Tetrahedron Letters No.57, pp. 4975–4978, 1970. Pergamon Press. Printed in Great Britain.

# THE STRUCTURE OF STEPHISOFERULINE, A NEW HASUBANAN ESTER ALKALOID FROM STEPHANIA HERNANDIFOLIA

S. Morris Kupchan and Matthew I. Suffness
Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901, and
Department of Pharmaceutical Chemistry, University of Wisconsin, Madison, Wisconsin 53706

(Received in USA 9 October 1970; received in UK for publication 9 November 1970)

Alkaloids which possess the rare hasubanan skeleton have been found to occur only in Stephania species. The structural elucidation of the first hasubanan ester alkaloid, stephavanine (from S. abyssinica), has recently been reported.[1] We report herein the isolation and structural elucidation of a new hasubanan ester-ketal alkaloid, stephisoferuline (1), and its interrelation with 4-demethylnorhasubanonine (2).[2]

The defatted roots and rhizomes of S. hernandifolia were extracted with methanol and then 30% aqueous methanol and the combined extracts were concentrated and triturated with 6% hydrochloric acid. The acid solution was extracted with ether and basified with ammonium hydroxide (pH 9). Extraction with chloroform gave the non-quaternary alkaloids, which were fractionated by continuous extraction with ether. The ether-soluble alkaloids were chromatographed on SilicAR-CC7 (Mallinckrodt). Elution with 2.5% methanol-chloroform gave fractions rich in stephisoferuline. Rechromatography on acid-washed alumina (Merck) with 2% methanol-chloroform as eluant followed by crystallization from chloroform-ether gave colorless needles of the chloroform solvate, $C_{29}H_{33}NO_9 \cdot 2/3\ CHCl_3$*: mp 133-135° (softens 101-102°); $[\alpha]_D^{32}$ + 48° (c 0.82, MeOH); $\lambda_{max}^{KBr}$ 2.84, 2.98, 3.38, 5.89 (unsaturated ester) μ; $\lambda_{max}^{EtOH}$ 229 mμ (sh) (ε 18,020), 287 mμ (ε 15,100), 325 mμ (ε 17,530); nmr ($CDCl_3$) τ 3.07-3.18 (3H, m, aromatic H from ester), 2.43 (1H, d (16), olefinic H), 3.32 (1H, d (8.5)) and

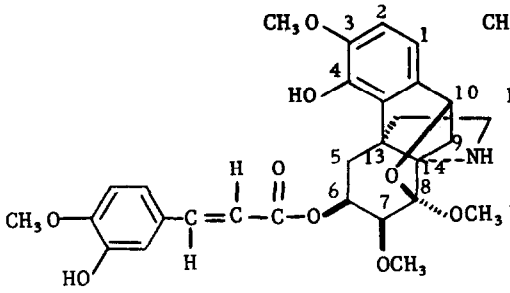
*All new crystalline compounds have been characterized by concordant elemental analyses.

3.58 (1H, d (8.5)) (C-1 and C-2 H), 4.63 (1H, m, C-6 H), 4.68 (1H, d (16), olefinic H), 5.12 (1H, d (5.5), C-10 H), 6.25 (1H, d (4), C-7 H), 6.08 (3H, s), 6.43 (3H, s) and 6.60 (6H, s) (4 x $OCH_3$); m/e 539 ($M^+$), 270, 248, 215, 194, 179, 133, 83.

