Synthesis of Isocoumarins

Part I. (±)-Mellein

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(±)-Mellein (ochracin) was synthesized from 4-bromo-7-methoxy-indanone via 3-methyl-8-hydroxyisocoumarin.

Mellein (I, (–)-3-methyl-8-hydroxy-3,4-dihydroisocoumarin) was first discovered by Nishikawa in 1933 as a metabolite of *Aspergillus melleus*.^{1,2)} In the same year, Yabuta and Sumiki established the identity of mellein with ochracin, a metabolite of *Aspergillus*

ochraceus isolated by them.^{3,4)}

Although (±)-mellein methyl ether (II) has been synthesized by Blair and Newbold,^{5,6)} no direct synthesis of (±)-mellein has been accomplished.

1) H. Nishikawa, *J. Agr. Chem. Soc. Japan*, **9**, 772 (1933).

2) H. Nishikawa, *ibid.*, **9**, 1059 (1933).

3) T. Yabuta and Y. Sumiki, *J. Agr. Chem. Soc. Japan*, **9**, 1264 (1933).

4) T. Yabuta and Y. Sumiki, *ibid.*, **10**, 703 (1954).

5) J. Blair and G. T. Newbold, *Chem. & Ind.*, **1955**, 93.

6) J. Blair and G. T. Newbold, *J. Chem. Soc.*, **1955**, 2871.

This paper describes a synthesis of ($\pm$)-mellein via 3-methyl-8-hydroxyisocoumarin (III) which itself has been obtained as a metabolite of *Marasmius ramealis* and correlated with ($\pm$)-mellein (I).^{7,8)}

4-Bromo-7-methoxyindanone (IV)⁹⁾ was nitrosated to give an α -oximinoketone (V), m.p. 233~236°C. The Beckmann rearrangement followed by alkaline hydrolysis of the oximinoketone (V) yielded 2-carboxy-3-methoxy-6-bromophenylacetic acid (VI), m.p. 183.5~184.5°C, which was debrominated by catalytic hydrogenation to give 2-carboxy-3-methoxyphenylacetic acid (VII), m.p. 165~166°C. The corresponding dimethyl ester (VIII) was partially saponified to give 2-carbomethoxy-3-methoxyphenylacetic acid (IX), m.p. 106~107°C. This half ester was converted into the corresponding acyl chloride (X). Condensation of the acyl chloride (X) with diethyl ethoxymagnesiummalonate followed by acid hydrolysis, decarboxylation and cyclization gave crude 3-methyl-8-methoxyisocoumarin (XI) as an oil. Treatment of the crude oil (XI) by refluxing with hydriodic acid gave needles of 3-methyl-8-hydroxyisocoumarin (III), m.p. 101~102°C. Comparison of the infrared and ultraviolet data of the synthetic material with the published data⁷⁾ proved the identity of our sample with the metabolite. The over-all yield of the isocoumarin (III) from the indanone (IV) was 14%.

An alternate route to the isocoumarin (III) was also investigated. The following procedure may serve as a new general route to 3-methyl-8-methoxyisocoumarins. The homophthalic acid (VII) was refluxed with acetic anhydride in the presence of sodium acetate. The reaction mixture was then diluted with

water while warm. The obtained crystalline product, m.p. 109.5~110.5°C, was assumed to be 3-methyl-8-methoxyisocoumarin (XI) by considering both analytical and spectral data. Refluxing of this substance with hydriodic acid gave 3-methyl-8-hydroxyisocoumarin (III) identified with an authentic sample by mixed melting point and infrared spectrum. This proved the assigned structure (XI) for the substance melting at 109.5~110.5°C. Direct formation of the isocoumarin ring from the homophthalic acid (VII) was thus accomplished. The possible intermediate in this one-step synthesis of the isocoumarin is either XII or XIII.¹⁰⁾ However, no further mechanistic study was attempted.

Conversion of 3-methyl-8-hydroxyisocoumarin (III) to ($\pm$)-mellein (I) was carried out as described by Bendz.⁷⁾ The infrared spectrum of the solution of the synthetic material (I), m.p. 37~38°C, was identical with that of the natural product kindly given us by Dr. N. Takahashi from the collection of Professors T. Yabuta and Y. Sumiki.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra refer to Nujol mulls for solid samples and liquid films for liquid samples.

