Synthetic Studies on the Benzofuran Derivatives. VI. Synthesis of Furano(2'', 3'' : 7, 8)-2'-methoxy-isoflavone Derivatives

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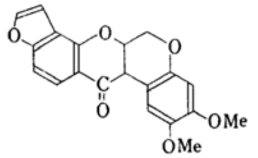
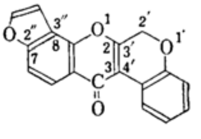
The structure of elliptone, the simplest member of rotenoids, has been established[1] to be a dimethoxy derivative of furano-chromanochromanone (I), but the synthesis of it and other rotenoids** is not yet achieved. Many efforts have hitherto been made on the synthesis of rotenoids, and recently the total synthesis of dihydrorotenone has been accomplished by Miyano and Matsui[2], who succeeded in the reduction of the chromenochromone system to give the chromanochromanone system. Therefore, it seems desirable for the synthesis of elliptone to prepare the furano-chromenochromone system, from which the furano-chromanochromanone system may be derived by reduction. For the preparation of chromenochromones, two methods are available —those are (a) by chromenochromone-ring formation of phenoxyacetic acid-2-(*o*-hydroxy)-acetophenones[3] and (b) by chromen-ring formation of 2-methyl[4] or 2-ethoxymethyl[5] derivatives of 2'-methoxy-isoflavones.



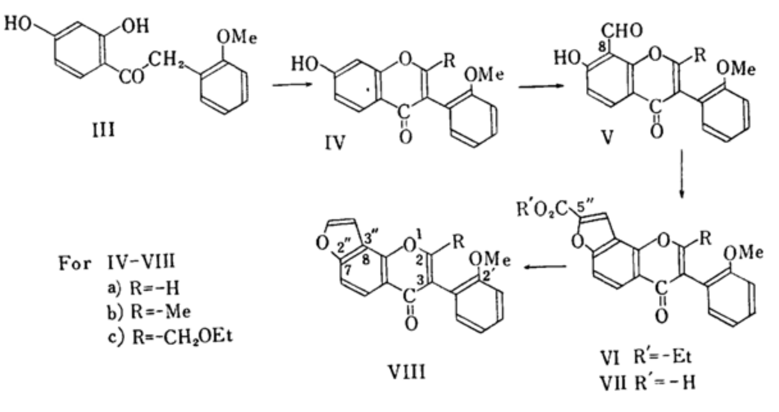
I



II

Following the latter method, the authors attempted to synthesize furano(2'', 3'' : 7, 8)-chromeno(3', 4' : 2, 3)chromone (II), and in this paper describe the preparation of three intermediate derivatives (VIIIa, b, c) of furano (2'', 3'' : 7, 8)-2'-methoxy-isoflavone.

Starting from three isoflavones (IVa, b, c), furan-ring was built up on the 7, 8-position of them smoothly by a similar method reported in the previous papers[6] as follows: the isoflavones IVa, b, c were formulated by the hexamine method to give 8-formyl derivatives (Va, b, c), which were converted into α-ethoxycarbonyl-furano derivatives (VIa, b, c) by the action of ethyl bromomalonate and potassium carbonate in acetone. Hydrolysis of the esters VIa, b, c under mild alkaline condition (aqueous sodium carbonate in acetone) furnished the corresponding acids VIIa, b, c which were decarboxylated in quinoline with the aid of copper catalyst



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1) S. H. Harper, *J. Chem. Soc.*, **1939**, 1099, 1424; ibid., **1942**, 587.

** Recentry, total synthesis of *dl*-deguelin has been reported by H. Fukami, J. Oda, G. Sakata and M. Nakajima (*Bull. Agr. Chem. Soc. Japan*, **24**, 327 (1960)). (added in proof).

2) M. Miyano und M. Matsui, *Chem. Ber.*, **91**, 2044 (1958); ibid., **92**, 2487 (1959); M. Matsui und M. Miyano, *Proc. Japan Acad.*, **35**, 175 (1959).

3) A. Robertson, *J. Chem. Soc.*, **1933**, 489, 1163.

4) T. R. Seshadri and S. Varadarajan, *Proc. Indian Acad. Sci.*, **37A**, 784 (1953).

5) A. C. Mehta and T. R. Seshadri, ibid., **42A**, 192 (1955).