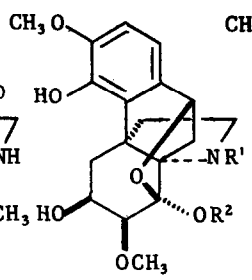
Hydrolysis of 1 in 2.5 N NaOH gave stephuline (2): mp 223-225°; $[\alpha]_D^{32}$ + 93° (c 0.55, MeOH); $\lambda_{max}^{KBr}$ 2.81, 3.03, 3.38, 3.50, 6.19, 6.73, 7.86 μ; $\lambda_{max}^{EtOH}$ 226 mμ (ε 8,200), 283 mμ (ε 1,850); m/e 363 ($M^+$), 217, 216, 215, 202, 184, 154. In the nmr spectrum of 2 ($CDCl_3$) the signal for the (C-6) proton on hydroxyl-bearing carbon appeared at τ 5.88 (1H, m). The other product isolated from the hydrolysis was isoferulic acid, identical in ir, uv, nmr, and mmp comparisons with an authentic sample. Methylation of 2 with formalin and sodium borohydride gave N-methylstephuline (3); mp 126-128°; $[\alpha]_D^{27}$ + 92° (c 0.54, $CHCl_3$); m/e 377 ($M^+$), 231, 230. The nmr spectrum of 3 ($CDCl_3$) showed a signal for the N-methyl group at τ 7.43 (3H, s) indicating the presence of a secondary amine in the parent compound. Treatment of stephuline (2) with dilute hydrochloric acid led to facile demethylation to give 8-demethylstephuline (4); mp 178-180° $[\alpha]_D^{26}$ + 107° (c 0.47, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.83, 3.32, 3.40, 6.73, 8.46, 9.27 μ; m/e 349 ($M^+$), 217, 216; nmr ($CDCl_3$) τ 6.22 (3H, s, $OCH_3$) and τ 6.48 (3H, s, $OCH_3$). Oxidation of 2 with Jones reagent in acetone gave 6-dehydrostephuline (5); mp 225-228° dec; $[\alpha]_D^{27}$ + 75° (c 0.27, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.82, 3.39, 3.52, 5.76 (unconj. ketone), 6.72, 6.80 μ; m/e 361 ($M^+$), 215, 214; nmr ($CDCl_3$) τ 5.72 (1H, s, C-7 H), 5.21 (1H, d (5.5), C-10 H), 6.15, 6.42, 6.50 (9H, 3 x $OCH_3$).

Acetylation of 2 with acetic anhydride-pyridine followed by acid treatment gave triacetyl derivative 6; mp 181-183°; $[\alpha]_D^{27}$ - 92° (c 0.29, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 3.32, 3.40, 3.46, 3.52, 5.70, 5.75, 6.08 μ; m/e 457 ($M^+$), 299, 257, 215; nmr ($CDCl_3$) τ 3.40 (1H, d (10)) and 4.18 (1H, d (10)) (C-10 and C-9 H), 4.45 (1H, m, C-6 H), 5.80 (1H, d (4), C-7 H), 6.20, 6.53 (6H, 2 x $OCH_3$), 7.67, 7.87, 8.30 (9H, 3 x $COCH_3$). The downfield shift of the signal for the C-7 proton supported assignment of the ketone to C-8. Hydrogenation of 6 over platinum gave triacetyl derivative 7: mp 199-201°; $[\alpha]_D^{26}$ + 16° (c 0.67, $CHCl_3$); m/e 459 ($M^+$), 431, 301, 259. Treatment of 7 with acetone dimethylacetal and p-toluenesulfonic acid in methanol gave the rearranged triacetyl derivative 8, as an amorphous solid which showed: $[\alpha]_D^{26}$ - 71° (c 0.57, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 3.30, 3.40, 5.65, 5.88, 6.06, 6.71, 7.10, 7.80, 8.14 μ; $\lambda_{max}^{MeOH}$ 270 mμ (ε 5,550); m/e 399 (M-60), 313, 301, 285, 271, 259; nmr ($CDCl_3$) τ 4.53 (1H, m, C-6 H), 6.25, 6.43 (6H, 2 x $OCH_3$), 7.70, 8.03, 8.82 (9H, 3 x $COCH_3$).

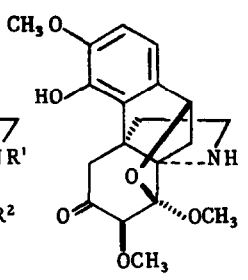
Since stephuline (2) has an unsubstituted position para to the phenolic hydroxyl (positive Gibbs test) the phenol could be located at either C-4 or C-1. From biogenetic considerations, C-4 was favored, since all but one of the hasubanan alkaloids recorded in the literature have oxygen substituents at C-4, whereas none have oxygen substituents at C-1.



