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DEHYDROAPORPHINES

A PROTONATION STUDY

A. VENKATESWARLU and M. P. CAVA*
Departments of Chemistry, University of Pennsylvania,* Philadelphia, PA 19174, U.S.A. and Wayne State University, Detroit, MI 48202, U.S.A.

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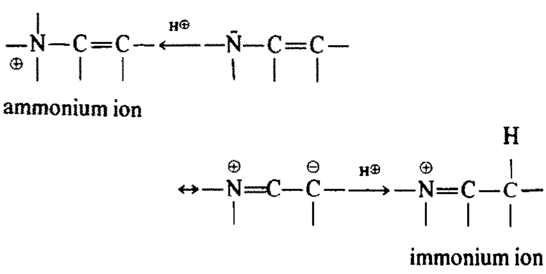
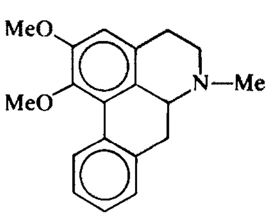
Abstract—The representative dehydroaporphines dehydronuciferine (**2**), dehydrodicentrine (**3**) and dehydroocopodine (**4**) initially undergo both N-protonation and C-protonation (at C-7) in CF_3COOH, the C-protonated immonium salts being formed almost completely under equilibration conditions. Applications of these observations to the synthesis of 7-deuteriodehydrodicentrine (**7**) and 6a,7,7-trideuterionuciferine (**8**) are described.

It is well known that enamines form salts with strong acids, proton addition taking place at either the nitrogen or the β-carbon of the mesomeric enamine system. The salts are usually immonium structures, but these may be secondary protonation products, ammonium salt formation occurring first.[1]



Structurally, the dehydroaporphines represent a special type of cyclic enamine, being in fact 9-aminophenanthrenes. The fact that dehydronuciferine (**2**) is readily reduced to nuciferine (**1**) only in the presence of mineral acid[2] suggested that the species being reduced was actually the corresponding immonium salt, and prompted us to carry out a protonation study of several representative dehydroaporphines. The compounds studied were dehydrodicentrine (**3**), dehydroocopodine (**4**) and dehydronuciferine (**2**).[3]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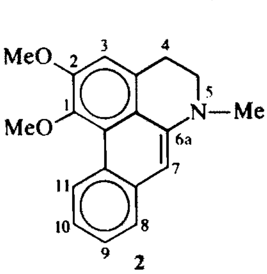

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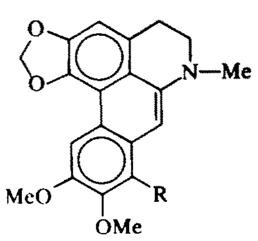
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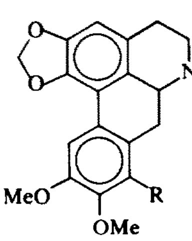
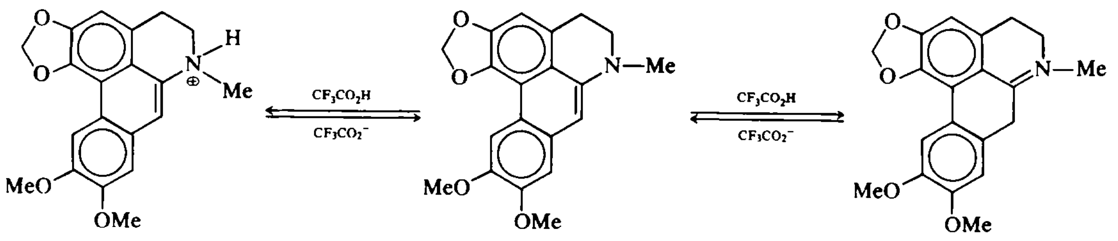
4: R = OMe


5: R = H
6: R = OMe

The NMR spectra of dehydroaporphines **3**, **4** and **2** in trifluoroacetic acid (CF_3COOH) showed features indicating the presence of both the C-protonated (C-7) and N-protonated species, with the former greatly predominating in the course of time. The spectra of the three compounds in $CDCl_3$ and in CF_3COOH were compared to estimate the extent of protonation at C-7 and at the tertiary N atom. The course of the protonation in each case was followed by measuring the NMR spectrum immediately, 25 min, 1.5 hr, 32 hr and 72 hr after dissolution of the compound in CF_3COOH. The results thus obtained were confirmed by deuterium exchange experiments involving a study of the NMR spectra similarly measured in deuterated trifluoroacetic acid (CF_3COOD). Table 1 summarizes the NMR data obtained for dehydrodicentrine (**3**) and dehydroocopodine (**4**) in $CDCl_3$ and CF_3COOH solutions.

