Tetrahedron. Vol. 26, pp. 3805 to 3808. Pergamon Press 1970. Printed in Great Britain

LEONTIFORMINE, A NEW 3-PIPERIDYL-(2)-QUINOLIZIDINE, FROM *LEONTICE LEONTOPETALUM* L.

N. M. MOLLOV and I. C. IVANOV
Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia, Bulgaria

(*Received in the UK* 10 *February* 1970; *Accepted for publication* 15 *April* 1970)

Abstract—*d*-Leontiformine (I), an alkaloid from *Leontice leontopetalum* L., is shown to be a new natural 3-piperidyl-(2)-quinolizidine. The structure has been established as 3-[N-formylpiperidyl-(2)] quinolizidine by physical methods and by synthesis.

THE plants of the genus *Leontice* (Berberidaceae) are a rich source of different types of alkaloids. The alkaloids found in *L. eversmannii*,[1-3] *L. albertii*,[1,4,5] and *L. darvasica*[6] are quinolizidine alkaloids of the matrine type (Table 1); the sparteine and cytisine types being found as well. The alkaloid taspine isolated from the same plants is a biphenyl one,[7] and the two known alkaloids from *L. leontopetalum*,[8] petaline and petaline methine, are of the benzylisoquinolinic type.[9]

Recently we investigated the tertiary base components of the fresh above-ground parts of *L. leontopetalum* L. from Bulgaria and isolated the tetrahydroprotoberberine alkaloid *l*-stylopine and the quinolizidine alkaloid *d*-lupanine.[15] A new quinolizidine

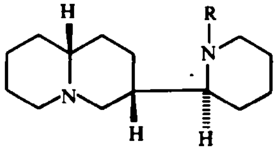
TABLE 1

Type	Alkaloid	Source
Matrine	Leontine = Isoleontine[3,10]	*L. eversmannii*
	Leontalbine[5,11]	*L. albertii*
	Leontalbinine[5]	*L. albertii*
	Albertine[12]	*L. albertii*
	d-Sophoridine[13]	*L. albertii*
	Darvasine[6]	*L. darvasica*
Sparteine	Pachicarpine = *d*-Sparteine	*L. eversmannii*
	l-Lupanine	*L. eversmannii*
Cytisine	N-methyl-cytisine	*L. albertii* *L. darvasica*
Biphenyl	Taspine	*L. eversmannii* *L. albertii* *L. darvasica*
With unknown structure	Leontamine[14]	*L. eversmannii*
	Leontidine (probably of the quinolizidine group)[16]	*L. eversmannii*

alkaloid leontiformine (I) was also found. We wish to report the structure of this alkaloid.

Leontiformine (I) is a colourless crystalline compound, m.p. 61–63° and $[\alpha]_D^{22} = +51 \cdot 9°$. Leontiformine hydrobromide is obtained as colourless platelets, m.p. 275–276° and $[\alpha]_D^{22} = +57 \cdot 7°$. The elemental analysis shows the formula $C_{15}H_{26}ON_2 . HBr$. The IR spectrum of I has an amide CO absorption band at 1660 cm^{-1} and two bands at 2740 and 2780 cm^{-1} for a *trans*-quinolizidine. In the NMR spectrum there are peaks for methylene and methine protons between 6·8 and 9 τ and two peaks at 1·77 and 1·86 τ with equal intensity due to one proton.

The LAH reduction of I yields an oily substance (II) with $[\alpha]_D^{22} = +63 \cdot 8°$ whose IR spectrum has no CO absorption band. In the NMR spectrum appears a singlet at 7·64 τ due to three protons of a tertiary N-Me group. The disappearance of the CO absorption band in the IR spectrum of II and the appearance of a N-Me group signal in the NMR spectrum of II supports the assumption that there is a tertiary N-formyl group in I. An attempt to hydrolyse I with concentrated hydrochloric acid led to the compound III, colourless needles, m.p. 46° and $[\alpha]_D^{22} = +2 \cdot 7°$. Conversely, I was obtained as a result of prolonged refluxing of III with formic acid.



