Estrogenic Biphenyls. VIII. Preparation and Estrogenic Activity of 4'-(1-Hydroxyalkyl)-4-methoxybiphenyls

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According to the hypothesis presented by Ōki and Urushibara[1)] to account for the estrogenic activity of non-steroidal compounds of the stilbene-bibenzyl type, the activity is closely associated with the molecular structure in that the development of strong action requires not only the presence of two active hydrogens or any groups capable of producing such in vivo at the optimum distance from each other, but also optimum thickness and width of the molecule. Therefore, the problems in studying the relation between the physiological action and the molecular structure in a homologous or an analogous series of compounds will be 1) the distance between the active hydrogen atoms in question, 2) the molecular thickness and width, and 3) the nature of the active hydrogens or the groups carrying them.

As for the biphenyl series Dodds and Lawson[2)] reported that 4, 4'-dihydroxybiphenyl (I) was almost inactive. As the recent X-ray crystallographical investigation[3)] of compound I revealed that the molecule of compound I has the unit cell constants of a = 10.54 Å, b = 5.36 Å and c = 7.59 Å, the distance between the two phenolic groups is apparently less than that between the two hydroxyl groups of steroidal hormones or stilbestrol in which the distance between the two oxygens was reported to be 15.5 Å[1b)]. Furthermore, the molecule of compound I is planar or nearly planar[4)] owing to the full conjugation of the biphenyl system and this is also considered to be unfavorable for the development of strong estrogenic activity. In this respect, 4-hydroxybiphenyl-4'-carboxylic acid (IIa) and its derivatives with two active hydrogens at a longer distance were prepared and found to be estrogenic[5)]. While this manuscript was in preparation, however, Y. Osawa[6)] observed that compound I, its dimethyl ether and derivatives were considerably active, compound I being active at 500 γ in 100% animals (ovariectomized mice), whereas compound IIa was active in 60% animals at the same level[7)]. Though the present author can give no comment on this contradiction in the activity of compound I, there might be another optimum distance of two active hydrogens.

The activity of 4-methoxybiphenyl-4'-carboxylic acid (IIb) was enhanced markedly by alkyl substitution, namely, by increasing the molecular thickness and width, and its dialkyl derivatives, in which positions 3' and either 2 or 6' were substituted, produced full estrus in 100% of the mice at a dose of 100 γ in spite of the methylation of the phenolic hydroxyl group[5)].

In connection with the third problem, 4'-hydroxymethyl-4-methoxybiphenyl (IIIa) has been prepared to obtain a confirmation for the postulation that a compound with a group other than carboxyl but carrying an active hydrogen will be similarly estrogenic, provided that it has two active groups at a similar distance.

A number of analogues of bisdehydrodoisynolic acid methyl ether (IVa), to which the compounds of the present series are structurally related, including the compounds with hydroxymethyl (IVb) and formyl (IVc) groups instead of the carboxyl, have been prepared[8a)] and found considerably active though slightly weaker than the carboxylic compound (IVa). The assumption that they are oxidized in vivo to IVa is quite probable and may serve as an explanation for the somewhat

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[1)] (a) M. Ōki and Y. Urushibara, This Bulletin, **25**, 109 (1952). (b) J. Grundy, *Chem. Revs.*, **57**, 281 (1957).

[2)] E. C. Dodds and W. Lawson, *Proc. Roy. Soc.*, *(London)*, **B125**, 222 (1938).

[3)] S. C. Wallwork and H. M. Powell, *Nature*, **167**, 1072 (1951).

[4)] Although electron diffraction data indicate the two benzene rings in biphenyl make an angle of about 45° in gas, X-ray diffraction analyses show that biphenyl is a planar molecule when it is solid[13)].

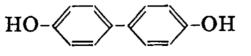
[5)] See T. Sato and M. Ōki, This Bulletin, **32**, 1289 (1959); also earlier papers of this series.

[6)] Y. Osawa, Doctorate Thesis, the University of Tokyo (1959).

[7)] M. Ōki and T. Sato, This Bulletin, **30**, 508 (1957).

