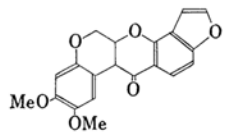
Synthetic Studies on the Benzofuran Derivatives. VIII. Synthesis of Furo[2,3-f]chromeno[3,4-b]chromone[*1]

By Yoshiyuki KAWASE and Chûji NUMATA

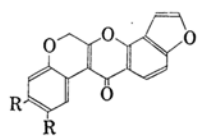
(Received October 20, 1961)

Miyano and Matsui[1] have succeeded in the reduction of chromenochromones to give chromanochromanones, and recently the total syntheses of rotenone[2], deguelin[3] and munduserone[4] have been accomplished by this method.

Therefore, it seems desirable for the synthesis of elliptone[5] (I), a kind of rotenoids, to prepare dehydroelliptone (II) because I may be obtained from II by the method mentioned above.



I



II) R=OMe
III) R=H

Now the synthesis of furo[2,3-f]chromeno-[3,4-b]chromone (III), the parent nucleus of II, has been carried out by two routes. Both routes started from 7-hydroxy-2'-methoxy-2-ethoxymethylisoflavone (IV), but differed from each other in the order of furan-ring construction and chromen-ring closure.

For the preparation of chromenochromones, two methods are available; those are by chromenochromone-ring formation of phenoxyacetic acid-2-(2-hydroxy)-acetophenone[6] (the Robertson's method) and by chromen-ring formation of 2-methyl[7] or 2-ethoxymethyl[8] derivatives of 2'-methoxyisoflavone (the Seshadri's method). In the latter method, Mehta and Seshadri reported that 7-hydroxy-2'-methoxy-2-ethoxymethylisoflavone (IV) was converted directly by the action of hydrogen bromide in acetic acid into 2', 7-dihydroxy-8-bromomethylisoflavone (VI) which was converted into 9-hydroxychromeno[3,4-b]chromone (VII), and Seshadri and Varadarajan reported that VII was also obtained by the action of potassium carbonate in acetone on 2', 7-dihydroxy-2-hydroxymethylisoflavone (V) which

*1 Brief report: Y. Kawase and C. Numata, *Chem. & Ind.*, **1961**, 1361.

1) M. Miyano and M. Matsui, *Bull. Agr. Chem. Soc. Japan*, **22**, 128 (1958); *Chem. Ber.*, **91**, 2044 (1958).

2) M. Miyano, A. Kobayashi and M. Matsui, *Bull. Agr. Chem. Soc. Japan*, **24**, 540 (1960); *Agr. Biol. Chem.*, **25**, 673 (1961).

3) H. Fukami, J. Toda, G. Sakata and M. Nakajima, *Bull. Agr. Chem. Soc. Japan*, **24**, 123 (1960); *Agr. Biol. Chem.*, **25**, 252 (1961).

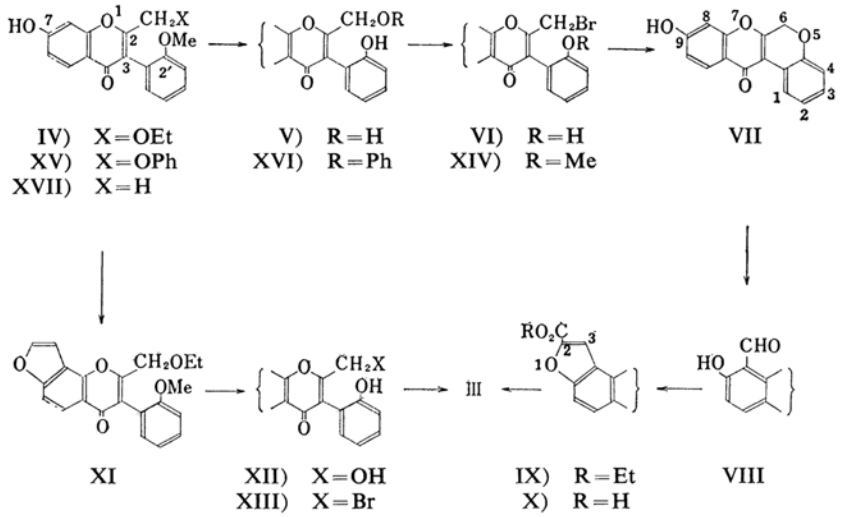
4) J. R. Herbert, W. D. Ollis and R. C. Russell, *Proc. Chem. Soc.*, **1960**, 177.

