A One-step Synthesis of the Phthalidylisoquinoline Alkaloids, Cordrastine and Hydrastine

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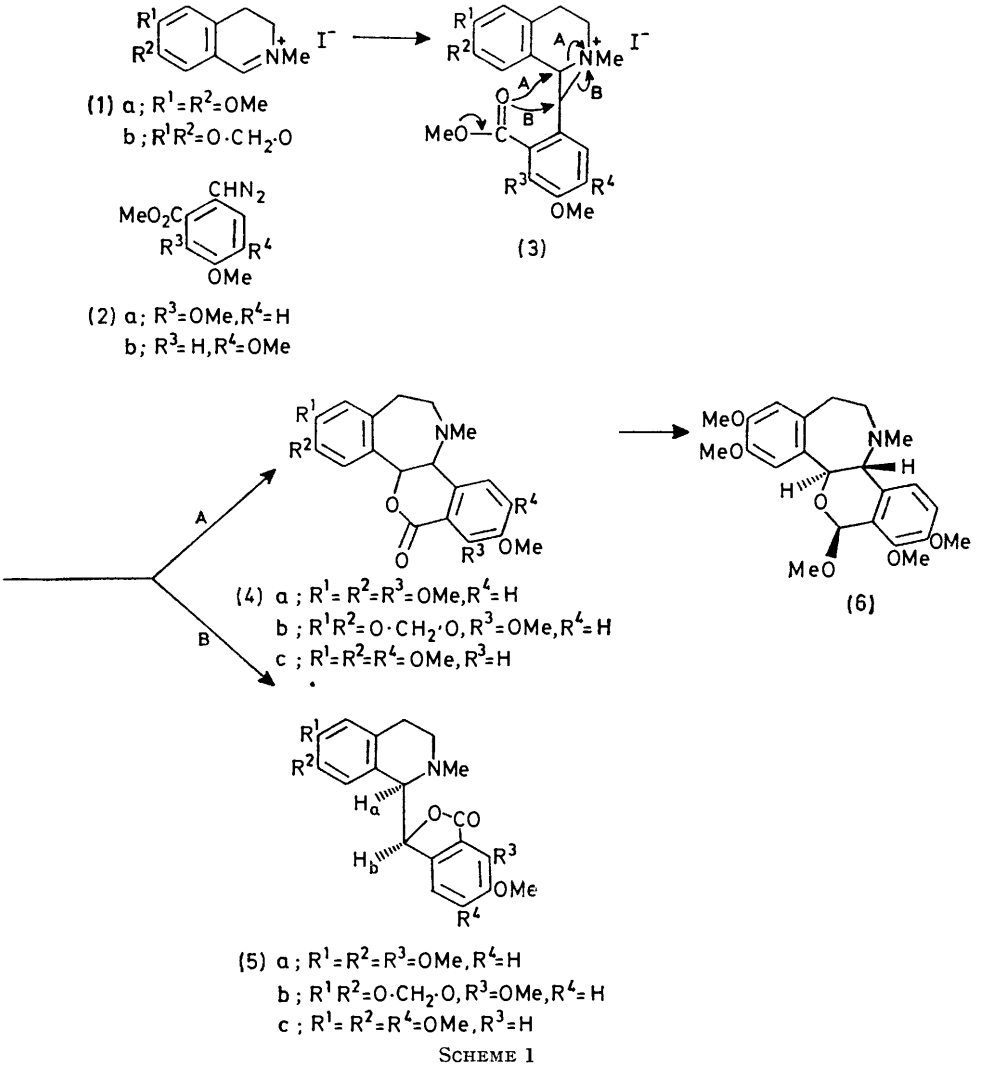
Cordrastine (5a) and hydrastine (5b) were synthesised by condensation of 3,4-dihydro-6,7-dimethoxy-2-methyl- (1a) and 3,4-dihydro-6,7-methylenedioxy-2-methyl-isoquinolinium (1b) salts, respectively, with methyl 6-diazomethyl-2,3-dimethoxybenzoate (2a) derived from 6,7-dimethoxyphthalimidine (16a). The reaction of (1a) with methyl 2-diazomethyl-4,5-dimethoxybenzoate (2b) gave the cordrastine isomer (5c).

