Tetrahedron Letters No. 39, pp 4001 - 4004, 1972. Pergamon Press. Printed in Great Britain.

Stepinonine, A New Dimeric Benzylisoquinoline - 2-Phenyl-s-homotetrahydroisoquinoline Alkaloid

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(Received in Japan 7 August 1972; received in UK for publication 21 August 1972)

In a previous paper[1)], one of the authors has reported the isolation of a new phenolic alkaloid, to which the tentative name, Base-B, has been given, from Stephania japonica Miers grown in Formosa. The present communication is concerned with the structure proof of this alkaloid which is now designated as stepinonine.

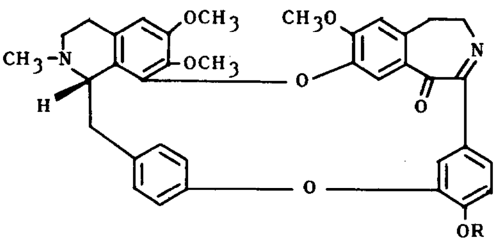
Stepinonine (Ia), m.p. 244-245°, 280° (dimorphism), $C_{36}H_{34}O_7N_2$[2)], $[\alpha]_D^{30}$ -28° (c=1.0, pyridine), $\nu_{max}^{CHCl_3}$: 3500 (OH) and 1663 (C=O) cm^{-1}, τ[3)]: 2.63-4.40 (arom. proton, 10 H), 6.04, 6.15 and 6.63 (OCH_3) and 7.46 ($N-CH_3$), was obtained as yellow prisms. Acetylation of (Ia) with Ac_2O-pyridine gave the monoacetate (Ib), m.p. 157°, the i.r. spectrum (KBr) of which showed the phenolic acetate band at 1767 cm^{-1} and no hydroxyl band. Reduction of (Ia) with $NaBH_4$ in methanol provided tetrahydrostepinonine (II), m.p. 173-174°, $C_{36}H_{38}O_7N_2 \cdot H_2O$, whose i.r. spectrum revealed no carbonyl band. Methylation of (II) with formalin-$NaBH_4$ afforded the N-methyl derivative (III), m.p. 164°, $C_{37}H_{40}O_7N_2$, M^+: m/e 624, τ ($CDCl_3$/pyridine=2:1): 6.32, 6.60 and 6.82 (OCH_3), 7.40 and 7.84 ($N-CH_3$). The signal due to the newly introduced N-methyl group appeared at abnormally higher field than that expected for the N-methyl group in the common tetrahydroisoquinoline derivatives, suggesting that this alkaloid may not be the known bisbenzylisoquinoline alkaloids. O-Methylation of (III) with diazomethane gave N,O-dimethyl-tetrahydrostepinonine (IV), m.p. 261-262°, $C_{38}H_{42}O_7N_2$.

Reductive fission reaction of (IV) with sodium in liq. ammonia gave two phenolic compounds. One of these, m.p. 142-144°, $[\alpha]_D^{24}$ +117° (c=1.0, $CHCl_3$)

was proved to be identical with the authentic specimen of S-armepavine (VII).[4] Another phenolic base, m.p. 204°, $C_{19}H_{23}O_4N$, $[\alpha]_D^{19}$ +20° (c=0.5, $CHCl_3$), was ethylated with diazoethane to give the hydro-3-benzazepine derivative (X), τ : 5.34 (C_1-H, d., J=1 cps), 6.59 (C_2-H, d., J=1 cps), 6.14 and 6.22 (OCH_3), 7.88 (N-CH_3) and 8.60 ($OCH_2C\underline{H}_3$), which was identified with the authentic sample of 4',7-dimethoxy-8-ethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepine-1-ol (racemate of X)[5] obtained through an unequivocal synthetic route, by direct comparison, establishing the structures of (IX) and (X).

