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Transformation of (±)-Ophiocarpine and (±)-13-Epiophiocarpine to (±)-α- and (±)-β-Hydrastine with Complete Retention of Configuration

(±)-α- and (±)-β-Hydrastine (3 and 4) were synthesized from (±)-ophiocarpine (1) and (±)-13-epiophiocarpine (2), respectively, with complete retention of configuration through a regioselective C_8–N bond cleavage.

Keywords——13-oxyberbines; phthalideisoquinoline alkaloids; interconversion; regioselective C–N bond cleavage; retention of configuration; ethyl chloroformate; PCC oxidation

Phthalideisoquinoline alkaloids have been shown to be biosynthesized from 13-oxyberbines with retention of configurations at C-13 and C-14 through a regioselective cleavage of C_8–N bond.[1] Although a number of papers concerning interconversion or total synthesis of phthalideisoquinoline alkaloids have so far been reported,[2] any conversion from 13-oxyberbines has not been achieved. Now we wish to report the first transformation of (±)-ophiocarpine (**1**) and (±)-13-epiophiocarpine (**2**) to (±)-α- and (±)-β-hydrastine (**3** and **4**), respectively, with complete retention of configuration by employing the method for a regioselective C–N bond cleavage using ethyl chloroformate.[3]

Reaction of (±)-*O*-acetylophiocarpine (**5**), derived from **1**,[4] with ethyl chloroformate at 70° for 3 days afforded the urethane (**6**) in an almost quantitative yield. Treatment of **6** with silver nitrate in aqueous acetone gave the alcohol (**7**, 66%, mp 229—230.5°, ν[5] 3430, 1730, 1665 cm^{-1}), which was oxidized with pyridinium chlorochromate (PCC) in methylene chloride to give the aldehyde (**8**, 94%, mp 154—154.5°, ν 2750 cm^{-1}). Partial hydrolysis of **8** with 10% sodium hydroxide in methanol at room temperature was accompanied by cyclization to give the lactol (**9**, 81%, ν 3550, 1680 cm^{-1}) as an inseparable mixture epimeric at C-14. Reduction of the acetal (**10**), derived from the lactol (**9**) in 87% yield, with lithium aluminum hydride in ether furnished two isomers, **11a** (55%, δ[5] 2.53) and **11b** (19%, δ 2.59).[6] Each of them afforded the same monoisomeric lactol [**12**, ν 3380 cm^{-1}, δ 6.36 (anomeric H)] by acid hydrolysis in an excellent yield. The PCC oxidation of **12** in the presence of sodium acetate gave (±)-α-hydrastine [**3**, 54%, mp 118—119°, *m/e* 383 (M^+), ν 1755 cm^{-1}].

A similar treatment of (±)-*O*-acetyl-13-epiophiocarpine (**13**), derived from **2**,[4,7] with ethyl chloroformate yielded the desired urethane (**14**, 47%, ν 1735, 1680 cm^{-1}) along with the regioisomer (**15**, 39%, ν 1730, 1685 cm^{-1}). Conversion of the former to (±)-β-hydrastine

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[1] A.R. Battersby, J. Staunton, H.R. Wiltshire, R.J. Francis, and R. Southgate, *J. Chem. Soc. Perkin I*, **1975**, 1147; A.R. Battersby, J. Staunton, H.R. Wiltshire, B.J. Bircher, and C. Fuganti, *ibid.*, **1975**, 1162.

[2] T. Kametani, "Total Synthesis of Natural Products," Vol. 3, ed. by J. ApSimon, John Wiley and Sons, Inc., New York, 1977, pp. 82—84; S.F. Dyke, "Rodd's Chemistry of Carbon Compounds," Vol. 4-H, ed. by S. Coffey, Elsevier Scientific Publishing Co., New York, 1978, Chapter 36; M. Shamma and J.L. Moniot, "Isoquinoline Alkaloids Research: 1972—1977," Plenum Press, New York, 1978, Chapter 24.

[3] M. Hanaoka, K. Nagami, and T. Imanishi, *Heterocycles*, **12**, 497 (1979). A similar cleavage using ethyl chloroformate-sodium iodide in acetone was recently reported without details by H. Rönsch, *Phytochemistry*, **16**, 691 (1977).

[4] M. Hanaoka, C. Mukai, and Y. Arata, *Heterocycles*, **6**, 895 (1977); Y. Kondo, H. Inoue, and J. Imai, *ibid.*, **6**, 953 (1977).