[8)] (a) J. Heer and Miesher, *Helv. Chim. Acta*, **30**, 777 (1947). (b) G. Anner and K. Miesher, ibid., **29**, 1071 (1946).

weaker activity. As methyl ketone IVd was found to be very weakly estrogenic[8b], it would be worthwhile to examine a compound with a secondary hydroxyl group which on oxidation would yield a ketone. Such compounds of the present series, namely, IIIb and IIIc have been synthesized. It appears of interest to note a similarity in the bond arrangement of compound IIIc, which is represented as V, with estradiol (VI). Rubin and Wishinsky[9] have already prepared compound VII as a bicyclic analogue of estradiol but not mentioned the activity.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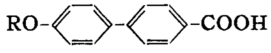
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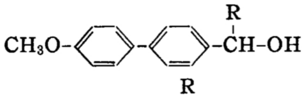
b CH_3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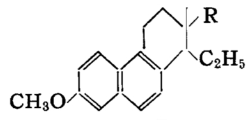
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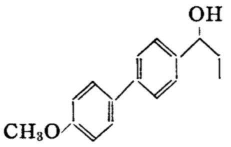
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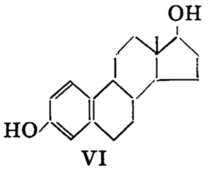
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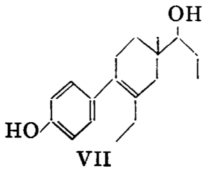
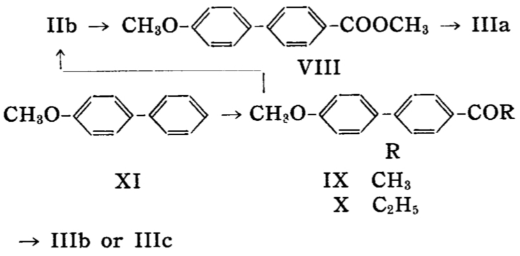

VII

Compound IIIa was obtained through reduction of methyl 4-methoxybiphenyl-4′-carboxylate (VIII)[10,11], prepared from compound IIb, with lithium aluminum hydride in ether. The alkyl homologues IIIb and IIIc were prepared by sodium borohydride reduction of 4′-acetyl-4-methoxybiphenyl (IX) and 4-methoxy-4′-propionylbiphenyl (X), respectively. The methoxyketone IX was prepared from 4-methoxybiphenyl (XI) by Friedel-Crafts reaction according to the literature[10,12]. Similar treatment of compound XI with propionyl chloride and aluminum chloride in carbon disulfide gave the ethyl ketone X, the structure being confirmed by oxidation to the corresponding carboxylic acid IIb likewise the methyl ketone IX[10].



Ultraviolet absorption spectra of these alcohols are recorded in Table I with the data of compounds IIb and XI. Compound IIIa showed a strong absorption at 264 mμ whereas the homologues IIIb and IIIc absorbed at 263 mμ. The curves are very similar and the intensities are nearly the same. As the hydroxymethyl group is only very weakly bathochromic[13], the absorption curves resemble that of 4-methoxybiphenyl (XI) and differ markedly from that of IIb, where additional conjugation with the carboxyl group is possible. These data are also taken as a confirmation of the structures.

TABLE I. ABSORPTION MAXIMA AND ESTROGENIC ACTIVITY

Compound	m. p. °C	λ_{max} mμ	log ε	Dose in γ (% of response in mice)
IIb	248~249	289	4.36	1000(50)
IIIa	158~159	264	4.32	1000(60)
b	122~123	263	4.34	200(80)
c	91~ 92	263	4.34	200(80)
XI	89	260	4.31	……

Compound IIIa was found to be estrogenic to 20% of mice at the dose of 500 γ and to 60% at 1 mg., being nearly equally active as compounds IIa[7] and IIb[14]. In compounds IIIb and IIIc, an increase in activity was encountered and they were active to 80% of animals at 200 γ level. It is noteworthy that the compounds which are secondary alcohols and racemic

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[9] M. Rubin and H. Wishinsky, *J. Am. Chem. Soc.*, **68**, 338 (1946).

[10] L. F. Fieser and C. K. Bradsher, ibid., **58**, 1738 (1936).

[11] L. C. Anderson and W. A. Fisher, ibid., **66**, 594 (1944).

[12] W. S. Johnson, C. D. Gutsche and R. O. Offenhauser, ibid., **68**, 1648 (1956).

[13] G. H. Beaven, D. M. Hall, M. S. Lesslie and E. E. Turner, *J. Chem. Soc.*, **1952**, 854; G. H. Beaven, D. M. Hall, M. S. Lesslie, E. E. Turner and G. R. Bird, ibid., **1954**, 131.

[14] T. Sato and M. Ōki, This Bulletin, **30**, 859 (1957).

are more active than the hydroxymethyl compound.

Experimental[15]

Methyl 4-Methoxybiphenyl-4′-carboxylate (VIII).—The methyl ester was obtained as colorless plates, m. p. 172~173°C, on esterification of 4-methoxybiphenyl-4′-carboxylic acid (IIb) in the usual way. Reported[10,11] melting point is 172~173°C.

