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TOTAL SYNTHESES OF OPTICALLY ACTIVE NATURAL ISOTETRANDRINE, PHAEANTHINE AND TETRANDRINE

Y. Inubushi and Y. Masaki

Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto, Japan

S. Matsumoto[1] and F. Takami[1]

Faculty of Pharmaceutical Sciences, Osaka University, Toyonaka, Japan

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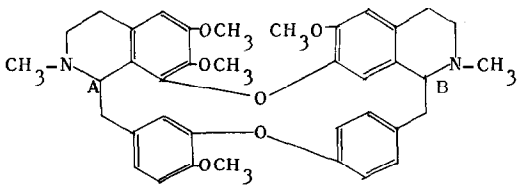
Attempts have been made to accomplish the total syntheses of the alkaloids possessing two asymmetric centers in the oxyacanthine-berbamine series of bis-benzylisoquinoline alkaloids, but unforeseen complications prevented the completion of the synthesis except an example of dl-cepharanthine by Tomita et al[2]. We describe here the first total syntheses of optically active natural alkaloids belonging to this series.

The starting material for these syntheses, O-benzyl-8-bromo-N-norlaudanine (2a: racemate) was synthesized from O-benzylhomoisovanillic acid and β-3-bromo-4,5-dimethoxyphenylethylamine by the usual manner, and then resolved via the dextrorotatory tartaric acid salt into the optically active base (2a), m.p. 99°, $[\alpha]_D$ -38° ($CHCl_3$). N-Methylation of the resolved base (2a) gave O-benzyl-8-bromo-laudanidine (2b). The structure and optical purity of the compound (2b) was assured by derivation of this base to R-(-)-laudanidine (3)[3].

The Ullmann condensation[4] of the base (2b) with N-t-butoxycarbonyl-β-phenylethylamine (4) afforded the compound (5a) as an amorphous powder*[5] in 50% yield[6]. Hydrogenolysis of the compound (5a), followed by the Ullmann condensation with methyl p-bromophenylacetate (6) gave N-t-butoxycarbonyl-carboxylic acid methyl ester (7a) as an amorphous powder* in 40% yield. The cycloamide* (9), an amorphous powder, $[\alpha]_D$ -153° ($CHCl_3$), was obtained in overall yield 54% from the compound (7a) by the method which had been successfully employed in the analogous lactam formation in the course of the synthesis of dl-cepharanthine[2], as shown in the reactions formulated (7a→7b→8→9). The Bischler-Napieralski reaction of the cycloamide afforded the 3,4-dihydro-

isoquinoline (10), m.p. 148-150°, $C_{37}H_{38}N_2O_6$, Calcd., C, 73.24 ; H, 6.31, Found, C, 73.47 ; H, 6.28, $[\alpha]_D$ +82° ($CHCl_3$) in 87% yield. The direction of the ring closure in this Bischler-Napieralski reaction can be ultimately settled by identification of the final product of this synthesis with isotetrandrine and phaeanthine. Reduction of the dihydrobase (10), with $NaBH_4$, followed by N-methylation gave a mixture (12) of isotetrandrine (1b)(ca. 60%) and phaeanthine (1a)(ca. 40%) in overall yield 70%. The ratio of these two alkaloids in the product (12) was estimated by comparing NMR spectrum of the mixture with that of natural isotetrandrine and phaeanthine, respectively, especially by the relative intensities of the signals due to the methoxyl and N-methyl groups.

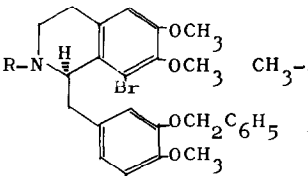
Separation of each diastereomer from the reaction mixture (12) was effected by the aid of different solubilities of isotetrandrine picrate and phaeanthine picrate. Thus, the less soluble phaeanthine picrate tended to crystallize, and the solution removed the crystalline picrate contained chiefly the isotetrandrine picrate. The synthesized phaeanthine picrate (1a: picrate), m.p. 245-250° (decomp.), $[\alpha]_D$ -98° (pyridine) was identical with the natural phaeanthine picrate[7], m.p. 245-250° (decomp.), $[\alpha]_D$ -116° (pyridine) in all respects. The free base (1a) from the picrate was also identical with natural phaeanthine in all respects. On the other hand, the free base (1b), m.p. 179-180°, $[\alpha]_D$ +136° ($CHCl_3$) from the solution was identified with natural isotetrandrine, m.p. 181°, $[\alpha]_D$ +146° ($CHCl_3$) by comparison of IR, NMR, t.l.c. and mixed melting point determination.



