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The Total Synthesis of (±)-Isoelliptone*1

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The condensation of 2′-hydroxy-4′,5′-dimethoxyfurano[3″,2″ : 6,7]isoflavone with ethyl bromoacetate in the presence of potassium carbonate gave the 2′-phenoxyacetate derivative. The subsequent treatment of this compound with dilute alkali gave isoelliptic acid. By the ring closure of the acid with acetic anhydride and anhydrous sodium acetate, or by the treatment of its ester with sodium methoxide, dehydroisoelliptone was obtained. The reduction of this compound with sodium borohydride, followed by Oppenauer oxidation, yielded isoelliptone, *via* a reduced compound, isoelliptol.

Isoelliptone[1] (erosone)[2] has been isolated, along with some rotenoids (*e.g.*, rotenone and pachyrrhizone), from yam beans (*Pachyrrhizus erosus*). Its chemical structure was shown to be an isomer of elliptone (I)[3] by Norton and Hansberry,[2] and has lately been identified as II on the basis of spectral studies by Ollis *et al.*[1,4] Derrisic acid derivatives are important intermediates in synthesizing some rotenoids (*e.g.*, munduserone,[5] rotenone,[6] deguelin[7] and elliptone[8]). These acids have been prepared from the corresponding phenols and ethyl (2-cyanomethyl-4,5-dimethoxyphenyl)acetate (III) by the Hoesch reaction. The preparation of the acetate III was, however, troublesome and did not give satisfactory results. Recntly, the present author has been reported a convenient method of synthesizing derrisic acid derivatives from the corresponding

*1 A part of this work had been preliminary communicated: *Experientia*, **25**, 789 (1969); presented at the Ube Local Meeting (June, 1969) of the Chemical Society of Japan.

1) W. D. Ollis, "Symposium on Phytochemistry," ed. by H. R. Arthur, Hong Kong Univ. Press, Hong Kong (1964), p. 128.

2) L. B. Norton and R. Hansberry, *J. Amer. Chem. Soc.*, **67**, 1909 (1945).

3) S. H. Harper, *J. Chem. Soc.*, **1939**, 1099, 1424; **1942**, 587, 593.

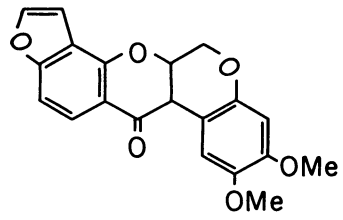
4) R. I. Reed and J. M. Wilson, *ibid.*, **1963**, 5949.

5) J. R. Herbert, W. D. Ollis and R. C. Russell, *Proc. Chem. Soc.*, **1960**, 176.

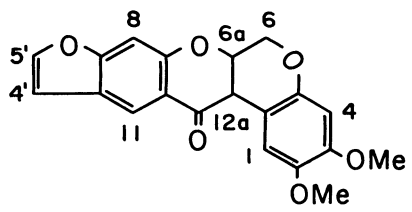
6) M. Miyano, A. Kobayashi and M. Matsui, *Bull. Agr. Chem. Soc. Jap.*, **24**, 540 (1960); **25**, 673 (1961).

7) H. Fukami, J. Oda, G. Sakata and M. Nakajima, *ibid.*, **24**, 327 (1960); **25**, 252 (1961).

8) H. Fukami, G. Sakata and M. Nakajima, *Agr. Biol. Chem.*, **29**, 82 (1965).



