Estrogenic Biphenyls. VI[1]. *2- and 6'-Alkyl Derivatives of 3'-Ethyl-4-methoxy-biphenyl-4'-carboxylic Acid*

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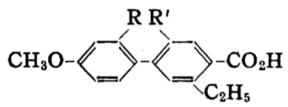
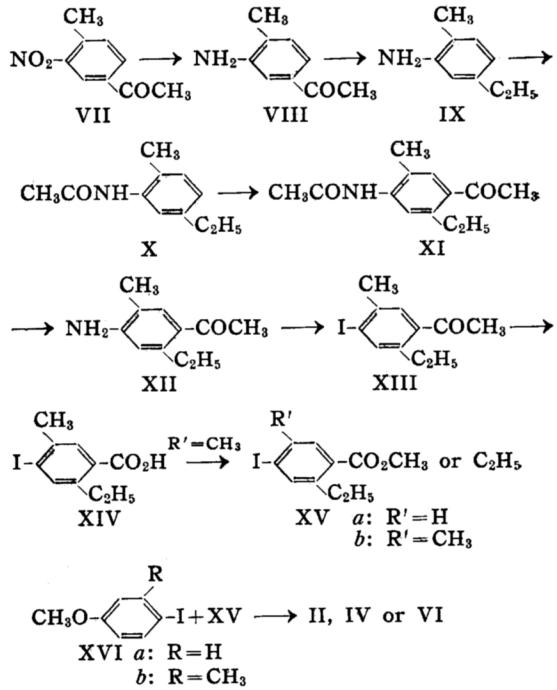
It was reported[2] that 3'-ethyl-4-methoxybiphenyl-4'-carboxylic acid (I) was fully estrogenic at the dose of 250 γ when injected subcutaneously to ovariectomized mice. Introduction of an additional ethyl group into position 2 or 6' of compound I increased the activity to a minimum active dose of 100 γ, thus 2,3'-diethyl-4-methoxybiphenyl-4'-carboxylic acid (III)[3] and 2',5'- (for 3',6')-diethyl-4-methoxybiphenyl-4'-carboxylic acid (V)[4] being the most active members of this series hitherto known. Enhancement of the estrogenic activity in compounds III and V in comparison with compound I was taken as an indication of a favorable molecular conformation in III and V as had already been observed in dialkylstilbestrol dimethyl ethers and related compounds[5]. The ethyl group introduced into position 2 or 6' was found to force the two benzene rings to a non-planar arrangement from the ultraviolet absorption spectra.



	R	R'		R	R'
I	H	H	IV	H	CH_3
II	CH_3	H	V	H	C_2H_5
III	C_2H_5	H	VI	CH_3	CH_3

The present communication deals with further studies on the effect of the 2- and 6'-alkyl substituents on the conformation and on the estrogenic activity of compound I and with the discussion on the relation between the physiological activity and the molecular structure in this series. 3'-Ethyl-4-methoxy-2-methylbiphenyl-4'-carboxylic acid (II) was prepared from 4-iodo-3-methylanisole (XVIb)[6] and ethyl 2-ethyl-4-iodobenzoate (XVa)[3] through the Ullmann reaction. The 6'-methyl isomer, namely, 5'-ethyl-4-methoxy-2'-methylbiphenyl-4'-carboxylic acid (IV), and the 2,6'-dimethyl derivative, namely, 5'-ethyl-4-methoxy-2,2'-dimethylbiphenyl-4'-carboxylic acid (VI), were prepared from methyl 2-ethyl-4-iodo-5-methylbenzoate (XVb) and the corresponding iodoanisoles (XVIa or b). The preparation of the ester XVb is shown in the accompanying diagram.



Modified Wolff-Kishner reduction[7] of 3-amino-4-methylacetophenone (VIII)[8] afforded 5-ethyl-2-methylaniline (IX) in an excellent yield which was acetylated in the usual manner to give 5-ethyl-2-methylacetanilide (X). The acetanilide was treated with acetyl chloride and aluminum chloride in carbon disulfide and resulting 4-acetamido-2-ethyl-5-methylacetophenone (XI) was refluxed with dilute hydrochloric acid to give 4-amino-2-ethyl-

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1) Part V: T. Sato, This Bulletin, **32**, 1130 (1959).
2) T. Sato and M. Ōki, ibid., **30**, 958 (1957).
3) M. Ōki and T. Sato, ibid., **30**, 508 (1957).
4) M. Ōki and T. Sato, ibid., **30**, 702 (1957).
5) M. Ōki and Y. Urushibara, ibid., **25**, 109 (1952).
6) T. Sato and M. Ōki, ibid., **30**, 859 (1957).
7) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946); **70**, 2802 (1948); **71**, 3301 (1949).
8) I. J. Rinkes, *Rec. trav. chim.*, **64**, 205 (1945).

5-methylacetophenone (XII). Diazotization of the aminoketone XII followed by treatment of the diazonium salt with potassium iodide yielded 2-ethyl-4-iodo-5-methylacetophenone (XIII), which was oxidized with sodium hypobromite to 2-ethyl-4-iodo-5-methylbenzoic acid (XIV). Esterification of compound XIV gave the desired ester XVb.

