petroleum ether raised the m.p. to a top value (somewhat dependent upon rate of heating) of 191–192°.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.8; H, 8.28. Found: C, 70.1; H, 8.14.

This acid, which dissolved readily in aqueous sodium bicarbonate solution, did not decolorize alkaline permanganate.

The methyl ester of the hydroxy acid VIIa, prepared with diazomethane, formed small, white, spherical aggregates of crystals from petroleum ether, m.p. 118–120°.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.6; H, 8.55. Found: C, 70.4; H, 8.47.

Lactone XI.—In another experiment, carried out as described above, the products of saponification of the residue that remained after removal of the anisole and unchanged keto ester VIa were extracted with warm potassium carbonate solution. A small portion failed to dissolve, and when this was dissolved in hot petroleum ether, the solution deposited colorless needles which, after another recrystallization from petroleum ether, melted at 102–102.5°, and gave analytical results in accord with those calculated for the lactone XI.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.4; H, 8.08. Found: C, 74.2; H, 7.90.

The infrared absorption spectrum of this compound showed a band at 1762 cm.$^{-1}$ which is attributable to a 6-membered lactone substituted at a bridgehead.

(b) With 2-Ethyl-4-methyl-4-carboxycyclohexanone (VIb).—A solution of the Grignard reagent from 22 g. (0.12 mole) of *p*-bromoanisole, prepared in a mixture of 20 ml. of ether and 50 ml. of tetrahydrofuran, was cooled in a Dry Ice–alcohol-bath to −30° and treated slowly with a solution of 9.4 g. (0.05 mole) of the keto acid VIb in 100 ml. of tetrahydrofuran. The mixture was allowed to warm to room temperature during the course of about 1.5 hours, and then hydrolyzed with ammonium chloride solution. The product was separated into a neutral fraction (14 g.) and an acidic fraction (23 g.) by partitioning between ether and sodium carbonate solution, and the acidic fraction was precipitated with dilute sulfuric acid. A solution of the acidic product in 95% alcohol, kept in the refrigerator for 10 days, deposited 2.57 g. of 2-methyl-3-ethyl-4-(*p*-anisyl)-4-hydroxycyclohexanecarboxylic acid (VIIb) as white crystals, m.p. 192°. The alcoholic filtrate from the hydroxy acid VIIb, after thorough drying over calcium chloride and paraffin in a vacuum desiccator, consisted of 18.4 g. of a viscous gum. This was esterified with 125 ml. of dry benzene, 250 ml. of absolute ethanol and 2 ml. of concd. sulfuric acid by boiling for 6 hours. By separating all residual acid from the esterification mixture with sodium carbonate solution, 2.5 g. of a semi-solid acid was obtained, which after two recrystallizations from dilute ethanol and methanol, respectively, melted at 157–158° and depressed the m.p. of 2-methyl-3-ethyl-4-(*p*-anisyl)-3-cyclohexenecarboxylic acid (IX) (the product of dehydration of the hydroxy acid VIIb with dry hydrogen chloride in benzene; see below) to 129–133°. Analysis, however, indicated the same empirical formula: Calcd. for $C_{17}H_{22}O_3$: C, 74.4; H, 8.08. Found: C, 74.6; H, 7.99.

This acid showed an ultraviolet absorption maximum at 254 mμ, ϵ 17,400.

The ester was subjected to vacuum distillation, giving 3.75 g. of 2-ethyl-3-methyl-4-carbethoxycyclohexanone (VIa) boiling at 145–147° at 12 mm., which furnished a semicarbazone, m.p. 188–189°, undepressed on admixture with an authentic sample of semicarbazone of VIa, and 11.65 g. of residue. The residue was dehydrated in 25 ml. of pyridine with 6 g. of thionyl chloride, and then saponified, as described below. The acid from this treatment crystallized from methanol; yield 1.82 g., m.p. 174–176.5°, and after one recrystallization from alcohol, 181–182°. This acid furnished a methyl ester with diazomethane, m.p. 78.5–79°, and was accordingly identified as 2-methyl-3-ethyl-4-(*p*-anisyl)-4-cyclohexenecarboxylic acid (VIIIb).

