

Studies on Orchidaceae Alkaloids

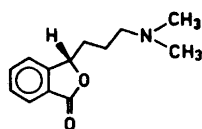
XXII.* Synthesis and Absolute Configuration of Pierardine.
Lactone-Betaine Isomerization of Shihunine

MAGNUS ELANDER, LARS GAWELL and KURT LEANDER

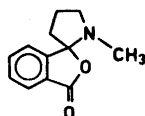
*Department of Organic Chemistry, University of Stockholm,
Sandåsgatan 2, S-113 27 Stockholm, Sweden*

(±)-Pierardine has been synthesised by reaction of the lithium salt of phthalaldehydic acid with 3-dimethylaminopropylmagnesium chloride, followed by lactonization. The natural occurring enantiomer (I) was obtained by recrystallisation of (±)-pierardine di-*O*-benzoyl-L-tartrate. On the basis of the CD curves of I, 3-propylphthalide derived from I and of 3*S*-butylphthalide, I is assigned the 3*S* configuration. The isolation of shihunine from *Dendrobium pierardii* Roxb. is reported. The possibility that shihunine is present in a betaine form in the plant is discussed.

In a recent publication² we reported the isolation and structural determination of pierardine (I), an alkaloid from *Dendrobium pierardii* Roxb.** The present communication reports the synthesis and absolute configuration of pierardine (I), and also the isolation of shihunine (II)³⁻⁵ from *D. pierardii*.



I pierardine



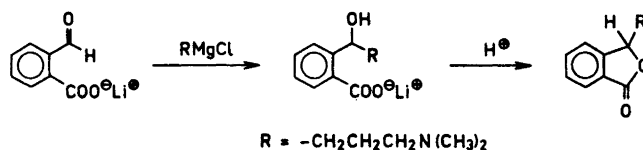
II shihunine

In the synthesis, the lithium salt of phthalaldehydic acid⁶ was reacted with 3-dimethylaminopropylmagnesium chloride⁷ in tetrahydrofuran, followed by lactonization.

The resulting (±)-pierardine was resolved by recrystallisation of its di-*O*-benzoyl-L-tartrate. Four recrystallisations from ethanol yielded the pure

* No. XXI of this series, see Ref. 1.

** Also known as *Dendrobium aphyllum* Roxb.



(-) enantiomer, indistinguishable (NMR, IR, MS, optical rotation) from an authentic sample of pierardine (I).

The absolute configuration of I was established by comparison of the CD curves (Fig. 1) of I and its transformation product 3-propylphthalide,² with that of 3*S*-butylphthalide, reported by Snatzke *et al.*⁸ From the similarity of the curves it is evident that the compounds have the same absolute configuration, and hence pierardine (I) is 3*S*-(3-dimethylaminopropyl)phthalide.

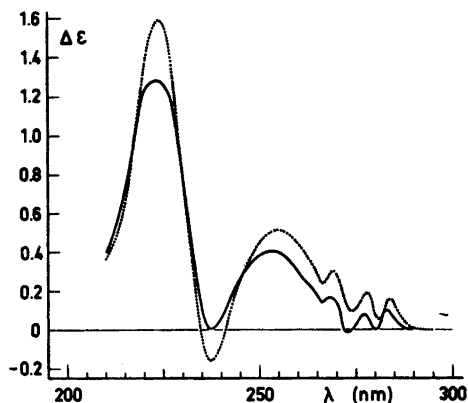
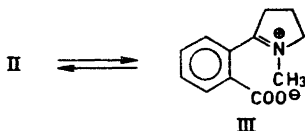


Fig. 1. CD curves of pierardine (I) (---), and 3*S*-propylphthalide (—) in methanol.

Shihunine (II), an alkaloid from *Dendrobium lohohense* Tang *et al.*,^{3,5} has been isolated from *D. pierardii*. Spectroscopic measurements show that shihunine in the crystalline state, or dissolved in non-polar solvents (chloroform, carbon tetrachloride, hexane), has the structure II. In water or methanol solutions, however, shihunine is rapidly and virtually completely converted into the betaine III, as supported by NMR (see Fig. 2), UV, and IR spectra.