[5] All infrared and proton magnetic resonance spectra were measured in chloroform and deuterochloroform, respectively.

[6] Stereochemistry of **11a** and **11b** remains undetermined.

[7] I.W. Elliott, *J. Heterocycl. Chem.*, **4**, 639 (1967).

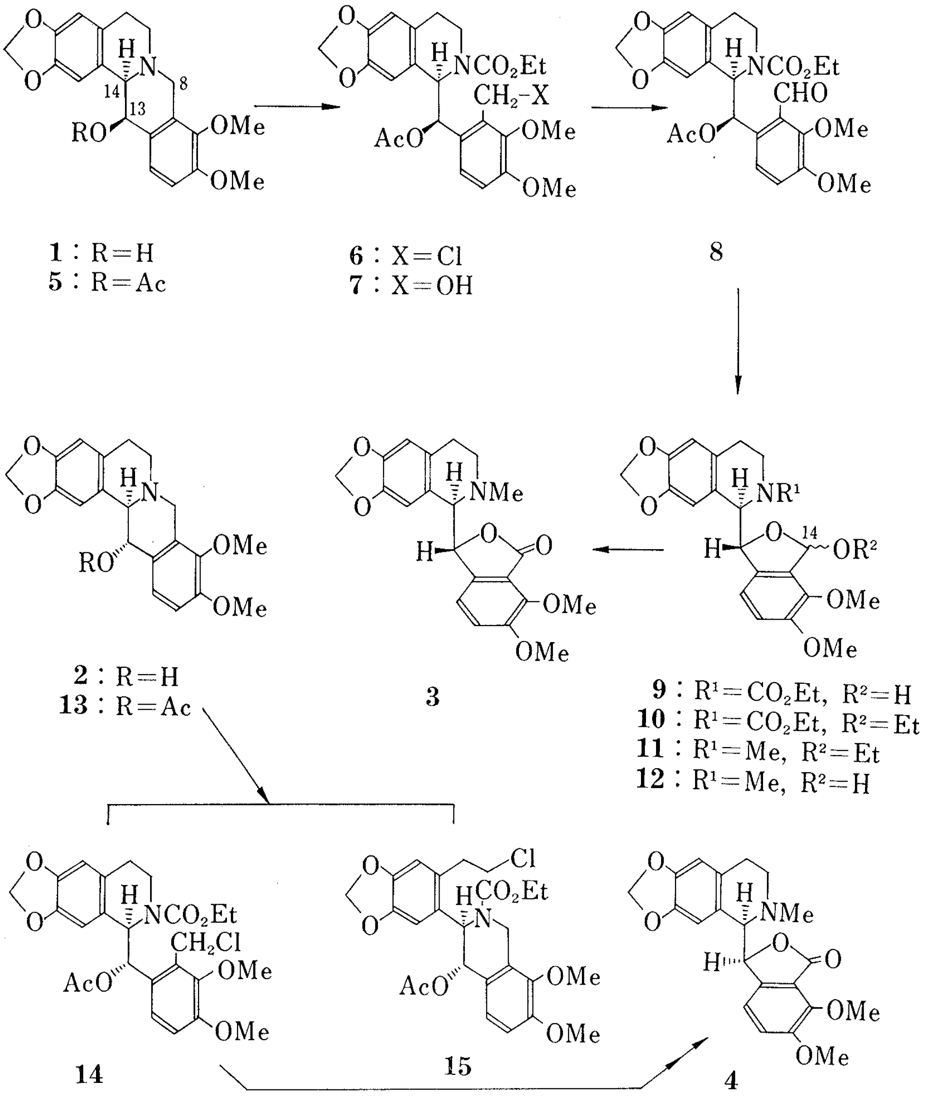

Chart 1

[**4**, mp 143.5—144°, *m/e* 383 (M^+), ν 1750 cm^{-1}] was also accomplished in the same manner described for (±)-α-hydrastine.

The synthetic (±)-α- and (±)-β-hydrastine were proved to be completely identical with the corresponding specimens[8] by thin-layer chromatography and spectral comparison. The first transformation of 13-oxyberbines into phthalideisoquinolines with retention of configuration is thus completed.

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[8] (−)-α-Hydrastine was obtained from commercially available (−)-β-hydrastine according to the method of M.A. Marshall, F.L. Pyman, and R. Robinson, *J. Chem. Soc.*, **1934**, 1315.