Reaction of Protoberberine-type Alkaloids. Part 13.[1] Biogenetic Conversion of Protoberberine Alkaloids into Phthalideisoquinoline Alkaloids [2]

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A new convenient and biogenetic-type conversion of the protoberberine alkaloids into the phthalideisoquinoline alkaloids is described. The phthalideisoquinoline 5,6-dimethoxy-3-(6,7-dimethoxyisoquinolin-1-yl)isobenzofuran-1(3*H*)-one (4) was derived from 8-norcoralyne chloride (1) *via* 13-oxidonorcoralyne (3) in a one-pot reaction consisting of dye-sensitized photo-oxygenation followed by treatment with sodium borohydride. The conversion of berberine chloride into (±)-β-hydrastine (21) was performed by a reaction sequence involving conversion of 8,13a-epidioxy-9,10-dimethoxy-2,3-methylenedioxy-13-oxo-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (9) into 1-(2-carboxy-3,4-dimethoxybenzoyl)-3,4-dihydro-6,7-(methylenedioxy)isoquinoline (11) using pyridinium chloride, followed by methylation and reductive cyclization.

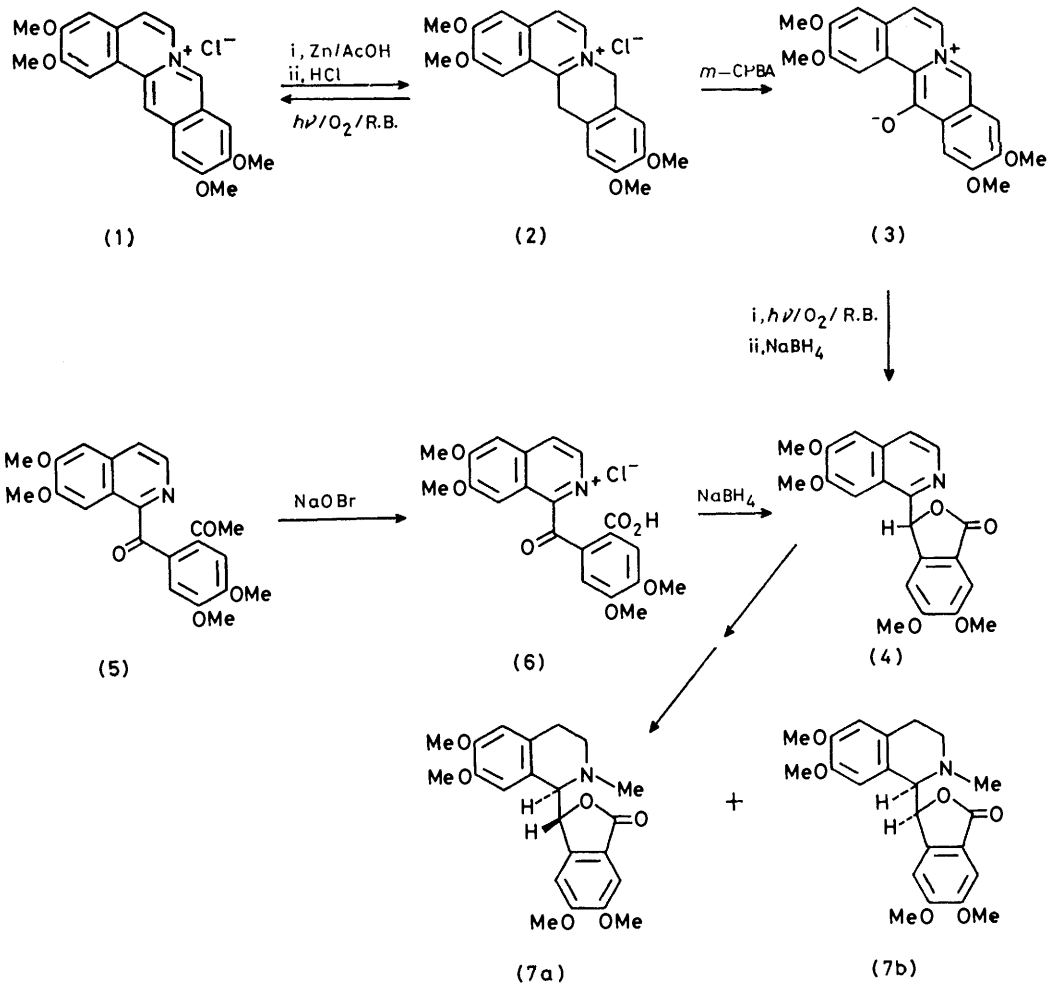
It has been shown that in plants the tetrahydroberberines are versatile biogenetic intermediates in the formation of more highly oxidized members,[3] *e.g.* phthalideisoquinoline-, spirobenzylisoquinoline-, protopine-, benzphenanthridine-, and benzazepine-type alkaloids. According to labelling experiments,[4] narcotine, a typical phthalideisoquinoline, has been ascertained to arise from a protoberberine alkaloid, sculerine, by its oxidative modification in *Papaver somniferum*. Receiving impetus from the elucidation of the biogenetic route, several attempts on the biogenetic conversion of protoberberine alkaloids into phthalideisoquinoline alkaloids have been reported recently.[2,5-8]

For the conversion, two key steps, introduction of the oxygen function on C-13 and oxidative cleavage of the bond between C-8 and N, are essential. We have previously shown that 7,8-dihydroprotoberberine derivatives are appropriate intermediates which can be oxygenated at C-8 and C-13, because of their propensity to quench singlet oxygen with regiospecificity.[1] We now describe a new convenient and biogenetic-type conversion of protoberberine alkaloids into phthalideisoquinoline alkaloids.

