The Dimer of $\Delta^{1(8)}$-Dehydropyrrolizidine and Its Reduction (1)

Kunihiro Sumoto, Shinichiro Fujii, Osamu Yamashita,
Takao Somehara and Seiji Miyano

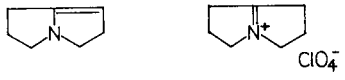
Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma, Nishi-Ku, Fukuoka, 814 Japan

Received September 22, 1980

The structure and reductions of the dimer of $\Delta^{1(8)}$-dehydropyrrolizidine are described.

J. Heterocyclic Chem., **18**, 413 (1981).

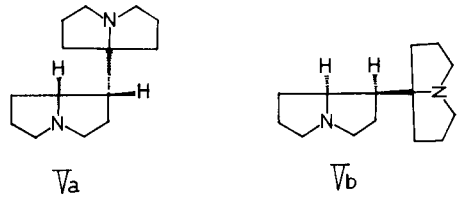
A few syntheses of $\Delta^{1(8)}$-dehydropyrrolizidine (I) and its perchlorate (II) (1-2) have appeared in the literature. However, thus far, none of these has described the formation of the dimeric compound of I. Recently, we have briefly noted the formation of a considerable amount of the dimeric compound on the redestillation of I (1), but the structure of the dimer has remained unpublished. We now established the structure of the dimer by chemical investigations and spectroscopic analyses. In this paper, we wish to deal with the structure as well as the reduction of the dimer.



I II

Scheme 1

The dimeric compound of I was prepared as a colorless oil, b.p. 165-166°/22 mm by the method described previously (1). The mass spectrum showed the correct molecular ion, m/e 218.1793 (M^+, $C_{14}H_{22}N_2$), and the ir spectrum showed a characteristic absorption band at 1685 cm^{-1} owing to heterocyclic enamines (3-4). Although signals in the nmr spectrum are too complicated for unequivocal analyses, the broad signal at δ 4.52 ppm, being assignable to the vinly proton of heterocyclic enamines (4-5), is characteristic. This signal, however, gave weak integration, the value of which was 0.12 H (6). Furthermore, treatment of the dimer with perchloric acid in ethanol afforded the monomeric form of the perchlorate II, $\Delta^{4(8)}$-dehydropyrrolizidinium perchlorate, in good yield. These experimental data, together with the dimerization process of enamines (4,7-8) and the isomerization of heterocyclic enamines (4-5) prompted us to propose the structure of the dimer III as the most reasonable one. It appears that the signal at δ 4.52 ppm is in good agreement with the isomerization between IIIa and IIIb, in which the contribution of the isomer IIIa is predominant. A similar tendency has been observed in the isomerization of 1-methyl-$\Delta^{1(10)}$-dehydroquinolizidine (IVa $\rightleftharpoons$ IVb) (5). The formation of the dimer III is considered as the same process reported in the dimerization of heterocyclic enamines (7-8).

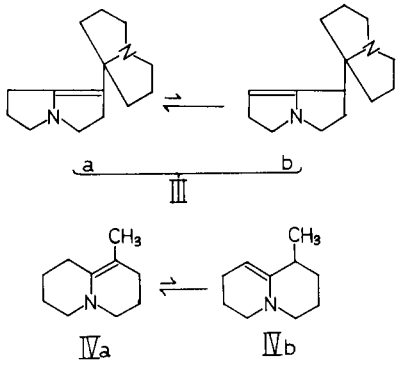


Va Vb

Scheme 3

In order to provide further information for the structure of the dimer III, reduction with formic acid and catalytic hydrogenation were carried out. Thus, when a mixture of the dimer III and formic acid was stirred at 60-70° for 3 hours, the reduced product, 1,8'-bipyrrolizidine (V), b.p. 132-133°/8 mm, was obtained in 49% yield. The mass spectrum afforded the correct molecular ion [m/e 220.1948 (M^+, $C_{14}H_{24}N_2$)], and both the strong absorption at 1685 cm^{-1} (ir) and the signal at δ 4.52 ppm (nmr) observed in the spectra of III disappeared. This phenomenon confirms the enamine structure (IIIa $\rightleftharpoons$ IIIb) of the dimer, because many enamines are usually reduced with formic acid (4). The gas chromatographic analyses of V showed that the product consisted of two isomers (Va and Vb), the isomer Va possessing a short retention time (198 seconds) (9) being predominant, and the ratio (Va/Vb) being 75/25.