2-Oximino-4-bromo-7-methoxyindanone (V). To a solution of 4-bromo-7-methoxyindanone (IV, 45.8g) and isoamyl nitrite (69 ml) in 99% ethanol (600 ml) was gradually added concd. hydrochloric acid (8.7 ml). The reaction mixture was kept at 45~50°C for 40 min. The precipitated crystals were collected and recrystallized from ethanol. Yield, 45g (87%). Pale yellow needles, m.p. 233~236°C (dec.). *Anal.* Found: C, 44.72; H, 3.13; N, 5.16. *Calcd.* for $C_{10}H_8O_3NBr$: C, 44.47; H, 2.98; N, 5.19%. $\nu_{\max}$. 3260, 1697, 1630, 1585 cm^{-1} .

2-Carboxy-3-methoxy-6-bromophenylacetic Acid (VI) To a solution of the oximino ketone (V, 23g) in 10% sodium hydroxide (215 ml) was added portionwise

7) G. Benz, *Arkiv. Kemi*, **14**, 511 (1959).

8) G. Bendz, *ibid.*, **15**, 131 (1960).

9) R. A. Barnes, E. R. Kraft and L. Gordon, *J. Am. Chem. Soc.*, **71**, 3523 (1949).

10) Since the acidity of methylene hydrogens of the homophthalic acid (VII) is greater than that of the methyl hydrogens of acetic acid, the intermediate XII seems to be the preferred one.

FIG. Infrared of Natural and Racemic Mellein.

Full line: natural mellein (Chloroform solution)
 Broken line: acemic mellein (Chloroform solution)

p-toluenesulfonyl chloride (27.3g) at 35~40°C with stirring. After the addition the mixture was kept at this temperature for 20 min. Then the temperature was raised to 100°C and sodium hydroxide (38g) was added to the reaction mixture. It was refluxed for 5 hrs., decolorized with charcoal, acidified with concd. hydrochloric acid (100 ml) and extracted with ethyl acetate. The extract was washed with brine, dried and evaporated to give 11.6 g (46.9%) of crystals. Needles from ethyl acetate, m.p. 183.5~184.5°C. *Anal.* Found: C, 42.05; H, 3.38. Calcd. for $C_{10}H_9O_5Br$: C, 41.55; H, 3.14%. $\nu_{\max}$. 3350, 1712, 1590 cm^{-1} .

2-Carboxy-3-methoxyphenylacetic Acid (VII) The bromo acid (VI, 10g) in aqueous sodium hydroxide (5.6g in 100 ml) was hydrogenated over Raney nickel W-7 (5g) at room temperature under atmospheric pressure until the hydrogen uptake ceased. The catalyst was filtered off and the filtrate concentrated and acidified. The precipitated diacid was collected. Further quantities of the product were obtained from the aqueous mother liquor by extraction with ethyl acetate. Yield, 7.1 g (97%). Needles from ethyl acetate, m.p. 165~166°C. *Anal.* Found: C, 57.01; H, 4.91. Calcd. for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80%. $\nu_{\max}$. 1708, 1669, 1595, 1583 cm^{-1} .

Methyl 2-Carbomethoxy-3-methoxyphenylacetate (VIII) The diacid (VII 8g) in ethyl acetate was esterified with ethereal diazomethane to give 8g(88%) of oily diester. This was employed for the next step without further purification.

2-Carbomethoxy-3-methoxyphenylacetic Acid (IX)

The diester (VIII, 8g) in ethanolic potassium hydroxide (3g in 90 ml 99% ethanol) was refluxed for an hour. After removal of the solvent, the residue was dissolved in water (7 ml) and acidified (10 ml cond. hydrochloric acid). The precipitated crystals were collected and the mother liquor was extracted with ethyl acetate. Concentration of the extract gave further amounts of the product. The product was recrystallized from benzene. Yield, 6.0g (80%). Elongated prisms from benzene, m.p. 106~107°C. *Anal.* Found: C, 59.16; H, 5.33. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40% $\nu_{\max}$. 1710, 1590 cm^{-1} . A small amount (0.2g) of 2-carboxy-3-methoxyphenylacetic acid was obtained as benzene insoluble fraction.