AZIRIDINES and their quaternary salts [1] are easily attacked by nucleophiles [2] or electrophiles [3] with formation of ring-opened amines; this type of reaction has been applied to a total synthesis of ibogamine and related alkaloids.[3] Moreover, an aziridine system is assumed to be an intermediate in the formation of a variety of naturally occurring heterocyclic compounds.[4]

[1] D. R. Crist and N. J. Leonard, *Angew. Chem.*, 1969, **81**, 953.
[2] N. J. Leonard and K. Jann, *J. Amer. Chem. Soc.*, 1962, **84**, 4806.
[3] W. Nagata, S. Hirai, T. Okamura, and K. Kawata, *J. Amer. Chem. Soc.*, 1968, **90**, 1650.
[4] T. Kametani and K. Fukumoto, *Heterocycles*, 1975, **3**, 931, and references cited therein.

We have reported the synthesis of isopavine [5] and benzazepine systems [6] by ring expansion of 3,4-dihydro-2-methylisoquinolinium salts with diazomethane, by way of aziridinium salt intermediates. As an extension of this work, we have investigated the reaction of 3,4-dihydro-6,7-dimethoxy-2-methyl- and 3,4-dihydro-6,7-methylenedioxy-2-methyl-isoquinolium salts (1) with 2-diazomethylbenzoates (2), in the hope of obtaining the rheadans (4) or the phthalidylisoquinolines (5). We report here one-step syntheses of cordrastine (5a) and hydrastine (5b) by this reaction.



SCHEME 1

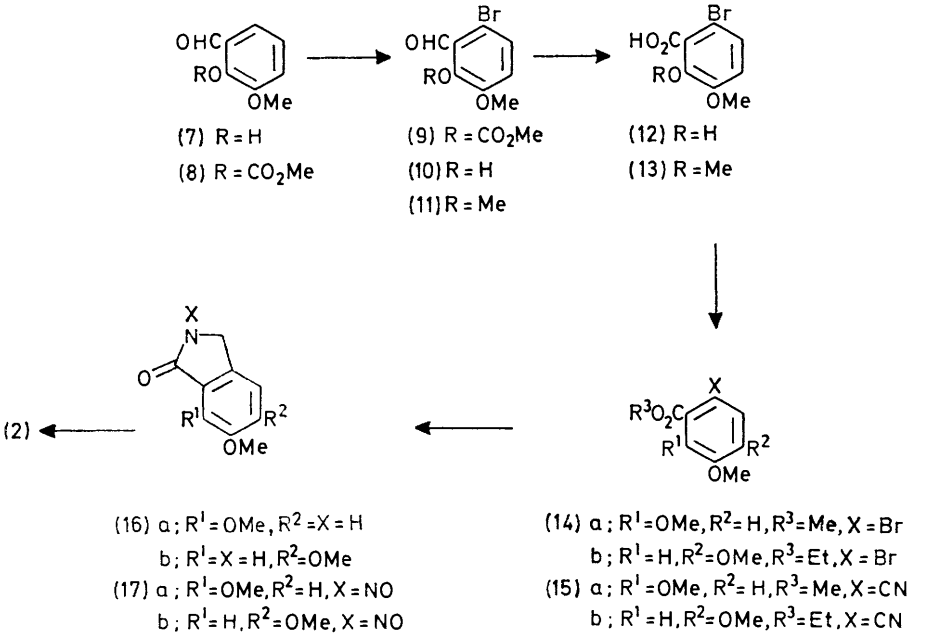
The synthetic route is summarised in Scheme 1. Thus it is possible that intramolecular nucleophilic attack of the carboxylate group on the aziridinium system (3) could take place by route A or B, leading to oxyalpinine (10a) [which has been converted into alpinine (6) by Manske [7]] or cordrastine (5a).

Ethyl 6-bromoveratrate [8] (14b) was treated with copper(I) cyanide in refluxing dimethylformamide for 4 h to give the corresponding cyanide (15b) in 85% yield, which was reduced over Raney nickel in ethanol at 80 °C under 80 atm of hydrogen to afford 5,6-dimethoxyphthalimidine (16b). Treatment of this product with sodium nitrite in concentrated hydrochloric acid at room temperature gave the *N*-nitrosophthalimidine (17b), which was treated with 5N-sodium methoxide in methanol by Oppé's method [9] to form the unstable diazomethylbenzoate (2b). An ethereal solution of this was added to the 3,4-dihydro-2-methylisoquinolinium iodide (1a) in methanol–chloroform (1 : 1, v/v), and the mixture was kept at room temperature for 2 days to give the phthalidylisoquinoline (5c) [10] (i.r. and n.m.r. data as

