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SYNTHESIS UTILIZING β-CARBONYL SYSTEM—II[1,2]

TOTAL SYNTHESIS OF (±)-ELAEOCARPINE AND (±)-ISOELAEOCARPINE

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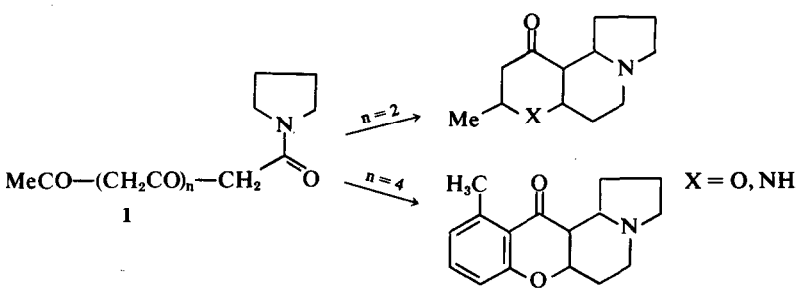
Abstract—Total synthesis of (±)-elaeocarpine (**2a**) and (±)-isoelaeocarpine (**2b**), the main constituents of elaeocarpus alkaloids, was accomplished by the use of the intermediate having a β-carbonyl system.

Johns *et al.* have recently isolated nineteen new alkaloids which are collectively named "Elaeocarpus alkaloids" from the plants of Elaeocarpus species (family Elaeocarpaceae) grown in New Guinea and have elucidated all of their structures.[3] One of the striking features of the elaeocarpus alkaloids is their biogenetic pathway.† It is plausible to speculate that a β-polyketomethylene system combined with a nitrogen donor plays an important role in the formation of these alkaloids and the framework of individual alkaloid produced is controlled by the length of the ketomethylene "C_2-units" involving in the tentative precursor depicted as a general formula (**1**) in Scheme 1.



SCHEME 1

We now wish to present the total synthesis of (±)-elaeocarpine (**2a**) and (±)-isoelaeocarpine (**2b**) utilizing the intermediate having a β-tricarbonyl system.

In 1964, we prepared 6-salicyloyl-cyclohexan-1,3-dione (**3**) by the condensation of the dianion of cyclohexan-1,3-dione and sodium methyl salicylate according to Hauser's procedure.[4] Although ring-chain tautomerism[5] was suggested between **3a** and **3b** in this compound, only the ring form (**3b**) was found to exist both in the solid state and in neutral solution on the basis of the spectral data. Since the compound (**3b**) is susceptible to dehydration to give the dihydroxanthone derivative (**4**), this reaction may be applicable to the synthesis of elaeocarpus alkaloids and the selective hydrogenation of the double bond formed at this point would cause the production of two stereoisomers corresponding to the $C_{6a} \sim C_{12a}$ relationship between elaeocarpine and isoelaeocarpine by one effort.

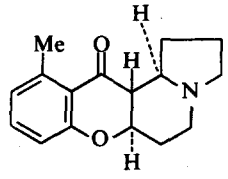
With these considerations in hand, we commenced first to connect a phenacyl and a pyrrolidinyl or pyrrolyl moieties.

The 1,3-dithiane derivative (**7**) was first prepared from 1-benzyloxycarbonyl-2-pyrrolidinemethanol (**5**) by oxidation with dicyclohexylcarbodiimide-pyridine-trifluoroacetic acid-dimethyl sulfoxide[6] followed by thioketalisation of the resultant aldehyde (**6**) in the presence of boron trifluoride-acetic acid in chloroform. Attempts to condense the anion of the thiane (**7**)[7] with 2-methoxy-6-methyl-benzoyl chloride[8] failed presumably because of the steric repulsion by the bulky substituents on both sides of each reaction center. In order to avoid this serious disadvantage the following Sörm modification was investigated. Benzoic acid was converted to the diazoketone (**10a**) via the acid chloride and this was allowed to react with excessive pyrrole at 50–60° in the presence of catalytic amount of

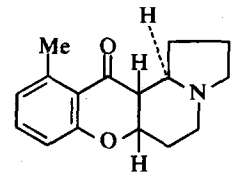
†Elaeocarpidine, an indole alkaloid, is the only exception in this discussion.

copper powder, giving the expected pyrrolylmethyl ketone (**11a**) in 30% yield. By use of the same procedure, several diazoketones (**10**) having substituents on the benzene ring were condensed with pyrrole or 1-(2-ethoxycarbonylethyl)-pyrrole effectively.[9] The structures of these pyrrole derivatives were proved by their NMR spectra which exhibited the presence of the methylene protons adjacent to the CO group at 5·64–5·89 τ (singlet) and the disappearance of one α-proton at the pyrrole ring around 3·30 τ, and by their IR spectra which showed a CO absorption around 1670–1690 cm^{-1}.

