Acknowledgment. We thank the N. L. Tartar Fund and the National Institutes of Health (RR07079) for support of this work and Dr. Charles Klopfenstein at the University of Oregon for acquisition of the 360-MHz ^1H NMR spectra.

Registry No. **2a**, 4370-49-4; **2b**, 87567-88-2; **2b** (diol), 87568-17-0; **2c**, 87567-89-3; **2d**, 87567-90-6; **2d** (diol), 87568-18-1; **6a**, 105-67-9; **6b**, 89-56-5; **7a**, 15191-36-3; **7b**, 17746-75-7; **8a**, 2785-75-3; **8b**, 6049-93-0; **9**, 87567-91-7; **10**, 513-81-5; **11a**, 2004-70-8; **11b**, 87567-92-8; **11c**, 74054-58-3; **12**, 87567-93-9; **13**, 87567-94-0; **14**, 87567-95-1; **15a**, 87567-96-2; **15b**, 87567-97-3; **16a**, 87567-98-4; **16b**, 87567-99-5; **17a**, 87637-78-3; **17b**, 87637-79-4; **18a**, 87568-00-1; **18b**, 87568-01-2; **19a**, 87637-80-7; **19b**, 87637-81-8; **20**, 87568-02-3; **21a**, 5747-07-9; **21b**, 87568-03-4; **22**, 87585-82-8; **23a**, 87568-04-5; **23b**, 87637-82-9; **24a**, 87568-05-6; **24b**, 87637-83-0; **25a**, 87568-06-7; **25b**, 87637-84-1; **26**, 87568-07-8; **27**, 87638-48-0; 4a,5,8,8a-tetrahydro-4,6,7,8a-tetramethylnaphthalene-1,2-dione, 32249-85-7; 4a,5,8,8a-tetrahydro-4,8,8a-trimethylnaphthalene-1,2-dione, 87568-08-9; 4a,5,8,8a-tetrahydro-3,4a,8-trimethylnaphthalene-1,2-dione, 87568-09-0; 6-acetoxy-4a,5,8,8a-tetrahydro-4,8,8a-trimethylnaphthalene-1,2-dione, 87568-10-3; 6-acetoxy-4a,5,8,8a-tetrahydro-3,4a,8-trimethylnaphthalene-1,2-dione, 87568-11-4; methyl 1,8a-dihydro-5,6-dioxo-2,3,8-trimethylnaphthalene-4a-(4*H*)-carboxylate, 87568-12-5; methyl 1,8a-dihydro-4,8-dimethyl-5,6-dioxonaphthalene-4a(4*H*)-carboxylate, 87568-13-6; methyl 2-acetoxy-1,8a-dihydro-4,8-dimethyl-5,6-dioxonaphthalene-4a(4*H*)-carboxylate, 87568-14-7; 4-chloro-5,8-dihydro-1-hydroxy-3,4a,8-trimethylnaphthalen-2(4a*H*)-one, 87568-15-8; 6-acetoxy-4-chloro-5,8-dihydro-1-hydroxy-3,4a,8-trimethylnaphthalen-2(4a*H*)-one, 87568-16-9; methyl 1-chloro-8,8a-dihydro-5,8a-dimethyl-4-hydroxy-3(5*H*)-oxonaphthalene-2-carboxylate, 87585-83-9; *o*-chloranil, 2435-53-2.

Supplementary Material Available: Analytical and spectral details of the Diels–Alder cycloaddition products of quinones **2a–d** with the model dienes, and the preparation of **22–27** (11 pages). Ordering information is given on any current masthead page.

A Pyrolytic Route to the Phthalide–Isoquinolines

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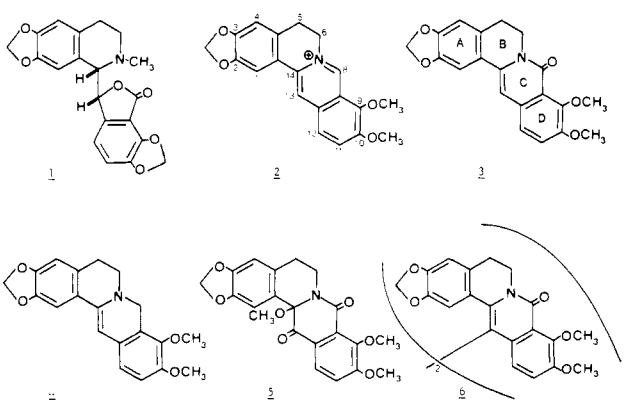
Pyrolysis of 8,13-dioxo-14-methoxycanadine (**5**) yields methyl keto ester **11** (35%), aromatic phthalide–isoquinoline **12** (15%), and (+)-chilenine (**13**, 7%). Methyl keto ester **11** can be reduced quantitatively to **12** with sodium borohydride. Catalytic reduction of **12** followed by N-methylation affords (±)-β-hydrastine (**18**) and (±)-α-hydrastine (**19**).