The contrasting information on the isomeric ratio of the products was obtained from the catalytic hydrogenation of the dimer III, in which the isomeric ratio (Va/Vb) was



III

Va Vb

Scheme 2

0022-152X/81/020413-02$02.25

1/99. Theoretically, it is expected that the reduction of the dimer III would give the two diastereomers, *cis*- and *trans*-1,8-hydrogens isomers. According to the information on the catalytic hydrogenation of 1-alkyl-$\Delta^{1(8)}$-dehydropyrrolizidine (10), we confirmed that the main product Vb from the catalytic hydrogenation has *cis*-1,8-hydrogens. The pure dipicrates of Va and Vb could be obtained by recrystallization (see Experimental) (12).

So far, no report dealing with dimeric pyrrolizidines has appeared, with the exception of cassipourine (11), a naturally occurring pyrrolidizine alkaloid containing four sulfur atoms. In terms of new genuine dimeric pyrrolizidine heterocycles, the structures of III, Va and Vb are quite interesting.

EXPERIMENTAL

Melting points are uncorrected. Ir spectra were recorded with a Hitachi-EPI-G-3 instrument. Nmr spectra were measured with a Hitachi-R-22 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained with a JEOL-01-SG instrument with a direct inlet system operating at 75 eV.

Preparation of the Dimer III.

The dimer III, b.p. 165-166°/22 mm, was prepared by the method described previously (1). The following spectroscopic data were obtained; ms: m/e 218.1793 (M^+, $C_{14}H_{22}N_2$); ir (film): 1685 cm^{-1} (enamine C=C), nmr (deuteriochloroform): δ 4.52 (b) and 1.40-3.40 (m, aliphatic protons) ppm. The broad signal at δ 4.52 ppm had a weak integral value (*ca.* 0.12 H) (6).

The treatment of this dimer with two molar amounts of perchloric acid (70%) in ethanol gave $\Delta^{4(8)}$-dehydropyrrolizidinium perchlorate (II) (1), m.p. 243° dec. (from ethanol), in 75% yield; ir (potassium bromide): 1700 cm^{-1} (iminium).

Anal. Calcd. for $C_7H_{12}ClNO_4$: C, 40.10; H, 5.77; N, 6.68. Found: C, 39.83; H, 5.80; N, 6.58.

Reduction of III with Formic Acid.

To the dimer III (2 g.) was added formic acid (1 g.) with stirring under ice-cooling. The mixture was stirred for 1 hour at room temperature, and then kept at 60-70° for 3 hours with stirring. After addition of 40% of aqueous sodium hydroxide (18 ml.) to the reaction mixture. The resulting mixture was extracted with ether, and the ether extract was washed with saturated sodium chloride, and dried over anhydrous magnesium sulfate. After evaporation of the solvent, the residue was distilled to give hydrogenated compound V, b.p. 132-133°/8 mm, in 49% yield as colorless oil. The isomer Va with a short retention time (198 seconds) was predominant, and the ratio (Va/Vb) was 75/25 by the gas chromatographic analysis (9); ms: m/e 220.1948 (M^+, $C_{14}H_{24}N_2$); ir (film): 1450, 1095 cm^{-1}, and no absorption at 1600-1700 cm^{-1}; nmr (deuteriochloroform): δ 1.20-3.50 (complicated multiplet, all aliphatic protons) ppm. The signal at δ 4.52 ppm observed in the nmr spectrum of III disappeared.

