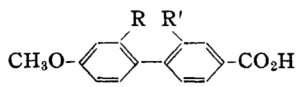
Estrogenic Biphenyls. V[1]. *Steric Effect in 2,2'-Dialkyl-4-methoxybiphenyl-4'-carboxylic Acids*

By Takeo SATO

(Received February 17, 1959)

Enhancement in the estrogenic activity of the 2- or 2'-alkyl homologs of 4-methoxybiphenyl-4'-carboxylic acid (I) in comparison with the parent compound I was attributed to the increase in the interplanar angle of the two benzene nuclei to attain a favorable conformation[2] for the development of the activity[3].



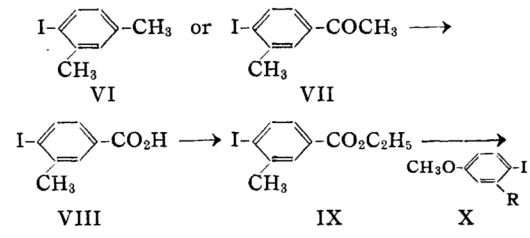
I: R=R'=H
II: R=CH_3, R'=H
III: R=H, R'=CH_3
IV: R=R'=CH_3
V: R=C_2H_5, R'=CH_3

The present author and Ōki also pointed out in the part III[4] of this series that the increase in the chain-length of the alkyl group at position 2 has little effect, as was deduced from the ultraviolet absorption spectra, and, consequently, essentially the same estrogenic potency was found in those compounds.

Since the minimum active dose in mice of the most potent compound of this series was found to be 100 γ, compared with 2.5 γ of stilbestrol dimethyl ether, it is considered that the methylene group at position 2 affords a steric effect which is not optimum for the development of the estrogenic potency as far as the biphenyl derivatives are concerned. Then the author sought higher estrogenic activity in more sterically hindered biphenyl derivatives.

4-Methoxy-2'-methylbiphenyl-4'-carboxylic acid (III) should have a similar conformation with 4-methoxy-2-methylbiphenyl-4'-carboxylic acid (II)[4], as was proved in 2,3'-diethyl-4-methoxybiphenyl-4'-carboxylic acid and 2',5'-diethyl-4-methoxybiphenyl-4'-carboxylic acid[5], because the steric interference by the methyl group must be equivalent at positions 2 and 2'. It is expected that the introduction of another alkyl group into position 2 of the compound III will give more steric interference and will result in a greater rotation of the benzene rings toward each other to relieve the steric hindrance. Thus the thicker models will be given.

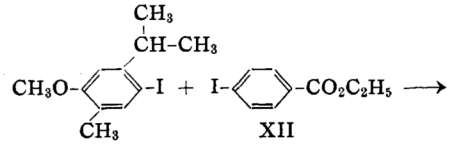
The method of preparation is illustrated in the following chart. Although 4-iodo-3-methylbenzoic acid (VIII) was obtained by Klingel[6] through a sequence of reactions starting from *o*-toluidine, the present author largely modified the method as is described in *Experimental Part*. The compound VIII is also obtainable through nitric acid oxidation[7] of 4-iodo-*m*-xylene (VI). The Ullmann reaction between appropriate 4-iodoanisoles (X) and ethyl 4-iodo-3-methylbenzoate (IX) followed by alkaline hydrolysis gave the desired biphenyls.



VI VII VIII IX X

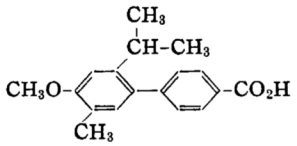
III, IV or V

As a reference compound 2-isopropyl-4-methoxy-5-methylbiphenyl-4'-carboxylic acid (XIII) was prepared from ethyl 4-iodobenzoate (XII) and 4-iodo-3-isopropyl-6-methylanisole (XI). The compound XIII is expected to involve greater rotation of the benzene nuclei toward each other than the corresponding straight-side-chain compounds because of the greater steric interference of the isopropyl group.



XI XII

1) Part IV: T. Sato and M. Ōki, This Bulletin, **30**, 958 (1957).
2) M. Ōki and Y. Urushibara, ibid., **25**, 109 (1952): See also J. Grundy, *Chem. Revs.*, **57**, 281 (1957).
3) M. Ōki and T. Sato, This Bulletin, **30**, 508 (1957).
4) T. Sato and M. Ōki, ibid., **30**, 859 (1957).
5) M. Ōki and T. Sato, ibid., **30**, 702 (1957).
6) J. Klingel, *Ber.*, **18**, 2687 (1885).
7) A. Grahl, ibid., **28**, 84 (1895).



XIII

The ultraviolet absorption maxima with the estrogenic activities in mice of the compounds I, II, III, IV, V and XIII are given in Table I.

