Reaction of Protoberberine-type Alkaloids. Part 12.[1] A Facile Method for Regiospecific Oxygenation and Excited Oxidative Ring-cleavage of Berberine Alkaloids[2]

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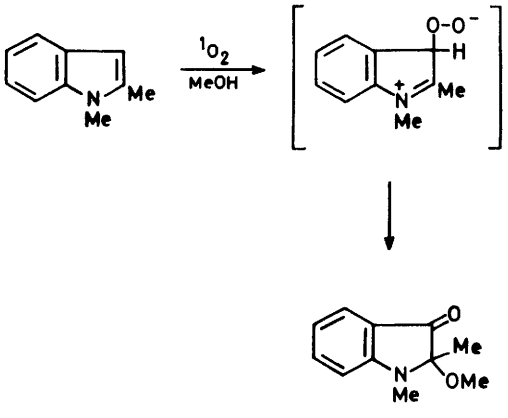
Regiospecific photo-oxygenation and photo-oxidative ring-cleavage of protoberberine alkaloids is described. Irradiation of a solution of dihydroberberine (1) in the presence of Rose Bengal under aerated conditions gave 13-oxidoberberine (3) along with berberine (2) in 80 and 7% yields, respectively. In contrast, 7,8-dihydrocoralyne (5) gave 13-oxidocoralyne (7) in nearly quantitative yield when an aerated solution of (5) was heated in the dark. Irradiation of a solution of (3) containing Rose Bengal with visible light afforded 8,13a-epidioxy-9,10-dimethoxy-2,3-(methylenedioxy)-13-oxo-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolozine (11) in 90% yield. Under the same conditions, however, (7) gave 2'-acetylpapaveraldine (14) in 88% yield. On the other hand, when an alcoholic solution of (5) or (7) containing sodium alkoxide was irradiated with a mercury lamp (Vycol filter) under bubbling oxygen, 6,7-dimethoxyisoquinolone (15) and 3-alkoxy-5,6-dimethoxy-3-methylisobenzofuran-1(3*H*)-one (17) or (18) were obtained in moderate yields. A reaction mechanism which involves the initial formation of an epidioxy-intermediate was evidenced by the fact that the photolysis of (7) was carried out in the presence of borohydride anion to give (15) and 5,6-dimethoxy-3-methylisobenzofuran-1(3*H*)-one (19). Irradiation of (11) in the same fashion gave berberal (20) and 2-(2-formyl-3,4-dimethoxybenzoyl)-3,4-dihydro-6,7-(methylenedioxy)isoquinolin-1(2*H*)-one (21) in 72% and 4% yields, respectively. Possible mechanisms are also presented.

Reduction of (3) with sodium borohydride gave (±)-ophiocarpine (9) and (±)-13-epiophiocarpine (10), with the ratio (9) : (10) varying depending upon the nature of the alcohol used as solvent. An interpretation which rationalizes these observations is suggested.

SINCE the pioneer work of Pyman was first reported,[3] many methods have been designed for the synthesis of C-13-oxygenated berberine alkaloids.[4-9] Recently, the synthetic utility of photo-oxygenation of cyclic enamines has been demonstrated in indole alkaloids.[10-14] In these cases, β-addition of singlet oxygen on the enamine is usually followed by rearrangement of a peroxide intermediate to furnish indoxyl derivatives (Scheme 1). We

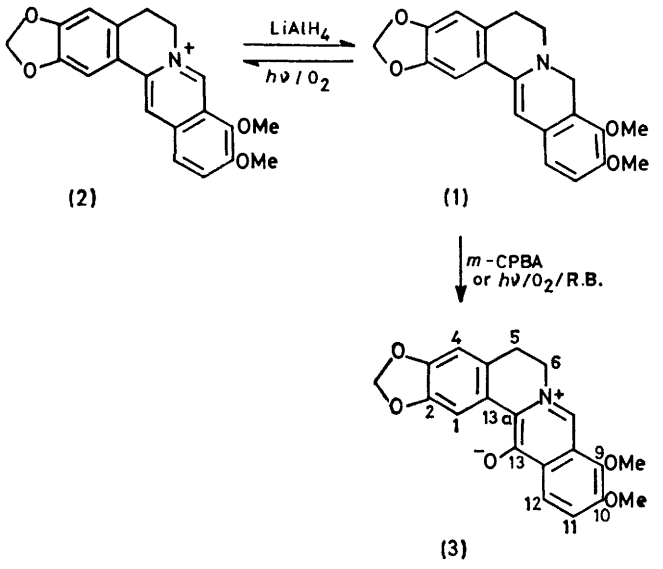


SCHEME 1

have now extended photo-oxygenation to 1,2-dihydroisoquinoline enamines. The present paper describes a general method for regiospecific introduction of an oxygen function at position 13 of protoberberine alkaloids by means of oxygenation. The synthetic significance of the C-13-oxygenated protoberberines in leading to other more highly oxygenated alkaloids is discussed. Additionally, because of the similarity of excited-state oxygenation with enzymic oxidation of isoquinoline alkaloids,[15,16] exhaustive oxygenation of protoberberine alkaloids, resulting in formation of isoquinolones and phthalides, is also described.

Oxygenation of Dihydroprotoberberines.—It is well known that 1,2-dihydroisoquinoline, a typical cyclic enamine, is readily auto-oxidized to isoquinoline. Dihydroberberine (1),[17,18] which involves a 1,2-dihydroisoquinoline moiety, was slowly auto-oxidized to berberine in solution,[19] the reaction being greatly accelerated by light. In contrast, when a solution of (1) in methanol containing Rose Bengal was irradiated with a medium-pressure mercury lamp (450 W) for 5 min under aerated conditions, 13-oxidoberberine (3) was obtained in 80% yield. In the absence of sensitizer, irradiation of (1) afforded berberine (2) (70%) along with a small quantity of (3) (8%) (Scheme 2). Compound (3) was identified by direct comparison with an authentic specimen.[4]