I



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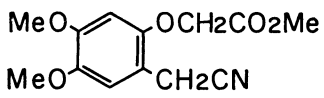
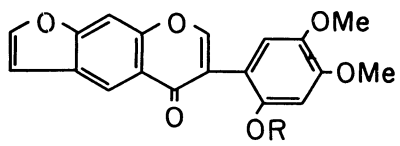
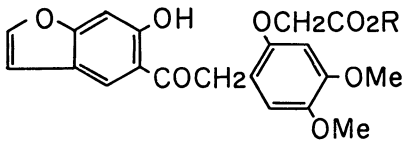


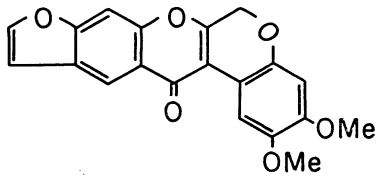
III



IV R=H
V R=CH_2CO_2Et



VI R=H
VII R=Me



VIII

2′-hydroxyisoflavone derivatives.[9,10] The present paper will describe the total syntehsis of (±)-II from 2′-hydroxy-4′,5′-dimethoxyfurano[3″,2″ : 6,7]-isoflavone (IV),[11,12] *via* isoelliptic acid (VI) or its methyl ester (VII).

The reaction of the 2′-hydroxyisoflavone (IV) with ethyl bromoacetate in the presence of anhydrous potassium carbonate in acetone gave a 2′-phenoxyacetate (V), mp 180—181°C, in a good yield. The treatment of V with alcoholic potassium hydroxide afforded an acid (VI), mp 216—217°C, which yielded its methyl ester (VII), mp 134—135°C, when treated with diazomethane in dioxane. The NMR spectrum*[2] of VII indicates the presence of a phenolic group at δ 12.36 ; this group is located at the position *ortho* to the carbonyl group and forms an intramolecular hydrogen bonding. Further, the signals of two methylene groups appear at δ 4.40 and 4.60 (Fig. 1). On the basis of these facts, the structure of VII was identified as 5-ω-(2-methoxycarbonylmethoxy - 4,5 - dimethoxyphenyl)acetyl - 6-hydroxycoumarone. The cyclization of the VI acid with acetic anhydride containing sodium acetate and a trace of acetic acid[13] gave dehydroisoelliptone (VIII), mp 266—268°C, in a poor yield (*ca.* 20%). The treatment of VII with sodium methoxide[14] was, however, found to be a suitable way to prepare it (yield: *ca.* 80%). The NMR spectrum of VIII exhibits the signals of olefinic protons at δ 6.95(1H, q, J=2.0 and 1.0 Hz, $C_{4'}$–H) and 7.77 (1H, d, J= 2.0 Hz, $C_{5'}$–H) due to a disubstituted furan ring. In addition, the signals of methoxyl, methylene, and aromatic protons are observed at δ 3.90_s, 4.00_s (each 3H, $OC\underline{H}_3$) ; 5.07_s (2H, $-C\underline{H}_2O-$); 6.59_s (1H, C_4–H), 7.59_s (1H, C_8–H), and 8.52_s and 8.59_s (each 1H, C_1– and C_{11}–H). According to the method of Miyano and Matsui,[15] VIII was reduced

9) K. Fukui, M. Nakayama and T. Harano, *Experientia*, **23**, 613 (1967).

10) T. Harano, *J. Sci. Hiroshima Univ., Ser. A-II*, **33**, 63 (1969).

11) V. Chandrashkar, M. Krishnamurti and T. R. Seshadri, *Tetrahedron*, **23**, 2505 (1967).

12) K. Fukui, M. Nakayama and T. Harano, This Bulletin, **42**, 199 (1969).

*2 The NMR spectra were measured with a Hitachi R-20 spectrometer, using tetramethylsilane as the internal standard (δ-values in $CDCl_3$); s, singlet; d, doublet; t, triplet; q, quartet.

13) S. Takei, S. Miyajima and M. Ono, *Ber.*, **65**, 1041 (1932).

14) N. Nakatani and M. Matsui, *Agr. Biol. Chem.*, **32**, 769 (1968).

15) M. Miyano and M. Matsui, *Bull. Agr. Chem. Soc. Jap.*, **22**, 128 (1958); *Chem. Ber.*, **91**, 2044 (1959).

