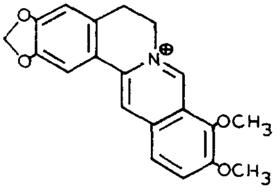
Tetrahedron Letters No. 43, pp 3787 - 3790, 1977. Pergamon Press. Printed in Great Britain.

AN UNUSUAL CARBON TO NITROGEN ACYL MIGRATION[1]

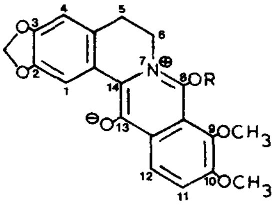
Jerome L. Moniot, Abd el Rahman H. Abd el Rahman[2] and Maurice Shamma*
Department of Chemistry, The Pennsylvania State University,
University Park, Pennsylvania 16802

(Received in USA 1 August 1977; received in UK for publication 7 September 1977)

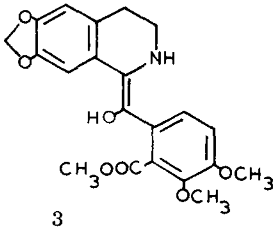
The known ylide 8-methoxyberberinephenolbetaine (2a) may be obtained either by ferricyanide oxidation[3] or by photolysis of berberine (1).[4] The unmasking of the potential carboxylic ester at C-8 by hydration in wet ether, a solvent in which it is only slightly soluble, has been shown to furnish the enamine 3. Subsequent N-methylation and reduction of 3 affords a mixture of the phthalideisoquinolines (±)-α and (±)-β-hydrastine.[3]



1



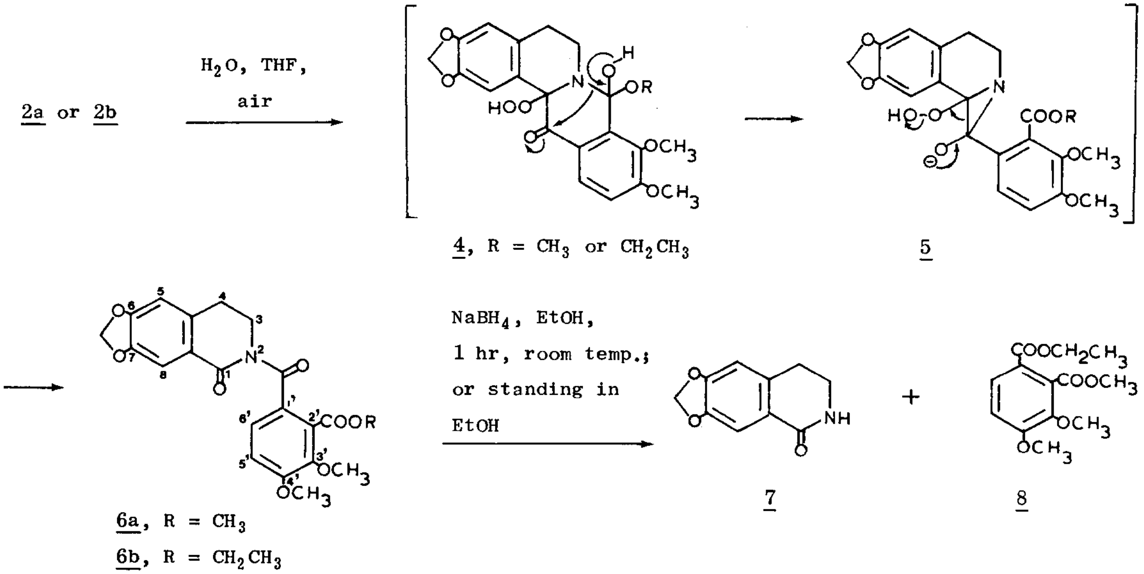
2a, R = CH_3
2b, R = CH_2CH_3



3

We now wish to report that hydration of 8-methoxyberberinephenolbetaine (2a) in wet THF, a solvent in which it is appreciably soluble, takes a different pathway and generates methyl isoanhydroberberilate (6a), $C_{21}H_{19}NO_8$, mp 143-144° (ether), $\nu_{max}^{CHCl_3}$ 1725 and 1685 cm^{-1}, in 80% yield.[5] Attempted reduction of this imidic methyl ester with sodium borohydride in ethanol resulted only in solvolysis with formation of noroxyhydrastinine (7) and 1-carboethoxy-2-carbomethoxy-3,4-dimethoxybenzene (8).[6] That carbon to nitrogen acyl migration had indeed occurred during treatment of 2a with wet THF was shown by hydration of 8-ethoxyberberinephenolbetaine (2b),[7] $C_{22}H_{21}NO_6$, HCl salt 187-188° dec. (MeOH-ether), to supply the corresponding imidic ethyl ester 6b, ethyl isoanhydroberberilate, $C_{22}H_{21}NO_8$, mp 141-142° (EtOH) in 85% yield.[8] These transformations indicate that the ester carbonyls in 6a and 6b are derived from the alkoxylated C-8 carbons of phenolbetaines 2a and 2b, respectively.

