Tetrahedron Letters,Vol.27,No.19,pp 2103-2106,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF A HYPOTHETICAL INTERMEDIATE IN THE BIOSYNTHESIS OF THE 13-METHYLBENZOPHENANTHRIDINE ALKALOIDS CORYNOLINE AND 14-EPICORYNOLINE AND THE B-SECOPROTOBERBERINE ALKALOID CORYDALIC ACID METHYL ESTER

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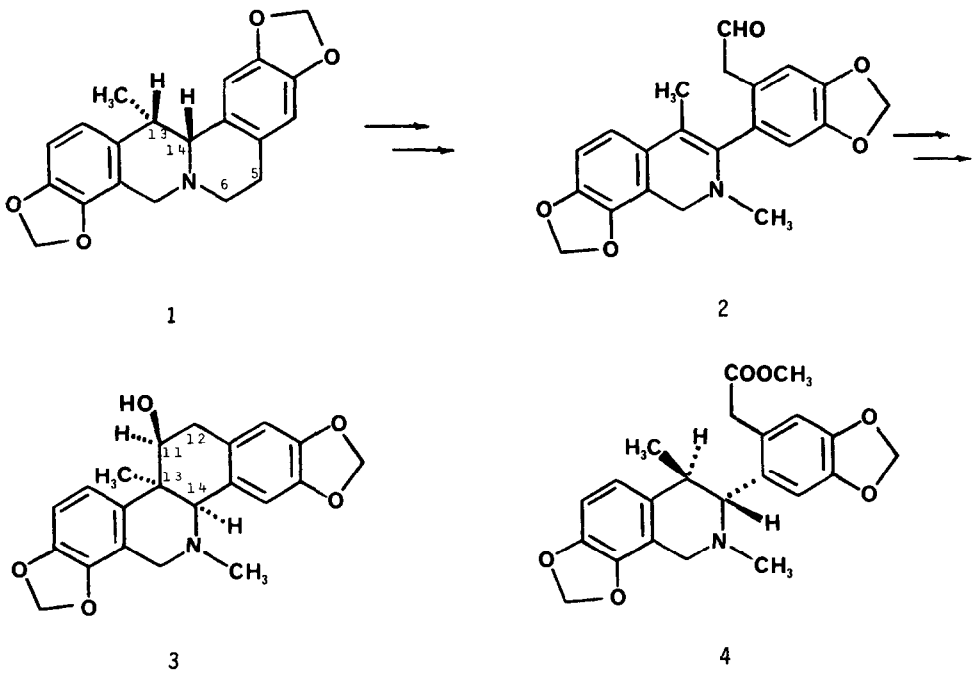
Abstract. A novel carbinolammonium chloride has been synthesized as a possible intermediate in the biosynthetic conversion of the 13-methylprotoberberine alkaloid (+)-tetrahydrocorysamine to the benzophenanthridine alkaloids (+)-corynoline, (+)-14-epicorynoline, and the B-secoprotoberberine alkaloid (+)-corydalic acid methyl ester.

The suggestion that the benzophenanthridines [e.g. (+)-corynoline **(3)**] arise biosynthetically from the protoberberines [e.g. (+)-tetrahydrocorysamine **(1)**][1] has been confirmed in several research groups.[2] There is general agreement that the transformation may proceed through an intermediate enamino aldehyde **2** (Scheme I), followed by an intramolecular nucleophilic addition of the enamine to the aldehyde and reduction of the resulting iminium ion.[2] The related isoquinoline alkaloid (+)-corydalic acid methyl ester **4** is presumably also derived from intermediate **2**.[3] Although evidence supporting the intermediacy of protoberberine N-methosalts,[2f,h] protopines,[2f] and 3-aryl-1,2,3,4-tetrahydroisoquinolines[3] has been presented in certain cases, the exact sequence of intermediates remains to be clarified. The transformation probably proceeds by initial N-methylation followed by oxidation of either C-6 or C-14. In view of this situation, we have executed the synthesis of the novel carbinolammonium structure **10** which would result from oxidation of C-6 of the N-methosalt derived from tetrahydrocorysamine (Scheme II).

The starting material **5** was previously obtained as an undesired cis diastereomer in the total synthesis of (±)-corydalic acid methyl ester.[4] Treatment of the nitrile **5** with methanol under acidic conditions afforded the methyl ester **6**. Selective reduction of the lactam functionality of **6** was performed with phosphorus oxychloride followed by sodium borohydride. Reduction of the ester group of **7** was carried out with diisobutylaluminum hydride at low temperature in methylene chloride solution,[5,6] resulting in the aldehyde **8** along with some of

