PHYTOESTROGENS

I. Syntheses Among Coumestan Derivatives: 8, 13-Diallylcoumestrol

A. A. Shamshurin, M. A. Yampol'skaya, and L. L. Simonova

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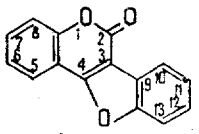
Recently, a group of phytoestrogens [1] of coumarin character, coumestrol (IX) [2], trifoliol [3], and medicagol [4], has been isolated from leguminous fodder plants (various types of clover and lucerne).

The common structural feature of these phytoestrogens is the "coumestan" skeleton (I) from which it is proposed to derive their nomenclature [5].

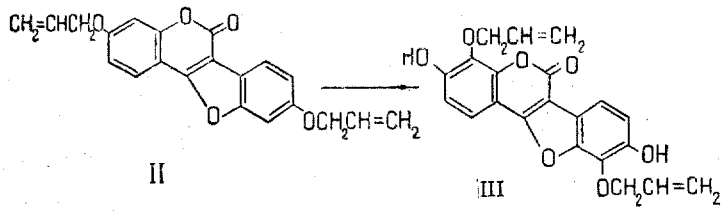


I

Then, for example, coumestrol (IX) will have the simple designation 7, 12-dihydroxycoumestan. Coumestrol possesses anabolic activity and has been patented as a growth stimulator for farm animals and poultry [6].

It is known that substances of the stilbestrol group are widely used as growth stimulators in animal husbandry abroad [1]. According to Kaiser [7], 3, 3'-alkenyl derivatives of stilbestrol, 3, 3'-diallylstilbestrol and 3, 3'-diallylhexestrol, stimulate the growth of animals still more. The estrogenic activity of these substances is many times less than that of stilbestrol. However, they possess a higher anabolic effect.

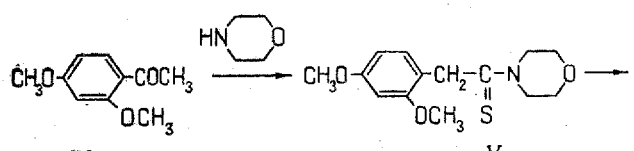
We decided to modify coumestrol by introducing C-allyl residues into its molecule and have obtained 8, 13-diallylcoumestrol (III). This was achieved by the allylation of coumestrol to 7, 12-diallyloxycoumestrol (II) and the Claisen rearrangement of the latter into (III). The fact that the rearrangement of the allyl group takes place into positions 8 and 13 and not 6 and 11 follows, for example, from the analogous rearrangement of the allyl ether of 4-methyl-7-hydroxycoumarin, which has a similar coumarinoresorcinol structure. In this case, 4-methyl-7-hydroxy-7-allylcoumarin is formed almost exclusively and not the 6-allyl derivative [8]:



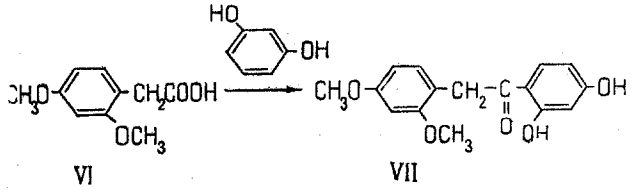
II III

Of the two variants of the synthesis of coumestrol described [9, 10], we adhered to Emerson and Bickoff's route and took up the problem of simplifying and shortening it by using a new variant of the production of the intermediates. In the Emerson-Bickoff synthesis these intermediates include ω-(2, 4-dimethoxyphenyl)-resacetophenone (VII), which they obtained from 2, 4-dimethoxyphenylacetonitrile. The synthesis of this ketone by the Emerson-Bickoff method is based on the use of the difficultly accessible 2, 4-dimethoxybenzaldehyde and takes place in five stages of which the last (the Hoesch reaction) takes place with a low yield.

