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OXIDATIVE RING CLEAVAGE OF CORALYNE ALKALOID

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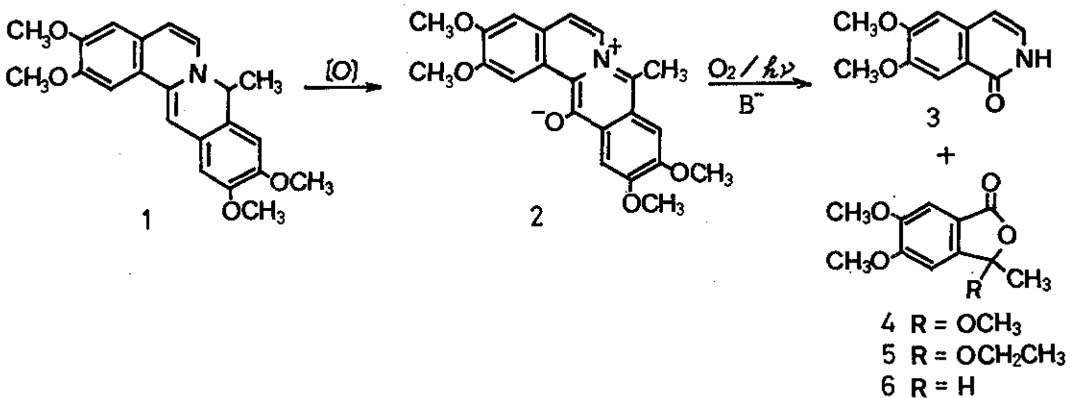
Oxygenation of coralyne alkaloid, a nonenzymic model of the oxygenase, has been investigated. A solution of dihydrocoralyne 1 or 13-hydroxycoralynium betaine 2 in the presence of sodium alkoxide was allowed to contact with air under illumination of visible light to give 6,7-dimethoxyisoquinolone-1 3 and the corresponding 3-methyl-3-alkoxy-5,6-dimethoxyphthalide 4 or 5. When the same autoxidation was carried out in the presence of borohydride anion, 3 and 3-methyl-5,6-dimethoxyphthalide 6 were obtained along with 13-hydroxycoralydine. Oxygenation of 2 in the presence of cuprous chloride led to 2'-acetylpapaveraldine 11. On the other hand, irradiation of 2 in chloroform in the presence of Rose Bengal gave a 1:1 mixture of 11 and 2'-carbomethoxypapaveraldine 12.

The mechanisms were also discussed.

The existence of the isoquinolone alkaloids together with the major berberine alkaloids in plants has been reported, and the possibility was recognized that the isoquinolone might be a result of enzymic oxidation of these major alkaloids[1]. However, the mode of oxidation of the berberine alkaloids in plants is little known at the present time. In this communication we report the oxygenation of coralyne alkaloid, a nonenzymic model of the dioxygenase[2], in which the products are dependent on a different excitation means of oxygen.