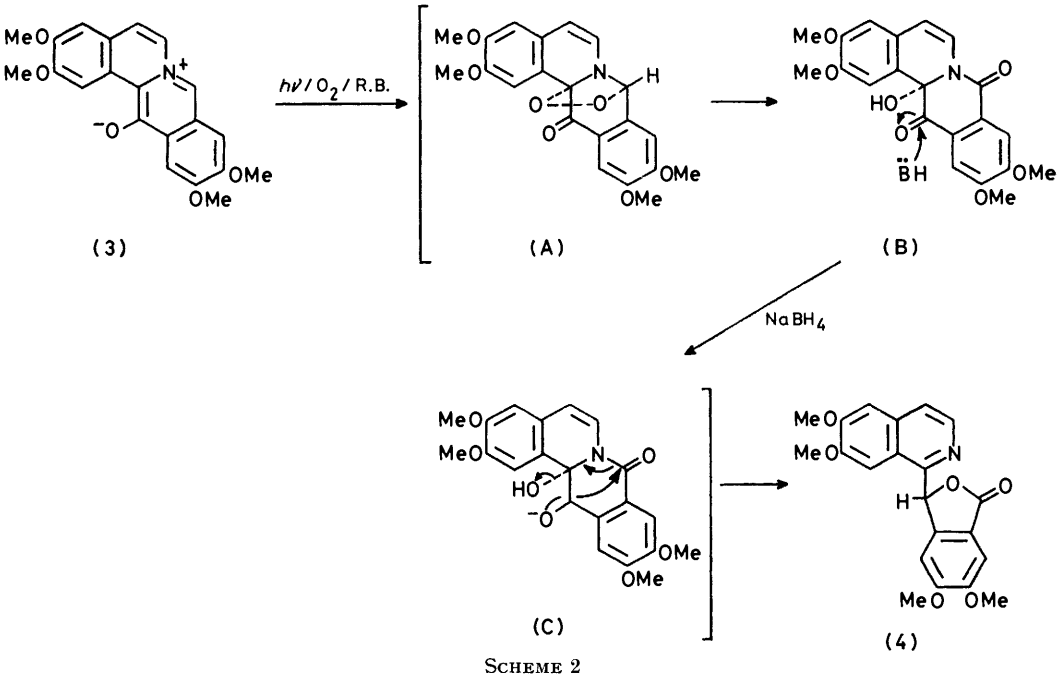
Synthetic efforts were directed first to deriving the hydrastine analogue (7) from the 8-norcoralyne salt (1). 8,13-Dihydro-2,3,10,11-tetramethoxydibenzo[*a*,*g*]quinolizinium chloride (2) was derived from reduction of (1) with deactivated zinc powder in 30% acetic acid [1] followed by treatment with 1% HCl. Oxygenation of (2), under the reaction conditions which yield 13-oxidocoralyne from 7,8-dihydrocoralyne in nearly quantitative yield,[1] did not yield 13-oxidonorcoralyne (3), but gave (1) in 88% yield. An additional selective method, photo-oxygenation in the presence of Rose Bengal,[1] was also ineffective with this compound. Treatment of (2) with *m*-chloroperbenzoic acid in degassed chloroform containing triethylamine at −20 °C afforded (3) in 73% yield. The spectral data of (3) showed a striking similarity to those of 13-oxidocoralyne. A solution of (3) in the presence of Rose Bengal was irradiated with a photo-flood lamp (375 W) for 10 min under aerated conditions, followed by addition of sodium borohydride to the solution. After being left for 30 min at ambient temperature, the reaction mixture was worked up as usual to provide 5,6-dimethoxy-3-(6,7-dimethoxyisoquinolin-1-yl)isobenzofuran-1(3*H*)-one (4) in approximately 70% yield (Scheme 1). Mass spectrometry and microanalysis confirmed the formula for (4). The structure of (4) was assigned on the basis of its spectral data and finally confirmed by an unambiguous synthesis. Oxidation of 2′-acetylpapaveraldine (5) with sodium hypobromite in dioxan, followed by acidification with concentrated HCl, afforded 2′-carboxypapaveraldine hydrochloride (6) in nearly quantitative yield. This was reduced with sodium borohydride in methanol and then the reaction mixture refluxed for 1 h at pH 6.5 to yield the phthalideisoquinoline (4), identical with the above synthetic material (Scheme 1). An acceptable mechanism for this reaction is shown in Scheme 2. With excited singlet oxygen, (3) produces a 1,3-dipolar adduct (A). The transient epidioxide (A) undergoes cleavage of the O–O bond to yield an amido-ketol (B). The amido-ketol (B) is then reduced efficiently by treatment with sodium borohydride followed by lactonization of an anionic intermediate (C) to yield the phthalideisoquinoline (4), which has already been converted into the hydrastin analogues (7a) and (7b) by Shamma *et al.*[8]

Extension of this biogenetic conversion of the coralyne-type alkaloid to the phthalideisoquinoline-type alkaloid could be expected to proceed in an analogous fashion for the berberine-type alkaloid. In the conversion of berberine into β-hydrastine, it seemed that the epidioxide (9) was the most suitable starting material. The preparation of (9) from berberine *via* 13-oxidoberberine (8) was reported in the preceding paper.[1] Treatment of (9) with pyridinium chloride in pyridine afforded three crystalline products, (10),† (11), and (12) in 40.0, 42.0, and 9.8% yields, respectively (Scheme 3). Compound (10) showed the composition $C_{20}H_{17}NO_7 \cdot H_2O$, established by means of microanalysis. The structure of (10) was determined from its spectral data, the i.r. spectrum of (10) indicating the presence of hydroxy,

† The structure (10), except for its stereochemistry, was reported for the decomposed product of oxybisberberine [5] by Shamma *et al.*[6] However, the physical and spectral properties of our compound (10) are different from those of Shamma's.