The phthalide–isoquinoline alkaloid (+)-bicuculline (**1**, Chart I) is a competitive antagonist of γ-aminobutyric acid (GABA), an important neurotransmitter in the mammalian nervous system.[1] The potential usefulness of (+)-bicuculline and other phthatlide–isoquinolines in this pharmacological area and the use of phthalide–isoquinolines as precursors in the synthesis of other isoquinoline alkaloids have prompted several investigations of new synthetic avenues for their preparation.[2]

Chart I



Specifically, we were interested in developing a simple and practical route to the phthalide–isoquinolines (±)-β-hydrastine (**18**) and (±)-α-hydrastine (**19**) starting with berberine (**2**), a common and inexpensive quaternary protoberberine alkaloid commercially available in ton quantities.

One of the "classical" reactions of berberine (**2**) is that it undergoes oxidation–reduction upon treatment with hydroxide base to supply in equal amounts oxyberberine (**3**) and the unstable dihydroberberine (**4**) which can readily be reoxidized to berberine.[3] It was also known that pyridinium chlorochromate oxidation of oxyberberine (**3**), followed by addition of methanol, supplied 8,13-dioxo-14-methoxycanadine (**5**).[4] Since **5** incorporates several of the structural features required for its transformation into a phthalide–isoquinoline, our efforts were focussed first

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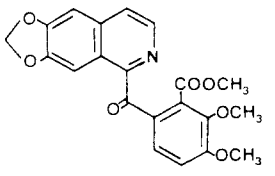
upon the generation of the highly oxidized intermediate **5** from oxyberberine (**3**) in satisfactory yields and second upon the pyrolysis of **5** in the hope that this would eventually lead to the formation of phthalide–isoquinolines.

Shortly after the initiation of our studies, we determined that room-temperature oxidation of oxyberberine (**3**) with pyridinium chlorochromate in methylene chloride for 5 h, followed by addition of methanol, furnished a 62% yield of compound **5**, rather than a 50% yield as previously indicated.[4] The improved yield was achieved by the addition of ether to the crude reaction product. This resulted in an immediate precipitation of chromium complexes which were filtered out (see Experimental Section).

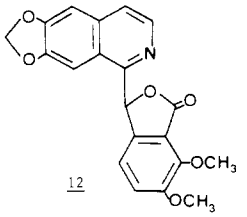
A hitherto unreported minor product, obtained in 20% yield, proved to be the new, high-melting, dimer bis[oxyberberine] **6** whose mass spectrum exhibits molecular ion m/z 700 which is also the base peak. The UV spectrum, [λ_{max} (MeOH) 228, 338 nm (log ϵ 4.69, 4.52)] resembles that of oxyberberine **4**: λ_{max} (MeOH) 225, 341 nm (log ϵ 4.50, 4.24). The ^{13}C NMR spectrum (Experimental Section) generally parallels that of oxyberberine (**3**), except that C-13 appears at 110.5 ppm in the spectrum of the dimer **6** and at 101.0 ppm in the spectrum of the monomeric species **3**.[5]

A possible mechanistic rationale for the formation of the desired 8,13-dioxo-14-methoxycanadine (**5**), as well as of the dimer **6**, is offered in Scheme I. The chromium complex **7** can break down in either of two ways. In the first route, the iminium chromium complex **8** derived from **7** can lead to the azaquinonium cation **9** whose solvation generates the isolable 8,13-dioxo-14-methoxycanadine (**5**). Alternatively, complex **7** can react with another mole of oxyberberine (**3**) to give rise to dimeric species **10** which through loss of two protons produces bis[oxyberberine] **6**.

