

SYNTHESIS OF 6:7:3':4'-TETRAMETHOXY ISOFLAVONE

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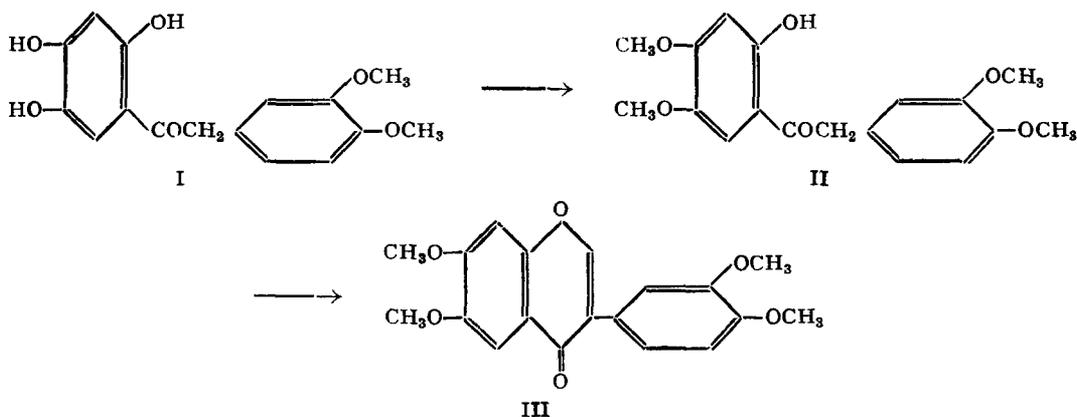
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MAXIMA Substance A was isolated from the roots of *Tephrosia maxima*¹ and assigned the structure 6:7:3':4'-dimethylene-dioxy isoflavone.² For confirmation of this structure, 6:7:3':4'-tetramethoxy isoflavone was required as a reference sample. This has now been prepared employing the following procedure:—

Adopting the method of Edwards³ for the preparation of homopiperonitrile, 3:4-dimethoxyphenyl pyruvic acid⁴ was converted through its oxime into 3:4-dimethoxyphenyl acetonitrile.⁵ This was condensed with hydroxyquinol⁶ (Hoesch reaction) to yield 2:4:5-trihydroxyphenyl-3:4-dimethoxy benzyl ketone (I). This ketone on methylation with dimethylsulphate and anhydrous potassium carbonate in acetone medium yielded 2-hydroxy-4:5:3':4'-tetramethoxy desoxybenzoin (II). The same desoxybenzoin was also obtained by the interaction of the trimethyl ether of hydroxy-quinol and homoveratroyl chloride^{7, 8} in the presence of anhydrous aluminium chloride (Friedel and Crafts reaction). During this reaction the methoxyl group in the hydroxyquinol nucleus which is *ortho* to the entrant carbonyl group underwent smooth demethylation to yield the desired *ortho*-hydroxy desoxy-benzoin (II) (*cf.*, Ballio and Pocchiari⁹). The trimethyl ether of hydroxyquinol (V) required in this connection was prepared by (i) the methylation of hydroxyhydroquinone triacetate with alkali and dimethylsulphate¹⁰ and (ii) by the oxidation of vanillin with hydrogen peroxide in alkaline medium¹¹ followed by methylation with dimethylsulphate. Samples of desoxybenzoin obtained by both the methods were identical in their melting points, colour reactions and solubility behaviour. The desoxybenzoin was smoothly converted into 6:7:3':4'-tetramethoxy isoflavone (III) by treatment with ethylformate in the presence of powdered sodium at 0°.¹²



EXPERIMENTAL

2:4:5-Trihydroxyphenyl 3:4-dimethoxybenzyl ketone

(a) *By Hoesch Reaction.*—To a solution of hydroxyquinol (10.5 g.) and 3:4-dimethoxyphenyl acetonitrile (10.7 g.) in absolute ether (50 c.c.) freshly fused zinc chloride (2 g.) was added. The mixture was cooled to 0° and dry hydrogen chloride gas was passed through it for 5 hours, rapidly during the first half an hour and at a moderate rate subsequently. The mixture was kept well-corked in an ice-chest for 48–72 hours. The ether layer was decanted off from the dark-green oily layer which was subsequently washed with fresh lots of absolute ether. Water (25 c.c.) was added and the solution containing the imino-hydrochloride was heated in a boiling water-bath for two hours. The dark-brown solid that separated was filtered and crystallised from dilute alcohol and subsequently from ethyl acetate-petroleum ether. The ketone was obtained as rhombs, m.p. 189–91° (Yield 0.25 g.). It gave an olive-green colour with alcoholic ferric chloride. It was soluble in aqueous sodium hydroxide giving an yellow solution changing over to orange-red and finally to reddish brown. It was soluble in aqueous sodium bicarbonate giving pale-yellow solutions (Found: C, 63.6; H, 4.6%; $C_{16}H_{16}O_6$ requires C, 63.2; H, 5.3%). The 2:4-dinitrophenylhydrazone of the phenolic ketone was prepared by refluxing the substance (25 mg. in 1 c.c. alcohol) with 2:4-dinitrophenylhydrazine (20 mg. in 5 c.c. alcohol) and a few drops of concentrated hydrochloric acid. The red solid obtained on working up the reaction product was crystallised from ethyl acetate-petroleum ether. It was obtained as rods, m.p. 207–08° (Found: C, 54.1; H, 4.5%; $C_{22}H_{20}O_9N_4$ requires C, 54.6; H, 4.1%).