III is readily retransformed into shihunine (II) by evaporating the solvent and drying the residue thoroughly.

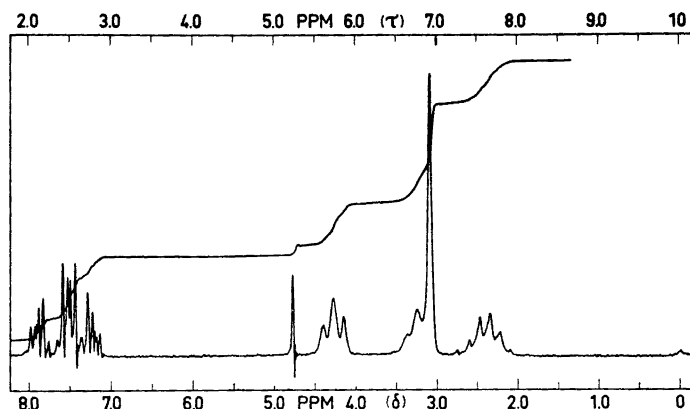


Fig. 2. NMR spectrum of shihunine in D_2O .

On the basis of the above evidence it seems probable that shihunine occurs as the betaine III in the plant, and that the lactone II is formed during the isolation procedure.

EXPERIMENTAL

Melting points are corrected. The optical rotations were measured on a Perkin-Elmer 141 polarimeter, the IR spectra on a Perkin-Elmer 257 instrument, the mass spectra on a Perkin-Elmer 270 instrument, and the NMR spectra on a Varian A60-A spectrometer, with TMS as internal reference.

Isolation of the alkaloids. Fresh plants of *Dendrobium pierardii* Roxb. (40 kg) were extracted with methanol (100 l). The extract was concentrated to 2 l, acidified and washed with carbon tetrachloride (4×0.5 l). The aqueous solution was made alkaline (pH 10) with sodium hydroxide and extracted with ether (6×0.5 l). The combined ether solutions were treated as previously described,² giving pierardine hydrochloride (8 g).

The alkaline aqueous solution was extracted with chloroform (15×1 l), and the combined chloroform solutions were evaporated to dryness at a bath temperature of 40° . The residue, which showed IR bands ($CHCl_3$) at $1745(s)$ and $1618(m)$ cm^{-1} , was filtered through neutral alumina (2.5×20 cm), using chloroform as eluent. Evaporation of the eluate to dryness and recrystallisation of the residue from ether at -20° afforded shihunine³⁻⁵ as colourless needles (13.2 g), m.p. $77-78^\circ$, $[\alpha]_{365-589}^{22} 0^\circ$ (c 12.0, chloroform), indistinguishable from an authentic sample (IR, MS, TLC). NMR spectrum ($CDCl_3$): τ 2.0–2.7 (m, 4 H), τ 6.4–7.2 (m, 2 H), τ 7.3–8.2 (m, 4 H), τ 7.88 (s, 3 H). NMR spectrum in D_2O , see Fig. 2. UV spectrum: λ_{max} (hexane) 278 nm ($\log \epsilon$ 2.89), 270.5 nm ($\log \epsilon$ 2.97), 264 nm ($\log \epsilon$ 2.87), 230.3 nm ($\log \epsilon$ 3.94), 223.7 nm ($\log \epsilon$ 4.03); λ_{max} (water) 215 nm ($\log \epsilon$ 4.13), $\lambda_{inflex.}$ 277 nm ($\log \epsilon$ 3.16), 270 nm ($\log \epsilon$ 3.23). IR spectrum: σ_{max} (KBr) 1750 cm^{-1} ; σ_{max} (CCl_4) 1777 cm^{-1} ; σ_{max} ($CHCl_3$) 1745 cm^{-1} ; σ_{max} (CH_3OH) $1680(w)$, $1618(s)$, $1595(m)$, $1565(m)$.

3-Dimethylaminopropylmagnesium chloride (IV). The Grignard reagent was prepared as described by Marxer *et al.*,⁷ using 3-dimethylaminopropylchloride (4.0 g), magnesium (0.80 g), and tetrahydrofuran (25 ml).

