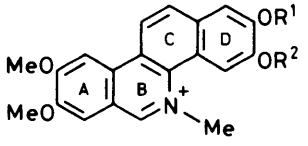
Studies on the Chemical Constituents of Rutaceous Plants. Part 62. Efficient Synthesis of Fagaronine, a Phenolic Benzo[*c*]phenanthridine Alkaloid[1] with Antileukaemic Activity

Hisashi Ishii,* Ih-Sheng Chen, and Tsutomu Ishikawa
Faculty of Pharmaceutical Sciences, Chiba University, 1—33, Yayoi-cho, Chiba, 260, Japan

Fagaronine (**2**), an antileukaemic hydroxybenzo[*c*]phenanthridine alkaloid, has been synthesized from the chalcone (**4a**) according to the synthetic sequence (Schemes 1–4). During the synthesis, the hydroxy group was protected in the form of its isopropoxy derivative.

It is well known that fully aromatised quaternary benzo[*c*]-phenanthridine alkaloids[2] occur naturally in Rutaceous and Papaveraceous plants. These alkaloids, particularly nitidine[3b] (1), a non-phenolic base, and fagaronine [3c,4] (**2**), a phenolic one, have attracted attention because of their antileukaemic properties.[3]

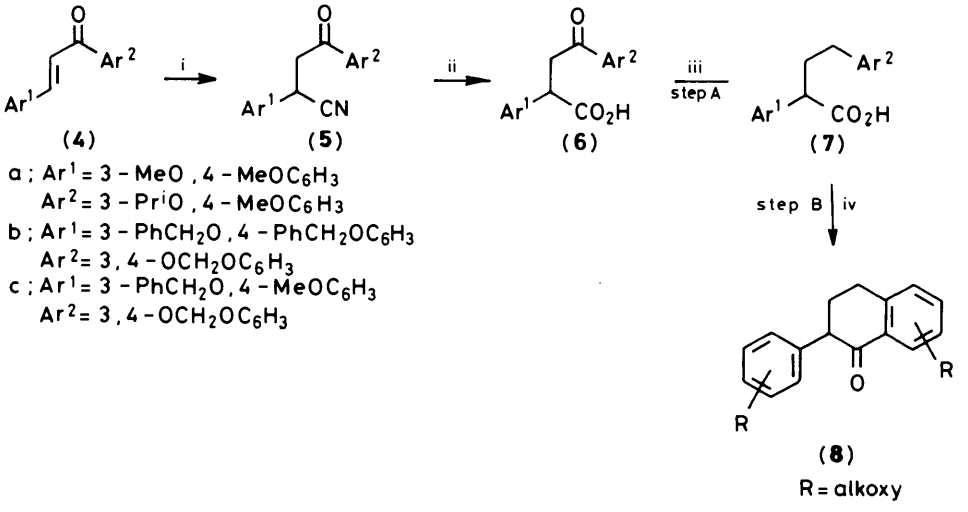


(**1**) $R^1, R^2 = CH_2$
(**2**) $R^1 = H, R^2 = Me$
(**3**) $R^1 = Pr^i, R^2 = Me$

In the previous papers,[5] we reported a versatile method for the synthesis of non-phenolic benzo[*c*]phenanthridine alkaloids from chalcones (**4**) *via* 2-aryl-1-tetralone derivatives (**8**) shown in Schemes 1—4. Ten alkaloids [5c,d] including six naturally occurring ones were synthesized by this method and the antitumour activities [5d] of these alkaloids against Sarcoma 180 were tested, their structure-activity relationships being discussed. However, it appears that our sequence was unsuitable for the synthesis of phenolic alkaloids, because the common groups used for protection of phenolic functions, such as benzyl or methoxymethyl groups, would be removed during hydrogenolysis of 2,4-bisaryl-4-oxobutyric acid (the oxo acid) (**6**) to 2,4-bisarylbutyric acid (the methylene acid) (**7**) (step A) or during the intramolecular acylation of the resulting methylene acid (**7**) with phosphorus oxychloride in chloroform to the tetralone (**8**) (step B). All trials [5b] to find conditions under which debenzylation would not occur during hydrogenolysis failed. The subsequent intramolecular Friedel-Crafts cyclisation of the benzyloxymethylene acids [5b] (**7b** and **7c**), which were prepared by re-benzylation of the hydrogenolysed products, to the tetralone derivatives was also unsuccessful. The situation challenged us to synthesize fagaronine (**2**) and other phenolic benzo[*c*]phenanthridine alkaloids. In a preliminary paper,[6] we reported the synthesis of fagaronine (**2**) *via* a synthetic sequence using an isopropoxy group, which was developed as a protecting group by Sargent and co-workers.[7] Here, we give full details of the experiments on this work.

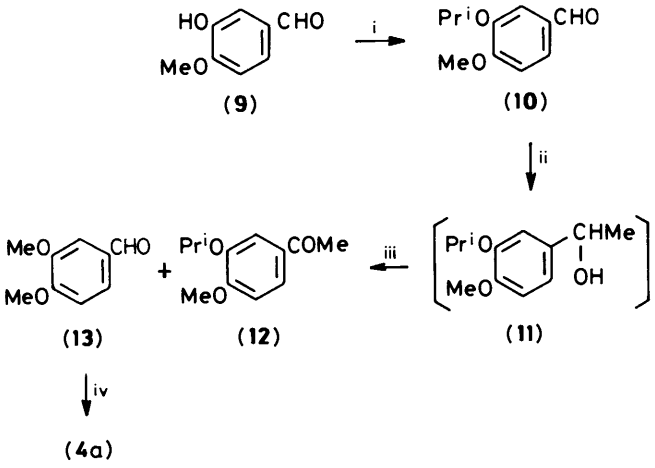
In 1972, fagaronine (**2**) was isolated by Farnsworth and co-workers [3c] from *Fagara zanthoxyloides* Lam., a Rutaceous plant, as a phenolic benzo[*c*]phenanthridine alkaloid which acts strongly against L1210 and P388 leukaemias in mice. Stermitz and co-workers [4a] later synthesized fagaronine (**2**) according to the Kessar method [8] through the photocyclisation of the anil derivative prepared by the condensation of 6-isopropoxy-7-methoxynaphthalen-1-amine and 2-bromoveratraldehyde.

