Estrogenic Biphenyls. III. 2-Alkyl-4-methoxybiphenyl-4'-carboxylic Acids

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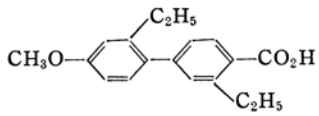
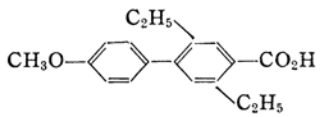
(Received June 3, 1957)

In the previous papers[1,2] of this series, it was reported that 2, 3'-diethyl-4-methoxybiphenyl-4'-carboxylic acid(I) and 2', 5'-diethyl-4-methoxybiphenyl-4'-carboxylic acid(II) were fully estrogenic at the doses of 100 γ when administered to ovariectomized mice. Enhancement of the estrogenic activity of compounds I and II, compared with that of 4-hydroxybiphenyl-4'-carboxylic acid(III), by the presence of the two ethyl groups was attributed to the steric effect causing the two benzene rings to rotate out of the otherwise coplanar structure and the increasing thickness of the molecules, which was shown by the hypsochromic effect in the ultraviolet absorption spectra.



I



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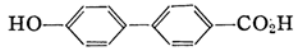
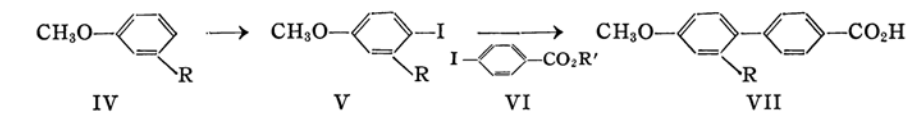


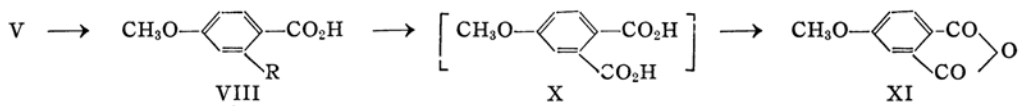
III

It is unknown, however, whether the introduction of ethyl groups into 4-hydroxy- or 4-methoxy-biphenyl-4'-carboxylic acid at positions 2 and 3' or 2' and 5' is the optimum substitution for developement of the estrogenic activity. Therefore, the authors hoped to find out first the most suitable alkyl group substituted at position 2 only of 4-methoxybiphenyl-4'-carboxylic acid.

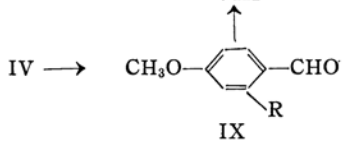
2-Alkyl-4-methoxybiphenyl-4'-carboxylic acids(VII) were synthesized in the following way. 3-Alkylanisoles(IV) were iodinated with iodine in the presence of yellow



IV V VI VII



VIII X XI



IX

R
a H
b CH_3
c CH_3CH_2
d $CH_3CH_2CH_2$

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1) M. Ōki and T. Sato, This Bulletin, **30**, 508 (1957).
2) M. Ōki and T. Sato, ibid., 702.

mercuric oxide[3]. The structures of 3-alkyl-4-iodoanisoles(V), compounds Va[3] and Vc[1] being known, were proved as follows:

The reaction of Grignard compound from 4-iodo-3-methylanisole (Vb) with solid carbon dioxide produced a carboxylic acid. It was identified with 4-methoxy-2-methylbenzoic acid (VIIIb) which was prepared by permanganate oxidation of 4-methoxy-2-methylbenzaldehyde (IXb), obtained from 3-methylanisole(IVb), zinc cyanide, hydrogen chloride and aluminium chloride[4]. The acid (VIIId) obtained from 4-iodo-3-propylanisole (Vd) in the same way was oxidized with potassium permanganate. The product was sublimed in vacuo to produce an anhydride, which was identical with 4-methoxyphthalic anhydride (XI) prepared from 4-methoxy-2-methylbenzoic acid (VIIIb). 3-Alkyl-4-iodoanisoles (V) and 4-iodobenzoic esters (VI) were submitted to the Ullmann reaction. Any unchanged materials were removed in vacuo when necessary, and hydrolysis of the condensation products gave the desired biphenyls (VII).

