Synthesis of 7-Hydroxy-2', 4', 5'-trimethoxyisoflavone and Related Compounds

By Kenji FUKUI, Mitsuru NAKAYAMA, Masayuki HATANAKA,
Tadao OKAMOTO and Yoshiyuki KAWASE

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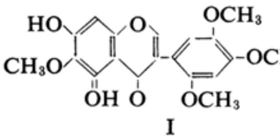
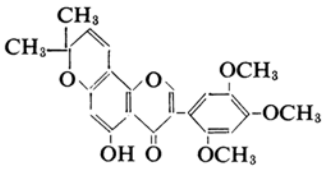
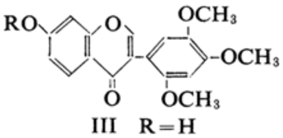
Little has been reported on isoflavones oxygenated at the 2'-, 4'- and 5'-positions. Caviunin⁽¹⁾ (I) and Harper's phenol (" toxicarol isoflavone ")⁽²⁾ (II) are the only known instances which occur naturally. We have, therefore, been interested in synthesizing 7-hydroxy-2', 4', 5'-trimethoxyisoflavone (III) and the corresponding 2-methyl derivative (IV) because of their structural resemblance to I and II.



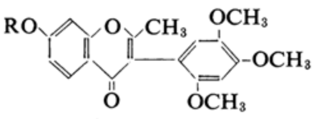
I



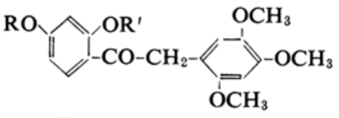
II



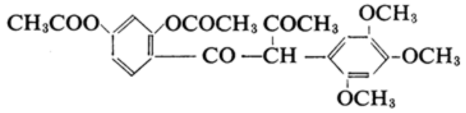
III $R=H$
X $R=CH_3CO$
XI $R=CH_3$



IV $R=H$
XII $R=CH_3CO$
XIII $R=CH_3$



V $R=R'=H$
VI $R=CH_3,\ R'=H$
VII $R=R'=CH_3$
VIII $R=C_6H_5CH_2,\ R'=H$
IX $R=R'=CH_3CO$



XIV

Hoesch condensation of resorcinol and 2, 4, 5-trimethoxybenzyl cyanide⁽³⁾ yielded 2, 4-dihydroxyphenyl 2, 4, 5-trimethoxybenzyl ketone (V) in discouraging yields under a variety of reaction conditions. The ketone V could, however, be prepared in a 46% yield by treating a mixture of resorcinol and homoasaronic acid (2, 4, 5-trimethoxyphenylacetic acid)⁽⁴⁾ with polyphosphoric acid. Zinc chloride in either the presence⁽⁵⁾ or absence of phosphorous oxychloride gave inferior yields of V. Ethers (VI–VIII) and a diacetate (IX) of V were prepared.

When the ketone V was treated with ethyl orthoformate in pyridine⁽⁶⁾, the desired isoflavone III was obtained in a 61% yield. An acetate (X) and a methyl ether (XI) of III were prepared.

Reaction of the ketone V with acetic anhydride in the presence of sodium acetate⁽⁷⁾ gave a cyclized acetate XII which could easily be hydrolyzed to 7-hydroxy-2', 4', 5'-trimethoxy-2-methylisoflavone (IV). A methyl ether (XIII) of IV was also obtained.

When the acetylation of the ketone V was carried out with acetyl chloride in pyridine at 0°C, a diketone XIV was produced. The alkaline hydrolysis of XIV was accompanied with a simultaneous ring closure to afford the methylisoflavone (IV), which was identical with the above-mentioned product.

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(3) J. Harley-Mason and A. H. Jackson, ibid., **1954**, 1165.

(4) A. Robertson and G. H. Rusby, ibid., **1935**, 1371.

(5) V. R. Shah, J. L. Bose and R. C. Shah, *J. Org. Chem.*, **25**, 677 (1960).

(6) V. R. Sathe and K. Venkataraman, *Current Sci.* (*India*), **18**, 373 (1949); *Chem. Abstr.*, **44**, 8916 (1950).

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Experimental*

2, 4-Dihydroxyphenyl 2, 4, 5-Trimethoxybenzyl Ketone (V). — *Hoesch Reaction*8). — A mixture of resorcinol (1.5 g.) and 2, 4, 5-trimethoxybenzyl cyanide (m. p., 84∼85°C)3) (1.0 g.) in anhydrous ether (60 ml.) was saturated with dried hydrogen chloride for a 3 hr. period at 0°C and then allowed to stand at room temperature for 4 days. The ethereal solution was decanted from the oily layer of ketimine hydrochloride which had separated. The oily layer was washed twice with dry ether (20 ml.) and then heated on a steam bath with water (30 ml.) for 1 hr. After cooling and standing, the product was collected and recrystallized from ethanol, giving V (m. p., 201∼202°C) (reported m. p., 201∼202°C8)) (colorless needles), which showed a reddish-brown ferric chloride reaction in ethanol; yield, 0.2 g. (13%).