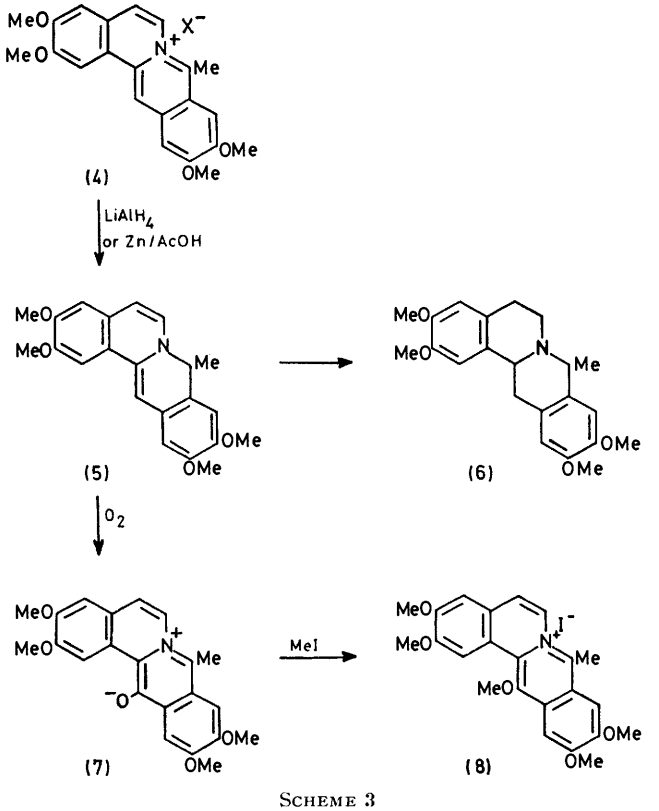
To evaluate its generality, we have applied photo-oxygenation to 7,8-dihydrocoralyne (5), a 5,6-dehydro-analogue of dihydroberberine. Although 7,8-dihydrocoralyne may be obtained by the usual lithium aluminium hydride reduction of the coralyne salt (4), it was prepared most effectively by partial reduction of (4) with zinc–acetic acid. Thus when the coralyne salt (4) was refluxed with deactivated zinc powder in 30% acetic acid, 7,8-dihydrocoralyne (5), $C_{22}H_{23}NO_4$, m.p. 184—186°, was obtained as the sole product in 86.5% yield. The n.m.r. spectrum of (5) in [$^2H_6$]benzene showed a doublet at δ 1.27 for the C-8 methyl protons and the spectral evidence fully supports structure (5) (see Experimental section). On the other hand, when fresh zinc powder (oxide-free) was used, reduction of (4) gave the usual perhydro-compound, coralydine (6), $C_{22}H_{27}NO_4$ (M^+ at *m/e* 369), m.p. 146—147° (lit.,[20] 146—148°), in



SCHEME 2

88% yield. Surprisingly, a solution of (5) in hot ethanol kept in the dark led to smooth auto-oxidation to the phenolic betaine (7) in nearly quantitative yield. The structure of (7) was assigned on the basis of spectral data (see Experimental section). The crucially important signals at δ 10.83 and 8.17 for the C-1 and C-12 aromatic protons showed the presence of the paramagnetic phenolate anion at C-13. In addition, the structure of (7) was unequivocally confirmed by its conversion into 13-methoxycoralyne iodide (8) which showed an additional n.m.r. methoxy-signal.

Although the exact mechanism is not known, the photo-oxygenation of (1) or (5) may be reasonably explained by a sequence involving nucleophilic attack of triplet or singlet oxygen at C-13 *via* the charge-transfer transient, followed by successive elimination of the C-8 and C-13 hydrogens to give the products (3) or (7) (Scheme 4). As described above, oxygenation of 7,8-dihydrocoralyne (5) proceeded under ground-state conditions and might be attributable to the low oxidation–reduction potential of (5).



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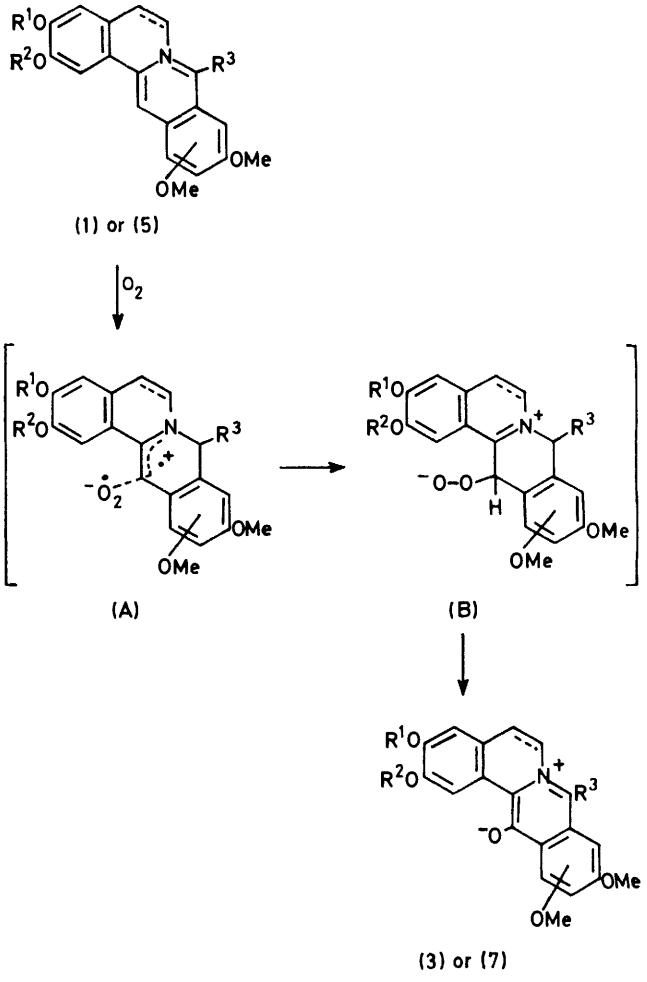


SCHEME 4

Reduction of 13-*Oxidoberberine* (3).—Reduction of phenolic betaines with sodium borohydride has proved to be an efficient method for synthesis of the 13-hydroxyprotoberberines.[4,5] However, in our hands reduction of (3) with sodium borohydride was affected by the nature of the alcohol used as solvent and the products were formed in varying quantities depending upon the acceptor number [21] of the solvent-alcohol. When the reduction was performed in methanol, (±)-ophiocarpine (13β-OH) (9) and (±)-13-epiophiocarpine [22] (13α-OH) (10) were obtained in 80% and 9% yields, respectively.

Reduction in ethanol afforded (9) and (10) in *ca.* 62% and 22% yields, respectively, and in n-propyl alcohol gave almost equal quantities of (9) (49%) and (10) (45%). These results, in the light of the acyclic push-pull mechanism,[23] can be interpreted as due to concurrent (formula C) or prior proton transfer (formula D) from the solvent-alcohol to carbonyl. The rise of the acceptor number (acidity) of the solvent probably increases the protonation of the carbonyl prior to attack of the borohydride anion, thus giving rise to the favourable transient D which is then reduced to borohydride anion to (9) under kinetic control. On the other hand, the reduction in n-propyl alcohol might proceed by a concurrent transfer of the solvent hydrogen and the borohydride anion to give a 1 : 1 mixture of (9) and (10) (Table 1).

On the basis of these results, 13-hydroxytetrahydroberberines were prepared directly from dihydroberberin

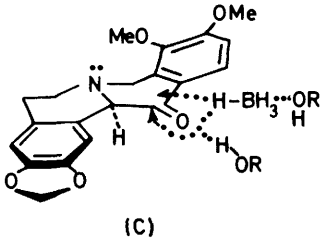
TABLE 1

Variation of product ratios with solvent for reduction of 13-oxidoberberine (3) with sodium borohydride

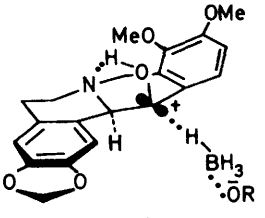
Solvent	Acceptor number	Product ratio (9) : (10)
methanol	41.3	9 : 1
ethanol	37.1	3 : 1
n-propanol	33.5	1 : 1

by a one-pot reaction. After photo-oxidation of (1) as described above, sodium borohydride was added to the reaction mixture to give (9) and (10) in good yields. Although several studies on the synthesis of 13-oxygenated berberine alkaloids have been reported, it is our opinion that the reaction described herein has a significant value as a synthetic method for the regiospecific oxygenation of berberine rings.

