



drastines was the isolation of the novel white crystalline oxidation dimer oxybisberberine, mp 215–216 °C dec (pyridine), in 60% yield from the ferricyanide oxidation of **1**.<sup>3</sup> This photosensitive dimer, which shows no carbonyl absorption in the ir, is stable in base, but rapidly and irreversibly cleaves in acid. When this breakdown is effected with methanolic hydrogen chloride, the products are berberine chloride (**1**), and orange colored 8-methoxyberberinephenolbetaine (**2**): C<sub>21</sub>H<sub>19</sub>NO<sub>6</sub>; mp 175–176 °C (ether);  $\lambda_{\max}^{\text{EtOH}}$  230, 262, 313, 359, 374, and 455 nm (log  $\epsilon$  4.50, 4.11, 4.09, 3.81, 3.80, and 3.83); NMR  $\delta$  2.90 (t, 2 H, C-5 CH<sub>2</sub>), 3.86 (s, 3 H, OCH<sub>3</sub>), 3.98 (s, 6 H, 2 × OCH<sub>3</sub>), 4.58 (t, 2 H, C-6 CH<sub>2</sub>), 5.86 (s, 2 H, OCH<sub>2</sub>O), 6.51 (s, 1 H, C-4 H), 7.35 (d, 1 H,  $J_{11,12} = 9$  Hz), 9.28 (d, 1 H,  $J_{11,12} = 9$  Hz, C-12 H), and 8.80 (s, 1 H, C-1 H).

Phenolbetaine **2** has the requisite oxygen function at C-13 as well as the potential carboxylic ester at C-8 for transformation to a phthalideisoquinoline. The unmasking of the C-8 carboxyl was achieved by simple hydration whereby a solution of **2** in water saturated ether at room temperature slowly decolorizes to furnish upon workup in 80% yield the hydrochloride salt of dehydronorhydrastine methyl ester (**3**): C<sub>21</sub>H<sub>21</sub>NO<sub>7</sub>·HCl·CH<sub>3</sub>OH; mp HCl salt 144–145 °C (MeOH–ether);  $\nu_{\max}^{\text{KBr}}$  1670 and 1735 cm<sup>-1</sup>;  $\lambda_{\max}^{\text{EtOH}}$  210, 228, 280, and 308 nm (log  $\epsilon$  4.50, 4.37, 4.20, and 4.19). The NMR spectrum of the free base (enol form) with  $\delta$  2.73 and 3.81 (2 t, 2 × 2H, CH<sub>2</sub>–CH<sub>2</sub>), 3.84, 3.92, and 3.96 (3 s, 3 × 3 H, 3 OCH<sub>3</sub>), 5.98 (s, 2 H, OCH<sub>2</sub>O), 6.70 and 7.03 (2 s, 2 × 1H, C-5 and C-8 H), and 7.04 (ABq, 2 H,  $J = 9$  Hz, ics = 10 Hz, C-2' and C-3' H) fully supported the structural assignment.<sup>4</sup> N-Alkylation of the free base **3** with methyl iodide in refluxing acetonitrile afforded, in quantitative yield, dehydronorhydrastine methyl ester (**4**): C<sub>22</sub>H<sub>23</sub>NO<sub>7</sub>; HI salt mp 167–168 °C (MeOH–ether);  $\nu_{\max}^{\text{CHCl}_3}$  1670 and 1735 cm<sup>-1</sup>. The free base (keto form) of **4** exhibited mp 125–127 °C (MeOH); NMR  $\delta$  2.22 (s, 3 H, N–CH<sub>3</sub>), 2.5–3.4 (m, 4 H, CH<sub>2</sub>–CH<sub>2</sub>), 3.45 (s, 1 H, C-1 H), 3.81, 3.83, and 3.97 (3 s, 3 × 3H, 3 OCH<sub>3</sub>), 5.83 (s, 2 H, OCH<sub>2</sub>O), 6.32 and 6.60 (2 s, 2 × 1H, C-8 and C-5 H), and 7.30 (ABq, 2 H,  $J = 9$  Hz, ics = 74 Hz, C-3' and C-2' H).

Direct sodium borohydride reduction of **4** in ethanol, followed by acid workup provided a 1:2 mixture of (±)- $\alpha$ -hydrastine (**5**) and (±)- $\beta$ -hydrastine (**6**) in 90% yield, spectrally identical with semisynthetic (–)- $\alpha$ -hydrastine and natural (–)- $\beta$ -hydrastine, respectively.<sup>5</sup>

Two pathways, therefore, are now available in the laboratory for cleavage of the critical N-7 to C-8 bond of berberinoids under conditions which could approximate in part the processes of nature. The first of these, namely, the quinone methide route, starts with a phenolic *N*-methyldehydroprotoberberine salt and leads to spirobenzylisoquinolines.<sup>6</sup> The second route, described herein, involves direct oxidation of an N-7 to C-8 immonium bond of a berberinoid salt to lead eventually to phthalideisoquinolines.<sup>7</sup>