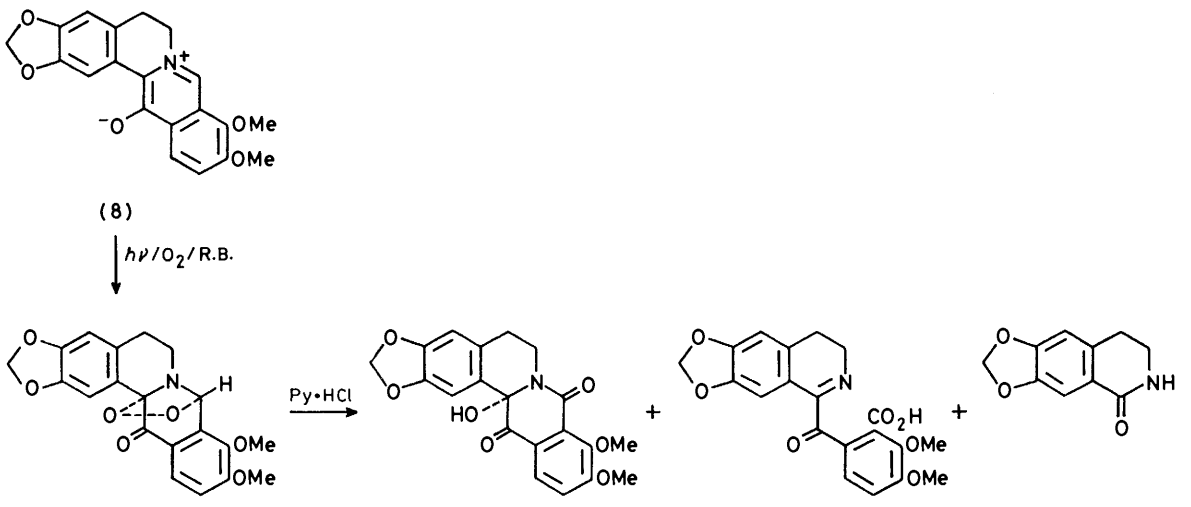


SCHEME 1



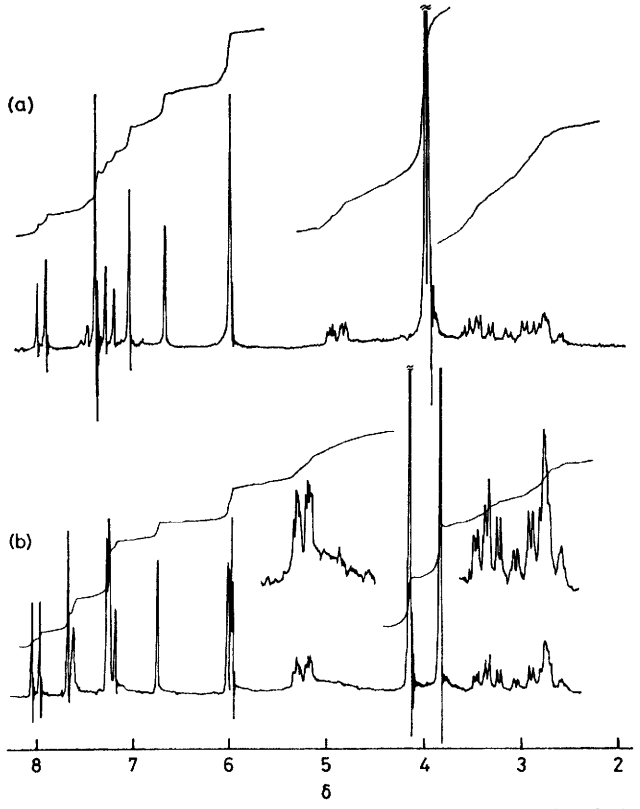
SCHEME 2

carbonyl, and amide groups. Typical ^1H n.m.r. spectra measured in $CDCl_3$ and in $[^2H_5]$pyridine are shown in Figure 1. The combination of the spectral data showed (10) to have a highly oxidized protoberberine skeleton.



SCHEME 3

The structure of (10) was further investigated by the following reactions. Compound (10), when heated in dry methanol, readily gave a methoxy-derivative (13). Addition of trace amounts of acid accelerated this reaction. Similarly, (13) reverted to (10) when kept in aqueous dioxan in the presence of a catalytic amount of concentrated HCl. These interconversions indicate the generation of an iminium intermediate (D). When (13) was reduced with sodium borohydride, a hydroxy-amide (14) was obtained. The n.m.r. spectrum of (14) showed the presence of a hydroxy-proton which was shown to couple with the 12-H ring proton by the double-resonance technique after addition of D_2O; its long-range coupling constant indicates an equatorial conformation for the 13-hydroxy-group. The carbonyl group of (10), consequently, must be situated at the 13-position of the protoberberine skeleton, confirming the structure (10).



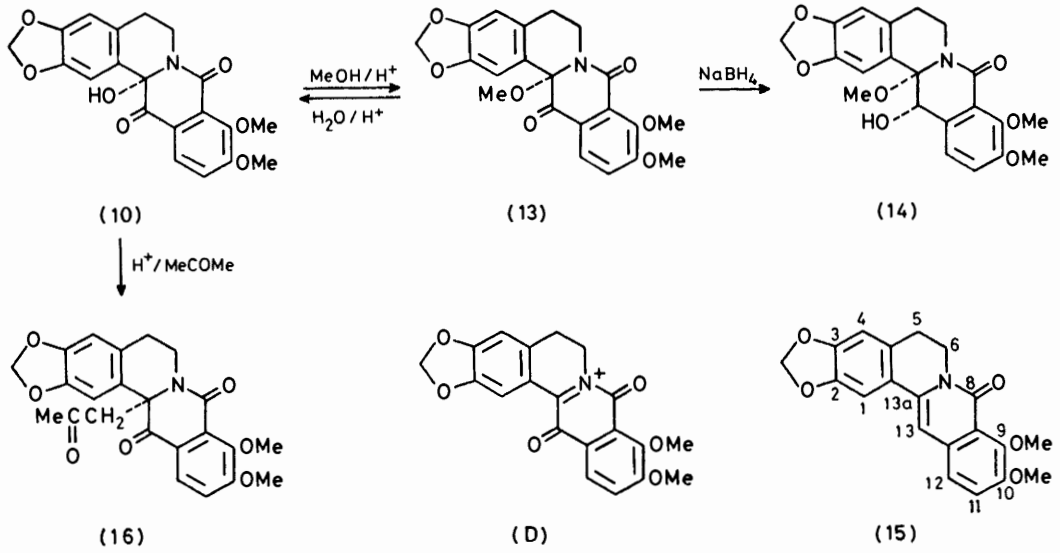
^1H N.m.r. spectra of 13a-hydroxy-9,10-dimethoxy-2,3-(methylenedioxy)-8,13-dioxo-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]-quinolizine (10) measured in (a) $CDCl_3$ and (b) $[^2H_5]$pyridine

Carbon-13 n.m.r. data of 8-oxoprotoberberine derivatives in $CDCl_3$ (p.p.m. from Me_4Si) [a,b]

Carbon	(15)	(10)	(13)	(16)
C-1	104.475 *	107.509 *	109.087 *	105.570 *
C-2	147.188 †	145.610 †	146.460 †	146.130 †
C-3	148.280 †	147.552 †	148.343 †	146.990 †
C-4	107.693 *	110.120 *	108.058 *	109.211 *
C-4a	123.468	124.075	122.920	124.500
C-5	28.515	29.061	28.940	28.030
C-6	39.193	36.038	38.465	37.070
C-8	159.871	161.210	161.696	159.868
C-9	149.251	149.071	149.678	149.375
C-10	151.192	159.084	159.443	159.689
C-11	118.735	114.911	115.032	115.093
C-12	122.192	126.380	124.133	124.194
C-12a	132.141	130.020	131.598	128.683
C-8a	129.714	124.075	124.499	126.563
C-13	101.200	189.051	188.323	191.230
C-13a	135.418	83.847	88.701	67.588
C-13b	119.158	124.075	124.497	125.349
C-9-OCH_3	61.460	61.156	61.520	61.278
C-10-OCH_3	56.667	56.181	56.302	56.182
C-13a-OCH_3			51.449	
$-O-CH_2-O-$	101.320	100.957	101.262	101.081
CH_3COCH_2-				29.547
CH_3COCH_2-				203.435
CH_3COCH_2-				55.575

[a] Assignments were made on the basis of off-resonance experiments and by comparison of the shifts of these compounds. [b] * or † indicates that the assignments may be reversed.

