Estrogenic Biphenyls. IV. 3′-Alkyl-4-methoxybiphenyl-4′-carboxylic Acids

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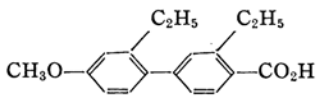
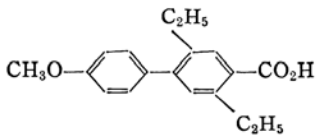
(Received July 22, 1957)

It has been found that 2,3′-diethyl-4-methoxybiphenyl-4′-carboxylic acid[1] (I) and 2′,5′-diethyl-4-methoxybiphenyl-4′-carboxylic acid[2] (II) are fully estrogenic to ovariectomized mice at the doses of 100 γ and that the enhanced estrogenic potency has been attributed to the presence of the two ethyl groups. In the previous paper[3], the role of the alkyl group of 2-alkyl-4-methoxybiphenyl-4′-carboxylic acids (III) in the estrogenic activity was studied and no significant difference was found in the activity of the members of this series.



I



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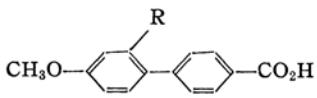
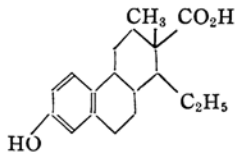


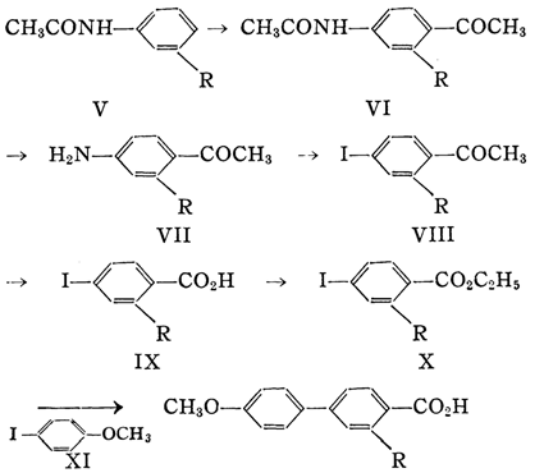
III



IV

Since these compounds are related structurally to doisynolic acid (IV), the effect of the alkyl group at position 3′ on the estrogenic activity is expected to be great[4]. Therefore the authors wished to find out the optimum alkyl group at position 3′ of 4-methoxybiphenyl-4′-carboxylic acid (III, R=H).

3′-Alkyl-4-methoxybiphenyl-4′-carboxylic acids (XII) were synthesized in the same way as compound I. All the compounds up to X where R is ethyl are known[1].



a: CH_3 b: C_2H_5 c: n-C_3H_7

m-Alkylacetanilide (V) was treated with acetyl chloride and aluminium chloride to give 4-acetamido-2-alkylacetophenone (VI), which was hydrolyzed to 2-alkyl-4-aminoacetophenone (VII). Diazotization of compound VII and treatment of the diazonium salt with potassium iodide yielded 2-alkyl-4-iodoacetophenone (VIII), which was oxidized with sodium hypobromite to produce 2-alkyl-4-iodobenzoic acid (IX). The ethyl ester (X) was prepared in the usual way. Compound X and *p*-iodoanisole (XI) were submitted to the Ullmann reaction and the product was hydrolyzed to produce the desired compound (XII).

The structure of 2-alkyl-4-iodobenzoic acid (IX_a and IX_b) was proved in the following way. Compound IX gave a dibasic acid (XIII) on oxidation with potassium permanganate and the acid (XIII) gave known 4-iodophthalic anhydride (XIV) on sublimation and then 4-iodophthalimide (XV)[5] when the compound XIV was treated with ammonia.

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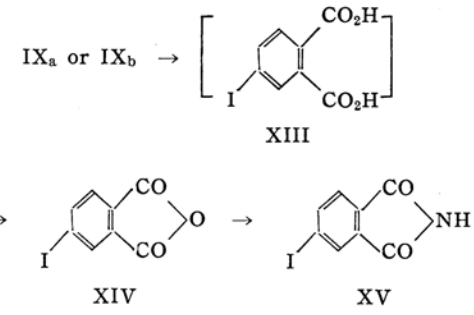
1) M. Ōki and T. Sato, This Bulletin, **30**, 508 (1957).
2) M. Ōki and T. Sato, ibid., **30**, 702 (1957).
3) T. Sato and M. Ōki, ibid., in press.
4) See K. Miescher, *Chem. Rev.*, **43**, 367 (1948).
5) A. Edinger, *J. prakt. Chem.*, (2), **53**, 375 (1896).



