THE SYNTHESIS OF dl-STEPORPHINE, 4-HYDROXYAPORPHINE TYPE ALKALOIDS.

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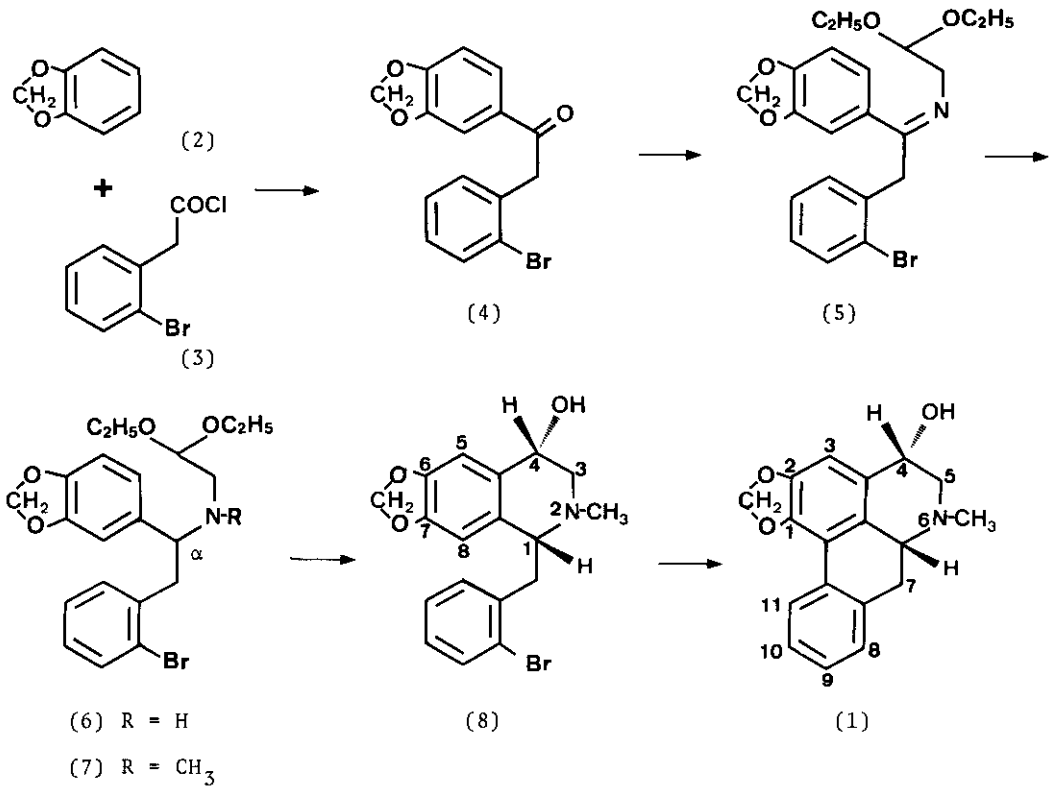
Abstract —— A 4-hydroxyaporphine type alkaloid, steporphine (1), has been stereospecifically synthesized for the first time.

Nine natural products of 4-hydroxyaporphine type alkaloids have been known[1,2]. Their structures, configuration and conformation have been determined by measurement of ^{1}H-NMR and specific rotation or ORD curve[2~4], and further confirmed by X-ray crystallographic analyses[5]. Until now, sntheses of this type of alkaloids have only consisted of the 4-hydroxylation by lead tetraacetate[6] or oxyvanadium trifluoride[7] of corresponding aporphine, which give dl-cataline. Their total synthesis has not been reported yet.

Two problems are encountered in synthesizing 4-hydroxy-1-benzyl-1,2,3,4-tetrahydroisoquinoline (4-OH-BTHIQ's) derivatives as starting materials for 4-hydroxyaporphine type alkaloids. One is the difficulty to prevent the direct formation of the isopavine type alkaloids and the other is the stereospecific selection of the configuration between C_1-H and C_4-H when these compounds (4-OH-BTHIQ's) are obtained from corresponding aminoacetaldehyde diethyl acetal derivatives by cyclization in concentrated hydrochloric acid. The first problem was solved by Dalton et al.[8], but the second problem was not solved even detailed study by Elliott et al.[9]. This communication reports the solution of both problems for the synthesis of 1-(2-bromobenzyl)-4-hydroxy-6,7-methylenedioxy-1,2,3,4,-tetrahydroisoquinoline (8) and the total synthesis of steporphine (1), which was isolated from *Stephania sasakii* Hayata (Menispermaceae)[10]. This is the first report of the total synthesis of an aporphine type alkaloid having a hydroxyl group at 4-position.



2-(o-Bromophenyl)-1-(3,4-methylenedioxy)acetophenone (4), prepared from 1,3-benzodioxole (2) and 2-bromophenylacetyl chloride (3) by carefully controlled Friedel-Crafts reaction, was condensed with aminoacetaldehyde diethyl acetal to give the corresponding ketimine (5). Eschweiler-Clarke N-methylation of α-(2-bromobenzyl)piperonylaminoacetaldehyde diethyl acetal (6), which is a reduction product of (5) with sodium borohydride, afforded N-methyl derivative (7) in more than 53.8% yield based on starting material (4). The derivative (7) was subjected to cyclization in concentrated hydrochloric acid as described by Bobbitt modifications cyclization[11] to afford 1-(2-bromobenzyl)-4-hydroxy-6,7-methylene-dioxy-1,2,3,4-tetrahydroisoquinoline (8) as colorless needless, mp 134∿135°C in 68.2% yield. The UV, IR, ^{1}H-NMR, MS spectra and elemental analyses of the compound showed that its formula was that of (8). In the ^{1}H-NMR spectrum, the signal which can be ascribed to hydrogen geminal to a hydroxyl group at C-4 appeared at δ 4.52 (m., change to triplet upon the addition of D_2O), and showed the cis relationship between C_1-H and C_4-H (in the case of the trans relationship, C_4-H

would be at δ 4.7∿4.8[9]). The signal of the aromatic proton at C-5 appeared at δ 6.82, which also proved the cis relationship between C_4-H and C_5-H (in the case of trans: C_5-H, above δ 7.05[9]). Accordingly, the performed alcoholic hydroxyl group was pseudoaxial by this cyclization.

Even when the mother liquor of the reaction product was carefully investigated, the diastereomer of compound (8) and corresponding isopavine type alkaloid were not found, showing that this cyclization has solved two problems for the synthesis of 1-(o-substituted benzyl)-4-hydroxy-1,2,3,4-tetrahydroisoquinoline derivative at one time. The explanation for the stereoselectivity is now under investigation.

Finally, irradiation of compound (8) in dilute hydrochloric acid and methanol as described for the photosynthesis of 7-hydroxyaporphine[12], produced dl-steporphine [(1), mp 172∿173°C, $C_{18}H_{17}NO_3$], which was identified by direct comparison of spectra (UV, IR, ^{1}H-NMR and MS) and TLC with those of the natural product.

This method can be adapted to the synthesis of other alkaloids of this type. This communication will be reported in the full paper.

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