

*Estrogenic Biphenyls. IX¹⁾. Optical Resolution
and Estrogenic Activity of
4'-(1-Hydroxypropyl)-4-methoxybiphenyl*

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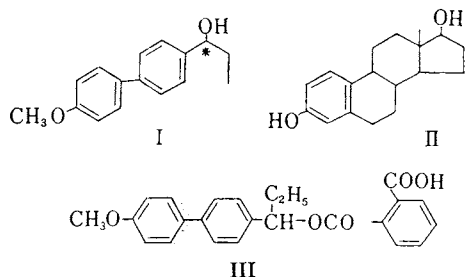
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As reported in the preceding paper of this series¹⁾, (4'-1-hydroxypropyl)-4-methoxybiphenyl (I) was moderately estrogenic when injected subcutaneously to ovariectomized mice. Since the location of the hydroxyl group attached to the asymmetric carbon atom in compound I corresponds to that of C₁₇-OH of estradiol (II) when the former is regarded as an aromatized BD-ring-lacking model of the latter, it has become of particular interest to examine the estrogenic activity of optically active form of compound I in comparison with the activities of epimeric estradiols, of which 17- β isomer represents more active form, being about 40 times more active than 17- α isomer.

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1) Part VIII: T. Sato, This Bulletin, 33, 5 (1960).

(\pm)-4'-(1-Hydroxypropyl)-4-methoxybiphenyl (I)¹⁾ was treated with phthalic anhydride in pyridine to produce (\pm)-4'-(1-hydroxypropyl)-4-methoxybiphenyl hydrogen phthalate (III), m. p. 164~165°C (Found: C, 76.64; H, 5.50. Calcd. for $C_{24}H_{21}O_5$: C, 76.58; H, 5.44%). It was converted into strychnine salt, which afforded a well crystallized optically active salt, m. p. 187~188.5°C (Found: N, 3.86. Calcd. for $C_{45}H_{44}N_2O_7$: N, 3.86%) with $[\alpha]_D^{19}$ -69.0° ($C=2$, 95% ethanol) through several recrystallization from ethanol. Combined mother liquors contained an oil which resisted attempts to induce crystallization.



The crystalline strychnine salt was treated with dilute hydrochloric acid to produce (+)-III, m. p. 149~153°C (Found: C, 76.10; H, 5.45. Calcd. for $C_{24}H_{21}O_5$: C, 76.58; H, 5.44%) having $[\alpha]_D^{17}$ +24.9° ($C=2$, 95% ethanol). Levorotatory alcohol (-)-I, m. p. 99~101.5°C (Found: C, 79.42; H, 7.65. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49%) with $[\alpha]_D^{14}$ -23.7° ($C=2$, 95% ethanol) was thus produced by the alkaline hydrolysis of (+)-III.

An attempt to obtain another alcohol with the opposite sign of rotation through cinchonine salt of the hydrogen phthalate III, m. p. 153~155.5°C, obtained by the hydrolysis of the oily strychnine salt mentioned above, failed owing to the unfavorable crystallizability of the salt.

Compound (-)-I, which was found to be active only in 20% of the test animals (ovariectomized mice) at the doses of 200 γ , had weaker estrogenic activity than (\pm)-I as the latter was active in 80% of the animals at the same level¹⁾. Although the reason why dextro- and levorotatory 3,4-bis-(*p*-hydroxyphenyl)-hexanes show different estrogenic potencies²⁾ is still obscure, the present finding which suggests that the levorotatory isomer is the poorer estrogen may be attributed to the absolute configuration about the carbon atom which carries the hydroxyl group.

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2) F. v. Wessely and H. Welleba, *Ber.*, **74**, 777 (1941).