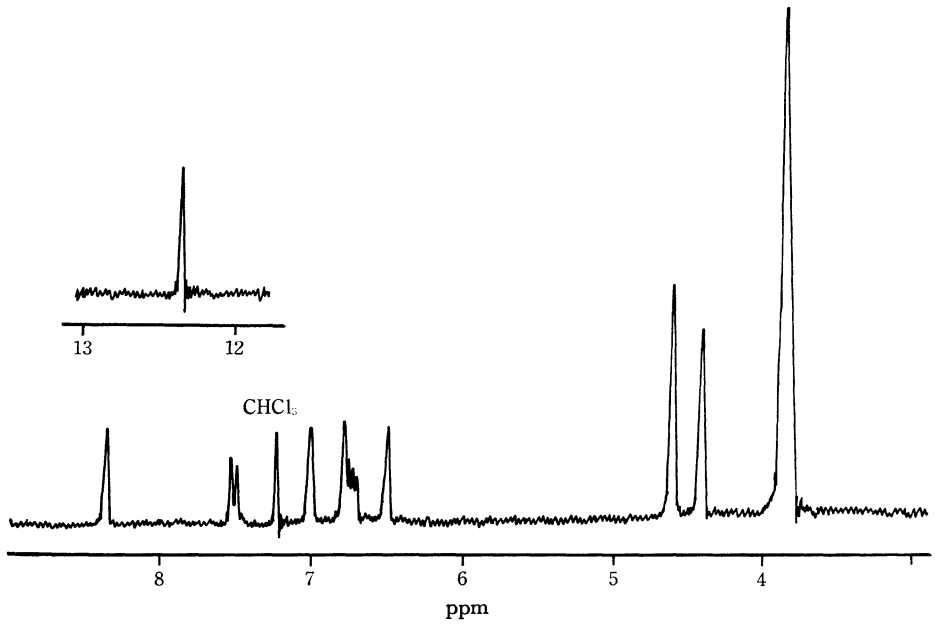


Fig. 1. The NMR spectrum of VII.

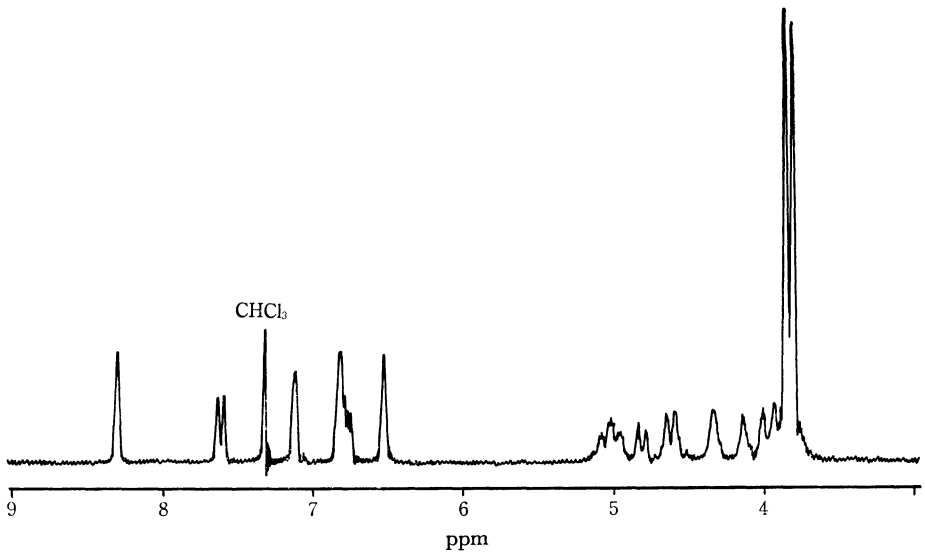


Fig. 2. The NMR spectrum of II.

with sodium borohydride in dioxane, subsequently, without any purification, Oppenauer oxidation gave (±)-isoelliptone (II), mp 215—216°C. The IR spectrum of II shows an absorption of the carbonyl at 1680 cm^{-1}. In the NMR spectrum of II, the signals due to the four protons in the positions 6, 6_a, and 12_a are observed at δ 3.9—5.2 as an ABCD system, and the signal of a proton in the position 1 shows an upper shift at δ 6.83 (Fig. 2).