As might be predicted from the interconversion of (10) and (13), the nucleophilic substitutions proceed under thermodynamic control *via* the iminium cation (D) to give a *trans*-quinolizidine isomer. Molecular models, iminium cation undergoes electrophilic attack of active methylene, it was not surprising that heating of (10) in acetone under strongly acidic conditions provided a condensation product (16).

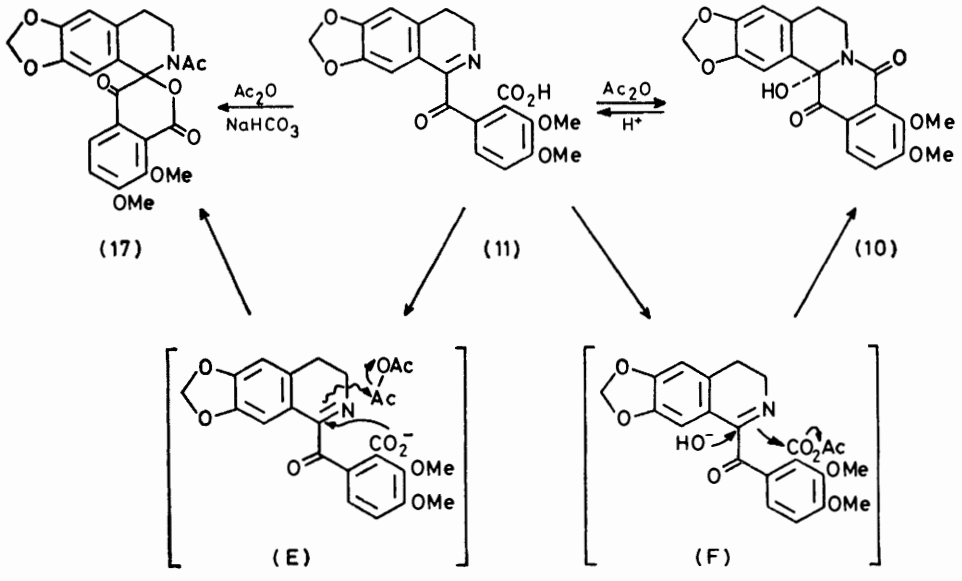


SCHEME 4

show that the axial substituent on C-13a in (10) or (13) projects so as to compress the C-6 carbon and 6-H_α. The evidence for the stereochemistry of (10) and (13) was afforded by the appearance of steric compression shifts [10] for each of the respective hydrogen and carbon resonances. In the ^1H n.m.r. spectra of (10) and (13), the 6-H_α signal showed unusual paramagnetic shifts in $CDCl_3$, while the ^{13}C n.m.r. spectra of these compounds showed the signals for the C-6 carbons to be shifted upfield in comparison with oxyberberine (15) (Table).

Since in the Mannich reaction it is believed that the

Compound (11) showed amphoteric character. Its i.r. spectrum indicated the presence of carboxy and conjugated carbonyl groups. Heating of (11) under reflux in acetic anhydride afforded (10), which reverted to (11) when heated in 25% sulphuric acid (Scheme 5).



SCHEME 5

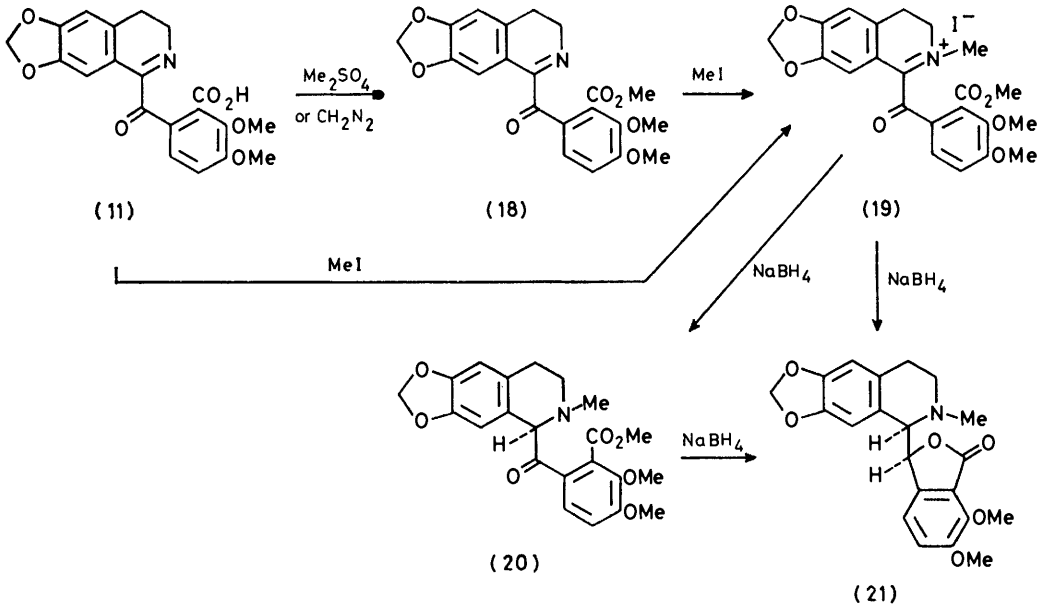
These observations permitted structure (11) to be assigned. On the other hand, when (11) was treated with acetic anhydride in aqueous acetone containing sodium hydrogen carbonate, (17) was obtained as the sole product. The u.v. spectrum of (17) was similar to that of (10). However, together with a molecular formula

which required one additional oxygen and two additional carbon atoms, its i.r. spectrum showed bands assigned to lactone, conjugated carbonyl, and *N*-acetyl groups. The molecular formula and the n.m.r. spectrum supported structure (17). Since (11) is an ambident compound, the favourable reaction depends upon the reaction conditions employed. A reasonable mechanism is shown in Scheme 5.