6) T. Matsumoto, Y. Kawase, M. Nanbu and K. Fukui, This Bulletin, **31**, 688 (1958); K. Fukui and Y. Kawase, ibid., **31**, 693 (1958).

to give furano(2″, 3″ : 7, 8)-2′-methoxy-isoflavone*** (VIIIa), furano(2″, 3″ : 7, 8)-2′-methoxy-2-methylisoflavone (VIIIb) and furano-(2″, 3″ : 7, 8)-2′-methoxy-2-ethoxymethylisoflavone (VIIIc) respectively. Attempts to prepare II from VIIIb or VIIIc are now in progress.

Experimental[7]

2, 4-Dihydroxyphenyl 2-Methoxybenzyl Ketone (III).—This ketone was prepared from resorcinol and *o*-methoxyphenylacetonitrile by the Hoesch reaction[4] or more conveniently from resorcinol and *o*-methoxy-phenylacetic acid by means of boron trifluoride[8]. M. p. 158~159°C (reported m. p. 159~160°C[4]).

7-Hydroxy-2′-methoxy-isoflavone (IVa).—A mixture of the ketone III (10 g.), ethyl orthoformate (20 ml.), piperidine (4 ml.) and pyridine (80 ml.) was refluxed for 8 hr. in an oil-bath. The resulting solution was cooled and acidified with dilute hydrochloric acid. The crystals formed were recrystallized from ethanol to give IVa, m. p. 226.5~227.5°C (reported m. p. 230~232°C[9]), having negative ferric reaction in ethanol; yield 6.6 g.

7-Hydroxy-2′-methoxy-8-formyl-isoflavone (Va).—A mixture of the isoflavone IVa (6 g.), hexamine (32 g.) and acetic acid (100 ml.) was heated in an oil bath (100°C) for 6 hr. The resulting hot solution was treated with hot dilute hydrochloric acid (1 : 1, 100 ml.) and again heated for 10 min., then allowed to stand overnight. The precipitates were collected, washed with water and dissolved in benzene, and the benzene solution was extracted with dilute aqueous sodium hydroxide. The product obtained by acidifying the alkaline solution was recrystallized from ethanol to give Va in faintly yellow colored microcrystals, m. p. 187~189°C, having a red ferric reaction in ethanol; yield 2.1 g.

Found: C, 68.40; H, 4.25. Calcd. for $C_{17}H_{12}O_5$: C, 68.92; H, 4.05%.

7-Hydroxy-2′-methoxy-8-formyl-2-methylisoflavone (Vb).—By the similar method as described for Va, 1.3 g. of Vb was obtained from 7-hydroxy-2′-methoxy-2-methylisoflavone[4] (IVb, m. p. 222~223°C, 3 g.), hexamine (16 g.) and acetic acid (50 ml.); m. p. 165.5~166.5°C (from ethanol) faintly yellow colored microcrystals, having a red ferric reaction in ethanol.

Found: C, 69.18; H, 4.67. Calcd. for $C_{18}H_{14}O_5$: C, 69.68; H, 4.52%.

7-Hydroxy-2′-methoxy-8-formyl-2-ethoxymethylisoflavone (Vc).—By the similar method, 1 g. of Vc was obtained from 7-hydroxy-2′-methoxy-2-ethoxymethylisoflavone[5] (IVc, m. p. 163~164°C, 1.5 g.), hexamine (8 g.) and acetic acid (25 ml.); m. p. 129~130°C (from 80% ethanol) faintly yellow colored microcrystals, having a red ferric reaction in ethanol.

Found: C, 68.04; H, 5.24. Calcd. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12%.

5″-Ethoxycarbonyl-furano(2″,3″:7,8)-2′-methoxy-isoflavone (VIa).—To a solution of the formyl-isoflavone Va (2 g.) and ethyl bromomalonate (2.2 g.) in anhydrous acetone (65 ml.) was added anhydrous potassium carbonate (7.8 g.), and the mixture was refluxed for 8 hr. in a steam bath. The resulting solution was filtered from precipitates and the solvent was distilled off. The residual oily product was recrystallized from ethanol to give VIa, m. p. 164.5°C, having a negative ferric reaction; yield 1.1 g.

Found: C, 69.12; H, 4.50. Calcd. for $C_{21}H_{16}O_6$: C, 69.23; H, 4.40%.

5″-Ethoxycarbonyl-furano(2″,3″:7,8)-2′-methoxy-2-methylisoflavone (VIb).—By the similar method as described for VIa, 1.2 g. of VIb was obtained from the formyl-isoflavone Vb (2 g.), ethyl bromomalonate (2.2 g.) and potassium carbonate (7.8 g.); m. p. 161.5~162.5°C (from ethanol), having a negative ferric reaction.

