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A STEREOSPECIFIC CONVERSION OF BERBERINE INTO (±)-β-HYDRASTINE[1]

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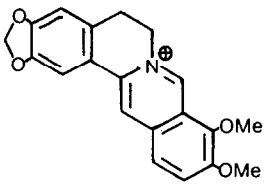
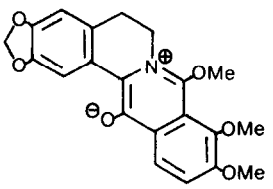
The conversion of berberine (1) into a 1:2 mixture of (±)-α-hydrastine (3) and (±)-β-hydrastine (4) through the intermediacy of 8-methoxyberberinephenolbetaine (2) has been recorded.[2] The betaine 2 can be obtained by means of the ferricyanide oxidation of berberine, followed by treatment with methanolic hydrogen chloride,[2] or alternatively by photooxidation of berberine.[3]



1



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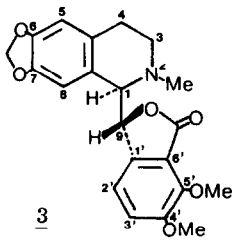

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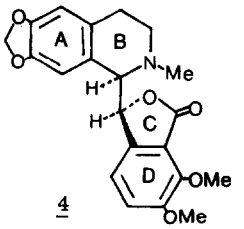
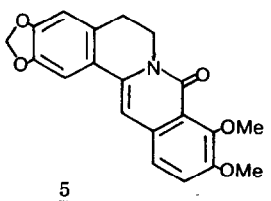


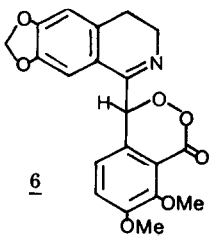
4

We now wish to present a new conversion of berberine which yields essentially pure (±)-β-hydrastine (4), practically unadulterated with the racemate of the non-naturally occurring base (-)-α-hydrastine (3). Short photooxidation of oxyberberine (5)[4] in benzene using a 450 watt Ace Glass medium high pressure lamp provided in 42% yield the γ-lactol 8, $C_{20}H_{17}NO_7$, mp 154-155° (Et_2O) or 160.5-162.5° ($CHCl_3$-Et_2O).[5] The formation of this lactol may be understood in terms of the intermediacy of the peroxylactone 6 which rearranges to the keto acid 7.[6]



5

hν, O_2,
benzene,
1 hr



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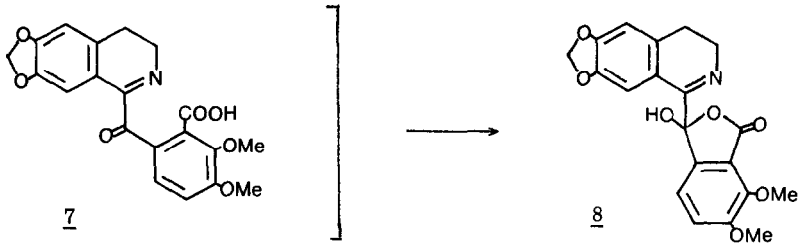
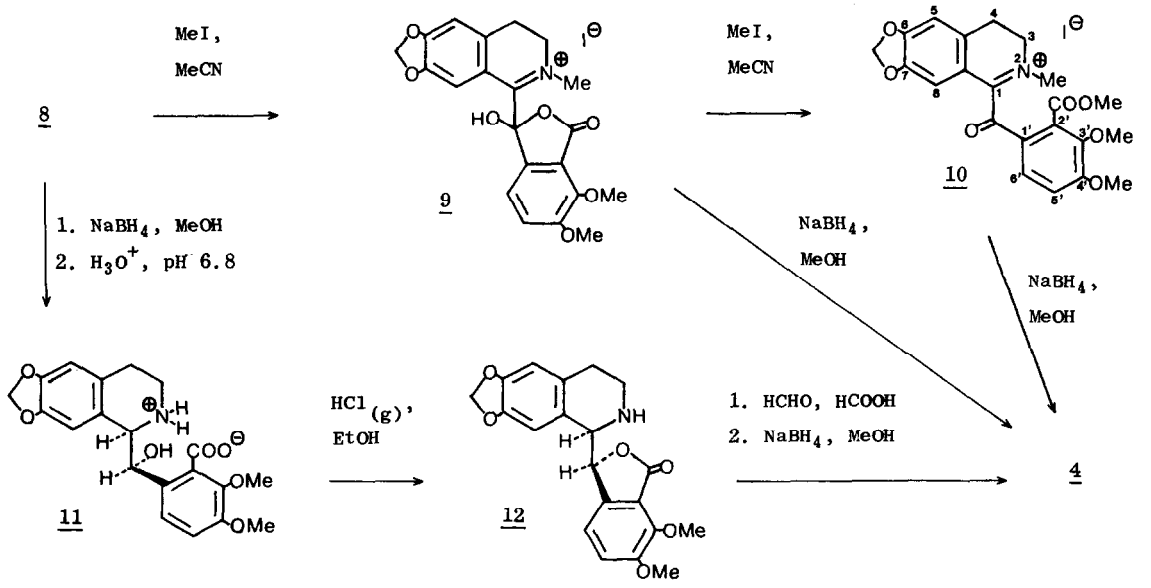


