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SULPHONATION OF β-CARBOLINES IN CONCENTRATED SULPHURIC ACID SOLUTIONS.

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Abstract- Solutions of harmane and N,N'-dimethylharmane in concentrated sulphuric acid (16–18M) conducted to the corresponding C-6 sulphonated derivatives.

β-Carboline (9H-pyrido[3,4-b]indole) (I) is the parent compound of an important class of heterocycles that are often found as the basic structural unit of some indole alkaloids of varied and potent biological activity.[1] In the last years, we have undertaken a series of studies on the prototropic equilibria of β-carboline alkaloids in order to gain insight into the chemistry and biochemistry of these compounds. Some of these results have recently been reported.[2-4]

In the context of such studies it was observed that unlike other β-carboline derivatives, solutions of fully aromatic β-carbolines in highly concentrated sulphuric acid were very unstable and therefore we were unable to make precise pK determinations. Sulphonations of β-carboline derivatives in these media are known from pioneering works on the chemistry of these compounds. However, in spite of the potential synthetic utility of such reactions they seem to be little explored and there is controversial about the structure of the sulphonated product.[5-7] Moreover, the reactions are of theoretical interest since the related compounds pyrrole, indole and carbazole are insensible towards sulphonation in concentrated sulphuric acid solutions. As it is well known, in these media pyrrole and indole protonate on α and β carbons, respectively and carbazole on nitrogen atom.[8-10]

Both synthetic and theoretical interest of these sulphonation processes induced us to extend our original investigations on the protonation equilibria of β-carboline alkaloids to examine with more detail these reactions. The recent study of prototropic equilibria of some Harmala alkaloids in concentrated sulphuric acid solutions reported by M. Krisnamurthy and S.K. Droga,[11] in which this process has not been mentioned, prompted us to report our preliminary results on the sulphonation of harmane (1-methyl-9H-pyrido[3,4-b]indole) (II) and its N,N'-dimethyl derivative (III).

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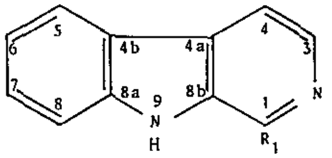
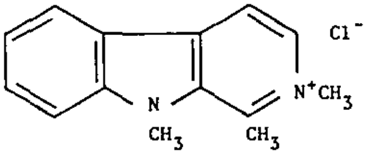


(I) β-carboline $R_1 = H$

(II) harmane $R_1 = CH_3$



(III) N,N'-dimethylharmane

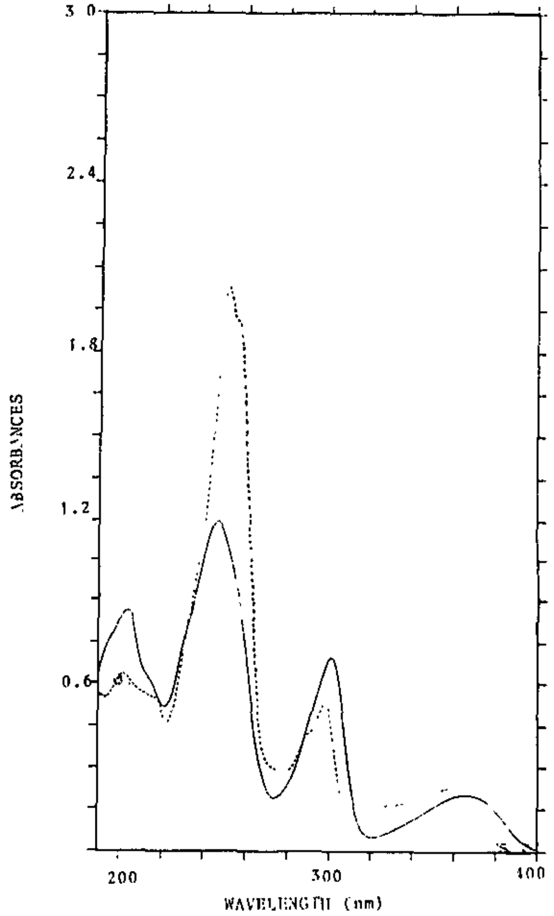


Fig. 1. Uv-Vis absorption spectra of harmane in (——) 0.1 M H_2SO_4 and (...) 18 M H_2SO_4.

The Uv-Vis and ^{13}C nmr absorption spectra of harmane did not show much change from 0.1 M up to 16 M solutions of sulphuric acid. In solutions of higher sulphuric acid concentrations, time dependent changes of the spectra were evident. These changes were irreversible and their rate depended upon sulphuric acid concentration (Fig.1). In 18 M sulphuric acid the reaction was completed in a few minutes. Dilution of these solutions with distilled water gave a white precipitate whose properties were very similar to those previously reported by Perkin and Robinson for sulphonated harmine.[5] This compound was very sparingly soluble in water and in common organic solvents, but it was readily soluble in potassium hydroxide solutions from which acids precipitated the original substance. It decomposes without melting about 300°C. The elemental analysis and mass spectrometry were in agreement with the formulae $C_{12}H_{10}N_2SO_3 \cdot 2H_2O$.