2-Carbomethoxy-3-methoxyphenylacetyl chloride (X) A. The half ester (IX, 2g) in purified chloroform (6 ml) was treated with phosphorus trichloride (3 ml). The mixture was kept at room temperature for 18 hrs. The upper chloroform layer was concentrated to yield oily product. Remaining phosphorus trichloride in the oil was removed by repeated addition and evaporation of purified chloroform. Yield, about 2g. This was employed for the next step without further purification. **B.** The half ester (IX, 0.7g) in chloroform (4 ml) was treated with thionyl chloride (2.2 ml) at 40~48°C for 2 hrs. Excess of thionyl chloride and chloroform were removed in vacuo to give an oil (0.7g).

3-Methyl-8-methoxyisocoumarin (XI) A. Ethyl ethoxymagnesiummalonate in ether (10 ml) was prepared from ethyl malonate (1.34g), magnesium (0.22g) and

ethanol (1.6 ml). Ethanol was removed from the mixture by codistillation with dry benzene. The residue was dissolved in dry ether (10 ml). To this solution was added the oily acyl chloride (X, 2g) in ether (10 ml). The mixture was refluxed for 30 min., cooled and treated with dilute sulfuric acid (1:10; 22 ml). The ethereal layer was separated, washed with water, dried and concentrated to give an oil, $\nu_{\max}$. 1732, 1582 cm^{-1} . This was dissolved in acetic acid (7 ml). To this was added concd. hydrochloric acid (5.8 ml) and the mixture refluxed for 6 hrs. After cooling, the mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried and concentrated to give 1.5g (88.3% from the half ester IX) of oil. $\nu_{\max}$. 1720, 1656, 1593, 1564 cm^{-1} . **B.** 2-Carboxy-3-methoxyphenylacetic acid (VII, 4.0g) in acetic anhydride (100 ml) was refluxed for 9 hrs. The solvent was removed in vacuo. The residue was dissolved in acetic anhydride (20 ml) containing sodium acetate (6.5g). The mixture was heated under reflux for 11 hrs. Then water (36 ml) was added while warm and the resulting dark solution decolorized with charcoal. The solution was diluted with water and extracted with ether (100 ml $\times$ 4). Removal of the solvent gave 2.2g of crystals. The product was purified by sublimation (bath temp.: 120~130°C, pressure: 8mmHg) followed by recrystallization from ethanol. Prisms, m.p. 109.5~110.5°C. *Anal.* Found: C, 69.92; H, 5.60. Calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_3$: C, 69.46; H, 5.30%. $\nu_{\max}$. 1723, 1661, 1595, 1565 cm^{-1} . $\lambda_{\max}$. (EtOH) $m\mu$ (log ϵ) 236

(4.43), 255 (4.16) 336 (3.85)

3-Methyl-8-hydroxyisocoumarin (III) Crude oily 3-methyl-8-methoxy-isocoumarin (XI, 1.5g) obtained by the above described procedure A was heated under reflux for 6 hrs. with acetic acid (22 ml) and hydriodic acid (d 1.7; 5.2 ml). The mixture was concentrated in vacuo, diluted with water (100 ml) and extracted with ethyl acetate. The organic layer was separated, washed with water, aqueous sodium thiosulfate and saturated brine. The dried extract was concentrated in vacuo to give 0.8g (58%) of crystals. Needles from methanol, m.p. 101~102°C. *Anal.* Found: C, 68.51; H, 4.69. Calcd. for $\text{C}_{10}\text{H}_8\text{O}_3$: C, 68.18; H, 4.58%. $\nu_{\max}$. 3070, 1680, 1644, 1610, 1568 cm^{-1} . $\lambda_{\max}$. (EtOH) $m\mu$ (log ϵ) 219 (4.45), 227 (4.50), 233 (4.47), 253.5 (4.21), 271 (3.98), 331 (3.88). Infrared and ultraviolet spectra were identical with the published data.⁷⁾ The crystalline isocoumarin (XI, 500 mg) obtained by the procedure B was demethylated as above to give 300 mg of crystals, identical in every respect with the above characterized substance.

($\pm$)-**Mellein (I).** 3-Methyl-8-hydroxyisocoumarin (III) was hydrolyzed with alkali, reduced with sodium borohydride and lactonized by acid to give ($\pm$)-mellein as described by Bendz.⁷⁾ Elongated prisms, m.p. 37~38°C. *Anal.* Found: C, 67.39; H, 5.70. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_3$: C, 67.40; H, 5.66%. Infrared spectrum was recorded in the text. $\nu_{\max}$. (Nujol) 3120, 3060, 1662, 1618, 1580, 810 cm^{-1} (CHCl_3). 3200, 1674, 1620, 1582, 810 cm^{-1} .