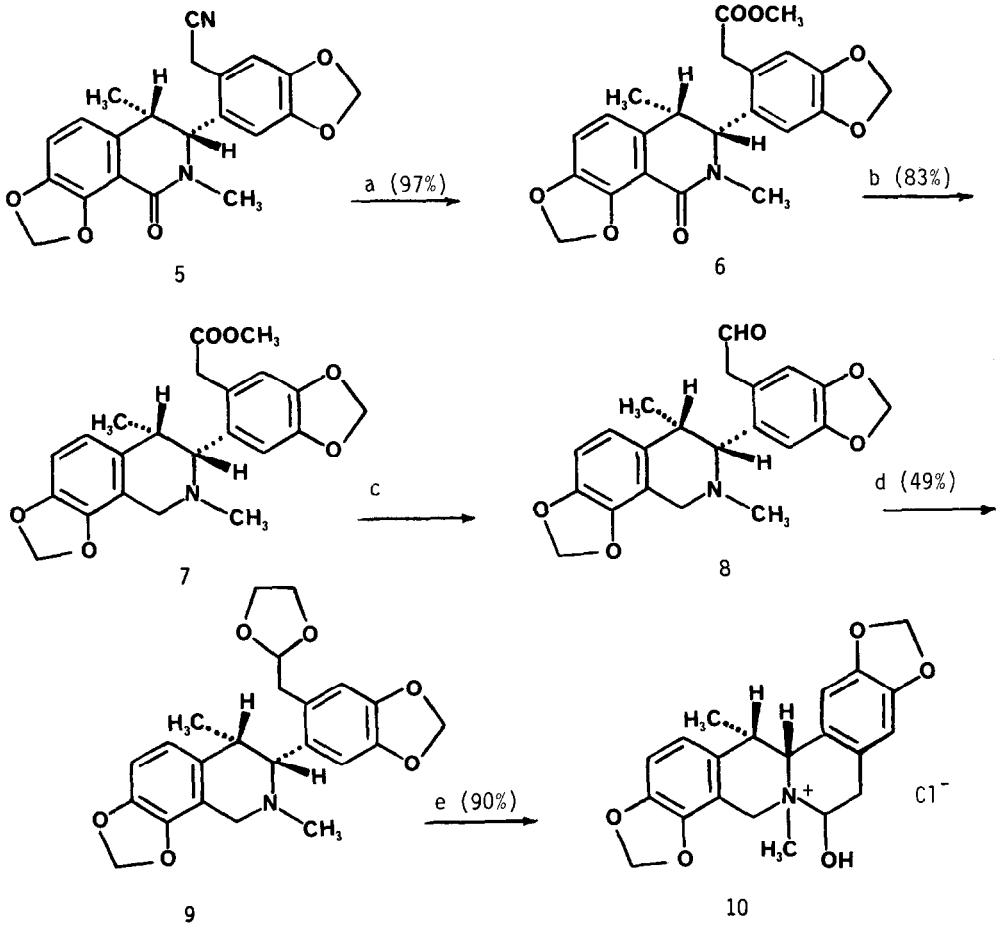
Scheme I



the corresponding alcohol. It became obvious during attempted purification that the amino aldehyde **8** was a very unstable substance, possibly because the acidity of the benzylic protons adjacent to the aldehyde and the basicity of the amino group facilitate an intermolecular aldol condensation reaction. The crude aldehyde **8** was therefore immediately converted to the ethylenedioxy acetal **9**, which could then be purified by silica gel chromatography, eluting with ethyl acetate-hexane (2:1). The acetal **9** itself is fairly unstable and prolonged storage is not advisable. In view of the fact that certain previously reported amino aldehydes were found to be extremely unstable except under acidic conditions[7], acetal **9** was hydrolyzed by a combination of aqueous hydrochloric acid and tetrahydrofuran, which produced a diastereomeric mixture of carbinolammonium chlorides **10.**

Four diastereomers of the carbinolammonium structure **10** are possible. The 200 MHz NMR spectrum of the crude product obtained after acid hydrolysis of the acetal **9** showed four singlets at δ 2.92, 3.02, 3.12, and 3.21 in an approximate ratio of 1:84:12:3, respectively. These signals have tentatively been assigned to the methyl groups of the four possible diastereomers. The major diastereomer[8] was purified by recrystallization from methanol. The relative configurations of the diastereomers, along with their possible equilibration and transformation into (+)-corynoline **(3)**, (+)-14-epicorynoline, and (+)-corydalic acid methyl ester **(4)** will be investigated.

Scheme II



[a]HCl, CH_3OH, -40 to -20 °C (2.25 h), 0 °C (17 h). [b](1) $POCl_3$, 60 °C (3 h); (2) $NaBH_4$, glyme, EtOH, 25 °C (12 h). [c]DIBAH, CH_2Cl_2, -78 °C (2 h). [d] $HOCH_2CH_2OH$, tosic acid, benzene, reflux (12 h). [e]HCl, THF 25 °C (0.5 h).

Analogous carbinolammonium structures have been reported from the transannular additions of tertiary amines to ketones under acidic conditions in ten-membered and also nine-membered rings found in certain protopine and pseudostrychnidine alkaloids, respectively.[9]

Acknowledgment. This investigation was supported by Grant GM30932, awarded by the National Institute of General Medical Sciences, DHHS.

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8. Mp 242-243 °C (dec); IR (KBr) 3400, 3000, 2900, 1490, 1475, 1450, 1380, 1255, 1135, 1050, 1020, 920 cm^{-1}; 80 MHz ^1H NMR (CF_3COOD) δ7.09 (s, 2 H), 6.93 (s, 1 H), 6.86 (s, 1 H), 6.13 (s, 4 H), 5.43 (t, 1 H, J = 7.5 Hz), 5.22 (d, 1 H, J = 5.3 Hz), 4.99 (d, 1 H, J = 15.8 Hz), 4.44 (d, 1 H, J = 15.8 Hz), 4.16 (m, 1 H), 3.43 (d, 2 H, J = 7.3 Hz), 3.07 (s, 3 H), 1.56 (d, 3 H, J = 7.4 Hz; CIMS, m/e (relative intensity) 368 ($M^+ - Cl^-$, 100).

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(Received in USA 21 January 1986)