Estrogenic Biphenyls. II. 2',5'-Diethyl-4-methoxybiphenyl-4'-carboxylic Acid

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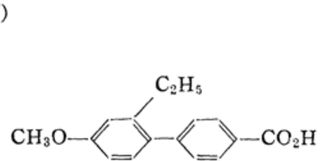
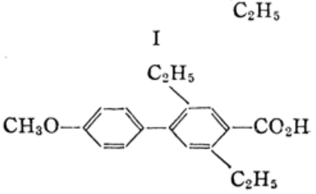
In the first paper1) of the present series it was reported that 2, 3'-diethyl-4-methoxybiphenyl-4'-carboxylic acid (I) is estrogenic and the activity can be explained on the basis of the postulation2) of the suitable distance between the two active hydrogen atoms and the suitable thickness of the molecule for an estrogen.



I



II

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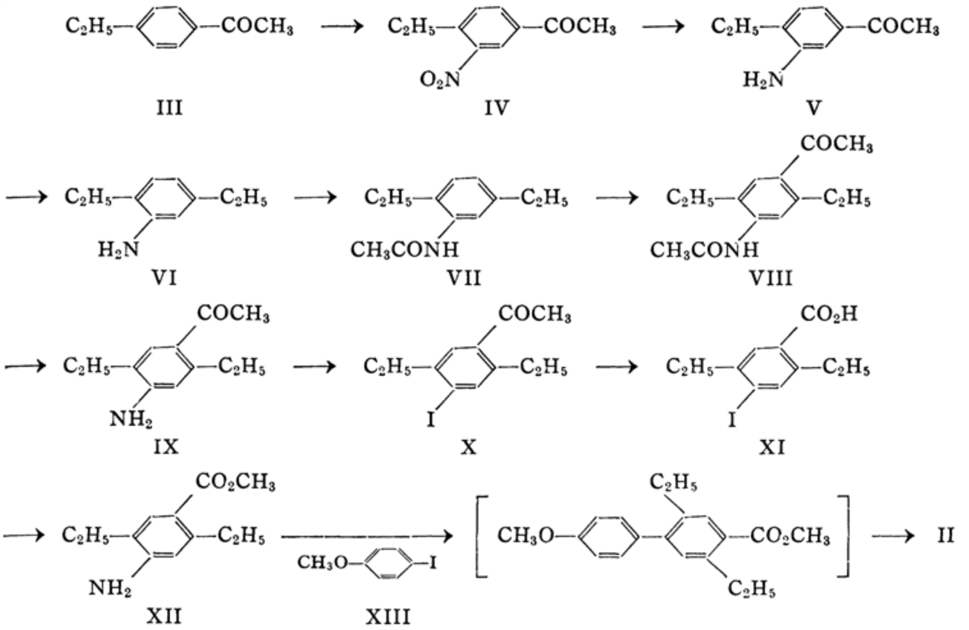
1) M. Ōki and T. Sato, This Bulletin, **30**, 508 (1957).

2) M. Ōki and Y. Urushibara, ibid., **25**, 109 (1952).



It is considered that the suitable thickness of compound I is obtained through the steric effect of the ethyl group at position 2, which causes a deformation of the coplanar structure, and thus increases the molecular thickness of the biphenyl system. As an ethyl group at position 2′ or 6′ should have the same steric effect as the one at position 2, 2′, 5′-diethyl-4-methoxybiphenyl-4′-carboxylic acid (II) has been prepared and tested on estrogenic activity.

Compound II was sythesized in the following way: nitration of 4-ethylacetophenone (III) gave 4-ethyl-3-nitroacetophenone (IV), which was reduced to the corresponding amine (V) with stannous chloride and hydrochloric acid. Modified Wolff-Kischner reduction of compound V yielded 2,5-diethylaniline (VI), of which acetylation product VII showed no depression of the melting point on admixture with the authentic specimen of 2,5-diethylacetanilide[3]. Reduction[3,4] of 2,5-diethylnitrobenzene to VI gave an unsatisfactory result especially on a larger scale, because of the instability of the nitro-compound to heat. Compound VII was treated with acetyl chloride and aluminium chloride and the product, 4-acetamido-2,5-diethylacetophenone (VIII), was hydrolyzed to yield 4-amino-2,5-diethylacetophenone (IX). Compound IX was converted into 2,5-dietyl-4-iodo-acetophenone (X) through a diazo-reaction and the iodo-ketone (X) was oxidized with sodium hypobromite to produce 2,5-diethyl-4-iodo-benzoic acid (XI). Methyl 2,5-diethyl-4-iodo-benzoate (XII) was prepared in the usual way. The ester (XII) and 4-iodoanisole (XIII) were submitted to the Ullmann reaction and the product was hydrolyzed and purified by chromatography through alumina.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMUM

Compound	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$
I	270	4.09
II	268	4.14

The ultraviolet absorption data of compounds I and II are shown in Table I. The absorption spectra of the two compounds were similar and suggested that the deformation in the biphenyl skeletons of these compounds is nearly the same.