XIII XIV XV

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA AND ESTROGENIC ACTIVITY OF 3'-ALKYL-4-METHOXYBIPHENYL-4'-CARBOXYLIC ACID (XII)

Compound	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	Minimum active dose in mice (γ)
XII_a	287	4.39	500
XII_b	286	4.36	250
XII_c	286	4.38	500

The ultraviolet absorption data and the estrogenic activity of compounds XII_a, XII_b and XII_c are given in Table I. All the members of the present series showed a strong absorption at about 286 mμ (log ε =4.36), while 4-methoxybiphenyl-4'-carboxylic acid (III, R=H) at 289 mμ, as previously reported[3]. The spectra of compounds XII and III (R=H) were expected to resemble, since substitution at position 3' was regarded to have little effect on the conformation of the biphenyl skeleton. However, it may be noted that a hypsochromic shift of the absorption maxima has been observed rather than a bathochromic shift which is common when an alkyl group is introduced into the benzene ring. Similar results have been noted by other workers, when alkyl substitution takes place at the ortho position to the carboxyl group of the benzoic acid[6-8] and have been explained on the basis of the steric effect of the alkyl group which enforces the carbonyl group to rotate and to lose resonance with the benzene ring.

The minimum active doses of the members of the series XII to produce full estrus were determined by the vaginal smear test with ovariectomized mice. The alkyl substitution at position 3' enhances the estrogenic activity of 4-methoxybiphenyl-4'-carboxylic acid, probably because of the increasing width of the molecule. It is noted, however, that the kinds of alkyl group show no remarkable difference in the estrogenic activity. This may be attributed to the similar molecular thickness, as is shown by the ultraviolet absorption.

6) S. D. Ross, *J. Am. Chem. Soc.*, **70**, 4039 (1948).
7) E. A. Fehner, ibid., **72**, 1404 (1950).
8) C. M. Moser and A. J. Kohlenberg, *J. Chem. Soc.*, **1951**, 804.

Experimental[9]

***m*-Propylacetanilide** (V_c). — *m*-Propylaniline[3] was treated with acetic anhydride in the usual way. The oily product distilled at 165—169°/3 mm. and solidified on cooling. Recrystallization from aqueous ethanol gave colorless needles, m. p. 51—52°. Yield 96% of the theoretical.

Anal. Found: N, 7.79. Calcd. for $C_{11}H_{15}ON$: N, 7.90%.

4-Acetamido-2-methylacetophenone (VI_a). —To a well-stirred mixture of 45 g. (0.30 mole) of *m*-methylacetanilide (V_a)[10], 43 g. (0.55 mole) of acetyl chloride, and 240 ml. of carbon disulfide, 142 g. (1.1 moles) of aluminium chloride was added in small portions in one hour. The mixture was then heated under reflux for one hour and allowed to stand at room temperature for another hour. The supernatant carbon disulfide layer was decanted off and the lower layer was poured into a mixture of cracked ice and hydrochloric acid. The precipitate was collected and used for the subsequent reaction without purification. The analytical sample was obtained by recrystallization from aqueous ethanol. Colorless needles, m. p. 135—136°.

Anal. Found: N, 7.40. Calcd. for $C_{11}H_{13}O_2N$: N, 7.33%.

4-Amino-2-methylacetophenone (VII_a). —A mixture of the crude VI_a and 300 ml. of dilute hydrochloric acid (1 : 1) was heated under reflux for two hours, and, after cooling, basified with aqueous sodium hydroxide. The organic material was extracted with ether and the ethereal extract was dried over potassium carbonate and concentrated to give crystals, which were recrystallized from benzene-petroleum ether. Pale yellow plates, m. p. 94—95°. Yield 29 g. or 64% of the theoretical based on the *m*-methylacetanilide.

Anal. Found: N, 9.18. Calcd. for $C_9H_{11}ON$: N, 9.15%.

4-Amino-2-propylacetophenone (VII_c). — Treatment of 140 g. (0.79 mole) of compound V_c with 70 g. (0.89 mole) of acetyl chloride and 300 g. (2.26 moles) of aluminium chloride in 700 ml. of carbon disulfide yielded a viscous oil. The mixture was extracted with benzene and the extract was heated under reflux with 500 ml. of hydrochloric acid (1 : 1) for two hours. The aqueous layer was separated and basified with sodium hydroxide. The base was extracted with ether and the extract was fractionated. Repeated fractionation gave an oil boiling at 155°/2 mm. which solidified on standing. The analytical sample was obtained by recrystallization from benzene-petroleum ether. Colorless needles, m.