The ultraviolet absorption data of compounds II, IV and VI are recorded in Table I together with those of compounds I[6], III[4] and V[4]. Compounds II and IV showed the K-band at 272 and 270 mμ, respectively, approximately in the regular intensities characteristic of this system. Hypsochromic shift of some 15 mμ caused by the introduction of the methyl substituent into an ortho position to the pivot bond is the result of an increase in the interplanar angle of the two benzene nuclei to relieve the steric hindrance. The shift is, however, smaller by 2 mμ than in the corresponding compounds with the ethyl group (III and V), and it agrees with the data of the present authors[6] and others[9]. It is noteworthy that the 6'-alkyl derivative of compound I gives an absorption maximum at a shorter wavelength than the 2-alkyl derivative whether the alkyl is methyl or ethyl. The result is in good agreement with the idea of hyperconjugation of the alkyl group with the carboxyl group through the benzene nucleus, with which the 2-alkyl derivative is favored[10]. In the 2,6'-dimethyl derivative (VI), no K-band maximum was found in the region examined but a shoulder at ca. 270 mμ was noticed. This is undoubtedly caused by further deterioration in conjugation of the biphenyl skeleton.

TABLE I. ULTRAVIOLET ABSORPTION MAXIMA[a] AND ESTROGENIC ACTIVITIES OF 2- AND 6'-ALKYL DERIVATIVES OF 3'-ETHYL-4-METHOXYBIPHENYL-4'-CARBOXYLIC ACID

Compound	λ, mμ	log ε	Active dose in mice, γ
I	286	4.36	250
II	272	4.13	100
III	270	4.09	100
IV	270	4.17	100[c]
V	268	4.14	100
VI	~270[b]	3.92	500

a) In 95% ethanol. b) ~: Indicates a shoulder. c) Active in 80% animals.

9) E. A. Braude, F. Sondheimer and W. F. Forbes, *Nature*, **173**, 117 (1954).
10) M. Ōki and H. Iwamura, unpublished work; also see Ref. 1.

The physiological data in Table I were obtained by the usual vaginal smear test with ovariectomized mice. The activities of the compounds with a methyl group were nearly the same as those with an ethyl group at the same position. The estrogenic potency is surely raised by the introduction of an alkyl group into position 2 or 6', but again no difference due to the change in the alkyl group was observed. Although the minimum active dose of compound VI to produce estrus in 100% animals was found to be 500 γ, it is not certain whether the excessive thickness of the molecule as indicated by the greater deterioration in conjugation really weakened the estrogenic activity of this compound, because it was active in 80% animals at 100 γ.

Experimental[11]

5-Ethyl-2-methylacetanilide (X).—A mixture of 149 g. (1 mol.) of 3-amino-4-methylacetophenone (VIII), obtained from 3-nitro-4-methylacetophenone (VII) according to Rinkes[8], 69 g. (1.1 mol.) of 80% hydrazine hydrate, 280 g. of potassium hydroxide and 1 kg. of diethylene glycol, was heated under reflux for two hours. Then the low boiling fraction was distilled off until the pot temperature reached 180°C. After the remaining mixture was refluxed for further three hours, the whole was steam-distilled and the distillate was combined with the low boiling fraction collected previously. The combined distillate was extracted with ether and the extract was dried over potassium carbonate. 5-Ethyl-2-methylaniline (IX) was obtained as a colorless liquid boiling at 78~79°C/3 mm. in 90% yield. The acetanilide X was obtained by acetylation with acetic anhydride, m. p. 136~137°C. The reported melting point is 138°C[8].

4-Acetamido-2-ethyl-5-methylacetophenone (XI).—To a well stirred suspension of 165 g. (0.93 mol.) of compound X in 78 g. (1 mol.) of acetyl chloride and 750 ml. of carbon disulfide, was added 415 g. (3.1 mol.) of anhydrous aluminum chloride in small portions in the course of one hour, while the mixture was gently refluxed. It was refluxed for another hour and then allowed to stand for two hours. The upper layer was decanted off and the viscous oil was decomposed with ice water and hydrochloric acid. The crystals were collected and recrystallized from aqueous ethanol to give 170 g. (79% yield) of colorless needles, m. p. 139~140°C.

Anal. Found: N, 6.56. Calcd. for $C_{13}H_{17}NO_2$: N, 6.39%.

4-Amino-2-ethyl-5-methylacetophenone (XII).—The acetamido compound XI was hydrolyzed with 1:1 aqueous hydrochloric acid. Colorless needles, m. p. 105~106°C, were obtained on recrystallization from benzene-petroleum ether.

11) All melting and boiling points are uncorrected.

Anal. Found: N, 8.22. Calcd. for $C_{11}H_{15}NO$: N, 7.91%.

