TOTAL SYNTHESIS OF (±)-CORYNOLINE AND (±)-6-OXOCORYNOLINE

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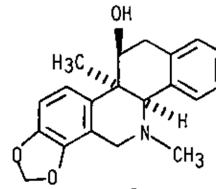
Abstract — The condensation of α-methyl-3,4-methylenedioxyhomophthalic anhydride (7) with piperonylidenemethylamine (8) is utilized as the key step in a total synthesis of (±)-corynoline (1) and (±)-6-oxocorynoline (2).

(±)-Corynoline,[1] (+)-corynoline (1),[2] and 6-oxocorynoline (2)[3] have been isolated from Corydalis incisa. The structure 1 of (±)-corynoline was proposed in 1963 on the basis of extensive chemical degradations, spectral evidence, and consideration of the biosynthesis.[4,5] It was subsequently confirmed by an X-ray analysis of the p-bromobenzoate.[6] The absolute configuration 1 of (+)-corynoline was determined by chemical correlation with (+)-14-epicorynoline (3),[2] whose absolute configuration was established by X-ray analysis.[7] The enamide photocyclization reaction was recently utilized as the key step in a total synthesis of (±)-corynoline (1).[8] We have lately been concerned with the possible extension of the methodology used in a synthesis of the related benzophenanthridine alkaloid (±)-chelidonine (4)[9] to the preparation of 13-methylated benzophenanthridines including (±)-corynoline (1). The critical question in this regard was whether or not the known reaction of homophthalic anhydrides with Schiff bases could be extended to the methylated derivative 7, thus creating the new quaternary center at C-4 present in the isoquinolone 9.

The trianion derived by treatment of 5 with three equivalents of lithium diisopropylamide in tetrahydrofuran-hexamethylphosphoramide at 0°C was methylated using methyl iodide. After acidic work-up, the homophthalic acid 6 was isolated in 42% yield. Cyclodehydration of 6 in refluxing acetyl chloride (6 h) gave the anhydride 7 in 78% yield. Condensation of the anhydride 7 with piperonylidenemethylamine (8) in methanol at room temperature for 1 h afforded the isoquinolone 9 [mp 238-240°C; NMR ($CDCl_3$-DMSO-d_6, 3:1) δ 9.67 (broad s, 1 H), 7.27 (d, 1 H, J = 8 Hz), 6.90 (d, 1 H, J = 8 Hz), 6.67 (m, 3 H), 6.13 (m, 2 H), 5.77 (s, 2 H), 4.60 (s, 1 H), 3.03 (s, 3 H), 1.77 (s, 3 H)] in 29% yield along with its trans diastereomer, which was also obtained in 66% yield. The C-methyl group of 9 appears at lower field (δ 1.77) than that of the trans diastereomer (δ 1.37). The diastereomeric isomer of 9 exhibits NMR ($CDCl_3$-DMSO-d_6, 3:1) signals at δ 9.33 (broad s, 1 H), 7.38-6.33 (m, 3 H), 6.95 (d, 1 H, J = 8 Hz), 6.72 (d, 1 H, J = 8 Hz), 6.20 (s, 2 H), 5.93 (s, 2 H), 4.92 (s, 1 H), 3.00 (s, 3 H), 1.37 (s, 3 H). The diazoketone 10 was obtained in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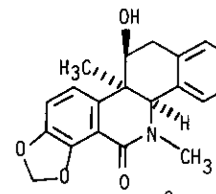
N
H
CH3

1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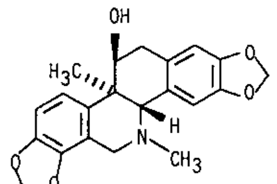
O

2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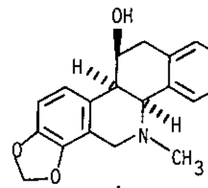
H
CH3