Photo-oxygenation of Phenolic Betaines.—The possibility of the phenolic betaines (3) and (7) acting as 1,3-dipolarophiles was suggested by the known ground-state reactivity of heteroaromatic betaines.[24] Both (3) and

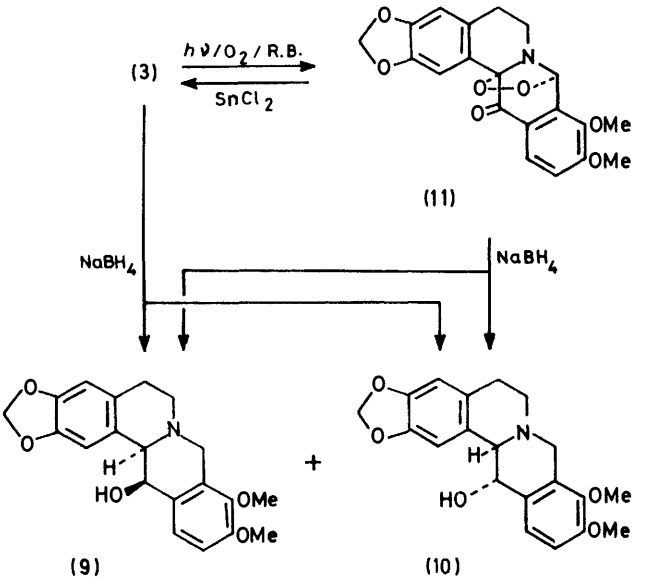


(C)



(D)

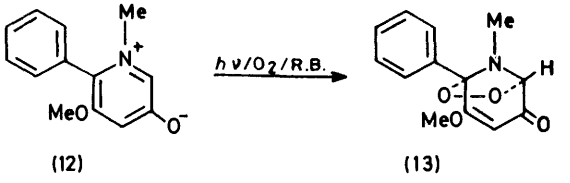
(7) were found in fact to be susceptible to photo-oxidation. When a solution of (3) in methanol was irradiated using a medium-pressure mercury lamp or exposed to sunlight, its visible absorption maximum disappeared within 10 min, the product being the new epidioxide derivative (11) in 42% yield. The preferred procedure was to irradiate a solution of (3) containing Rose Bengal with a photo-flood lamp at 0 °C. The reaction mixture was then evaporated *in vacuo* below 10 °C to give (11) in *ca.* 90% yield. Mass spectrometry and microanalysis confirmed the formula $C_{20}H_{17}NO_7$ for (11). The i.r. spectrum of (11) displayed an absorption for a conjugated carbonyl group at 1 690 cm^{-1} and lacked that for a hydroxy-group. The u.v. spectrum showed absorption maxima at 226, 269, and 309 nm. Its n.m.r. spectrum in [$^2H_6$]acetone revealed the presence of two methylene groups, two methoxys, a methylenedioxy, a methine proton, and four aromatic ring protons. A highly deshielded singlet appearing at δ 6.54 was consistent with the chemical shift of the proton on the carbon bearing the oxygen and nitrogen atoms. Treatment of (11) with tin(II) chloride resulted in formation of (3) in 80% yield. Reduction of (11) with sodium borohydride gave a mixture of (9) and (10), identical with authentic samples (Scheme 5). Combination of the



SCHEME 5

spectral data with the evidence from the chemical conversions indicated the structure of (11) to be 8,13a-epidioxy-9,10-dimethoxy-2,3-(methylenedioxy)-13-oxo-5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine.

Tamura *et al.* have recently reported[25] the photo-oxygenation of 5-methoxy-1-methyl-6-phenylpyridinium-3-olate (12) to give the similar 1,3-dipolar cyclo-adduct (13) (Scheme 6). However, when a methanolic solution

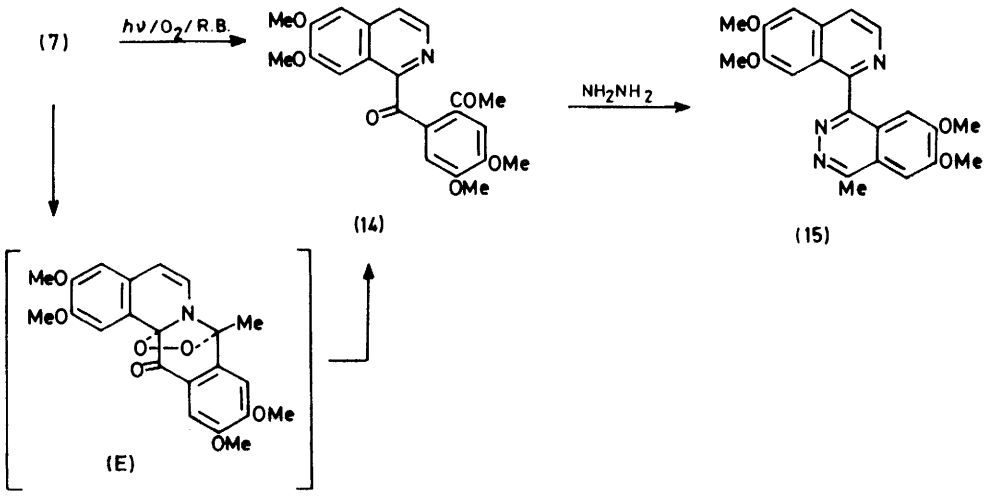


SCHEME 6

of (7) containing Rose Bengal was irradiated in the same fashion, a papaveraldine derivative (14) was obtained instead of the expected epidioxide; (14) was also obtained by treatment of (7) with 1.2 equivalents of *m*-chloroperbenzoic acid, but in lower yield. The n.m.r. spectrum of (14) showed a singlet at δ 2.31 assigned to an

acetyl group and the i.r. spectrum displayed acetyl carbonyl absorptions at 1 670 and 1 355 cm^{-1}. Treatment of (14) with hydrazine hydrate gave the expected phthalazine derivative (15) which was characterized by the absence of a carbonyl absorption in its i.r. spectrum. Thus the structure of (14) was deduced to be 1-(2-acetyl-3,4-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline (2′-acetylpapaveraldine). The oxidative cleavage of (7) methoxide, the photo-oxidation of (7) gave (16) and 3-ethoxy-5,6-dimethoxy-3-methylisobenzofuran-1(3*H*)-one (18) in *ca.* 45 and 30% yields, respectively.

