HETEROCYCLES, Vol. 6, No. 7, 1977

A SIMPLE CONVERSION OF NORCORALYNE INTO PHTHALIDEISOQUINOLINE

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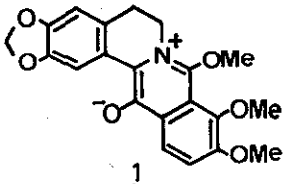
A new simple conversion of the berberine type alkaloid into the phthalideisoquinoline alkaloid was described by a sequence involving intramolecular rearrangement of the 8,13a-epidioxy intermediate B *via* the three-membered cyclic peroxide D, to 2'-carboxypapaveraldine which was reduced with $NaBH_4$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

As has been predicted by biogenetic interrelationships[1], an elegant conversion of berberine into α- and β-hydrastine was achieved recently[2], in which 13-hydroxy-8-methoxyberberinium phenolbetaine 1 was utilized as a profitable key substance.



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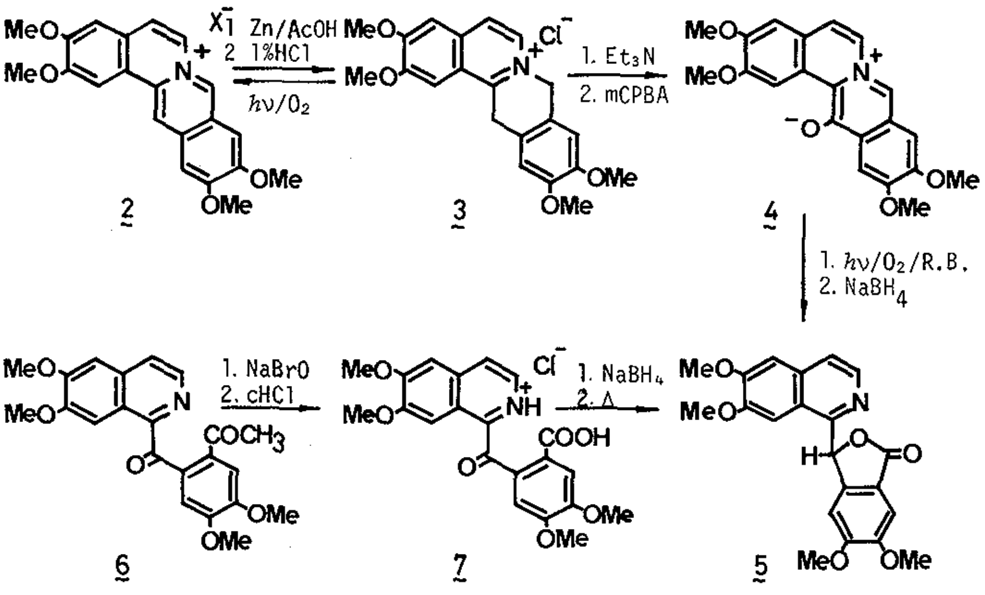
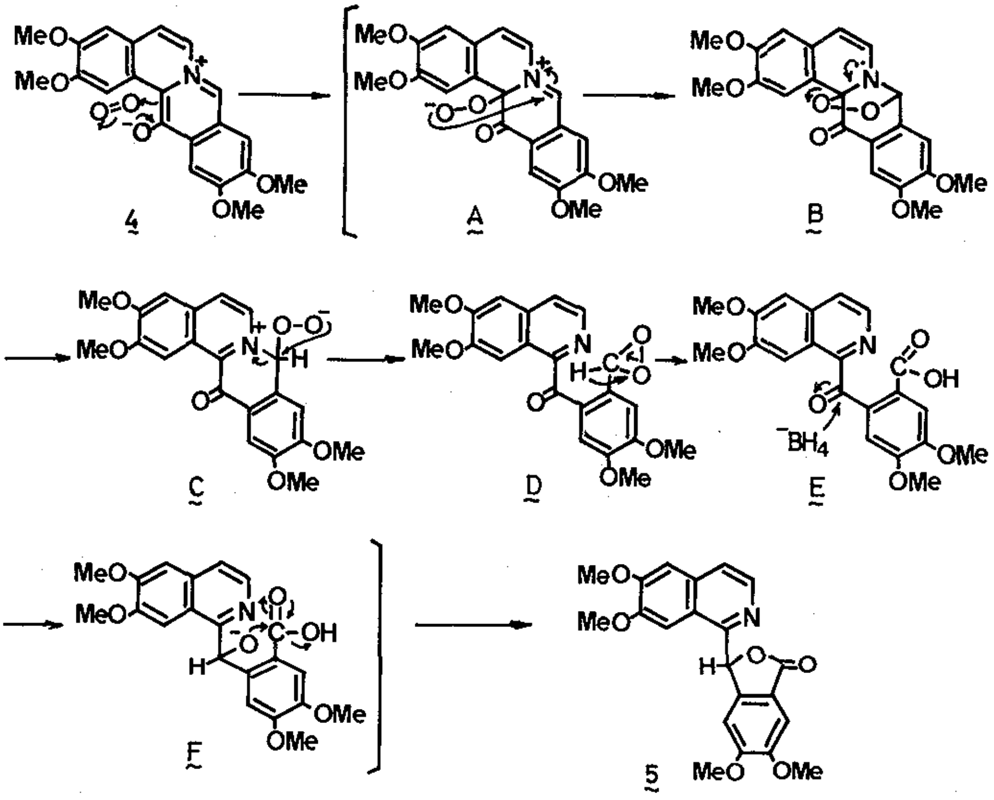
We have recently demonstrated regiospecific autoxidation of dihydrocoralyne to 13-hydroxycoralynium phenolbetaine, which was readily converted to the 2'-substituted papaveraldine derivatives under the controlled oxygenation conditions[3,4]. In this communication we wish to report a new convenient and