The third minor product (12) was identified as norhydrastinine [10] from its spectral data.

air. The mixture was heated under reflux for 90 min. After cooling and removal of the metal, the solution was concentrated *in vacuo* to give a yellow syrup. To the residue was added successively with stirring H_2O (10 ml) and 1% HCl (250 ml). Pale yellow needles which were deposited were collected and recrystallized from methanol to afford (2) as yellow needles, m.p. 213—215° (decomp.) (lit.,[13] 212—215°), identical (i.r. and n.m.r. spectra) with authentic material.[14]

2,3,10,11-*Tetramethoxydibenzo*[a,g]*quinolizinium*-13-*olate* (13-*Oxidonorcoralyne*) (3).—A solution of the dibenzo-



SCHEME 6

To complete the reaction sequence, two objectives, *N*-methylation and reductive lactonization had to be accomplished. We achieved the conversion of (11) into the final (±)-β-hydrastine (21) as follows. Methylation of (11) with dimethyl sulphate or diazomethane gave a methyl ester (18). On the other hand, methylation of (11) with methyl iodide in dry tetrahydrofuran provided a quarternary base (19),[11] which was treated with sodium borohydride to afford, *via* the tetrahydro-ester (20), (±)-β-hydrastine (21), identical with a specimen of natural (—)-β-hydrastine [11] with respect to all spectral data (n.m.r., u.v., i.r., and mass spectra) and t.l.c. behaviour (Scheme 6).

EXPERIMENTAL

M.p.s were determined on a Yamato model MP-21 apparatus. I.r. spectra were recorded on a Shimazu IR-7G grating spectrophotometer, and u.v. spectra on a Hitachi 124 spectrometer. N.m.r. data were obtained using Hitachi H-60 and JNM PS-100 spectrometers with tetramethylsilane as internal standard. Mass spectra were obtained on a Hitachi RMU-7 and M-52G spectrometer.

8,13-*Dihydro*-2,3,10,11-*tetramethoxydibenzo*[a,g]*quinolizinium Chloride* (2).—To a solution of 2,3,10,11-tetramethoxydibenzo[*a*,*g*]quinolizinium chloride (norcoralyne) [12] (1) (4.98 g, 12.9 mmol) in 30% AcOH (300 ml) was added zinc powder (10 g) deactivated by storage in contact with quinolizinium chloride (2) (202 mg, 0.522 mmol) in hot $CHCl_3$ (100 ml) was placed in a three-necked flask fitted with a dropping funnel, a thermometer, and a three-way stopcock connected to a water-aspirator and a source of nitrogen gas. After cooling, the system was replaced with nitrogen gas by evacuation and filling with nitrogen several times. The flask was cooled with ice–salt to —20 °C. Triethylamine (0.2 ml) and a solution of *m*-chloroperbenzoic acid (70% purity; 202 mg) in $CHCl_3$ (18 ml) were successively introduced to the flask *via* the dropping funnel with vigorous stirring. The mixture was further stirred for 15 min at room temperature and then powdered K_2SO_3 (70 mg) was added. After removal of inorganic material the solution was concentrated *in vacuo* to give a syrup. Methanol (2 ml) was added to the residue and within a few minutes yellow crystals separated out, which were collected and crystallized from methanol to afford 13-*oxidonorcoralyne* (3) (140 mg, 73.4%) as yellow needles, m.p. 183—185° (Found: C, 68.9; H, 5.45; N, 3.75. $C_{21}H_{19}NO_5$ requires C, 69.05; H, 5.25; N, 3.85%), δ ($CDCl_3$ + CD_3OD) 3.84, 3.93, 4.12, and 4.18 (each 3 H, s, ArO*Me*), 6.80 and 6.91 (each 1 H, s, ArH), 7.11 (1 H, d, *J* 8 Hz, ArH), 7.94 (1 H, s, ArH), 7.76 (1 H, d, *J* 8 Hz, ArH), and 10.39 (1 H, s, ArH), $\lambda_{max.}$ (EtOH) 227 (log ε 4.48), 237sh (4.45), 264 (4.51), 284 (4.50) 296sh (4.40), 319 (4.27), 408sh (4.13), 428 (4.30), and 453 nm (4.38), *m/e* 365 (M^+), 350, and 141.

Auto-oxidative Dehydrogenation of 8,13-*Dihydronorcoralyne* (2) *to Norcoralyne* (1).—A solution of the chloride (2) (154

mg, 0.396 mmol) was brought to pH 8 by addition of a drop of ammonia. After the mixture had been stirred for 2 h in the presence of air at room temperature, it was brought to pH 1 by addition of a few drops of 10% HCl. The yellow precipitate was collected and recrystallized from methanol to give norcoralyne chloride (1) (135 mg, 88.4%) as yellow needles, m.p. 235—237° (decomp.) (lit.,[12] 235—237°).

1-(2-*Carboxy*-4,5-*dimethoxybenzoyl*)-6,7-*dimethoxyisoquinolinium Chloride* (6).—To 2′-acetylpapaveraldine (5) (502 mg, 1.27 mmol), dissolved in dioxan (10 ml), was added dropwise with stirring at 0 °C over a period of 10 min cold sodium hypobromite solution [prepared by dissolving NaOH (3.02 g) and Br_2 (1 ml) in H_2O (16.7 ml)]. The mixture was warmed to room temperature and stirred for an additional 1 h. The resulting bromoform was removed by extraction with ether (10 ml × 3) and a solution of Na_2SO_3 (200 mg) in H_2O (10 ml) was added to the cooled (ice–water) reaction mixture. Concentrated HCl (1 ml) was added dropwise to the solution when a yellow precipitate separated out which was filtered off and washed with 1% HCl and ether. After drying in a desiccator, the precipitate was recrystallized from methanol containing 1% HCl to yield 2′-carboxypapaveraldine hydrochloride (6) (528 mg, 96.1%) as yellow needles, m.p. 198—200° (Found: C, 55.9; H, 4.95; N, 3.35. $C_{21}H_{20}NO_7Cl·H_2O$ requires C, 55.8; H, 4.9; N, 3.1; Cl, 7.85%), δ ([$^2H_6$]DMSO) 3.90 (9 H, s, ArO*Me*), 4.00 (3 H, s, ArO*Me*), 7.27, 7.46, and 7.69 (each 1 H, s, ArH), 8.01 (1 H, d, *J* 8 Hz, ArH), 8.22 (1 H, s, ArH), and 8.35 (1 H, d, *J* 8 Hz, ArH), $\nu_{max.}$ (KBr) 1 665 cm^{-1}, $\lambda_{max.}$ (EtOH) 234 (log ε 4.34), 262 (4.07), 312 (3.85), and 353 nm (3.48).