We described above that irradiation of (7) with a photo-flood lamp in the presence of Rose Bengal gave 2′-acetylpapaveraldine (14) in 80% yield and showed the epidioxide (E) as a likely intermediate in the reaction. Although the epidioxide (E) has still not been isolated, a



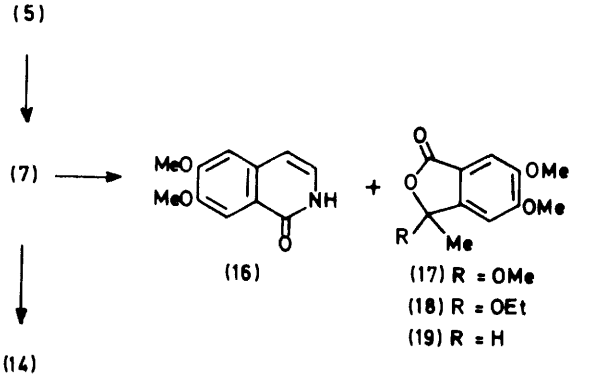
SCHEME 7

would be initiated by formation of the epidioxide intermediate (E) (Scheme 7).

The epidioxide (11) has usefulness not only as a precursor of oxygenated protoberberine alkaloids, but as an intermediate in the synthesis of the phthalideisoquinoline alkaloids. These results are reported in the following paper.

Photochemical Ring-cleavage of Phenolic Betaines.— Naturally occurring isoquinolone alkaloids are regarded as arising from enzymic oxidation of benzylisoquinoline and/or berberine alkaloids.[26] Although there is no experimental evidence on the mode of cellular oxidation of protoberberine alkaloids, it is anticipated that they would be metabolized oxidatively. We now describe the oxidative ring cleavage of these alkaloids; this imitates the concept of the enzymic oxidation.

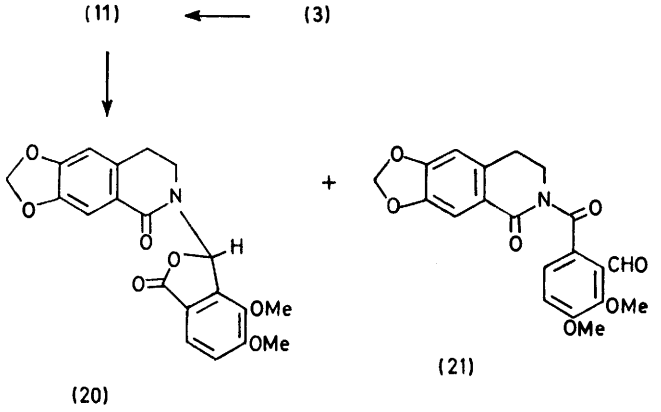
A solution of 7,8-dihydrocoralyne (5) in hot methanol was kept for 2 h when sodium methoxide was added. The solution was irradiated with a medium-pressure mercury lamp equipped with a Vycol filter under aerated conditions to give 6,7-dimethoxyisoquinolone (16)[27] and 3,5,6-trimethoxy-3-methylisobenzofuran-1(3*H*)-one (17) in 47.5 and 35.0% yields, respectively. Undoubtedly the photo-oxidative cleavage of (5) to (15) and (16) proceeds *via* initial formation of 13-oxidocoralyne (7), because the same reaction occurred when a solution of (7) in methanol in the presence of sodium methoxide was irradiated with a medium-pressure mercury lamp under bubbling oxygen (Scheme 8). Analogously, when a sodium ethoxide–ethanol solution was used in place of sodium more detailed mechanism is required to clarify the photochemical properties of the epidioxide. Therefore, as another example the irradiation of the epidioxide (11) was performed. When a solution of (11) was irradiated through a Vycol filter, two products, berberal (20)[28] and 2-(2-formyl-3,4-dimethoxybenzoyl)-3,4-dihydro-6,7-(methylenedioxy)isoquinolin-1(2*H*)-one (21) were obtained in 72.0% and 3.8% yields, respectively (Scheme 9). The



SCHEME 8

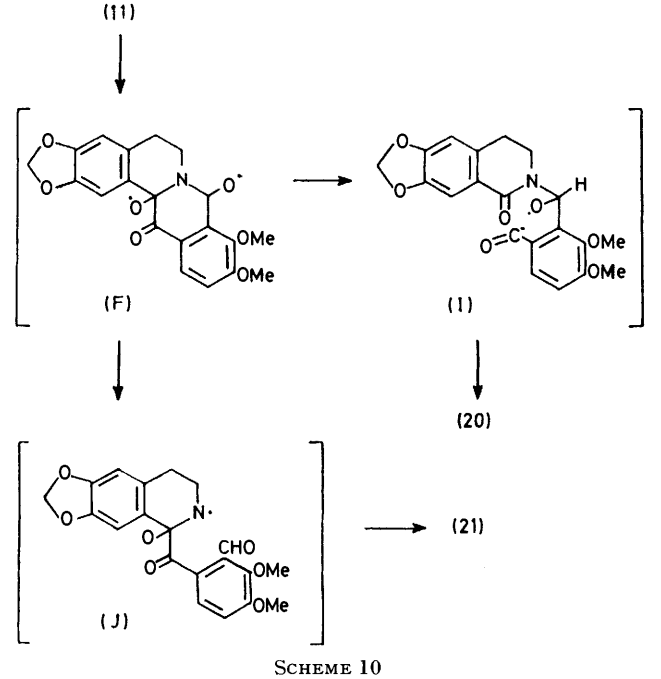
structure of (21) was deduced on the basis of its i.r. and, particularly, its n.m.r. spectral data, in which a singlet at δ 10.45 was assigned as an aldehydic proton. We consider that the photolysis of (11) must be initiated by homolytic cleavage of the O–O bond to generate the biradical (F), which is transformed into the biradicals

(I) or (J) with accompanying cleavage of the bond between C-13 and C-13a or of the bond between N and C-8, respectively. The biradical (I) gives the predominant product, berberal (20), while (J) permits rearrangement of the benzoyl moiety, leading to the aldehyde (21) (Scheme 10). Photolysis of (11) in the presence of a source of anions gave 3,4-dihydro-6,7-(methylenedioxy)isoquinolin-1(2*H*)-one (noroxyhydrastinine) and the phthalide derivative [29] as in the case of photolysis of 13-oxidocoralyne (7).



SCHEME 9

The epidioxide (11) was transformed into (20) and (21) by heat. This transformation takes place even in the crystalline state at room temperature. Under thermal conditions, the biradical intermediate (I) and (J) might



SCHEME 10

be formed in similar equilibrium concentrations to yield a 1 : 1 mixture of (20) and (21). The same transformation was observed in the case of treatment of (11) with ferrous ion.[30] The yields of (20) and (21) for the photolysis, thermolysis, and rearrangement with ferrous ion are given in Table 2.

