A SYNTHESIS OF DIHYDROISOOSTHOL. NOTE ON THE CONSTITUTION OF OSTHOL.

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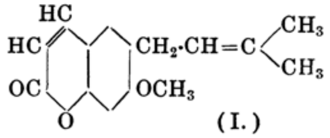
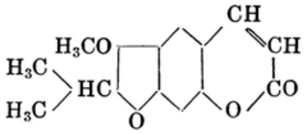
Received July 20th, 1933. Published September 28th, 1933.

A fish-poison, Osthol, was first isolated from the root of *Imperatoria Ostruthium* by Herzog and Krohn⁽¹⁾, who, however, did not determine its constitution. This (I) was suggested last year by Butenandt and Marten⁽²⁾, from its relation to peucedanin (II) and from the formation of acetone and ostholic acid (III) by its oxidation with chromic acid.


(I.)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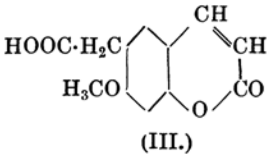
(III.)

The present work has been undertaken to synthesise dihydro-osthol in the following scheme:—

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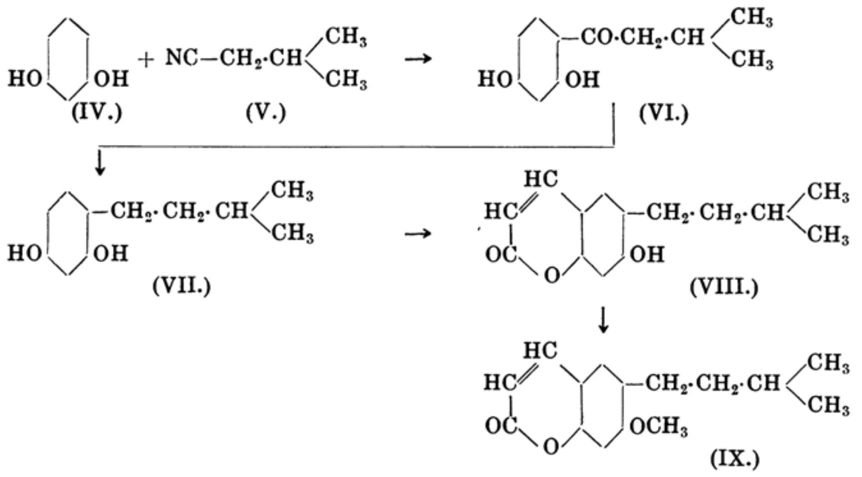
(1) *Arch. Pharm.*, **247** (1909), 553.

(2) *Ann.*, **495** (1932), 187.



In 1926, Dohme and his collaborators(3) synthesised the ketone (VI) by means of a condensation of isovaleric acid with resorcinol in the presence of zinc chloride. The present author attempted to synthesise it by condensing resorcinol with isovaleronitrile by the Hoesch reaction. However, when dry hydrogen chloride gas was passed into a mixture of isovaleronitrile and resorcinol in ethereal solution in the presence of zinc chloride, neither precipitate nor oily substance was separated. This phenomenon is very different from the ordinary Hoesch reaction. After hydrolysing the reaction product, many attempts were made to obtain the desired ketone in the crystalline state, but without success. In order to prove the presence of the ketone, the crude product was converted into its oxime, m.p. 203–205°C. As Dohme and his collaborators(3) had not synthesised this oxime, the present author synthesised ketone (VI) according to their method, and converted it into its oxime for comparison's sake. Both the oximes melted at the same temperature, and no depression of the melting point was caused on mixing them. The formation of 2: 4-dihydroxyphenyl isobutyl ketone having been thus confirmed, the crude ketone was next reduced to 2: 4-dihydroxyisovaleryl benzene (VII) by means of amalgamated zinc and hydrochloric acid, and the resulting compound was converted into 6-isoamyl-7-hydroxycoumarine (VIII) according to the Pechmann reaction. 6-Isoamyl-7-hydroxycoumarine was finally methylated with diazomethane or with methyl iodide and caustic alkali, when 6-isoamyl-7-methoxycoumarine, m.p. 61–62°C. was obtained. This melting point differs by about 20°C. from that of dihydro-osthol.

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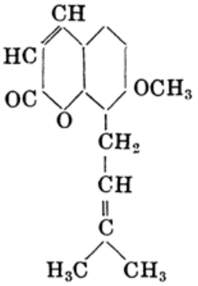
(3) *J. Amer. Chem. Soc.*, **48** (1926), 1690.

The constitution of dihydro-osthol appears therefore to be different from that of (IX) as suggested by Butenandt and his collaborator⁽⁴⁾. This fact receives strong support from the recent work of Späth and Peste⁽⁵⁾, who advanced the view that osthol has the structure (X) in contrary to formula (I), for they isolated 2: 6-dihydroxytoluene as its decomposition product.



(X.)

