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Total Synthesis of Stereoisomeric Mixture of Magnoline

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Sir:

Magnoline, $C_{36}H_{40}N_2O_6$, m.p. 179° , occurs in the leaves of *Magnolia fuscata* Andr., which grows on the Caucasian shores of the Black Sea. It is a yellow, crystalline, optically active substance forming vitreous salts with hydrogen halides (1). The structure (I) of magnoline was established by Proskurnina and Orekhoff (2). Furthermore, berbaminine, $C_{36}H_{40}N_2O_6$, m.p. $190-191^\circ$, was isolated from *Berberis amurensis* Rupr. var. *japonica* (Regel) Rehd. *forma Bretschneideri* (Rehd.) Ohwi by Tomita and Kugo (3) and its structure assigned as I by chemical methods (4, 5). Furthermore, it was established that berbaminine is a phenolic base belonging to the dauricine type and that *O*-methylberbaminine, *O*-methylauricine, and *O*-methylmagnoline are optical isomers indicated by the same structural formula (II).

The purpose of the present investigation was to study the cyclization of the diamide (VIII and IX) in order to obtain the corresponding dihydroisoquinoline derivative (X and XI) and its dimethiodide (XII and XIII) as possible intermediates for the synthesis of stereoisomeric mixture of magnoline, namely, berbaminine (I).

Ethoxycarbonylation (6) of the dicarboxylic acid (III), which was used as a starting material in case of total synthesis of dauricine (7), gave the acid (IV) as colorless needles (from ether), m.p. $127-129^\circ$.

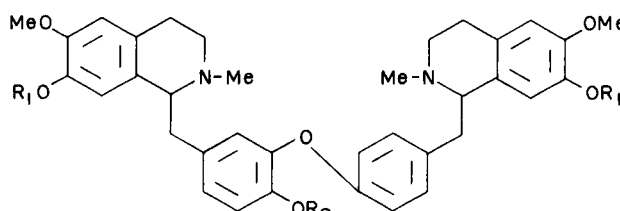
Anal. Calcd. for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 60.72; H, 4.74.

Chlorination of IV with thionyl chloride gave the acid chloride (V) in an excellent yield, which was used in the following reaction without purification.

Schotten-Baumann reaction of 4-benzyloxy-3-methoxyphenethylamine (VI) (6) with the preceding acid chloride (V) afforded the diamide (VIII), whose infrared spectrum showed ethoxycarbonyl and amidocarbonyl bands ($C=O$) at 1760 and 1660 cm^{-1} , respectively. Bischler-Napieralski reaction of the above diamide (VIII) with phosphoryl chloride in benzene gave the dihydroisoquinoline derivative (X), which was converted into the dimethiodide (XII). Reduction of compound (XII) with sodium borohydride in chloroform-methanol gave the tetrahydroisoquinoline derivative (XIV), whose de-ethoxycarbonylation yielded the substance (XV) on refluxing with

an ethanolic potassium hydroxide solution. Recrystallization of XV from ethanol-water gave a colorless powder, m.p. $100-110^\circ$.

Anal. Calcd. for $C_{50}H_{52}N_2O_6 \cdot 1.5\text{ H}_2\text{O}$: C, 74.69; H, 7.27; N, 3.47. Found: C, 74.52; H, 6.86; N, 3.38.