The unusual migration involved in going from 2a to 6a can be rationalized in terms of the mechanism indicated below, in which the ylide 2a is first hydrated and air oxidized to the peroxide 4. Subsequent formation of aziridine 5, followed by loss of hydroxide anion, would then lead to the product.[9] A parallel mechanism can be invoked for the conversion of 2b to 6b.



4, R = CH_3 or CH_2CH_3

5

6a, R = CH_3

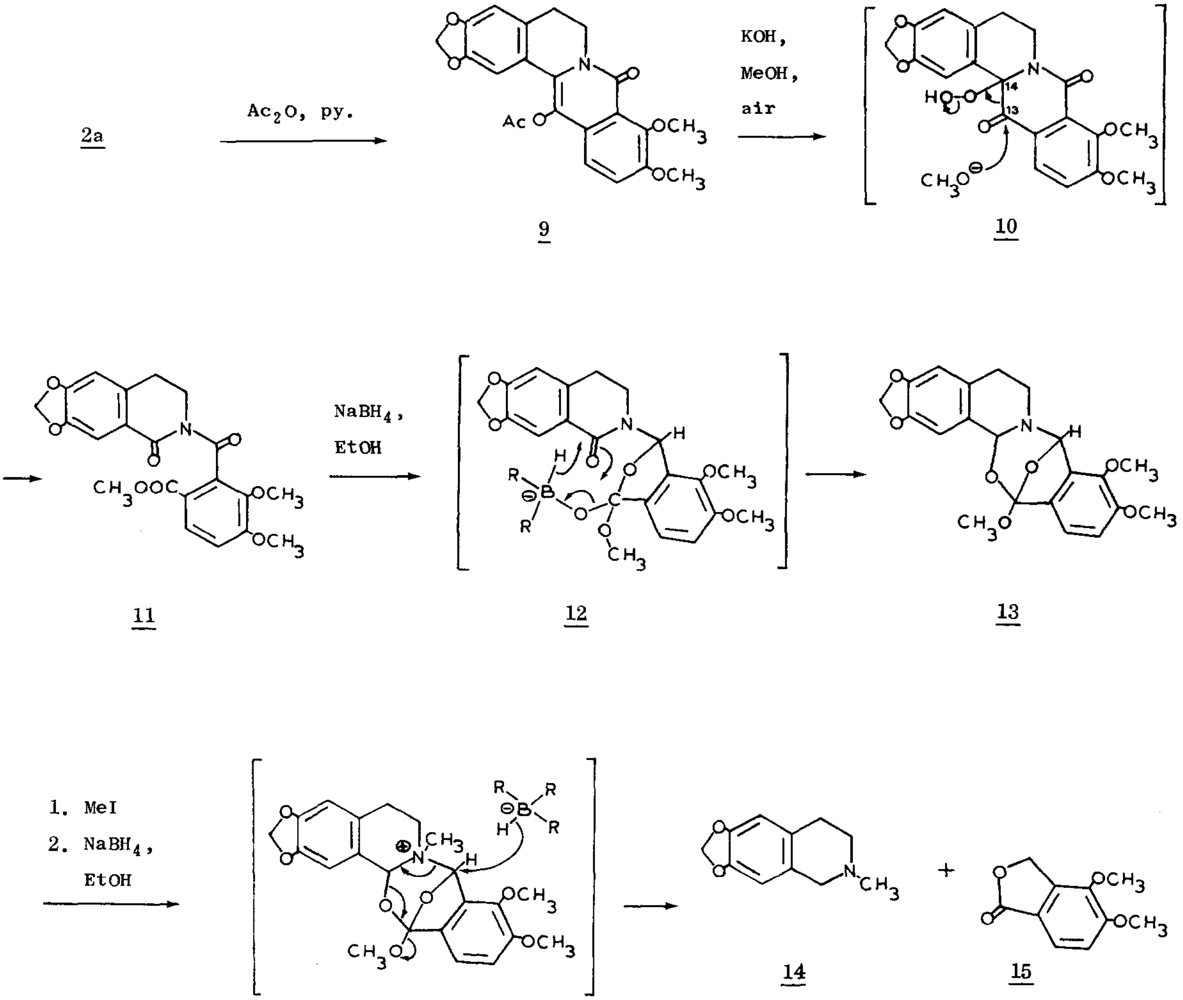
6b, R = CH_2CH_3

7

8

To further insure that a rearrangement had indeed occurred when 2a was subjected to wet THF, 2a was treated with acetic anhydride in pyridine, and the resulting 13-acetoxyoxyberberine (9), $C_{22}H_{19}NO_7$, mp 175-176° (MeOH) or 237-238° ($CHCl_3$), λ_{max}^{EtOH} 313sh, 343, 368sh and 386sh (log ϵ 4.52, 4.74, 4.65 and 4.54), obtained in 95% yield,[10] was heated with potassium hydroxide in methanol. The known methyl anhydroberberilate (11), $C_{21}H_{19}NO_8$, mp 185-186° (MeOH) (lit. 178-179° from HOAc),[11] obtained by this procedure is spectrally and chromatographically different from the isomeric methyl anhydroisoberberilate (6a).