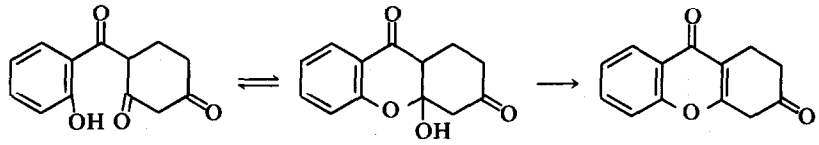
Dieckmann condensation of the ketone (**11c**) in boiling benzene using sodium hydride afforded the indolizinone (**12**) in the expected fashion. In con-



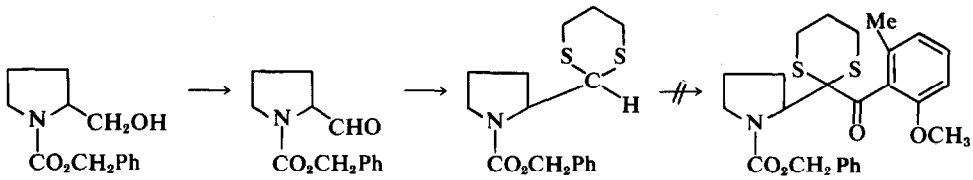
2a



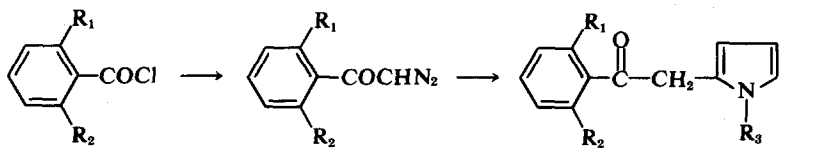
2b



3a **3b** **4**



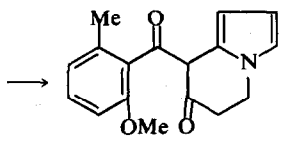
5 **6** **7** **8**



9a: $R_1 = R_2 = H$
9b: R_1 = Me, R_2 = OMe

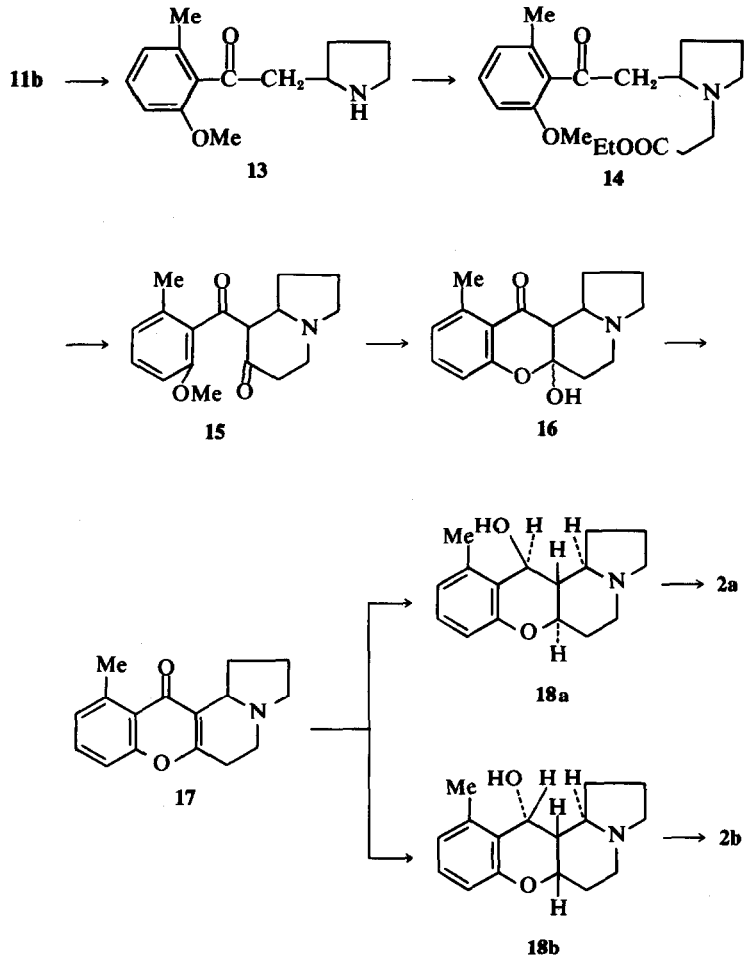
10

11a: $R_1 = R_2 = R_3 = H$
11b: R_1 = Me, R_2 = OMe, $R_3 = H$
11c: R_1 = Me, R_2 = OMe, $R_3 = CH_2—CH_2—CO_2Et$