I: R = CHO
II: R = Me
III: R = H

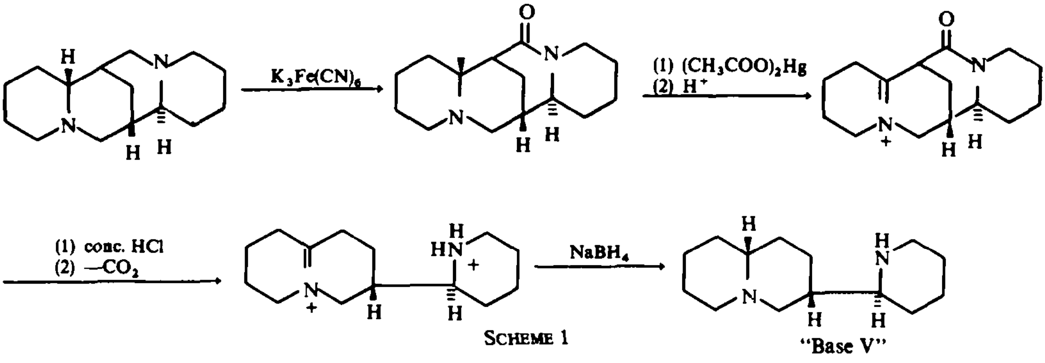
The IR spectra of all these compounds (I–III) contain the absorption bands for a *trans*-quinolizidine. If the presence of *trans*-quinolizidine system is assumed to be in I, the formyl group should be in the remaining part of the molecule where the second N atom is included. Taking into account the nature of the second N atom the remaining C and H atoms (C_5H_9N) probably participate in a piperidine ring system.

All the properties of leontiformine agree with 3-[N-formylpiperidyl-(2)]quinolizidine as its structure. This compound has been obtained by Bohlmann *et al.* by t-butylhydroperoxide oxidation of the mono- and diperchlorate of 5,6-dehydrosparteine.[17] The IR spectra of I and 3-[N-formylpiperidyl-(2)]quinolizidine are identical.

The problem concerning the configuration of I was resolved by comparison of III with the four possible racemates of 3-piperidyl-(2)-quinolizidine synthesized and identified by Bohlmann[18] following the route of Sorm *et al.*[19] Accordingly the IR spectra III is identical with the racemate *C* whose *l*-enantiomere is the so-called "Base V" obtained also by Bohlmann.[18] We synthesized the "Base V" starting from *l*-17-oxosparteine according to Bohlmann[18, 20] as shown in scheme 1.

The IR spectra of the so-prepared "Base V" and III are indistinguishable. The m.ps are also the same. Since the optical rotations of the two compounds are equal and of opposite sign, we concluded that the "Base V" is the *l*-enantiomere and the compound III the *d*-enantiomere.

Until 1956 it was considered that the alkaloid pusilline presented a 3-piperidyl-(2)-quinolizidine but Marion *et al.*[20] proved it is identical with *l*-β-isosparteine. Recently the methyl ester of 3-piperidyl-(2)-quinolizidine-5-carboxylic acid (aphillic acid) was



SCHEME 1

isolated from *Anabasis aphilla* L.[23] The leontiformine, found by us, is a second representative of the 3-piperidyl-(2)-quinolizidine group of alkaloids.

