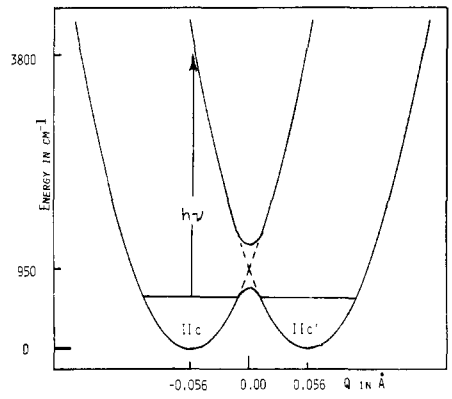

Figure 2. Potential surface and ground-state vibrational level for the interconversion of IIc and IIc'. Q = reaction coordinate = $\sqrt{2}[R_{CO}(12) - 1.26\ Å] = \sqrt{2}[1.26\ Å - R_{CO}(9)]$.

characterize small amplitude vibrations of the two structures independent of one another. These zeroth-order surfaces may in turn be constructed from knowledge of the force constants for equivalent vibrations in analogous monofunctional molecules. For this case the problem is vastly simplified by the fact that the internal coordinates of greatest importance are just the two C–O bond lengths in each structure, R_{CO} (9) and R_{CO} (12). Thus, conversion of IIc to IIc' requires little more than compressing R_{CO} (9) and stretching R_{CO} (12). The zeroth-order surface for this motion is readily calculated from the force constants derived from the spectra of the monoketones and their respective anion radicals.[5] The portion of this surface along the reaction coordinate is shown in Figure 2 (solid lines). In the region where the zeroth-order surfaces cross (dotted lines), the true states will be mixed, splitting the degeneracy. This establishes the height of the barrier and the position of a low lying electronic excited state. If we adopt 0.08 Å as the difference between R_{CO} (9) and R_{CO} (12)[6] at the minima, the barrier is calculated to be $\lesssim 950\ cm^{-1}$.

As a consequence of this very low barrier, molecular vibrations involving change in R_{CO} (9) and R_{CO} (12) must be strongly anharmonic. Both the vibrational splittings and the selection rules for dipolar transitions between them should deviate greatly from the monofunctional cases. Also, local solvation inhomogeneities should result in fluctuations in the barrier height (and therefore the vibrational states) resulting in the observed line broadening. Calculation of the vibrational states for the full two-dimensional surface are currently in progress.

As shown in Figure 2, there should exist an electronic transition at about 3800 cm^{-1}[7] (the exact value depending upon the vibrational levels). In fact, the electronic spectrum of II includes a strong absorption at very long wavelength (λ_{max} 1590 nm in Me_2SO, λ_{max} 1700 nm in CH_3CN, ϵ 4030).[8] Applying the correction for the solvent effect proposed by Hush,[4] we obtain 4018 cm^{-1} as the "gas phase" optical intervalence transition, in surprisingly good agreement.[9]

It is interesting to note the possibility that the ground vibrational state for the fluxional system may exceed the barrier for interconversion. If such were the case, the nuclear configuration would effectively be symmetrical and it is ironic that this may be the case even in the absence of strong transannular interaction.[10]

Acknowledgment. We are grateful for advice from Professors John C. Light and Karl Freed, and to the National Science Foundation for financial support (MPS75-00935).

References and Notes

(1) Data from cyclic voltammetry in $(CH_3)_2SO$, 0.10 M $(CH_3)_4NPF_6$.
(2) The cell represents a modified version of that described by W. R. Heineman, J. N. Burnett, and R. W. Murray, *Anal. Chem.*, **40**, 1974 (1968).
(3) That the spectrum does represent the anion radical is supported by (i) the reversible oxidation to I, (ii) the observation of isosbestic points when the electrode was held at intermediate potentials, and (iii) Beer's law behavior for the corresponding electronic absorption spectrum, vide infra.
(4) N. S. Hush, *Prog. Inorg. Chem.*, **8**, 391 (1967).
(5) These are 13.0 and 10.6 mdyn/Å for the ketones and radical anions, respectively.
(6) Bond lengths of 1.22 and 1.30 Å were used for the ketone and radical anions, respectively. The latter is based on an INDO calculation for indanone radical anion.
(7) This transition is analogous to the intervalence transition characteristic of binuclear mixed valence complexes.[11]
(8) None of the radical anions in Table I absorbed beyond the visible.
(9) It should be pointed out that an error in the extrapolation of solvent effects could be as great as $\pm 1000\ cm^{-1}$.
(10) This interaction is apparently not negligible since the reduction potential of I is 0.27 V more positive than the equivalent monoketone.
(11) C. Creutz and H. Taube, *J. Am. Chem. Soc.*, **95**, 1086 (1973); G. M. Tom and H. Taube, *ibid.*, **97**, 5310 (1975); R. W. Callahan, G. M. Brown, and T. J. Meyer, *ibid.*, **96**, 7830 (1974).

