Tetrahedron Letters No. 49, pp 4273 - 4276, 1977. Pergamon Press. Printed in Great Britain.

NEW FACETS OF PROTOBERBINOID CHEMISTRY: THE 8,13-DIOXOBERBINES

Maurice Shamma, Jerome L. Moniot and David M. Hindenlang,

Department of Chemistry, The Pennsylvania State University,

University Park, Pennsylvania 16802

(Received in USA 18 July 1977; received in UK for publication 13 October 1977)

It has previously been shown that methanolic hydrogen chloride cleaves oxybisberberine, the crystalline ferricyanide oxidation dimer of berberine (4), to afford 8-methoxyberberinephenol-betaine.[1,2] We have now found that cleavage of oxybisberberine[3] with pyridine hydrochloride in pyridine, followed by aq acid work-up, gives in nearly quantitative yield a 1:1 molar ratio of 4 and the highly oxygenated, colorless, derivative 5, $C_{20}H_{17}NO_7$, mp 133-134° (ether); $\nu_{max}^{CHCl_3}$ 1720 and 1670 cm^{-1}; λ_{max}^{MeOH} 342, 368 and 382 nm (log ε 4.79, 4.56 and 4.41); pmr δ2.6-3.0 (br. m, 2H, CH_2-5), 3.88 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.4-5.0 (br. m, 2H, CH_2-6), 5.88 (s, 2H, OCH_2O), 6.53 (s, 1H, H-4), 6.93 (s, 1H, H-1), 7.10 and 7.74 (ABq, 2H, J = 8.5 Hz, H-11 and 12).[4] This 8,13-dioxo-14-hydroxyberbine incorporates the unusual juxtaposition of functional groups best described as a homoannular α-ketocarbinolamide (R-C(=O)-C(OH)-N-C(=O)-R') which undergoes a variety of chemical transformations depending upon cleavages about the core atom C-14.

Cleavage of the C-14 to OH bond of 5 occurs in the presence of methanolic hydrogen chloride whereupon a deep violet solution of the immonium salt 2 is formed. Evaporation of the solvent generates in quantitative yield the O-methylated derivative 1, $C_{21}H_{19}NO_7$, mp 126° (ether); $\nu_{max}^{CHCl_3}$ 1725 and 1665 cm^{-1}; pmr δ3.17 (s, 3H, OCH_3-14).[5]

When a concentrated solution of the immonium salt 2 is allowed to stand in strong mineral acid, 5 can serve as a nucleophile to quench the immonium species, thus supplying dimer 3, $C_{40}H_{32}N_2O_{13}$, mp 154-155° decomp. ($CHCl_3$); $\nu_{max}^{CHCl_3}$ 1710 br., 1660 and 1650 cm^{-1}.[6] Subsequent treatment of either 1 or 3 with concentrated hydrochloric acid, dilution with water, and extraction with chloroform, effects the regeneration of the original 8,13-dioxoberbine 5.