12

SCHEME 2



SCHEME 2 (cont.)

formity with the structure, this compound showed a characteristic IR band around 1610–1589 cm^{-1} due to the conjugated chelation of β-dicarbonyl system. Nevertheless, attempt to cleave the OMe group at this stage was fruitless because of the unstability of the pyrrole ring towards acidic reagents. Catalytic hydrogenation of **12** to obtain the pyrrolidine ring also failed owing to the production of various hydrogenated compounds.

On the contrary, the pyrrole derivative (**11b**) was readily converted to the pyrrolidinylmethyl ketone (**13**) by catalytic hydrogenation over platinum oxide in 78% yield. Marked unreactivity of the CO group in **13** may be ascribable again to the difficulty of the catalyst surface to approach the CO function hindered by the neighboring bulky groups. Ethyl acrylate was then added to **13** in refluxing acetonitrile, yielding the aminoester (**14**) as a colorless oil in 81% yield. This ester was submitted to the Dieckmann condensation,[10] furnishing, after chromatographic separation using silica gel, the indolizidinone (**15**). The structure of this compound was followed by the IR spectrum which showed a Bohlmann's band at 2780 cm^{-1} and by its positive ferric reaction. When boron tribromide was added to **15** in dichloromethane at room temperature, fission of the OMe group took place accompanied with spontaneous ring closure, yielding the chromanone derivative (**16**)[11] in 52% yield. Although the configuration of the OH group at C_{6a} was not certain, **16** was further treated with boiling methanolic hydrochloric acid to afford the chromone (**17**) expectedly.

Since the attempts to reduce the $C_{6a} \sim C_{12a}$ double bond of **17** was unsuccessful, efforts were now made to obtain the saturated alcohol (**18**) as a preliminary step. Sodium borohydride reduction of **17** in refluxing ethanol gave, after chromatographic purification, two isomeric alcohols in a ratio of about 7 : 1.[12]

Opportunely, the Australian workers have obtained all of four possible stereoisomeric alcohols

concerning C_{3a}, C_{12} and C_{12a} from elaeocarpine and isoelaeocarpine by reduction with sodium borohydride or subsequent epimerisation with aqueous hydrochloric acid.[3a]

The NMR spectral comparison indicated our major (C_{12}-H, 7·74τ, d, J = 6·5 Hz.) and minor (C_{12}-H, 5·38τ, d, J = 7·4 Hz) products were ascribable to the authentic alcohols (**18b** and **18a**), respectively.

Finally, the alcohol (**18a**) was oxidized with chromium trioxide in acetic acid at room temperature to give **2a**, m.p. 81–82° identical in all respects with the natural product. By use of the same procedure, the alcohol (**18b**) was led to the compound of m.p. 75–76°, the IR spectrum of which coincided completely with that of natural isoelaeocarpine.

Incidentally, some differences on the m.ps of isoelaeocarpine and its reduction product (**18b**) were pointed out between natural and synthetic series. This discrepancy may be due to the fact that the natural product was not completely racemic.[3a]

EXPERIMENTAL

M.ps are uncorrected. The IR spectra were recorded with a JASCO IR-E spectrometer. The UV spectra were determined using a Hitachi EPS-2U spectrometer. The NMR spectra were obtained with a JEOL JNM-MH-60 spectrometer with TMS as the internal standard. The mass spectra were measured with a Hitachi RMS-4 spectrometer.