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA AND ESTROGENIC ACTIVITY OF 2-ALKYL-4-METHOXYBIPHENYL-4′-CARBOXYLIC ACID (VII)

Compound	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	Minimum active dose in mice (γ)
VIIa[5]	289	4.36	1000*
VIIb	224 280	4.27 4.17	200
VIIc	222 278	4.28 4.10	500
VIId	224 278	4.28 4.13	250

* Active in 50% animals.

The ultraviolet absorption data and the estroganic activity of compounds VIIa, VIIb, VIIc, and VIId are given in Table I. 4-Methoxybiphenyl-4′-carboxylic acid (VIIa) showed a strong absorption at 289 mμ, while its homologs (VIIb, c, d) possessed absorption at about 278 mμ. It can be deduced from the spectral study that the introduction of an alkyl group into position 2 modifies the coplanar conformation of the biphenyl skeleton, because the observed hypsochromic shift and decrease in K-band intensity in the present series (VII) can be attributed to the non-planar conformation of the system, if the wave length of the maximum absorption depends on the extent of conjugation. Further, it may be inferred that the deterioration in conjugation in the series (VII) is similar regardless of the length of the alkyl chains, and then, it may be assumed that the first methylene group only interferes with the benzene rings. The present observation is in good agreement with others[6]. Namely, it is known that by a single substitution at position 2 of biphenyl a little change occurs in the ultraviolet absorption and the K-band appears, though the maximum shifts to a shorter wave length and the intensity diminishes, and that 2-methylbiphenyl absorbs at 237 mμ and 2-ethylbiphenyl at 233 mμ while biphenyl itself does at 249 mμ.

The minimum active doses of the members of the series VII to produce full estrus were determined by the vaginal smear test with ovari-ectomized mice. The substances in oil solution were injected subcutaneously. 4-Hydroxybiphenyl-4′-carboxylic acid (III) produced estrus in 60% of the test animals at the dose of 500 γ but the assay could not be carried out at 1 mg. dose because of its small solubility in oil[1]. On the other hand, compound VIIa was found to be active to 40% and 50% of the animals at the doses of 500 γ and 1 mg., respectively. Natural estrogens, hexestrol, and stilbestrol, lose potency markedly when they are converted into methyl ethers[7], while there is no remarkable difference in estrogenic activity between a free phenol and its methyl ether of the type of doisynolic acid[8] or allenolic acid[9]. 4-Hydroxybiphenyl-4′-carboxylic acid, and presumably its 2-alkylhomologs, fall in the latter category both in the two functional groups and in the effect of the methylation of the hydroxyl group. It is striking, however, that the kind of the alkyl group gives almost no difference in the estrogenic activity in contrast to the case of dialkylstilbestrol dimethyl ethers[10]. This may be understood on the basis of the molecular thickness being similar irrespective of the kind

3) M. P. Brenans, *Bull. Soc. chim. France*, [3] **25**, 819 (1901).
4) R. Adams and E. Montgomery, *J. Am. Chem. Soc.*, **46**, 1518 (1924).
5) Prepared according to the method given by L. F. Fieser and C. K. Bradsher, ibid., **58**, 1738 (1936).
6) E. A. Braude, F. Sondheimer and W. F. Forbes, *Nature*, **173**, 117 (1954) : R. A. Friedel, M. Orchin and L. Reggel, *J. Am. Chem. Soc.*, **70**, 199 (1948) : C. D. Freedman, ibid., **77**, 6223 (1955).
7) U. V. Solmssen, *Chem. Rev.*, **37** 481 (1945).
8) K. Miescher, ibid., **43**. 367 (1948),
9) See A. Horeau and Jacque, *Bull. Soc. chim. France*, **1945**, 1001 and the following papers.
10) M. Ōki and Y. Urushibara, This Bulletin, **25**, 109 (1952).

of the alkyl group as judged from the ultraviolet absorption, provided that the molecular thickness is mainly given by the rotated benzene rings.