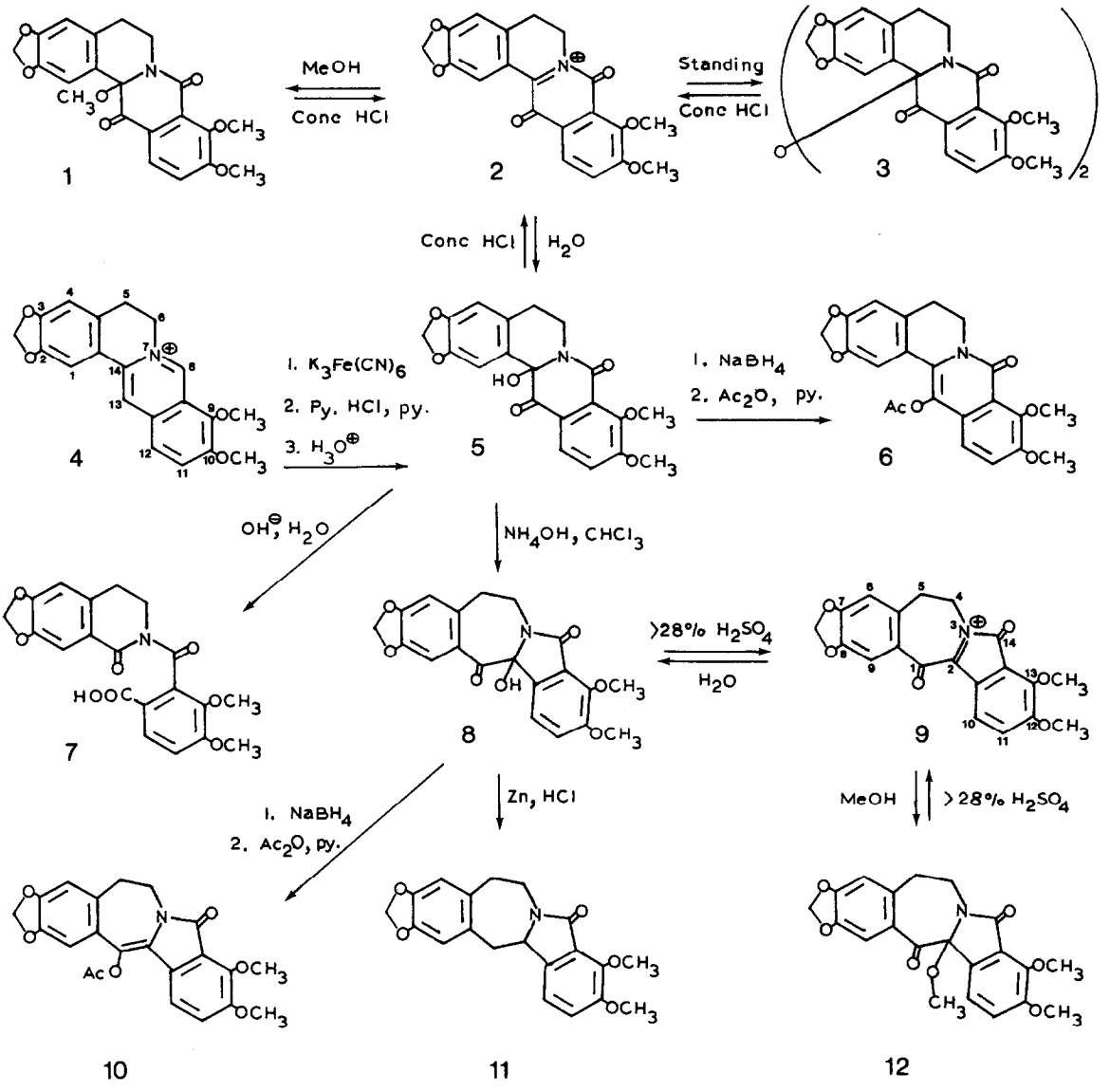
Fission of the C-13 to C-14 bond of 5 is readily achieved in the presence of aq. sodium hydroxide which promotes rapid oxidative cleavage to furnish in good yields Perkin's anhydroberberilic acid (7), as well as its further hydrolysis product, the known bicyclic lactam noroxyhydrastinine.[7]

The N-7 to C-14 bond of 5 is ruptured non-oxidatively by the action of weak base. Treatment of a chloroform solution of 5 with ammonium hydroxide results in a quantitative carbonyl-carbinol rearrangement with formation of aporhoeadane 8, $C_{20}H_{17}NO_7$, mp 154-155° (MeOH); $\nu_{max}^{CHCl_3}$ 1720 and 1700 cm^{-1}; λ_{max}^{MeOH} 275 and 314 nm (log ε 3.81 and 3.94); pmr δ2.6-4.2 (br. m, 4H, CH_2-CH_2), 3.80 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.00 (br. s, 1H, OH), 5.91 (s, 2H, OCH_2O), 6.63 (s, 1H, H-4), 6.73 (s, 1H, H-1), 6.94 and 7.42 (ABq, 2H, J = 8 Hz, H-11 and 12), which incorporates a heteroannular α-ketocarbinolamide grouping.[8] As in the case of 5, the angular C-2 hydroxyl can be exchanged under acidic conditions. However, in contrast to 2, the blue-black immonium form 9 requires >28% sulfuric acid before it is formed in appreciable concentration. Quenching with methanol then provides the O-methylaporhoeadane 12, $C_{21}H_{19}NO_7$, mp 146-147° (MeOH); pmr δ3.01 (s, 3H, OCH_3-2). The heteroannular α-ketocarbinolamide 8 is more stable than its homoannular analog 5, and does not undergo base mediated oxidative cleavage or rearrangement.