9) All melting and boiling points are uncorrected.
10) F. Beilstein and Al Kuhlberg, *Ann.*, **156**, 66 (1870).

p. 77.5—79°. Yield 53 g. or 38% of the theoretical.

Anal. Found: N, 7.88. Calcd. for $C_{11}H_{15}ON$: N, 7.90%.

The acetyl compound (VII_c) was obtained in the usual way. Colorless plates, m. p. 95.5—96°, were obtained on recrystallization from aqueous ethanol.

Anal. Found: N, 6.74. Calcd. for $C_{13}H_{17}O_2N$: N, 6.39%.

2-Alkyl-4-iodoacetophenones (VIII). — The general procedure is described by an example of the preparation of 4-iodo-2-methylacetophenone. The diazonium salt solution prepared from 30 g. (0.2 mole) of compound VII_a, dilute sulfuric acid (42 g. or 0.42 mole of sulfuric acid and 100 ml. of water) and 14 g. (0.2 mole) of sodium nitrite in 30 ml. of water, was slowly added to a solution of 50 g. (0.3 mole) of potassium iodide in 70 ml. of water. Stirring was continued for thirty minutes at a low temperature and then at 50—60° for two hours. The mixture was extracted with ether and the ethereal extract was washed with aqueous sodium hydroxide, aqueous sodium thiosulfate, and water. 4-Iodo-2-methylacetophenone boiled at 134—138°/4 mm. and solidified on long standing. The analytical sample was obtained by recrystallization from petroleum ether. Colorless prisms, m. p. 23—24°. Yield 27 g. or 52% of the theoretical.

Anal. Found: C, 41.40; H, 3.13. Calcd. for C_9H_9OI: C, 41.56; H, 3.49%.

4-Iodo-2-propylacetophenone ($VIII_c$) was obtained in 51% yield from the corresponding amine (VII_c). Brown oil, b. p. 158—159°/8 mm. Since the purification of this compound was a tedious process, the crude product was used for the subsequent reaction without purification.

2,4-Dinitrophenylhydrazone of 4-Iodo-2-methylacetophenone ($VIII_a$). — Recrystallized from ethanol-ethyl acetate. Orange plates, m. p. 167—168°.

Anal. Found: N, 12.50. Calcd. for $C_{15}H_{13}O_4N_4I$: N, 12.73%.

2,4-Dinitrophenylhydrazone of 4-Iodo-2-propylacetophenone ($VIII_c$). — Recrystallized from ethanol-ethyl acetate. Deep-orange plates, m. p. 160—161°.

Anal. Found: N, 11.86. Calcd. for $C_{17}H_{17}O_4N_4I$: N, 11.97%.

2-Alkyl-4-iodobenzoic Acids (IX). — The general procedure is given by an example of the preparation of 4-iodo-2-methylbenzoic acid (IX_a) as follows. To a well stirred sodium hypobromite solution, prepared from 65 g. (0.36 mole) of bromine, 50 g. (1.25 moles) of sodium hydroxide and 250 ml. of water, a solution of 25 g. (0.096 mole) of compound $VIII_a$ in 130 ml. of dioxan was added in one hour. The temperature was kept below 10° during the addition and then at 50—60° for one hour. The excess of hypobromite was decomposed with sodium sulfite and the mixture was steam-distilled to remove bromoform. The remaining solution was acidified with hydrochloric acid and the product was recrystallized from aqueous ethanol. Colorless needles, m. p. 169—170.5°. Yield 20 g. or 79% of the theoretical.

Anal. Found: C, 36.74; H, 2.53. Calcd. for $C_8H_7O_2I$: C, 36.66; H, 2.69%.

4-Iodo-2-propylbenzoic acid (IX_c) was obtained in 80% yield. Colorless needles, m. p. 127—128°.

Anal. Found: C, 41.60; H, 3.50. Calcd. for $C_{10}H_{11}O_2I$: C, 41.41; H, 3.82%.