The signal of the formyl proton in the NMR spectrum of leontiformine (I) is split. This effect may result from the hindered rotation around the C—N bond in the formamide I. Two conformations are possible and they cause different chemical shifts.[21]

EXPERIMENTAL

The m.ps were taken on a Kofler hot-stage. IR spectra were measured as liquid films with a UNICAM SP 200 G Spectrophotometer. NMR spectra were recorded on a JEOL JNM 60 S instrument in $CDCl_3$. The chemical shifts are expressed as τ units and are referred to TMS as the internal standard. The optical rotations were determined in EtOH on a QUICK-JOUAN polarimeter.

d-*Leontiformine* (I) is a colourless crystalline compound, m.p. 61–63° and $[\alpha]_D^{22} = +51{\cdot}9°$ ($c = 0{\cdot}26$); IR: ν 1660 (amide C=O), 2740 and 2780 cm^{-1} (trans-quinolizidine); NMR 1·77 and 1·86 (both 1H).

d-*Leontiformine*. HBr yields colourless platelets, m.p. 275–276° (EtOH/Me_2CO) and $[\alpha]_D^{22} = +57{\cdot}7°$ ($c = 0{\cdot}39$). (Found: C, 54·23; H, 8·06; N, 8·32. $C_{15}H_{26}ON_2$. HBr requires: C, 54·38; H, 8·21; N, 8·45%).

LAH reduction of I. A mixture of I (60 mg), dry ether (15 ml) and LAH (0·2 g) was stirred and refluxed for 12 hr. Then 1 ml water was added and the mixture extracted with ether. After drying over Na_2SO_4 the solvent was evaporated. Compound II was obtained as a colourless liquid (40 mg) with $[\alpha]_D^{22} = +63{\cdot}8°$ ($c = 0{\cdot}31$); IR: ν 2715, 2795 cm^{-1} (*trans*-quinolizidine); NMR: 7·64 (3H singlet).

Acidic hydrolysis of I. 200 mg of I. HBr in 5 ml conc HCl were refluxed for 16 hr. The soln was concentrated *in vacuo*, NaOH aq was added till an alkaline and then extracted with ether. After removal of solvent, 115 mg of III were obtained as colourless needles, m.p. 46° (light petroleum), $[\alpha]_D^{22} = +2{\cdot}7°$ ($c = 0{\cdot}22$); IR (identical to that of "Base V"[18]): ν 2745, 2785 cm^{-1} (*trans*-quinolizidine), 3300 cm^{-1} (broad, NH).

Formic acid reaction of III. Compound III (50 mg) was refluxed with 3 ml 98% formic acid for 16 hr. The soln was made alkaline (NaOH aq) and extracted with ether. The dried (Na_2SO_4) ether extract on removal of solvent left 30 mg of a liquid substance, identical (IR and TLC) with I.

Synthesis of l-3-piperidyl-2-quinolizidine

(a) *l-17-Oxosparteine*. *l*-Sparteine (2 ml) in 25 ml acetone was added to a soln of 50 g KOH and 50 g $K_3Fe(CN)_6$ in 600 ml water. The reaction mixture was stirred at room temp and every 15 min 0·5 g $K_3Fe(CN)_6$ were added until complete oxidation of the sparteine (TLC control). The product was extracted with ether and the residue after removal of solvent was passed through a basic Al_2O_3 column. A colourless crystalline substance (1·0 g, m.p. 82–84°) was obtained by elution with ether which was identical (m.p., IR[22]) with *l*-17-oxospateine.

(b) *5,6-Dehydro-17-oxosparteine*. *l*-17-Oxosparteine (1 g) was heated under reflux at 80° for 4 hr with 6 g of $(AcO)_2Hg$ in 50 ml 5% aq acetic acid (perhaps such a long heating is unnecessary because the ppt of $(AcO)_2Hg_2$ formed almost immediately). After cooling, the ppt was filtered off and the excess Hg ions were removed by H_2S. The filtrate was made alkaline (NaOH aq) and extracted with $CHCl_3$. The $CHCl_3$ soln was dried (Na_2SO_4) and evaporated *in vacuo* to leave a pale yellow oil which in air changed quickly into dark-red resin.

