Communications to the Editor

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EFFECT OF 3,3'-DIHYDROXY-α,β-DIETHYLDIPHENYLETHANE ON CORONARY AND MESENTERIC ARTERIES ISOLATED FROM GUINEA-PIGS

Yoshihiko Inamori,*,[a] Hiroshi Tsujibo,[a] Hiroko Hachiken,[b] Yasuyoshi Miki[b] and Shoji Takemura[b]
Osaka University of Pharmaceutical Sciences,[a] Kawai, Matsubara-shi, Osaka 580, Japan and Faculty of Pharmaceutical Sciences, Kinki University,[b] Kowakae, Higashiosaka-shi, Osaka 577, Japan

3,3'-Dihydroxy-α,β-diethyldiphenylethane (I), the isomer of hexestrol (II), showed strong coronary vasodilator effect (ED_{50}: 1.0 μg/heart) on the isolated guinea-pig heart. The action of I was stronger than those of II (ED_{50}: 9.0 μg/heart) and 3,3'-dihydroxy-α,β-diethylstilbene (ED_{50}: 4.3 μg/heart), the starting material of I. Compound I also had a cardiotonic effect and a relaxing action on the contraction of guinea-pig mesenteric artery due to KCl and norepinephrine at a low concentration of 10^{-6}- 10^{-5}M. It should be emphasized that compound I, in addition to the lack of hormonal side effect, had a stronger effect on guinea-pig coronary and mesenteric artery.

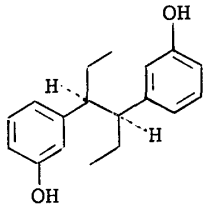
KEYWORDS ———— 3,3'-dihydroxy-α,β-diethyldiphenylethane; 3,3'-dihydroxy-α,β-diethylstilbene; hexestrol; diethylstilbestrol; oxystilbene-related compound; coronary vasodilator action; mesenteric artery; relaxing action; hormonal side effect

It has been reported that oxystilbene-related compounds such as 3,3',4,5'-tetrahydroxystilbene,[1,2] 3,4-*O*-isopropylidene-3,3',4,5'-tetrahydroxystilbene,[3,4] diethylstilbestrol (IV, Chart 1)[5,6,8] 3,3'-dihydroxy-α,β-diethylstilbene (III, Chart 1)[7,8] and hexestrol (II, Chart 1)[6,9] had the following biological activities: coronary vasodilator action, antifungal activity, ichthyotoxicity, phytogrowth-inhibitory activity and hypotensive effect. Among the oxystilbene-related compounds tested, compound III has already reported to have no hormonal side effect.[10] In this respect, the above-mentioned activities of III and its derivatives are of considerable interest.

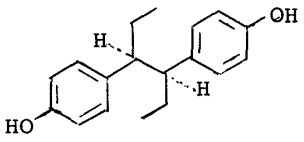
Therefore, we synthesized the derivatives of III to obtain more active substances. As a result, 3,3'-dihydroxy-α,β-diethyldiphenylethane (I, Chart 1), the dihydro-compound of III, was found to have a strong effect on guinea-pig coronary and mesenteric artery. Compound I which is the dihydro-compound of III, is considered to have no hormonal side effect.

Here, we report the coronary vasodilator action of I and its effect on the mesenteric artery isolated guinea-pig.

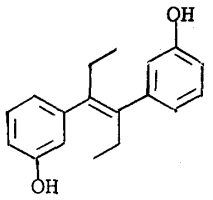
The effect of compound I on the isolated guinea-pig heart was examined by the Langendorff method. The results are summarized in Table I. Compound I had strong



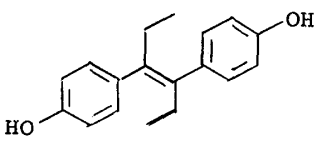
3,3'-dihydroxy-α,β-diethyldiphenylethane (I)



hexestrol (II)



3,3'-dihydroxy-α,β-diethylstilbene (III)



diethylstilbestrol (IV)

Chart 1

coronary vasodilator action. This action was weaker than IV[5,6] and stronger than II,[6] III[7] and the papaverine used as standards. Compound I, like III,[7] had a cardiotonic effect (Fig. 1). Although the positive inotropic effect of I was transient, its effect (170%) was stronger than that (150%) of papaverine (100% before treatment). The effect of I on isolated guinea-pig heart should be emphasized. From these results, it was found that compound I, in addition to the loss of hormonal side effect , showed strong vasodilator action on the isolated guinea-pig heart.

Table I. Cardiac Effect of 3,3'-Dihydroxy-α,β-diethyldiphenylethane (I) on the Isolated Guinea-Pig Heart

Compound	Coronary vasodilation (ED_{50}: μg/heart)	Cardiotonic effect
I	1.0	p.i.
II[6]	9.0	n.e.
III[7]	4.3	p.i.
IV[5,6]	0.26	n.e.
Papaverine	7.0	p.i.