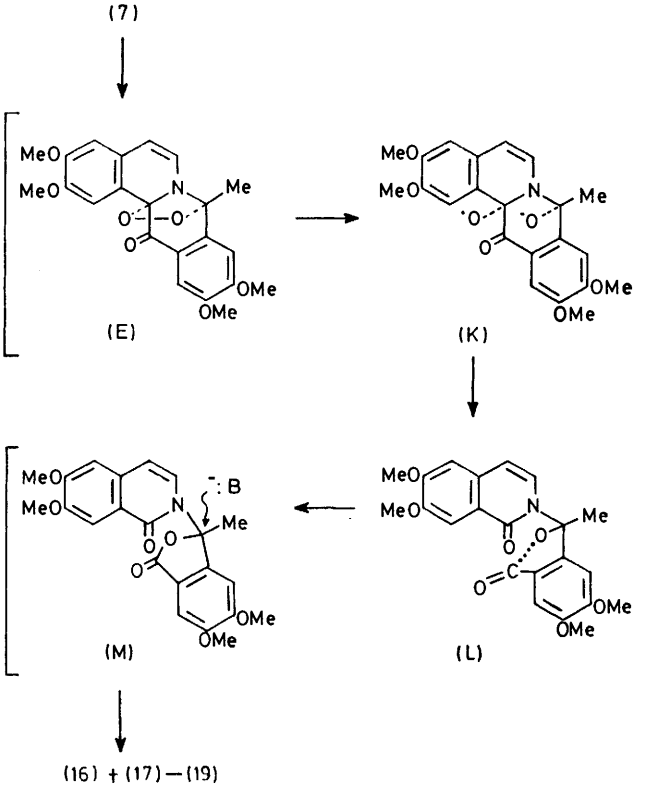
On the basis of these results the proposed mechanism for the photo-oxidative degradation of (7) is shown in Scheme 11. The phthaloylisoquinolone intermediate (M) is hydrolysed in the final step by concomitant attack of the nucleophile to yield the isoquinolone (16) and the corresponding phthalide. The mechanism is further

TABLE 2

Product yields for ring-cleavage of the epidioxide (11)

Method	Yield (%) (20)	(21)
hν	72.0	3.8
heat	43.6	45.8
$FeSO_4$	60.1	33.2

supported by the fact that the photolysis of (7) was carried out in methanol in the presence of sodium borohydride to give (16) and 5,6-methoxy-3-methylisobenzofuran-1(3*H*)-one (19) [31] in *ca.* 26 and 16% yields, respectively. In the final step of the mechanism, the



SCHEME 11

borohydride anion attacks the intermediate (M) to give the isoquinolone (15) and the phthalide (19). Irradiation of (7) in a caustic alkaline solution gave (15) as the only isolable product.

The mechanism of cellular oxidation of the berberine alkaloids is still unknown. However, taking into account the similarity between the biotransformation of benzylisoquinoline alkaloids [32-36] and their oxidative

cleavage with singlet oxygen,[15,16] the cellular degradation of the berberine alkaloids might be brought about by a mechanism similar to that described in this paper.

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 Hitachi RMU-7 and M-52G mass spectrometers.

Photo-oxidative Dehydrogenation of Dihydroberberine (1) *to Berberine* (2).—A solution of dihydroberberine (1) (118 mg, 0.350 mmol) in $CHCl_3$ (40 ml) was irradiated for 5 min with a medium-pressure mercury lamp (Ushio UM452, 450 W) equipped with a Pyrex filter in a water-cooled immersion apparatus under a stream of oxygen. Removal of the solvent *in vacuo* gave a syrup which crystallized from methanol–benzene (16 ml; 1 : 15 v/v) to afford a yellow precipitate. Recrystallization from methanol containing 1% HCl afforded berberine chloride (2) (91 mg, 70.0%) as yellow needles, m.p. 204—206° (decomp.). After removal of (2) the mother-liquor was concentrated *in vacuo* and the residue subjected to preparative t.l.c. ($CHCl_3$–methanol, 9 : 1 v/v) to yield 13-oxidoberberine (3) (10 mg, 8.0%), m.p. 261—263° (lit.,[4] 263°).

Dye-sensitized Photo-oxygenation of Dihydroberberine (1) *to 13-Oxidoberberine* (3).—A mixture of dihydroberberine (1) (106 mg, 0.316 mmol), methanol (150 ml), and Rose Bengal (1 mg) was irradiated with a medium-pressure mercury lamp (Ushio UM452, 450 W) equipped with a Pyrex filter in a water-cooled immersion apparatus under a stream of oxygen. The mixture was concentrated under reduced pressure to afford yellow needles. After removal of the needles by filtration, the filtrate was concentrated to give a second crop of yellow needles. Recrystallization of the combined crude crystals from methanol furnished 13-oxidoberberine (3) (89 mg, 80.0%) as yellow needles, m.p. 261—263° (lit.,[4] 263°). The mother-liquor after removal of (3) was concentrated *in vacuo* and 1% HCl (1 ml) was added to the residue whereupon a yellow precipitate was deposited. Filtration and recrystallization from H_2O afforded berberine chloride (2) (8.3 mg, 7.0%) as yellow needles, m.p. 204—206° (decomp.).

2,3,10,11-*Tetramethoxy*-8-*methyl*-8H-*dibenzo*[a,g]*quinolizine* (7,8-*Dihydrocoralyne*) (5).—To a solution of coralyne sulphoacetate (4)[37] (4.04 g, 8.02 mmol) in 30% AcOH (100 ml) was added zinc powder (6.05 g) deactivated by storage in air for several months. The mixture was heated under reflux for 75 min. After cooling and removal of zinc, the solution was evaporated *in vacuo*. The residue was diluted with ice-water (200 ml) and concentrated ammonia solution (10 ml). The resulting yellow solution was extracted with $CHCl_3$ (150 ml × 3). The combined $CHCl_3$ layer was dried over Na_2SO_4 and evaporated *in vacuo* to give a yellowish brown syrup, which recrystallized from ethanol to yield 7,8-dihydrocoralyne (5) (2.53 g, 86.5%), m.p. 184—186° (lit.,[37a] 200°), as fine yellow crystals, δ ([$^2H_6$]benzene) 1.27 (3 H, d, *J* 7 Hz, 8-Me), 3.44, 3.54, 3.56, and 3.62 (each 3 H, s, ArO*Me*), 4.49 (1 H, q, *J* 7 Hz, 8-H), 5.68 (1 H, d, *J* 8 Hz, 5-H), 6.13 (1 H, d, *J* 8 Hz, 6-H), 5.96 (1 H, s, 3-H), and 6.35, 6.38, 6.55, and 7.13 (each 1 H, s, ArH), *m/e* 365 (M^+), 350, and 334.