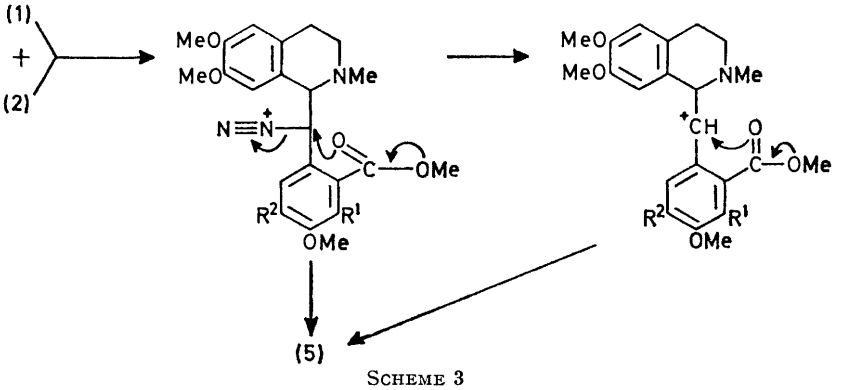
[5] T. Kametani and K. Ogasawara, *Chem. and Pharm. Bull. (Japan)*, 1973, **21**, 893; T. Kametani, S. Hirata, and K. Ogasawara, *J.C.S. Perkin I*, 1973, 1466.
[6] T. Kametani, S. Hirata, F. Satoh, and K. Fukumoto, *J.C.S. Perkin I*, 1974, 2509.
[7] K. Orito, R. H. Manske, and R. Rodrigo, *J. Amer. Chem. Soc.*, 1974, **96**, 1944.
[8] A. Bruggink and A. McKillop, *Angew. Chem.*, 1974, **86**, 349.
[9] A. Oppé, *Ber.*, 1913, **46**, 1095.
[10] M. Shamm and V. St. Georgiev, *Tetrahedron Letters*, 1974, 2339.

reported [11]) in 10—15% yield after purification by silica gel column chromatography. No rheadan-type compound (4c) was detected.

This method was applied to a synthesis of cordrastine (5a) as follows. Methoxycarbonylation of 2-hydroxy-3-methoxybenzaldehyde (7) with methyl chloroformate and triethylamine in benzene gave the non-phenolic aldehyde (8), which was converted into 3-bromo-2-formyl-6-methoxyphenyl methyl carbonate (9) by bromination in the presence of iron and sodium acetate in acetic acid at room temperature. Hydrolysis with sodium hydroxide in boiling aqueous methanol afforded 6-bromo-2-hydroxy-3-methoxybenzaldehyde (10), which was treated with dimethyl sulphate and potassium carbonate to give 6-bromo-2,3-dimethoxybenzaldehyde (11) in 90% yield. Oxidation of the aldehyde (10) with silver oxide and sodium hydroxide afforded 6-bromo-2-hydroxy-3-methoxybenzoic acid.[12] Methylation of (12) with diazomethane gave methyl 6-bromo-2,3-dimethoxybenzoate (13), which was also synthesised by oxidation of (11) with silver oxide, followed by methylation with diazomethane. Cyanation of this bromide (13) with copper(I) cyanide, followed by hydrogenation of the resulting cyanide (15a) over Raney nickel, afforded 6,7-dimethoxyphthalimidine (16a). *N*-Nitrosation of (16a) with sodium nitrite and concentrated hydrochloric acid provided (17a), which was treated with sodium methoxide by Oppé's method [9] to yield the diazo-benzoate (2a). Condensation of this with 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide (1a) gave, in 10—15% yield, cordrastine (5a), characterised as the picrate. The i.r. and n.m.r. spectra of the free base were identical with those of an authentic sample. In the above reaction no oxyalpinigenine (4a) could be detected.



SCHEME 2



SCHEME 3

Similarly, condensation of the diazo-compound (2a) with 3,4-dihydro-6,7-methylenedioxy-2-methylisoquinolinium iodide (1b) afforded, in 15% yield, hydrastine (5b), which was identical with an authentic sample (i.r.,

[11] T. Kametani, S. Hirata, M. Ihara, and K. Fukumoto, *Heterocycles*, 1975, **3**, 405.