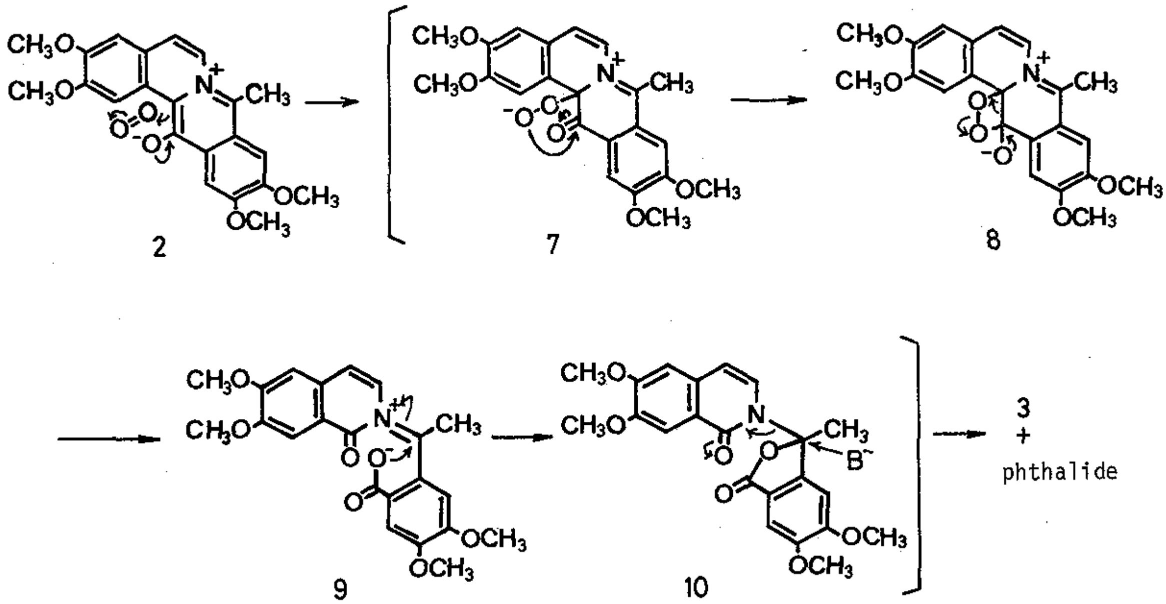


Scheme 1

A solution of dihydrocoralyne[3] 1 in hot methanol was kept for 2 hr at pH 8 and to the solution subsequently was added sodium methoxide. The solution was allowed to stand under illumination of a photoflood lamp to give 6,7-dimethoxyisoquinolone-1 3, $C_{11}H_{11}O_3N$, mp 244-245° (lit.[4], mp 237°), and 3-methyl-3,5,6-trimethoxyphthalide[5] 4, $C_{12}H_{14}O_4$, mp 150-152°, in moderate yields. 3: IR (KBr) cm^{-1}: 3450 (>NH), 1658 and 1632 (amido carbonyl). UV (EtOH) nm (log ε): 246 (4.26), 253 (sh, 4.00), 268 (3.45), 278 (3.48), 290 (3.51), 310 (3.25), 322 (3.35) 335 (3.24). NMR ($CDCl_3$) ppm: 1.75 (1H, br.s, >NH), 4.01 (3H, s, $-OCH_3$), 4.04 (3H, s, $-OCH_3$), 6.46 (1H, d, J=8 Hz, Ar-CH=CH-N<), 6.88 (1H, s, Ar-H), 7.10 (1H, br. d, J=8Hz, Ar-CH=CH-N<), 7.75 (1H, s, Ar-H). MS m/e: 205 (M^+). 4: IR (KBr) cm^{-1}: 1745 (lactone carbonyl). UV (EtOH) nm (log ε): 221 (4.14), 257 (3.71), 293 (3.60), 300 (sh, 3.57). NMR ($CDCl_3$) ppm: 1.80 (3H, s, $-CH_3$), 3.07 (3H, s, $-OCH_3$), 3.93 (3H, s, Ar-OCH_3), 6.80 (1H, s, Ar-H), 7.20 (1H, s, Ar-H). MS m/e: 238 (M^+). Similar oxidation accompanied by cleavage of the hetero-ring was observed by the addition of caustic alkali in aqueous solution, but the corresponding phthalide could not be isolated.

It is considered that the oxidative cleavage of **1** proceeds *via* the initial formation of the phenolbetaine **2**. Our previous work has demonstrated that **1** is oxidized to **2** in quantitative yield under the physiological conditions[3]. A solution of **2** in methanol containing sodium methoxide was allowed to contact with air under illumination of visible light to give **3** and **4** in approximately 50% and 30% yields, respectively (Scheme 1). When sodium ethoxide-ethanol solution was used in the place of sodium methoxide, the autoxidation of **2** gave **3** and 3-ethoxy-3-methyl-5,6-dimethoxyphthalide **5**, $C_{13}H_{16}O_4$, oil, in approximately 45% and 30% yields, respectively. **5**: IR ($CHCl_3$) cm^{-1}: 1753 (lactone carbonyl). UV (MeOH) nm (log ε): 223 (4.14), 261 (3.62), 293 (3.50), 300 (sh, 3.48). NMR ($CDCl_3$) ppm: 1.15 (3H, t, J=8 Hz, $-OCH_2C\underline{H}_3$), 1.82 (3H, s, $-C\underline{H}_3$), 3.10 (1H, dq, J_{gem}=9 Hz, J_{vic}=8 Hz, $-OC\underline{H}H-CH_3$), 3.44 (1H, dq, J_{gem}=9 Hz, J_{vic}=8 Hz, $-OCH\underline{H}-CH_3$), 6.90 (1H, s, Ar-$\underline{H}$), 7.30 (1H, s, Ar-H). MS m/e: 250 (M^+).