After some preliminary attempts, an isopropoxy group was developed to protect the phenolic function in our synthetic sequence. Treatment of isovanillin (**9**) with isopropyl bromide and potassium carbonate in *N*,*N*-dimethylformamide gave isopropylisovanillin [9] (**10**) (88.0%). Grignard reaction of isopropylisovanillin (**10**) with methylmagnesium iodide followed by oxidation with Jones reagent afforded 3-isopropoxy-4-methoxyacetophenone [10] (**12**) (64.8%). Aldol condensation of the



(**4**) (**5**) (**6**) (**7**)
a; Ar^1 = 3-MeO, 4-$MeOC_6H_3$; Ar^2 = 3-Pr^iO, 4-$MeOC_6H_3$
b; Ar^1 = 3-$PhCH_2O$, 4-$PhCH_2OC_6H_3$; Ar^2 = 3,4-$OCH_2OC_6H_3$
c; Ar^1 = 3-$PhCH_2O$, 4-$MeOC_6H_3$; Ar^2 = 3,4-$OCH_2OC_6H_3$
(**8**)
R = alkoxy

Scheme 1. *Reagents:* i, KCN/AcOH/$EtOCH_2CH_2OH$; ii, NaOH/EtOH; iii, H_2/Pd-C/AcOH; iv, $POCl_3/CHCl_3$

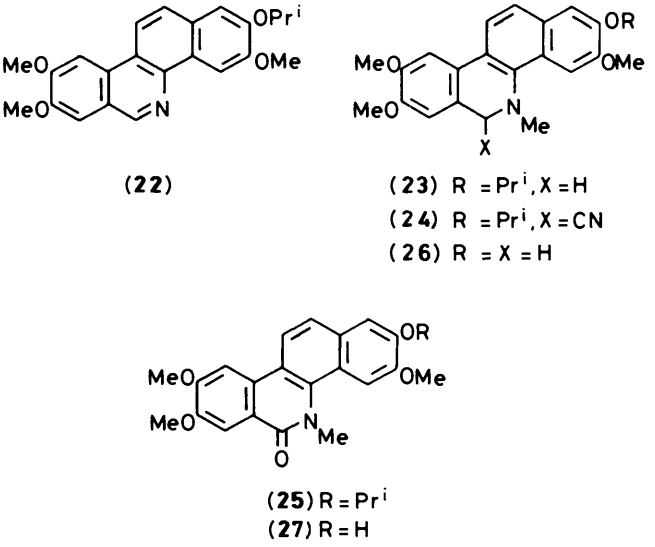


Scheme 2. *Reagents:* i, $Pr^iBr/K_2CO_3/DMF$; ii, MeMgI; iii, Jones reagent; iv, NaOH/EtOH

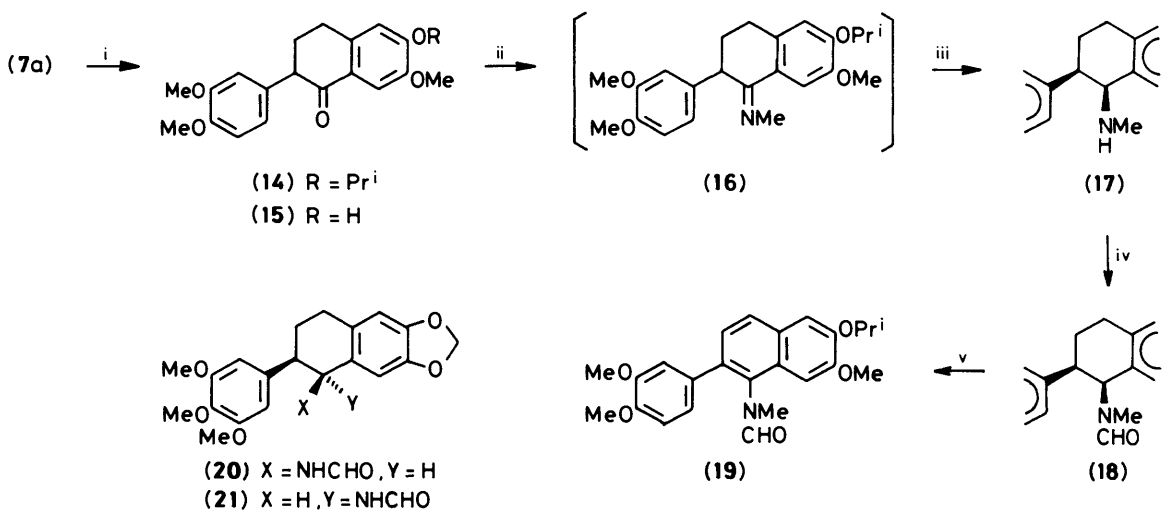
acetophenone (**12**) with veratraldehyde (**13**) and sodium hydroxide in aqueous ethanol gave the oily chalcone (**4a**), quantitatively. Hydrocyanation of the chalcone (**4a**) with potassium cyanide and acetic acid in 2-ethoxyethanol gave 2,4-bisaryl-4-oxobutyronitrile (the oxo nitrile) (**5a**) (75.5%). The hydrolysis of the oxo nitrile (**5a**) with sodium hydroxide in aqueous ethanol for 7.5 h under reflux afforded the oxo acid (**6a**) (95.9%). Catalytic hydrogenation of the oxo acid (**6a**) over 10% palladium–charcoal provided the methylene acid (**7a**) quantitatively.

The intramolecular Friedel–Crafts reaction of the methylene acid (**7a**) with phosphorus oxychloride in chloroform was achieved by reaction at 80 °C for 2.5 h. The mixture of products was separated into two fractions, neutral and phenolic, in 71.0 and in 5.8% yield, respectively. The neutral fraction gave the desired isopropoxytetralone (**14**). The phenolic fraction provided another tetralone (**15**) having a phenolic function, instead of an isopropoxy group, indicating that the isopropoxy group of the former tetralone (**14**) was cleaved under the conditions of the cyclisation. These results demonstrate that an isopropoxy group acts as a protecting group for a phenolic function in our reaction sequence.