[12] S. Sugasawa, *J. Pharm. Soc. Japan*, 1934, **54**, 295. In this paper, it was reported that the acid was not crystallised.

n.m.r., and mass spectra), and was characterised as the picrate.

The formation of this type of phthalidylisoquinoline presumably proceeds *via* the aziridinium salt (3) by route B in Scheme 1; the isolation of azirino[2,3-*a*]isoquinoline methiodides and the formation of benzazepines from hydrastinine and diazoalkanes has been reported.[13,14] However, the lack of formation of the oxyrheadans (4) suggests that the mechanism shown in Scheme 3 is also a possibility.

EXPERIMENTAL

N.m.r. spectra were measured with a JNM-PMX-60 spectrophotometer, i.r. spectra (for solutions in chloroform) with a Hitachi 215 spectrophotometer, and mass spectra with a Hitachi RMU-7 spectrometer.

2-*Formyl*-6-*methoxyphenyl Methyl Carbonate* (8).—To a solution of 2-hydroxy-3-methoxybenzaldehyde (7) (25 g) in benzene (300 ml) containing triethylamine (17 g), methyl chloroformate (20 g) was added dropwise with stirring at 5—10 °C. Stirring was continued for 2 h at room temperature. The benzene layer was washed with water, 10% hydrochloric acid, and water, dried (Na_2SO_4), and evaporated to give (8) as an *oil*, b.p. 150° at 5 mmHg (Found: C, 57.1; H, 4.75. $C_{10}H_{10}O_5$ requires C, 57.15; H, 4.8%), $\nu_{max.}$ 1 760 (C=O) and 1 690 cm^{-1} (C=O), δ(CCl_4) 3.79 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 7.10—7.33 (3 H, m, ArH), and 10.07 (1 H, s, CHO).

3-*Bromo*-2-*formyl*-6-*methoxyphenyl Methyl Carbonate* (9).—To a stirred solution of the aldehyde (8) (20 g) in acetic acid (200 ml) containing a catalytic amount of iron powder was added a solution of bromine (22 g) in acetic acid (100 ml) dropwise at room temperature. After continuous stirring for 5 h, the mixture was poured into water and extracted with chloroform. The organic layer was washed with water, 5% sodium thiosulphate solution, and water, dried (Na_2SO_4); and evaporated to afford a pale reddish solid; recrystallisation from propan-2-ol gave the *bromide* (9) (22.5 g) as needles, m.p. 120—122° (Found: C, 41.85; H, 3.35. $C_{10}H_9BrO_5$ requires C, 41.55; H, 3.15%), $\nu_{max.}$ 1 760 (C=O) and 1 690 cm^{-1} (C=O), δ($CDCl_3$) 3.78 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 7.07 (1 H, d, *J* 8 Hz, ArH), 7.47 (1 H, d, *J* 8 Hz, ArH), and 10.22 (1 H, s, CHO).

6-*Bromo*-2-*hydroxy*-3-*methoxybenzaldehyde* (10).—A mixture of the aldehyde (9) (38 g), 10% sodium hydroxide (200 ml), and methanol (750 ml) was refluxed for 2 h, then evaporated. The residue was acidified with concentrated hydrochloric acid and extracted with chloroform. The extract was washed with water and dried (Na_2SO_4). The solvent was distilled off to give the product (10) (24 g) as a pale yellowish powder, which was recrystallised from propan-2-ol to afford *needles*, m.p. 93—95° (Found: C, 41.6; H, 3.05. $C_8H_7BrO_3$ requires C, 41.85; H, 3.2%), $\nu_{max.}$ 1 635 cm^{-1} (C=O), δ($CDCl_3$) 3.88 (3 H, s, OCH_3), 6.88 (1 H, d, *J* 9 Hz, ArH), and 7.08 (1 H, d, *J* 9 Hz, ArH).