Found: C, 64.10; H, 5.82. Calcd. for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70%.

Nencki Reaction. — A mixture of homoasaronic acid (m. p., 102∼103°C)4) (1.0 g.) and freshly fused zinc chloride (0.4 g.) was heated at 130∼140°C for 30 min. After resorcinol (1.5 g.) had been added, the mixture was kept at the same temperature for 2 hr. Upon working up the reaction mixture, 0.4 g. (31%) of V was obtained. M. p. and mixed m. p., 199∼200°C.

With Phosphorus Oxychloride-Zinc Chloride. — A mixture of resorcinol (2.0 g.), homoasaronic acid (1.5 g.), phosphorus oxychloride (20 ml.) and freshly fused zinc chloride (6.0 g.) was heated at 50∼60°C for 2 hr. The product was recrystallized from ethanol, giving V (m. p. and mixed m. p., 197∼199°C); yield, 0.6 g. (24%).

With Poly(phosphoric Acid).—A mixture of resorcinol (1.5 g.), homoasaronic acid (1.0 g.) and poly(phosphoric acid) (n=2.5) (10 g.) was warmed on a steam bath for 15 min. The dark red solution was then poured into ice-water. The resulting product was recrystallized from ethanol, giving V (m. p. and mixed m. p., 201∼202°C); yield, 0.65 g. (46%).

2-Hydroxy-4-methoxyphenyl 2, 4, 5-Trimethoxybenzyl Ketone (VI). — *With Diazomethane.* — The treatment of V (0.5 g.) in acetone (60 ml.) with an ethereal solution of diazomethane (prepared from 0.5 g. of nitrosomethylurea) gave VI as colorless needles (m. p., 135∼136°C (from ethanol)); yield, 0.5 g. (96%).

Found: C, 64.91; H, 6.15. Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07%.

With Methyl Iodide.—To a solution of V (1.0 g.) and methyl iodide (0.2 ml.) in acetone (30 ml.) was added potassium carbonate (2.0 g.); the mixture was then refluxed for 70 min. The product was recrystallized from ethanol, giving VI (m. p. and mixed m. p., 135∼136°C); yield, 1.0 g. (96%).

2, 4-Dimethoxyphenyl 2, 4, 5-Trimethoxybenzyl Ketone (VII). — To a solution of V (1.0 g.) and dimethyl sulfate (1.0 ml.) in acetone (50 ml.) was added potassium carbonate (5.0 g.); the mixture was then refluxed for 6.5 hr. to provide VII (m. p., 110∼111°C) (colorless needles from ethanol); yield, 1.0 g. (91%).

Found: C, 65.89; H, 6.58. Calcd. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40%.

2-Hydroxy-4-benzyloxyphenyl 2, 4, 5-Trimethoxybenzyl Ketone (VIII).—A mixture of V (1.0 g.), benzyl chloride (1.0 g.) and potassium carbonate (5.0 g.) in acetone (50 ml.) was refluxed for 8 hr. Recrystallization from ethanol gave VIII in the form of colorless needles, (m. p. 149∼150°C); yield, 1.2 g. (94%).

Found: C, 70.55; H, 5.99. Calcd. for $C_{24}H_{24}O_6$: C, 70.57; H, 5.92.

2, 4-Diacetoxyphenyl 2, 4, 5-Trimethoxybenzyl Ketone (IX). — The treatment of V (0.1 g.) in pyridine (5.0 ml.) with acetic anhydride (2.0 ml.) at room temperature gave IX as colorless prisms (m. p., 134∼135°C (from ethanol)); yield, 0.12 g. (95%).

Found: C, 62.23: H, 5.58. Calcd. for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51.

7-Hydroxy-2′, 4′, 5′-trimethoxyisoflavone (III).— To a solution of V (0.8 g.) and ethyl orthoformate (2.0 ml.) in pyridine (10 ml.) was added piperidine (0.5 ml.); the mixture was then refluxed for 10 hr. The resulting solution was cooled and acidified with dilute hydrochloric acid. The precipitate was recrystallized from ethanol, giving III (m. p., 244∼245°C) (colorless microcrystals), with a negative ferric chloride reaction in ethanol; yield, 0.5 g. (61%). IR: 3320∼3200 (broad) (OH), 1640 cm^{-1} (γ-pyrone). UV: λ_{max}^{EtOH} mμ (log ε): 241 (4.35), 249 (4.35), 300 (4.24).