The present author proposes to designate the synthetical 6-isoamyl-7-methoxycoumarine as "dihydroisoosthol."

Experimental.

2:4-Dihydroxyphenyl Isobutyl Ketoxime, $C_4H_9C(=NOH)C_6H_3(OH)_2$. Isovaleronitrile (3.3 gr.) and resorcinol (3 gr.) were dissolved in 40 c.c. of absolute ether, and after adding two grams of freshly fused and powdered zinc chloride, a gentle stream of dry hydrogen chloride was passed into the mixture. The ethereal solution was first separated into two layers. The upper layer was colourless, whilst the lower one was reddish. After a short time, the former was redissolved in the latter, and the solution became viscous and reddish. After the solution has been saturated with hydrogen chloride, it was allowed to stand overnight, and the ether was then evaporated. The oily residue was warmed with 50 c.c. of water on a water-bath for half an hour, and, after cooling, the product was extracted several times with ether, and the ethereal solution was washed with water, dried, and evaporated. The oily substance (A) thus separated was dissolved in a concentrated solution of potassium hydroxide (10 gr.), mixed with a concentrated solution of hydroxylamine hydrochloride (6 gr.), and allowed to stand overnight. The mixture was acidified with dilute hydrochloric acid, when a precipitate (0.6 gr.) was deposited. It was recrystallised from dilute methyl

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(4) *Ann.*, **495** (1932), 187.

(5) *Ber.*, **66** (1933), 754.

alcohol with the addition of animal charcoal, from which it separated in the form of colourless plates, m.p. 203–205°C.

Anal.: Subst. = 5.694 mg. N_2 = 0.325 c.c. at 15°C. and 757.7 mm.
Found: N = 6.80%.
Calc. for $C_{11}H_{15}O_3N$: N = 6.73%.

It is soluble in acetone and in alcohol, but only slightly so in benzene, and insoluble in chloroform, carbon tetrachloride, water and ether. Its alcoholic solution gave a violet coloration with ferric chloride.

The ketone prepared by the method of Dohme and his collaborators was converted into the oxime under the same conditions as those in the above experiment, when the oxime melted at 203–205°C., and no depression of the melting point by admixture with the above-mentioned oxime resulted.

2 : 4-Dihydroxy-isoamylbenzene (VII). The crude oil (A) was reduced with zinc amalgam and hydrochloric acid by the same method as that used by Dohme and his collaborators(6). The purified substance melted at 61–62.5°C. Dohme and his collaborators(6) gave 61–62.5°C. as its melting point.

6-Isoamyl-7-hydroxycoumarine (VIII). Seven grams of 2 : 4-dihydroxy-isoamylbenzene were thoroughly mixed with 5.5 gr. of malic acid, and, to this mixture, 12 c.c. of concentrated sulphuric acid (D. 1.84) were added. The whole was warmed for a short time on a sand-bath, which had been previously heated. After the reaction mixture had been cooled, it was mixed with finely crushed ice and allowed to stand overnight, when it solidified to a greyish mass. It was separated by decantation, well washed with water, and recrystallised several times from dilute methyl alcohol with the addition of animal charcoal, from which it separated in the form of colourless needles, melting at 108–110°C. The yield was 5.1 gr. after one crystallisation.

Anal.: Subst. = 3.487; CO_2 = 9.223; H_2O = 2.11 mg.
Found: C = 72.24; H = 6.80%.
Calc. for $C_{14}H_{16}O_3$: C = 72.37; H = 6.94%.

6-Isoamyl-7-methoxycoumarine (Dihydroisoosthol) (IX).

(1) An ethereal solution of diazomethane prepared from 2 c.c. of nitrosomethylurethane was added to a methyl alcoholic solution of 0.2 gr. of 6-isoamyl-7-hydroxycoumarine and allowed to stand for a short time

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(6) *J. Amer. Chem. Soc.*, **48** (1926), 1691.

After the removal of the solvents from the reaction mixture, the resinous residue was digested with a dilute solution of caustic alkali, and allowed to stand for two or three hours, when the methylated product was separated as a precipitate, which was collected, washed with water, and recrystallised from dilute methyl alcohol with the addition of animal charcoal.

(2) 6-Isoamyl-7-hydroxycoumarine (0.2 gr.), methyl iodide (1 gr.), potassium hydroxide (0.05 gr.) and methyl alcohol (5 c.c.) were mixed and boiled for two hours under a reflux condenser. After the removal of the alcohol, the resinous reaction mixture was purified in the same way as (1).

The purified specimen in each experiment crystallised in the form of colourless plates, m.p. 61–62°C.

Anal.: Subst. = 3.260; CO_2 = 8.769; H_2O = 2.224 mg.
Found: C = 73.36; H = 7.63%.
Calc. for $C_{15}H_{18}O_3$: C = 73.12; H = 7.37%.

In conclusion, the present author wishes to express his hearty thanks to Professor Hiroshi Nomura for his kind guidance and encouragement during this investigation.

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