Synthesis of Some Isocoumarin Derivatives

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Piericidins A and B, natural insecticides, have been isolated from mycellia of *Streptomyces mobaraensis*.^{1,2)} Later, some other metabolites such as piericidin X, A-, B- and X-substance have been isolated from the same fungus, and A- and B-substance identified³⁾ as 3-methyl-6,7-dimethoxy-8-hydroxyisocoumarin

(Ia) and 3-methyl-7-methoxy-6,8-dihydroxyisocoumarin (reticulol,⁴⁾ Ib), respectively. This paper describes the synthesis of A-substance (Ia), as well as the preparation of some 3-alkoxyisocoumarins.

3-(3',4',5'-Trimethoxyphenyl)-propionic acid (II) was prepared from gallic acid by the

- a $R_1=OH, R_2=R_3=OCH_3$
- b $R_1=R_3=OH, R_2=OCH_3$
- c $R_1=R_2=R_3=OCH_3$
- d $R_1=R_3=OCH_3, R_2=H$
- e $R_1=OH, R_2=H, R_3=OCH_3$
- f $R_1=R_2=R_3=H$

- a $R_1=OCH_3, R_2=R_3=H$
- b $R_1=OCH_3, R_2=H, R_3=Et$
- c $R_1=R_2=H, R_3=Et$
- d $R_1=R_3=H, R_2=CH_3$

- a $R=OCH_3$
- b $R=H$

- a $R_1=OH, R_2=R_3=OCH_3$
- c $R_1=R_2=R_3=OCH_3$
- d $R_1=R_3=OCH_3, R_2=H$
- e $R_1=OH, R_2=H, R_3=OCH_3$
- f $R_1=R_2=R_3=H$

method of Koo⁵¹ with some modifications.* II was converted to 5,6,7-trimethoxy-1-indanone (III) by heating with polyphosphoric acid. According to the method applied to the synthesis of mellein by Matsui *et al.*,⁶¹ III was treated with isoamyl nitrite to give 5,6,7-trimethoxy-2-oximino-1-indanone (IV), mp 189~190°C, which was converted to 2-carboxy-3,4,5-trimethoxyphenylacetic acid (Va), mp 151°C by the Beckmann rearrangement followed by alkali hydrolysis, and then Va was refluxed in acetic anhydride for 2 hr to give 3-methyl-6,7,8-trimethoxyisocoumarin (Ic). A milder reaction condition than that used by Matsui *et al.* is enough for the conversion of Va to Ic. This reaction condition could be used for the synthesis of 3-methylisocoumarin (If) and 3-methyl-6,8-dimethoxyisocoumarin (Id)⁷¹ from the corresponding homophthalic acid derivatives. Hydrolysis of Ic with hydriodic acid yielded 3-methyl-6,7-dimethoxy-8-hydroxyisocoumarin (Ia). This was identical with A-substance isolated from *Streptomyces mobaraensis* in all respects, melting point, IR, NMR and mass spectra. The over-all yield of Ia from II was 53%.

In the course of this synthesis, we found that a half ester of Va (Vb) was converted to 3-ethoxy-6,7,8-trimethoxyisocoumarin (VIa) by refluxing in acetic anhydride. By this method 3-ethoxy-6,8-dimethoxyisocoumarin (VIb) was also prepared.

On heating with 28% ammonia in sealed tube at 100°C, 3-methylisocoumarin derivatives (Ia, c, d, e, f) were transformed into the corresponding 1-hydroxyisoquinoline derivatives (VIIa, c, d, e, f) in good yield.

EXPERIMENTAL

All melting points were uncorrected. IR spectra

were determined with a JASCO IRS-KCl spectrophotometer in nujol mulls for solid samples. NMR spectra were run with JNM-4H 100 spectrometer in CDCl₃ unless otherwise stated and chemical shifts are expressed in τ value. Mass spectra were obtained by RMU-6L equipped with a direct inlet system: electron accelerating voltage, 70 eV; chamber temperature, 200~310°C.

3-(3',4',5'-Trimethoxyphenyl)-propionic acid (II). To the solution of ethyl 3-(3',4',5'-trimethoxyphenyl)-3-oxopropionate (10 g) in toluene (100 ml) were added amalgamated zinc (3 g) and 21% hydrochloric acid (70 ml) and the reaction mixture was refluxed for 48 hr and then extracted with ethyl acetate. Evaporation of the solvent afforded a mixture (5.7 g) of II and its ester, which was hydrolysed with 2 N sodium hydroxide solution at 100°C for 1 hr. The aqueous solution was extracted with ethyl acetate at pH 3. Crude crystals of II obtained by evaporation of the solvent were recrystallized from ethyl acetate-hexane into needles (4.5 g), mp 102~103°C. IR ν cm⁻¹: 1710, 1590, 1510. NMR (in CD₃COCD₃) τ : 7.37 (2H, t), 7.17 (2H, t), 6.31 (3H, s), 6.20 (6H, s), 3.45 (2H, s). MS: M⁺, *m/e* 240.