Found: C, 65.62; H, 5.18. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%.

The acetylation of III with acetic anhydride and pyridine at room temperature gave the acetate (X) (m. p., 156∼157°C) (colorless needles from ethanol). IR: 1752 (acetate), 1659 cm^{-1} (γ-pyrone).

Found: C, 64.72; H, 5.11. Calcd. for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90%.

2′, 4′, 5′, 7-Tetramethoxyisoflavone (XI). — This ether XI was prepared from V (0.15 g.) with dimethyl sulfate in acetone. Recrystallization from ethanol yielded colorless plates (m. p., 190∼191°C); yield, 0.12 g. (80%). IR: 1639 cm^{-1} (γ-pyrone).

Found: C, 66.62; H, 5.42. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30%.

7-Acetoxy-2′, 4′, 5′-trimethoxy-2-methylisoflavone (XII).—A mixture of V (1.0 g.) and anhydrous sodium acetate (2.0 g.) in acetic anhydride was refluxed for 18 hr. The cooled mixture was poured into ice-water. An oil separated and solidified on cooling. Recrystallization of the solid from ethyl acetate or ethanol gave XII (m. p., 177∼178°C) (colorless needles), with a negative ferric chloride reaction in ethanol; yield, 1.0 g. (83%). IR: 1756 (acetate), 1645 cm^{-1} (γ-pyrone).

Found: C, 65.79; H, 5.31. Calcd. for $C_{21}H_{20}O_7$: C, 65.61; H, 5.24%.

2, 4-Diacetoxyphenyl α-Acetyl-2, 4, 5-trimethoxybenzyl Ketone (XIV).—Into a solution of V (2.0 g.) in pyridine (40 ml.) acetyl chloride (3.0 ml.) was

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** All melting points are uncorrected; the infrared spectra were meaured in Nujol.

8) This procedure is based on a private communication from Hiroshi Fukami of the Department of Agricultural Chemistry, Kyoto University.

added with stirring at 0°C. After having been left standing for 24 hr. at 0°C, the reaction mixture was poured into ice-water. The resulting solid mass was collected by filtration and dried. Recrystallization from ethanol gave XIV (m. p., 164∼165°C) (colorless prisms), with a negative ferric chloride reaction in ethanol; yield, 2.2 g. (78%).

Found: C, 62.12; H, 5.45. Calcd. for $C_{23}H_{24}O_9$: C, 62.16; H, 5.44%.

2-Hydroxy-2′,4′,5′-trimethoxy-2-methylisoflavone (IV).—*By Hydrolysis of XII.*—*i) With Sulfuric Acid:* A solution of XII (0.55 g.) in ethanol (50 ml.) was refluxed with concentrated sulfuric acid (0.3 ml.) for 4 hr. After evaporation of the solvent, the residue was triturated with water. The resulting solid was recrystallized from ethanol giving IV (m. p., 246∼247°C) (colorless microcrystals); yield, 0.47 g. (96%). IR: 3248 (OH), 1637 cm^{-1} (γ-pyrone). UV: λ_{max}^{EtOH} mμ (log ε): 242 (4.37), 250 (4.37), 296.5 (4.30).

Found: C, 66.65; H, 5.43. Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30%.

The acetylation of IV with acetic anhydride and pyridine gave the acetate (XII) (m. p. and mixed m. p., 177∼178°C).

ii) With Sodium Carbonate: A mixture of XII (0.25 g.) and 10% aqueous sodium carbonate (10 ml.) was refluxed for 2 hr. Upon acidification of the hydrolyzate with dilute hydrochloric acid, a precipitate formed. Recrystallization from ethanol gave IV (m. p., 246∼248°C, which was identical with that of the above sample); yield, 0.1 g. (48%).

By Hydrolysis of XIV.—XIV (1.0 g.) was treated with sodium carbonate in a manner similar to that described above. Recrystallization from ethanol gave IV (m. p., 246∼247°C); yield, 0.5 g. (38%).

2′,4′,5′,7-Tetramethoxy-2-methylisoflavone (XIII).—This ether XIII was prepared from (0.20 g.) with dimethyl sulfate in acetone. Recrystallization from ethanol gave colorless microcrystals (m. p., 189∼190°C); yield, 0.20 g. (96%). IR: 1641 cm^{-1} (γ-pyrone).

Found: C, 67.38; H, 5.73. Calcd. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66%.

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Department of Chemistry
Faculty of Science
Hiroshima University
Higashi-sendamachi, Hiroshima
(K. F., M. N. & M. H.)

Faculty of Literature and Science
Toyama University
Gofuku, Toyama
(T. O. & Y. K.)