Treatment of a solution of the isopropoxytetralone (**14**) in dry chloroform containing titanium tetrachloride with methylamine gas at −5—0 °C afforded the labile Schiff base (**16**) which led directly to a crude oily amine (**17**) (99.1%) on treatment with sodium borohydride in methanol [δ 3.17 (1 H, dt, *J* 12.0, 3.5 Hz, C-2) and 3.61 (1 H, d, *J* 3.5 Hz, C-1)]. In an earlier report,[11] we described the preparation of the related *cis*- (**20**) and *trans*- (**21**) amines and confirmed that, in the ^1H n.m.r. spectrum, the 1-H, 2-H coupling constant of the *cis*-isomer (**20**) is 3.4 Hz and that of the *trans*-isomer (**21**) is 9.6 Hz. On the basis of the spectral evidence, therefore, we suggest that the resulting oily amine (**17**) has the *cis*-configuration.



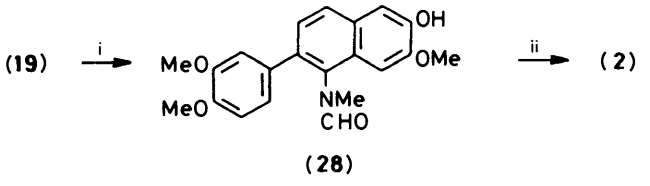
A solution of the amine (**17**) in chloroform was treated with freshly prepared chloral[5c,12] to give the *cis*-formamide (**18**) (88.1%). Dehydrogenation of the latter with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in benzene provided the aromatised formamide (**19**) (87%), which upon treatment with phosphorus oxychloride in acetonitrile (Bischler-Napieralski reaction) gave *O*-isopropylfagaronine (**3**) chloride quantitatively. The identity of the latter was confirmed by characterization of its norbase (**22**), dihydrobase (**23**), ψ-cyanide (**24**), and oxybase (**25**) derivatives, which were prepared by general methods.[5c,d] Difficulties were encountered in the next step of the synthesis in that there were problems in isolating fagaronine (**2**) from the reaction mixtures resulting from cleavage of the



Scheme 3. *Reagents:* i, $POCl_3/CHCl_3$; ii, $MeNH_2/TiCl_4/CHCl_3$; iii, $NaBH_4/MeOH$; iv, $CCl_3CHO/CHCl_3$; v, DDQ/C_6H_6

isopropoxy group from *O*-isopropylfagaronine (**3**) with a variety of reagents. We therefore looked for another reaction pathway of fagaronine (**2**) from the aromatised formamide (**19**).

Since boron trichloride–methylene dichloride was reported[7] to cleave selectively isopropoxy groups in the presence of methoxy groups, we applied this reagent to the aromatised formamide (**19**) and obtained the desired phenol (**28**) (56.2%). In extending our studies we also found that treatment of the isopropoxy aromatised formamide (**19**) with concentrated sulphuric acid in acetic acid also gave cleavage of the isopropoxy group (**28**) (80.7%) a finding of interest since it was expected, and subsequently verified,[13] that methylenedioxy groups would be expected to be left unaffected under such conditions. This is important since many natural benzo[*c*]-phenanthridine alkaloids bear methylenedioxy groups.



(28)

Scheme 4. *Reagents:* i, H_2SO_4/AcOH; ii, $POCl_3$/MeCN

Bischler-Napieralski treatment of compound (**28**) gave fagaronine (**2**) chloride, which was identical with an authentic sample of natural material.[3c] Characterization of the synthetic fagaronine (**2**) was achieved on its dihydrobase (**26**).

Since some phenolic oxybases occur in nature, oxyfagaronine (**27**) (57.8%) was prepared by treatment of the *O*-isopropyloxy-fagaronine (**25**) with sulphuric acid in acetic acid.

In conclusion, while Stermitz and co-workers[4a] synthesized fagaronine (**2**) from 2,3-dihydroxynaphthalene as a starting material in 5.2% overall yield, our synthetic sequence provided it in 15.7% yield based on the starting isovanillin (**9**).

Experimental

All m.p.s were measured on a micro melting-point hot-stage (Yanagimoto) and are uncorrected. I.r. spectra were recorded in Nujol on a Hitachi 215 spectrometer. ^{1}H N.m.r. spectra were recorded on a Hitachi R-24B spectrometer (60 MHz) in deuteriochloroform, unless otherwise stated, with tetramethylsilane as internal reference. All NH and OH signals were confirmed by disappearance of their signals after addition of deuterium oxide. JEOL JNM-4H-100 (100 MHz) and JEOL JNM-FX-270 (270 MHz) spectrometers were also used. For t.l.c. and preparative t.l.c., silica gel GF_{254} (Merck) was used. Products were identified by i.r., mixed m.p., and t.l.c.

3-*Isopropoxy*-4-*methoxybenzaldehyde* (**10**).—A suspension of isovanillin (**9**) (50.0 g), isopropyl bromide (46.2 ml), and potassium carbonate (72.8 g) in *N*,*N*-dimethylformamide (125 ml) was stirred at room temperature for 40 h, poured into a large quantity of water, and extracted with diethyl ether. The ethereal solution was washed with 5% aqueous sodium hydroxide, dried (K_2CO_3), and evaporated to dryness. The oily residue was purified by distillation at 110—113 °C (1 mmHg) [lit.,[9] b.p. 123—124 °C (2 mmHg)] to give a colourless oil (56.2 g); $\nu_{max.}$(neat) 1 690 cm^{-1}; δ 1.38 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.92 (3 H, s, OMe), 4.63 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 6.96 (1 H, d, *J* 8.5 Hz, 5-H), 7.42 (1 H, d, *J* 2.0 Hz, 2-H), 7.44 (1 H, dd, *J* 8.5 and 2.0 Hz, 6-H), and 9.83 (1 H, s, CHO).