1-Benzyloxycarbonyl-2-formylpyrrolidine (**6**). To a mixture of 1-benzyloxycarbonyl-2-pyrrolidinemethanol (30·6 g), DMSO (163 ml), benzene (195 ml), pyridine (10·4 ml) and trifluoroacetic acid (5·20 ml), was added dicyclohexylcarbodiimide (80·7 g) gradually. After stirring at room temp for 16 hr, the mixture was treated with 10% HCl and the separated N,N'-dicyclohexyl urea was filtered off. The filtrate was diluted with H_2O, extracted with C_6H_6, washed with H_2O and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a brown oil which was purified by column chromatography on silica gel with Et_2O to afford **6** (23·5 g, 77·5%) as a pale yellow oil; IR (liquid) cm^{-1}: 1722, 1685.

1-Benzyloxycarbonyl-2-(1,3-dithian-2-yl) pyrrolidine (**7**). A mixture of **6** (22·5 g), propane-1,3-dithiol (13·7 g), catalytic amount of BF_3-etherate and glacial AcOH in $CHCl_3$ (500 ml) was heated under reflux for 17 hr. After being cooled, the mixture was washed with H_2O, with 1% NaOH aq and dried (Na_2SO_4). The residue obtained by evaporation of the solvent was distilled under reduced pressure to give **7** (21·3 g, 65·1%) as a pale yellow oil, b.p. 189–200° (0·2 mm); IR (liquid) cm^{-1}: 1685; NMR ($CDCl_3$)τ: 2·64 (s, 5H), 4·85 (s, 2H). (Found: C, 59·22; H, 6·64; N, 4·32; S, 19·74. Calcd. for $C_{16}H_{21}NO_2$: C, 59·49; H, 6·54; N, 4·64; S, 19·80%).

Condensation of Diazoketones **10** *and pyrroles.* A typical condensation was carried out as follows. To the diazoketone (**10b**) prepared from 2-methoxy-6-methylbenzoyl chloride (43·0 g) and excessive diazomethane (about 4 molar equivs) in Et_2O were added pyrrole (1·10 g) and Cu powder (1·0 g), and the whole was heated at 60° for 2·5 hr. After the brisk evolution of N_2 gas ceased, the mixture was filtered and the filtrate was evaporated *in vacuo* to give a brown oil. This was chromatographed on silica gel using n-hexane-Et_2O (2 : 1).

A fraction which showed a single spot by TLC check [silica gel plate, Et_2O-n-hexane (2 : 1)] was evaporated to give a solid. Recrystallization from isopropyl ether gave **11b** (17·9 g, 33%) as colorless needles, m.p. 91–92°; IR (nujol) cm^{-1}: 3350, 1697; NMR ($CDCl_3$)τ: 5·88 (s, 2H), 6·15 (s, 3H), 7·91 (s, 3H), 3·23 (m, 1H), 3·82 (m, 1H), 3·97 (m, 1H). (Found: C, 73·49; H, 6·59; N, 6·02. Calcd. for $C_{14}H_{15}NO_2$: C, 73·34; H, 6·59; N, 6·11%.)

By use of the same procedure, **11a** was obtained from **10a** and pyrrole as colorless plates (30% yield), m.p. 137°; IR (nujol) cm^{-1}: 3300, 1661; NMR ($CDCl_3$)τ: 3·17 (m, 1H), 3·82 (m, 2H), 5·64 (s, 2H). (Found: C, 77·92; H, 5·84; N, 7·65. Calcd. for $C_{12}H_{11}NO$: C, 77·81; H, 5·99; N, 7·56%.)

Similarly, **11c** was obtained from **10b** and 2-ethoxycarbonylethyl pyrrole as a pale yellow oil (13% yield); IR (liquid) cm^{-1}: 1719, 1690; NMR ($CDCl_3$)τ: 3·33 (m, 1H), 3·91 (m, 1H), 4·10 (m, 1H), 5·89 (s, 2H), 5·85 (t, 2H, J = 7·5 Hz), 5·85 (q, 2H, J = 7 Hz), 6·16 (s, 3H), 7·93 (s, 3H), 8·77 (t, 3H, J = 7 Hz).

8-(2-Methoxy-6-methylbenzoyl)-5,6-dihydro-7(8H)-indolizinone **12**. A soln of **11c** (1·05 g) in anhyd C_6H_6 (10 ml) was added to a suspension of NaH (63% oil dispersion, 0·26 g) in C_6H_6 (30 ml) and the mixture was refluxed under N_2 gas for 5 hr. After being cooled, the mixture was neutralized with AcOH, washed with H_2O and dried (Na_2SO_4). Removal of the solvent left an oil, which was chromatographed on silica gel plates using Et_2O-n-hexane (1 : 1) to afford a solid **12** (0·29 g, 16·6%). Recrystallization from Et_2O-n-hexane have pale yellow prisms, m.p. 83–84°; IR (nujol) cm^{-1}: 1610, 1580; NMR ($CDCl_3$)τ: 3·53 (m, 1H), 4·15 (m, 1H), 5·23 (m, 1H), 5·89 (t, 2H, J = 7 Hz), 6·30 (s, 3H), 7·10 (t, 2H, J = 7 Hz), 7·84 (s, 3H). (Found: C, 72·00; H, 6·34; N, 4·91. Calcd. for $C_{17}H_{17}NO_3$: C, 72·06; H, 6·05; N, 4·94%.)