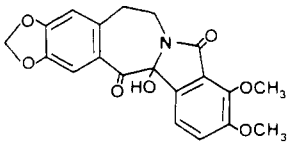
Following several abortive attempts, it was eventually found that pyrolysis of 8,13-dioxo-14-methoxycanadine (**5**) at 175 °C for 20 min at reduced pressure consistently yielded three products which were separated and identified as the new methyl keto ester **11** (35%), the known aromatic



11



12

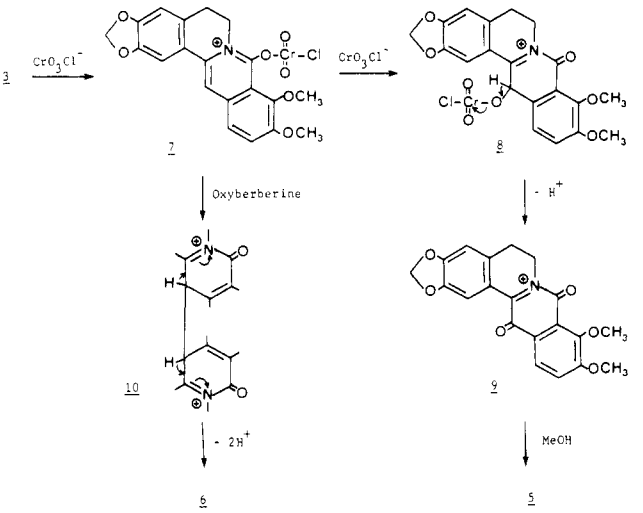


13

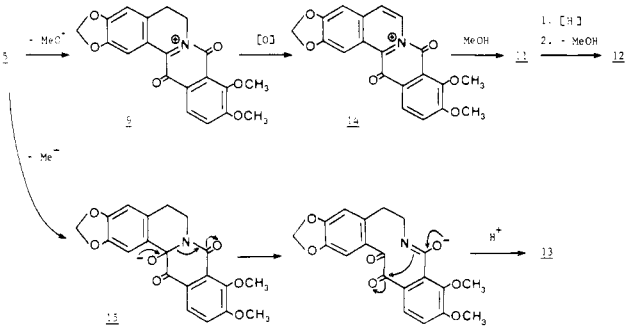
phthalide–isoquinoline **12** (15%).[6] and the known alkaloid (±)-chilenine (**13**, 7%).[7]

The IR spectrum of the methyl keto ester **11**, which is the major product of the pyrolysis, displays ν_{max} ($CHCl_3$) 1730 and 1660 cm^{-1}. The first absorption infers the presence of an ester group, while the second is consistent with an imino ketone functionality.[8] The ^1H NMR spectrum is well-defined and is listed in the Experimental

Scheme I. Pyridinium Chlorochromate Oxidation of Oxyberberine (3)



Scheme II. Pyrolysis of 8,13-Dioxo-14-methoxycanadine (5)



Section. A salient feature of this spectrum is the two doublets situated at δ 7.61 and 8.41 (J = 5.5 Hz) due to aromatization of ring B. Finally, the mass spectrum of **11** shows a small molecular ion m/z 395, while the base peak m/z 336 is due to loss of carbomethoxyl from the molecule.

Sodium borohydride reduction of **11** led quantitatively to the aromatic phthalide–isoquinoline **12**,[6] for a 50% overall yield of **12** from intermediate **5**.

A possible mechanism for the formation of the methyl keto ester **11** and the aromatic phthalide–isoquinoline **12** is presented in Scheme II. Azaquinonium cation **9**, formed readily through loss of methoxide ion, can suffer oxidation to afford the aromatic iminium species **14**. Methanolysis of ring C provides the imino keto ester **11**. Reduction and lactonization would then supply the aromatic phthalide–isoquinoline **12**. The formation of (±)-chilenine (**13**) as a minor product of the pyrolysis may be understood in terms of anion **15** as indicated.

At this stage, the remaining challenge was simply to reduce and N-methylate aromatic phthalide–isoquinoline **12** so as to provide an analogue of bicuculline (**1**). Indeed, reduction of **12** with hydrogen and Adams catalyst in the presence of perchloric acid gave rise to (±)-nor-β-hydrastine (**16**) (35%) and (±)-nor-α-hydrastine (**17**, 31%).[9] N-Methylation of these secondary amines by the formaldehyde–sodium borohydride method generated the required (±)-β-hydrastine (**18**) and (±)-α-hydrastine (**19**) in high yields.

The advantage of the present approach is that the racemic hydrastines may now be prepared from berberine

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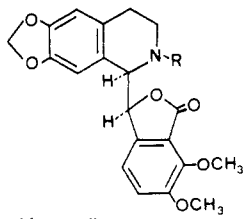
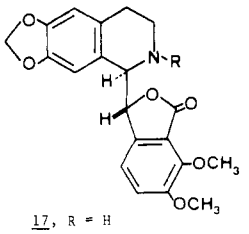


16, R = H
18, R = CH_3



17, R = H
19, R = CH_3

(1) in six well-defined and easy steps. The overall yield of phthalide–isoquinolines is on the order of 7% or better.