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

6) A. Robertson, ibid., **1933**, 489, 1163.

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

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



was prepared from 7-hydroxy-2'-methoxy-2-methylisoflavone (XVII) through four steps.

But in the author's experiments, the hydroxybromomethyl compound VI was not obtained directly from IV but only the 2'-methyl ether (XIV) of VI was obtained by the procedure reported by Mehta and Seshadri, and also some attempts to obtain the 2-halomethyl analog of VI from IV by the action of other reagents (e. g. hydrochloric, hydrobromic or hydroiodic acid in acetic acid or pyridine hydrochloride) resulted in a failure. Further, the 2-phenoxy analog (XV) of IV was not affected by hydrogen bromide in acetic acid, and was converted into only the 2'-demethylated compound XVI by the action of anhydrous aluminum chloride.

On the other hand, IV was readily converted by the action of anhydrous aluminum chloride into the trihydroxy compound V which had been, with difficulty, prepared from XVII. But it proved to be impossible to convert this compound V directly into the chromenochromone VII by the procedure reported by Seshadri and Varadarajan, and also by other dehydrating reagents (e. g. *p*-toluenesulfonic acid in benzene, concentrated sulfuric acid, polyphosphoric acid, acetic anhydride, and tosyl or thionyl chloride in pyridine). Therefore, the trihydroxy compound V was made to react with hydrogen bromide in acetic acid to give the hydroxybromomethyl compound VI smoothly, which was readily converted into the chromenochromone VII*2 by the action of potassium carbonate in acetone.

Then, constructing the chromenochromone-ring by the above-mentioned modification of the Seshadri's method and building up the furan-ring by a method analogous to that reported previously for isoflavones[9], the authors synthesized the furochromenochromone III from IV as follows:

In one route, the chromenochromone VII was formylated by the hexamine method to give the 8-formyl compound VIII, which was converted into furochromenochromone-2-carboxylic acid (X) by the action of ethyl bromomalonate and potassium carbonate followed by alkaline hydrolysis. Decarboxylation of this acid X furnished the furochromenochromone III, slightly red colored microcrystals, m. p. 239.5~240°C.

In the other route, the furochromenochromone III was obtained more smoothly by the chromen-ring closure of 2'-methoxy-2-ethoxymethylfuro-[2,3-f] isoflavone (XI), its preparation from the isoflavone IV was reported in the previous paper[9]: Furoisoflavone XI was treated with aluminum chloride in nitrobenzene not in benzene to give the dihydroxy compound XII, which was converted into the bromo compound XIII and then finally into III, slightly orange colored microneedles, m. p. 241.5~242.5°C, identical with the other sample. The structure of III and of the other intermediates was confirmed by ultraviolet and infrared spectroscopy and by microanalysis.

Experimental*3

7-Hydroxy-2'-methoxy-2-bromomethylisoflavone (XIV).—A mixture of IV (1 g.), acetic acid (10 ml.) and hydrogen bromide-acetic acid (50%, 10 ml.) was allowed to stand over night, then the mixture

*2 This VII was also prepared by the Robertson's method.

9) T. Matsumoto et al., This Bulletin, 31, 688 (1958); Y. Kawase and K. Fukui, ibid., 31, 693 (1958); Y. Kawase et al., ibid., 33, 1240 (1960).

*3 Melting points are uncorrected and infrared spectra were measured in Nujol unless otherwise noted.

was heated for 45 min. on a steam-bath with the addition of more hydrogen bromide-acetic acid (50%, 10 ml.). Ice water was added to the cooled solution, and the solid products obtained were recrystallized from ethanol to give XIV in colorless microcrystals, m. p. 192~193°C, which gave a positive Beilstein test.

Found: C, 57.22; H, 3.79. Calcd. for $C_{17}H_{13}O_4Br$: C, 56.53; H, 3.63%.

7-Hydroxy-2'-methoxy-2-phenoxymethylisoflavone (XV).—To a solution of 2,4-dihydroxyphenyl 2-methoxybenzyl ketone (2.6 g.) in pyridine (50 ml.) was added phenoxyacetyl chloride (5 g.) drop by drop with ice cooling and stirring. By the usual treatment of the mixture, XV was obtained in colorless microcrystals, m. p. 232~233°C (from ethanol); yield 1.25 g. (33.5%).

Found: C, 73.34; H, 4.86. Calcd. for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85%.