Each value represents the mean of 3 guinea-pig hearts. Animals: Male hartley strain guinea-pig (body weight: 400-500 g). The guinea-pig heart were rapidly isolated and perfused with Krebs-Henseleit solution according to the Langendorff method. Drugs (0.1 ml in 10% DMSO) were administered directly into the perfusion solution through a connecting rubber tube. DMSO (10%) had no effect on coronary vasodilation. Transducer: Force Diplacement Transducer 45196 (SAN-EI Instrument Co., Ltd.) and MPU-0.5-0-3 (Nihon Kohden Kogyo Co., Ltd.).
The relative potency of the test compounds was determined as that perfusion pressure which induced vasodilation by 50% of the maximum response produced by papaverine at 33 μg/heart (ED_{50}).
n.e.: no effect, p.i.: positive inotropic effect.

In this respect, the coronary vasodilator action of I was noteworthy. The action of I was stronger than that of II, the basic skeleton of coralgil, a coronary vas-

odilator. Since 1970, the use of coralgil was discontinued because of the severe side effects of phospholipidosis on the liver[11] and lung[12] cells and the foam cell syndrome.[13] From these results, the coronary vasodilator action of I should be emphasized. The action of I may be intrinsic to oxystilbene-related compounds from the following two standpoints: 1) Compounds, II,[6] III,[7] IV,[5,6] 3,3',4,5'-tetrahydroxystilbene (ED_{50}: 13.0 μg/heart)[2] and 3,4-*O*-isopropylidene-3,3',4,5'-tetrahydroxystilbene (ED_{50}: 4.3 μg/heart)[3,4] had the coronary vasodilator action and 2) Rhapontigenin,[14] rhaponticin,[14] and piceid[14] had the same action.

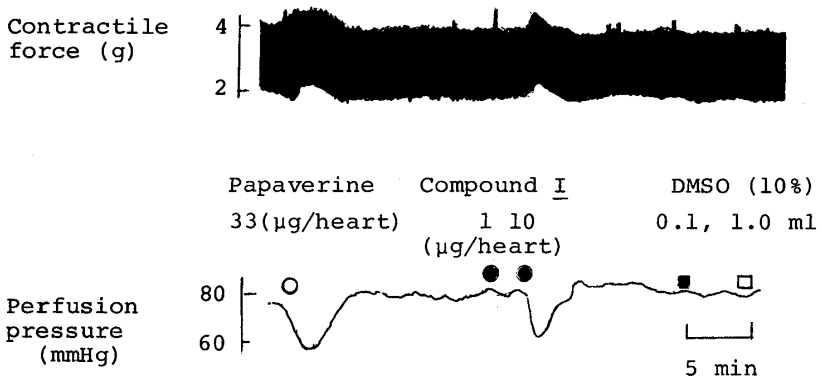


Fig. 1. Effect of 3,3'-Dihydroxy-α,β-diethyldiphenylethane (I) on Contractile Force and Perfusion Pressure in Isolated Guinea-pig Heart

Next, we examined the effect on the contraction of guinea-pig mesenteric artery induced by 60 mM^+ K and 10^{-5} M norepinephrine (NE). As shown in Fig. 2, compound I showed strong relaxing action on both contractile agents at a low concentration of 10^{-5}-10^{-6}M. Phloroglucinol,[15] curcumine[16] and magnolol[17] having a polyphenol structure in common with I, also relax the smooth of rats. The results indicate that the phenolic hydroxyl groups play an important role on the relaxing action of smooth muscle.

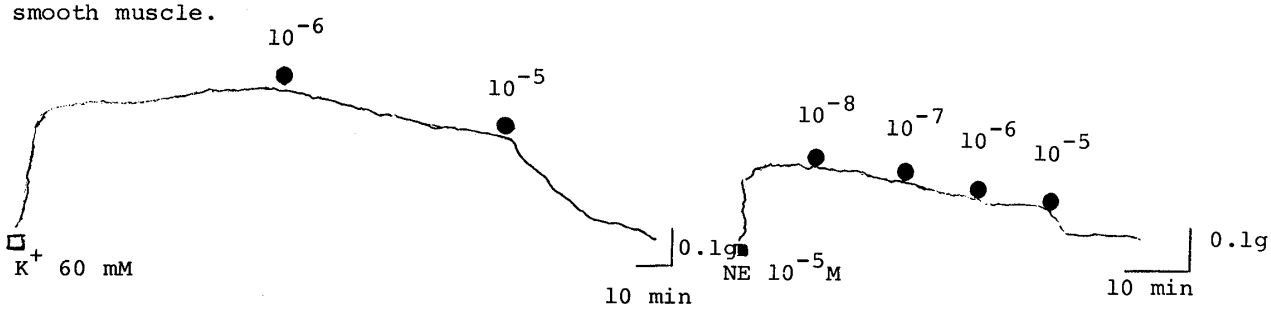


Fig .2. Effect of 3,3-Dihydroxy-α,β-diethyldiphenylethane (I) on Contraction of Guinea-pig Mesenteric Artery to 60 mM^+ and 10^{-5}M Norepinephrine (NE)

Further studies on the relaxing action of many oxystilbene-related compounds in the smooth muscle are in progress.

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