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An Alternative Synthesis of Stereoisomeric Mixture of Magnoline by Ullmann Reaction (Studies on the Syntheses of Heterocyclic Compounds. CCXLVIII[1])

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Magnoline, $C_{36}H_{40}O_6N_2$, mp 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 acitve substance forming vitreous salts with hydrogen halides.[3] The sturcture of magnoline (I) was established by Proskurnina and Orekhov.[4] Furthermore, berbamunine, $C_{36}H_{40}O_6N_2$, mp 190—191°, was isolated from *Berberis amurensis* Rupr. var. *japonica* (Regel) Rehd. *forma Bretschneideri* (Rehd.) Ohwi by Tomita and Kugo[5] and its structure assigned as I by chemical methods.[6,7] Furthermore, it was established that berbamunine is a phenolic base belonging to the dauricine type and that O-methylmagnoline, O-methylberbamunine, and O-methyldauricine (II) are optical isomers indicated by the same structural formula[8,9,10]. Moreover, Kunitomo[11] has revealed the absolute configurations of magnoline and berbamunine according to the relation of L-(+)-laudanosine.[12]

Since we have already reported a synthesis of stereoisomeric mixture of magnoline (I) through the diamide in a previous paper,[13] we wish to report a synthesis of I by Ullmann reaction of *dl*-7,4′-O,O-dibenzyl-3′-bromo-N-methylcoclaurine (III)[14]with *dl*-7-O-benzyl-N-methylcoclaurine (IV)[15] as an alternative synthesis of I.

Ullmann reaction by heating both specimens (III) and (IV) at 150—155° in an oil-bath in the presence of pyridine, copper powder, potassium carbonate, and potassium iodide in a current of nitrogen gave a stereoisomeric mixture of our expected O-benzylmagnoline. During the above reaction, it was examined by thin-layer chromatography whether the spots of the compounds (III) and (IV) have disappeared or not. It took 45 hr for only the latter spot to appear in thin-layer chromatography (TLC). Alumina column chromatography

1) Part CCXLVII: T. Kametani, K. Ogasawara, T. Terui, K. Yamaki, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **16**, 1584 (1968),
2) Location: *a) No. 85, Kita-4-bancho, Sendai*; *b) No. 600, Kashiwagi-4-chome, Shinjuku, Tokyo.*
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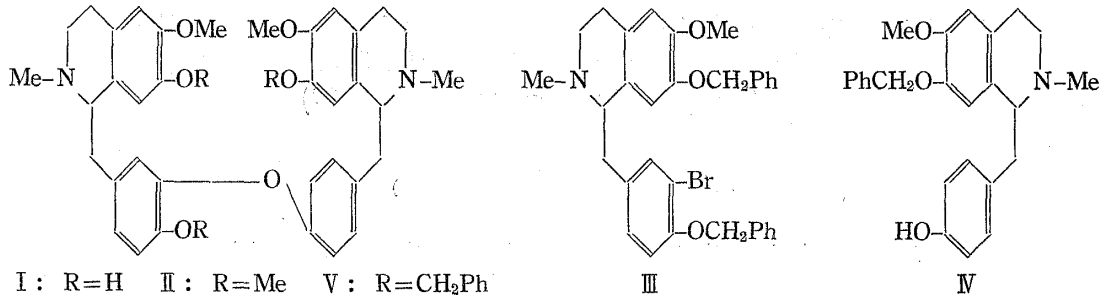
of the reaction mixture afforded O,O,O-tribenzylmagnoline (V), which was characterized as its dipicrate, mp 113—120° (decomp.).



I: R=H II: R=Me V: R=CH_2Ph III IV

Chart 1

Removal of the benzyl groups by hydrolysis with an ethanolic hydrochloric acid solution afforded our expected compound (I) as a pale brown powder, mp 122—129°, which was elucidated beyond doubt by infrared (IR) and nuclear magnetic resonance (NMR) spectra.

The natural magnoline and berbamunine were not available for comparison. Accordingly, methylation of the stereoisomeric mixture of synthetic magnoline, namely, berbamunine with diazomethane in ethanol–ether gave O,O,O-trimethylmagnoline, namely, O,O,O-trimethylberbamunine (II), whose IR spectrum was superimposable on that of natural O-methyldauricine[13] in chloroform.

The dipicrate of our synthetic O,O,O-trimethylmagnoline was also characterized as a yellow powder, mp 143—145° (decomp.) (sinters at 127°). The IR spectra of the picrate of both specimens were identical. Thus, an alternative synthesis of the stereoisomeric mixture of magnoline, namely, berbamunine has been accomplished.

Experimental[16]

Stereoisomeric Mixture of O,O,O-Tribenzylmagnoline (V) (O,O,O-Tribenzylberbamunine)——A mixture of 3.5 g of III, 3 g of IV, 0.4 g of Cu powder, 1.2 g of K_2CO_3, 0.3 g of KI, and 10 ml of pyridine was heated with stirring at 150—155° in an oil-bath for 45 hr in a current of N_2. After the reaction, the solvent was distilled off to give a dark brown residue, which was dissolved in benzene. The resultant solution was filtered in order to remove the impurities, washed with 5% NaOH aq. solution and water, dried on Na_2SO_4, and evaporated to give a brown oil, which was chromatographed on Al_2O_3 (200—300 mesh) using benzene as solvent.