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.38; H, 8.20.

The total yield of products from the Grignard reaction was, therefore, 24.5% of the theoretical (2.56 g. of hydroxy acid VIIb and 4.32 g. of two unsaturated acids).

Dehydration of the Hydroxy-acid (VIIb). (a) With Thionyl Chloride.—A solution of 200 mg. of the methyl ester VIIa in 0.58 g. of pyridine was cooled in an ice-bath and treated with 0.10 g. of thionyl chloride. The mixture was then heated on the steam-bath for ten minutes, diluted with water, and acidified with dilute sulfuric acid. The oily product which separated (methyl 2-methyl-3-ethyl-4-(*p*-anisyl)-4-cyclohexenecarboxylate, VIIIa) soon crystallized. The yield was 185 mg., m.p. 60°. Recrystallization from dilute methanol raised the m.p. to a constant value of 78.5–79.5°.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 75.0; H, 8.09. Found: C, 74.5; H, 8.11.

Saponification of the above ester gave 2-methyl-3-ethyl-4-(*p*-anisyl)-4-cyclohexenecarboxylic acid (VIIIb) which, after recrystallization from alcohol, melted at 181–182.5°, depressed the m.p. of the hydroxy-acid to 174–175°.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.7; H, 8.03.

This acid forms a sodium and a potassium salt which are sparingly soluble in cold water, freely soluble in hot water, and which decolorize 1% aqueous potassium permanganate rapidly.

(b) With Boron Fluoride in Ether.—One hundred milligrams of 2-methyl-3-ethyl-4-(*p*-anisyl)-4-hydroxycyclohexanecarboxylic acid (VIIb) was dissolved in 5–10 ml. of anhydrous ether and treated at room temperature with 1 ml. of commercial boron fluoride etherate (40% solution in ether). After 4 hours, the ether solution was washed with water and evaporated to dryness, leaving 96 mg. of dark colored, oily crystals, which, after recrystallization from ethyl acetate, formed colorless prisms melting at 178–179.5°. The assignment of the structure as 2-methyl-3-ethyl-4-(*p*-anisyl)-4-cyclohexenecarboxylic acid (VIIIb) was made on the basis of the ultraviolet absorption maximum at 241 mμ (ϵ 11,025) and from the product of ozonolysis.

(c) **With Dry Hydrogen Chloride in Benzene.**—A Grignard reaction was carried out, using one equivalent of the keto-acid IVa and two of *p*-anisylmagnesium bromide, in the manner described above. After decomposing the magnesium salts with dilute sulfuric acid, the organic products were dissolved in benzene, filtered, and the benzene solution dried. It was then chilled in an ice-bath, saturated with dry halogen chloride, and allowed to stand at room temperature for four hours. The solvent was removed on the steam-bath in a current of air, leaving a residue which, after recrystallization from ethyl acetate, melted at 158.5–159°. Further recrystallization did not raise the m.p.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.4; H, 8.09. Found: C, 73.9; H, 7.83.

This product, 2-methyl-3-ethyl-4-(*p*-anisyl)-3-cyclohexenecarboxylic acid (IX), like its double-bond isomer VIIIb, also formed sparingly soluble sodium and potassium salts, whose dilute aqueous solutions decolorized permanganate. Its ultraviolet absorption maximum was at 230 mμ (ϵ 10,740). Mixtures of VIIIb and IX melted unsharply between the lower and higher ranges.

(d) **With *p*-Toluenesulfonic Acid in Acetic Acid.**—One hundred milligrams of the hydroxy acid VIIb was boiled in 2.2 ml. of acetic acid with about 15 mg. of *p*-toluenesulfonic acid for 5 minutes. The solution, which became pale blue, was diluted with water just short of permanent turbidity. Eighty milligrams of white needle-like crystals melting at 165–166° were deposited. The process was repeated on the same 80 mg., giving 70 mg., m.p. 160–161°. A mixture of this product IX with the sample obtained from the dehydration with HCl in benzene (above) melted at 159–160°. The infrared spectra were identical.