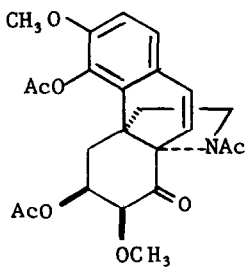
1



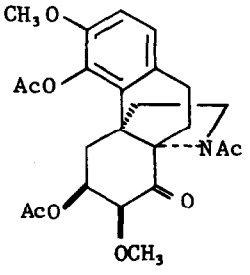
2; $R^1$=H, $R^2$=$CH_3$
3; $R^1$=$R^2$=$CH_3$
4; $R^1$=$R^2$=H



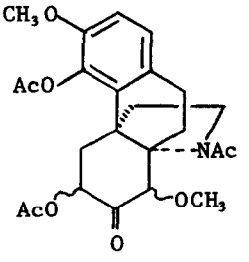
5



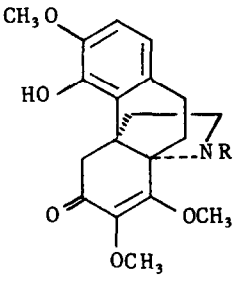
6



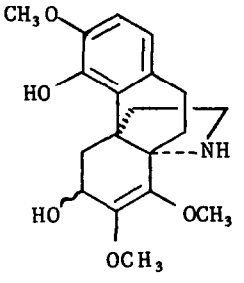
7



8



9; R=H
10; R=$CH_3$



11a and 11b

4-Demethylnorhasubanonine (9) has been interrelated with 10, the structure of which (as well as absolute configurations at all centers) has been determined unequivocally by X-ray crystallographic analysis.[2] Reduction of 4-demethylnorhasubanonine (9) with sodium borohydride gave the C-6 epimeric alcohols 11a and 11b. The less polar, axial alcohol, 11a, showed: mp 181-182°; $[\alpha]_D^{32}$ - 114° (c 0.85, MeOH); $\lambda_{max}^{KBr}$ 2.80, 2.94, 3.39, 7.78, 9.30 μ; m/e 347 ($M^+$); nmr ($D_5$-pyridine) τ 5.12 (1H, t (5), C-6 H), 5.95, 6.18, 6.30 (9H, 3 x $OCH_3$). The more polar, equatorial alcohol, 11b, showed: mp 214-215° dec; $[\alpha]_D^{32}$ - 100° (c 0.97, MeOH); $\lambda_{max}^{KBr}$ 2.90, 3.06, 3.39, 7.78, 9.18, 9.51 μ; m/e 347 ($M^+$); nmr ($D_5$-pyridine) τ 5.38 (1H, t (6), C-6 H), 6.05, 6.23, 6.27 (9H, 3 x $OCH_3$). Acetylation of either 11a or 11b gave products which were converted on standing in chloroform solution to triacetyl derivative 8, as shown by mixture tlc, sign of optical rotation, and superimposable ir, uv, and mass spectra.

This correlation via 8 established the molecular structure of stephisoferuline, the relative stereochemistry at C-8, C-10, C-13, and C-14, and the absolute configuration of the molecule. The stereochemistry at C-6 was demonstrated by means of borohydride reduction of 6-dehydrostephuline (5), which gave the natural alcohol 2 in quantitative yield. Examination of molecular models of 5 supports the view that attack by hydride from the equatorial (α) direction is highly favored; hence, the natural alcohol, stephuline, could be assigned the C-6-β-(axial)-hydroxyl configuration. Thus, independent chemical, spectral, and crystallographic arguments led to firm assignment of identical stereochemistry at five of the six asymmetric centers of stephisoferuline (1) and stephavanine.[1] The close stereochemical similarity of the alkaloids and their occurrence in the same genus suggest their biogenesis by analogous processes, and support the β-(equatorial)-configuration for the C-7 methoxyl group of stephisoferuline.

Acknowledgements: The authors acknowledge with thanks receipt of the dried plant material from Dr. R. E. Perdue, Jr., U. S. Department of Agriculture, Beltsville, Md., in accordance with the program developed with the U.S.D.A. by the Cancer Chemotherapy National Service Center (CCNSC), and financial support from the National Heart Institute under Grant No. HE-13184. M.I.S. was a National Institutes of Health Predoctoral Fellow, 1966-1969.

References

1. S. M. Kupchan, M. I. Suffness, R. J. McClure, and G. A. Sim, J. Amer. Chem. Soc., in press.
2. S. M. Kupchan, M. I. Suffness, D. N. J. White, A. T. McPhail, and G. A. Sim, J. Org. Chem., 33, 4529 (1968).