

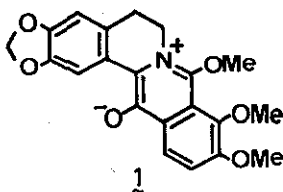
A SIMPLE CONVERSION OF NORCORALYNE INTO PHTHALIDEISOQUINOLINE

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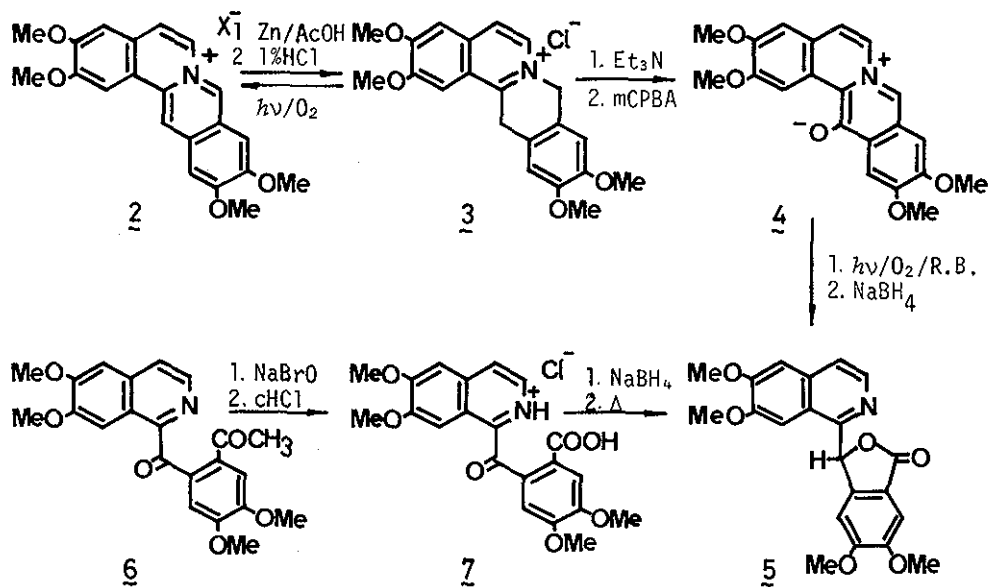
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A new simple conversion of the berberine type alkaloid into the phthalideisoquinoline alkaloid was described by a sequence involving intramolecular rearrangement of the 8,13a-epidioxy intermediate B *via* the three-membered cyclic peroxide D, to 2'-carboxypapaveraldine which was reduced with NaBH_4 to give the phthalideisoquinoline 5.

As has been predicted by biogenetic interrelationships¹, an elegant conversion of berberine into α - and β -hydrastine was achieved recently², in which 13-hydroxy-8-methoxyberberinium phenolbetaine 1 was utilized as a profitable key substance.



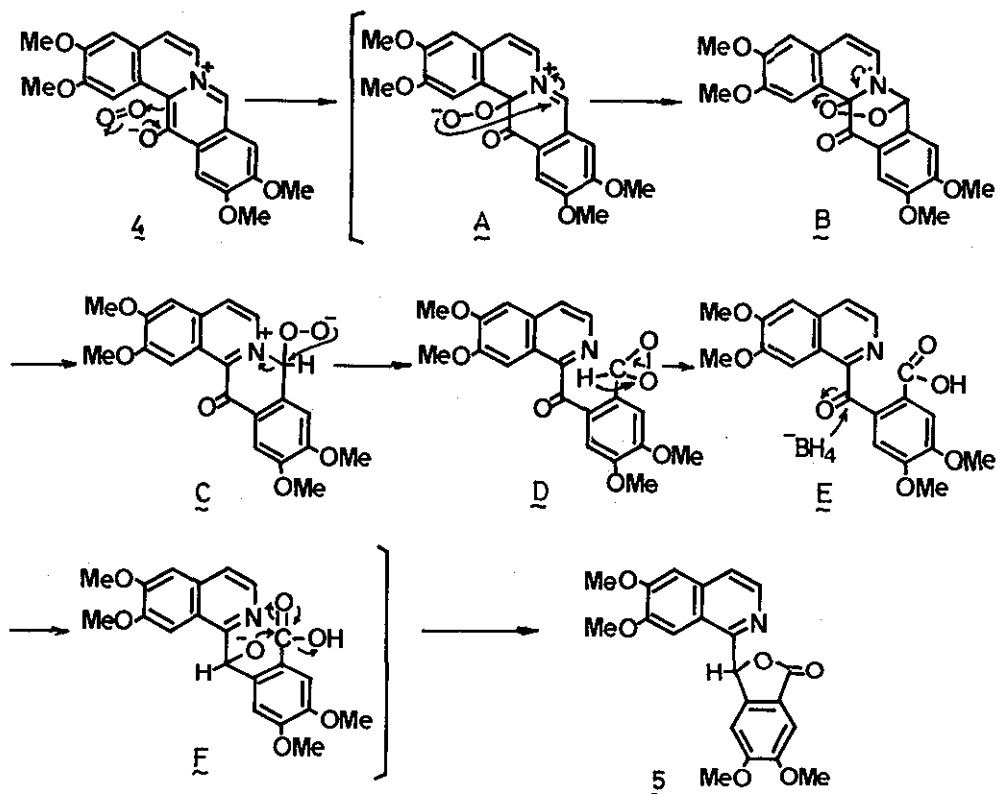
We have recently demonstrated regiospecific autoxidation of dihydrocoralyne to 13-hydroxycoralyinium phenolbetaine, which was readily converted to the 2'-substituted papaveraldine derivatives under the controlled oxygenation conditions^{3,4}. In this communication we wish to report a new convenient and