3-*Isopropoxy*-4-*methoxyacetophenone* (**12**).–(i) 1-(3-*Isopropoxy*-4-*methoxyphenyl*)*ethanol* (**11**): A solution of 3-isopropoxy-4-methoxybenzaldehyde (**10**) (10.0 g) in dry diethyl ether (60 ml) was dropwise added to an ethereal solution of methylmagnesium iodide which was prepared from magnesium metal (3.20 g) and methyl iodide (9.8 ml) in dry diethyl ether (40 ml) below 5 °C with stirring. The mixture was stirred at room temperature for 1.5 h, after which the resulting precipitate was filtered off and washed with dry hexane. A suspension of the precipitate in water (250 ml) was decomposed by addition of 20% aqueous ammonium chloride (90 ml) and then extracted with diethyl ether. The ethereal solution was dried (K_2CO_3) and evaporated to give oily residue (8.97 g); $\nu_{max.}$(neat) 3 400 cm^{-1}; δ 1.34 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 1.43 (3 H, d, *J* 6.0 Hz, CH*Me*), 2.30 (1 H, s, OH), 3.80 (3 H, s, OMe), 4.62 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 4.78 [1 H, q, *J* 6.0 Hz, ArC*H*(O)Me], and 6.87—7.00 (3 H, m, ArH).

(ii) 3-*Isopropoxy*-4-*methoxyacetophenone* (**12**): Jones reagent[5a] (34 ml) was added to a solution of the crude oil (8.93 g) in acetone (180 ml) below 10 °C with stirring and the mixture was stirred at room temperature for 3 h. After decomposition of the excess of reagent with methanol (12 ml), the mixture was poured into water and extracted with diethyl ether. The ethereal solution was washed with 5% aqueous sodium hydroxide, dried (K_2CO_3), and evaporated to dryness. Recrystallization of the residue from diethyl ether–hexane gave colourless prisms (5.95 g), m.p. 55.5—56.5 °C (lit.,[10] m.p. 56 °C). The crude material which was obtained from the mother liquor was purified by distillation at 110—120 °C (1 mmHg) followed by recrystallization from diethyl ether–hexane to give an additional amount of the above material (0.987 g) (total amount 6.93 g) (Found: C, 69.3; H, 7.8. Calc. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.7%); $\nu_{max.}$ 1 660 cm^{-1}; δ 1.36 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 2.52 (3 H, s, COMe), 3.89 (3 H, s, OMe), 4.60 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 6.84 (1 H, d, *J* 9.0 Hz, 5-H), 7.51 (1 H, d, *J* 2.0 Hz, 2-H), and 7.53 (1 H, dd, *J* 9.0 and 2.0 Hz, 6-H).

3′-*Isopropoxy*-3,4,4′-*trimethoxychalcone* (**4a**).—To a mixture of 3-isopropoxy-4-methoxyacetophenone (**12**) (23.0 g) and veratraldehyde (**13**) (18.3 g) in ethanol (206 ml) was added 10% aqueous sodium hydroxide (20.5 ml). The mixture was stirred at room temperature for 20 h, after which it was poured into a large volume of water and extracted with benzene. The organic layer was dried (K_2CO_3) and evaporated under reduced pressure to give an oil (39.3 g). Since all crystallization attempts failed, this material was employed in the next step without any further purification; $\nu_{max.}$($CHCl_3$) 1 650 cm^{-1}; δ (100 MHz) 1.39 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.91 (6 H, s, 2 × OMe), 3.93 (3 H, s, OMe), 4.65 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 6.87 (1 H, d, *J* 9.0 Hz, 5- or 5′-H), 6.89 (1 H, d, *J* 9.0 Hz, 5′- or 5-H), 7.16 (1 H, dif. s, 2-H), 7.22 (1 H, dd, *J* 9.0 and 2.0 Hz, 6-H), 7.37 (1 H, d, *J* 15.0 Hz, CH=C*H*CO), 7.61 (1 H, dif. s, 2′-H), 7.64 (1 H, dd, *J* 9.0 and 2.0 Hz, 6′-H), and 7.73 (1 H, d, *J* 15.0 Hz, ArC*H*=CH).

2-(3,4-*Dimethoxyphenyl*)-4-(3-*isopropoxy*-4-*methoxyphenyl*)-4-*oxobutyronitrile* (**5a**).—To a solution of the chalcone (**4a**) (39.3 g) in 2-ethoxyethanol (178 ml) was added acetic acid (7.6 ml) at 100 °C. An aqueous solution of potassium cyanide (16.9 g) in water (31.5 ml) was then added to the solution at 117—118 °C and the mixture stirred at the same temperature for 4.5 min. It was then cooled to room temperature and poured onto ice–water. The resulting solid mass was filtered off and washed with ice–water until the washings showed pH 7. Recrystallization of the crude material from chloroform–methanol afforded colourless prisms (31.9 g), m.p. 148—149 °C (Found: C, 68.9; H, 6.5; N, 3.7. $C_{22}H_{25}NO_5$ requires C, 68.9; H, 6.6; N, 3.65%); $\nu_{max.}$ 2 245 and 1 670 cm^{-1}; δ(100 MHz) 1.35 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.39 (1 H, dd, *J* 18.0 and 7.0 Hz, CHC*H*$_A$H$_B$-CO), 3.65 (1 H, dd, *J* 18.0 and 7.0 Hz, CHCH$_A$*H*$_B$CO), 3.84 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.89 (3 H, s, OMe), 4.49 (1 H, t, *J* 7.0

Hz, ArC*H*CH_2), 4.58 (1 H, septet, *J* 6.0 Hz, OC*H*Me_2), 6.76—7.04 (4 H, m, ArH), and 7.42—7.60 (2 H, m, ArH).

2-(3,4-*Dimethoxyphenyl*)-4-(3-*isopropoxy*-4-*methoxyphenyl*)-4-*oxobutyric Acid* (**6a**).—The nitrile (**5a**) (26.6 g) was dissolved in aqueous ethanol [water (296 ml) and ethanol (128 ml)] containing sodium hydroxide (27.4 g) and the mixture refluxed for 7.5 h under argon. The mixture was then cooled, diluted with water, washed with diethyl ether, and acidified with 10% hydrochloric acid. The precipitate was filtered off and recrystallized from benzene–hexane to give colourless prisms (26.7 g), m.p. 135—137 °C (Found: C, 65.3; H, 6.45. $C_{22}H_{26}O_7$ requires C, 65.7; H, 6.5%); $\nu_{max.}$ 3 100—2 600br, 1 700, and 1 670 cm^{-1}; δ (100 MHz) 1.34 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.24 (1 H, dd, *J* 18.0 and 4.0 Hz, CHC$H_A$$H_B$CO), 3.81 (1 H, dd, *J* 18.0 and 10.0 Hz, CHC$H_A$$H_B$CO), 3.85 (3 H, s, OMe), 3.87 (3 H, s, OMe), 3.90 (3 H, s, OMe), 4.23 (1 H, dd, *J* 10.0 and 4.0 Hz, ArC*H*CH_2), 4.59 (1 H, septet, *J* 6.0 Hz, OC*H*Me_2), 6.65 (1 H, br s, COOH), 6.75—7.04 (4 H, m, ArH), 7.53 (1 H, s, 2′-H), and 7.58 (1 H, dd, *J* 10.0 and 2.0 Hz, 6′-H).