TABLE I. ULTRAVIOLET ABSORPTION MAXIMA AND ESTROGENIC ACTIVITIES OF 4-METHOXY-BIPHENYL-4'-CARBOXYLIC ACID DERIVATIVES

Compound	K-Band maxima λ, mμ	log ε	Active dose in mice, γ (%)
I	289	4.36	1000 (50)
II	280	4.17	200 (100)
III	271	4.21	
IV			100 (80)
V			100 (60)
XIII	273	4.06	

The ultraviolet absorption maximum of the compound III is located at 271 mμ and the curve is similar with that of compound II. The hypsochromic shift in the type of the compound III compared with the compound II is always observed and may be attributed to the hyperconjugation of the methyl group[8]. The compound XIII, even though the bulkiness of the isopropyl group is expected to exert a greater steric interference and to cause a greater deterioration in conjugation, still possesses a strong K-band of the biphenyl system. The hypsochromic shift of the absorption maximum of the compound XIII, which can be compared with the compound II in term of hyperconjugation, can be attributed to the deterioration in conjugation, since the methyl group at position 5 is known to have little effect on the ultraviolet absorption[9]. On the other hand, the compounds IV and V show weak absorption at about 280 mμ, possess instead the strong absorption at about 230 mμ, indicating the two moieties of the biphenyl system absorb the light almost independently. Thus the two benzene nuclei in the compounds IV and V are considered nearly perpendicular to each other.

The estrogenic activity in ovariectomized mice was determined by the vaginal smear test. It is striking to find out that the estrogenic potency is not greatly altered by the introduction of the alkyl groups into position 2 and/or posititon 2', but it is evident that the estrogenic action is enhanced by the introduction of the alkyl groups.

Experimental[10]

4-Amino-3-methylacetophenone. — To a well stirred mixture of 115 g. (0.77 mol.) of *o*-acetotoluidide, 70 g. (0.89 mol.) of acetyl chloride and 700 ml. of carbon disulfide, was added 350 g. (2.62 mol.) of anhydrous aluminum chloride in small portions in the course of one hour, during which time the whole was gently refluxed on a bath. The refluxing was continued for one hour and the viscous oil at the bottom, after cooling, was decomposed with an excess of concentrated hydrochloric acid. The acidic mixture was hydrolyzed by refluxing for two hours without isolation of the acetamido compound. The solution was made alkaline with sodium hydroxide and the organic material was extracted with ether. The ethereal solution was washed as usual and evaporated to give 44 g. (38% of the theoretical) of 4-amino-3-methylacetophenone, colorless needles, which melted at 110°C on recrystallization from benzene-petroleum ether. The reported melting point is 102°C[5].

Anal. Found: N, 9.52. Calcd. for $C_9H_{11}NO$: N, 9.39%.

4-Iodo-3-methylacetophenone (VII).—To a diazonium solution obtained from 16 g. (0.11 mol.) of 4-amino-3-methylacetophenone, 30 ml. of concentrated sulfuric acid, 100 ml. of water and 7 g. (0.10 mol.) of sodium nitrite in minimum quantity of water, was added a solution of 17 g. (0.1 mol.) of potassium iodide in 20 ml. of water in the course of 10 min. Stirring was continued for thirty minutes below 10°C and then at 50°C for one hour. The mixture was extracted with ether and the ethereal extract was successively washed with aqueous sodium hydroxide, aqueous sodium thiosulfate and water. The iodo-acetophenone boiled at 146~148°C/8 mm. and solidified on standing. Pale yellow crystals, m. p. 42~43°C. Yield, 15.5 g. or 60% of the theoretical. It was prepared by Klingel[6] in the same way and the reported melting point was 39°C.

4-Iodo-3-methylbenzoic acid (VIII).—A solution of 45 g. (0.17 mol.) of iodoketone VII in 170 ml. of dioxane was dropped slowly into a sodium hypobromite solution, made from 56 g. (1.4 mol.) of sodium hydroxide, 82 g. (0.51 mol.) of bromine and 450 ml. of water, at the temperature below 10°C. After the excess of sodium hypobromite was decomposed with sodium bisulfite and bromoform was removed by steam distillation, the solution was acidified to give a crystalline substance, which was recrystallized from ethanol-water. Colorless needles, m. p. 198~199°C. Yield, 39 g. (88% of the theoretical). According to

8) Private communication from Dr. M. Ōki, the University of Tokyo.

9) T. Sato and M. Fujii, unpublished work.

10) All melting and boiling points are uncorrected. The microanalyses were carried out by Mr. Mizushima to whom the author's thanks are due.

Klingel[6] the same acid, m. p. 203~204°C, was obtained by chromic acid oxidation of the iodoketone VII.