Scheme 1

biogenetic type conversion of 2,3,10,11-tetramethoxydibenzo[a,g]quinolizinium chloride⁵ (norcoralyne) 2 into 5,6-dimethoxy-3-(6,7-dimethoxyisoquinolin-1-yl)phthalide 5. Although 8,13-dihydro-2,3,10,11-tetramethoxydibenzo[a,g]quinolizinium chloride⁶ (dihydronorcoralynium chloride) 3, which was obtained by the partial reduction of norcoralyne 2 with zinc powder and 30% acetic acid followed by treatment with 1% HCl in 88% yield, was susceptible to photooxidation under the conditions described previously^{3,4}, the product was 2 instead of the desired 13-hydroxy-2,3,10,11-tetramethoxydibenzo[a,g]quinolizinium phenolbetaine (13-hydroxy-norcoralynium phenolbetaine) 4. However, the addition of *m*-chloroperbenzoic acid to a degassed solution of 3 in chloroform containing triethylamine gave 4, mp 183-185°, in 73% yield. The spectral results of 4⁷ were shown as follows; UV (MeOH) nm (log ϵ): 227 (4.48),

237 (sh, 4.45), 264 (4.51), 284 (4.50), 296 (sh, 4.40), 319 (4.27), 408 (sh, 4.13), 428 (4.30), 453 (4.38). NMR ($\text{CDCl}_3 + \text{CD}_3\text{OD}$) δ (ppm): 3.84 (3H, s, $-\text{OCH}_3$) 3.93 (3H, s, $-\text{OCH}_3$), 4.12 (3H, s, $-\text{OCH}_3$), 4.18 (3H, s, $-\text{OCH}_3$), 6.80 (1H, s, Ar-H), 6.91 (1H, s, Ar-H), 7.11 (1H, d, $J=8$ Hz, Ar-H), 7.76 (1H, d, $J=8$ Hz, Ar-H), 7.94 (2H, s, $2 \times$ Ar-H), 10.39 (1H, s, Ar-H). MS (m/e): 365 (M^+), 350.



A solution of 4 in a mixture of chloroform and methanol was exposed to sun-light (of winter in Sendai) for 8 min in the presence of Rese Bengal and NaBH_4 was subsequently added to the solution. After being held for 30 min at ambient temperature, the reaction mixture was worked up as a usual manner to provide the phthalideisoquinoline 5, mp 192-194° (lit.⁸ mp 190-192°) in

approximately 70% yield (Scheme 1). The structure of the phthalideisoquinoline 5 was evidenced unequivocally by the following synthetic manner: oxidation of 2'-acetylpapaveraldine³ 6 with NaBrO in dioxane, followed by acidification with conc. HCl afforded 2'-carboxypapaveraldine hydrochloride 7, mp 198-200° (decomp) in nearly quantitative yield. The spectral results of 7 were shown as follows; UV (EtOH) nm (log ε): 234 (4.34), 262 (sh, 4.07), 312 (3.85), 353 (3.48). IR (KBr) cm⁻¹: 1665 (Ar-CO-Ar). NMR (d₆-DMSO) δ (ppm): 3.90 (9H, s, 3x-OCH₃), 4.00 (3H, s, -OCH₃), 7.27 (1H, s, Ar-H), 7.46 (1H, s, Ar-H), 7.69 (1H, s, Ar-H), 8.22 (1H, s, Ar-H), 8.01 (1H, d, J=8 Hz, Ar-H), 8.35 (1H, d, J=8 Hz, Ar-H). Reduction of 7 with NaBH₄ in methanol followed by heating for 1 hr yielded the phthalideisoquinoline 5 which is identical with above synthetic material (Scheme 1).

The formation of 5 from 4 implicates the 8,13a-epidioxy intermediate B, which undergoes intramolecular rearrangement to the three-membered cyclic peroxide D (Scheme 2). The analogous intermediates have been postulated in the mode of photooxidation of 13-hydroxycoralynium phenolbetaine⁴ by us. It is suggestive for these postulated intermediates that we recently isolated a stable 8,13a-epidioxy compound in the course of photooxidation of 13-hydroxyberberinium phenolbetaine⁹.

In conclusion, this procedure provides a facile convenient synthesis of the phthalideisoquinoline, in which another example concerning cleavage of an N⁷-C⁸ immonium bond is shown. The phenolbetaine 4, an analog of 1, is easily photooxidized to result the analogous cleavage in compound 1.

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