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TOTAL SYNTHESIS OF AMURINE

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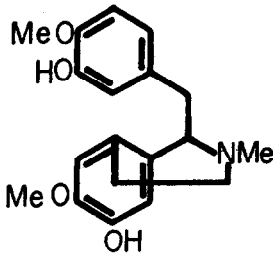
In 1957, Barton suggested that morphinandienone (salutaridine) (I) would be a key intermediate in biogenesis of morphine (II).[1] The synthesis of this dienone (I) with phenol oxidation of reticuline (III), the isolation of salutaridine (I) from Nature and the several feeding experiments by Barton and Battersby proved the Barton's hypothesis to be true.[2] On the other hand, several morphinandienone alkaloids, flavinantine (IV)[3] and amurine (V)[4], were isolated from Nature, and the phenol oxidation played an important role in the biogenesis of these type alkaloids. However, amurine and flavinantine would not be synthesised with phenol oxidation[5,6] in the laboratory on the ground of their structures since the former alkaloid (V) has a methylenedioxy group and the latter one (IV) has a phenolic hydroxyl group at the m-position to the oxidative coupling. We are currently investigating the general syntheses of the alkaloids[7,8] and wish to report the total synthesis of amurine (V) with the modified Pschorr reaction.

1-(2-Amino-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (VI), which was synthesised by usual method[9], was diazotised with a slightly excess of 10 % sodium nitrite solution and 1N sulphuric acid at 0° and the resulting diazonium salt was decomposed and coupled at 70°. The careful work up involving silica gel chromatography with chloroform-methanol (v/v 98 : 2) as an eluant, followed by alumina chromatography using benzene-chloroform (v/v 95 : 5) as an eluant, gave a small amount of (±)-dicentrine (VII) and (±)-amurine (V) in 1.23 % yield, the latter of which was confirmed by the following evidence.



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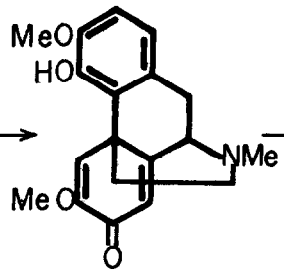

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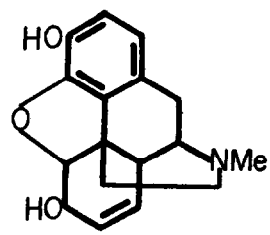

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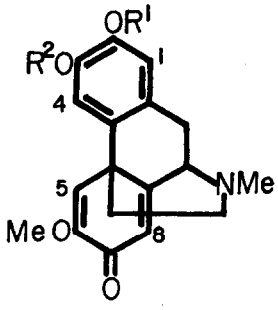
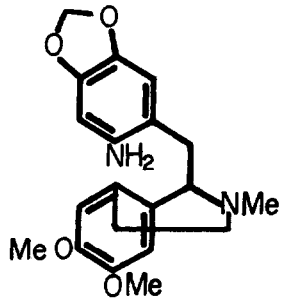


(Ⅳ) R^1=Me, R^2=H

(Ⅴ) R^1+R^2=$-CH_2-$



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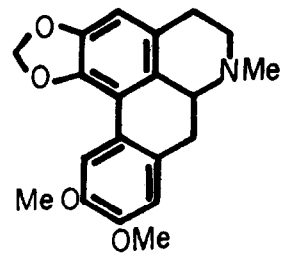

(Ⅶ)

The microanalysis of its methiodide (m.p. 222 - 224°) and the mass spectrometry of free base (M^+ : m/e 325) verified the molecular formula of $C_{19}H_{19}NO_4$ and it showed $\nu_{max}^{CHCl_3}$ 1675, 1645, 1620 and 1482 cm^{-1}, λ_{max}^{MeOH} 240 mμ (log ε: 4.24) and 290 mμ (log ε: 3.95), whose data well supported a cross-conjugated α-methoxycyclohexadienone system.[7,8,10,11] The n.m.r. spectrum (τ in $CDCl_3$) showed the presence of two methyl groups at 7.56 (singlet, NMe, 3H) and 6.21 (singlet, OMe, 3H), methylene protons at 4.09 (triplet, J = ~1 cps, $-OC\underline{H}_2O-$, 2H), two olefinic protons at 3.72 (singlet, C_8-H, 1H) and 3.68 (singlet, C_5-H, 1H) and two aromatic protons at 3.41 (singlet, C_1-H, 1H) and 3.18 (singlet, C_4-H, 1H).

The synthetic dienone and natural amurine were proved to be identical by i.r. (in $CHCl_3$) and n.m.r. (in $CDCl_3$) spectra and chromatographic comparison (R_f 0.60 ± 0.05; WAKOGEL, 0.2 mm; $CHCl_3$: MeOH = 5 : 1). These facts reveal that total synthesis of amurine (V) has been accomplished. Further studies on the same method of various aminoisoquinolines are in progress, particularly aimed at the synthesis of salutaridine (I).

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REFERENCES

1 D. H. R. Barton and T. Cohen, 'Festschrift Arthur Stoll', p. 114 (1957).

2 D. H. R. Barton, G. W. Kirby, W. Steglich, G. M. Thomas, A. R. Battersby, T. A. Dobson, and H. Ramuz, J. Chem. Soc., 2423 (1965); D. H. R. Barton, D. S. Bhakuni, R. James, and G. W. Kirby, J. Chem. Soc. (C), 128 (1967) and references cited herein.

3 C. Chamber and K. L. Stuart, Chem. Comm., 328 (1968).

4 H. Flentje, W. Döpke, and P. W. Jeffs, Naturwiss., 52, 259 (1965).

5 T. Kametani and K. Fukumoto, Japanese J. Pharm. & Chem., 35, 425 (1963); Farumasia, 4, 144 (1968).

6 A. I. Scott, Quart Revs., 19, 1 (1968).

7 T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, Chem. Comm., in press (1968).

8 T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, Chem. Comm., in press (1968).

9 Z. Kitasato and H. Shishido, Ann., 527, 176 (1937).

10 T. Kametani, H. Yagi, F. Satoh, and K. Fukumoto, J. Chem. Soc. (C), 271 (1968).

11 T. Kametani, F. Satoh, H. Yagi, and K. Fukumoto, J. Org. Chem., 33, 690 (1968).