Experimental Section

General Experimental Procedures. Melting points are uncorrected. ^1H spectra are at 200 or at 360 MHz, and ^{13}C spectra are at 50.32 MHz. Thin-layer chromatography (TLC) was on Merck silica gel F-254 plates. The solvent system used was methylene chloride–methanol (96:4 v/v) unless indicated otherwise.

Oxyberberine (3). Berberine chloride (**2**; 20 g, 0.059 mol) was dissolved in boiling water, and the temperature was brought to 80 °C. To the solution was added a potassium hydroxide solution (300 g of KOH in 50 mL of H_2O). A precipitate immediately rose to the top. The gummy solid was collected and refluxed in concentrated KOH solution for 10 h. The mixture was filtered and the solid washed with water. The solid was loaded on a silica gel column in chloroform. Elution was carried out with an increasingly polar mixture of methanol in chloroform. The band which showed a blue fluorescence under long-wavelength UV light was collected and crystallized from chloroform to give the product: 6.00 g (32%); mp 201–203 °C (lit.[3] mp 198–200 °C); IR ν_{max} $CHCl_3$ 1648 cm^{-1}.

Oxidation of Oxyberberine (3) with Pyridinium Chlorochromate. Oxyberberine (500 mg, 1.4 mmol) was added to a solution of pyridinium chlorochromate (650 mg, 3.0 mmol) in dry methylene chloride (20 mL) and stirred at room temperature for 5 h. Anhydrous ether was added, and the mixture was allowed to stand 10 min and then filtered. The residue was washed with ether. Evaporation of the ethereal solution gave a greenish residue to which was added methanol (75 mL). The mixture was stirred for 6 h. The white precipitate, **5**, was collected and recrystallized from methanol: 250 mg (46%); mp 125–126 °C (lit.[2a] mp 126 °C, ether).

The mother liquor was purified by TLC. Under long-wavelength UV light, the dark blue fluorescent higher band (R_f 0.70) gave **5** (90 mg, 16%). The lower band (R_f 0.26) which showed a faint blue fluorescence was collected and recrystallized from methanol to furnish **6**: 100 mg, (20%); mp 339 °C; IR ν_{max} ($CHCl_3$) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 and 2.50 (2 dt, J_1 = 14.0 Hz, J_2 = 3.8 Hz, 2 H, H-5), 3.15 and 5.11 (2 dt, J_1 = 14.0 Hz, J_2 = 4.0 Hz, 2 H, H-6), 3.94 (s, 3 H, OCH_3), 4.13 (s, 3 H, OCH_3), 5.79 (dd, J_{gem} = 2.0 Hz, 2 H, OCH_2O), 6.19 (s, 1 H, H-1), 6.42 (s, 1 H, H-4), 7.06 and 7.11 (AB q, J = 9.0 Hz, 2 H, H-11 and H-12); ^{13}C NMR ($CDCl_3$) δ 29.5 (t, C-5), 40.4 (t, C-6), 56.4 (q, 10-OCH_3), 61.6 (q, 9-OCH_3), 101.0 (t, OCH_2O), 106.7 (d, C-1), 108.4 (d, C-4), 110.5 (s, C-13), 118.6 (d, C-11), 119.7 (d, C-12), 122.2* (s, C-8a), 123.6* (s, C-12a), 133.1** (s, C-4a), 133.3** (s, C-14a), 135.9 (s, C-14), 145.2*** (s, C-10), 147.2*** (s, C-2), 149.5*** (s, C-3), 151.7*** (s, C-9), 159.7 (s, C-8); MS, m/z 700 (100) $(M)^+$, 685 (59), 671 (31), 350 (10), 335 (5), 321 (5), 306 (6) (the ^1H and ^{13}C NMR chemical shift values for dimer **6** are for half of this symmetrical molecule); high-resolution mass spectrum, calcd for $C_{40}H_{32}O_{10}N_2$ m/z 700.2056, found m/z 700.2045.

Pyrolysis of 5. Compound **5** (100 mg, 0.25 mmol) was heated at 175 °C for 20 min under a 10–15-mmHg pressure. The sublimate was collected (5 mg, 5%) and crystallized from methanol to give **13**, mp 154 °C (lit.[2a,7] mp 155 °C, methanol).