5,6,7-Trimethoxy-1-indanone (III). 3-(3',4',5'-Trimethoxyphenyl)-propionic acid (II, 4 g) was added to polyphosphoric acid (50 g) and the mixture was heated at 60°C for 1 hr and poured into ice water. The solution was extracted with ether. The solid obtained by evaporation of the solvent was purified through silicic acid column chromatography. Elution with ethyl acetate-benzene (1:99) afforded III (2.9 g), mp 107~108°C. IR ν cm⁻¹: 1685, 1590. NMR τ : 7.50 (2H, t), 7.00 (2H, t), 6.25 (3H, s), 6.07 (6H, s), 3.15 (1H, s). MS: M⁺, *m/e* 222.

5,6,7-Trimethoxy-2-oximino-1-indanone (IV). 5,6,7-Trimethoxy-1-indanone (III, 2.8 g) was nitrosated with isoamyl nitrite (4 ml) in the same way as that described by Matsui *et al.* Crude IV was crystallized into needles (2.7 g), mp 189~190°C. IR ν cm⁻¹: 3240, 1710, 1650, 1590. NMR (in CD₃COCD₃) τ : 7.22 (2H, s), 6.20 (3H, s), 6.02 (6H, s), 3.05 (1H, s), -1.31 (1H, s). MS: M⁺, *m/e* 251.

2-Carboxy-3,4,5-trimethoxyphenylacetic acid (Va). The Beckmann rearrangement followed by alkali hydrolysis was conducted in the same way as that of Matsui *et al.* From IV (0.3 g), Va (0.26 g) was obtained.

* In the process of the preparation of II, reduction of ethyl 3-(3',4',5'-trimethoxyphenyl)-3-oxopropionate with palladium charcoal was unsuccessful in our hand. We used the Clemmensen reduction in this conversion.

Mp 151°C. IR ν cm⁻¹: 2600, 1720, 1685, 1590. MS: M⁺, *m/e* 270.

3-Methyl-6,7,8-trimethoxyisocoumarin (Ic). 2-Carboxy-3,4,5-trimethoxyphenylacetic acid (Va, 0.26 g) was refluxed in acetic anhydride (10 ml) at 130°C for 2 hr and then acetic anhydride was removed *in vacuo*. The resulting residue was dissolved in ethyl acetate and the ethyl acetate solution was washed with sodium bicarbonate solution, dried with anhyd. sodium sulfate and concentrated to give crude crystals of Ic (0.25 g), which was recrystallized from ethyl acetate-hexane into rods, mp 118°C. IR ν cm⁻¹: 1700, 1670, 1600, 1560. NMR τ : 7.80 (3H, s), 6.13 (3H, s), 6.09 (3H, s), 6.05 (1H, s), 3.93 (1H, s), 3.50 (1H, s). MS: M⁺, *m/e* 250. This compound was identical with the methyl ether of A-substance in all respects.

3-Methyl-6,7-dimethoxy-8-hydroxyisocoumarin (Ia). 3-Methyl-6,7,8-trimethoxyisocoumarin (Ic, 50 mg) was heated at 130°C for 2 hr in a solution of acetic acid (0.66 ml) and hydriodic acid (d 1.6, 0.02 ml). The reaction mixture was concentrated *in vacuo* and diluted with water (4 ml) and the aqueous solution was extracted with ethyl acetate. The organic layer was washed with water, 5% aqueous sodium thiosulfate and sat. brine, successively. The solvent was removed *in vacuo* to give crude crystals of Ia (39 mg), which were recrystallized from ethyl acetate-hexane, mp 193°C. IR ν cm⁻¹: 1680, 1640, 1560, 1520. NMR τ : 7.70 (3H, s), 6.10 (3H, s), 6.05 (3H, s), 3.75 (1H, s), 3.60 (1H, s), -1.05 (1H, s). MS: M⁺, *m/e* 236. This compound was identical with A-substance in all respects.

3-Methylisocoumarin (If) and 3-methyl-6,8-dimethoxyisocoumarin (Id). Homophthalic acid or 2-carboxy-3,5-dimethoxyphenylacetic acid⁷¹ (1.5 g) was refluxed in acetic anhydride (15 ml) for 2 hr to yield If (0.57 g) or Id (0.91 g). If: Mp 72°C. IR ν cm⁻¹: 1740, 1670, 1620, 1580. NMR τ : 7.80 (3H, s), 3.90 (1H, s), 2.73~2.40 (3H, m), 1.91 (1H, d). MS: M⁺, *m/e* 160. Id: Mp 157~158°C. IR ν cm⁻¹: 1715, 1670, 1605, 1570. NMR τ : 7.75 (3H, s), 6.08 (3H, s), 6.02 (3H, s), 3.92 (1H, s), 3.70 (1H, d), 3.60 (1H, d). MS: M⁺, *m/e* 220.