The treatment of N,N'-dimethylharmane under similar conditions gave a similar product. This indicated that sulphonation took place on carbon as previously suggested by Kermack and coworkers.[6] The definitive evidence for sulphonation on carbon was supported for the replacement of a strong doublet in the non-decoupled ^{13}C nmr spectra of harmane and N,N'-dimethylharmane by a small singlet upon acidification in 18 M sulphuric acid. The position of sulphonation was fixed at C-6 by comparison of the ^{13}C nmr spectra of harmane, N,N'-dimethylharmane and their sulphonated derivatives in 4 M potassium hydroxide solutions and on the basis of empirical substituent effects on chemical shifts (Table 1).

Table 1. ^{13}C Nmr spectra of harmane, N,N'-dimethylharmane and sulphonated harmane in various media.[a]

	Harmane				Sulphonated Harmane	N,N'-Dimethylharmane	
C-atom	DMSO	0.1M $H_2SO_4^b$	18M H_2SO_4	4M KOH[c]	4M KOH[c]	DMSO	18M H_2SO_4
1	142.3	138.6	140.7	143.0*	147.1*	141.4	142.5
3	137.6	128.7	131.0	130.1	131.0	135.1	136.7
4	112.6	116.6	117.3	111.4	113.2	115.6	117.4
4a	127.1	133.7	135.7	126.3	128.5	134.6	137.0
4b	121.3	119.8	120.5	121.1	121.6	123.7	120.6
5	121.7	121.7	125.1	119.7	119.3	121.8	125.0
6	119.2	121.4	129.8	115.0	132.4	120.0	129.6
7	127.8	131.8	130.0	124.1	122.9	131.8	129.8
8	112.0	113.2	115.4	114.1	116.7	113.0	115.3
8a	140.5	143.2	146.5	149.5	153.0	143.7	146.6
8b	134.7	131.6	134.6	144.1*	147.6*	131.1	133.2
$CH_3(-C_1)$	20.6	16.3	16.9	18.7	20.2	15.8	16.2
$CH_3(-N_2)$						53.1	60.8
$CH_3(-N_9)$						44.9	46.2

[a] ^{13}C Nmr spectra were run at 50.2 MHz in a Varian XL-200 spectrometer. Chemical shifts are reported with respect to TMS. The spectra in 18M H_2SO_4 and 4M KOH were run using the ^{13}C resonance of benzene-d_6 at 128.0ppm as an external standard (coaxial tube). The chemical shift assignments were tentatively made using the data from reference (14) and with the aid of the non-decoupled spectra and APT techniques. Signals marked with asterisks can be interchanged.

[b] In this medium harmane is protonated on the pyridinic nitrogen atom.[12]

[c] In these media harmane and sulphonated harmane are deprotonated at the NH pyrrolic group.[4]

Chemical reactivity is also in favour of this assignment because C-6 is the most reactive position in other electrophilic substitution reaction of β-carbolines.[13] It is interesting to note that C-6 has also been assigned as the protonation site of Harmala alkaloids in concentrated sulphuric acid solutions.[11] However, our experimental results do not provide evidence for the existence of such cationic species in these media.

It does not seem worthwhile at this point to speculate on the mechanism of β-carboline ring sulphonation. Further kinetic studies are in progress and they will be reported along with a more comprehensive study of the sulphonation reactivity of other β-carboline derivatives.

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REFERENCES

1. H.P. Husson, Alkaloids, 1985, **26**, 1.
2. Manuel Balón, Carmen Carmona, and Domingo González, *Tetrahedron*, 1985, **41**, 4706.
3. J. Hidalgo Toledo, M. Balón Almeida, M.A. Muñoz Perez, and M.C. Carmona Guzmán, *Tetrahedron*, 1986, **42**, 1497.
4. M.A. Muñoz, M.C. Carmona, J. Hidalgo, and M. Balón, *J. Chem. Soc. Perkin Trans II*, 1986, 1573.
5. W.H. Perkin and R.Robinson, *J. Chem. Soc.*, 1919, **115**, 933.
6. W.O. Kermack, W.H. Perkin, and R.Robinson, *J. Chem. Soc.*, 1922, **121**, 1872.
7. V. Hasenfratz, *Ann. Chim. (Paris)*, 1927, **7**, 151.
8. R.A. Jones and G.P. Bean, "The Chemistry of Pyrroles", Academic Press, London, 1977.
9. R.J. Sundberg, "The Chemistry of Indoles", Academic Press, New York and London, 1970.
10. J.A. Joule, *Adv. Heterocycl. Chem.*, 1984, **35**, 83.
11. M. Krishnamurthy and S.K. Droga, *J. Chem. Soc. Perkin Tarns II*, 1986, 1247.
12. O.S. Wolfbeis, E. Fúrlinger, and R. Wintersteiger, *Monatsh. Chem.*, 1982, **113**, 509.
13. R.A. Abramovitch and I.D. Spencer, *Adv. Heterocycles Chem.*, 1964, **3**, 79.
14. a) H. Wagner and T. Nestler, *Tetrahedron Letters*, 1978, **31**, 2777.
    b) C.A. Coune, L.J.G. Angenot, and J. Denoël, *Phytochem.*, 1980, **19**, 2009.
    c) D.H. Welti, *Magn. Reson. in Chem.*, 1985, **23**, 872.
    d) K. Koike, Y. Sakamoto, and T. Ohmoto, *Org. Magn. Reson.*, 1984, **22**, 471.

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