Department of Chemistry, Fisk University

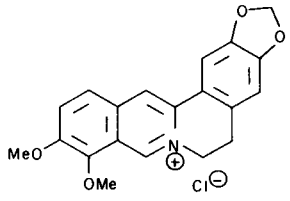
Conversion of Berberinium Chloride to the Stereoisomeric Ophiocarpines

I. W. Elliott, Jr. (1)

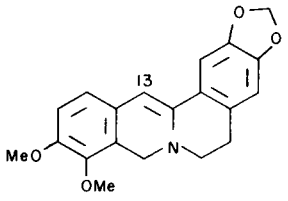
As part of a program of new synthetic approaches to isoquinoline alkaloids we describe herein the preparation of *dl*-ophiocarpine (III) from berberinium chloride (I). The steps involved reduction of berberinium chloride to dihydroberberine (II) and hydration of II by Brown's hydroboration-alkaline peroxide method.

Barton, Hesse and Kirby mention without experimental details that sodium borohydride in pyridine reduces berberinium chloride to dihydroberberine (2). By contrast, the berberinium salt, like other *N*-alkylisoquinolinium ions, is reduced by sodium borohydride in aqueous alcohol to the tetrahydro derivative (3,4). In practice the work-up of the reduction mixture was facilitated by using a smaller volume of pyridine than in the model reaction described by Barton, and the product was isolated simply by dilution with water rather than by a tedious ether extraction of the slightly soluble dihydroberberine.

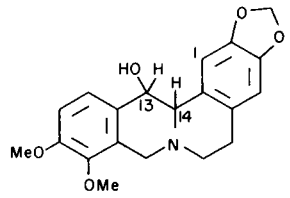
In projecting the hydration of II there were two problems of concern: first, whether the addition of diborane, and consequently of water, would be anti-Markownikoff as predicted to place the hydroxyl group at *C*-13 in II; and, secondly, since both addition of diborane and the subsequent oxidation are known to occur predominantly *cis*, whether only 13-epiophiocarpine (IIIb) would be formed. Previous syntheses of ophiocarpine from dehydronorhydrastine (IV) by Govindachari and coworkers (5) and the later stereochemical refinements by Ohta, Tani and Morozumi (6) in which the absolute configuration was established for ophiocarpine show that the natural alkaloid is the *cis* isomer (IIIa), described with reference to the two hydrogen atoms at positions 13 and 14. The diastereoisomer with the epimeric configuration at *C*-13, called 13-epiophiocarpine by Ohta or "ophiocarpine b" by Govindachari, is correspondingly the *trans* compound.



I

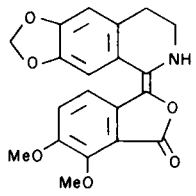


II



IIIa (H-13 and H-14 cis)

IIIb (H-13 and H-14 trans)



IV

The crude ophiocarpine preparation was separated into two racemates by the differential solubility in ethanol. The ratio of epiophiocarpine (IIIb) to ophiocarpin (IIIa) was approximately 4:1. The formation of even minor quantities of ophiocarpine may be due to relative steric effects in the products involving the hydroxyl group. Epiophiocarpine is acetylated more slowly than ophiocarpine (5); in the NMR spectra Ohta showed an apparent interaction between an aromatic ring proton and the hydroxyl group in epiophiocarpine that was not present in ophiocarpine; and models reveal greater crowding between the equatorial hydroxyl group and the proton at position 1 in IIIb.

EXPERIMENTAL

Dihydroberberine.

Berberinium chloride dihydrate (7.0 g.) was dried at 80° under reduced pressure over phosphorus pentoxide for 8 hours. The dried salt (5.0 g.) was added to a suspension of sodium borohydride (0.6 g.) in dry pyridine (30 ml.) at room temperature. After 20 minutes more sodium borohydride (0.5 g.) was added, and the solution was allowed to stand 30 minutes. The reaction mixture was stirred into 800 ml. of ice water to give a pale yellow solid, 4.8 g., m.p. 152-158°. Recrystallization of the crude product from benzene-ligroin (b.p. 30-60°) gave 3.3 g. of light orange prismatic crystals, m.p. 157-158° (lit. (7) m.p. 157-159° with prior decomposition at 146°).

Ophiocarpine and 13-Epiophiocarpine.

Dihydroberberine (3.3 g.) was treated with diborane in tetrahydrofuran solution (35 ml., 1 molar concentration), and the originally yellow solution quickly faded. The solution was allowed

to stand at room temperature four hours and cautiously hydrolized with water and treated with 20% sodium hydroxide (40 ml.) and 30% hydrogen peroxide (35 ml.). The two-phase mixture was stirred magnetically for 3 hours, then boiled gently to remove excess tetrahydrofuran. After cooling, the yellow solid was collected and heated while still damp with ethanol (60 ml.). Not all of the solid dissolved, but the hot mixture was filtered. The undissolved solid (fraction A, 0.3 g.) had m.p. 245° dec. Recrystallization from ethanol containing a little dimethylformamide raised the m.p. to 256-258° with preliminary darkening at 240°. Fraction A was identified as *dl*-ophiocarpine (lit. (5) m.p. 252°); the infrared spectrum showed a broad band at 3.0 μ.

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.63; H, 5.97; N, 3.99.

An acetyl derivative of ophiocarpine, prepared in pyridine with acetic anhydride on a steam bath (1 hour) followed by recrystallization from aqueous methanol, was isolated as colorless needles, m.p. 176-177° (lit. (5) m.p. 172-174°).

Anal. Calcd. for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.72; H, 5.80; N, 3.84.

The filtrate, after removal of ophiocarpine (fraction A) was diluted with water and cooled. There was obtained 1.2 g. of 13-epiophiocarpine (fraction B), m.p. 158-160°. Several recrystallizations from aqueous methanol gave the product reproducibly with m.p. 166-168°, and from chloroform-methanol a recrystallized sample melted at 170-172°. Recrystallization of fraction B from benzene-petroleum ether gave colorless needles, m.p. 178-179° (lit. (5) m.p. 176°).

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.50; H, 5.97; N, 3.99.

13-Epiophiocarpine (ophiocarpine b) was acetylated as described; the purified compound had m.p. 185-186° (lit. (5) m.p. 186°).

Anal. Calcd. for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.27; H, 5.78; N, 3.63.

REFERENCES

(1) Presented at the First International Congress of Heterocyclic Chemistry, Albuquerque, New Mexico, June 12-15, (1967). Acknowledgment is made to the Faculty Reasearch Fund of Fisk University for support of this work.

(2) D. H. R. Barton, R. H. Hesse and G. W. Kirby, *J. Chem. Soc.*, 6479 (1965).

(3) R. Mirza, *ibid.*, 4400 (1957).

(4) S. Bose, *J. Indian Chem. Soc.*, 32, 450 (1955); W. Awe, H. Wichmann, and R. Buerhop, *Chem. Ber.*, 90, 1997 (1957); I. Sallay and R. H. Ayers, *Tetrahedron*, 19, 1397 (1963).

(5) T. R. Govindachari and S. Rajadurai, *J. Chem. Soc.*, 557 (1957); T. R. Govindachari, S. Rajadurai, M. Sobramanian and N. Viswanathan, *ibid.*, 2943 (1957).

(6) M. Ohta, H. Tani and S. Morozumi, *Tetrahedron Letters*, 859 (1963).

(7) B. Witkop, *J. Am. Chem. Soc.*, 78, 2873 (1956).

Received September 5, 1967 Nashville, Tennessee 37203