2,3,10,11-*Tetramethoxy*-8-*methyl*-13-*oxidodibenzo*[a,g]*quinolizinium* (13-*Oxidocoralyne*) (7).—An ethanolic solution (400 ml) of 7,8-dihydrocoralyne (5) (2.00 g, 5.47 mmol) was heated under reflux in the presence of air for 2 h. After cooling, fine orange needles were deposited which were collected and the mother-liquor was concentrated to give a second crop, total yield 1.93 g (92.8%). Recrystallization from ethanol provided orange needles of 13-*oxidocoralyne* (7), m.p. 191—193° (Found: C, 69.55; H, 5.75; N, 3.4. $C_{22}H_{21}NO_5$ requires C, 69.65; H, 5.6; N, 3.7%), δ ($CDCl_3$) 2.80 (3 H, s, 8-Me), 3.98 (6 H, s, ArO*Me*), 4.17 and 4.22 (each 3 H, s, ArO*Me*), 6.83 and 6.96 (each 1 H, s, ArH), 7.14 (1 H, d, *J* 9 Hz, 5-H), 7.82 (1 H, d, *J* 9 Hz, 6-H), 8.17 (1 H, s, 12-H), and 10.83 (1 H, s, 1-H), *m/e* 379 (M^+), 364, and 348. $\lambda_{max.}$ (MeOH) 230sh (log ε 4.54), 236 (4.55), 264 (4.43), 288 (4.37), 323 (4.24), 411 (4.00), 439 (4.09), and 466 nm (4.15). To a solution of (7) (100 mg, 0.266 mmol) in ethanol (20 ml) was added 10% HCl (1 ml). 13-Hydroxy-2,3,10,11-tetramethoxydibenzo[*a,g*]quinolizinium chloride (103 mg, 0.248 mmol), m.p. 248—250° (decomp.), separated out within a few minutes as yellow needles which were collected by filtration, $\lambda_{max.}$ (EtOH) 215 (log ε 4.07), 224 (4.06), 236sh (3.90), 260sh (3.89), 270sh (4.02), 280sh (4.18), 288 (4.24), 304 (4.22), 314 (4.22), 330 (4.16), 367 (3.45), 394sh (3.61), 419 (3.88), 442 (4.01), and 470sh nm (3.39).

2,3,10,11-*Pentamethoxydibenzo*[a,g]*quinolizinium Iodide* (13-*Methoxycoralyne Iodide*) (8).—To a suspension of 13-oxidocoralyne (7) (504 mg, 1.32 mmol) in $CHCl_3$ (5 ml) was added methyl iodide (1 ml) and the mixture was heated at 90 °C in a sealed tube for 2 h. After cooling, the yellow precipitate was collected and recrystallized from ethanol to afford 13-*methoxycoralyne iodide* (8) as fine yellow needles (484 mg, 70.3%), m.p. 182—184° (decomp.) (Found: C, 52.8; H, 4.3; N, 2.8. $C_{23}H_{24}NO_5I$ requires C, 53.0; H, 4.65; N, 2.7%), δ ([$^2H_6$]DMSO) 2.50 (3 H, s, 8-Me), 3.96 (6 H, s, ArO*Me*), 4.00, 4.13, and 4.18 (each 3 H, s, ArO*Me*), 7.57 (2 H, s, ArH), 7.81 (1 H, s, ArH), 7.90 (1 H, d, *J* 8 Hz, 5-H), 8.86 (1 H, d, *J* 8 Hz, 6-H), and 8.97 (1 H, s, ArH), $\lambda_{max.}$ (EtOH) 221 (log ε 4.24), 235sh (4.09), 244sh (3.96), 288 (4.28), 305 (4.34), 316 (4.37), 331 (4.28), 367 (3.54), 390sh (3.51), 414 (3.83), and 436 nm (3.98).

Reduction of 13-*Oxidoberberine* (3) *with Sodium Borohydride.*—(*a*) To a methanolic solution (400 ml) of 3-oxidoberberine (3) (1.00 g, 2.85 mmol) was added $NaBH_4$ (1.00 g) and the mixture left overnight at room temperature. The precipitate was recrystallized from methanol–$CHCl_3$ to afford (±)-ophiocarpine (9) (810 mg, 80.0%) as colourless needles, m.p. 272—273° (lit.,[4] 272—273°). The mother-liquor was concentrated *in vacuo* and the resulting residue extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated aqueous NaCl and dried (Na_2SO_4). After removal of the $CHCl_3$, the residue was recrystallized from methanol to provide (±)-13-epiophiocarpine (10) (92.5 mg, 9.1%) as colourless needles, m.p. 183—185° (lit.,[22] 176—178°), δ ($CDCl_3$) 2.26 (1 H, br s, 13-OH), 2.75 (2 H, m, 5-H_2), 3.12 (2 H, m, 6-H_2), 3.48 (1 H, d, *J* 8.5 Hz, 13a-H), 3.66 (1 H, d, *J* 16 Hz, 8β-H), 3.88 and 3.90 (each 3 H, s, ArO*Me*), 4.13 (1 H, d, *J* 16 Hz, 8α-H), 4.70 (1 H, br d, *J* 8.5 Hz, 13-H), 5.96 (2 H, s, $-OCH_2O-$), 6.64 (1 H, s, 4-H), 6.90 (1 H, d, *J* 8 Hz, 11-H), 7.29 (1 H, d, *J* 8 Hz, 12-H), and 7.45 (1 H s, 1-H), *m/e* 355 (M^+), 337 ($M^+ - H_2O$), 177, and 165, $\nu_{max.}$ (KBr) 3 300 (OH), 2 740, and 2 780 cm^{-1} (Bohlmann band).

(*b*) To an ethanolic solution (40 ml) of (3) (226 mg, 0.644 mmol) was added $NaBH_4$ (143 mg) and the mixture left

overnight at room temperature. Work-up as described above afforded (9) (142 mg, 61.9%), m.p. 272—273°, and (10) (51 mg, 22.4%), m.p. 183—185°.

(*c*) To a propanolic solution (40 ml) of (3) (201 mg, 0.573 mmol) was added $NaBH_4$ (135 mg) and the mixture allowed to stand at room temperature overnight. Work-up as described above afforded (9) (101 mg, 49.8%) and (10) (93 mg, 45.6%).

8,13a-*Epidioxy*-9,10-*dimethoxy*-2,3-(*methylenedioxy*)-13-*oxo*-5,6,13,13a-*tetrahydro*-8H-*dibenzo*[a,g]*quinolizine* (11).—A mixture of 13-oxidoberberine (3) (100 mg, 0.285 mmol), Rose Bengal (1.0 mg), $CHCl_3$ (2 ml), and methanol (100 ml) was irradiated with a photo-flood lamp (Toshiba, 375 W) at 0 °C for 1 h under a stream of oxygen. The solvent was evaporated off at <10 °C and the red residue collected (98 mg, 89.8%). Recrystallization from methanol yielded the *epidioxide* (11) as colourless prisms, m.p. 100.5—101.5° (Found: C, 62.3; H, 4.7; N, 3.5. $C_{20}H_{17}NO_7$ requires C, 62.65; H, 4.45; N, 3.65%), δ ([$^2H_6$]acetone) 2.80 (2 H, m, 5-H_2), 3.25 (2 H, m, 6-H_2), 3.88 (3 H, s, ArO*Me*) 3.98 (each 3 H, s, 2 ArO*Me*), 6.01 (2 H, s, $-OCH_2O-$), 6.54 (1 H, s, 8-H), 6.71 (1 H, s, 1- or 4-H), 6.82 (1 H, s, 1- or 4-H), 7.20 (1 H, d, *J* 8 Hz, 11-H), and 7.75 (1 H, d, *J* 8.5 Hz, 12-H), *m/e* 383 (M^+), 354, 338, 324, 220, 193, and 190, $\nu_{max.}$ (KBr) 1 690 cm^{-1} (conj. carbonyl), $\lambda_{max.}$ (EtOH) 226 (log ε 4.49), 269 (4.04), and 309 nm (3.93).

