Tetrahedron Letters No. 18, pp 1415 - 1418, 1976. Pergamon Press. Printed in Great Britain.

DEHYDROPROTOBERBERINIUM SALTS AS SYNTHETIC INTERMEDIATES[1]

Maurice Shamma and Leland A. Smeltz,
Department of Chemistry, The Pennsylvania State University,
University Park, Pennsylvania 16802

(Received in USA 4 February 1976; received in UK for publication 23 March 1976)

Although a variety of dehydroprotoberberinium salts incorporating skeleton <u>2</u> are known,[2] their synthetic utility has so far remained essentially unexplored. We have determined that dehydroprotoberberinium salts are versatile synthetic intermediates which can be utilized (a) to functionalize protoberberines at C-5, and (b) to carry out the unusual cleavage of the aromatic protoberberine nucleus at the N-7 to C-8 bond.[3]

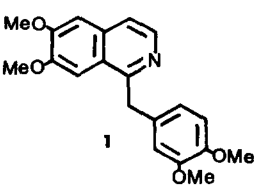
The known dehydroprotoberberinium salt 2,3,10,11-tetramethoxydibenzo [a,g] quinolizinium chloride (<u>2a</u>), readily available from papaverine (<u>1</u>),[4] was reduced with $NaBH_4$ in dry pyridine to afford in nearly quantitative yield the unstable yellow-orange dihydro derivative <u>3</u> which without purification was treated with dilute hydrochloric acid to provide in 87% yield the isoquinolinium salt <u>4</u>, $C_{21}H_{22}NO_4Cl$, m.p. 212-215^0 (decomp.) (1% aq. HCl). Yellow <u>4</u> is a new type of protoberberinium salt, completely aromatic in rings A, B, and D, but partially reduced in ring C. It is stable in acid solution, but reverts back to <u>3</u> rapidly in base, or slowly upon standing in the solid state. Nmr (DMSO-d_6, 60 MHz) δ3.83 (6H, s, 2 $OC\underline{H}_3$), 4.07 (3H, s, $OC\underline{H}_3$), 4.13 (3H, s, $OC\underline{H}_3$), 4.96 (2H, broad s, $ArC\underline{H}_2$), 5.77 (2H, broad s, $ArC\underline{H}_2N^+$), 7.16 (1H, s, Ar<u>H</u>), 7.28 (1H, s, Ar<u>H</u>), 7.74 (1H, s, Ar<u>H</u>), 7.97 (1H, s, Ar<u>H</u>), and 8.40 (2H, q, J = 6.5 Hz, i.c.s. = 28.5 Hz, C-5 and 6 Ar<u>H</u>); ν_{max}^{Nujol} 1515, 1609 and 1630 cm^{-1}.

Reduction of <u>4</u> with $NaBH_4$ in dry pyridine led to the unstable and previously unknown enamine <u>5</u>, 5-dehydronorcoralydine, which was used directly for functionalization at C-5. Thus hydroboration of <u>5</u> in THF followed by treatment with 30% H_2O_2-20% NaOH supplied a separable mixture of the diastereoisomeric C-5 hydroxylated tetrahydroprotoberberines <u>6</u> and <u>7</u> in 45 and 30% yield, respectively.[5]

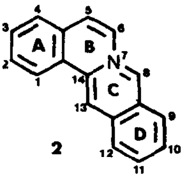
Acetylation of the enamine 5 with acetyl chloride in pyridine gave rise to the C-5 acetyl derivative 8, $C_{23}H_{25}NO_5$, m.p. 197-199° (methanol), $\nu_{max}^{CHCl_3}$ 1596 cm^{-1}, in 60% yield. Alternatively, treatment of enamine 5 with methyl iodide followed by $NaBH_4$ in methanol reduction furnished the C-5 methylated tetrahydroprotoberberine 9, $C_{22}H_{27}NO_4$, m.p. 163-165° (benzene-heptane), as well as the enamine methiodide salt 10, $C_{22}H_{26}NO_4I$, m.p. 175° (decomp.) (benzene) in 24 and 57% yield, respectively.

Besides their use in functionalization at C-5, dehydroprotoberberinium salts can be utilized as intermediates in the cleavage of the N-7 to C-8 bond of berberinium systems. Treatment of 2a with refluxing 20% aq. KOH led quantitatively to the yellow oxy derivative 11, $C_{21}H_{19}NO_5$, m.p. 258° (ethanol). When this pyridone was in turn refluxed in a saturated methanolic KOH solution, and the reaction mixture carefully neutralized, the product proved to be the ring opened colorless zwitterionic salt 12, $C_{21}H_{21}NO_6$, recrystallized from chloroform, λ_{max}^{EtOH} 241, 292, 311 sh and 327 nm (log ϵ 4.84, 3.87, 3.75 and 3.74), $\nu_{max}^{CHCl_3}$ 1565 (broad) and 3460 (broad) cm^{-1}. Upon heating to establish the melting point, a crystalline transformation to yellow needles occurred. The determined m.p. of 258° actually corresponds to that of the oxy derivative 11, so that 12 dehydrates to 11 upon heating, as also indicated by comparative tlc. The stable methyl ester 13, $C_{23}H_{29}NO_6$, m.p. 127-128° (ether), $\nu_{max}^{CHCl_3}$ 1708 cm^{-1}, was obtained by treatment of the salt 12 with methyl iodide in acetonitrile at 40°, followed by $NaBH_4$ reduction in methanol.

