[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Synthesis of Tectorigenin Dimethyl Ether

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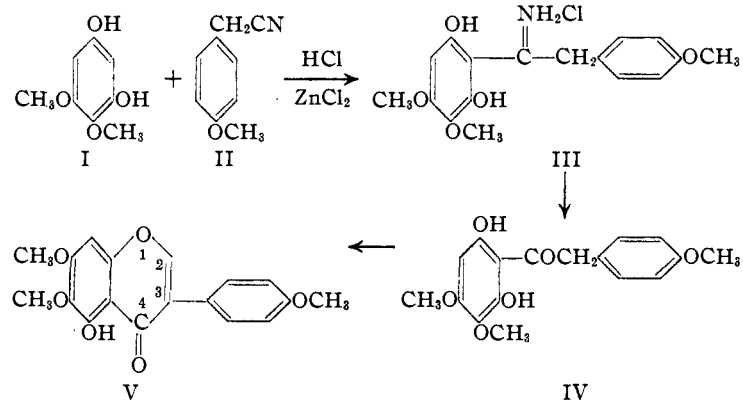
An isoflavone structure has been suggested for tectorigenin, the aglucone of the naturally occurring glucoside, tectoridin. This structure was deduced from its degradation products,[1] absorption spectra[2] and general chemical properties.[2,3] Two other possible substituted coumaran structures were shown to be quite different from the natural aglucone.[4] The present paper reports the synthesis of the dimethyl ether of tectorigenin (V).

The starting materials are 4,5-dimethoxyresorcinol (I) and homoanisonitrile (II). The first was prepared by the sequence: guaiacol → 4,6-dinitroguaiacol → 3,5-dinitroveratrole → 3,5-diaminoveratrole → 4,5-dimethoxyresorcinol, according to the directions of Baker and Robinson.[5] Homoanisonitrile has been synthesized repeatedly by a number of methods; for instance, recently by Julian and Sturgis, and by Lapine.[6] The direct chloromethylation of anisole to *p*-methoxybenzyl chloride[7] followed by reaction with sodium cyanide[8] in the presence of an emulsifying agent to promote rapid reaction of the chloride with the cyanide was found to be a time saving procedure, although the yields were low (29%).

Condensation of 4,5-dimethoxyresorcinol (I) with homoanisonitrile (II) was effected by means of hydrogen chloride and zinc chloride. Hydrolysis of the intermediate iminohydrochloride (III) yielded the substituted desoxybenzoin (IV). A Claisen condensation of the latter compound with ethyl formate and sodium followed by acidification yielded 5-hydroxy-4′,6,7-trimethoxyisoflavone (V). This compound melted at the same temperature as dimethyltectorigenin[4] and a melting point of a mixture of the two samples showed no depression. The acetyl derivative of the synthetic isoflavone (V) was identical with the acetate prepared from the methylated tectorigenin.[4]

In the first step in the above synthesis, the Hoesch reaction is shown taking place in the 2-position of 4,5-dimethoxyresorcinol (I) rather than the 6-position. The reactivity of the 2-position in substituted resorcinols of this type has been previously pointed out by Baker and Robinson[5] who have shown that 3,4,5-trimethoxyphenylaceto-



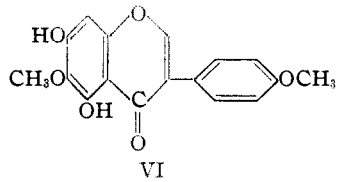
nitrile condenses in the 2-position. Methoxyacetonitrile also reacted with the 2-position of 4,5-dimethoxyresorcinol.[9] Hence it seems very probable that the condensation with homoanisonitrile also takes place in the 2-position especially since the properties of the isoflavone (V) indicate an hydroxyl group in the 5-position.[4]

The second step in the synthesis of tectorigenin dimethyl ether involves the Claisen condensation with ethyl formate and ring closure with the 6-hydroxyl of the substituted desoxybenzoin (IV) and not with the 2-hydroxyl. The fact that ring closure in compounds of this type always appears to involve the unhindered 6-hydroxyl group has been well established by previous work by Baker and Robinson,[5] Bargellini[10] and Chapman, Perkin and Robinson.[11]

The present synthesis of tectorigenin dimethyl

(1) Shibata, *J. Pharm. Soc. Japan*, **47**, 380 (1927).
(2) Asahina, Shibata and Ogawa, *ibid.*, **48**, 1087 (1928).
(3) Mannich, Schumann and Lin, *Arch. Pharm.*, **275**, 317 (1937).
(4) Shriner, Matson and Damschroder, THIS JOURNAL, **61**, 2322 (1939).
(5) Baker and Robinson, *J. Chem. Soc.*, 152 (1929).
(6) Julian and Sturgis, THIS JOURNAL, **57**, 1126 (1935); Lapine, *Bull. soc. chim.*, **6**, 390 (1939).
(7) Quelet and Anglade, *Compt. rend.*, **203**, 262 (1936).
(8) Cannizzaro, *Ann.*, **117**, 243 (1861); Levy, *Ann. chim.*, **9**, 5 (1938).
(9) Baker, Nodzu and Robinson, *J. Chem. Soc.*, 74 (1929).
(10) Bargellini, *Gazz. chim. ital.*, **45**, 69 (1915); **49**, 47 (1919).
(11) Chapman, Perkin and Robinson, *J. Chem. Soc.*, 3015 (1927).

ether coupled with the fact that iretol (2,4,6-trihydroxyanisole) is one of the degradation products of tectorigenin[1] shows that tectorigenin possesses the isoflavone structure (VI).