Reaction of the Epidioxide (11) *with Stannous Chloride.*—To a solution of the epidioxide (11) (100 mg, 0.261 mmol) in tetrahydrofuran (10 ml) was added a solution of $SnCl_2$ (50 mg) in H_2O (2 ml) with vigorous stirring at 0 °C. The mixture was stirred at room temperature for 20 min, and then concentrated *in vacuo*. The residue was suspended in H_2O (10 ml) and extracted with CH_2Cl_2 (10 ml × 3). The combined CH_2Cl_2 layer was washed with saturated NaCl and dried (Na_2SO_4). After removal of the solvent, the residue was recrystallized from methanol to provide the phenol-betaine (3) (68 mg, 74.2%) as yellow needles, m.p. 261—263° (lit.,[4] 263°).

Reduction of the Epidioxide (11) *with Sodium Borohydride.*—To a suspension of the epidioxide (11) (50 mg, 0.131 mmol) in methanol (5 ml) was added $NaBH_4$ (30 mg) and the mixture allowed to stand at room temperature for 2 h. The colourless needles which were deposited were collected and recrystallized from methanol to provide (±)-ophiocarpine (9) (39 mg, 82.8%) as colourless needles, m.p. 272—273° (lit.,[4] 272—273°). The mother-liquor was concentrated *in vacuo* and the resulting residue extracted with $CHCl_3$. The $CHCl_3$ layer was washed with saturated NaCl and dried (Na_2SO_4). After removal of the solvent, the residue was recrystallized from methanol to provide (±)-13-epiophiocarpine (10) (3 mg, 6.7%) as colourless needles, m.p 183—185° (lit.,[22] 176—178°).

1-(2-*Acetyl*-3,4-*dimethoxybenzoyl*)-6,7-*dimethoxyisoquinoline* (2′-*Acetylpapaveraldine*) (14).—(*a*) A mixture of 13-*oxidocoralyne* (7) (500 mg, 1.32 mmol), Rose Bengal (5 mg), CH_2Cl_2 (10 ml), and methanol (200 ml) was irradiated with a photo-flood lamp (Toshiba, 375 W) at 0 °C for 1 h under a stream of oxygen. The reaction mixture was concentrated *in vacuo* to give coloured crystals which were subjected to chromatography on alumina (5 g). Elution with AcOEt and recrystallization from methanol gave 2′-acetylpapaveraldine (14) (459 mg, 88.0%) as colourless prisms, m.p. 203—205° (Found: C, 69.5; H, 5.55; N, 3.8. $C_{22}H_{21}NO_6$ requires C, 69.65; H, 5.6; N, 3.7%), δ ($CDCl_3$) 2.31, 3.93, 3.96, 4.00, and 4.08 (each 3 H, s, ArO*Me*), 7.01, 7.11, and 7.15 (each 1 H, s, ArH), 7.50 (1 H, d, *J* 6 Hz, 4-H), 8.17 (1 H, d, *J* 6 Hz, 3-H), and 8.45 (1 H, s, ArH), *m/e* 395 (M^+), 352 ($M^+ - COCH_3$), $\nu_{max.}$ (KBr) 1 670 (conj. carbonyl) and 1 355 cm^{-1} (CH_3CO), $\lambda_{max.}$ (EtOH) 237 (log ε 4.41), 314 (3.66), and 326 nm (3.66).

(*b*) The stirred suspension of 13-oxidocoralyne (7) (1.04 g, 2.75 mmol) in CH_2Cl_2 (150 ml) was cooled to −20 °C in a ice–salt-bath and a solution of *m*-chloroperbenzoic acid (70% purity; 660 mg, 3.84 mmol) in CH_2Cl_2 (25 ml) was added dropwise with stirring over 20 min. Stirring was continued at room temperature for 40 min. The reaction mixture was then washed with 10% ammonia (50 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give a residue which was recrystallized from methanol to yield (14) (705 mg, 67.4%) as colourless prisms, m.p. 203—205°.

1-(6,7-*Dimethoxy*-4-*methylphthalazin*-1-*yl*)-6,7-*dimethoxyisoquinoline* (15).—A mixture of 2′-acetylpapaveraldine (14) (196 mg, 0.500 mmol), hydrazine hydrate (30 mg, 0.600 mmol), $CHCl_3$ (3 ml), and ethanol (3 ml) was heated under reflux for 1 h. After evaporation the residue was recrystallized from ethanol to yield (15) as colourless crystals (161 mg, 82.3%), m.p. 229—231° (Found: C, 67.35; H, 5.5; N, 11.0. $C_{22}H_{21}N_3O_4$ requires C, 67.5; H, 5.4; N, 10.75%), δ ($CDCl_3$) 3.02 (3 H, s, Ar*Me*), 3.77 (6 H, s, ArO*Me*), 3.99 and 4.03 (each 3 H, s, ArO*Me*), 7.09 (2 H, s, ArH), 7.23 (2 H, s, ArH), 7.56 (1 H, d, *J* 6 Hz, 4-H), and 8.45 (1 H, d, *J* 6 Hz, 3-H), *m/e* 391 (M^+), 376, and 360, $\nu_{max.}$ (KBr) 1 620 and 1 610 cm^{-1} (>C=N–).

Photo-oxidative Ring-cleavage of 13-*Oxidocoralyne* (7) *with Sodium Methoxide.*—A mixture of 13-oxidocoralyne (7) (100 mg, 0.263 mmol), sodium (70 mg), and dry methanol (25 ml) was irradiated for 10 min with a medium-pressure mercury lamp (Ushio UM452, 450 W) equipped with a Vycol filter in an ice–water-cooled immersion apparatus under a stream of oxygen. After neutralization with 10% HCl, the reaction mixture was concentrated *in vacuo*. The residue was suspended in H_2O (10 ml) and extracted with AcOEt (20 ml × 3). The combined AcOEt layer was washed with saturated NaCl, dried (Na_2SO_4), and evaporated to give a syrup, preparative t.l.c. ($CHCl_3$–10% methanol: two elutions) of which afforded 6,7-dimethoxyisoquinolone (16) (25.6 mg, 47.5%), m.p. 244—245° (from $CHCl_3$–benzene) (lit.,[27] 237°) (Found: C, 64.3; H, 5.45; N, 6.9. $C_{11}H_{11}NO_3$ requires C, 64.45; H, 5.4; N, 6.85%), δ ($CDCl_3$) 1.75 (1 H, br s, >NH), 4.01 and 4.04 (3 H, s, ArO*Me*), 6.46 (1 H, d, *J* 8 Hz, 4-H), 6.88 (1 H, s, 5-H), 7.10 (1 H, d, *J* 8 Hz, 3-H), and 7.75 (1 H, s, 8-H), $\nu_{max.}$ (KBr) 3 450 (>NH) and 1 658 cm^{-1} (amide), $\lambda_{max.}$ (EtOH) 246 (log ε 4.26), 253sh (4.00), 268 (3.45), 278 (3.48), 290 (3.51), 310 (3.25), 322 (3.35), and 335 nm (3.24), *m/e* 205 (M^+), 190, 176, and 162, and 3,5,6-*trimethoxy*-3-*methylisobenzofuran*-1(3H)-*one* (17) (22 mg, 35.0%), m.p. 150—152° (from ethanol) (Found: C, 60.7; H, 5.8. $C_{12}H_{14}O_5$ requires C, 60.5; H, 5.9%), δ ($CDCl_3$) 1.80 (3 H, s, 3-Me), 3.07 (3 H, s, 3-OMe), 3.93 (6 H, s, ArO*Me*), 6.80 (1 H, s, 4-H), and 7.20 (1 H, s, 7-H), $\nu_{max.}$ (KBr) 1 745 cm^{-1} (lactone), $\lambda_{max.}$ (EtOH) 221 (log ε 4.14), 257 (3.71), 293 (3.60), and 300(sh) nm (3.57, *m/e* 238 (M^+), 223, and 207.