2-(3,4-*Dimethoxyphenyl*)-4-(3-*isopropoxy*-4-*methoxyphenyl*)-*butyric Acid* (**7a**).—A solution of the oxo acid (**6a**) (4.50 g) in acetic acid (146 ml) containing 1% aqueous palladium chloride solution [5b] (18 ml) and Norit (1.62 g) was hydrogenated at room temperature and atmospheric pressure until absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. After addition of water, the residue was extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure to give a pale brownish product (4.33 g). Purification of a part of this material by preparative t.l.c. with chloroform–methanol (15:1, v/v) gave colourless needles, m.p. 103—104 °C, which were recrystallized from diethyl ether–hexane (Found: C, 68.2; H, 7.2. $C_{22}H_{28}O_6$ requires C, 68.0; H, 7.3%); $\nu_{max.}$ 1 685 cm^{-1}; $\nu_{max.}$($CHCl_3$) 1 710 cm^{-1}; δ (100 MHz) 1.33 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 1.91—2.70 (4 H, m, 3- and 4-H_2), 3.30—3.58 (1 H, m, 2-H), 3.78 (3 H, s, OMe), 3.86 (6 H, s, 2 × OMe), 4.47 (1 H, septet, *J* 6.0 Hz, OC*H*Me_2), 6.60—7.00 (6 H, m, ArH), and 8.70 (1 H, br s, COOH).

The crude material was used in the subsequent reaction without purification.

Intramolecular Friedel-Crafts Reaction of the Methylene Acid (**7a**) *with Phosphorus Oxychloride in Chloroform.*—A mixture of the crude methylene acid (**7a**) (11.2 g) and phosphorus oxychloride (14.3 ml) in chloroform (26.3 ml) was heated at 78—80 °C for 2.5 h. The mixture was poured onto ice–water, made alkaline with 5% aqueous sodium hydroxide, and extracted with diethyl ether. The ethereal solution was washed with 5% aqueous sodium hydroxide, dried (K_2CO_3), and evaporated to dryness.

(*a*) 2-(3,4-*Dimethoxyphenyl*)-6-*isopropoxy*-7-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (**14**): Recrystallization of the residue from benzene–hexane gave colourless prisms (7.59 g), m.p. 121—122 °C (Found: C, 71.6; H, 7.1. $C_{22}H_{26}O_5$ requires C, 71.3; H, 7.1%); $\nu_{max.}$ 1 670 cm^{-1}; δ 1.43 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 2.20—2.60 (2 H, m, 3-H_2), 2.80—3.17 (2 H, m, 4-H_2), 3.70 (1 H, t, *J* 8.0 Hz, 2-H), 3.85 (6 H, s, 2 × OMe), 3.88 (3 H, s, OMe), 4.67 (1 H, septet, *J* 6.0 Hz, OC*H*Me_2), 6.60—6.86 (4 H, m, ArH), and 7.57 (1 H, s, 8-H).

(*b*) 2-(3,4-*Dimethoxyphenyl*)-6-*hydroxy*-7-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (**15**): The above sodium hydroxide solution separated from the ethereal layer and the washings were combined, acidified with 10% hydrochloric acid, and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure. Recrystallization of the residue from methanol gave colourless prisms (0.551 g), m.p. 170—172 °C (Found: C, 69.6; H, 6.1. $C_{19}H_{20}O_5$ requires C, 69.5; H, 6.1%); $\nu_{max.}$ 3 415 and 1 670 cm^{-1}; δ 2.20—2.60 (2 H, m, 3-H_2), 2.77—3.15 (2 H, m, 4-H_2), 3.68 (1 H, t, *J* 8.0 Hz, 2-H), 3.84 (6 H, s, 2 × OMe), 3.92 (3 H, s, OMe), 6.14 (1 H, br s, OH), 6.55—6.86 (4 H, m, ArH), and 7.56 (1 H, s, 8-H).

cis-2-(3,4-*Dimethoxyphenyl*)-6-*isopropoxy*-7-*methoxy*-N-*methyl*-1,2,3,4-*tetrahydronaphthalen*-1-*amine* (**17**).—A solution of the tetralone (**14**) (9.35 g) in dry chloroform (93 ml) was added to an ice-cooled solution of methylamine (21 g) in dry chloroform (93 ml). The mixture was then added dropwise to a solution of titanium tetrachloride (2.8 ml) in dry chloroform (93 ml) at −5—0 °C during 20 min with stirring. It was then stirred at room temperature for 2 h and subsequently refluxed for 30 min. The inorganic material was filtered off and washed with dry chloroform and the filtrate and the washings combined to give upon evaporation under reduced pressure (**16**) as a yellow oil (13.1 g). This was dissolved in dry methanol (280 ml) and sodium borohydride (1.89 g) was gradually added to it with stirring at room temperature. The mixture was further stirred at room temperature for 1.5 h and then evaporated under reduced pressure. After addition of water, the mixture was extracted with diethyl ether. The ethereal solution was dried (K_2CO_3) and evaporated to give a yellow oil * (9.64 g); $\nu_{max.}$(KBr) 3 310 cm^{-1}; δ(270 MHz) 1.37 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 1.41 † (1 H, s, NH), 1.94—2.02 (1 H, m, 3-H), 2.23 (3 H, s, NMe), 2.36—2.49 (1 H, m, 3-H), 2.75—2.98 (2 H, m, 4-H_2), 3.17 (1 H, dt, *J* 12.0 and 3.5 Hz, 2-H), 3.61 (1 H, d, *J* 3.5 Hz, 1-H), 3.85 (3 H, s, OMe), 3.86 (3 H, s, OMe), 3.88 (3 H, s, OMe), 4.51 (1 H, septet, *J* 6.0 Hz, OC*H*Me_2), 6.69 (1 H, s, ArH), 6.79 (1 H, s, ArH), 6.83 (1 H, s, Ar H), and 6.85 (2 H, s, ArH).

