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NEW ELECTROREDUCTIVE SYNTHESIS OF PHTHALIDE ALKALOIDS[1)]

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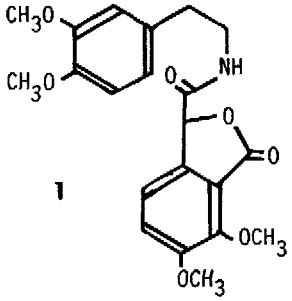
Electroreduction of 2-methyl-3,4-dihydro-6,7-dimethoxy-isoquinolinium salt in the presence of 3-bromomeconine afforded Cordrastine. The method of cross coupling of immonium salts with *bromophthalides was also applicable to other phthalide alkaloids.*

Since the versatile potentiality of our new electroreductive cross coupling reaction between immonium salts and benzylic type bromides was confirmed in our previous work,[2)] we have extended the coupling *reaction to practical syntheses of some important* phthalide alkaloids which are hitherto known to be synthesized through troublesome multistage methods.[3—6)] One of the most difficult points in the previous syntheses is the preparation of the compounds like **1**,[6)] which can be ring closed to phthalide alkaloids using so-called Bishler-Napieralsky type reaction.



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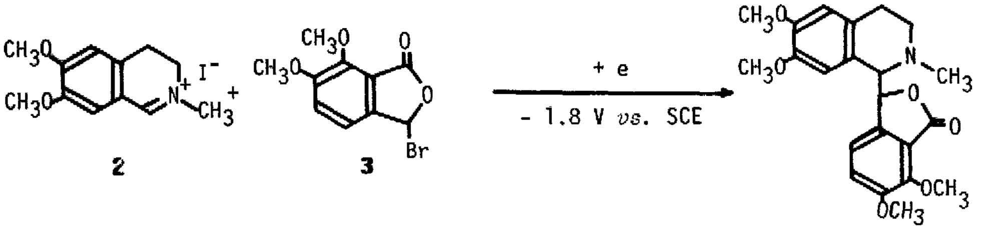
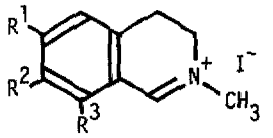
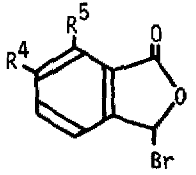
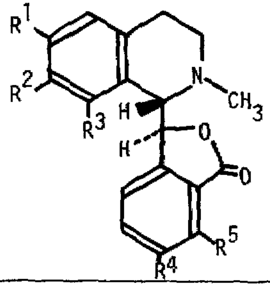
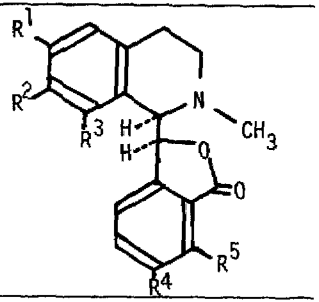
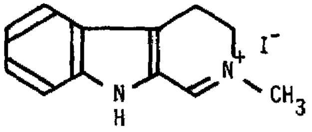
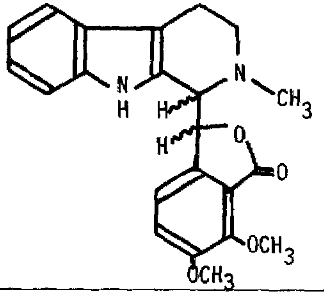
In our new electroreductive method, the synthesis of both components such as **2**[7)] and **3**[8)] is much easier than that of **1**, and the coupling reaction shown in equation (1) can be performed under very mild reaction conditions and the yields are reasonably good as given in Table 1.



..........(1)

A typical experimental procedure is shown below exemplifying the synthesis of Cordrastine I and II. A solution of 2-methyl-3,4-dihydro-6,7-dimethoxy-isoquinolinium iodide **2** (2 mmol) and 3-bromomeconine **3** (4 mmol) in dry DMF (40 mL) was used as catholyte, whereas anolyte was a solution of tetraethylammonium *p*-toluenesulfonate (3 g) in dry DMF (10 mL). The reaction was carried out at room temperature under the conditions of controlled potential (-1.8 V *vs.* SCE) using platinum electrodes. The presence of a lead plate in the reaction system was desirable,though its role was not clear but assumed to be a scavenger of bromide ion or any other active bromine species. After 3 *F*/mol of electricity was passed through the cell,