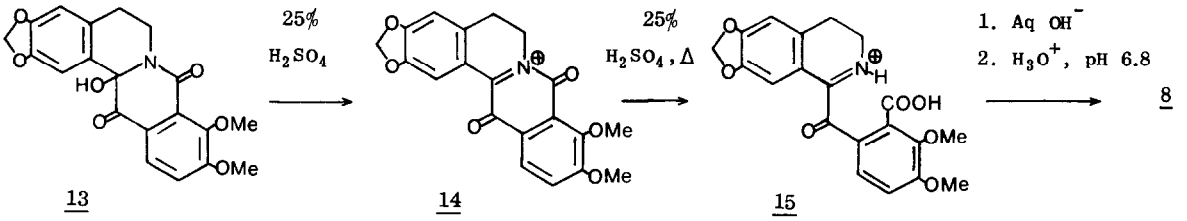
7 8

N-Methylation of 8 with methyl iodide in acetonitrile at room temperature for 2-4 hr gave the immonium salt 9, $C_{21}H_{20}NO_7$, mp 178-180° decomp. (CH_3CN). If the N-methylation were carried out for a longer reaction time (24 hr) or under reflux for 4 hr, the immonium keto ester 10, $C_{22}H_{22}NO_7$, mp 141-142° (CH_3CN),[7] was isolated. Sodium borohydride reduction of 9 or 10 proceeded in a stereospecific manner to generate (±)-β-hydrastine (4), mp 151-152° (MeOH),[8] in 95% yield from 8, accompanied by only a faint trace (<1%) of (±)-α-hydrastine (3).

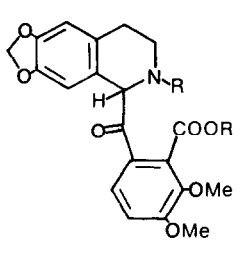
Alternatively, direct sodium borohydride reduction of the γ-lactol 8, followed by work-up at pH 6.8 led to the amino acid 11, mp 181-183° ($CHCl_3$), ν_{max}^{KBr} 1595 cm^{-1}, which gave rise to the known (+)-nor-β-hydrastine (12), mp 156-158° ($CHCl_3$), $\nu_{max}^{CHCl_3}$ 1760 cm^{-1}, upon acidification.[9] N-Methylation with formaldehyde and formic acid, followed by treatment with sodium borohydride to ensure complete reduction, then supplied (±)-β-hydrastine (4) in 35% yield from the γ-lactol 8.



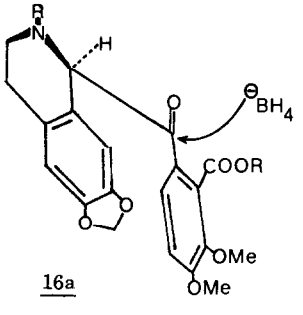
A separate route to the key γ-lactol 8 involves the known 8,13-dioxo-14-hydroxycanadine (13) derived from berberine (1).[10] Treatment of 13 with 25% aq sulfuric acid produced instantaneously the deep violet immonium salt 14 which upon heating in situ at 70° for 2 hr hydrolyzed to the water soluble yellow immonium keto acid 15. Neutralization and extraction then supplied the γ-lactol 8 in 90% overall yield from 13.