This material was characterized as a picrate: yellow prisms, m.p. 163—166 °C (chloroform–methanol) (Found: C, 56.4; H, 5.6; N, 9.1. $C_{23}H_{31}NO_4$·$C_6H_3N_3O_7$ requires C, 56.7; H, 5.6; N, 9.1%).

cis-2-(3,4-*Dimethoxyphenyl*)-6-*isopropoxy*-7-*methoxy*-1-(N-*methylformamido*)-1,2,3,4-*tetrahydronaphthalene* (**18**).—The freshly prepared chloral [5c,12] (b.p. 97 °C, 4.9 ml) was added to a solution of the naphthalen-1-amine (**17**) (9.63 g) in dry chloroform (97 ml) at room temperature with stirring. The mixture was refluxed for 3 h, poured into water, and extracted with chloroform. The chloroform solution was dried (K_2CO_3) and evaporated under reduced pressure. Recrystallization of the residue from benzene–hexane gave colourless prisms (9.10 g), m.p. 147—149 °C (Found: C, 69.8; H, 7.6; N, 3.4. $C_{24}H_{31}NO_5$ requires C, 69.7; H, 7.6; N, 3.4%); $\nu_{max.}$ 1 670 cm^{-1}; δ (100 MHz) 1.38 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 1.88—2.30 (2 H, m, 3-H_2), 2.51 (3 H, s, NMe), 2.80—3.32 (3 H, m, 2-H and 4-H_2), 3.76 (3 H, s, OMe), 3.85 (6 H, s, 2 × OMe), 4.53 (1 H, septet, *J* 6.0 Hz, OC*H*Me_2), 4.62 (1 H, d, *J* 4.5 Hz, 1-H), 6.50 (1 H, s, 5-H), 6.62—6.75 (3 H, m, ArH), 6.83 (1 H, dif. d, *J* 9.0 Hz, 6′-H), 7.59 * (7/8 H, s, NCHO), and 7.76 ‡ (1/8 H, s, NCHO).

2-(3,4-*Dimethoxyphenyl*)-6-*isopropoxy*-7-*methoxy*-1-(N-*methylformamido*)*naphthalene* (**19**).—A solution of DDQ (9.89 g) in dry benzene (90 ml) was added to a solution of the *cis*-formamide (**18**) (6.00 g) in dry benzene (180 ml) at room temperature. The mixture was refluxed for 2 h. The resulting

* This oil was solidified with time and a portion of the resulting solid was recrystallized from methanol–diethyl ether to give colourless prisms, m.p. 33—52 °C.

† The NH signal overlapped with those of an isopropyl group. However, the presence of the signal was confirmed by disappearance of the NH signal after addition of deuterium oxide.

‡ This compound showed two spots on t.l.c. [benzene–ethyl acetate (1:1, v/v)], thought to be due to the presence of rotational isomers.[5c]

precipitate was filtered off and the filtrate was evaporated under reduced pressure. The residue was suspended in 5% aqueous sodium hydroxide and the suspension was extracted with chloroform. The chloroform solution was washed with 5% aqueous sodium hydroxide, dried (K_2CO_3), and evaporated under reduced pressure. Recrystallization of the residue from chloroform–methanol or benzene–hexane gave colourless prisms (5.17 g), m.p. 181—183 °C* (Found: C, 70.5; H, 6.7; N, 3.4. $C_{24}H_{27}NO_5$ requires C, 70.4; H, 6.65; N, 3.4%); $\nu_{max.}$($CHCl_3$) 1 670 cm^{-1}; δ 1.46 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 2.95† (3/8 H, s, NMe), 3.05† (21/8 H, s, NMe), 3.87 (3 H, s, OMe), 3.91 (3 H, s, OMe), 3.94 (3 H, s, OMe), 4.74 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 6.74—6.97 (3 H, m, ArH), 7.00 (1 H, s, 5-H), 7.20 (1 H, s, 8-H), 7.33 (1 H, d, *J* 8.0 Hz, 4-H), 7.72 (1 H, d, *J* 8.0 Hz, 3-H), 8.18† (7/8 H, s, NCHO), and 8.38† (1/8, s, NCHO).

O-*Isopropylfagaronine* (2-*Isopropoxy*-3,8,9-*trimethoxy*-5-*methylbenzo*[c]*phenanthridinium*) (**3**) *Chloride*.—A mixture of the aromatised formamide (**19**) (1.00 g) and phosphorus oxychloride (1.5 ml) in acetonitrile (40 ml) was refluxed for 30 min. The mixture was poured into ice–water. The resulting precipitate was filtered off and washed with chilled water and benzene. Recrystallization of the precipitate from methanol gave yellow prisms (1.04 g), m.p. 274—277 °C (lit.,[4a] m.p. 265—267 °C); δ(CF_3CO_2H) 1.57 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 4.22 (6 H, s, 2 × OMe), 4.33 (3 H, s, OMe), 4.90—5.26 (1 H, m, OC*H*Me$_2$), 5.07 (3 H, s, NMe), 7.64 (1 H, s, 1-H), 7.74 (1 H, s, 7-H), 8.20 (2 H, s, 4- and 10-H), 8.21 (1 H, d, *J* 9.0 Hz, 12-H), 8.56 (1 H, d, *J* 9.0 Hz, 11-H), and 9.38 (1 H, br s, 6-H).