(c) *l-3-Piperidyl-(2)-quinolizidine ("Base V")*. The crude 5,6-dehydro-17-oxosparteine in acetone soln was converted into its perchlorate with conc perchloric acid. After removal of acetone, 15 ml conc HCl was added and the soln was heated in an autoclave for 30 hr at 170°. The HCl was removed *in vacuo* to dryness. The residue was dissolved in 20 ml MeOH–H_2O (1 : 1) and after 1 g of $NaBH_4$ had been added the mixture was heated for 5 min on a steam bath. The product was extracted with ether, the ether evaporated and the residue passed through a basic Al_2O_3 column. It was eluted with ether and ether—1% MeOH. A colourless crystalline compound (145 mg, m.p. 46°) was obtained which was identical with 3-piperidyl-(2)-quinolizidine ("Base V")[18] by IR spectra and m.ps.

The so-prepared "Base V" is identical with III by IR, TLC and m.p. The optical rotation of "Base V" however, is − 2·7 while that of III is + 2·7°.

REFERENCES

[1] S. Yu. Yunusov and L. G. Sorokina, *Zh. Obshch. Khim.* **19**, 1955 (1949)

[2] T. F. Platonova, A. D. Kuzovkov and P. S. Massagetov, *Ibid.* **23**, 880 (1953)

[3] T. F. Platonova and A. D. Kuzovkov, *Ibid.* **26**, 283 (1956)

[4] S. Iskandarov, R. N. Nuriddinov and S. Yu. Yunusov, *Dokl. Akad. Nauk Uzb. SSR* **21**(12), 32 (1964)

[5] S. Iskandarov, R. N. Nuriddinov and S. Yu. Yunusov, *Khim. Prir. Soedin.* **3**, 26 (1967)

[6] S. Iskandarov and S. Yu. Yunosov, *Ibid.* **2**, 132 (1969)

[7] T. F. Platonova, A. D. Kuzovkov and Yu. N. Sheinker, *Zh. Obshch. Khim.* **26**, 2651 (1956)

[8] J. McShefferty, P. F. Nelson, J. L. Paterson, J. B. Stenlake, and J. P. Todd, *J. Pharm. Pharmacol.* **8**, 1117 (1956)

[9] N. J. McCorkindale, D. S. Magrill, M. Martin-Smith, S. J. Smith, and J. B. Stenlake, *Tetrahedron Letters* No. 51, 3841 (1964)

[10] F. Rulko and N. F. Proskurnina, *Zh. Obshch. Khim.* **31**, 308 (1961)

[11] S. Iskandarov, R. N. Nuriddinov and S. Yu. Yunusov, *Khim. Prir. Soedin.* **1**, 66 (1966)

[12] S. Iskandarov and S. Yu. Yunusov, *Ibid.* **2**, 137 (1968)

[13] D. Kamalitdinov, S. Iskandarov and S. Yu. Yunusov, *Ibid.* **5**, 352 (1967)

[14] A. P. Orekhov and R. A. Konovalova, *Arch. Pharm.* **270**, 329 (1932)

[15] P. P. Panov, N. M. Mõllov and L. Panova, *C.R. Acad. Sci. Bulgare* in press

[16] Sui Jen-shen and A. D. Kuzovkov, *Zh. Obshch. Khim.* **33**, 2067 (1963); *Ibid.* **34**, 1669 (1964)

[17] F. Bohlmann, E. Winterfeldt and G. Boroschewski, *Chem. Ber.* **93**, 1953 (1960)

[18] F. Bohlmann, *Ibid.* **92**, 1798 (1959)

[19] J. Ratusky and F. Sorm, *Collection* **19**, 107 (1954)

[20] R. Greenhalg and L. Marion, *Canad. J. Chem.* **34**, 456 (1956)

[21] J. W. Emsley, J. Freeney and L. H. Sutcliffe, *High Resolution NMR Spectroscopy* p. 553. Pergamon Press, Oxford (1965)

[22] F. Bohlmann, *Chem. Ber.* **91**, 2160 (1958)

[23] Kh. A. Aslanov, S. Z. Mukhamedzhanov and A. S. Sadykov, *Nauch. tr., Tashkent. Gos. Univ.* No. **286**, 71 (1966)