The treatment of the product V with two molar amount of picric acid in ethanol gave the dipicrate as yellow crystals in 90% yield. Recrystallization of the crude dipicrate from dimethylformamide/isopropyl alcohol afforded the pure dipicrate of Va (*trans*-1,8-hydrogens), m.p. 285° dec.

Anal. Calcd. for $C_{26}H_{30}O_{14}N_8$: C, 46.02; H, 4.46; N, 16.51. Found: C, 46.01; H, 4.48; N, 16.51.

Catalytic Hydrogenation of III.

To the mixture of the dimer III (5.01 g.) and platinum oxide (0.016 g.) as a catalyst in anhydrous ether (35 ml.) was absorbed hydrogen at atmospheric pressure by the usual manner. After absorption of equivalent molar amount of hydrogen, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. Distillation of the residue affords the hydrogenated compound, b.p. 178-180°/21 mm, in 72% yield. The isomer Vb (*cis*-1,8-hydrogens) posssessing a long retention time (273 seconds) was obtained as the main product, and the ratio (Va/Vb) was 1/99 by the gas chromatographic analysis (9); ms: m/e 220.1905 (M^+, $C_{14}H_{24}N_2$), ir (film): 1450, 1095, 1085 cm^{-1}, and no absorption at the 1600-1700 cm^{-1} region, nmr (deuteriochloroform): δ 1.20-3.50 (complicated multiplet, all aliphatic protons) ppm. The signal at δ 4.52 ppm observed in the nmr spectrum of III could not be detected. The treatment of this hydrogenated compound with two molar amount of picric acid afforded pure dipicrate of Vb, m.p. 221-223° (from dimethylformamide/isopropyl alcohol in 88% yield.

Anal. Calcd. for $C_{26}H_{30}O_{14}N_8$: C, 46.02; H, 4.46; N, 16.51; H, 4.50; N, 16.16.

REFERENCES AND NOTES

(1) Part II in the series on studies of pyrrolizidines and related compounds. For Part I, see S. Miyano, T. Somehara, M. Nakao and K. Sumoto, *Synthesis,* 701 (1978), and references cited therein.

(2) Y. Arata, K. Tanaka, S. Yoshifuji and S. Kanatomo, *Chem. Pharm. Bull.,* **27**, 981 (1979).

(3) N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, *J. Am. Chem. Soc.,* **77**, 439 (1955).

(4) A. G. Cook, "Enamine: Synthesis, Structure, and Reactions", Marcal Dekker, New York and London, 1969, related references cited therein.

(5) M. G. Reinecke and L. R. Kray, *J. Org. Chem.,* **31**, 4215 (1966).

(6) Based on the total integration of the other protons (δ 1.40-3.40 ppm), on the assumption that the number of these protons are 22.

(7) Y. Arata, H. Kato and T. Shioda, *Yakugaku Zasshi,* **88**, 614 (1968).

(8) N. J. Leonard and A. G. Cook, *J. Am. Chem. Soc.,* **81**, 5627 (1959); N. J. Leonard and F. P. Hauck, Jr., *ibid.,* **79**, 5279 (1957).

(9) Measured from injection time on a Yanaco G-180 instrument with a 1.5 m x 3 mm column (10% Thermon-1000 + 3% potassium hydroxide Chromosorb W 80/100 AW-DMCS) at 1.2 kg./cm^2 nitrogen flow pressure, and at 230° column temperature.

(10) For example, the catalytic hydrogenation of 1-methyl-$\Delta^{1(8)}$-dehydropyrrolizidine results in (±)-heliotridane (*cis*-1,8-hydrogens) in good yield and with high stereoselectivity (*ca.* 90%). This result will be described in the future communication.

(11) R. G. Cook, F. L. Warren and D. H. Williams, *J. Chem. Soc. C,* 286 (1967); W. G. Wright and F. L. Warren, *ibid.,* 283 (1967).

(12) The purity of each of them was 100% by gaschromatographic analysis of these free bases. Both nmr spectra (1.20-3.50 ppm) were, however, too complicated for unequivocal analysis.