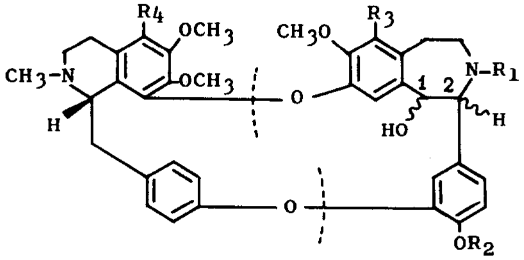
The position of a hydroxyl group in stepinonine and the linking fashion connecting two moieties were established as follows. O-Ethylation of (III) with diazoethane, followed by oxidation of the resulting non-phenolic base (V), m.p. 255-260°, $C_{39}H_{44}O_7N_2 \cdot H_2O$, with $KMnO_4$ in aqueous acetone provided the ethoxydiphenyl ether dicarboxylic acid (VI), m.p. 276-280°, which was identified with the authentic sample[6] by direct comparison. Stepinonine therefore is built up of armepavine (VII) and the hydro-3-benzazepine moiety linked by two diphenyl ether linkages in the "head to head" and "tail to tail" manner.

In order to establish the attached position of a diphenyl ether linkage at the armepavine moiety (C_5 or C_8), deuteration experiment, followed by the reductive fission with sodium in liq. ammonia was performed.[7] Thus, treatment of the compound (V) with C_2H_5OD - D_2O - 3% DCl at 125-130° for 100 hr gave the dideuterated product (XII) which was then subjected to the reductive fission to afford two phenolic compounds. One is identified with an authentic sample of S-[5-D]-armepavine (VIII).[7] The other (XI), m.p. 181-184°, M^+ : m/e 344, was methylated with diazomethane to derive the compound (XIII), the structure of which was certified by the comparison with the synthetic sample of 7,8-dimethoxy-4'-ethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepine-1-ol (racemate of XIV).[5] It is thus evident that the armepavine moiety and the hydro-3-benzazepine moiety must link at the C_8 position of the former and the oxygen function at the C_8 position of the latter. Therefore, stepinonine must have the structure (Ia). Stepinonine is the first example of the alkaloid possessing this type of the dimeric structure.

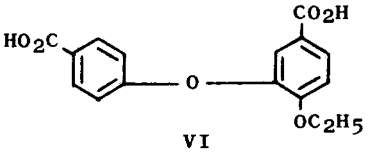


Ia R=H

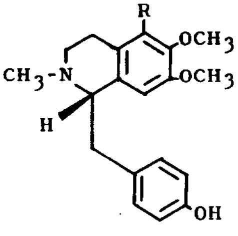
Ib R=$OCOCH_3$



	R_1	R_2	R_3	R_4
II	H	H	H	H
III	CH_3	H	H	H
IV	CH_3	CH_3	H	H
V	CH_3	C_2H_5	H	H
XII	CH_3	C_2H_5	D	D

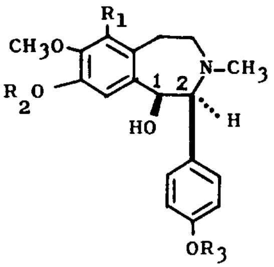


VI



VII R=H

VIII R=D



	R_1	R_2	R_3
IX*	H	H	CH_3
X*	H	C_2H_5	CH_3
XI*	D	H	C_2H_5
XIII*	D	CH_3	C_2H_5
XIV	H	CH_3	C_2H_5

* The absolute configurations at C_1 and C_2 chiral centers remain equivocal but the cis relationship of these centers was estimated by comparing the coupling constants of protons concerned with those of the related compounds5) (cis: J_{H_1,H_2}=1 cps ; trans: J_{H_1,H_2}=8 cps).

REFERENCES and REMARKS

1) M. Tomita and T. Ibuka, *YAKUGAKU ZASSHI*, **83**, 996 (1963).

2) Correct analytical data were obtained for the compounds shown by the molecular formulas.

3) Unless otherwise stated, the n.m.r. spectra were measured on Varian A-60 Spectrometer in $CDCl_3$ with TMS as an internal standard.

4) M. Tomita and E. Fujita, *Chem. Pharm. Bull.*, **1**, 101 (1953).

5) Syntheses of these compounds will be stated in a full paper. Cf. Y. Inubushi, T. Harayama, and K. Takeshima, *Chem. Pharm. Bull.*, **20**, 689 (1972).

6) M. Tomita and T. Ibuka, *YAKUGAKU ZASSHI*, **83**, 940 (1963).

7) Y. Inubushi, T. Kikuchi, T. Ibuka, and I. Saji, *Tetrahedron Letters*, **1972**, 423.