Compound II in oil was injected subcutaneously to ovariectomized mice. The minimum active dose to produce full estrus in 100% of the animals was found to be 100γ and the same as that of compound I[1].

Experimental[5]

4-Ethyl-3-nitroacetophenone (IV).—4-Ethylacetophenone (III) was prepared from ethylbenzene and acetyl chloride according to the method

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[3] W. J. Gaudion, W. H. Hook and S. G. P. Plant, *J. Chem. Soc.*, **1947** 1631.

[4] A. Voswinkel, *Ber.*, **22**, 315 (1889)

[5] All melting and boiling points are uncorrected. The authors are indebted to Dr. Y. Osawa of the University of Tokyo for microanalyses.

described by Mowry et. al.[6]. One mole or 148 g. of compound III was dropped into 300 ml. of concentrated sulfuric acid with good stirring, while the temperature was kept below 5° by adding solid carbon dioxide. A mixed acid consisting of 80 ml. of nitric acid (d : 1.42) and 120 ml. of concentrated sulfuric acid was dropped into the sulfuric acid solution of the ketone (III) in forty-five minutes, the temperature being kept below 0° by adding solid carbon dioxide. The mixture was stirred for further ten minutes and poured into 2.5 l. of ice-water. The supernatant layer was decanted off and the lower one was dissolved in ether. The ethereal solution was washed with aqueous sodium hydroxide and then with water and dried over calcium chloride. Fractional distillation gave a pale yellow oil boiling at 135—136°/1 mm. which solidified at 0° and melted at the room temperature. Yield 164 g. or 85%, of the theoretical.

Anal. Found: N, 7.46%. Calcd. for $C_{10}H_{11}O_3N$: N, 7.25%.

3-Amino-4-ethylacetophenone (V). — When a mixture of 193 g. (1 mole) of compound IV, 750 g. (3.3 moles) of stannous chloride and 1.2 l. (6.6 moles) of dilute hydrochloric acid (1 : 1) was stirred, a spontaneous reaction set in and the mixture began to boil. The homogenous solution was allowed to cool and was basified with an excess of 33% aqueous sodium hydroxide. The organic material was extracted with ether and the combined extracts were dried over potassium carbonate. After the solvent was evaporated, the product distilled over at 144-145°/2 mm. as a pale yellow oil. Yield 147 g. or 90% of the theoretical.

Anal. Found: N, 8.76%. Calcd. for $C_{10}H_{13}ON$: N, 8.58%.

2, 5-Diethylaniline (VI).—A solution of 163 g. (1 mole) of the amino-ketone (V), 120 g. (1.6 moles) of 80% hydrazine hydrate and 280 g. of potassium hydroxide in 1 kg. of diethylene glycol was heated under reflux for one hour and the reflux condenser was then replaced by a downward condenser. Distillation was continued until the remainder in the flask attained the temperature of 200°, and it was heated again for thirty minutes. The reaction mixture was cooled and steam-distilled. The oily product was extracted with ether and the extract was dried over potassium hydroxide. Distillation gave a colorless oil boiling at 120—125°/20 mm. Reported boiling points of 2, 5-diethylaniline are 122°/13 mm[3] and 140—142°/20 mm.[4]. Yield 134 g. or 90% of the theoretical. The acetylation product (VII) was recrystallized from aqueous alcohol and melted at 150—151°. Reported melting point of 2, 5-diethylacetanilide (VII) is 154°[3].

4-Acetamido-2, 4-diethylacetophenone (VIII).—To a boiling suspension of 95.5 g. (0.5 mole) of compound VII in 56 g. (0.8 mole) of acetyl chloride and 400 ml. of carbon disulfide, was added 160 g. (1.2 moles) of aluminum chloride with stirring at such a rate that the mixture boiled briskly. The reaction mixture was refluxed with stirring for one hour and then allowed to stand for two hours at the room temperature. The supernatant carbon disulfide layer was decanted off and the lower layer was decomposed by pouring into ice-water in which 200 ml. of concentrated hydrochloric acid had been added. The crystals were collected and recrystallized from aqueous alcohol. Colorless prisms, m.p. 149.5—150°. Yield 100 g. or 90% of the theoretical.

Anal. Found: N, 6.25%. Calcd. for $C_{14}H_{19}O_2N$: N, 6.00%.

4-Amino-2, 5-diethylaetophenone (IX). — A mixture of 111.5 g. (0.5 mole) of the acetyl compound (VIII) and 600 ml. of dilute hydrochloric acid (1 : 1) was heated under reflux for two hours and basified with sodium hydroxide after cooling. The crystals were collected and recrystallized from benzene-petroleum ether. Colorless needles, m. p. 72.5—73°. Yield 71.6 g. or 75% of the theoretical.