O-*Isopropylnorfagaronine* (2-*Isopropoxy*-3,8,9-*trimethoxybenzo*[c]*phenanthridine*) (**22**).—*O*-Isopropylfagaronine (**23**) chloride (0.050 g) was heated at 150 °C under reduced pressure (1 mmHg) for 18 h. Recrystallization of the residue from chloroform–methanol gave colourless prisms (0.040 g), m.p. 275—277 °C (lit.,[4a] m.p. 270—272 °C) (Found: C, 73.4; H, 6.2; N, 3.7. Calc. for $C_{23}H_{23}NO_4$: C, 73.2; H, 6.1; N, 3.7%); δ(CF_3CO_2H) 1.57 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 4.22 (6 H, s, 2 × OMe), 4.34 (3 H, s, OMe), 5.02 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 7.61 (1 H, s, 1-H), 7.81 (1 H, s, 7-H), 8.18 (1 H, d, *J* 9.0 Hz, 12-H), 8.19 (1 H, s, ArH), 8.24 (1 H, s, ArH), 8.52 (1 H, d, *J* 9.0 Hz, 11-H), and 9.42‡ (1 H, d, *J* 8.0 Hz, 6-H).

O-*Isopropyldihydrofagaronine* (2-*Isopropoxy*-3,8,9-*trimethoxy*-5-*methyl*-5,6-*dihydrobenzo*[c]*phenanthridine*) (**23**).—To a solution of *O*-isopropylfagaronine (**23**) chloride (0.081 g) in methanol (19 ml) was added portionwise sodium borohydride (0.031 g) with stirring. The mixture was stirred at room temperature for 30 min. After addition of water, the mixture was extracted with chloroform and the extract dried (K_2CO_3) and evaporated under reduced pressure. Recrystallization of the residue from chloroform–methanol gave colourless prisms (0.046 g), m.p. 199—202 °C (Found: C, 73.4; H, 6.9; N, 3.6. $C_{24}H_{27}NO_4$ requires C, 73.3; H, 6.9; N, 3.6%); δ 1.47 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 2.63 (3 H, s, NMe), 3.94 (3 H, s, OMe), 3.99 (3 H, s, OMe), 4.03 (3 H, s, OMe), 4.15 (2 H, s, 6-H_2), 4.70 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 6.79 (1 H, s, 7-H), 7.14 (1 H, s, 1-H), 7.31 (1 H, s, 10-H), 7.46 (1 H, d, *J* 9.0 Hz, 12-H), 7.64 (1 H, s, 4-H), and 7.72 (1 H, d, *J* 9.0 Hz, 11-H).

O-*Isopropylfagaronine* ψ-*Cyanide* (6-*Cyano*-2-*isopropoxy*-3,8,9-*trimethoxy*-5-*methyl*-5,6-*dihydrobenzo*[c]*phenanthridine*) (**24**).—To a solution of *O*-isopropylfagaronine (**3**) chloride (0.151 g) in water (15 ml) was added potassium cyanide (0.060 g) at 50 °C. The mixture was stirred for 1.5 h at the same temperature, after which it was diluted with water and extracted with chloroform. The extract was dried (K_2CO_3), and evaporated under reduced pressure and the residue recrystallized from chloroform–methanol to give colourless prisms (0.110 g), m.p. 203 °C (decomp.) (softened at 191 °C) (Found: C, 71.7; H, 6.3; N, 6.6. $C_{25}H_{26}N_2O_4$ requires C, 71.75; H, 6.3; N, 6.7%); δ (100 MHz) 1.47 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 2.64 (3 H, s, NMe), 3.96 (3 H, s, OMe), 4.00 (3 H, s, OMe), 4.03 (3 H, s, OMe), 4.71 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 5.12 (1 H, s, 6-H), 6.97 (1 H, s, ArH), 7.14 (1 H, s, ArH), 7.32 (1 H, s, 10-H), 7.52 (1 H, d, *J* 9.0 Hz, 12-H), 7.58 (1 H, s, 4-H), and 7.68 (1 H, d, *J* 9.0 Hz, 11-H).

O-*Isopropyloxyfagaronine* (2-*Isopropoxy*-3,8,9-*trimethoxy*-5-*methylbenzo*[c]*phenanthridin*-6(5H)-*one*) (**25**).—To a solution of the ψ-cyanide (**24**) (0.056 g) in hexamethylphosphoric triamide (1 ml) was added sodium hydride (52.9% sodium hydride in mineral oil; 0.012 g). The mixture was then stirred at room temperature for 2.5 h, after which the same amount of sodium hydride was added to the mixture. The mixture was stirred for further 1.5 h and then poured into a large volume of water and extracted with ethyl acetate. The organic layer was washed with water, dried (K_2CO_3), and evaporated under reduced pressure. Recrystallization of the residue from chloroform–methanol gave colourless prisms (0.045 g), m.p. 194—196 °C (Found: C, 71.2; H, 6.35; N, 3.3. $C_{24}H_{25}NO_5$ requires C, 70.7; H, 6.2; N, 3.4%); $\nu_{max.}$($CHCl_3$) 1 635 cm^{-1}; δ 1.47 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.99 (3 H, s, NMe or OMe), 4.03 (6 H, s, 2 × OMe or OMe and NMe), 4.08 (3 H, s, NMe or OMe), 4.76 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 7.18 (1 H, s, 1-H), 7.52 (1 H, d, *J* 9.0 Hz, 12-H), 7.60 (2 H, s, ArH), 7.90 (1 H, s, 7-H), and 7.97 (1 H, d, *J* 9.0 Hz, 11-H).

2-(3,4-*Dimethoxyphenyl*)-6-*hydroxy*-7-*methoxy*-1-(N-*methylformamido*)*naphthalene* (**28**).—(a) *With boron trichloride:* Boron trichloride (0.374 g) in dry methylene chloride (10.7 ml) was ice-cooled and added (1.65 ml) to a solution of the isopropoxynaphthylamide (**19**) (0.100 g) in dry methylene chloride (1.8 ml) at −40 °C under argon with stirring. The mixture was stirred at the same temperature for 2 h and then set aside at −10 °C overnight. A small volume of water was added to the mixture which was then diluted with methylene chloride (20 ml). The organic layer was separated from the aqueous layer and extracted with 5% aqueous sodium hydroxide. The aqueous sodium hydroxide solution was acidified with 10% hydrochloric acid and extracted with methylene chloride. The extract was then dried ($MgSO_4$) and evaporated under reduced pressure. Recrystallization of the residue from methanol gave colourless prisms (0.051 g), m.p. 209—210 °C (Found: C, 68.4; H, 5.9; N, 3.8. $C_{21}H_{21}NO_5$ requires C, 68.65; H, 5.8; N, 3.8%); $\nu_{max.}$ 3 185, 1 660, and 1 650 cm^{-1}; δ 3.05 (3 H, s, NMe), 3.86 (3 H, s, OMe), 3.90 (3 H, s, OMe), 3.99 (3 H, s, OMe), 6.09 (1 H, br s, OH), 6.80—6.98 (3 H, m, ArH), 7.00 (1 H, s, 5-H), 7.31 (1 H, s, 8-H), 7.34 (1 H, d, *J* 9.0 Hz, 4-H), 7.71 (1 H, d, *J* 9.0 Hz, 3-H), and 8.18 (1 H, s, NCHO).

