Reactions of Active Methylene Compounds. VI. A New Synthesis of Coumestrol, 6,7'-Dihydroxycoumarino (3',4':3,2) coumarone

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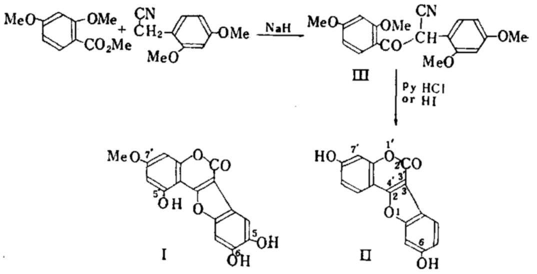
It has been reported that naturally occurring wedelolactone[1] (I) and coumestrol[2] (II) are 5,5',6-trihydroxy-7'-methoxy and 6,7'-dihydroxy derivatives of coumarino (3',4':3,2)coumarone, respectively. The synthesis of coumarino(3',4':3,2) coumarones has been achieved by the action of hydrobromic acid[3] or pyridine hydrochloride[4] on 3-(2'-methoxyphenyl)-4-hydroxycoumarin derivatives; wedelolactone trimethylether[3,4], from which wedelolactone[5] was derived, was prepared by this method, and coumestrol has recently been synthesized by the action of aniline hydrochloride or hydriodic acid on 3-(2',4'-dimethoxyphenyl)-4,7-dihydroxycoumarin[6].

Another synthetic route to coumarino-(3',4':3,2)coumarone was reported by Chatterjea and Roy, which involves the action of hydrobromic acid on 2-methoxybenzoyl-2-methoxyphenylacetonitrile[7].

The author also has achieved independently the synthesis of 3-phenyl-4-hydroxycoumarins[8] and coumarino (3',4':3,2)coumarones[9] from methoxy derivatives of benzoyl-phenylacetonitrile or corresponding ester by the action of hydrobromic or hydriodic acid or pyridine hydrochloride or anhydrous aluminum chloride.

Now, the synthesis of coumestrol has been carried out by the action of pyridine hydrochloride or hydriodic acid on 2,4 dimethoxybenzoyl-2,4-dimethoxyphenyl-acetonitrile(III). The acetate of coumestrol thus obtained, m.p. 227~228°C (uncorrected), was identical with the sample, m.p. 227~228°C (uncorrected), which was kindly sent by Dr. Emerson.



Experimental[10]

Ester Condensation.—To a solution of methyl 2,4-dimethoxybenzoate (3.5 g.) and 2,4-dimethoxyphenylacetonitrile (3 g., prepared by azlactone-method[11]) in anhydrous benzene (100 cc.), sodium hydride (ca. 0.6 g.) was added, and the mixture was heated on an oil bath (ca. 95~100°C) for 4 hr. under anhydrous condition, most of the benzene having been distilled off in the meantime. After being well cooled, the mixture was treated with a small amount of ethanol to destroy the excessive sodium hydride, and then diluted with water. Insoluble starting materials being extracted with ether (from the residue of the ether solution, 1.5 g. of the nitrile was recovered through crystallization from methanol), the alkaline solution was acidified and the separated product was collected, washed with aqueous sodium bicarbonate solution and recrystallized from ethanol to give III in colorless needles, m. p. 97~98°C; yield 2.4 g. or 40% (yield was raised to 70% when recovery of the nitrile was taken into account).

Anal. Found: C, 67.01; H, 5.72; N, 4.25. Calcd. for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61; H, 4.10%.

Coumestrol.—(*a*) *By pyridine hydrochloride.*—A mixture of III (0.7 g.) and anhydrous pyridine hydrochloride (3.5 g.) was refluxed for 40 min.

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[1] T. R. Govindachari et al., *J. Chem. Soc.*, **1956**, 629; ibid., **1957**, 545.

[2] E. M. Bickoff et al., *Science*, **126**, 969 (1957); *J. Agr. Food Chem.*, **6**, 536 (1958); *J. Am. Chem. Soc.*, **80**, 3969 (1958).

[3] W. J. Bowyer, A. Robertson and W. Whalley, *J. Chem. Soc.*, **1957**, 542.

[4] T. R. Govindachari et al., ibid., **1957**, 548.

[5] N. R. Krishnaswamy and T. R. Seshadri, *J. Sci. Ind. Research (India)*, **16B**, 268 (1957); [*Chem. Abstr.*, **52**, 376 (1958)].

[6] O. H. Emerson and E. M. Bickoff, *J. Am. Chem. Soc.*, **80**, 4381 (1958).

[7] J. N. Chatterjea and S. K. Roy, *J. Indian Chem. Soc.*, **34**, 98 (1957); [*Chem. Abstr.*, **51**, 16445 (1957)]; cf. J. N. Chatterjea and S. K. Roy, *J. Indian Chem. Soc.*, **34**, 155 (1957); [*Chem. Abstr.*, **52**, 1987 (1958)].

[8] Y. Kawase, This Bulletin, **31**, 440 (1958); ibid., **32**, 9, 11 (1959); *Experientia*, **14**, 435 (1958).

[9] A report will appear in this bulletin afterwards.

[10] Melting points are uncorrected.

[11] P. C. Mitter and S. S. Maitra, *J. Indian Chem. Soc.*, **13**, 236 (1936).

on an oil bath (ca. 220~230°C) in a carbon dioxide atmosphere under anhydrous condition. The cooled mixture was warmed with dilute hydrochloric acid on a steam bath for 30 min. The separated precipitates were crystallized from ethanol to give light brown microcrystals (m. p. of this was very high); yield ca. 0.2 g.

Anal. Found: C, 67.35; H, 3.18. Calcd. for $C_{15}H_8O_5$: C, 67.17; H, 3.01%.

The acetate prepared by pyridine-acetic anhydride method was colorless needles (from acetic acid), m. p. 227~228°C, and was identical with the sample from Dr. Emerson, m. p. 227~228°C (corrected m. p. is reported to be 235~236°C).

Anal. Found: C, 64.51; H, 3.59. Calcd. for $C_{19}H_{12}O_7$: C, 64.77; H, 3.43%.

(*b*) *By hydriodic acid.* — A mixture of III (0.8 g.), hydriodic acid (d=1.7, 15 cc.), acetic acid (7.5 cc.) and acetic anhydride (7.5 cc.) was refluxed for 2 hr. on an oil bath (ca. 140°C) under a carbon dioxide atmosphere. The cooled solution was diluted with dilute aqueous sodium bisulfite solution, and the precipitates were crystallized from ethanol to give a red product (ca. 0.1 g.), the acetate, m. p. 225.5~226.5°C, which was identical with the other sample.

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