2-Methoxy-6-methylphenyl pyrrolidin-2-ylmethyl ketone (**13**). A soln of **11b** (5·60 g) in glacial AcOH (56 ml) was shaken with H_2 at room temp and atm pressure in presence of PtO_2 (0·2 g). About 1·2 moles H_2 was absorbed during 7 hr and the absorption stopped. The catalyst was removed and the solvent was evaporated *in vacuo*. The residue was dissolved in 10% HCl aq and the water layer, after shaking with C_6H_6 once, was made alkaline with $NaHCO_3$. The separated oil was taken up in $CHCl_3$, washed with H_2O, worked up in the usual way and the oil was chromatographed on silica gel using a mixture of $CHCl_3$–MeOH (3 : 1). The main fraction showed a single spot by TLC check gave **13** (4·37 g, 78%) as a colorless oil; IR (liquid) cm^{-1}: 3280, 1680; NMR ($CDCl_3$)τ: 6·18 (s, 3H), 7·77 (s, 2H). The hydrochloride, m.p. 172–175° (MeOH–Et_2O). (Found: C, 62·15; H, 7·19; Cl, 13·24; N, 5·05. Calcd. for $C_{14}H_{20}ClNO_2$: C, 62·33; H, 7·47; Cl, 13·14; N, 5·19%.)

2-Methoxy-6-methylphenyl 1-(2-ethoxycarbonylethyl)-pyrrolidin-2-yl ketone (**14**). A soln of **13** (2·75 g) and ethyl acrylate (2·00 g) in MeCN (50 ml) was refluxed for 8 hr and then the solvent was evaporated under reduced pressure. The residue was dissolved in AcOEt and the soln was passed through a chromato-column packed with silica gel. The eluent gave **14** (3·19 g, 81·17%) as a colorless oil; IR (liquid) cm^{-1}: 1720, 1680; NMR ($CDCl_3$)τ: 5·86 (q, 2H, J = 7 Hz), 6·18 (s, 3H), 7·77 (s, 3H), 8·75 (t, 3H, J = 7 Hz); mass spectrum = *m/e* 333 (M^+).

8-(2-*Methoxy*-6-*methylbenzoyl*)7-*indolizidionone* (**15**). To a stirred suspension of NaH (63% oil dispersion, 0·137 g) in dry toluene (10 ml) was added under N_2 a soln of **14** (0·5 g) in dry toluene (10 ml), and the whole was boiled under reflux for 11 hr. After being cooled, the mixture was neutralized with glacial AcOH and the resulting soln was washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent gave an oil, which was purified by means of column chromatography on silica gel using $CHCl_3$–MeOH (9 : 1) to afford **15** (0·27 g, 62·6%) as a pale yellow oil; IR (liquid) cm^{-1}: 1700–1600 (conjugated chelation of β-diketones) NMR ($CDCl_3$)τ: 7·75 (br, s, 3H), 6·20 (s, 3H); mass spectrum = *m/e* 287 (M^+). The picrate; m.p. 181–183° (MeOH). (Found: C, 53·47; H, 4·56; N, 10·69. Calcd. for $C_{23}H_{24}N_4O_{10}$: C, 53·49; H, 4·68; N, 10·85%).

1,2,3,5,6,6a,12a,12b-*Octahydro*-6a-*hydroxy*-11-*methyl*-12H-[1]*benzopyrano*[2,3-g]*indolizin*-12-*one* (**16**). To a stirred soln of **15** (3·85 g) in dichloromethane (150 ml) placed in an ice bath was added BBr_3 (7 ml) and the mixture was allowed to stand at room temp for 3 days. The mixture was poured on ice-water and made alkaline with $NaHCO_3$. The organic layer was worked up in the usual way and the residue was recrystallized from Et_2O to give **16** (1·90 g, 51·9%) as colorless prisms, m.p. 139–140·5°; IR (nujol) cm^{-1}: 3410, 1660; NMR ($CDCl_3$)τ: 7·38 (s, 3H); UV λ_{max}^{EtOH} mμ (ε): 256 (6600), 316 (2200); mass spectrum = *m/e* 273 (M^+). (Found: C, 70·46; H, 6·82; N, 4·90. Calcd. for $C_{16}H_{19}NO_3$: C, 70·31; H, 7·01; N, 5·31%.)