Table 1. Electroreductive Synthesis of Phtahlide Alkaloids

Immonium Salts		Bromophthalides		Products[a] and Yields		
	+		$\xrightarrow{+e}$		+	
$R^1{=}R^2{=}OCH_3$, $R^3{=}H$		$R^4{=}R^5{=}H$		40%		28%
$R^1{=}R^2{=}OCH_3$, $R^3{=}H$		$R^4{=}R^5{=}OCH_3$		42% (Cordrastine I)[4]		35% (Cordrastine II)[4]
$R^1 + R^2 = OCH_2O$, $R^3{=}H$		$R^4{=}R^5{=}OCH_3$		35%		30% (Hydrastine)[4]
$R^1{=}R^2{=}R^3{=}OCH_3$		$R^4{=}R^5{=}OCH_3$		57%[b]		
$R^1 + R^2 = OCH_2O$, $R^3{=}OCH_3$		$R^4{=}R^5{=}OCH_3$		57%[b] (*dl*-Noscapine)		
		$R^4{=}R^5{=}OCH_3$				50%[b]

a) Products were identified by NMR and IR and/or elemental analysis.

b) A mixture of erythro and threo isomers.

the solvent was removed by evaporation. To the residue, dilute aqueous hydrochloric acid was added, and nonbasic impurities were extracted with ether (50 mL). The acidic aqueous layer was made alkaline with potassium hydroxide and extracted with three portions of methylene dichloride (100 mL), and the combined organic layer was dried over magnesium sulfate. After it was filtered, solvent was evaporated, and the residue was subjected to column chromatography (Silica Gel $CHCl_3/CH_3OH$) to get the products, Cordrastine I (0.84 mmol) and Cordrastine II[4-6] (0.70 mmol). Cordrastine I : IR (KBr) ν_{max} 1745 cm^{-1}, NMR (70% $CDCl_3$—30% CCl_4) δ 2.58 (3H, s, N-CH_3), 2.0-3.2 (4H, m, C-3 and C-4 H's), 3.61 (3H, s, -OCH_3), 3.70 (6H, s, 2-OCH_3's), 3.76 (3H, s, -OCH_3), 3.93 (1H, d, J=3.4 Hz, C-1 H), 5.41 (1H, d, J=3.4 Hz, C-1'H), 6.18 (1H, s, C-5 H), 6.53 (1H, s, C-8 H), 6.81 and 7.14 (2H, ABq, J=8.5 Hz, C-6' and C-7' H's respectively), m.p. 156-157 ° from CH_3OH (lit.[3] 155-156 °), Rf 0.6 (5% methanolic chloroform). Cordrastine II : IR (KBr) ν_{max} 1755 cm^{-1}, NMR (70% $CDCl_3$—30% CCl_4) δ 2.53 (3H, s, N-CH_3), 2.0-3.2 (4H, m, C-3 and C-4 H's), 3.64 (3H, s, -OCH_3), 3.80 (3H, s, -OCH_3), 3.82 (3H, s, -OCH_3), 3.97 (3H, s, -OCH_3), 4.00 (1H, d, J=3.5 Hz, C-1 H), 5.43 (1H, d, J=3.5 Hz, C-1'H), 6.27 (1H, s, C-8 H), 6.47 (1H, s, C-5 H), 6.40 and 6.98 (2H, ABq, J=8.0 Hz, C-7' and C-6' H's respectively), Rf 0.3 (5% methanolic chloroform). Cordrastine II was converted into its picrate, which was recrystallized from methanol-acetone, m.p. 205 ° (dec.) (lit.[3] 202 °, dec.).

Above compounds were identified by comparison of their spectroscopic and Physical constants with those of authentic samples.

As clearly shown in Table 1, our electroreductive method is really versatile and promissing.

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References and Notes

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4) V. Smula, N. E. Cundasawmy, H. L. Holland, and D. B. Maclean, *Can. J. Chem.*, **51**, 3287 (1973).

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6) Kerekes and Bognar, *J. Prakt. Chem.*, **313**, 923 (1971).

7) The isoquinolinium salt was made by addition of methyl iodide to 3,4-dihydro-6,7-dimethoxyisoquinoline in THF. After filtration, the filtrate was washed with *n*-hexane, and dried under vacuum.

8) Starting from meconine,$^{9)}$ 3-bromomeconine was prepared according to the usual method.$^{10)}$ IR (KBr) ν_{max} 1750 cm^{-1}, NMR (50% $CDCl_3$—50% CCl_4) δ 7.10, 7.15 (3H, two singlet, aromatic and C-3 H's), 4.05 (3H, s, $-OCH_3$), 3.87 (3H, s, $-OCH_3$), m.p. 129-131 °.

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