Isomerization of VIIIb to IX.—Three and two-tenths grams of 2-methyl-3-ethyl-4-cyclohexenecarboxylic acid (VIIIb), dissolved in 120 ml. of benzene, was saturated at room temperature with gaseous hydrogen chloride and the solution kept at room temperature for 5 hours. The solvent was evaporated on the steam-bath at atmospheric pressure and the residue recrystallized from ethyl acetate, giving 2.84 g. of 2-methyl-3-ethyl-3-cyclohexenecarboxylic acid, m.p. 158.5–159°.

The same isomerization was accomplished by heating the acid VIIIb in 20 volumes of acetic acid with one-fourth its weight of *p*-toluenesulfonic acid, allowing the solution to stand overnight, and finally crystallizing the product by diluting with water. In this experiment the product melted at 159–161°.

Ozonolysis of VIIIb and IX.[8]—Ozone was passed through a solution of 0.275 g. of each of the isomeric acids VIIIb and IX dissolved in 5 ml. of acetic acid and 5 ml. of ethyl acetate at about −10° (ice–salt-bath) until an estimated 1.1 equivalents had been absorbed. Then 0.5 ml. of water and 0.2 ml. of 30% hydrogen peroxide was added to the solution, which was kept at room temperature overnight.

The acids were isolated by diluting with water, extracting with ether, washing out most of the acetic acid, extracting with acidic products into 2% sodium hydroxide, acidifying the latter and re-extracting it with ether, and finally drying and evaporating the ether. The acids were obtained in 90–94% yield as waxy solids; the one from VIIIb crystallized from an acetone–petroleum ether (Skellysolve B) mixture, m.p. 169–170°.

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88; neut. equiv., 161. Found: C, 62.46; H, 6.93; neut. equiv., 221.

The acid from IX could not be crystallized.

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; neut. equiv., 306. Found: C, 66.62; H, 6.98; neut. equiv., 285.

1,2-Dimethyl-3-ethyl-4-(*p*-anisyl)-4-cyclohexenecarboxylic Acid (X).—To 912 mg. of the methyl ester VIIIa, m.p. 78.5–79.5°, was added a slight excess of ethereal triphenylmethylsodium[9] in one portion, whereupon the red color faded rapidly. After 30 minutes a large excess of methyl iodide was added and the mixture was allowed to stand overnight; 1.5 ml. of glacial acetic acid was added, the ether solution washed with water and sodium carbonate solution, dried and evaporated. The residue was saponified by refluxing for 22 hours with 2 ml. of 42% potassium hydroxide solution in 30 ml. of alcohol. The alkaline solution was diluted with water, extracted with ether, treated with a stream of carbon dioxide and filtered. The filtrate was acidified with hydrochloric acid, which precipitated the product X as snow-white crystals, m.p. 158–160°, in a yield of 730 mg. (80%). After two recrystallizations from methanol the latter melted at 173–173.5°, and depressed the melting point of the starting acid to below 155°; λ_{max} 241, ϵ 11,130.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 75.0; H, 8.39. Found: C, 74.7; H, 8.21.

Acknowledgments.—We are indebted to Dr. J. L. Johnson and staff for the spectral data and their interpretations. Our thanks are also due to Dr. George Slomp for helpful discussions of this work. Analyses were performed by Mr. C. H. Emerson, Mr. W. A. Struck and the staff of the Physics Department of these laboratories.

KALAMAZOO, MICHIGAN

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[8] This procedure for oxidative ozonolysis was patterned after one described by R. B. Turner, THIS JOURNAL, **72**, 579 (1950).

[9] C. R. Hauser and B. E. Hudson, Jr., "Organic Reactions," Vol. 1 John Wiley and Sons, Inc., New York, N. Y., 1942, p. 266.