6-*Bromo*-2,3-*dimethoxybenzaldehyde* (11).—To a solution of the phenol (10) (27 g) in dimethylformamide (100 ml) containing potassium carbonate (32 g) was added dimethyl sulphate (18 g), dropwise at 100—120 °C with stirring. Stirring was continued for 4 h at the same temperature. After cooling, the mixture was poured into water and extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give a pale reddish solid; recrystallisation from propan-2-ol gave (11) (22 g) as *needles*, m.p. 71—73° (Found: C, 44.1; H, 3.65. $C_9H_9BrO_3$ requires C, 44.35; H, 3.95%), $\nu_{max.}$ 1 695 cm^{-1} (C=O), δ 3.85 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 6.93 (1 H, d, *J* 8 Hz, ArH), 7.30 (1 H, d, *J* 8 Hz, ArH), and 10.24 (1 H, s, CHO).

6-*Bromo*-2,3-*dimethoxybenzoic Acid* (13).—To a solution of the aldehyde (11) (4.1 g) and silver nitrate (3.0 g) in water (20 ml) was added 20% sodium hydroxide (20 ml) dropwise with stirring during 30 min at 80—90° C. After continuous stirring for 30 min at the same temperature, the mixture was filtered, and the filtrate was acidified with concentrated hydrochloric acid and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a powder; recrystallisation from benzene–n-hexane afforded the *carboxylic acid* (3.0 g) as needles, m.p. 83—85° (Found: C, 41.6; H, 3.65. $C_9H_9BrO_4$ requires C, 41.4; H, 3.45%), $\nu_{max.}$ 1 725 cm^{-1} (C=O), δ($CDCl_3$) 3.83 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 6.80 (1 H, d, *J* 9 H z, ArH), and 7.26 (1 H, d, *J* 9 Hz, ArH).

6-*Bromo*-2-*hydroxy*-3-*methoxybenzoic Acid* (12).—The oxidation of the aldehyde (10) (2 g) was carried out in the same manner as the synthesis of (13) to give the carboxylic acid (1.8 g) as a gum, which was used without further purification.

Methyl 6-*Bromo*-2,3-*dimethoxybenzoate* (14a).—A mixture of the acid (13) (3 g) and an excess of diazomethane in ether was kept overnight at room temperature. The solvent and the excess of diazomethane were evaporated off and the residue was extracted with chloroform. The organic layer was washed with water, 5% sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and evaporated to afford the *ester* (14a) (2.8 g) as an oil (Found: C, 44.25; H, 4.3. $C_{10}H_{11}BrO_4$ requires C, 43.65; H, 4.05%), $\nu_{max.}$ 1 725 cm^{-1} (C=O), δ($CDCl_3$) 3.82 (3 H, s, OCH_3), 3.91 (3 H, s, OCH_3), 6.79 (1 H, d, *J* 9 Hz, ArH), and 7.15 (1 H, d, *J* 9 Hz, ArH).

The reaction of the acid (13) (1 g) with an excess of diazomethane in ether also gave the ester (14a) (0.8 g), identical with the sample just described.

Methyl 6-*Cyano*-2,3-*dimethoxybenzoate* (15a).—A solution of the ester (14a) (7.0 g) and copper(I) cyanide (3.5 g) in dimethylformamide (30 ml) was refluxed for 4 h with stirring. The mixture was poured into water, acidified with concentrated hydrochloric acid, and then extracted with benzene. The extract was washed with water, dried (Na_2SO_4), and evaporated to afford a pale yellowish solid; recrystallisation from ethanol gave the *cyanide* (15a) (4.8 g) as needles, m.p. 137—140° (Found: C, 59.6; H, 5.1; N, 6.3. $C_{11}H_{11}NO_4$ requires C, 59.7; H, 5.0; N, 6.35%), $\nu_{max.}$ 2 230 (C≡N) and 1 715 cm^{-1} (C=O), δ($CDCl_3$) 3.88 (3 H, s, OCH_3), 3.94 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 6.97 (1 H, d, *J* 9 Hz, ArH), and 7.39 (1 H, d, *J* 9 Hz, ArH).

6,7-*Dimethoxyphthalimidine* (16a).—A solution of the cyanide (15a) (5.0 g) in ethanol (50 ml) was hydrogenated over Raney nickel (2 g) at 80 °C under 80 atm of hydrogen until uptake ceased. The mixture was filtered and the filtrate was evaporated to give a solid; recrystallisation from propan-2-ol afforded the *lactam* (16a) (3.5 g) as needles, m.p. 140—141° (Found: C, 62.05; H, 5.75; N, 7.2. $C_{10}H_{11}NO_3$ requires C, 62.15; H, 5.7; N, 7.25%), $\nu_{max.}$ 3 450 (NH) and 1 680 cm^{-1} (C=O), δ($CDCl_3$) 3.88 (3 H,

[13] R. O. Bernhard and V. Snieckus, *Tetrahedron*, 1971, **27**, 2091.