Experimental[11]

3-Propylaniline. A mixture of 130 g. (0.87 mole) of 3-aminopropiophenone, prepared from 3-nitropropiophenone according to Kenford and Simpson[12], 120 g. (1.8 moles) of 72% hydrazine hydrate, 280 g. of potassium hydroxide and 700 ml. of diethylene glycol, was heated under reflux for one hour. The reflux condenser was replaced by a downward condenser. Distillation was continued until the pot temperature rose to 190° and the mixture was maintained at this temperature for three hours. Then the mixture was steam-distilled. The combined distillate was extracted with ether and the extract was dried over potassium carbonate. Distillation gave a colorless oil boiling at 102—107°/8 mm. Yield 113 g. or 96% of the theoretical. The reported boiling point is 118—119°/12—13 mm.[13]

The picrate, prepared in the usual way, melted at 155—156°. The reported melting point is 155°[13].

Anal. Found: N, 15.83. Calcd. for $C_{15}H_{16}N_4O_6$: N, 16.09%.

3-Alkyl-4-iodoanisole (V). The general procedure is described by an example of the preparation of 4-iodo-2-methylanisole. To a solution of 28 g. (0.23 mole) of 3-methylanisole (IVb)[14] in 46 ml. of ethanol were alternatively added 58 g. (0.23 mole) of iodine and 60 g. (0.28 mole) of yellow mercuric oxide in small portions during ten to fifteen minutes, while the reaction mixture was kept at the temperature below 25° and the flask was well swirled. Then the mixture was heated under reflux for ten minutes, cooled, and filtered with suction. The filtrate was diluted with water and the oil was extracted with ether. The ethereal extract was washed with aqueous potassium iodide, dried over calcium chloride, and fractionally distilled. 4-Iodo-2-methylanisole (Vb) boiled at 123—125°/7 mm. and solidified on cooling. The analytical sample was obtained by recrystallization from ethanol. Colorless needles, m. p. 43—45°. Yield 31 g. or 54% of the theoretical.

Anal. Found: I, 51.26. Calcd. for C_8H_9OI: I, 51.18%.

3-Ethyl-4-iodoanisole (Vc) was prepared as described elsewhere[1].

4-Iodo-2-propylanisole (Vd) was obtained from 2-propylanisole (IVd)[15]. Colorless oil, b. p. 120—121°/4 mm. Yield 62%.

Anal. Found: C, 43.77; 4.85. Calcd. for $C_{10}H_{13}IO$: C, 43.50; H, 4.75%.

4-Methoxy-2-methylbenzoic Acid (VIIIb). *A. From 4-Methoxy-2-methylbenzaldehyde (IXb).* The benzaldehyde, prepared according to Adams and Montgomery[4], was oxidized with aqueous potassium permanganate to give colorless plates melting at 173°. The reported melting point is 176°[16].

Anal. Found: C, 65.23; H, 6.11. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07%.

B. From 4-Iodo-2-methylanisole (Vb). 4-Methoxy-2-methylphenylmagnesium iodide was prepared in the usual way from 5 g. of compound Vb, 0.6 g. (0.029 atom) of magnesium turnings and 50 ml. of ether. Solid carbon dioxide was added to this solution and the product was decomposed with dilute hydrochloric acid. The acid in the ethereal layer was taken up in aqueous sodium bicarbonate and the aqueous solution was acidified with hydrochloric acid. The acid was recrystallized from aqueous ethanol. Colorless plates, m. p. 176—177°. Yield 2 g. or 60% of the theoretical. The melting point did not depress when this compound was mixed with 4-methoxy-2-methylbenzoic acid.

4-Methoxy-2-propylbenzoic Acid (VIIId). 4-Methoxy-2-propylphenylmagnesium iodide, prepared from 7 g. (0.025 mole) of compound Vd and 0.8 g. (0.033 atom) of magnesium in 50 ml. of ether was treated with solid carbon dioxide and the reaction mixture was worked up as in the preparation of compound VIIIb. Colorless plates, m. p. 106—107°, were obtained on recrystallization of the product from aqueous ethanol. Yield 2 g. or 41% of the theoretical.

Anal. Found: C, 68.03; H, 7.46. Calcd. for $C_{11}H_{14}O_3$; C, 68.02; H, 7.27%.

4-Methoxyphthalic anhydride (XI). *A. From 4-Methoxy-2-methylbenzoic Acid (VIIIb).* The acid VIIIb was oxidized according to Shall[16] and the dicarboxylic acid (X) was sublimed in vacuo. Colorless needles, m. p. 88—90°. The reported melting point is 93°.

