THE STRUCTURE OF (+)-ISOCORYNOLINE

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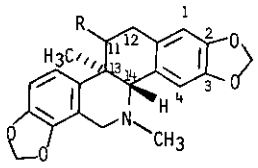
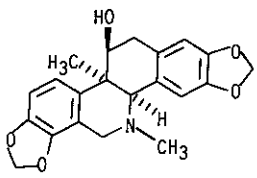
Abstract - (±)-14-Epicorynoline (5) and (±)-13-epicorynoline (4) are synthesized from a common intermediate 13. The identity of (+)-isocorynoline with (+)-14-epicorynoline is also demonstrated.

In 1973 the isolation of a variety of alkaloids from Corydalis incisa was reported.[1] These included two benzophenanthridines, (+)-isocorynoline and (+)-acetylisocorynoline, which were assigned structures 1 and 2. However, in a recent review of isoquinoline alkaloids, (+)-acetylisocorynoline was depicted as structure 3.[2] We are not aware of any evidence which supports the relative configuration assignment of the acetoxy-bearing carbon atom C-11 as shown in structure 3. In fact, the melting points of the two metabolites, (+)-isocorynoline (1, mp 232-233°C) and (+)-acetylisocorynoline (2, mp 205-207°C), are suspiciously close to those recorded for (+)-14-epicorynoline (5, mp 235-236°C, also known as base II) and (+)-14-epicorynoline acetate (6, mp 204-206°C).[3,4] Consequently, there appears to be some confusion regarding the identity of isocorynoline. The structures of 5 and 6 have been established beyond doubt by chemical correlation of (+)-14-epicorynoline (5) with (+)-corynoline (7) and also by an X-ray analysis of (+)-14-epicorynoline bromoacetate.[4,5] The present communication describes total syntheses of (±)-14-epicorynoline (5) and (±)-13-epicorynoline (4). These synthetic materials have now been compared with naturally occurring (+)-isocorynoline.

Deprotonation of compound 8[6] with lithium diisopropylamide in tetrahydrofuran-hexamethylphosphoramide at -78°C yielded an anion which on alkylation with methyl iodide gave the product 9 in 71% yield. Alkaline hydrolysis of 9 and cyclodehydration of 10 in refluxing acetyl chloride afforded the anhydride 11. Condensation of the anhydride 11 with piperonylidenemethylamine in benzene at room temperature provided the isoquinolone 12 [mp 165-167°C; NMR ($CDCl_3$) δ 8.30 (s, 1H, exchangeable with D_2O), 6.88 (d, 1 H, J = 8 Hz), 6.66 (d, 1 H, J = 8 Hz), 6.61-6.33 (m, 3 H), 6.14 (s, 2 H), 5.88 (s, 2 H), 4.77 (s, 1 H), 2.99 (s, 3 H), 1.37 (s, 3 H)] in 85% yield. The C-methyl group 12 appears at higher field (δ 1.37) than that of its diastereomer (δ 1.77), which was obtained when the condensation was performed at room temperature in methanol. Treatment of the acid chloride of 12 with diazomethane in diethyl ether at -10°C to room temperature during 1 h afforded the diazoketone 13 in 69% yield. Subjection of the diazoketone 13 to trifluoroacetic acid at 0°C for 1 min gave the benzophenanthridine 14 (mp 265-267°C) in 42% yield.