5,6-*Dimethoxy*-3-(6,7-*dimethoxyisoquinolin*-1-*yl*)*isobenzofuran*-1(3H)-*one* (4).—(*a*) A solution of 13-oxidonorcoralyne (3) (100 mg, 0.273 mmol) in $CHCl_3$–methanol (100 ml; 1 : 19 v/v) containing Rose Bengal (1 ml) was irradiated with a photo-flood lamp (Toshiba, 375 W) for 10 min at 0 °C under a stream of oxygen. $NaBH_4$ (75 mg) was added and the solution left to stand at room temperature for 30 min. After removal of the solvent the residue was extracted with $CHCl_3$ (15 ml × 3) and the combined $CHCl_3$ layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated *in vacuo* to give a syrup. Recrystallization from ethanol gave the ketone (4) (72.3 mg, 69.6%) as colourless crystals, m.p. 192—194° (lit.,[8] 190—192°). The spectral data of (4) were identical with those reported.[8]

(*b*) To a solution of the chloride (6) (235 mg, 0.585 mmol) in methanol (15 ml) was added $NaBH_4$ (121 mg) in small portions with stirring. After the mixture had been stirred for 15 min at room temperature, the solution was concentrated to dryness under reduced pressure. The residue was dissolved in H_2O and the solution subjected to an Amberlite XAD-2 column, which was washed with H_2O to neutrality. Elution with methanol and concentration to 10 ml was followed by heating under reflux for 1.5 h in the presence of a catalytic amount of HCl. After cooling, colourless crystals deposited which were collected and recrystallized from methanol to yield (4) (205 mg, 91.9%) as colourless needles, m.p. 192—194° (lit.,[8] 190—192°).

Treatment of the Epidioxide (9) *with Pyridinium Chloride*.—A mixture of 13-oxidoberberine [1] (8) (1.03 g, 2.93 mmol), *Rose* Bengal (10 mg), pyridine (300 ml), and concentrated HCl (6 ml) was irradiated with a photo-flood lamp (Toshiba, 375 W) for 1 h at 0 °C under a stream of oxygen. After the mixture had been stirred for additional 1 h at room temperature, the solution was concentrated under reduced pressure to give a reddish brown residue, which was then suspended in H_2O (30 ml) and extracted with $CHCl_3$ (50 ml × 3). The combined $CHCl_3$ layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to give a syrup (1.2 g) which was chromatographed on silica gel (40 g). Elution with $CHCl_3$–acetone (10 : 1) afforded first 13a-*hydroxy*-9,10-*dimethoxy*-2,3-(*methylenedioxy*)-8,13-*dioxo*-5,6,13,13a-*tetrahydro*-8H-*dibenzo*[a,g]*quinolizine* (10) (449 mg, 40.0%) which was recrystallized from ether to give colourless needles, m.p. 151—153° (Found: C, 60.0; H, 4.35; N, 3.3. $C_{20}H_{17}NO_7·H_2O$ requires C, 59.85; H, 4.75; N, 3.5%), δ ($CDCl_3$) 2.50—2.92 (2 H, m, 5-H_2), 3.00—3.60 (1 H, m, 6-H), 3.93 and 3.95 (each 3 H, s, ArO*Me*), 4.85 (1 H, m, 6-H), 5.95 (2 H, s, $-OCH_2O-$), 6.63 (1 H, s, 4-H), 7.00 (1 H, s, 1-H), 7.18 (1 H, d, *J* 8 Hz, 11-H), and 7.89 (1 H, d, *J* 8 Hz, 12-H), $\nu_{max.}$ (KBr) 3 270 (OH), 1 720 (ArCO), and 1 635 cm^{-1} (amido), $\lambda_{max.}$ (CH_2Cl_2) 238 (log ε 4.35), 267 (3.90), 291 (3.86), and 323 nm (3.83), *m/e* 365, 350, 320, 193, 172, and 165. Further elution with $CHCl_3$–acetone (10 : 1) afforded 3,4-dihydroxy-6,7-(methylenedioxy)-1-isoquinolone (norhydrastinine) (12) which was recrystallized from methanol–H_2O to give colourless crystals, m.p. 187—188° (lit.,[10] 185—187°). The final eluate with $CHCl_3$–acetone (2 : 1) afforded 1-(2-*carboxy*-3,4-*dimethoxybenzoyl*)-3,4-*dihydro*-6,7-(*methylenedioxy*)*isoquinoline* (11) (493 mg, 42.0%) which was recrystallized from CH_3CN to yield colourless plates, m.p. 160—162° (Found: C, 60.0; H, 4.8; N, 3.6. $C_{20}H_{17}NO_7·H_2O$ requires C, 59.85; H, 4.75; N, 3.5%), δ ([$^2H_5$]pyridine) 2.57 (2 H, t, *J* 9 Hz, 4-H_2), 3.77 (3 H, s, ArO*Me*), 3.80 (2 H, m, 3-H_2), 4.07 (3 H, s, ArO*Me*), 5.97 (2 H, s, $-OCH_2O-$), 6.64 (1 H, s, 5-H), 7.04 (1 H, d, *J* 9 Hz, 5′-H), 7.53 (1 H, s, 8-H), and 7.87 (1 H, d, *J* 9 Hz, 6′-H), $\nu_{max.}$ (KBr) 3 480, 1 710, and 1 665 cm^{-1}, $\lambda_{max.}$ (MeOH) 220 (log ε 4.41), 286 (4.11), and 304 nm (4.01), *m/e* 365, 350, 335, 193, and 165.

9,10,13a-*Trimethoxy*-2,3-(*methylenedioxy*)-8,13-*dioxo*-5,6,13,13a-*tetrahydro*-8H-*dibenzo*[a,g]*quinolizine* (13).—The hydroxy-diketone (10) (100 mg, 0.261 mmol) was heated under reflux in dry methanol (5 ml) for 15 min. After cooling, colourless needles were deposited and were collected; the mother-liquor was concentrated to yield a second crop of the *trimethoxy-compound* (13) (total yield 95 mg, 91.5%), m.p. 158—159° (Found: C, 63.1; H, 5.0; N, 3.35. $C_{21}H_{19}NO_7$ requires C, 63.45; H, 4.9; N, 3.55%), δ ($CDCl_3$) 2.60—3.00 (2 H, m, 5-H_2), 3.00—3.40 (1 H, m, 6-H), 3.19 (3 H, s, 13a-OCH_3), 3.97 and 4.00 (3 H, s, ArO*Me*), 5.04 (1 H, m, 6-H), 5.97 (2 H, s, $-OCH_2O-$), 6.65 (1 H s, 4-H), 7.00 (1 H, s, 1-H), 7.16 (1 H, d, *J* 9 Hz, 11-H), and 7.77 (1 H, d, *J* 9 Hz, 12-H), $\nu_{max.}$ (KBr) 1 710 and 1 650 cm^{-1}, $\lambda_{max.}$ (MeOH) 236 (log ε 4.38), 262sh (4.00), 290 (3.99), and 324 nm (3.85), *m/e* 397 (M^+), 382, 365, 338, 204, 191, and 175.