VI

Experimental

Homoanisonitrile.—One hundred fifty grams of anisole, 150 g. of 40% formalin, 15 cc. of petroleum ether, and 15 g. of zinc chloride were placed in a three-necked flask equipped with a mercury-sealed stirrer. The flask was placed in an ice-bath, and hydrogen chloride gas was added with stirring at such a rate that the temperature remained at 15°. After one hour and fifteen minutes the gas addition was stopped, and 30 g. of cracked ice was added. The stirring was continued for five minutes. After stopping the stirring, an oily layer rose to the top of the solution. This layer was separated, dissolved in 200 cc. of benzene, and washed with 100 cc. of 10% sodium carbonate. The benzene solution was then washed once with 100 cc. of water and added to a solution of 70 g. of sodium cyanide in 180 cc. of water. One gram of sodium laurylsulfate (Dupanol WA) was added and stirring and heating were started. The benzene was distilled out by steam developed in the flask. After the distillation of the benzene was complete the condenser, which had been set downward for distillation, was raised to a vertical position and the solution heated at the boiling point until the solution had boiled with stirring, a total of three and one-half hours. After cooling, the solution was extracted with 800 cc. of ether in three portions. The ether solution was dried with sodium sulfate, and the ether was distilled off. The residue was distilled under diminished pressure. The first fraction (26 g.) was anisole b. p. 53–55° at 20 mm. The second fraction was homoanisonitrile b. p. 154–56° at 20 mm. Sixty grams (29%) of the nitrile was obtained.

The first step in this synthesis must be carried out quickly. The chloromethylanisole must be freed from hydrogen chloride and added to the sodium cyanide as quickly as possible. Otherwise polymerization or hydrolysis of the chloromethylanisole to methoxybenzyl alcohol occurs.

2,6-Dihydroxy-3,4-dimethoxy-α-(*p*-methoxyphenyl)-acetophenone (IV).—A 1.45-g. quantity of 4,5-dimethoxyresorcinol, 1.8 g. of homoanisonitrile, and 0.5 g. of anhydrous zinc chloride were dissolved in 60 cc. of dry ether. Dry hydrogen chloride gas was passed into the solution at 0°. The hydrogen chloride was added rapidly for one hour, then slowly for two hours. The flask was then stoppered and allowed to stand overnight. After the flask had stood for twenty hours, 100 cc. of dry ether was added and the flask again allowed to stand overnight. The ether was then poured off the viscous oil and the oil washed with dry ether. Approximately 100 cc. of 10% hydrochloric acid was added to the oil and the solution boiled under reflux for one-half hour. After cooling, the solution was extracted with ether and the ether solution dried with anhydrous sodium sulfate. Removal of the ether left a red oil which became crystalline upon the addition of methyl alcohol. Recrystallization from methyl alcohol gave 0.8 g. (29%) of white crystals melting at 116.5°.

Anal. Calcd. for $C_{17}H_{18}O_6$: C, 64.15; H, 5.66. Found: C, 64.32; H, 5.99.

Dimethyltectorigenin.—To 0.20 g. of powdered sodium at 0° was added 0.28 g. of 2,6-dihydroxy-3,4-dimethoxy-α-(*p*-methoxyphenyl)-acetophenone in 4.5 cc. of redistilled ethyl formate. The mixture was stirred for four and one-half hours at 0°. Then about 10 g. of crushed ice was added, and the stirring was continued for three hours. After the solution had stood overnight without stirring so that the ethyl formate had evaporated, the solid was filtered off. This solid was dissolved in pyridine and precipitated with water. Repeated precipitation gave 0.04 g. (14%) of light tan colored microscopic needles m. p. 186°. Recrystallization of this material from methanol gave silvery white needles melting at 188°. A mixed melting point of this material with a sample of dimethyltectorigenin prepared by Matson[4] (from natural tectorigenin) gave no alteration in melting point.

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.87. Found: C, 65.69; H, 5.06.

Dimethyltectorigenin Acetate.—In 0.6 cc. of dry pyridine was dissolved 0.026 g. of dimethyltectorigenin and 0.26 cc. of acetic anhydride. The stoppered tube was allowed to stand at room temperature for three days. Then 5 cc. of water was added to the mixture. After standing several hours light tan crystals had formed. These were purified by dissolving in pyridine and precipitating with water. After several crystallizations silvery-white crystals melting at 213° were obtained. A mixed melting point of this material with a sample of dimethyltectorigenin acetate, prepared by Matson[4] (from natural tectorigenin) gave no alteration in melting point.

Anal. Calcd. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.86. Found: C, 65.00; H, 4.95.

In order to establish the validity of the use of melting points of mixtures in the isoflavone field, five different synthetic isoflavones were found to exhibit depressions in melting point when any two of them were mixed together.

Summary

A synthesis of tectorigenin dimethyl ether has been carried out which provides additional evidence that tectorigenin possesses the isoflavone structure.

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