[14] B. Göbar and G. Engelhardt, *Pharmazie*, 1969, **24**, 423.

s, OCH_3), 4.06 (3 H, s, OCH_3), 4.12 (2 H, s, $ArCH_2{\cdot}N$), and 7.04 (2 H, s, ArH).

6,7-*Dimethoxy*-2-*nitrosophthalimidine* (17a).—To a stirred solution of the lactam (16a) (1 g) in concentrated hydrochloric acid (8 ml) was added a solution of sodium nitrate (1.4 g) in water (10 ml), dropwise, at 0 °C. After continuous stirring for 10 min, the precipitate was collected, washed with water, and recrystallised from ethanol to give the nitroso-compound (17a) (0.8 g) as yellowish *needles*, m.p. 145—147° (Found: C, 53.9; H, 4.6; N, 12.55. $C_{10}H_{10}N_2O_4$ requires C, 54.05; H, 4.55; N, 12.6%), $\nu_{max.}$ 1 680 cm^{-1} (C=O), δ($CDCl_3$) 3.88 (3 H, s, OCH_3), 4.12 (3 H, s, OCH_3), 4.23 (2 H, s, $ArCH_2{\cdot}N$), 7.04 (1 H, d, *J* 8 Hz, ArH), and 7.26 (1 H, d, *J* 8 Hz, ArH).

Ethyl 2-*Cyano*-4,5-*dimethoxybenzoate* (15b).—A solution of the bromobenzoate (14b) (7 g) and copper(I) cyanide (3.5 g) in dimethylformamide was refluxed for 4 h. The mixture was poured into water, then treated with concentrated hydrochloric acid, and extracted with benzene. The organic layer was washed with water and dried (Na_2SO_4). Removal of the solvent left a pale yellowish solid, which was recrystallised from ethanol to give the *cyanide* (15b) (4.5 g) as needles, m.p. 118—119° (Found: C, 61.45; H, 5.35; N, 5.75. $C_{12}H_{13}NO_4$ requires C, 61.25; H, 5.55; N, 5.95%), $\nu_{max.}$ 2 230 (C≡N) and 1 705 cm^{-1} (C=O), δ($CDCl_3$) 1.46 (3 H, t, *J* 8 Hz, $CH_3{\cdot}CH_2$), 3.98 (6 H, s, 2 × OCH_3), 4.46 (2 H, q, *J* 8 Hz, $CH_3{\cdot}CH_2$), 7.17 (1 H, s, ArH), and 7.57 (1 H, s, ArH).

4,5-*Dimethoxyphthalimidine* (16b).—Catalytic reduction of the cyanide (15b) (5 g) was carried out as described in the synthesis of (16a); recrystallisation of the product from ethanol afforded (16b) (3.8 g) as *needles*, m.p. 229—231° (Found: C, 62.05; H, 5.75; N, 7.3. $C_{10}H_{11}NO_3$ requires C, 62.15; H, 5.75; N, 7.25%), $\nu_{max.}$ 3 450 (NH) and 1 680 cm^{-1} (C=O), δ($CDCl_3$) 3.88 (2 H, s, CH_2), 3.90 (6 H, s, 2 × OCH_3), 6.91 (1 H, s, ArH), and 7.53 (1 H, s, ArH).

5,6-*Dimethoxy*-2-*nitrosophthalimidine* (17b).—The nitroso-compound (17b) was obtained from the lactam (16b) (1 g) by the same procedure as in the preparation of (17a). Recrystallisation from ethanol afforded yellowish *needles* (0.8 g), m.p. 128—129° (Found: C, 54.0; H, 4.5; N, 12.6. $C_{10}H_{10}N_2O_4$ requires C, 54.05; H, 4.55; N, 12.6%), $\nu_{max.}$ 1 680 cm^{-1} (C=O), δ($CDCl_3$), 3.88 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3), 3.96 (2 H, s, $CH_2{\cdot}N$), 6.92 (1 H, s, ArH), and 7.52 (1H, s, ArH).