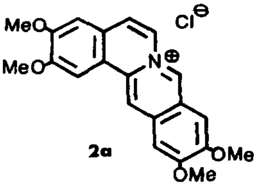
Significantly, we have also found that the above ring opening reaction of the oxy derivative 11 cannot be duplicated with oxyberberine[6] (14) which lacks the C-5,6 double bond, and is essentially stable to methanolic base. The present characterization of the tricyclic benzylisoquinolines 12 and 13, therefore, represents the first known opening of ring C of an aromatic protoberberine system with formation of an isolable amino acid derivative.[7]



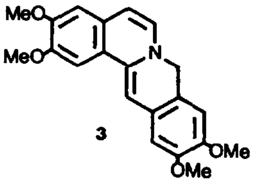
1

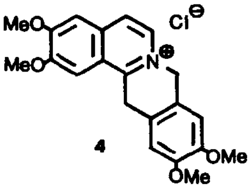


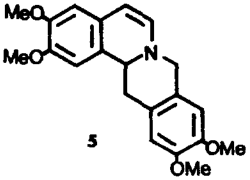
2

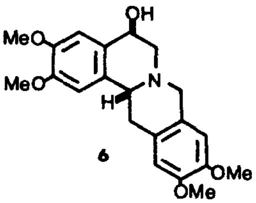


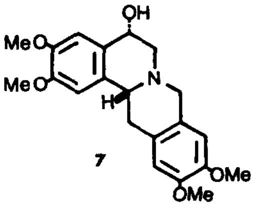
2a

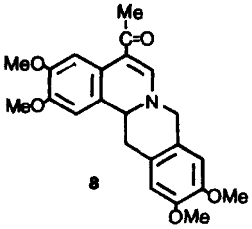

3

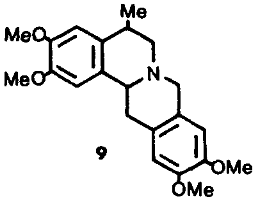

4

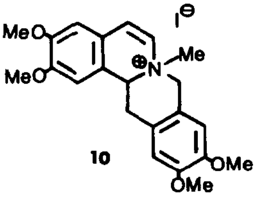

5

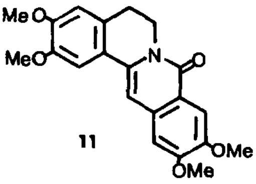

6

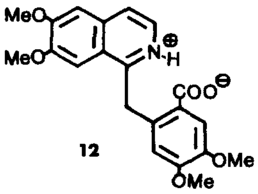

7

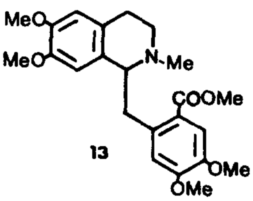

8

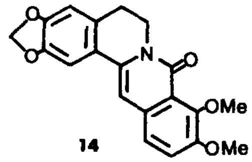

9


10


11


12


13


14

References

1. This project was supported by NIH research grant CA-11450, awarded by the National Cancer Institute, PHS/DHEW. The authors are grateful to Professor S.F. Dyke for providing spectra of authentic alcohol 7. Acceptable combustion elemental analyses were obtained on all stable new compounds. The composition of all new compounds prepared was confirmed by high resolution mass spectrometry using an AEI MS-902 instrument.
2. C.K. Bradsher and N.L. Dutta, J. Amer. Chem. Soc., 82, 1145 (1960); and J. Org. Chem., 26, 2231 (1961).
3. For the cleavage of the N-7 to C-8 bond of protoberberine salts resulting in formation of naphthalene derivatives see M. Shamma, L.A. Smeltz, J.L. Moniot and L. Tőke, Tetrahedron Letters, 44, 3803 (1975).
4. T. Kametani, M. Takeshita, F. Satoh and K. Nyu, J. Pharm. Soc. Japan, 94, 478 (1974).
5. The previously known preparation of alcohols 6 and 7 involves a total synthesis utilizing a Pomeranz-Fritsch cyclization: S.F. Dyke, D.W. Brown, M. Sainsbury and G. Hardy, Tetrahedron, 27, 3495 (1971). See also S.F. Dyke and E.P. Tiley, Tetrahedron, 31, 561 (1975), for a synthesis of the alkaloid berberastine, which corresponds to 5-hydroxyberberine, by the Pomeranz-Fritsch method.
6. A.R. Pinder in Chemistry of Carbon Compounds, Vol. IV^{C}, ed. by E.H. Rodd, Elsevier Publishing Co., Amsterdam (1960), p. 1923.
7. For a systematic polarographic study of the reaction of protoberberinium and other ammonium salts with hydroxide anion, but without isolation of products, see V. Šimanek, V. Preininger, S. Hegerová and F. Šantavy, Coll. Czech. Chem. Commun., 37, 2746 (1972).