## References and Notes

- (1) This research was supported by Grant HL-12971 from the National Institutes of Health. Acceptable combustion elemental analyses were obtained for compounds **2**–**4**. NMR spectra were at 60 MHz in CDCl<sub>3</sub>.
- (2) W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 305 (1910). See also R. Robinson, "Structural Relations of Natural Products", Clarendon Press, Oxford, 1955, p 88.
- (3) The exact structure of oxybisberberine is in the process of being determined by x-ray crystallography.
- (4) We have found that the known compound berberinephenolbetaine (J. Iwasa and S. Naruto, *J. Pharm. Soc. Jpn.*, **86**, 534 (1966); *Chem. Abstr.*, **65**, 12247b (1966)) also decolorizes when subjected to these same hydrolytic conditions. However, hydration does not proceed in a straightforward manner, and numerous highly oxidized products are obtained. These will be discussed at a later date.
- (5) R. D. Haworth and A. R. Pinder, *J. Chem. Soc.*, 1776 (1950); R. D. Haworth, A. R. Pinder, and R. Robinson, *Nature (London)*, **165**, 529 (1950); see also W. H. Perkin, Jr., J. N. Rây, and R. Robinson, *J. Chem. Soc.*, **127**, 740 (1925).
- (6) M. Shamma and C. D. Jones, *J. Am. Chem. Soc.*, **92**, 4943 (1970); M.

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- (7) Attention should be called, however, to the important finding that in *Papaver somniferum* the tetrahydroprotoberberine base (–)-scoulerine labeled at C-14 leads to the phthalideisoquinoline (–)- $\alpha$ -narcotine also mostly labeled at the corresponding site (A. R. Battersby, M. Hirst, D. J. McCaldin, R. Southgate, and J. Staunton, *J. Chem. Soc. C*, 2163 (1968); A. R. Battersby and M. Hirst, *Tetrahedron Lett.*, 669 (1965); and A. R. Battersby, R. J. Francis, M. Hirst, R. Southgate, and J. Staunton, *Chem. Commun.*, 602 (1967)). It follows that in the plant (–)-scoulerine must suffer oxidation of the N-7 and C-8 bond while the integrity of the C-14 asymmetric center is essentially maintained.

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## Reactions of Silyl Enol Ethers and Lactone Enolates with Dimethyl(methylene)ammonium Iodide. The Bis- $\alpha$ -methylenation of Pre-Vernolepin and Pre-Vernomenin

Sir:

Recently we described the synthesis of bisnorvernolepin (**1**) and bisnorvernomenin (**2**) in 17 steps from 1,3-butadiene.<sup>1</sup> Since the first total synthesis of *dl*-vernolepin (**3**)<sup>2</sup> and *dl*-vernomenin (**4**)<sup>2</sup> of Grieco and co-workers<sup>3,4</sup> had involved transformation of a mixture of **1** and **2** into **3** and **4**, which was then separated into individual components, our preparation of homogeneous **1** and **2** constituted a technical total synthesis of the racemates **3** and **4**.

Although the  $\alpha$ -methylenation of lactones has received considerable study,<sup>5a-c</sup> culminating in the bis- $\alpha$ -methylenation of bisnordeoxyvernolepin<sup>7</sup> and thence of **1** and **2**,<sup>3</sup> we were desirous of augmenting this capability in the context of converting a vicinal hydroxybutyrolactone such as **5** into its  $\alpha$ -methylene derivative **6** without protection of the hydroxyl.

This objective arose from practical considerations. Preliminary efforts to convert **1** into its OTHP derivative afforded only a 70% yield of relatively pure product.<sup>8</sup> A 71% yield was recorded for the conversion of the OTHP derivatives of **3** and **4** into the final products.<sup>3</sup> Thus, this type of protection, deprotection maneuver appears to result in the loss of ca. one-half of the difficulty won tricyclic material, apart from the less than ideal efficiency of the bis- $\alpha$ -methylenation process.

Our attentions focused on a Mannich approach. Such a route would avoid differentiating between a hydroxyl group<sup>9</sup> that must be retained and one which must be used for further functionalization. The specific<sup>10</sup> Mannich agent used was dimethyl(methylene)ammonium iodide (**7**), a nicely crystalline salt first prepared and used by Eschenmoser in another context.<sup>11</sup> Before relating the successful application of **7** to the stated objective, we describe some new chemistry which should serve to stimulate other applications of this highly reactive and interesting reagent.

Compound **7**, which is insoluble in methylene chloride, reacts instantaneously with a solution of 1-trimethylsilyloxy-cyclohexene in this solvent to produce a salt which must be formulated as **8** on the basis of its spectral properties:  $\delta$  CDCl<sub>3</sub> 0.25 (s, 9), 3.03 (s, 3), 3.70 (s, 2) (no vinylic hydrogens);  $\lambda_{\max}^{\text{CHCl}_3}$  6.02  $\mu$  (silyl enol ether). Reaction of **8** with aqueous HCl gives Mannich salt **9**, which affords the well known **10** (87% overall yield) after neutralization. The ability to perform a Mannich reaction on a silyl enol ether<sup>12,13</sup> without catalysis and with restoration of the double bond to its original site is a valuable observation in terms of trapping possibilities.

We have demonstrated the utility of this chemistry as a route to steroids. Reductive silylation<sup>14a</sup> of **11**<sup>14b</sup> affords **12**. This reacts at room temperature with **7** to afford a silyl enol ether