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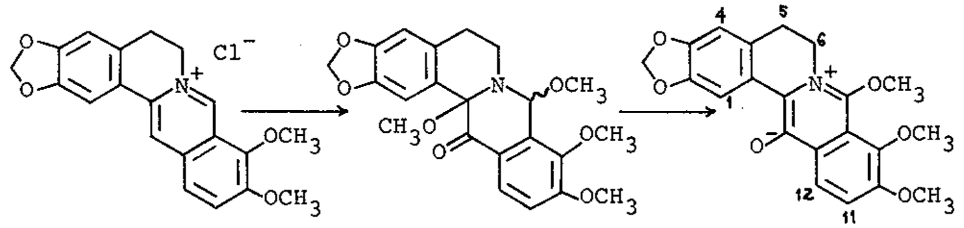
PHOTO-OXYGENATION OF BERBERINE. A NOVEL CONVERSION OF BERBERINE TO (±)-OPHIOCARPINE, (±)-α- AND (±)-β-HYDRASTINE[1]

Miyoji Hanaoka*, Chisato Mukai, and Yoshio Arata
Faculty of Pharmaceutical Sciences, Kanazawa University
Takara-machi, Kanazawa 920, Japan

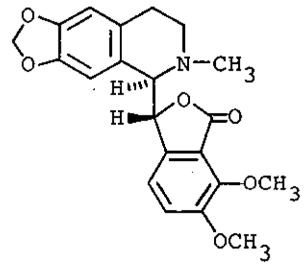
Photo-oxygenation of berberinium chloride(I) afforded 8-methoxyberberinephenolbetaine(III), which had been already converted to (±)-α- and (±)-β-hydrastine(IV and V). Sodium borohydride reduction of III yielded (±)-ophiocarpine(IX) and (±)-13-epi-ophiocarpine(X).

The protoberberine alkaloids have been shown to be a precursor of the phthalideisoquinoline alkaloids[2] and ophiocarpine was proved to be biosynthesized from tetrahydroberberine.[3] Recently berberine(I) was converted to (±)-α- and (±)-β-hydrastine(IV and V) via 8-methoxyberberinephenolbetaine(III), the key intermediate.[4] The present communication deals with the novel and convenient synthesis of III from I by photo-oxygenation and the transformation of III into (±)-ophiocarpine(IX).

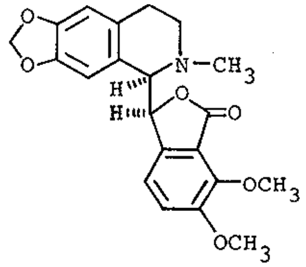
Irradiation(400W high-pressure Hg lamp, with Pyrex filter) of I in methanol containing rose bengal and sodium methoxide in a stream of oxygen for 45 min afforded the precipitate(II)[59%, mp 126-130°, ν_{max}^{KBr} cm^{-1}: 1690(C=O), λ_{max}^{EtOH} nm(log ε): 230(4.16), 291 (4.12)], recrystallization of which from methanol gave quantitatively orange colored 8-methoxyberberinephenolbetaine(III)[mp 176-