2-Hydroxy-4:5:3':4'-tetramethoxy desoxy benzoin

2:4:5-Trihydroxyphenyl-3:4-dimethoxy benzyl ketone (1.0 g.) dissolved in dry acetone (150 c.c.) was refluxed with dimethyl sulphate (2 c.c.) (excess) and anhydrous potassium carbonate (4.0 g.) for 8 hours. The potassium salts were filtered off and washed with warm acetone (2×20 c.c.). The solvent was distilled off from the filtrate and the pale-yellow residue obtained was treated with 5% aqueous sodium bicarbonate to remove the unreacted ketone. The pale-yellow tetramethyl ether was filtered and crystallised first from alcohol and subsequently from benzene-petroleum ether. Colourless thin rods, m.p. 135–137°, were obtained (Yield 0.7 g.). The substance gave an emerald-green colour with alcoholic ferric chloride. It was soluble in aqueous sodium hydroxide giving a pale-yellow solution. It was insoluble in aqueous sodium carbonate. (Found: C, 65.5; H, 6.3; OCH₃, 35.6%. C₁₈H₂₀O₆ requires C, 65.1; H, 6.0; OCH₃, 37.4%.)

(b) *By Friedel and Crafts Reaction.*—Homoveratroyl chloride (15.0 g.) was dissolved in absolute ether (150 c.c.) and treated with hydroxyquinol trimethyl ether (12.0 g.) in ether (50 c.c.). Then anhydrous aluminium chloride (20.0 g.) was carefully added in small amounts. The contents were refluxed over a water-bath for 8 hours. After cooling, the ether layer was separated and the reddish-brown aluminium chloride complex decomposed by the addition of hydrochloric acid (1:2; 90 c.c.) and heating on the steam-bath for an hour. The aqueous solution was extracted with ether and combined with the original ether layer. The combined ether extract was washed with hydrochloric acid (1:2; 20 c.c.) and with water (20 c.c.). The ether layer was extracted twice with 10% aqueous sodium hydroxide. The aqueous alkaline extract was acidified carefully with concentrated hydrochloric acid and repeatedly extracted with ether. The ether layer was washed with water, dried over anhydrous magnesium sulphate and distilled. The dark-brown residue was macerated with alcohol (5–10 c.c.). The pale-yellow solid that separated was filtered and crystallised from benzene-petroleum ether when 2-hydroxy-4:5:3':4'-tetramethoxy desoxybenzoin was obtained as colourless thin rods, m.p. 136–38° (Yield 2.0 g.). It gave an emerald-green colour with alcoholic ferric chloride. It did not depress the melting point of the ketone obtained by the Hoesch condensation of hydroxyquinol and 3:4-dimethoxy acetonitrile (Found: C, 65.5; H, 6.1%; C₁₈H₂₀O₆ requires C, 65.1; H, 6.0%).

6:7:3':4'-Tetramethoxy isoflavone

A solution of 2-hydroxy-4:5:3':4'-tetramethoxy desoxybenzoin (0.4 g.) in freshly distilled ethyl formate (15 c.c.) was cooled to 0° and added in small

portions with stirring to powdered sodium (0.4 g.). The mixture was stirred for an hour more keeping the flask in ice-salt mixture. The flask was corked and left in the ice-chest for two days. Pieces of ice and concentrated hydrochloric acid (10 c.c.) were added to the mixture with stirring. The flask was then corked and left overnight at room temperature. Unreacted ethylformate was removed by distillation under reduced pressure. The solid that separated on cooling was filtered, macerated with cold alcohol and again filtered. It was then crystallised twice from rectified spirit. The tetramethoxy isoflavone was obtained as colourless rectangular prisms, m.p. 188–89° (Yield 100 mg.). It did not give any colour with alcoholic ferric chloride. It was insoluble in sodium hydroxide, sodium carbonate and sodium bicarbonate solutions (Found: C, 66.4; H, 5.6; OCH₃, 34.7%; C₁₉H₁₈O₆ requires C, 66.7; H, 5.3; OCH₃, 36.2%).

SUMMARY

The synthesis of 6:7:3':4'-tetramethoxy isoflavone is described.

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