In view of this complexity, we did not consider other methods [7, 12] for the synthesis of 2, 4-dimethoxyphenylacetonitrile, the precursor of the ketone (VII), and synthesized coumestrol from the readily accessible dimethyl derivative of resacetophenone (IV) as follows:

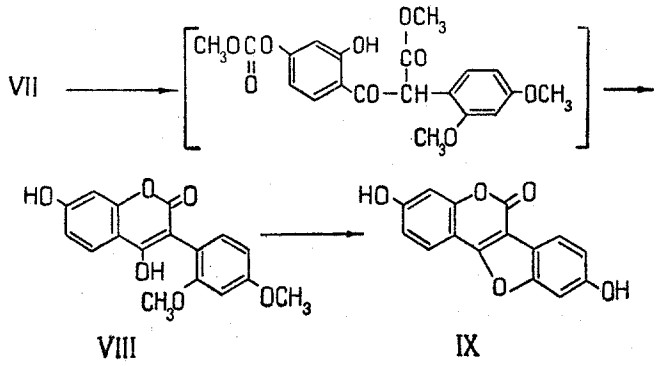


IV V



VI VII

By Willgerodt's reaction (modified by Kindler), 2, 4-dimethoxyacetophenone (IV) was converted into 2, 4-dimethoxyphenylacetic acid (VI) and this was condensed with resorcinol. Under these circumstances, the isolation of the intermediate morpholide (V) is unnecessary (although it can be isolated). Then the synthesis of ω-(2, 4-dimethoxyphenyl)-resacetophenone (VII) involves only two stages [13]. The ketone (VII) obtained was then cyclized with methyl chloroformate by Emerson and Bickoff's method, with some variations in preparative details, to form 3-(2, 4-dimethoxyphenyl)-4, 7-dihydroxycoumarin (VIII), which was demethylated with aniline hydrochloride, and with the simultaneous closing of the furan ring, converted into coumestrol (IX):



VIII IX

Because of the difficulty of purification, the coumestrol was not isolated but was subjected to allylation as the unpurified product. The resulting 7, 12-diallyloxycoumestrol (II) was rearranged in cymene to the final product, 8, 13-diallylcoumestrol (III).

Experimental

2, 4-Dimethoxyacetophenone (IV). The compound was obtained by the stepwise methylation of resacetophenone with dimethyl sulfate in a strongly alkaline medium, bp 131-134°C (1 mm).

2, 4-Dimethoxyphenylacetic acid (VI). A mixture of 9.5 g of 2, 4-dimethoxyacetophenone, 2.5 g of sulfur and 7 g of morpholine was heated for 10 hr at the boiling point of the base. Without the isolation of the thiomorpholide, a solution of 14 g of caustic potash in 140 ml of water was added to the reaction mixture and it was hydrolyzed by boiling (9 hr). The hydrolyzate was cooled, filtered, and acidified with concentrated hydrochloric acid. After cooling, the crude acid that had deposited was separated off, washed with water, and, after preliminary purification with activated carbon, recrystallized from water. This gave 5.6 g (about 55%) of pure product with mp 107-107.5°C.

Found, %: C 61.24; H 6.15. Calculated for $C_{10}H_{12}O_4$, %: C 61.22: H 6.16.

The thiomorpholide (V). In another experiment, to isolate the thiomorpholide the reaction with the same ratio of reagents as in the previous experiment was broken off at the hydrolysis stage. The hot reaction mixture was poured into 10 ml of hot ethanol. The solution was left in the refrigerator and the crude morpholide which deposited was separated off, washed with cooled alcohol, and recrystallized from chloroform. Yield 8.1 g, mp 118-119°C.

Found, %: N 11.29. Calculated for $C_{14}H_{19}NO_3S$, %: N 11.33.

ω-(2, 4-Dimethoxyphenyl)-resacetophenone (VII). A mixture of 3 g of 2, 4-dimethoxyphenylacetic acid, 1.7 g of resorcinol, 6 g of fused zinc chloride, and 4.6 g of phosphorus oxychloride was heated on a water bath at

50°C for 24 hr. The mixture was decomposed with ice water, and the crude product was separated off and crystallized from toluene. This gave 3.6 g of the ketone (83%) with mp 149-150°C. Literature data for (VII): mp 156°C [9].