B. From 2-Ethyl-4-methoxybenzoic Acid (VIIIc)[1]. A solution of 500 mg. of compound VIIIc, 3 g. of potassium permanganate and 1 ml. of 10% sodium hydroxide in 60 ml. of water, was heated under reflux for three hours. Sulfur dioxide was bubbled into the mixture and the resulting solution was extracted with ether for five hours. After concentration of the ethereal extract, the residue was heated in vacuo and the crystalline material was collected. The compound melted at 90—90.5° and showed no depression of the melting point on admixture with the authentic specimen of 4-methoxyphthalic anhydride obtained from 4-methoxy-2-methylbenzoic acid as described above.

C. *From 4-Methoxy-2-propylbenzoic Acid (VIIId).* The acid VIIId was treated in the same way as described above. The ahnydride obtained melted at 85—86° and showed no depression of the melting point when mixed with the authentic 4-methoxyphthalic anhydride.

2-Alkyl-4-methoxybiphenyl-4'-carboxylic Acid (VII). 4-Iodobenzoic esters (VI) were

11) All melting and boiling points are uncorrected.
12) J. R. Kenford and J. E. Simpson, *J. Chem. Soc.*, **1948**, 354.
13) R. Long and K. Schofield, ibid., **1953**, 2066.
14) c. f. G. S. Hiers and F. D. Hager, *Org. Synth.*, Coll. Vol. **1**, 58 (1940).
15) 3-Propylanisole was prepared from the corresponding phenol which was obtained by the diazo-reaction of 3-propylaniline.
16) C. Shall, *Ber.*, **12**, 816 (1879).

obtained from 4-iodobenzoic acid in the usual way. Methyl ester, m. p. 113—114° [17] and ethyl ester, b. p. 154°/16 mm.[18] were prepared.

For the general procedure of the preparation, 4-methoxy-2-methylbiphenyl-4'-carboxylic acid (VIIb) is described as follows. To a well stirred mixture of 10 g. (0.040 mole) of 4-iodo-3-methylanisole (Vb) and 5 g. (0.019 mole) of methyl 4-iodobenzoate, 15 g. of activated copper bronze[19] was added in twenty-five minutes, the temperature being kept at 240—250°. The reaction mixture was then heated at 280—290° for twenty-five minutes and extracted with acetone after cooling. The solvent was removed by distillation and the residue was hydrolyzed by refluxing with a mixture of 50 ml. of 10% aqueous sodium hydroxide and 100 ml. of ethanol for two hours. Ethanol was evaporated and the residue was diluted with 500 ml. of water. The oily insoluble material was removed by filtration with the aid of active charcoal and the filtrate was acidified with hydrochloric acid. The precipitate was collected and boiled with acetic acid, and any insoluble material was removed by filtration. The extract was concentrated and the residue was again treated with boiling benzene. The filtrate gave brown crystals, which yielded colorless plates, m. p. 211—212°, on recrystallization from benzene. Yield 0.4 g. or 9% of the theoretical.

Anal. Found: C, 74.05; H, 5.76. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83%.

2-Ethyl-4-methoxybiphenyl-4'-carboxylic Acid (VIIc). It was obtained from compounds Vc and VI ($R'=C_2H_5$). It was necessary to remove any unchanged ester in vacuo before hydrolysis for easier purification of the desired material. The acid was finally recrystallized from aqueous ethanol. M. p. 173.5—174.5°. Yield about 7% of the theoretical.

Anal. Found: C, 74.56; H, 6.21. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29%.

4-Methoxy-2-propylbiphenyl-4'-carboxylic Acid (VIId). It was prepared in the same way as described for compound VIIc, starting from 4-iodo-2-propylanisole (Vd) and ethyl 4-iodobenzoate. M. p. 175.5—176°. Yield about 8% of the theoretical.

Anal. Found: C, 75.52; H, 7.03. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%

Ultraviolet Absorption Spectra. They 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 his encourgement throughout this work and to 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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17) P. P. T. Sah and Chang-lin Hsü, *Rec. Trav. Chim.*, **59**, 349 (1940).
18) K. Kindler, *Ann.*, **450**, 1 (1926).
19) E. C. Kleiderer and R. Adams, *J. Am. Chem. Soc.*, **55**, 4219 (1933).