Synthesis of (\pm)-pierardine. Lithiumhydride (0.30 g, 87 % purity) was added in small portions to phthalaldehydic acid⁶ (3.75 g) in tetrahydrofuran (25 ml). The mixture was refluxed for 1 h, cooled, and IV (prepared from 0.80 g Mg) in tetrahydrofuran (30 ml) was added dropwise under stirring. The solution obtained was refluxed for 1.5 h, acidified with hydrochloric acid (pH 2), and then heated at 90° for 1 h. The reaction mixture was washed with ether (2×75 ml), made alkaline (pH 10) and extracted with chloroform

(4 × 100 ml). The extract was dried (Na_2SO_4) and concentrated, leaving a pale yellow oil (4.75 g), which was dissolved in ether and treated with hydrogen chloride in ether. The precipitate (5.35 g) was recrystallised twice from ethanol, giving (\pm)-pierardine hydrochloride (4.85 g), m.p. 185–186°. (Found: C 61.2; H 7.20; Cl 13.8; N 5.45; O 12.6. Calc. for $\text{C}_{13}\text{H}_{16}\text{ClNO}_2$: C 61.1; H 7.09; Cl 13.9; N 5.48; O 12.5). From the hydrochloride, (\pm)-pierardine was obtained as a colourless oil, indistinguishable (NMR, MS, IR, TLC, GLC) from an authentic sample.

Resolution of (\pm)-pierardine. Solutions of (\pm)-pierardine (0.97 g) and di-*O*-benzoyl-L-tartaric acid (1.64 g) in ether were mixed. The precipitate (2.30 g) was recrystallised four times from ethanol, giving pierardine di-*O*-benzoyl-L-tartrate (0.65 g), m.p. 156°, $[\alpha]_{578}^{22} - 113^\circ$ (c 0.58, methanol). (Found: C 64.5; H 5.30; N 2.66; O 27.8. Calc. for $\text{C}_{31}\text{H}_{31}\text{NO}_{10}$: C 64.5; H 5.41; N 2.43; O 27.7.) The tartrate was dissolved in a mixture of methanol and hydrochloric acid, and the solution was washed with ether (4 × 5 ml). The aqueous layer was made alkaline (pH 10) and extracted with ether (3 × 5 ml). Evaporation of the solvent from the dried ether solution afforded pierardine (I), $[\alpha]_{\text{D}}^{22} - 68^\circ$ (c 0.66, chloroform).

Acknowledgements. We are indebted to Prof. Yasuo Inubushi, Kyoto, Japan, for a sample of shihunine. We thank Dr. Björn Lünig for his interest in this work, Dr. Rolf Håkansson for measuring the CD spectra, and Mr. Jörgen Lönngren for measuring the mass spectra. A fellowship from *Stiftelsen Bengt Lundqvists Minne* to one of us (K. L.) is gratefully acknowledged. This work was supported by the *Swedish Natural Science Research Council*.

REFERENCES

1. Elander, M. and Leander, K. *Acta Chem. Scand.* **25** (1971) 717.
2. Elander, M., Leander, K. and Lünig, B. *Acta Chem. Scand.* **23** (1969) 2177.
3. Inubushi, Y., Tsuda, Y., Konita, T. and Matsumoto, S. *Chem. Pharm. Bull. Tokyo* **12** (1964) 749.
4. Onaka, T. *Yakugaku Zasshi* **85** (1965) 839.
5. Inubushi, Y., Ysuda, Y., Konita, T. and Matsumoto, S. *Chem. Pharm. Bull. Tokyo* **16** (1968) 1014.
6. *Org. Syn. Coll. Vol.* **2** (1944) 523.
7. Marxer, A., Salzmann, U. and Hofer, F. *Helv. Chim. Acta* **52** (1969) 2351.
8. Snatzke, G., Wollenberg, G., Hrbek, J., Sastavy, F., Blaha, K., Klyne, W. and Swan, R. J. *Tetrahedron* **25** (1969) 5059.

Received June 30, 1970.