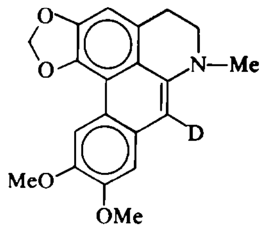
The NMR spectrum of dehydrodicentrine (**3**) in CF_3COOH, taken immediately on dissolution, showed the presence of two species in the ratio of 1:3. Spectra obtained at subsequent time intervals showed a continuous increase in the percentage of the major species, which reached a maximum of over 95% at the end of 72 hr. The major species was assigned the immonium structure (i.e. the C-protonated salt **3B**) on the basis of its benzylic proton signal, the other peaks attributable to **3B** being revealed by their intensity relative to the benzylic peak. The C-protonated species **3B** was thus assigned the major peaks which included a three-proton N-Me singlet at unusually low field (δ 3.80), a two-proton broad singlet (δ 4.40) due to the benzylic protons at C-7 and three one-proton singlets in the aromatic region (δ 6.91, 7.09 and 8.32) for the protons at C-3, C-8 and C-11, respectively. The minor ammonium species **3A** showed the expected C-7 olefinic proton as a singlet at δ 6.49; the N-Me appeared at rather low field (δ 3.53) as a broad signal consistent with the N-protonated formulation, while the three aromatic singlets were clearly distinguishable from those of the C-protonated species **3B**.

The protonation assignments thus made were supported by the NMR spectrum of **3** in CF_3COOD which showed that exchange occurred at C-7, with equilibration reaching completion within 72 hr. Consequently, the peak due to



3A **3** **3B**

the benzylic protons at C-7 was absent in the spectrum taken at the end of this period. Consistent with this observation, the product recovered from the CF_3COOD solution by treatment with anhydrous potassium carbonate under aprotic conditions was shown to be the C-7 deuterated compound **7** by its NMR spectrum in $CDCl_3$, which showed the complete absence of the C-7 proton at δ 6.47. Also worthy of note, the NMR spectrum of **3** in CF_3COOD showed the N-methyl of the N-deuterated species as a sharp singlet (δ 3.51) in contrast to the broad signal observed for the corresponding N-protonated species **3A**.



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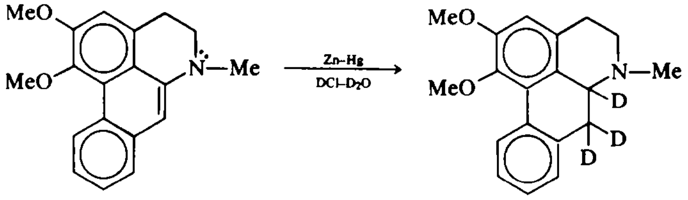


2 **8**

Dehydronuciferine (**2**) similarly studied by NMR showed features analogous to those of dehydrodicentrine (**3**) with respect to protonation and deuterium exchange. As predicted, reduction of **2** with amalgamated zinc in DCl–D_2O solution afforded, in 86% yield, 6a,7,7-trideuterionuciferine (**8**). This result confirmed the protonation at C-7 and also showed the reversibility of the process.

The NMR spectrum of dehydroocopodine (**4**) in $CDCl_3$ showed the C-7 proton at a lower field (δ 6.83) than that observed for this proton (δ 6.47) in the NMR spectrum of dehydrodicentrine (**3**). The low-field shift of the C-7 proton in the case of **4** may be attributed to deshielding caused by the anisotropic effect of the OMe oxygen at C-8.

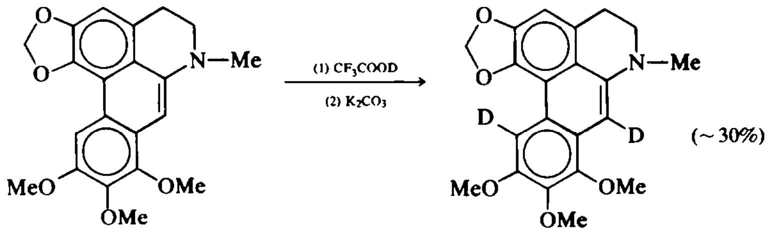
The NMR spectra of dehydroocopodine (**4**) in CF_3COOH taken at various periods indicated the protonation equilibration process occurs much more rapidly than with dehydrodicentrine (**3**) and dehydronuciferine (**2**). Thus, the spectrum taken after 1.5 hr showed the presence almost exclusively of the C-protonated species. The formation of this species is probably particularly favored in the case of **4** because of steric factors, since the structural change from the enamine form to the immonium form brought about by C-7 protonation would result in the release of steric interactions between the C-8 OMe and the C-7 proton. In accord with a reluctance of the C-7 deuterated species to return to the enamine form, the NMR spectrum of **4** in CF_3COOD showed only partial exchange at C-7 even after 32 hr, but surprisingly, 100% deuterium incorporation at C-11. The NMR spectrum taken after 72 hr showed no significant increase in deuterium exchange at C-7. Work-up of the CF_3COOD solution with anhydrous potassium carbonate under