1a (A:R, B:R) Phaeanthine

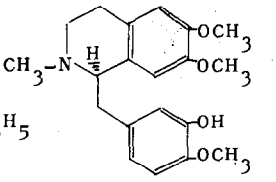
1b (A:R, B:S) Isotetrandrine

1c (A:S, B:S) Tetrandrine



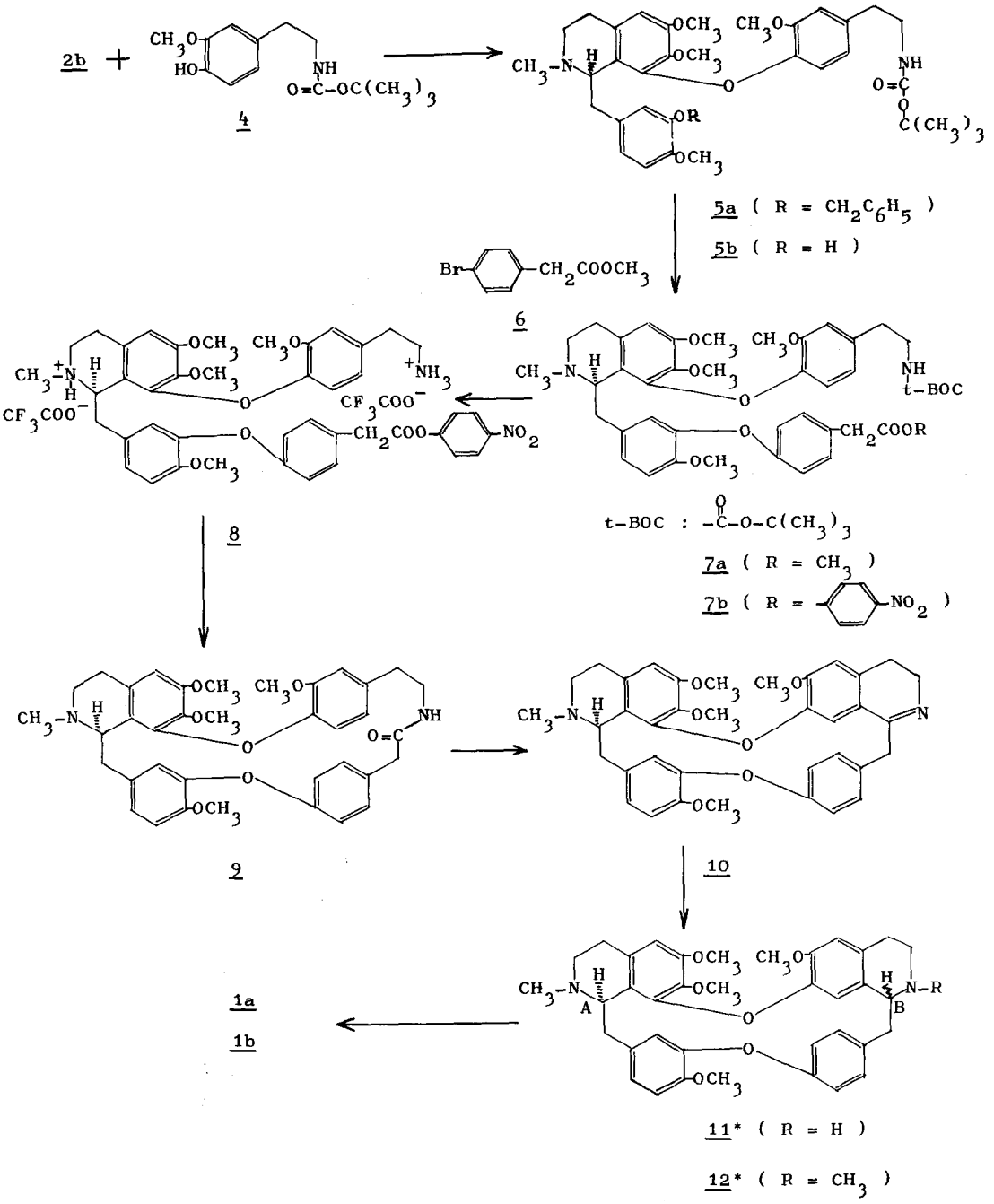
2a (R = H)

2b (R = CH_3)



3

R-(-)-Laudanidine



* Diastereomeric mixture with respect to the B-center.

Prior to this synthetic work starting from optically active O-benzyl-8-bromo-laudanidine (2b), the same synthetic sequence from the racemic base (2b: racemate) was achieved. In the latter case, reduction of 3,4-dihydroisoquinoline (10: racemate), obtained as an intermediate, with Zn-dil.H_2SO_4 in ethanol, followed by N-methylation proceeded stereoselectively to give dl-tetrandrine (1c: racemate). Since dl-tetrandrine has been isolated from the natural source and resolved into the optically active form (1c)[8], the present synthesis implies the total synthesis of optically active tetrandrine.

The synthetic route described in this communication seems to offer promise of a general synthetic route for the alkaloids of the oxyacanthine-berbamine series.

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3) M. Tomita, J. Kunitomo, Yakugaku Zasshi, 82, 734 (1962).

4) The Ullmann condensation was carried out in pyridine solution with solid K_2CO_3 and CuO was effectively employed as catalyst.

5) IR and NMR spectra of an amorphous powder or an oily substance marked with an asterisk showed reasonable patterns for the corresponding structure to each compound and homogeneity was also verified by thinlayer chromatography and NMR spectrum measurements.

6) The yield in each reaction in this communication is calculated from the starting material subtracted the recovered material.

7) Phaeanthine picrate was derived from limacine in our laboratory.

8) S.M. Kupchan, N. Yokoyama, B.S. Thyagarajan, J. Pharm. Sci., 50, 164 (1961).