2-Ethyl-4-iodo-5-methylacetophenone (XIII).—To a diazonium salt solution obtained from 32 g. (0.18 mol.) of compound XII, 39 ml. of concentrated sulfuric acid, 54 ml. of water and 13 g. (0.19 mol.) of sodium nitrite in a minimum quantity of water, was added a solution of 31 g. (0.19 mol.) of potassium iodide in a small amount of water. Stirring was continued for 30 min. at a low temperature and then at 50~60°C for two hours. The mixture was extracted with ether and the extract was washed with aqueous sodium hydroxide, aqueous sodium thiosulfate and water. The iodoacetophenone was obtained in a 50% yield as a brown oil boiling at 127~128°C/2.5 mm. On standing it solidified and colorless needles melting at 51~52°C were obtained on recrystallization from petroleum ether.

Anal. Found: I, 43.88. Calcd. for $C_{11}H_{13}IO$: I, 44.08%.

2,4-Dinitrophenylhydrazone.—It was obtained as orange needles, m. p. 165~166°C, on recrystallization from ethyl acetate.

Anal. Found: N, 11.54. Calcd. for $C_{18}H_{19}IN_4O_4$: N, 11.62%.

2-Ethyl-4-iodo-5-methylbenzoic Acid (XIV).—To a well stirred sodium hypobromite solution prepared from 28 g. (0.18 mol.) of bromine, 20 g. (0.50 mol.) of sodium hydroxide and 120 ml. of water, was added a solution of 17 g. (0.057 mol.) of compound XIII in 60 ml. of dioxan in one hour. The temperature was kept below 10°C during the addition and then at 50~60°C for one hour. After excessive hypobromite was decomposed with sodium sulfite, the whole was steam-distilled. The remaining solution was acidified with hydrochloric acid and the product was recrystallized from aqueous ethanol. Colorless needles, m. p. 157~158°C, were obtained in 90% yield.

Anal. Found: I, 44.41. Calcd. for $C_{10}H_{11}IO_2$: I, 43.77%.

Methyl 2-Ethyl-4-iodo-5-methylbenzoate (XVb).—The acid XIV was esterified in the usual manner. The ester, b. p. 125°C/2.5 mm., was obtained in a 78% yield.

Anal. Found: I, 42.08. Calcd. for $C_{11}H_{13}IO_2$: I, 41.76%.

3'-Ethyl-4-methoxy-2-methylbiphenyl-4'-carboxylic Acid (II).—With vigorous stirring 15 g. (0.24 atom) of copper bronze activated by Kleiderer and Adams' method[12] was added in small portions to a mixture of 9 g. (0.036 mol.) of 4-iodo-2-methylanisole (XVIb) and 5 g. (0.016 mol.) of ethyl 2-ethyl-4-iodobenzoate[3] over a period of 30 min., while the temperature was maintained at 215~220°C. The mixture was then heated to 280~285°C and was stirred for 30 min. at that temperature. After cooling, the whole was extracted with boiling acetone and the extract was refluxed with 40 ml. of 10% aqueous sodium hydroxide and 70 ml. of ethanol for two hours. A part of ethanol was removed by distillation and the residue was diluted with water to make up 500 ml. and an insoluble oil was removed by extraction with ether. The aqueous layer was acidified with hydrochloric acid and the acid mixture thus collected was extracted with hot benzene. On concentration of the solution it afforded a crude product, which on repeated recrystallization from aqueous ethanol gave 500 mg. of colorless needles melting at 150.5~151°C.

Anal. Found: C, 75.32; H, 6.80. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%.

5'-Ethyl-4-methoxy-2'-methylbiphenyl-4'-carboxylic Acid (IV).—The Ullmann reaction was carried out in the same way as described above with 15 g. (0.064 mol.) of 4-iodoanisole (XVIa), 9 g. (0.030 mol.) of methyl 2-ethyl-4-iodo-5-methylbenzoate (XVb) and 20 g. (0.32 atom) of activated copper bronze. The temperature for the addition of copper bronze was 230~240°C and then raised to 280~290°C. The acidic portion was digested with ether and the ethereal solution was passed through an alumina column. The elute was evaporated and repeated recrystallization of the residue from ethanol gave colorless needles melting at 188~189°C. It weighed 900 mg.

Anal. Found: C, 75.35; H, 6.51. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%.

5'-Ethyl-4-methoxy-2,2'-dimethylbiphenyl-4'-carboxylic Acid (VI).—The reaction was carried out in the same way as described for the preparation of II, with 18 g. (0.073 mol.) of compound XVIb, 10 g. (0.033 mol.) of compound XVb and 30 g. (0.47 atom) of activated copper bronze. The reaction temperatures were the same as in the preparation of IV. The acetone extract was distilled under reduced pressure to remove any unchanged materials, and the distillate up to 190°C/5 mm. was discarded. Colorless plates, melting at 127~128°C after recrystallization from ethanol-water, were obtained by handling the residue of vacuum distillation as described before. It weighed 600 mg.

Anal. Found: C, 76.27; H, 7.39. Calcd. for $C_{18}H_{20}O_3$; C, 76.03; H, 7.09%.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra were measured with a Hitachi photo-electric spectrophotometer Model EPU-2. The samples were dissolved in 95% ethanol.

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