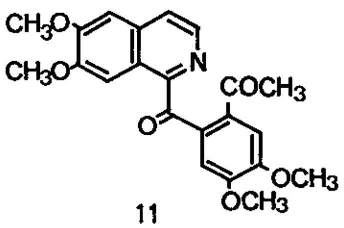
The autoxidative degradation of **2** is rationalized by addition of singlet oxygen to form a peroxide intermediate **7**, which could cleave *via* 1,2-dioxetane[6] **8** and hydrolyze by concomitant attack of the nucleophile to **3** and the corresponding phthalide (Scheme 2). The mechanism is further supported by the fact that the oxygenation of **2** was carried out in methanol in the presence of sodium borohydride to give **3** and 3-methyl-5,6-dimethoxyphthalide **6**, $C_{11}H_{12}O_4$, mp 101-102° (lit.[7], 100-101°), together with 13-hydroxycoralydine, $C_{22}H_{27}O_4N$, mp 185-187°, in 26%, 16%, and 4% yields, respectively. **6**: IR (KBr) cm^{-1}: 1730 (lactone carbonyl). UV (EtOH) nm (log ε): 221 (4.11), 257 (3.67), 293 (3.58), 300 (sh, 3.52). NMR ($CDCl_3$) ppm: 1.60 (3H, d, J=7 Hz, $>CH-C\underline{H}_3$), 3.92 (3H, s, $-OC\underline{H}_3$), 3.96 (3H, s, $-OC\underline{H}_3$), 5.43 (1H, q, J=7 Hz, Ar-$\overset{|}{C}\underline{H}$-O), 6.98 (1H, s, Ar-$\underline{H}$), 7.22 (1H, s, Ar-$\underline{H}$). In the final step of the mechanism, the borohydride anion attacks to the amido-lactone intermediate **10** to give the phthalide **6**. When the same reaction was carried out in the solution previously deactivated by acetone, the



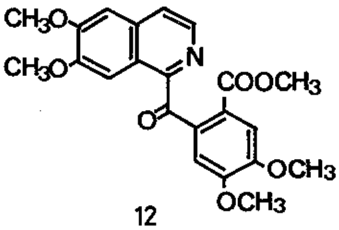
Scheme 2

products, 3 and 4, were exactly analogous to the autoxidation in sodium methoxide-methanol solution.

Of interest the oxidation of 2 in DMF in the presence of cuprous chloride which catalyzed the activation of molecular oxygen[8,9], yielded 2'-acetylpapaveraldine[3] 11 in quantitative yield. Since single oxygen is inserted in 2, the most likely intermediate, the peroxide 13, formed *via* rearrangement of 7, should exist before final ring opening (Scheme 3). When irradiation of 2 in chloroform in the presence of Rose Bengal was performed, a 1:1 mixture of 11 and 2'-carbomethoxypapaveraldine 12, $C_{22}H_{21}O_7N$, mp 210-212°, was obtained. 12: IR (KBr) cm^{-1}: 1705 (ester carbonyl), 1675 (Ar-CO-Ar), 1438 and 1355 (carbomethoxy). UV (EtOH) nm (log ε): 235 (4.43), 260 (sh, 4.20), 298 (3.70), 343 (3.68). NMR ($CDCl_3$) ppm: 3.20 (3H, s, $-COOC\underline{H}_3$), 4.00 (6H, s, $-OC\underline{H}_3$), 4.07 (3H, s, $-OC\underline{H}_3$), 4.13 (3H, s, $-OC\underline{H}_3$), 7.08 (1H, s, Ar-$\underline{H}$), 7.18 (1H, s, Ar-$\underline{H}$), 7.20 (1H, s, Ar-$\underline{H}$),



11



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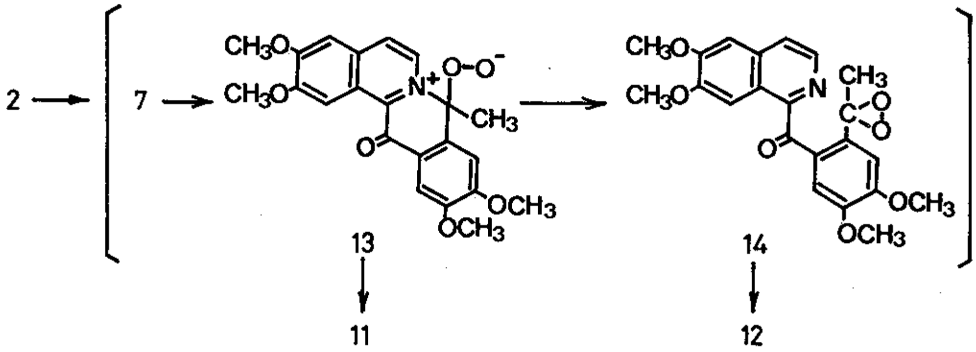

Scheme 3

8.64 (1H, s, Ar-H), 7.55 (1H, d, J=7 Hz, -CH=CH-N<), 8.54 (1H, d, J=7 Hz, -CH=CH-N<). MS m/e: 411 (M^+), 396, 380, 368, 352. The mechanism of formation of **12** involves simultaneous cyclization of **13** to a three-membered cyclic peroxide **14** (Scheme 3).

The analogous oxidative ring cleavage has been extended to the berberine alkaloids[10].

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