13-*Hydroxy*-9,10,13a-*trimethoxy*-2,3-(*methylenedioxy*)-8-*oxo*-5,6,13,13a-*tetrahydro*-8H-*dibenzo*[a,g]*quinolizine* (14).—To a methanolic solution (5 ml) of compound (13) (51 mg, 0.128 mmol) was added $NaBH_4$ (23 mg) and the mixture was left to stand at room temperature for 2.5 h. The colourless needles which deposited were filtered off (14 mg, 0.035 mmol) and the filtrate was carefully neutralized with 1% aqueous HCl at 0 °C and then concentrated under reduced pressure to dryness. The residue was suspended in H_2O (1 ml) and extracted with $CHCl_3$ (3 ml × 3). The combined $CHCl_3$ layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated under reduced pressure to give a syrup. Recrystallization from methanol yielded the *hydroxy-ketone* (14) (22 mg, 42.9%) as colourless needles, m.p. 142—144° (Found: C, 62.85; H, 5.2; N, 3.4.

$C_{21}H_{21}NO_7$ requires C, 63.15; H, 5.3; N, 3.5%), δ ($CDCl_3$) 2.33 (1 H, d, *J* 10 Hz, disappeared after addition of D_2O, 13-OH), 2.65—2.90 (3 H, m, 5-H_2 and 6-H), 3.05 (3 H, s, 13a-OMe), 3.86 and 3.96 (3 H, s, ArO*Me*), 4.48 (1 H, dd, J_1 10, J_2 1 Hz, changed to doublet after addition of D_2O; 13-H), 5.16 (1 H, m, 6-H), 5.90 (1 H, d, *J* 2 Hz, −O−C*H*H−O−), 5.96 (1 H, d, *J* 2 Hz, −O−CH*H*−O−), 6.66 (1 H, s, 4-H), 7.01 (1 H, d, *J* 9 Hz, 11-H), 7.03 (1 H, s, 1-H), 7.31 (1 H, dd, J_1 9, J_2 1 Hz, changed to doublet by irradiation of dd at δ 4.48), $\nu_{max.}$ (KBr) 3 450 (OH) and 1 635 cm^{-1} (amide), $\lambda_{max.}$ (MeOH) 232sh (log ε 4.28), 290 (3.82), 308sh cm (3.36), *m/e* 367, 342, 338, 324, 308, and 165.

13a-*Acetonyl*-9,10-*dimethoxy*-2,3-(*methylenedioxy*)-8,13-*dioxo*-5,6,13,13a-*tetrahydro*-8H-*dibenzo*[a,g]*quinolizine* (16).—To a solution of the hydroxy-diketone (10) (203 mg, 0.530 mmol) in acetone was added 30% H_2SO_4 (2 ml). The mixture was heated under reflux for 15 min. After cooling the precipitate was filtered off. The filtrate was neutralized with 10% $NaHCO_3$ and then concentrated under reduced pressure. The residue was extracted with AcOEt (10 ml × 3) and the combined AcOEt layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to give a crystalline residue. Recrystallization from methanol afforded the condensation product (16) (195 mg, 87.0%) as colourless crystals, m.p. 190—191° (Found: C, 65.45; H, 5.1; N, 3.25. $C_{23}H_{21}NO_7$ requires C, 65.2; H, 5.0; N, 3.3%), δ ($CDCl_3$) 2.12 (3 H, s, COMe), 2.58—3.00 (1 H, m, 5-H), 3.00—3.40 (2 H, m, 5- and 6-H), 3.57 (1 H, d, *J* 18 Hz, 13a-C*H*H−CO−), 3.90 (1 H, d, *J* 18 Hz, 13a-CH*H*−CO−), 4.01 (6 H, s, ArO*Me*), 5.18 (1 H, m, 6-H), 5.92 (1 H, d, *J* 1 Hz, −OC*H*HO−), 5.98 (1 H, d, *J* 1 Hz, −O−CH*H*−O−), 6.62 (1 H, s, 4-H), 7.22 (1 H, d, *J* 8 Hz, 11-H), 7.28 (1 H, s, 1-H), and 8.01 (1 H, d, *J* 8 Hz, 12-H), $\nu_{max.}$ (KBr) 1 720 (ketone), 1 675 (conjugated ketone, and 1 650 cm^{-1} (amide), $\lambda_{max.}$ (MeOH) 237 (log ε 4.45), 279sh (4.10), 290 (4.11), and 319 cm (3.97), *m/e* 423 (M^+), 380, 367, 366, and 165.

Conversion of the Diketone (10) *into the Acid* (11).—A suspension of compound (10) (105 mg, 0.274 mmol) in 25% H_2SO_4 was heated at 70 °C for 2 h. After cooling, the reaction mixture was neutralized with $Ba(OH)_2$. The white precipitate was filtered off and the filtrate repeatedly extracted with $CHCl_3$. The combined $CHCl_3$ layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was recrystallized from MeCN to yield compound (11) (88 mg, 83.9%) as colourless plates, m.p. 160—162°.

Conversion of the Acid (11) *into the Diketone* (10).—A mixture of compound (11) (100 mg, 0.261 mmol) and Ac_2O (1 ml) was heated on a boiling water-bath for 3 min. The excess of AC_2O was removed by evaporation under reduced pressure and the residue was subjected to column chromatography on silica gel (5 g). Elution with $CHCl_3$–acetone (10 : 1) afforded compound (10) (92 mg, 92.0%) which was recrystallized from ether–$CHCl_3$ to yield needles, m.p. 151—153°.