Found, %: C 67.22; H 5.38. Calculated for $C_{10}H_{16}O_5$, %: C 66.65; H 5.59.

3-(2, 4-Dimethoxyphenyl)-4, 7-dihydroxycoumarin (VIII). A mixture of 1.24 g of ω-2, 4-dimethoxyphenyl-resacetophenone (VII), 0.75 ml of methyl chloroformate, 3.15 g of dry potassium carbonate, and 28 ml of acetone was boiled on a water bath for 4 hr. After cooling, the reaction mixture was diluted to twice its volume with water and was acidified with dilute (1:1) hydrochloric acid. The oil which separated out – a white substance solidifying in the refrigerator – was filtered off, and the filtrate was evaporated. The combined residue, amounting to 1.35 g, was dissolved in 20 ml of methanol, alizarin yellow was added, the solution was heated to the boil in an atmosphere of nitrogen, and 20% caustic soda added in drops until the mixture became bright orange (pH ~ 11). Then it was heated for a further 10 min, cooled, diluted with a twofold volume of water, acidified with hydrochloric acid, and the precipitate was filtered off. After several recrystallizations from alcohol, 0.95 g (67%) of a substance with mp 260-261°C was obtained. Literature data for (VIII): mp 263-264°C [9].

7, 12-Diallyloxycoumestrol (II). A mixture of 1.2 g of 3-(2, 4-dimethoxyphenyl)-4, 7-dihydroxycoumarin (VIII) and 2.5 g of aniline hydrochloride was heated for 3.5 hr on an oil bath at 210-230°C in a current of CO_2. After cooling, the aniline hydrochloride was washed out with water and the dark red resinification products were removed by washing with acetone. The crude product was dried and, without purification, was boiled for 4 hr with 0.9 g of allyl bromide and 3 g of calcined potassium carbonate in 30 ml of anhydrous acetone. The mixture was cooled and diluted with water, and the red-brown precipitate was collected on a filter, dried, dissolved in benzene, and purified on a column of alumina. About 0.5 g of 7, 12-diallyloxycoumestrol was isolated as light white needles, mp 167°C (from a mixture of benzene and petroleum ether).

Found, %: C 72.35; H 4.64. Calculated for $C_{21}H_{16}O_5$, %: C 72.40; H 4.63.

8, 13-Diallylcoumestrol (III). A mixture of 0.8 g of 7, 12-diallyloxycoumestrol and 12 ml of cymene was boiled for 10 hr. The solvent was distilled off at 65-70°C (20 mm), the dark resinous residue was dissolved in benzene, and the solution passed through a column containing 20 g of alumina for purification. The benzene was evaporated off and the now lighter-colored residue was twice recrystallized from isopropanol. This gave yellowish crystals with mp 345-347°C.

Found, %: C 72.33; H 4.65. Calculated for $C_{21}H_{16}O_5$, %: C 72.40; H 4.63.

8, 13-Diallylcoumestrol acetate. A mixture of 50 mg of (III), 3 ml of acetic anhydride, and 1 g of fused sodium acetate was boiled for 5 min. The mixture was poured into ice water. The precipitate was collected on a filter and crystallized from acetone. The white needles had mp 262-263°C.

Found, %: C 69.46; H 4.64. Calculated for $C_{25}H_{20}O_7$, %: C 69.43; H 4.66.

Summary

A new method for the production of ω-(2, 4-dimethoxyphenyl)-resacetophenone, the basic intermediate in the synthesis of the phytoestrogen coumestrol by Emerson and Bickoff's method, has been described. The new variant of the production of this substance shortens the synthesis of coumestrol by a factor of 2. 7, 12-Diallyloxycoumestrol has been isomerized by a Claisen rearrangement into 8, 13-diallylcoumestrol.

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Institute of Chemistry, AS MoldavSSR