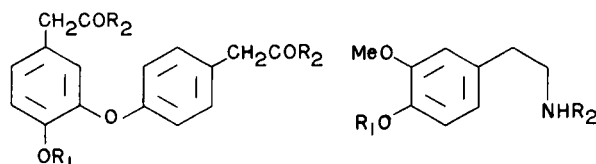
I: $R_1=R_2=H$

II: $R_1=R_2=Me$

XIV: $R_1=CH_2Ph$; $R_2=CO_2Et$

XV: $R_1=CH_2Ph$; $R_2=H$

XVI: $R_1=R_2=CO_2Et$



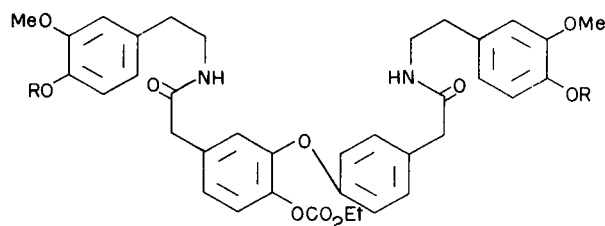
III: $R_1=H$; $R_2=OH$

IV: $R_1=CO_2Et$; $R_2=OH$

V: $R_1=CO_2Et$; $R_2=Cl$

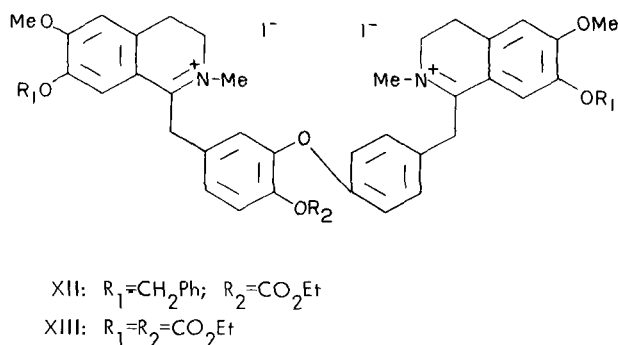
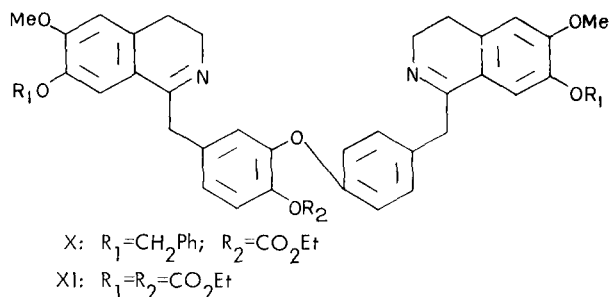
VI: $R_1=CH_2Ph$; $R_2=H$

VII: $R_1=H$; $R_2=ZnCl$



VIII: $R=CH_2Ph$

IX: $R=CO_2Et$



Since debenzoylation of XV under various conditions resulted in failure, synthesis of the diamide (IX) was examined as follows: Schotten-Baumann reaction of 4-hydroxy-3-methoxyphenethylamine, which was obtained by basification of the compound (VII) (8) with 1 *N* sodium hydroxide solution, with the acid chloride (V) in chloroform, followed by ethoxycarbonylation, afforded the diamide (IX), which showed a maximum at 3400 cm^{-1} (NH) and both carbonyl bands at 1760 cm^{-1} (ester) and 1665 cm^{-1} (amide). Bischler-Napieralski reaction of the diamide (IX) with phosphoryl chloride in benzene gave the dihydroisoquinoline derivative (XI), which was converted into the dimethiodide (XIII) on being allowed to stand in methyl iodide in the presence of nitrogen. Reduction of the compound (XIII) with sodium borohydride in methanol-chloroform gave the tetrahydroisoquinoline derivative (XVI). Removal of the ethoxycarbonyl radical by hydrolysis with an ethanolic sodium hydroxide solution afforded compound (I) as a yellow powder, m.p. 145° (sinters at 135°) (9), whose infrared spectrum showed a maximum at 3500 cm^{-1} (OH) and *N*-methyl radical at 2770 and 2830 cm^{-1} (in chloroform). Recrystallization of

the picrate of compound (I) from methanol-ether gave a yellow powder, m.p. $140\text{--}145^\circ$.

Anal. Calcd. for $\text{C}_{36}\text{H}_{40}\text{N}_2\text{O}_6 \cdot 2\text{C}_6\text{H}_3\text{N}_3\text{O}_7$: C, 54.65; H, 4.40; N, 10.62. Found: C, 55.00; H, 4.63; N, 10.58.

The natural magnoline and berbaminine were not available for comparison. Accordingly, methylation of the stereoisomeric mixture of synthetic magnoline, namely, berbaminine with diazomethane gave *O*-methylmagnoline, namely *O*-methylberbaminine (II), whose infrared spectrum was superimposable on that of natural *O*-methyldauricine (II) in chloroform. The latter natural product was obtained by methylation of natural dauricine donated by Dr. R. H. F. Manske as a yellow powder, m.p. 145° (sinters at 130°).

Anal. Calcd. for $\text{C}_{39}\text{H}_{46}\text{N}_2\text{O}_6 \cdot 2\text{C}_6\text{H}_3\text{N}_3\text{O}_7 \cdot 4\text{H}_2\text{O}$: C, 52.39; H, 5.21; N, 5.96. Found: C, 51.98; H, 5.26; N, 5.99.

The infrared spectra of the picrate of both specimens were identical. Since magnoline and berbaminine are optical isomers, a total synthesis of the stereoisomeric mixture (I) of magnoline, namely berbaminine has been accomplished.

We express our deep gratitude to Dr. R. H. F. Manske for a gift of natural darucine.

REFERENCES

- (1) N. F. Proskurnina and A. P. Orekhoff, *Bull. Soc. Chim.*, 5, 1357 (1938); *Chem. Abstr.*, 33, 1439 (1939).
- (2) N. F. Proskurnina and A. P. Orekhoff, *J. Gen. Chem. (U.S.S.R.)*, 10, 707 (1940); *Chem. Abstr.*, 35, 2520 (1941).
- (3) M. Tomita and T. Kugo, *Yakugaku Zasshi*, 75, 753 (1955).
- (4) M. Tomita and T. Kugo, *ibid.*, 77, 1075 (1957).
- (5) M. Tomita and T. Kugo, *ibid.*, 77, 1079 (1957).
- (6) J. Finkelstein, *J. Am. Chem. Soc.*, 73, 550 (1951).
- (7) T. Kametani and K. Fukumoto, *Tetrahedron Letters*, 2772 (1964); *J. Chem. Soc.*, 6141 (1964); *Chem. Pharm. Bull.*, 14, 73 (1966).
- (8) T. Kametani, S. Takano, and E. Karibe, *Yakugaku Zasshi*, 83, 1035 (1963).
- (9) This m.p. was measured on a hot stage apparatus after the sample had been dried over phosphorus pentoxide at $50^\circ/13\text{ mm.}$ for 3 days.

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