Anal. Found: N, 7.38%. Calcd. for $C_{12}H_{17}ON$: N, 7.32%.

2, 5-Diethyl-4-iodoacetophenone (X). — A diazonium salt solution prepared from 95.5 g. (0.5 mole) of compound IX, 150 g. (1.5 moles) of concentrated sulfuric acid, 300 ml. of water and 35 g. (0.5 mole) of sodium nitrite in a minimum quantity of water was gradually added to a warm solution of 166 g. (1 mole) of potassium iodide in 200 ml. of water. The mixture was warmed at 50° for thirty minutes. The heavy oil was extracted with ether and the ethereal extract was washed with water, with aqueous sodium thiosulfate, and again with water, and dried over calcium chloride. Fractional distillation under nitrogen atmosphere gave a pale yellow oil boiling at 136°/2 mm. Yield 91 g. or 60% of the theoretical.

Anal. Found: I, 42.00%. Calcd. For $C_{12}H_{15}OI$: I, 42.29%.

This compound is unstable and quickly discolors on exposure to air. The 2, 4-dinitrophenylhydrazone was recrystallized from alcohol-ethyl acetate. Orange leaflets, m. p. 150—151°.

Anal. Found: N, 11.49%. Calcd. for $C_{17}H_{17}O_4N_4I$: N, 11.62%.

2, 5-Diethyl-4-iodobenzoic Acid (XI). — A solution of 30.2 g. (0.1 mole) of the iodo-ketone (X) in 150 ml. of dioxane was dropped into a sodium hypobromite solution prepared from 56 g. (1.4 moles) of sodium hydroxide, 72 g. (0.45 mole) of bromine and 300 ml. of water in one hour, at the temperature below 10° and with continuous stirring. The excess of sodium hypobromite was decomposed with sodium bisulfite and bromoform was removed by steam-distillation. After cooling, the solution was acidified with hydrochloric acid, and the crystalline substance was recrystallized from aqueous alcohol. Colorless needles, m. p. 134—135°. Yield 25 g. or 82% of the theoretical.

Anal. Found: I, 42.21%. Calcd. for $C_{11}H_{13}O_2I$: I, 41.76%.

Methyl-2, 5-diethyl-4-iodobenzoate (XII).—A solution of 30.1 g. of the acid (XI) in 100 ml. of methanol was saturated with dry hydrogen

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[6] D. T. Mowry, M. Renoll and W. E. Huber, *J. Am. Chem. Soc.*, **68**, 1105 (1946).

chloride at 0° and the mixture was warmed on a water bath for two hours. The reaction mixture was poured into water and extracted with ether. The extracts were washed with aqueous sodium bicarbonate and dried over potassium carbonate. The ester boiled at 137°/1 mm. Yield 27 g. or 87% of the theoretical.

Anal. Found: I, 40.20%. Calcd. for $C_{12}H_{15}O_2I$: I,39.89%.

4-Methoxy-2′, 5′-diethylbiphenyl-4′-carboxylic Acid (II).—To a well stirred mixture of 10 g. (0.043 mole) of 4-iodoanisole (XIII), prepared by iodination of anisole[7], and 5 g. (0.016 mole) of compound XII, heated at 240—250°, was added 15 g. (0.235 atom) of copper bronze activated by iodine[8] in portions in twenty minutes. The temperature was then raised to 280° and the mixture was stirred for forty minutes at that temperature. After cooling, the reaction mixture was extracted with acetone and the solvent was evaporated. To the residue was added 50 ml. of 10% sodium hydroxide in 50% aqueous alcohol, and the mixture was heated under reflux for two hours, and then diluted with 500 ml. of water. The insoluble material was filtered off with the aid of active charcoal. The filtrate was acidified with hydrochloric acid and the crystalline substance was collected. The crude acid was dissolved in ether and purified by passing the solution through an alumina column and eluting with the same solvent. Colorless needles, m. p. 161—162°. Yield 0.6 g. or 11% of the theoretical amount based on the used iodoester (XII).

Anal. Found: C, 76.28: H, 7.36%. Calcd. for $C_{18}H_{20}O_3$: C, 76.03: H, 7.09%.

Ultraviolet Absorption Spectra.—The specimens were submitted to measurements in 95% alcohol by the use of Hitachi Photoelectric Spectro photometer Model EPU-2. 2, 3′-Diethyl-4-methoxybiphenyl-4′-carboxylic acid (I) was prepared as described in the previous paper[1].

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[7] M. P. Brenans, *Bull. chim. soc. France*, [3] **25**, 819 (1901).

[8] E. C. Kleiderer and R. Adams, *J. Am. Chem. Soc.*, **55**, 4225 (1933).