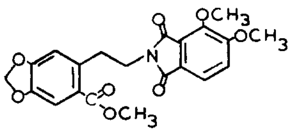
Sodium borohydride reduction of 11 unexpectedly furnished in 50% yield the methyl orthoester 13, $C_{21}H_{21}NO_7$, mp 171-172° (ether), which shows no carbonyl absorption in the infrared, and may be formed through intramolecular participation of the hydridoborate 12.[12] N-Methylation of the methyl orthoester 13 succeeded by reduction with sodium borohydride supplied the known compounds hydrohydrastinine (14) as well as pseudomeconine (15), mp 124-125° (water) (lit. mp 123-124° from water).[11]



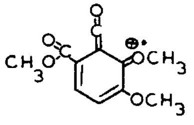
It is worth noting here the difference between the two key intermediates 4 and 10, both of which incorporate an α-hydroperoxyketone moiety. The hydroxyl group at C-8 in species 4 furnishes the required source of electrons for the rearrangement to take place. On the other hand, 10 is a lactam which preferentially undergoes nucleophilic attack at C-13 by the methoxide anion with subsequent cleavage of the C-13 to C-14 bond to give rise to methyl anhydroberberilate (11).

References

1. This project was supported by Grant HL-12971 from the National Institutes of Health. Acceptable combustion and/or high resolution mass spectral analyses were obtained on all new compounds. NMR spectra are at 60 MHz in $CDCl_3$.
2. Permanent address: Chemistry Department, Mansura University, Mansura, Egypt.
3. J.L. Moniot and M. Shamma, *J. Am. Chem. Soc.*, **98**, 6714 (1976).
4. M. Hanaoka, C. Mukai and Y. Arata, *Heterocycles*, **6**, 895 (1977).
5. NMR spectrum of **6a** δ3.00 (t, 2H, J = 7 Hz, $ArCH_2$), 3.71 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.04 (t, 2H, J = 7 Hz, CH_2N), 5.98 (s, 2H, OCH_2O), 6.67 (s, 1H, H-5), 7.43 (s, 1H, H-8), 6.91 and 7.19 (ABq, 2H, J = 8.5 Hz, H-5' and H-6', respectively). MS m/e 413 (M^+, 50), 382 (90), 364 (5), 354 (40), 223 (100), 193 (5), 191 (30) and 177 (20).
6. Compound **8**, $C_{13}H_{16}O_6$, is an oil, nmr δ1.27 (t, 3H, $\underline{CH_3}CH_2$), 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.33 (q, 2H, $CH_3\underline{CH_2}$), 6.93 (d, 1H, J = 8 Hz, ArH), 7.80 (d, 1H, J = 8 Hz, ArH). MS m/e 268 (M^+, 100), 237 (20), 223 (90) and 208 (80).
7. Obtained by cleavage of oxybisberberine (Ref. 3 above) with ethanolic hydrogen chloride.
8. Significantly, solvolysis of **6b** in methanol furnishes the known 1-carbomethoxy-2-carboethoxy-3,4-dimethoxybenzene, mp 86-87° (MeOH). The compound was first prepared by A. Kirpal, *Monatsh.*, **35**, 677 (1914), who found mp 88° (EtOH-H_2O).
9. Compound **3** was recovered unchanged after stirring for 72 hr in wet THF, so that **3** is not an intermediate in the conversion of **2a** to **6a**.
10. Alternative treatment of **2a** with methyl iodide in acetonitrile affords the known 13-methoxyoxyberberine, $C_{21}H_{19}NO_6$, mp 194-195° (MeOH), $\nu_{max}^{CHCl_3}$ 1650 and 1600 cm^{-1}, briefly described by Y. Sawa and T. Ikegawa, Japanese patent 75 19,795; *Chem. Abstr.*, **83**, 43574w (1975).
11. W.H. Perkin, Jun., *J. Chem. Soc.*, **57**, 992 (1890). In this paper, which was written almost 90 years ago, Perkin assigned to methyl anhydroberberilate the isomeric structure **A**. However, the mass spectrum with a base peak m/e 223 ($C_{11}H_{11}O_5$) supports expression **11**.



A



m/e 223

12. NMR of **13** δ3.10 (t, 2H, J = 7 Hz, $ArCH_2$), 3.30 (t, 2H, J = 7 Hz, CH_2N), 3.67 (3H, orthoester OCH_3), 3.76 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.95 (s, 1H, $N\text{-}\underset{\underline{H}}{\overset{O}{C}}\text{-}Ar$), 5.05 (s, 1H, $N\text{-}\underset{\underline{H}}{\overset{O}{C}}\text{-}Ar$), 5.90 (s, 1H, ArH), 7.20 (s, 1H, ArH), 7.13 and 7.55 (ABq, 2H, J = 8.5 Hz, H-11 and 12).