Methyl 6-*Diazomethyl*-2,3-*dimethoxybenzoate* (2a).—To a stirred solution of 5N-sodium methoxide in methanol (2 mol. equiv.) was added the nitroso-compound (17a) (300 mg) in small portions during 2 h at room temperature. Stirring was continued for 15 min, and the mixture was treated with carbon dioxide gas and filtered. The filtrate was concentrated to half volume, poured into water, and extracted with ether. The ethereal layer was washed with sodium chloride solution and dried (K_2CO_3) [$\nu_{max.}$ 2 055 (N_2) and 1 715 cm^{-1} (C=O)], and this solution was used without further purification.

(±)-*Cordrastine* (5a).—A mixture of 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolium iodide (1a) (500 mg) in methanol–chloroform (1 : 1 v/v; 20 ml) and the above diazo-compound in ether was kept at room temperature for 2 days. The solvent was then removed and the residue was chromatographed on silica gel (30 g). Elution with benzene–ethyl acetate (1 : 1 v/v) gave (±)-cordrastine as a gum (70 mg), $\nu_{max.}$ 1 750 cm^{-1} (C=O), δ($CDCl_3$) 2.57 (3 H, s, NCH_3), 3.36 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 3.87 (3 H, s, OCH_3), 4.05 (3 H, s, OCH_3), 5.57 (1 H, d, *J* 4 Hz, $ArCH{\cdot}O$), 6.29 (1 H, s, ArH), 6.52 (1 H, d, *J* 8 Hz, ArH), 6.58 (1 H, s, ArH), and 7.06 (1 H, d, *J* 8 Hz, ArH). The picrate formed yellowish needles (from ethanol), m.p. 198—199° (lit.,[15,16] 202°).

(±)-*Hydrastine* (5b).—The reaction of 3,4-dihydro-6,7-methylenedioxy-2-methylisoquinolinium iodide (1b) (1.5 g) with the diazo-compound (2a) [from the nitroso-compound (1 g)], carried out similarly, gave (±)-hydrastine as a gum (220 mg), $\nu_{max.}$ 1 755 cm^{-1} (C=O), δ($CDCl_3$) 2.53 (3 H, s, NCH_3), 3.86 (3 H, s, OCH_3), 4.03 (3 H, s, OCH_3), 5.43 (1 H d, *J* 4 Hz, $ArCH{\cdot}O$), 5.79 (2 H, s, $O{\cdot}CH_2{\cdot}O$), 6.40 (1 H, s, ArH), 6.53 (1 H, s, ArH), 6.46 (1 H, d, *J* 8 Hz, ArH), and 7.03 (1 H, d, *J* 8 Hz, ArH); the picrate formed yellowish needles (from ethanol), m.p. 210—212°.

Methyl 2-*Diazomethyl*-4,5-*dimethoxybenzoate* (2b).—To a stirred solution of sodium methoxide (2 mol. equiv.) in methanol was added the nitroso-compound (17b) (600 mg) in portions at room temperature during 2 h. The mixture was worked up as described for the preparation of (2a). The product showed $\nu_{max.}$ 2 055 (N_2) and 1 705 cm^{-1} (C=O), and the ethereal solution was used without purification.

5,6-*Dimethoxy*-3-(1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*methylisoquinolin*-1-*yl*)*phthalide* (5c).—A mixture of the diazo-compound (2b) in ether and 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide (1a) (900 mg) was kept at room temperature for 2 days. The solvent was then removed and the residue was chromatographed on silica gel. Elution with benzene–ethyl acetate (1 : 1 v/v) gave an oil, which was recrystallised from ethanol to afford the phthalidylisoquinoline (5c) (160 mg), m.p. 166—167° (lit.,[10] 157—159°), $\nu_{max.}$ 1 755—1 750 cm^{-1}, δ($CDCl_3$) 2.58 (3 H, s, NCH_3), 3.78 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 3.92 (6 H, s, 2 × OCH_3), 4.07 (1 H, d, *J* 4 Hz, H_a), 5.56 (1 H, d, *J* 4 Hz, H_b), 6.18 (1 H, s, ArH), and 6.48 (1 H, s, ArH), identical with an authentic sample.[11]

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[15] R. D. Haworth and A. R. Pinder, *J. Chem. Soc.*, 1950, 1776.
[16] V. Smula, N. E. Cundasawmy, H. O. Holland, and D. B. MacLean, *Canad. J. Chem.*, 1973, **51**, 3287.