(b) *With concentrated sulphuric acid in acetic acid.* A solution of the isopropoxynaphthylamide (**19**) (1.00 g) in acetic acid (80 ml) containing concentrated sulphuric acid (2.5 ml) was refluxed for 10 min under argon. The mixture was poured into a large volume of water and extracted with benzene. The benzene solution was extracted with 5% aqueous sodium hydroxide and the latter was then acidified with 10% hydrochloric acid and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated to dryness under reduced pressure.

* When methanol was used as a recrystallization solvent this material melted at 147—150 °C at once, resolidified again, and finally melted at this temperature.

† See footnote on preceding page.

‡ Since the ^1H n.m.r. spectrum of this material was measured in trifluoroacetic acid, the signal of its 6-H was observed as a doublet due to coupling with N^+-H of the resulting salt.

Recrystallization of the residue from methanol–diethyl ether gave colourless prisms (0.724 g), m.p. 209—210 °C. This material was identical with a sample which was prepared by treatment of the isopropoxynaphthylamide (**19**) with boron trichloride in dry methylene chloride.

Fagaronine (2-*Hydroxy*-3,8,9-*trimethoxy*-5-*methylbenzo*[c]-*phenanthridinium*) (**2**) *Chloride*.—A mixture of the phenolic formamide (**28**) (0.488 g) in acetonitrile (19.5 ml) and phosphorus oxychloride (0.83 ml) was refluxed for 30 min. After cooling, the resulting precipitate was filtered off and washed with benzene. Recrystallization of the precipitate from methanol–ethyl acetate gave yellow needles (0.446 g), m.p. 276 °C (193—195 °C*) [lit.,[3c] m.p. 255 °C (202 °C*); m.p. 260—261 °C (198—200 °C*)[4a]]; $\nu_{max.}$(KBr) 3 375 cm^{-1}; δ(CF_3CO_2H) 4.22 (6 H, s, 2 × OMe), 4.33 (3 H, s, OMe), 5.07 (3 H, s, NMe), 7.69 (1 H, s, ArH), 7.73 (1 H, s, ArH), 8.10 (1 H, s, ArH), 8.16 (1 H, d, *J* 9.0 Hz, 12-H), 8.19 (1 H, s, ArH), 8.52 (1 H, d, *J* 9.0 Hz, 11-H), and 9.38 (1 H, s, 6-H). This material was identical with an authentic sample of naturally occurring fagaronine (**2**) chloride.[3c]

Dihydrofagaronine (2-*Hydroxy*-3,8,9-*trimethoxy*-5-*methyl*-5,6-*dihydrobenzo*[c]*phenanthridine*) (**26**).—Sodium borohydride (0.024 g) was added portionwise to a solution of fagaronine (**2**) chloride (0.060 g) in methanol (8 ml) at room temperature with stirring. After being stirred at room temperature for 30 min, the mixture was evaporated under reduced pressure. The residue was suspended in 5% hydrochloric acid and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure. Recrystallization of the residue from chloroform–methanol gave colourless prisms (0.037 g), m.p. 196—200 °C (Found: C, 71.55; H, 6.1; N, 3.9. $C_{21}H_{21}NO_4$ requires C, 71.8; H, 6.0; N, 4.0%); $\nu_{max.}$ 3 400 cm^{-1}; δ 2.61 (3 H, s, NMe), 3.92 (3 H, s, OMe), 3.97 (3 H, s, OMe), 4.03 (3 H, s, OMe), 4.13 (2 H, s, 6-H_2), 6.02 (1 H, br s, OH), 6.77 (1 H, s, 7-H), 7.22 (1 H, s, ArH), 7.29 (1 H, s, ArH), 7.44 (1 H, d, *J* 8.5 Hz, 12-H), 7.62 (1 H, s, 4-H), and 7.68 (1 H, d, *J* 8.5 Hz, 11-H).

Oxyfagaronine {2-*Hydroxy*-3,8,9-*trimethoxy*-5-*methylbenzo*-[c]*phenanthridin*-6(5H)-*one*} (**27**).—A solution of the *O*-isopropyloxyfagaronine (**25**) (0.050 g) in acetic acid (5 ml) containing concentrated sulphuric acid (0.03 ml) was refluxed for 5.5 h under argon. The mixture was poured into a large volume of water and extracted with benzene. The benzene solution was extracted with 5% aqueous sodium hydroxide and the latter then acidified with 10% hydrochloric acid and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. Recrystallization of the residue from chloroform–methanol gave slightly pink prisms (0.026 g), m.p. 273—275 °C (Found: C, 68.8; H, 5.3; N, 3.8. $C_{21}H_{19}NO_5$ requires C, 69.0; H, 5.2; N, 3.8%); $\nu_{max.}$ 3 490 and 1 645 cm^{-1}; δ ($CDCl_3$–CD_3OD; 270 MHz) 4.06 (9 H, s, NMe and 2 × OMe or 3 × OMe), 4.12 (3 H, s, OMe or NMe), 7.29 (1 H, s, 1-H), 7.58 (1 H, d, *J* 8.7 Hz, 12-H), 7.62 (1 H, s, ArH), 7.63 (1 H, s, ArH), 7.92 (1 H, s, 7-H), and 8.01 (1 H, d, *J* 8.7 Hz, 11-H).

* This material melted at this temperature at once followed by resolidification, then melting again.

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