The brown residue was purified by TLC. Three bands, R_f 0.64, 0.55, 0.46, were significant. The higher band, which was dark blue under short-wavelength UV light, yielded **11**: 35 mg (35%); mp 170–171 °C (methanol); UV λ_{max} (MeOH) 240, 282, 303, 328 nm (log ϵ 4.99, 4.77, 4.45, 4.33); ^1H NMR ($CDCl_3$) δ 3.74 (s, 3 H, $COOCH_3$), 3.93 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 6.12 (s, 2 H, OCH_2O), 6.93 and 7.44 (AB q, J = 8.7 Hz, 2 H, ring D Ar H), 7.14 (s, 1 H, ring A Ar H), 7.74 (s, 1 H, ring A Ar H), 7.61 and 8.41 (AB q, J = 5.5 Hz, ring B Ar H); MS, m/z (relative intensity) 395 (1, M^+), 364 [6] $(M - OCH_3)^+$, 352 (23), 337 (31), 336 [100, $M - COOCH)^+$], 320 (15), 223 (10), 172 (6), 148 (5); high-resolution mass spectrum, calcd for $C_{21}H_{17}NO_7$ m/z 395.1160, found m/z 395.0967.

The middle band (R_f 0.55), which showed a light blue fluorescence under short-wavelength UV light, was collected and crystallized from methanol to furnish **12**: 15 mg (15%); mp 206–207 °C (methanol) [lit.[6] mp 204–207 °C (methylene chloride–hexane)]; IR ν_{max} (KBr) 1753 cm^{-1}; UV λ_{max} (MeOH) 242, 246, 293, 318, 331 nm (log ϵ 4.26, 4.24, 3.70, 3.79, 3.78).

The lower R_f band corresponded to (±)-chilenine (**13**, 2 mg, 2%).

Reduction of Methyl Keto Ester 11. Sodium borohydride (130 mg, 3.42 mmol) was added in portions to **11** (200 mg, 0.51 mmol) in methanol (20 mL) at 0 °C, and the mixture stirred for 1 h. The workup gave **12** (183 mg, 100%).

Catalytic Reduction of 12. A solution of **12** (100 mg, 0.27 mmol) in ethanol (25 mL) containing 10 drops 70% perchloric acid was hydrogenated over Adams catalyst (50 mg) at 35 psi of H_2 for 10 h. The workup produced a mixture of **16** and **17**. Preparative TLC with benzene–methanol (4:1) afforded **16** [35 mg (35%); R_f 0.35] and **17** [31 mg (31%); R_f 0.53]. Recrystallization of **16** from methanol gave colorless crystals, mp 169 °C (lit.[6] mp 168–173 °C, EtOH). Recrystallization of **17** from methanol yielded coloreless crystals, mp 204–205 °C [lit.[6] mp 202–205 °C (EtOH)].

N-Methylation of a Mixture of (±)-16 and (±)-17. The mixture of **16** and **17** (50 mg, 0.13 mmol) obtained from the catalytic reduction of **12** was dissolved in 37% aqueous formaldehyde (2 mL), and the solution was heated for 2 h at 110 °C. Evaporation of the solvent in vacuo left a solid which was dissolved in hot methanol. The solution was cooled in an ice bath, and excess sodium borohydride (40 mg, 1.05 mmol) was added cautiously. Stirring was continued for 30 min at 0 °C. The products were separated by TLC with benzene–methanol (4:1) to yield **18** [24 mg; R_f 0.58; mp 150 °C (methanol) [lit.[10] mp 151–153 °C (ethanol)]] and **19** [22 mg; R_f 0.72; mp 161 °C (methanol) [lit.[2a] mp 162–163 °C (methanol)]].

N-Methylation of 16 and 17. (±)-Nor-β-hydrastine (**16**; 10 mg, 0.08 mmol) was N-methylated by using aqueous formaldehyde (1 mL), MeOH (10 mL), and sodium borohydride (8 mg, 0.21 mmol) as above to give 9 mg of (±)-β-hydrastine (**18**). Similarly, 13 mg of (±)-nor-α-hydrastine (**17**) yielded 11.8 mg of (±)-α-hydrastine (**19**).

Acknowledgment. This research was supported by Grant CHE-8210699 from the National Science Foundation. We are grateful to Dr. G. Manikumar for assistance in the early stages of this project.

Registry No. **2**, 633-65-8; **3**, 549-21-3; (±)-**5**, 71733-96-5; **6**, 87586-23-0; **11**, 71733-98-7; (±)-**12**, 87586-24-1; (±)-**13**, 71700-15-7; (±)-**16**, 66408-36-4; (±)-**17**, 68780-76-7; (±)-**18**, 60594-55-0; (±)-**19**, 60827-73-8.

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