These data are in accord with those reported by Ollis *et al.*[16] and by Crombie and Lown.[17] Furthermore, in the mass spectrum*3 of II the parent ion peak (M^+) appears at m/e=352 and the fragment ions are observed at 192, 191, 177, 161, 160, 149, 134, 131, 121, and 106. This mass spectrum is identical with that of natural isoelliptone, which has been previously reported by Reed and Wilson.[4]

16) W. D. Ollis, C. A. Rhodes and I. O. Sutherland, *Tetrahedron*, **23**, 4741 (1967).

17) L. Crombie and J. W. Lown, *J. Chem. Soc.*, **1962**, 775.

*3 The mass spectrum was measured by a Hitachi RMU-6E Mass Spectrometer.

Experimental*4

4′, 5′-Dimethoxy-2′-ethoxycarbonylmethoxyfurano[3″,2″: 6,7]isoflavone (V). A mixture of 4′,5′-dimethoxy-2′-hydroxyfurano[3″,2″:6,7]isoflavone (IV) (1.1 g), ethyl bromoacetate (700 mg), and anhydrous potassium carbonate (4.0 g) in acetone (80 m*l*) was refluxed for 24 hr. After the inorganic precipitates had been filtered off, the solvent was condensed to 10 m*l* and the residual solution was diluted with water. The separated solid was collected, washed with water, and then crystallized from ethanol to give V as colorless needless; mp 180—181°C; yield, 1.1 g. IR: 1725, 1653 cm^{-1} (C=O); UV: λ_{max}^{EtOH} mμ (log ε): 237 (4.54) 297 (4.10).

Found: C, 65.02; H, 4.70%. Calcd for $C_{23}H_{20}O_8$: C, 65.09; H, 4.75%.

Isoelliptic Acid (5-ω-(2-Carboxymethoxy-4,5-dimethoxyphenyl)acetyl-6-hydroxycoumarone) (VI). A mixture of V (1.0 g) and a 10% potassium hydroxide solution (40 m*l*) in ethanol (100 m*l*) was refluxed on an oil bath for 2 hr. The solvent was then removed as much as possible and acidified with 10% hydrochloric acid. After the separated solid had been extracted with ethyl acetate, the extract was washed with water and dried on sodium sulfate. The solvent was removed and the residual solid was crystallized from ethanol to give VI as yellow prisms; mp 216—217°C; yield, 800 mg. This substance gave a green color with alcoholic ferric chloride. IR: 3250 (OH), 1730, 1640 cm^{-1} (C=O); UV: λ_{max}^{EtOH} mμ (log ε): 233 (4.56), 278 (4.02), 340 (3.81).

Found: C, 62.04; H, 4.83%. Calcd for $C_{20}H_{18}O_8$: C, 62.17; H, 4.70%.

Methyl Ester (VII) of VI. To a solution of VI (1.0 g) in refreshed dioxane (100 m*l*), the ethereal diazomethane was added; the mixture was then allowed to stand overnight. The solvent was removed under reduced pressure to dryness, and the residue was crystallized from ethanol to give VII as light yellow needles; mp 134—135°C; yield, 950 mg. This substance gave a green color with alcoholic ferric chloride. IR: 1760, 1640 cm^{-1} (C=O); UV: λ_{max}^{EtOH} mμ (log ε): 236 (4.52), 264_i*5 (3.83), 281 (4.03), 334 (3.83). NMR: 383_s (9H), 6.51_s, 6.80_s, 7.01_s, 8.37_s (each 1 H), 6.75_q (1 H, J=2.0 and 1.0 Hz), 7.52_d (1 H, J=2.0 Hz).

Found: C, 62.96; H, 5.20%. Calcd for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04%.