4′-Hydroxymethyl-4-methoxybiphenyl (IIIa).—To an ethereal slurry made from 100 mg. (0.0026 mol.) of lithium aluminum hydride and 20 ml. of ether, a solution of 240 mg. (0.001 mol.) of compound VIII in 100 ml. of ether was added over a period of 10 min. with efficient stirring. The reaction mixture was gently refluxed on a bath for one hour and then allowed to stand. After the excessive reagent was decomposed with water, 50 ml. of 10% sulfuric acid was added and the aqueous layer was extracted with ether. The ethereal solution was successively washed with water, aqueous sodium hydroxide and water. On evaporation of the solution and recrystallization of the residue from benzene yielded 100 mg. of colorless plates, m. p. 158~159°C.

Anal. Found: C, 78.80; H, 7.06. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59%.

Phenylurethan.—It was prepared in the usual way as colorless plates melting at 140~141°C on recrystallization from carbon tetrachloride.

Anal. Found: N, 4.42. Calcd. for $C_{21}H_{19}O_3N$: N, 4.20%.

4′-Acetyl-4-methoxybiphenyl (IX). — 4-Methoxybiphenyl (XI), prepared[16] by decomposition of *N*-nitrosoacetanisidide in benzene, was acetylated with acetyl chloride and aluminum chloride in carbon disulfide. Recrystallization from isopropyl alcohol gave compound IX, m. p. 152~153°C. Reported melting point is 153~154°C[10,12].

4-Methoxy-4′-propionylbiphenyl (X).—To a mixture of 15g. (0.082 mol.) of compound XI, 13g. (0.098 mol.) of anhydrous aluminum chloride and 100 ml. of carbon disulfide, 8.0 g. (0.086 mol.) of propionyl chloride was added in the course of twenty minutes, while the reaction mixture was gently refluxed. After stirring and refluxing for additional thirty minutes, the mixture was decomposed with ice water containing hydrochloric acid. The product was washed repeatedly with cold ether and recrystallized from ethanol, colorless plates, m. p. 146~147°C. Yield, 11 g. (56% of the theoretical).

Anal. Found: C, 79.86; H, 6.84. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

On oxidation with potassium permanganate and sodium hydroxide, compound X yielded a carboxylic acid, which did not depress the melting point of an authentic specimen of 4-methoxybiphenyl-4′-carboxylic acid (248~249°C).

2, 4-Dinitrophenylhydrazone.—It was prepared in the usual way and recrystallized from ethyl acetate, deep red plates, m. p. 201~202°C.

Anal. Found: N, 13.42. Calcd. for $C_{22}H_{20}O_5N_4$: N, 13.33%.

4′-(1-Hydroxyethyl)-4-methoxybiphenyl (IIIb).—To a suspension of 3 g. (0.016 mol.) of compound IX in 200 ml. of methanol, 0.5 g. (0.013 mol.) of sodium borohydride and 50 ml. of methanol was added in the course of 10 min. After the addition was complete, the mixture was warmed to 60°C and stirred for two hours. Aqueous sodium hydroxide was added and a part of methanol was removed on a steam bath. The residue was diluted with water and the solid was collected. Recrystallization from aqueous ethanol gave 2.5 g. (68% of the theoretical) of colorless plates, melting at 122~123°C.

Anal. Found: C, 78.62; H, 6.97. Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06%.

Phenylurethan. — Colorless plates, melting at 162~163°C, on recrystallization from carbon tetrachloride.

Anal. Found: N, 3.82. Calcd. for $C_{22}H_{21}O_3N$: N, 4.03%.

4′-(1-Hydroxypropyl)-4-methoxybiphenyl (IIIc).—In the same way as described above, 10 g. (0.042 mol.) of compound X in 400 ml. of methanol was reduced with 1.5 g. (0.040 mol.) of sodium borohydride in 100 ml. of methanol to yield 7.5 g. (74% of the theoretical) of colorless plates, melting at 91~92°C on recrystallization from aqueous ethanol.

Anal. Found: C, 79.28; H, 7.37. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49%.

Phenylurethan.—It was prepared in the usual way and recrystallized from carbon tetrachloride, colorless plates, m. p. 165~166°C.

Anal. Found: N, 3.96. Calcd. for $C_{23}H_{23}O_3N$: N, 3.88%.

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

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[15] All melting points are uncorrected. The author wishes to thank Mr. T. Mizushima of this laboratory for microanalyses.

[16] J. W. Haworth and D. H. Hey, *J. Chem. Soc.*, **1940**. 361.