Scheme 1

biogenetic type conversion of 2,3,10,11-tetramethoxydibenzo[a,g]quinolizinium chloride[5] (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 chloride[6] (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 photoxidation 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 degased solution of **3** in chloroform containing triethylamine gave **4**, mp 183-185°, in 73% yield. The spectral results of **4**[7] 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 ($CDCl_3$+CD_3OD) δ(ppm): 3.84 (3H, s, -OC$\underline{H}_3$) 3.93 (3H, s, -OC$\underline{H}_3$), 4.12 (3H, s, -OC$\underline{H}_3$), 4.18 (3H, s, -OC$\underline{H}_3$), 6.80 (1H, s, Ar-$\underline{H}$), 6.91 (1H, s, Ar-$\underline{H}$), 7.11 (1H, d, J=8 Hz, Ar-$\underline{H}$), 7.76 (1H, d, J=8 Hz, Ar-$\underline{H}$), 7.94 (2H, s, 2×Ar-$\underline{H}$), 10.39 (1H, s, Ar-$\underline{H}$). MS (m/e): 365 (M^+), 350.



Scheme 2

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'-acetylpapaveraldine[3] 6 with NaBrO in dioxane, followed by acidification with conc. HCl afforded 2'-carboxylpapaveraldine hydrocholoride 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 (d_6-DMSO) δ (ppm): 3.90 (9H, s, 3×-OCH_3), 4.00 (3H, s, -OCH_3), 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 $NaBH_4$ 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 posturated in the mode of photoxidation of 13-hydroxycoralynium phenolbetaine[4] by us. It is suggestive for these posturated intermediates that we recently isolated a stable 8,13a-epidioxy compound in the course of photoxidation of 13-hydroxyberberinium phenolbetaine[9].

In conclusion, this procedure provides a facile convenient synthesis of the phthalideisoquinoline, in which another example concerning cleavage of an N^7-C^8 immonium bond is shown. The phenolbetaine 4, an analog of 1, is easily photoxidized to result the analogous cleavage in compound 1.

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Received, 20th April, 1977