Sodium borohydride reduction of 8, followed by O-acetylation with acetic anhydride in pyridine, proceeds with concomitant elimination of the angular hydroxyl group to supply the highly fluorescent acetoxyenamide 10, $C_{22}H_{19}NO_7$, mp 213-214° (MeOH); $\nu_{max}^{CHCl_3}$ 1775 and 1710 cm^{-1}; λ_{max}^{MeOH} 263sh, 274sh, 303 and 377 nm (log ε 3.84, 3.85, 3.86 and 4.32); pmr δ2.42 (s, 3H, CH_3COO), 6.64 and 6.87 (2s, 2H, H-4 and 1), 7.08 and 7.50 (ABq, 2H, J = 8.5 Hz, H-11 and 12). This transformation stands in analogy to similar reduction and acetylation of 5 which leads to the acetoxypyridone 6,[9] $C_{22}H_{19}NO_7$, mp 175-176° (MeOH), $\nu_{max}^{CHCl_3}$ 1775 and 1658 cm^{-1}; λ_{max}^{MeOH} 313sh, 343, 368sh and 386sh nm (log ε 4.52, 4.74, 4.65 and 4.54); pmr δ2.32 (s, 3H, CH_3COO), 7.16 and 7.33 (ABq, 2H, J = 8.5 Hz, H-11 and 12) and 7.47 (s, 1H, H-1). As a final structural confirmation of 8, its zinc in hydrochloric acid reduction gives rise to the known aporhoeadane 11, mp 228-229° (MeOH), in 35% yield.[10]

The present oxidation of berberine at C-8, C-13 and C-14, and the formation of rearranged products such as the aporhoeadane 8, have some analogy in nature. Tetrahydroprotoberberines are known to be converted in plants into benzazepine containing alkaloids such as the rhoeadines.[11] The conversion of 5 to 8 is also reminiscent of the ring expansion which must be involved in the biogenesis of the dimeric benzylisoquinoline alkaloid stepinonine.[12]

Acknowledgments:- This project was supported by NIH research grant HL-12971, awarded by the National Heart, Lung and Blood Institute, PHS/DHEW. The authors are endebted to Miss Tina M. Kravetz for technical assistance.


MeOH
Conc HCl
Standing
Conc HCl
Conc HCl
H_2O
1. $K_3Fe(CN)_6$
2. Py. HCl, py.
3. $H_3O^{\oplus}$
1. $NaBH_4$
2. Ac_2O, py.
$OH^{\ominus}$, H_2O
NH_4OH, $CHCl_3$
>28% H_2SO_4
H_2O
Zn, HCl
1. $NaBH_4$
2. Ac_2O, py.
MeOH
>28% H_2SO_4
1
2
3
4
5
6
7
8
9
10
11
12

References

1. J.L. Moniot and M. Shamma, J. Am. Chem. Soc., 98, 6714 (1976). All structural 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. 8-Methoxyberberinephenolbetaine has recently been prepared by an alternate route involving photooxidation of berberine: M. Hanaoka, C. Mukai and Y. Arata, Heterocycles, 6, 895 (1977).
3. An x-ray crystallographic investigation of the structure of oxybisberberine is in progress.
4. Alternatively, aq acid hydrolysis of the known 8-methoxyberberinephenolbetaine to 13-hydroxy-8-oxoberberine, mp 216-217° (MeOH), followed by air oxidation in pyridine, affords 5 in high yield. In addition, the known compound berberinephenolbetaine upon hydration in wet ether gives rise to a complex mixture of oxidation products including 1, 5, 7 and 8.
5. Addition of methanol in the work-up of the pyridine hydrochloride in pyridine cleavage of oxybisberberine furnishes compound 1 directly.
6. The pmr spectrum of 3 exhibits δ2.5-3.5 (br. m, 4H, CH_2-5), 4.2-5.0 (br. m, 4H, CH_2-6), 3.87, 3.89 and 3.92 (3s, 3H, 3H, 6H, 4 OCH_3), 5.84 and 5.93 (2s, 2H, 2H, 2 OCH_2O), 6.49, 6.59, 6.93 and 6.99 (4s, 4H, arom. H), 7.07 and 7.72 (ABq, 2H, J = 8.5 Hz, H-11 and 12), and 7.09 and 7.72 (ABq, 2H, J = 8.5 Hz, H-11 and 12); ms m/e 748 (M^+) (2), 382 (base), and 366 (80).
7. W.H. Perkin, jun., and R. Robinson, J. Chem. Soc., 97, 305 (1910).
8. The term aporhoeadane refers to the isoindolo-[2,3-c][3]-benzazepine skeleton present in compounds 8, 10, 11 and 12.
9. 13-Acetoxy-8-oxoberberine (6) is also obtained by acetic anhydride in pyridine treatment of oxybisberberine (50% yield) or 8-methoxyberberinephenolbetaine (>90% yield).
10. S. Teitel, W. Klötzer, J. Borgese and A. Brossi, Can. J. Chem., 50, 2022 (1972).
11. For a review on the rhoeadine alkaloids see M. Shamma, The Isoquinoline Alkaloids, Academic Press, New York (1972), p. 399.
12. T. Ibuka, T. Konoshima and Y. Inubushi, Chem. Pharm. Bull., Tokyo, 23, 114 (1975), and 23, 133 (1975).