2',7-Dihydroxy-2-phenoxymethylisoflavone (XVI).—Anhydrous aluminum chloride (1.5 g.) was added to a solution of XV (0.5 g.) in benzene (or nitrobenzene), and the mixture was refluxed for 2.5 hr. on a steam-bath. The solvent was removed (by steam-distillation in the case of nitrobenzene), and the cooled residue was treated with ice water and hydrochloric acid. Next day, the precipitates were collected, washed with water, dissolved in aqueous sodium carbonate, and the alkaline solution was filtered and acidified. The crystaline products obtained were recrystallized from ethyl acetate or from dilute ethanol to give XVI in colorless microcrystals, m. p. 218~220°C; yield 0.2 g. (40%). IR: 3600, 3000 (broad) (OH), 1630 cm^{-1} (γ-pyrone).

Found: C, 73.03; H, 4.75. Calcd. for $C_{22}H_{16}O_5$: C, 73.33; H, 4.44%.

2',7-Dihydroxy-2-hydroxymethylisoflavone (V).—Powdered anhydrous aluminum chloride (12 g.) was added to a solution of IV (4 g.) in benzene (200 ml.) or in nitrobenzene (100 ml.), and the mixture was treated similarly as described for XVI. The product obtained from the sodium carbonate soluble part was crystallized from dilute ethanol to give V in colorless microcrystals, m. p. 225~226°C (decomp.)*4, identical with the sample kindly sent from Seshadri; yield 3 g. (86%). IR: 3200 (OH), 1630 cm^{-1} (γ-pyrone) (KBr).

Found: C, 67.56; H, 4.35. Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.22%.

2',7-Dihydroxy-2-bromomethylisoflavone (VI).—A mixture of V (2.2 g.), acetic acid (22 ml.) and hydrogen bromide-acetic acid (50%, 33 ml.) was heated gradually to 100°C (20 min.) and kept for 45 min. at the temperature. Ice water was added to the cooled solution, and the crystalline product obtained was washed with water and with ethyl acetate, then was recrystallized from ethanol to give VI in colorless microcrystals, m. p. 221~224°C (decomp.)*5, which gave a positive Beilstein test and was identical with the sample from Seshadri; yield 2.1 g. (82%).

9-Hydroxychromeno[3,4-b]chromone (VII).—Anhydrous potassium carbonate (9 g.) was added to a solution of VI (0.9 g.) in anhydrous acetone (300 ml.), and the mixture was refluxed for 4 hr. and then for further 6 hr. with the addition of more potassium carbonate (9 g.). The solvent was distilled off, and the residue was dissolved in water, filtered and acidified. The crystalline product obtained was recrystallized from ethanol to give VII in colorless needles, m. p. 245~250°C (decomp.), identical with the sample prepared by the Robertson's method; yield 0.7 g. (quantitative).

UV λ_{max}^{EtOH} mμ (log ε): 270 (5.02), 297 (4.55).

9-Hydroxy-8-formylchromeno[3,4-b]chromone (VIII).—A mixture of VII (1.5 g.), hexamine (8 g.) and acetic acid (60 ml.) was heated on a steam-bath for 6 hr. and then for further 10 min. with the addition of hot hydrochloric acid (20%, 27 ml.). The crystalline product obtained from the cooled solution was recrystallized from ethyl acetate to give VIII in slightly yellow colored needles, m. p. 261~262°C, which gave a red ferric chloride reaction; yield 0.7 g. (40%). IR: 1730 (CHO), 1630 cm^{-1} (γ-pyrone).

Found: C, 69.18; H, 3.69. Calcd. for $C_{17}H_{10}O_5$: C, 69.39; H, 3.43%.

Furo[2,3-f]chromeno[3,4-b]chromone-2-carboxylic Acid (X).—Anhydrous potassium carbonate (4 g.) was added to a solution of VIII (0.9 g.) and ethyl bromomalonate (1.2 g.) in anhydrous acetone (130 ml.), and the mixture was refluxed for 8.5 hr. Acetone was distilled off, and the residual product was crystallized from ethanol to give ethyl furo-[2,3-f]chromeno[3,4-b]chromone-2-carboxylate (IX) in slightly brown colored microcrystals, m. p. 225~226°C; yield 0.4 g. (36%).

A mixture of this ester IX (0.4 g.), acetone (115 ml.) and 5% aqueous sodium hydroxide (30 ml.) was refluxed for 3 hr. The resulting mixture was acidified by hydrochloric acid, acetone was distilled off, and the crystaline product was collected and recrystallized from ethanol to give X in orange colored plates, m. p. 300°C (decomp.); yield 0.25 g. (68%). IR: 3500, 3320, 1700 (CO_2H), 1630 cm^{-1} (γ-pyrone).