Dehydroisoelliptone (VIII). *a) With Acetic Anhydride-Anhydrous Sodium Acetate.* A mixture of VI (700 mg), acetic anhydride (15 m*l*), anhydrous sodium acetate (450 mg), and acetic acid (0.7 m*l*) was warmed at 120°C for 20 min. After the reaction mixture had been cooled, it was poured into ice water. The separated solid was then collected, washed with water, a large amount of a saturated sodium bicarbonate solution, and water again, and then dried under reduced pressure. The solid was chromatographed on silica gel (*ca.* 10 g) in dichloromethane and crystallized from dichloromethane-ethanol (1: 1 v/v) to give VIII as light yellow microneedles; mp 266—268°C; yield, 200 mg. IR: 1633 cm^{-1} (C=O); UV: λ_{max}^{EtOH} mμ (log ε): 237.5 (4.51), 273 (4.39), 307 (4.30).

Found: C, 68.40; H, 4.09%. Calcd for $C_{20}H_{14}O_6$: C, 68.57; H, 4.03%.

b) With Sodium Methoxide. To a refluxing solution of VII (0.9 g) in anhydrous methanol (90 m*l*), a sodium methoxide solution (prepared from 50 mg of Na and 5 m*l* of anhydrous methanol) was added dropwise for 30 min period. The mixture was refluxed for 3 hr and then allowed to stand overnight. The crystals which had been deposited were dissolved in dichloromethane, passed through a short column of silica gel (*ca.* 10 g), and crystallized from dichloromethane-ethanol (1: 1 v/v) to give VIII as light yellow needles; mp 265—267°C; yield, 750 mg. This compound was identical in all respects with the sample described above a).

Isoelliptone (II). A solution of sodium borohydride (100 mg) in absolute ethanol (10 m*l*) was added to a solution of VIII (200 mg) in dioxane (10 m*l*). The mixture was warmed at 50—60°C for 30 min and then allowed to stand overnight at room temperature. Acetone (20 m*l*) was added to the reaction mixture to decompose the excess reducing agent, and the solvent was removed under reduced pressure to dryness. The residual solid was dissolved in chloroform, washed with water, and dried on calcium chloride. The evaporation of chloroform under reduced pressure furnished crude isoelliptol; without any purification, this product was employed in the next reaction. Aluminum isopropoxide (4.0 g) was added to a solution of the crude isoelliptol in absolute benzene (40 m*l*) and refreshed acetone (30 m*l*), after which the mixture was gently refluxed for 12 hr. The reaction mixture was cooled, diluted with benzene (200 m*l*), washed with diluted sulfuric acid and water, and then dried on calcium chloride. After the solvent had then been removed under reduced pressure to dryness, the solid was chromatographed on silica gel (*ca.* 5 g) in dichloromethane and then crystallized from dichloromethane-ethanol (1: 1 v/v) to give II as colorless needles; mp 215—216°C; yield, 90 mg. IR: 1680 cm^{-1} (C=O); UV: λ_{max}^{EtOH} mμ (log ε): 236 (4.59), 254.5 (4.09), 276 (4.01), 300_s*6 (3.80), 335 (3.55); $\lambda_{max}^{CHCl_3}$ mμ (log ε): 280 (4.03), 344 (3.55). NMR: 3.78_s, 3.82_s (each 3 H), 6.54_s, 6.83_s, 7.12_s, 8.30_s (each 1 H), 6.80_q (1 H, J=2.0 and 1.0 Hz), 7.61_d (1 H, J=2.0 Hz).

Found: C, 68.14; H, 4.73%. Calcd for $C_{20}H_{16}O_6$: C, 68.18; H, 4.58%.

The author wishes to express his deep thanks to Professor Kenji Fukui, Hiroshima University, for his encouragement throughout the course of this work.

*4 All the melting points are uncorrected. The infrared spectra were measured in nujol, while the ultraviolet spectra were measured in an ethanol and a chloroform solution.

*5 i=inflection.

*6 s=shoulder.