Table 1. NMR data (δ units): Dehydrodicentrine (**3**) and dehydroocopodine (**4**)

Compound	N-Methyl protons	Methoxyl protons†			Methylenedioxy protons	Aromatic protons			
		C_8	C_9	C_{10}		C_3	C_7	C_8	C_{11}
3 in $CDCl_3$	3.02	—	3.98	3.98	6.13	6.82	6.47	6.99	8.52
3 in CF_3COOH									
(**A**) N-Protonated species	3.53	—	4.13	4.16	~6.35	7.43	7.30	7.75	8.78
(**B**) C-Protonated species	3.80	—	4.03	4.06	6.35	6.91	4.39‡	7.08	8.32
4 in $CDCl_3$	3.07	4.02	3.97	4.00	6.15	6.89	6.83	—	8.26
4 in CF_3COOH									
(**A**) N-Protonated species	3.53	4.22	4.15	4.20	~6.36	7.33	8.10	—	8.68
(**B**) C-Protonated species	3.83	4.15	4.06	4.13	6.36	6.96	4.33‡	—	8.20

†Assignments may be interchanged.

‡Benzylic protons (a broad signal integrating for 2 H).



4 **9**

aprotic conditions afforded the free base (**9**) which was shown by its NMR spectrum ($CDCl_3$) to contain 100% of deuterium at the C-11 position, but only ~30% deuterium at C-7.

The acid-catalyzed deuterium incorporation at C-11 of dehydroocopodine (**4**) is indicative of a very facile electrophilic substitution at this position.

EXPERIMENTAL

All m.ps were determined in open tubes using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Mass spectra were determined using an Atlas CH-4 instrument. NMR spectra were obtained in the solvents indicated using a Varian A60-A instrument; chemical shifts are reported as ppm (δ) downfield from TMS. CF_3COOD was prepared by the slow addition of an equivalent amount of reagent grade trifluoroacetic anhydride to 99.5% pure D_2O.

6a,7,7-*Trideuterionuciferine* (**8**). Dehydronuciferine **2** (0.06 g) was added to a mixture of amalgamated Zn in DCl-D_2O (prepared by shaking a suspension of 0.5 g Zn dust in a soln of 35 mg mercuric chloride in 1 ml D_2O, followed by treatment with 6 ml 2.5 N DCl in D_2O) at 60°. After being stirred for 20 min, 6 N DCl-D_2O soln (2 ml) was added and the mixture was heated at 60° with stirring for another 30 min. The supernatant soln was decanted and the residue was washed with D_2O (2 × 5 ml). The combined soln was cooled, basified with anhyd K_2CO_3 and was then extracted with dry CCl_4 (5 × 15 ml). The extract, after washing with D_2O (10 ml), was dried (K_2CO_3) and evaporated. Crystallization of the residue from ether-petroleum ether afforded **8** as white crystals (0.057 g, 86%): m.p. 134–136.5°; NMR spectrum: δ 2.50 (3 H, NCH_3), 2.52 ~ 3.20 (4 H, methylene H at C-4 and C-5), 3.64, 3.86 (2 × 3 H, 2 OCH_3), 6.58 (1 H, C-3 H), 7.17–7.26 (3 H, C-8, C-9, and C-10 H), and 8.33 (1 H, C-11 H); *m/e* 298, *m/e* calcd. for $C_{19}H_{18}D_3NO_2$: 298.

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REFERENCES

[1] For a review of enamine protonation, see K. Blaha and O. Cervinka, *Advances in Heterocyclic Chemistry*, (Edited by A. R. Katritzky and A. J. Boulton) Vol. 6. pp. 183–186. Academic Press, New York, N.Y. (1966).

[2] M. P. Cava, M. J. Mitchell, S. C. Havlicek, A. Lindert and R. J. Spangler, *J. Org. Chem.* **35**, 175 (1970).

[3] M. P. Cava, A. Venkateswarlu, M. Srinivasan and D. L. Edie, *Tetrahedron* **28**, 4299 (1972).