1,2,3,5,6,12b-*Hexahydro*-11-*methyl*-12H-[1]*benzopyrano*[2,3-g]*indolizin*-12-*one* (**17**). A soln of **16** (1·08 g) and 40% methanolic HCl (50 ml) was refluxed for 3 hr. After evaporating the solvent *in vacuo*, the residue was dissolved in water (50 ml). The water layer, after treating with decolorizing carbon, made alkaline with $NaHCO_3$ and the separated oil was worked up in the usual way. Removal of the solvent left a solid which was recrystallized from Me_2CO to yield **17** (0·86 g, 87·1%) as colorless plates, m.p. 102–103°; IR (nujol) cm^{-1}: 2800, 1630; NMR ($CDCl_3$)τ: 7·14 (s, 3H); UV λ_{max}^{EtOH} mμ (ε): 230 (49000), 308 (12000); mass spectrum = *m/e* 255 (M^+). (Found: C, 75·09; H, 6·60; N, 5·28. Calcd. for $C_{16}H_{17}NO_2$: C, 75·27; H, 6·71; N, 5·49%).

Sodium borohydride reduction of **17**. A soln of **17** (0·54 g) and $NaBH_4$ (1·1 g) in EtOH (30 ml) was refluxed for 8 hr with the addition of an equal amount of $NaBH_4$ in the middle of the reaction time. After evaporating the EtOH, H_2O (30 ml) was added to the residue, and the soln was taken up in $CHCl_3$. Removal of the solvent left an oil, which was purified by column chromatographic separation over alumina using Et_2O-n-hexane. From the first eluate, (±) **18a** was obtained (0·03 g, 5·6%) as colorless prisms, m.p. 192–193° (Et_2O); IR (nujol) cm^{-1}; 3130, 2740; NMR ($CDCl_3$)τ: 7·60 (s, 3H), 5·83 (d, 1H, J = 7·5 Hz); mass spectrum = *m/e* 259 (M^+). (Found: C, 73·56; H, 8·05; N, 5·14. Calcd. for $C_{16}H_{21}NO_2$: C, 74·10; H, 8·16; N, 5·40%). The second eluate gave (±) **18b** (0·22 g, 40·7%) as colorless prisms, m.p. 168–169° (Et_2O); IR (nujol) cm^{-1}: 3130, 2740; NMR ($CDCl_3$)τ: 7·55 (s, 3H), 4·78 (d, 1H, J = 6·5 Hz). (Found: C, 73·89; H, 8·11; N, 5·27. Calcd. for $C_{16}H_{21}NO_2$: C, 74·10; H, 8·16; N, 5·40%).

(±)-*Isoelaeocarpine* (**2b**). To a stirred soln of **18b** (0·17 g) in AcOH (10 ml), a soln of CrO_3 (0·30 g) in AcOH (40 ml) was added dropwise at room temp. After stirring for 3 hr, MeOH (3 ml) was added to the mixture to destroy excess CrO_3 and then the solvent was evaporated *in vacuo*. The residue was made alkaline with $NaHCO_3$ and the resulting mixture was extracted with $CHCl_3$ 3 times. The combined organic layer was worked up in the usual way and the resulting solid was recrystallized from n-pentane giving **2b** (0·092 g, 54·1%) as colorless prisms, m.p. 75–76°. (Found: C, 74·96; H, 7·54; N, 5·45. Calcd. for $C_{16}H_{19}NO_2$: C, 74·68; H, 7·44; N, 5·44%). The IR spectrum measured in $CHCl_3$ soln and the R_f value on the TLC (silica gel plates, Et_2O-MeOH in 9 : 1) of this compound were coincided with those of the natural product.

(±)-*Elaeocarpine* (**2a**). By use of the same procedure described above, **18a** was converted to **2a**. This compound was obtained as colorless prisms, m.p. 81·5–82° (n-pentane) and was identified with the natural product by their IR spectra and the TLC comparison.

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