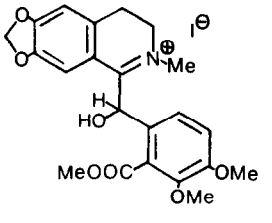
The high degree of stereospecificity observed in each of the above sodium borohydride treatments is rationalized on the premise that reduction of the imine or immonium double bond proceeds first to furnish species 16 which exists in the preferred conformation 16a. Application of Cram's rule[11] with approach of the borohydride anion from the less hindered side of the ketone leads to the products obtained. This stereospecific reduction stands in contrast to that of dehydrohydrastine methyl ester hydroiodide (17) which proceeds to 3 and 4 with marginal specificity.[2] Salt 17 incorporates a hydroxyl group adjacent to the immonium double bond, which can complex with the borohydride anion and thus allow for neighboring group participation during the reduction.



16, R = H or Me



16a



17

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References

1. All spectral assignments are supported by concordant combustion and/or high resolution mass spectral analyses. All pmr spectra were run in $CDCl_3$ with TMS as internal standard.
2. J.L. Moniot and M. Shamma, J. Am. Chem. Soc., 98, 6714 (1976).
3. M. Hanaoka, C. Mukai and Y. Arata, Heterocycles, 6, 895 (1977).
4. Oxyberberine is readily prepared from berberine by refluxing with aq potassium hydroxide for 3 hr. W.H. Perkin, jun., J. Chem. Soc., 722 (1918).
5. Compound 8 exhibits $\nu_{max}^{CHCl_3}$ 3200, 1773 and 1675 cm^{-1}; λ_{max}^{EtOH} 238, 290 and 300 sh nm (log ε 1.78, 1.62 and 1.58); pmr δ2.70 (br. t, 2H, J = 7.5 Hz, CH_2-4), 3.82 (br. t, 2H, J = 7.5 Hz, CH_2-3), 3.94 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 5.90 (s, 2H, OCH_2O), 6.34 (s, 1H, H-5), 6.68 (s, 1H, H-8), 7.07 and 7.19 (ABq, 2H, J = 8.5 Hz, ring D arom. H); ms m/e 383 (M^+), 365, 208 and 173 (base).
6. The intimate details of the mechanism involved in the photooxidation of 5 to 8 would be the subject of a separate investigation.
7. Salt 10 iodide exhibits $\nu_{max}^{CHCl_3}$ 1740 and 1670 cm^{-1}; λ_{max}^{EtOH} 240 sh, 257 sh, 310 and 388 nm (log ε 4.31, 4.23, 4.19 and 3.87); pmr δ2.5-3.5 (br. m, 2H, CH_2-4), 3.83 (s, 3H, N^+-CH_3), 3.91 (s, 3H, OCH_3), 4.01 (s, 6H, OCH_3 and $COOCH_3$), 4.2-5.0 (br. m, 2H, CH_2-3), 6.12 (s, 2H, OCH_2O), 6.79 (s, 1H, H-5), 6.88 (s, 1H, H-8), 7.29 and 8.49 (ABq, 2H, J = 8.5 Hz, ring D arom. H); ms m/e 412 (M^+), 397, 381, 223 and 190 (base).
8. R.D. Haworth and A.R. Pinder, J. Chem. Soc., 1776 (1950); and R.D. Haworth, A.R. Pinder and R. Robinson, Nature (London), 165, 529 (1950).
9. T.R. Govindachari and S. Rajadurai, J. Chem. Soc., 557 (1957). Compound 12 exhibits $\nu_{max}^{CHCl_3}$ 1760 cm^{-1}; pmr δ2.53 (t, 2H, J = 4 Hz, H-4), 2.79 (t, 2H, J = 4 Hz, H-3), 3.09 (s, 1H, NH), 3.87 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 4.68 (d, 1H, J = 3.5 Hz, H-1), 5.73 (d, 1H, J = 3.5 Hz, H-9), 5.96 (s, 2H, OCH_2O), 6.62 (s, 2H, H-5 and 8), 6.35 and 7.05 (ABq, 2H, J = 8.5 Hz, ring D arom. H); ms m/e 369 (M^+), 193 and 176 (base).
10. M. Shamma, J.L. Moniot and D.M. Hindenlang, Tetrahedron Lett., in press.
11. D.J. Cram and F.A. Abd Elhafez, J. Am. Chem. Soc., 74, 5828 (1952).