Anal. Found: C, 36.72; H, 2.72. Calcd. for $C_8H_7O_2I$: C, 36.66; H, 2.69%.

Ethyl 4-iodo-3-methylbenzoate (IX).—The iodobenzoate was obtained as a colorless oil boiling at 145~147°C/8 mm. by usual esterification of the acid VIII.

Anal. Found: C, 41.21; H, 3.79. Calcd. for $C_{10}H_{11}O_2I$: C, 41.41; H, 3.82%.

4-Methoxy-2'-methylbiphenyl-4'-carboxylic acid (III).—As a general procedure of the Ullmann reaction, the preparation of 4-methoxy-2'-methylbiphenyl-4'-carboxylic acid (III) is described. To a well-stirred mixture of 3 g. (0.010 mol.) of ethyl 3-methyl-4-iodobenzoate (IX) and 10 g. (0.043 mol.) of 4-iodoanisole (X, R=H), 10 g. (0.16 atom) of copper bronze, activated by Kleiderer and Adams' method[11], was added in 20 min. at 220~230°C. The reaction mixture was then heated to 270~280°C for 25 min. and extracted with acetone after cooling. The extract was hydrolyzed by refluxing with a mixture consisting of 50 ml. of 10% sodium hydroxide solution and 100 ml. of ethanol for about two hours. The solvent was evaporated and the residue was diluted with water. Insoluble dimethoxybiphenyl was removed by filtration. On acidification, the filtrate afforded an acid mixture, which was purified by chromatography on alumina. Repeated recrystallizations from ethanol gave 500 mg. of colorless needles, m. p. 183~184°C.

Anal. Found: C, 73.92; H, 5.59. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83%.

2, 2'-Dimethyl-4-methoxybiphenyl-4'-carboxylic acid (IV).—The dimethylbiphenyl was prepared from compound IX and 4-iodo-3-methylanisole (X, R=CH_3)[4]. It was necessary to remove unchanged starting materials in vacuo before hydrolysis for the easier purification of the product. The acid was obtained as colorless prisms on recrystallization from ethanol-water, m. p. 142~144°C.

Anal. Found: C, 74.99; H, 6.39. Calcd. for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29%.

2-Ethyl-4-methoxy-2'-methylbiphenyl-4'-carboxylic acid (V).—It was prepared from IX and 3-ethyl-4-iodoanisole (X, R=C_2H_5)[3]. Removal of the unchanged materials in vacuo was required and the distillate up to 180°C/5 mm. was discarded. Colorless needles, m. p. 139~140°C were obtained on recrystallization from benzene-petroleum ether.

Anal. Found: C, 75.55; H, 6.75. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%.

2-Isopropyl-5-methyl-4-iodoanisole (XI). — To a solution of 80 g. (0.49 mol.) of carvacrol methyl ether in 100 ml. of ethanol were alternatively added 130 g. (0.51 mol.) of iodine and 130 g. (0.60 mol.) of yellow mercuric oxide in small portions in the course of 30 min., while the mixture was well stirred and cooled in ice-water below 20°C. Stirring was continued for an additional 30 min. The mixture was heated on a water bath for 10 min. and filtered with suction. After the filtrate was diluted with water, the heavy oil was extracted with ether. The ethereal solution was washed with aqueous potassium iodide and dried over calcium chloride. The product boiling at 130~150°C/6~7 mm. was collected and then refractionated. The pure compound was obtained as brown oil, b. p. 135~137°C/6 mm.

Anal. Found: C, 46.16; H, 5.21. Calcd. for $C_{11}H_{15}OI$: C, 45.53; H, 5.21%.

2-Isopropyl-4-methoxy-5-methylbiphenyl-4'-carboxylic acid (XIII). — It was prepared from the compound XI and ethyl 4-iodobenzoate (XII). After hydrolysis the acidic portion was extracted with ethanol and the extract was recrystallized from ethanol to give colorless plates, m. p. 227.5~229°C.

Anal. Found: C, 76.06; H, 6.98. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09%.

Ultraviolet absorption spectra. — They were measured with a Hitachi photoelectric spectrophotometer Model EPU-2, the compounds being in dissolved 95% ethanol.

The author wishes to express his hearty thanks to Professor Y. Urushibara, the University of Tokyo, Professor K. Hata, Tokyo Metropolitan University, and Dr. M. Ōki for their kind guidance and encouragement throughout this study and to the members of the Research Department, Teikoku Hormone Manufacturing Co., Ltd., Kawasaki, for bioassays. The author is also indebted to the Ministry of Education for the Grant in Aid for Fundamental Scientific Research.

Department of Chemistry
Faculty of Science
Tokyo Metropolitan University
Setagaya-ku, Tokyo

11) E. C. Kleiderer and R. Adams, *J. Am. Chem. Soc.*, **55**, 4219 (1933).