3-Methyl-6-methoxy-8-hydroxyisocoumarin (Ie). 3-Methyl-6,8-dimethoxyisocoumarin (Id, 0.5 g) was hydrolysed with hydriodic acid to give (Ie, 0.45 g) in the same condition as in the hydrolysis of Ic. Mp

155°C. IR ν cm⁻¹: 1695, 1655, 1580, 1530. NMR (in CD₃COCD₃) τ : 7.78 (3H, s), 6.14 (3H, s), 3.66 (1H, s), 3.62 (2H, s), -1.10 (1H, s). MS: M⁺, *m/e* 206.

3-Ethoxy-6,8-dimethoxyisocoumarin (VIb). 2-Carboxy-3,5-dimethoxyphenylacetic acid (0.1 g) was dissolved in abs. ethanol (2 ml) and a few drop of conc. sulfuric acid was added to it. The solution was refluxed for 30 min and water (50 ml) was added. The aqueous solution was extracted with ethyl acetate. Evaporation of the solvent afforded the half ester (Vc, 50 mg), mp 111°C. IR ν cm⁻¹: 1735, 1660, 1605, 1570. NMR τ : 8.72 (3H, t), 6.15 (3H, s), 6.05 (2H, s), 6.02 (3H, s), 5.83 (2H, q), 3.52 (2H, d). MS: M⁺, *m/e* 268. This structure was confirmed by the comparison of its IR spectra with that of Vd⁷¹ which was obtained by alkali hydrolysis of the dimethyl ester. The half ester (Vc, 50 mg) was refluxed in acetic anhydride for 2 hr. After acetic anhydride was removed *in vacuo*, water was added and the aqueous solution was extracted with ethyl acetate. Evaporation of the solvent afforded VIb (48 mg), mp 114°C. IR ν cm⁻¹: 1725, 1645, 1600, 1560. NMR τ : 8.75 (3H, t), 6.17 (3H, s), 6.04 (3H, s), 5.85 (2H, q), 3.55 (2H, s). MS: M⁺, *m/e* 250.

3-Ethoxy-6,7,8-trimethoxyisocoumarin (VIa). 2-Carboxy-3,4,5-trimethoxyphenylacetic acid (Va, 1 g) was converted to the half ester (Vb), which was treated with acetic anhydride to give VIa (0.3 g). Vb: Mp 91°C. IR ν cm⁻¹: 1735, 1675, 1590, 1570. NMR τ : 8.72 (3H, t), 6.12 (3H, s), 6.07 (3H, s), 6.05 (2H, s), 5.95 (3H, s), 5.85 (2H, q). MS: M⁺, *m/e* 298. VIa: Mp 82°C. IR ν cm⁻¹: 1730, 1650, 1590, 1545. NMR (in CD₃COCD₃) τ : 8.61 (3H, t), 6.21 (3H, s), 6.11 (3H, s), 6.05 (3H, s), 5.90 (2H, q), 4.32 (1H, s). MS: M⁺, *m/e* 280.

Preparation of 1-hydroxyisoquinoline derivatives. 3-Methylisocoumarin derivatives (Ia, c, d, e, f) was dissolved in 28% ammonia (50 ml) and the solution was heated in a sealed tube at 100°C for 5 hr. The cooled solution was extracted with ethyl acetate. Evaporation of the solvent afforded 3-methyl-1-hydroxyisoquinoline derivatives (VIIa, c, d, e, f) in 90% yield. VIIa: Mp 225°C. IR ν cm⁻¹: 1660, 1620, 1530. NMR τ : 7.68 (3H, s), 6.08 (6H, s), 3.78 (1H, s), 3.65 (1H, s), -1.24 (1H, s), -2.51 (1H, s). MS: M⁺, *m/e* 235. VIIc: Mp 230°C. IR ν cm⁻¹: 1670, 1635, 1560, 1520. NMR τ : 7.68 (3H, s), 6.08 (9H, s), 3.80 (1H, s), 3.65 (1H, s), -1.50 (1H, s).

MS: M^+ , m/e 249. VIIId: Mp 229°C. IR ν cm^{-1} : 1640, 1610, 1560. NMR τ : 7.70 (3H, s), 6.18 (3H, s), 6.10 (3H, s), 3.92 (1H, s), 3.68 (2H, s), -1.10 (1H, s). MS: M^+ , m/e 219. VIIe: Mp 228°C. IR ν cm^{-1} : 1650, 1620, 1550. NMR: (in $\text{C}_5\text{D}_5\text{N}$) τ : 7.77 (3H, s), 6.25 (3H, s), 3.77 (1H, s), 3.47 (1H, d), 3.28 (1H, d), -2.70 (1H, s), -4.00 (1H, s). MS: M^+ , m/e 205. VIIIf: Mp 210°C. IR ν cm^{-1} : 1660, 1640, 1600, 1550. NMR τ : 7.61 (3H, s), 3.72 (1H, s), 2.67 (1H, s), 2.57 (1H, s), 2.47 (1H, d), 1.67 (1H, d), -1.73 (1H, s). MS: M^+ , m/e 159.

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