4-Iodophthalimide (XV). (A). From 4-Iodo-2-propylbenzoic Acid (IX_d).—A mixture of 1 g. of compound IX_d, 5 g. of potassium permanganate, and 80 ml. of water, was heated under reflux for eighteen hours. Sulfur dioxide was bubbled into the mixture and the resulting solution was extracted with ether for five hours. The ethereal extract was dried over anhydrous magnesium sulfate and evaporated. The residue was distilled and 800 mg. of pale yellow prisms, m. p. 111—112°, were obtained. A purer sample of 4-iodophthalic anhydride (XIV) was obtained by sublimation in vacuo. Colorless prisms, m. p. 114—116°. The reported melting point is 123°[5].

A mixture of the crude 4-iodophthalic anhydride (500 mg.) and 1 ml. of 28% aqueous ammonia was heated over a free flame to remove excess of ammonia and water and the residue was sublimed in vacuo. 4-Iodophthalimide was obtained in pale yellow plates melting at 226—228°. Yield 400 mg. or 80% of the theoretical. Reported melting point is 222—224°[5].

Anal. Found: N, 5.08. Calcd. for $C_8H_4O_2NI$: N, 5.13%.

(B) From 4-Iodo-2-methylbenzoic Acid (IX_a).—Compound IX_a was treated in the same way as described above. Pale yellow plates melting at 224—226° were obtained and showed no depression of the melting point when mixed with another specimen of 4-iodophthalimide described above.

Ethyl 2-Alkyl-4-iodobenzoates (X).—The general procedure is exemplified by the preparation of ethyl 4-iodo-2-methylbenzoate (X_a) as follows. A solution of 20 g. of compound IX_a in 200 ml. of ethanol was saturated with hydrogen chloride and the mixture was heated under reflux for six hours. The solution was concentrated and diluted with water. Extraction with ether followed by fractionation gave the pure ester boiling at 141—144°/4 mm. Yield 17 g. or 78% of the theoretical.

Anal. Found: C, 41.87; H, 4.07. Calcd. for $C_{10}H_{11}O_2I$: C, 41.40; H, 3,82%.

Ethyl 2-ethyl-4-iodobenzoate (X_b) was prepared as described elsewhere[1]. Ethyl 4-iodo-2-propylbenzoate (X_c) was obtained in 77% yield. B. p. 179—182°/16 mm.

Anal. Found: C, 45.72; H, 4.74. Calcd. for $C_{12}H_{15}O_2I$: C, 45.30; H, 4.75%.

3'-Alkyl-4-methoxybiphenyl-4'-carboxylic Acids (XII).—The general procedure of synthesis was illustrated by the following example. A mixture of 18.6 g. (0.079 mole) of *p*-iodoanisole (XI)[11] and 10.0 g. (0.035 mole) of compound X_a, was heated at 220—228° with stirring and 30 g. (0.47 atom) of activated copper bronze[12] was

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

12) E. C. Kleiderer and R. Adams, *J. Am. Chem. Soc.*, **55**, 4291 (1933).

added over a period of twenty-five minutes. The temperature was kept at 220—230° for ten minutes and then at 280° for forty minutes. The reaction mixture was extracted with acetone and the solvent was evaporated. The residue was refluxed with a mixture of 100 ml. of 10% aqueous sodium hydroxide and 200 ml. of ethanol for six hours. The mixture was concentrated and the residue diluted with water. Insoluble material was removed by filtration and the filtrate was acidified with hydrochloric acid. The crystalline material was collected and boiled with benzene. Removal of the insoluble material followed by concentration gave the desired product. 4-Methoxy-3'-methylbiphenyl-4'-carboxylic acid (XII_a) was obtained in colorless needles, m.p. 199.5—200°, on recrystallization from aqueous ethanol. Yield 1.0 g. or 12% of the theoretical.

Anal. Found: C, 74.35; H, 5.55. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83%.

3'-Ethyl-4-methoxybiphenyl-4'-carboxylic acid (XII_b) was obtained in 15% yield. Colorless needles, m. p. 182—183°.

Anal. Found: C, 74.82; H, 6.57. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29%.

4-Methoxy-3'-propylbiphenyl-4'-carboxylic acid (XII_c) was obtained in 16% yield. Colorless needles, m. p. 170.5—171°.

Anal. Found: C, 75.85; H, 6.63. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%.

Ultraviolet Absorption Spectra. — These were measured by using Hitachi Photo-electric Spectrophotometer Model EPU-2. Substances were dissolved in 95% ethanol.

The authors wish to express their hearty thanks to Professor Y. Urushibara of the University of Tokyo for encouragement throughout this work and to the Research Department of Teikoku Hormone Manufacturing Co., Kawasaki, for bio-assay. The authors' thanks are also due to the Ministry of Education for the Grant in Aid for Fundamental Research.

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