7,8-*Dimethoxy*-1,4-*dioxoisochroman*-3-*spiro*-1′-(2′-*acetyl*-1′,2′,3′,4′-*tetrahydro*-6′,7′-*methylenedioxyisoquinoline*) (17).—To a solution of the acid (11) (100 mg, 0.261 mmol) in acetone (5 ml) was added 25% aqueous $NaHCO_3$ (0.5 ml). The solution was left to stand at room temperature for 10 min when Ac_2O (3 ml) was added. The mixture was heated on a boiling water-bath for 10 min, and then evaporated *in vacuo* to remove the excess of Ac_2O. The residue was extracted with $CHCl_3$ (10 ml × 3) and the combined $CHCl_3$ layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure to give a syrup which was recrystallized from methanol to yield compound (17) (102 mg, 91.9%) as colourless needles, m.p. 194—196° (Found: C, 62.2; H, 4.45; N, 3.0. $C_{22}H_{19}NO_8$ requires C, 62.1; H, 4.5; N, 3.3%), δ ($CDCl_3$) 2.25 (3 H, s, >N−CO−Me), 2.81 (1 H, dd, J_1 16, J_2 3 Hz, 4′-*H*H), 3.16 (1 H, dd, J_1 12, J_2 5 Hz, 3′-*H*H), 3.44 (1 H, dd, J_1 16, J_2 5 Hz, 4′-H*H*), 3.70 (1 H, dd, J_1 12, J_2 3 Hz, 3′-H*H*), 4.05 and 4.08 (3 H, s, ArO*Me*), 5.90 (1 H, d, *J* 1 Hz, −O−C*H*H−O−), 5.95 (1 H, d, *J* 1 Hz, −O−C*H*H−O−), 6.51 (1 H, s, 8′-H), 6.71 (1 H, s, 5′-H), 7.30 (1 H, d, *J* 9 Hz, 5-H), and 7.87 (1 H, d, *J* 9 Hz, 6-H), $\nu_{max.}$ (KBr) 1 740 (lactone), 1 690 (conjugated ketone), and 1 650 (amide) cm^{-1}, $\lambda_{max.}$ (CH_2Cl_2) 240 (log ε 4.43), 283sh (4.13), 289 (4.18), and 322 nm (3.98), *m/e* 409, 365, 350, 336, 320, 306, 292, 265, 193, and 165.

3,4-*Dihydro*-(3,4-*dimethoxy*-2-*methoxycarbonylbenzoyl*)-6,7-(*methylenedioxy*)*isoquinoline* (18).—(*a*) To a methanolic solution (1 ml) of the acid (11) (121 mg, 0.316 mmol) was added Me_2SO_4 (0.25 ml). The mixture was heated on a boiling water-bath for 1 h and then evaporated under reduced pressure to remove the methanol. The residue was extracted with AcOEt (10 ml × 3) and the combined AcOEt layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated *in vacuo* to give a syrup. The syrup was chromatographed on silica gel (6 g). Elution with $CHCl_3$ afforded compound (18) (115 mg, 91.7%) as an oil, δ ($CDCl_3$) 2.73 (2 H, t, *J* 8 Hz, 4-H_2), 3.82 (3 H, s, $ArCO_2Me$), 3.84 (2 H, m, 3-H_2), 3.91 and 3.95 (3 H, s, ArO*Me*), 5.98 (2 H, s, $-OCH_2O-$), 6.70 (1 H, s, 8-H), 6.94 (1 H, d, *J* 9 Hz, 5′-H), 7.00 (1 H, s, 5-H), and 7.61 (1 H, d, *J* 9 Hz, 6′-H), $\nu_{max.}$ ($CHCl_3$) 1 730 (ester) and 1 665 cm^{-1} (conjugated ketone), $\lambda_{max.}$ ($CHCl_3$) 241 (log ε 4.24), 280 (4.18), and 309 nm (4.20), *m/e* 397 (M^+), 367, 365, 352, 336, 320, 223, 193, and 165.

(*b*) To a methanolic solution of compound (11) (50 mg, 0.130 mmol) was added a solution of diazomethane in ether (2 ml) prepared in the usual way. Evaporation of the solvent afforded compound (18) (52 mg, 100%).

3,4-*Dihydro*-1-(3,4-*dimethoxy*-2-*methoxycarbonylbenzoyl*)-2-*methyl*-6,7-(*methylenedioxy*)*isoquinolinium Iodide* (19).—(*a*) To a solution of the acid (11) (150 mg, 0.392 mmol) in dry tetrahydrofuran (15 ml) was added methyl iodide (1 ml). After the mixture had been left to stand at room temperature for 2 days, the solution was evaporated under reduced pressure to give a residue. Recrystallization from MeCN afforded compound (19) (203 mg, 96.1%) as yellow crystals, m.p. 141—142° (lit.,[11] 141—142°). The spectral data of (19) were identical with those reported.[11]

(*b*) To a solution of (18) (202 mg, 0.510 mmol) in MeCN (5 ml) was added methyl iodide (1 ml). The mixture was allowed to stand at room temperature overnight and then evaporated *in vacuo*. Recrystallization of the residue from MeCN afforded compound (19) (268 mg, 97.7%) as yellow crystals, m.p. 141—142°.

1,2,3,4-*Tetrahydro*-1-(3,4-*dimethoxy*-2-*methoxycarbonylbenzoyl*)-2-*methyl*-6,7-(*methylenedioxy*)*isoquinoline* (20).—To a methanolic solution (2 ml) of compound (19) (100 mg, 0.186 mmol) was added $NaBH_4$ (10 mg, 0.264 mmol) and the reaction mixture allowed to stand at room temperature for 30 min. After careful neutralization with dilute HCl, the mixture was concentrated *in vacuo* at <20 °C to yield a residue which was suspended in H_2O (5 ml) and extracted with AcOEt (5 ml × 3). The combined AcOEt layer was dried (Na_2SO_4) and evaporated *in vacuo* to give a syrup.

Recrystallization from methanol afforded the *keto-ester* (20) (70 mg, 91.1%) as colourless crystals, m.p. 147—149° (Found: C, 63.9; H, 5.8; N, 3.45. $C_{22}H_{23}NO_7$ requires C, 63.9; H, 5.6; N, 3.4%), δ ($CDCl_3$) 2.32 (3 H, s, NMe), 2.20—3.30 (4 H, m, $ArCH_2CH_2N$), 3.81 (3 H, s, ArO*Me*), 3.84 (3 H, s, $ArCO_2Me$), 3.93 (3 H, s, ArO*Me*), 4.27 (1 H, s, Ar–CH–N<), 5.83 (2 H, s, $-OCH_2O-$), 6.48 and 6.61 (each 1 H, s, ArH), and 6.74 and 7.85 (each 1 H, d, *J* 8 Hz, ArH), $\nu_{max.}$ (KBr) 1 720 (ester) and 1 675 cm^{-1} (conjugated ketone), $\lambda_{max.}$ (CH_2Cl_2) 230 (log ε 4.26), 278 (4.07), and 295 nm (4.06), *m/e* 413 (M^+) and 190.

(±)-β-*Hydrastine* (21).—To a methanolic solution (5 ml) of compound (19) (200 mg, 0.371 mmol) was added $NaBH_4$ (70 mg, 1.85 mmol). After the mixture had been left at room temperature for 30 min, it was worked up in the usual way to provide (±)-β-hydrastine (21) (140 mg, 95.5%), m.p. 151—152° (lit.,[11] 151—152°). The spectral data of (21) were identical with those of (−)-β-hydrastine.

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