Found: C, 69.97; H, 4.96. Calcd. for $C_{22}H_{18}O_6$: C, 69.84; H, 4.76%.

5″-Ethoxycarbonyl-furano(2″,3″:7,8)-2′-methoxy-2-ethoxymethylisoflavone (VIc).—By the similar method, 1 g. of VIc was obtained from the formyl-isoflavone Vc (1.5 g.), ethyl bromomalonate (1.7 g.) and potassium carbonate (6 g.); m. p. 177.5~178.5°C (from ethanol), having a negative ferric reaction.

Found: C, 68.55; H, 5.33. Calcd. for $C_{24}H_{22}O_7$: C, 68.24; H, 5.25%.

5″-Carboxy-furano(2″, 3″ : 7, 8)-2′-methoxy-isoflavone (VIIa).—A mixture of the ester VIa (0.8 g.), acetone (40 ml.) and 5% aqueous sodium carbonate (30 ml.) was refluxed for 3 hr. Dilute hydrochloric acid (20 ml.) was added to the resulting mixture, and acetone was distilled off. The precipitates were collected and recrystallized from ethanol; m. p. 273.5~274°C, having a negative ferric reaction; yield 0.6 g.

Found: C, 67.83; H, 3.65. Calcd. for $C_{19}H_{12}O_6$: C, 67.86; H, 3.57%.

5″-Carboxy-furano(2″, 3″ : 7, 8)-2′-methoxy-2-methylisoflavone (VIIb).—By the similar method as described for VIIa, 1.1 g. of VIIb was obtained from the ester VIb (1.2 g.), acetone (50 ml.) and 5% aqueous sodium carbonate (50 ml.); m. p. 294°C (from ethanol), having a negative ferric reaction.

Found: C, 68.41; H, 4.02. Calcd. for $C_{20}H_{14}O_6$: C, 68.57; H, 4.00%.

5″-Carboxy-furano(2″, 3″ : 7, 8)-2′-methoxy-2-ethoxymethylisoflavone (VIIc).—By the similar method, 0.3 g. of VIIc was obtained from the ester VIc (0.5 g.), acetone (20 ml.) and 5% aqueous sodium carbonate (20 ml.); m. p. 233~234°C (from ethanol), having a negative ferric reaction.

Found: C, 67.21; H, 4.57. Calcd. for $C_{22}H_{18}O_7$: C, 67.00; H, 4.60%.

Furano(2″,3″ : 7,8)-2′-methoxy-isoflavone (VIIIa).—A mixture of the acid VIIa (0.5 g.), copper powder (0.3 g.) and quinoline (20 ml.) was heated while stirring in an atmosphere of nitrogen for 20 min.

*** It has recently been reported that munetone is 5″-isopropyl derivative of VIIIa by N. L. Dutta (*J. Indian Chem. Soc.*, **36**, 165 (1959)).

[7] Melting points are uncorrected, and the products are colorless microcrystals unless otherwise noted.

[8] Private communication from H. Fukami of the Agricultural Department of Kyoto University.

[9] P. K. Grover and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **38A**, 122 (1953).

at 190~200°C until evolution of carbon dioxide ceased. Quinoline was distilled off by steam-distillation, and the residual product was dissolved in ethyl acetate, filtered from copper, and washed with dilute sulfuric acid and dilute aqueous sodium hydroxide. Evaporation of ethyl acetate gave VIIIa, m. p. 182°C (from ethyl acetate and then from ethanol), having a negative ferric reaction; yield 0.3 g.

Found: C, 74.04; H, 4.20. Calcd. for $C_{18}H_{12}O_4$: C, 73.97; H, 4.11%.

Furano(2'',3'':7,8)-2'-methoxy-2-methylisoflavone (VIIIb).—By the similar method as described for VIIIa, 0.6 g. of VIIIb was obtained from the acid VIIb (1 g.), copper powder (0.5 g.) and quinoline (35 ml.); m. p. 168°C (from ethyl acetate and then from ethanol), having a negative ferric reaction.

Found: C, 74.33; H, 4.64. Calcd. for $C_{19}H_{14}O_4$: C, 74.51; H, 4.58%.

Furano(2'', 3'' : 7, 8)-2'-methoxy-2-ethoxymethylisoflavone (VIIIc).—By the similar method, 0.5 g. of VIIIc was obtained from the acid VIIc (1 g.), copper powder (0.5 g.) and quinoline (35 ml.); m. p. 119~120°C (from ethyl acetate and then from ethanol), having a negative ferric reaction.

Found: C, 72.18; H, 5.21. Calcd. for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18%.

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