Photo-oxidative Ring-cleavage of 13-*Oxidocoralyne* (7) *with Sodium Ethoxide.*—A mixture of 13-oxidocoralyne (7) (100 mg, 0.263 mmol), sodium (70 mg), and dry ethanol (25 ml) was irradiated for 10 min as described above. Usual work-up afforded (16) (29 mg, 54.4%) and 3-*ethoxy*-5,6-*dimethoxy*-3-*methylisobenzofuran*-1(3H)-*one* (18) (31 mg, 46.0%) as an oil (Found: C, 62.0; H, 6.5. $C_{13}H_{16}O_5$

requires C, 61.9; H, 6.4%), δ ($CDCl_3$) 1.15 (3 H, t, *J* 8 Hz, OCH_2CH_3), 1.82 (3 H, s, 3-Me), 3.00—3.60 (2 H, m, OCH_2-CH_3), 3.97 and 4.02 (each 3 H, s, ArO*Me*), 6.90 (1 H, s, 4-H), and 7.30 (1 H, s, 7-H), $\nu_{max.}$ ($CDCl_3$) 1 755 cm^{-1} (lactone), $\lambda_{max.}$ (EtOH) 223 (log ε 4.14), 261 (3.62), 293 (3.50), and 300(sh) nm (3.48), *m/e* 252 (M^+).

Photo-oxidative Ring-cleavage of 13-*Oxidocoralyne* (7) *with Sodium Borohydride.*—A mixture of 13-oxidocoralyne (7) (1.00 g, 2.64 mmol), sodium borohydride (3.00 g), and methanol (500 ml) was irradiated for 20 min using the same procedure. Usual work-up afforded (16) (140 mg, 26.0%) and 5,6-dimethoxy-3-methylisobenzofuran-1(3*H*)-one (19) (86 mg, 16.3%), m.p. 101—102° (lit.,[26] 100—101°).

Photo-oxidative Ring-cleavage of 13-*Oxidocoralyne* (7) *with Sodium Hydroxide.*—A mixture of 13-oxidocoralyne (7) (100 mg, 0.264 mmol), sodium hydroxide (3.0 g), and methanol (100 ml) was irradiated for 20 min under the same fashion. Work-up as above afforded (16) (16 mg, 0.078 mmol, 29.6%).

Photo-cleavage of the Epidioxide (11).—A solution of the epidioxide (11) (100 mg, 0.261 mmol) in methanol was irradiated for 10 min with a medium-pressure mercury lamp (Ushio UM452, 450 W) equipped with a Vycol filter. The solution was concentrated *in vacuo* and the residue chromatographed on silica gel (8 g). Elution with $CHCl_3$ afforded 3-[3,4-dihydro-1-oxo-6,7-(methylenedioxy)-2*H*-isoquinolin-2-yl]-4,5-dimethoxy-1(3*H*)-isobenzofuranone (berberal) (20) (72 mg, 72.0%) which was recrystallized from methanol as colourless needles, m.p. 153—155° (lit.,[28] 148—150°), δ ([$^2H_6$]benzene) 2.25 (2 H, t, *J* 7 Hz, $ArCH_2CH_2N<$), 2.59 (1 H, dd, J_1 7, J_2 14 Hz, $ArCH_2CHHN<$), 2.86 (1 H, dd, J_1 7, J_2 14 Hz, $ArCH_2CHHN<$), 3.35 and 3.61 (each 3 H, s, ArO*Me*), 5.37 (2 H, s, $-OCH_2O-$), 6.13 (1 H, s, $-COO-CH-N<$), 6.50 and 7.43 (each 1 H, d, *J* 8 Hz, ArH), and 7.73 and 7.82 (each 1 H, s, ArH), $\nu_{max.}$ (KBr) 1 760 (lactone) and 1 650 cm^{-1} (amide). Further elution with $CHCl_3$ afforded 2-(2-*formyl*-3,4-*dimethoxybenzoyl*)-3,4-*dihydro*-6,7-(*methylenedioxy*)*isoquinolin*-1(2*H*)-*one* (21) (4 mg, 3.8%), m.p. 156—158° (from ether) (Found: C, 62.55; H, 4.5; N, 3.9. $C_{20}H_{17}NO_7$ requires C, 62.65; H, 4.45; N, 3.65%), δ ($CDCl_3$) 3.07 (2 H, t, *J* 6 Hz, $ArCH_2CH_2N<$), 3.97 and 4.03 (each 3 H, s, ArO*Me*), 4.33 (2 H, t, *J* 6 Hz, $ArCHCH_2N<$), 6.01 (2 H, s, $-OCH_2O-$), 6.70 (1 H, s, ArH), 7.00 and 7.23 (each 1 H, d, *J* 8.5 Hz, ArH), 7.36 (1 H, s, ArH), and 10.42 (1 H, s, CHO), $\nu_{max.}$ (KBr) 1 685 (ArCHO) and 1 675 cm^{-1} (amide), $\lambda_{max.}$ (MeOH) 264 (log ε 4.21) and 312 nm (3.89), *m/e* 383 (M^+), 354 (M^+ — CHO), 220, 193, 176, and 165.

Reaction of the Epidioxide (11) *with Ferrous Sulphate.*—To a solution of $FeSO_4$ (200 mg) in H_2O (10 ml) was added a solution of the epidioxide (11) (103 mg, 0.269 mmol) in tetrahydrofuran (10 ml) with vigorous stirring at 0 °C. The $CHCl_3$ layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and evaporated *in vacuo* to give an oil which was chromatographed on silica gel (15 g). Elution with $CHCl_3$ afforded (i) the aldehyde (21) (34 mg, 33.2%), m.p. 156—158° (from ether), and (ii) berberal (20) (62 mg, 60.1%), m.p. 153—155° (from methanol).

Transformation of the Epidioxide (11) *into Berberal* (20) *and the Aldehyde* (21).—The epidioxide (11) (225 mg, 0.587 mmol) was transformed into berberal (19) and the aldehyde (20) during storage for several months at room temperature. The mixture was chromatographed on silica gel (16 g). Elution with $CHCl_3$ afforded (i) the aldehyde (21) (103 mg, 0.269 mmol, 45.8%) which was recrystallized from ether to give colourless needles, m.p. 156—158°, and (ii) berberal (20) (98 mg, 43.6%) which was recrystallized from methanol to give colourless needles, m.p. 153—155°.

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