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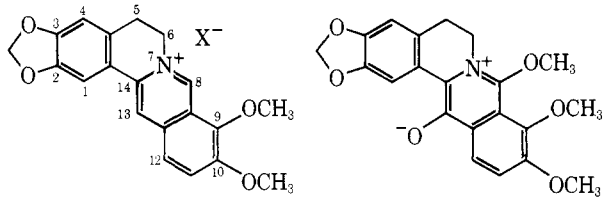
Received June 11, 1976

The Conversion of Berberine into (±)-α- and (±)-β-Hydrastine[1]

Sir:

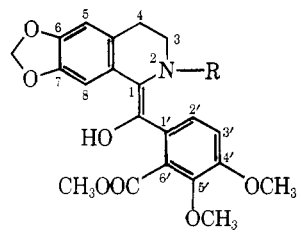
A useful landmark in the topography of ideas concerning biogenetic interrelationships among monomeric isoquinoline alkaloids can be traced back to 1910 when William H. Perkin, Jr., and Sir Robert Robinson observed that: "These (berberine and phthalideisoquinoline) alkaloids are, indeed, so closely related as to suggest that hydrastine is either formed in the plant from berberine, or that they are both derived from some common parent."[2] We now wish to report the first known in vitro conversion of berberine (**1**) into (±)-α-hydrastine (**5**) and (±)-β-hydrastine (**6**) by a simple and efficient route which may emulate in part the biogenetic process.

The key to the transformation of berberine (**1**) to the hy-

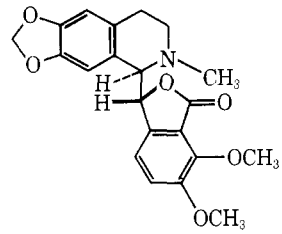


1

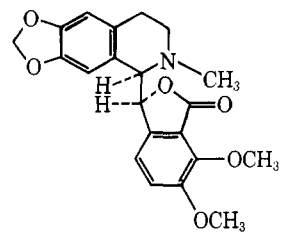
2



3, R = H
4, R = CH_3



5



6

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**.[3] 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**): $C_{21}H_{19}NO_6$; mp 175–176 °C (ether); λ_{max}^{EtOH} 230, 262, 313, 359, 374, and 455 nm (log ϵ 4.50, 4.11, 4.09, 3.81, 3.80, and 3.83); NMR δ 2.90 (t, 2 H, C-5 CH_2), 3.86 (s, 3 H, OCH_3), 3.98 (s, 6 H, 2 × OCH_3), 4.58 (t, 2 H, C-6 CH_2), 5.86 (s, 2 H, OCH_2O), 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**): $C_{21}H_{21}NO_7$·HCl·CH_3OH; mp HCl salt 144–145 °C (MeOH–ether); ν_{max}^{KBr} 1670 and 1735 cm^{-1}; λ_{max}^{EtOH} 210, 228, 280, and 308 nm (log ϵ 4.50, 4.37, 4.20, and 4.19). The NMR spectrum of the free base (enol form) with δ 2.73 and 3.81 (2 t, 2 × 2H, CH_2–CH_2), 3.84, 3.92, and 3.96 (3 s, 3 × 3 H, 3 OCH_3), 5.98 (s, 2 H, OCH_2O), 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.[4] N-Alkylation of the free base **3** with methyl iodide in refluxing acetonitrile afforded, in quantitative yield, dehydrohydrastine methyl ester (**4**); $C_{22}H_{23}NO_7$; HI salt mp 167–168 °C (MeOH–ether); $\nu_{max}^{CHCl_3}$ 1670 and 1735 cm^{-1}. The free base (keto form) of **4** exhibited mp 125–127 °C (MeOH); NMR δ 2.22 (s, 3 H, N–CH_3), 2.5–3.4 (m, 4 H, CH_2–CH_2), 3.45 (s, 1 H, C-1 H), 3.81, 3.83, and 3.97 (3 s, 3 × 3H, 3 OCH_3), 5.83 (s, 2 H, OCH_2O), 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 (±)-α-hydrastine (**5**) and (±)-β-hydrastine (**6**) in 90% yield, spectrally identical with semisynthetic (−)-α-hydrastine and natural (−)-β-hydrastine, respectively.[5]

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*-methyldihydroprotoberberine salt and leads to spirobenzylisoquinolines.[6] 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.[7]

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 $CDCl_3$.

(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. Shamma and J. F. Nugent, *Tetrahedron*, **29**, 1265 (1973).

(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 (−)-α-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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Received May 24, 1976

Reactions of Silyl Enol Ethers and Lactone Enolates with Dimethyl(methylene)ammonium Iodide. The Bis-α-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.[1] Since the first total synthesis of *dl*-vernolepin (**3**)[2] and *dl*-vernomenin (**4**)[2] of Grieco and co-workers[3,4] 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 α-methylenation of lactones has received considerable study,[5a–c] culminating in the bis-α-methylenation of bisnordeoxyvernolepin[7] and thence of **1** and **2**,[3] we were desirous of augmenting this capability in the context of converting a vicinal hydroxybutylrolactone such as **5** into its α-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.[8] A 71% yield was recorded for the conversion of the OTHP derivatives of **3** and **4** into the final products.[3] 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-α-methylenation process.

Our attentions focused on a Mannich approach. Such a route would avoid differentiating between a hydroxyl group[9] that must be retained and one which must be used for further functionalization. The specific[10] Mannich agent used was dimethyl(methylene)ammonium iodide (**7**), a nicely crystalline salt first prepared and used by Eschenmoser in another context.[11] 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-trimethylsilyloxycyclohexene in this solvent to produce a salt which must be formulated as **8** on the basis of its spectral properties: δ $CDCl_3$ 0.25 (s, 9), 3.03 (s, 3), 3.70 (s, 2) (no vinylic hydrogens); $\lambda_{max}^{CHCl_3}$ 6.02 μ (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[12,13] 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[14a] of **11**[14b] affords **12**. This reacts at room temperature with **7** to afford a silyl enol ether