Found: C, 66.33; H, 3.68. Calcd. for $C_{19}H_{10}O_6 \cdot 1/2\,H_2O$: C, 66.47; H, 3.23%.

2'-Hydroxy-2-hydroxymethylfuro[2,3-f]isoflavone (XII).—Powdered aluminum chloride (1.2 g.) was added to a solution of 2'-methoxy-2-ethoxymethylfuro[2,3-f]isoflavone[9] (XI)*6 (0.4 g.) in nitrobenzene (30 ml.), and the mixture was heated for one hour on a steam-bath. The resulted solution was treated with a little dilute hydrochloric acid, nitrobenzene was removed by steam-distillation, and the residue was extracted with ethyl acetate. The ethyl acetate solution was washed with dilute hydrochloric acid and then extracted with 5% aqueous sodium hydroxide. The precipitates obtained by acidifying the alkaline solution were recrystallized from ethanol to give XII in colorless microcrystals, m. p. 224~225°C; yield 0.2 g. (50%). IR: 3280 (OH), 1630 cm^{-1} (γ-pyrone).

Found: C, 70.32; H, 4.25. Calcd. for $C_{18}H_{12}O_5$: C, 70.12; H, 3.93%.

*4 Melting point was 212~214°C (decomp.) when the temperature was raised slowly.

*5 Melting point was 212~214°C (decomp.) when the temperature was raised slowly.

*6 M. p. 119~120°C; UV λ_{max}^{EtOH} mμ (log ε): 240 (4.98), 307 (4.14); IR: 1640 cm^{-1} (γ-pyrone) (KBr).

2'-Hydroxy-2-bromomethylfuro[2,3-f]isoflavone (XIII).—A mixture of XII (0.15 g.), acetic acid (2 ml.) and hydrogen bromide-acetic acid (50%, 3 ml.) was treated similarly as described for VI. The product was recrystallized from ethyl acetate to give XIII in colorless microcrystals, m.p. 210°C (decomp.), which gave a positive Beilstein test; yield 0.1 g. (60%). IR: 3380, 3190 (OH), 1630 cm^{-1} (γ-pyrone).

Found: C, 58.46; H, 3.06. Calcd. for $C_{18}H_{11}O_4Br$: C, 58.24; H, 2.98%.

Furo[2,3-f]chromeno[3,4-b]chromone (III).—*a) From the Acid X.*—A mixture of X (0.2 g.), copper powder (0.1 g.) and quinoline (10 ml.) was heated on an oil-bath (190~210°C) for 20 min. under nitrogen gas stream with stirring until the evolution of carbon dioxide ceased. The resulting mixture was filtered from copper, quinoline was removed by steam-distillation, and the crystalline product obtained was dissolved in ethyl acetate. The ethyl acetate solution was washed successively with dilute sulfuric acid, aqueous sodium hydroxide and water. The solvent was removed and the residual product was crystallized from ethanol then from ethyl acetate to give III in slightly red colored microcrystals, m.p. 239.5~240°C, identical with the other sample; yield 0.1 g. (70%).

b) From the Furoisoflavone XIII.—Anhydrous potassium carbonate (1.2 g.) was added to a solution of XIII (0.12 g.) in acetone (40 ml.), and the mixture was refluxed for 4 hr. and then for further 4 hr. with the addition of potassium carbonate (1.2 g.). Acetone was removed from the filtered solution, and the residual product was treated with dilute hydrochloric acid. Recrystallization from ethanol then from ethyl acetate furnished III in slightly orange colored microneedles, m.p. 241~242.5°C. UV λ_{max}^{EtOH} $m\mu$ ($\log \varepsilon$): 264 (4.93), 304 (4.48); IR: 1630 cm^{-1} (γ-pyrone).

Found: C, 74.26; H, 3.67; Mol. wt. (Rast), 300. Calcd. for $C_{18}H_{10}O_4$: C, 74.48; H, 3.47%; Mol. wt., 290.

The authors are grateful to Dr. Mitsuru Nakayama for assistance, to the members of the Faculty of Pharmacology of this University for microanalysis and to the members of the Institute of Agricultural Chemistry of Kyoto University for microanalysis and infrared spectroscopy.

Faculty of Literature and Science
Toyama University
Gofuku, Toyama