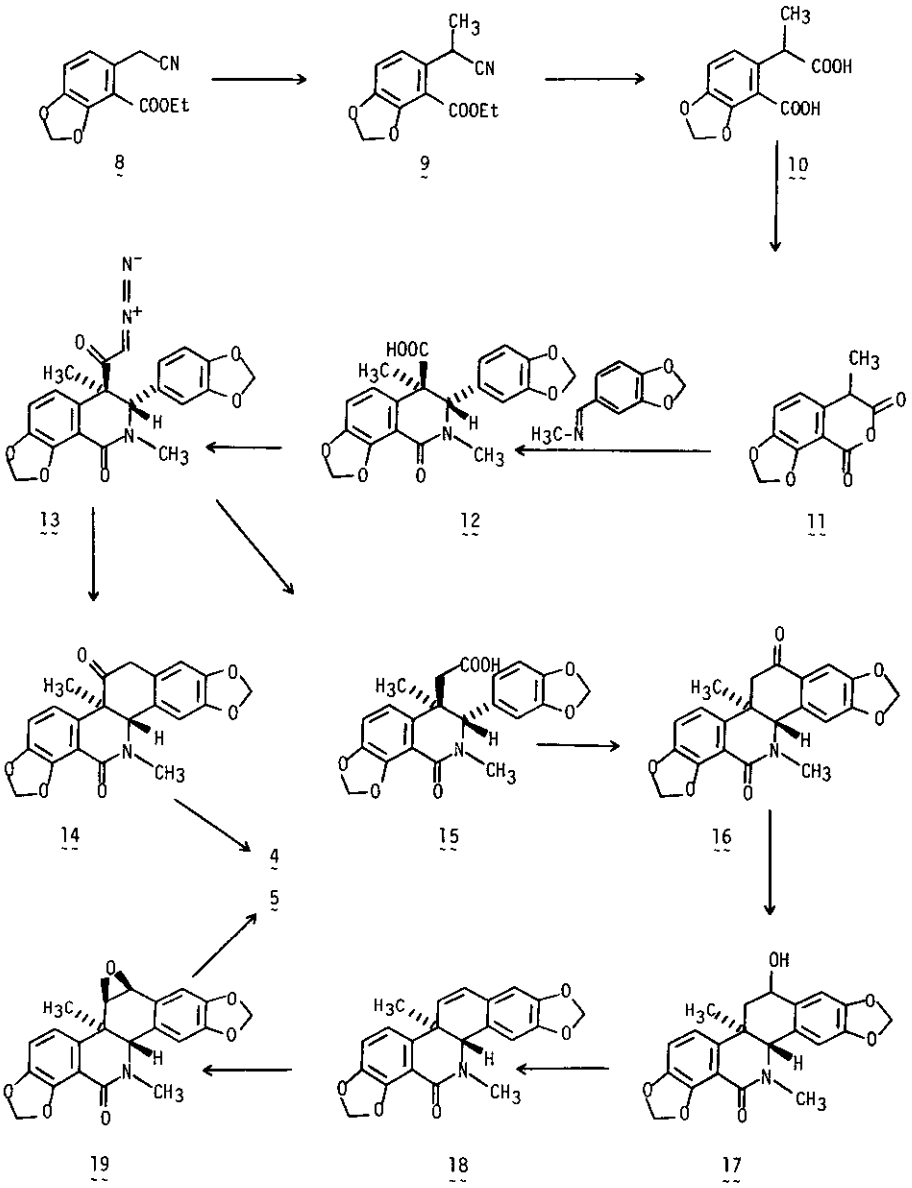
7

1, R= ~~ OH
2, R= ~~ OAc
3, R= |||| OAc
4, R= |||| OH
5, R= ▬ OH
6, R= ▬ OAc

Reduction of 14 with lithium aluminum hydride in refluxing dioxane provided compound 4 in 89% yield. Comparison of the 470 MHz ^{1}H NMR spectra of our synthetic compound 4 and authentic (+)-isocorynoline[7] revealed that (+)-isocorynoline is not (+)-4.

Several unsuccessful attempts were then made to convert compound 4 to (±)-14-epicorynoline (5). Treatment of 4 with triphenylphosphine, diethyl azodicarboxylate, and formic acid in tetrahydrofuran[8] gave back the starting material even when the mixture was heated at reflux. Efforts to displace the mesylate of the alcohol with a variety of oxygen-containing nucleophiles including potassium nitrite in dimethylsulfoxide or N,N-dimethylformamide,[9] tetra-n-butylammonium formate in acetone,[10] potassium acetate in hexamethylphosphoramide, and potassium hydroxide in ethanol uniformly resulted in the reisolation of the starting material and the alcohol 4. Efforts to introduce a double bond between C-11 and C-12 by dehydration of 4 with thionyl chloride in pyridine[4] or phosphorus oxychloride in pyridine[11] went unrewarded.

The diazoketone 13 was then subjected to an Arndt-Eistert synthesis which furnished the homologous acid 15 in 83% yield. Subjection of 15 to a mixture prepared by dissolving phosphorus pentoxide in methanesulfonic acid at 45°C gave the Friedel-Crafts product 16 in 84% yield.[12] Reduction of 16 with sodium borohydride in isopropanol at room temperature provided a mixture of alcohols 17. Dehydration of the major diastereomer with p-toluenesulfonic acid in refluxing benzene gave the alkene 18. The overall yield in the conversion of 16 to 18 was 79%. (±)-14-Epicorynoline (5, mp 174-176°C) was then obtained from 18 in 64% yield upon treatment of 18 with m-chloroperbenzoic acid in methylene chloride at room temperature for 2 h followed by reduction of the intermediate 19 using lithium aluminum hydride in refluxing tetrahydrofuran. The 470 MHz ^{1}H NMR spectrum of our synthetic compound 5 proved to be identical with that of both (+)-isocorynoline and (+)-14-epicorynoline.[13] This is the first total synthesis of (±)-14-epicorynoline.[14]


CN
COOEt
8
CH3
CN
COOEt
9
CH3
COOH
COOH
10
CH3
11
HOOC
H3C
H3C-N
12
N⁻
N⁺
13
COOH
15
16
4
5
OH
17
18
19

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7. We are grateful to Dr. G. Nonaka, Kyushu University, for a sample of (+)-isocorynoline.
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13. We are indebted to Dr. N. Takao, Kobe Women's College of Pharmacy, for a sample of (+)-14-epicorynoline.
14. All of the intermediates reported in this communication gave satisfactory IR, ^{1}H NMR, and mass spectra.

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