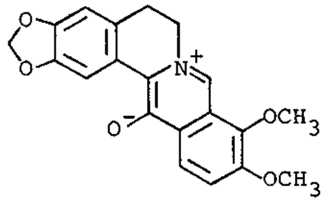
I II III



IV



V

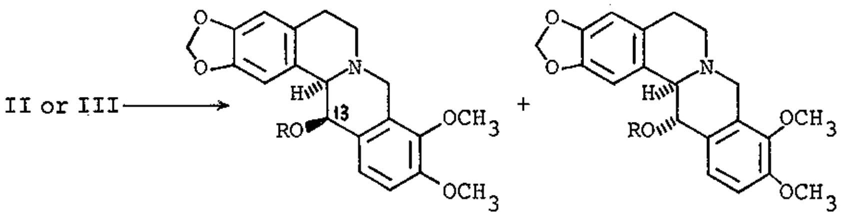


VI

178°, *m/e*: 381 ($M^{\bullet}$), λ_{max}^{EtOH} nm(log ε): 235(4.22), 262(4.15), 317(4.13), 361.5(3.92), 377(4.12), 464(4.13), δ: 2.90(t, 2H, *J*=6 Hz, H_2-5), 3.90(s, 3H, OCH_3), 4.02(s, 6H, OCH_3 x 2), 4.58(t, 2H, *J*=6 Hz, H_2-6), 5.91(s, 2H, OCH_2O), 6.58(s, 1H, H-4), 7.40(d, 1H, *J*=9 Hz, H-11), 8.42(d, 1H, *J*=9 Hz, H-12), 8.80(s, 1H, H-1)].[5] Catalytic hydrogenation of III over platinum oxide afforded berberinephenolbetaine (VI) along with 13-hydroxytetrahydroberberine. The betaine(VI) was proved to be identical with the authentic specimen[6] by mixed mp and infrared spectral comparison. Although II has not been fully characterized, its structure might be that as depicted on the basis of its lability and ready conversion to III,[7] and further confirmation of its structure is now in progress.

Since the betaine(III) has been already converted into (±)-α- and (±)-β-hydrastine(IV and V) in an excellent yield,[4] the present photo-oxygenation of I amounts to a formal synthesis of IV and V.

Sodium borohydride reduction of II or III, followed by acetylation[8] with acetic anhydride in pyridine afforded (±)-O-acetylophiocarpine(VII)[87%, mp 178.5-179.5° (lit.[9] mp 172-174°), m/e: 397(M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1728(C=O), δ: 1.80(s, 3H, $COCH_3$), 6.46(d, 1H, J=3 Hz, H-13)[10]] and (±)-O-acetyl-13-epi-ophiocarpine(VIII) [6%, mp 187-188° (lit.[9] mp 186°), m/e 397(M^+), $\nu_{max}^{CHCl_3}$ cm^{-1}: 1732 (C=O), δ: 2.21(s, 3H, $COCH_3$), 6.10(d, 1H, J=8 Hz, H-13)[10]], both of which were hydrolyzed with 5% aqueous sodium hydroxide in methanol to give (±)-ophiocarpine(IX)[100%, mp 248-251° (lit.[9] mp 252°), m/e: 355(M^+)] and (±)-13-epi-ophiocarpine(X)[91%, mp 181-183° (lit.[9] mp 176°), m/e: 355(M^+)], respectively. The synthetic (±)-ophiocarpine was proved to be identical with the authentic specimen[6] by mixed mp and infrared spectral comparison.



VII: R=Ac
IX: R=H

VIII: R=Ac
X: R=H

The present transformation of berberine to 8-methoxyberberinephenolbetaine provides a simple and general method for the synthesis of the phthalideisoquinoline and 13-hydroxyprotoberberine alkaloids.[11]

REFERENCES

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2. A. R. Battersby, J. Staunton, H. R. Wiltshire, R. J. Francis, and R. Southgate, J. Chem. Soc. Perkin I, 1975, 1147 and references cited therein.
3. P. W. Jeffs and J. D. Scharver, J. Am. Chem. Soc., 98, 4301 (1976).
4. J. L. Moniot and M. Shamma, J. Am. Chem. Soc., 98, 6714(1976).
5. The published data for III[4]; mp 175-176°, λ_{max}^{EtOH} nm(log ε): 230 (4.50), 262(4.11), 313(4.09), 359(3.81), 374(3.80), 455(3.83), δ: 2.90(t, 2H), 3.86(s, 3H), 3.98(s, 6H), 4.58(t, 2H), 5.86(s, 2H), 6.51(s, 1H), 7.35(d, 1H), 9.28(?)(d, 1H), 8.80(s, 1H).
6. The authentic specimen was synthesized according to the literature; T. Takemoto and Y. Kondo, Yakugaku Zasshi, 82, 1413(1962).
7. Dissolution of II in $CDCl_3$ produced immediately a deep orange color. The NMR spectrum of this solution was found to be identical with that of III.
8. Separation of VII and VIII was much easier than that of IX and X.
9. T. R. Govindachari and S. Rajadurai, J. Chem. Soc., 1957, 557.
10. The published NMR data[12]; (-)-VII δ: 1.78, 6.46, (-)-VIII δ: 2.23, 6.07.
11. Photo-oxygenation conversion of dihydroberberine to the betaine (VI) and conversion of dihydrocoralyne to phthalideisoquinoline were recently presented; Y. Kondo and J. Imai, The 97th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1977.
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