3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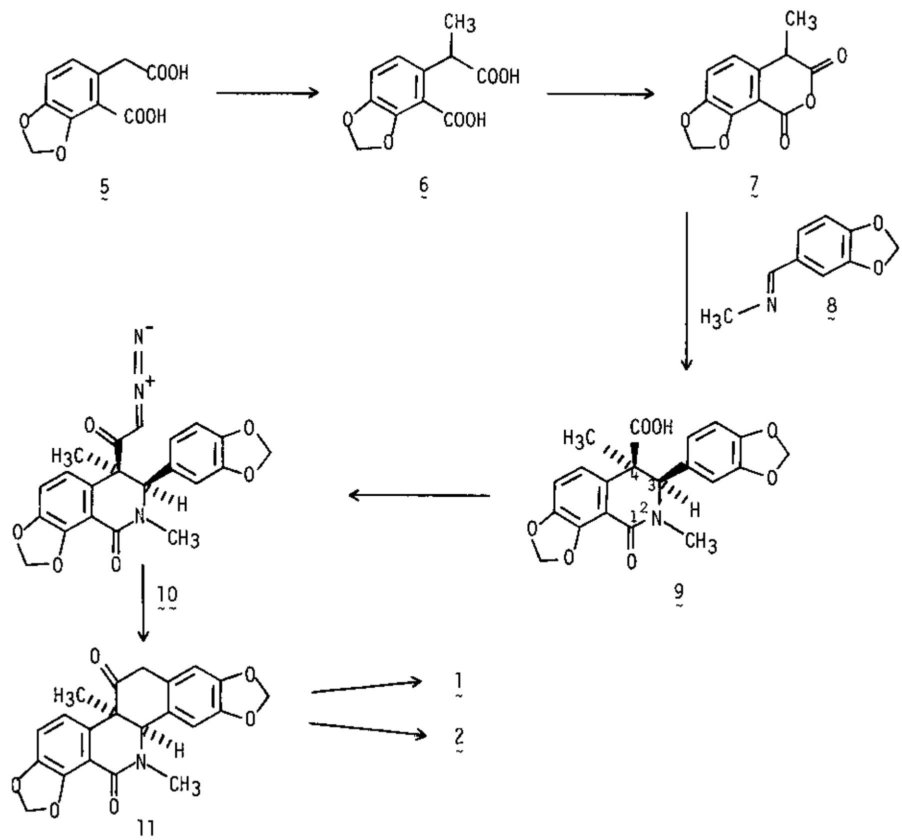
CH3

4


COOH
COOH
5
CH3
COOH
COOH
6
CH3
O
7
H3C
N
8
N-
N+
H3C
N
H
CH3
10
H3C
COOH
4
3
2
1
N
H
CH3
9
O
H3C
N
H
CH3
11
1
2

80% yield when a benzene solution of the acid chloride of 9 was added dropwise to a solution of diazomethane in diethyl ether at -10°C. Treatment of compound 10 with trifluoroacetic acid at 0°C for 10 min gave the benzophenanthridine 11 (mp 220-221°C) in 37% yield.[10] Reduction of 11 with lithium aluminum hydride in tetrahydrofuran at room temperature for 17 h afforded (±)-corynoline (1, mp 216-217°C, lit[1] mp 216-217°C) in 69% yield. The 470 MHz ^{1}H NMR spectrum of our synthetic (±)-corynoline is identical with that of an authentic sample.[11] Subjection of compound 11 to sodium borohydride in refluxing methanol for 1 h gave (±)-6-oxocorynoline (2, mp 310-312°C). The 470 MHz ^{1}H NMR spectrum of our synthetic (±)-6-oxocorynoline (2) also compares favorably with that of the natural product.[12]

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REFERENCES AND NOTES

1. C. Tani and N. Takao, Yakugaku Zasshi, 1962, 82, 594.
2. N. Takao, M. Kamigauchi, and K. Iwasa, Tetrahedron, 1979, 35, 1977.
3. G. Nonaka and I. Nishioka, Chem. Pharm. Bull., 1975, 23, 521.
4. N. Takao, Chem. Pharm. Bull., 1963, 11, 1306.
5. N. Takao, Chem. Pharm. Bull., 1963, 11, 1312.
6. T. Kametani, T. Honda, M. Ihara, H. Shimanouchi, and Y. Sasada, Tetrahedron Lett., 1972, 3729.
7. N. Takao, M. Kamigauchi, K. Iwasa, K. Tomita, T. Fujiwara, and A. Wakahara, Tetrahedron Lett., 1974, 805.
8. I. Ninomiya, O. Yamamoto, and T. Naito, J. C. S. Perkin I, 1980, 212.
9. M. Cushman, T.-C. Choong, J.T. Valko, and M.P. Koleck, J. Org. Chem., 1980, 45, 5067.
10. D.J. Beames and L.N. Mander, Aust. J. Chem., 1974, 27, 1257.
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