Removal of the first eluate gave a brown syrup whose Beilstein test was positive. Thin-layer chromatography [Wakogel B-5, thickness, 0.25 mm, $CHCl_3$–MeOH (10:1)] gave one spot which showed the same *Rf* value as the starting material (III). In this case the thin-layer chromatogram (TLC) using $CHCl_3$–MeOH (10:1) showed *Rf* 0.66 and the IR spectra of both specimens were identical in $CHCl_3$.

Removal of the second $CHCl_3$ eluate afforded 0.8 g of a brown syrup, which was extracted with hot *n*-hexane. The preceding extract was distilled to give 0.6 g of a pale yellowish brown syrup, whose TLC showed *Rf* 0.51 in case of elution with $CHCl_3$–MeOH (10:1). On the other hand, *Rf* value of IV showed 0.36 in the same TLC as above. NMR (ppm) ($CDCl_3$): 2.46 (3H, singlet, N-CH_3), 2.50 (3H, singelt, N-CH_3), 3.85 (6H, singlet, 2OCH_3), 6.24 (1H, C_8-H), 6.28 (1H, C_8-H), 6.60—7.37 (24H, aromatic protons). Purification of dipicrate from benzene—*n*-hexane gave a yellow amorphous powder, mp 113—120° (decomp.) (sinters at 108°). *Anal.* Calcd. for $C_{57}H_{58}O_6N_2 \cdot 2C_6H_3O_7N_3$: C, 62.53; H, 4.87; N, 8.46. Found: C, 62.33; H, 5.01; N, 8.21.

Stereoisomeric Mixture of Magnoline (Berbamunine) (I)——A mixture of 0.3 g of the above compound (V), 15 ml of EtOH, and 15 ml of conc. HCl was refluxed for 2.5 hr in a current of N_2. After the reaction removal of the solvent *in vacuo* in a current of N_2 afforded a dark brown residue, which was basified with conc. NH_4OH aq. solution and extracted with $CHCl_3$. The extract was washed with saturated NaCl aq. solution, dried on Na_2SO_4, and evaporated *in vacuo* in a current of N_2 to give 0.15 g of a brown syrup, which was purified by silica gel (100 mesh) chromatography. After the elution with $CHCl_3$, removal of the eluates, $CHCl_3$–MeOH (10:1) and $CHCl_3$—MeOH (5:1). afforded 48 mg of a pale brown powder, whose TLC [Wakogel

16) All melting points were not corrected.

B–5, $CHCl_3$–MeOH (5:1)] showed one spot (*Rf*: 0.30). Purification from $CHCl_3$—*n*–hexane gave a colorless powder, mp 122—129° (sinters at 114°). *Anal.* Calcd. for $C_{36}H_{40}O_6N_2 \cdot \frac{1}{2}H_2O$[17]: C, 71.38; H, 6.82; N, 4.63. Found: C, 71.26; H, 6.93; N, 4.64. IR cm^{-1} (KBr): ν_{OH} 3300—3540 (broad). NMR (ppm) ($CDCl_3$): 2.39 (6H, singlet, 2N–CH_3); 3.75 (6H, singlet, 2OCH_3); 6.15 (1H, C_8–H); 6.23 (1H, C_8–H); 6.45—7.13 (9H, aromatic protons).

Stereoisomeric Mixture of O,O,O-Trimethylmagnoline (II) (O,O,O-Trimethylbergamumine)——To a solution of 43 mg of synthetic magnoline mentioned above in 15 ml of EtOH was added a solution (50 ml) of an excess of CH_2N_2 in ether, and the mixture was allowed to stand at 3° for 48 hr. After filtration, removal of the solvent *in vacuo* in a current of N_2 afforded 40 mg of II as a brown syrup, whose dipicrate was recrystallized from $CHCl_3$—*n*–hexane to give a yellow powder, mp 143—145° (decomp.) (sinters at 127°). $C_{39}H_{46}O_6N_2 \cdot 2C_6H_3ON_3 \cdot 1H_2O$[17] *Anal.* Calcd. for: C, 54.93; H, 4.88; N, 10.05. Found: C, 55.21; H, 4.51; N, 10.03. The IR spectrum (in $CHCl_3$) of this dipicrate was superimposable on that of the sample[13] obtained by methylation of natural dauricine, followed by treatment with picric acid.

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17) This was dried on P_2O_5 at 60° for 48 hr *in vacuo*.

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Synthesis of Stereoisomeric Mixture of Daurinoline (Studies on the Syntheses of Heterocyclic Compounds. CCXLIX[1])

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Daurinoline (II),[3] $C_{37}H_{42}O_6N_2 \cdot H_2O$, was isolated from *Menispermum dauricum* DC. (Japanese name "Kohmorikazura") as a minor new phenolic base of biscoclaurine type alkaloid, besides dauricine[4] (I) and menisperine[5] (V). This base was obtained as non-crystallizable, pale yellow powder, whose methylation with diazomethane gave the known O–methyldauricine (III). Futhermore, ethylation with diazoethane gave O,O–diethyldaurinoline, whose cleavage reaction with metallic sodium in liquid ammonia afforded D–(–)–O–ethylarmepavine as a non–phenolic base and D–(–)–6–ethoxy–1,2,3,4–tetrahydro–1–(4–hydroxybenzyl)–7–methoxy–2–methylisoquinoline as a phenolic base[3]. These facts confirmed the structure of daurinoline as II.

We now report the synthesis of the stereoisomeric mixture of daurinoline by the application of a Ullmann reaction between two tetrahydroisoquinoline derivatives, XII and XIII.

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