BIOGENETIC-TYPE SYNTHESIS OF CLIVIMINE FROM CLIVACETINE

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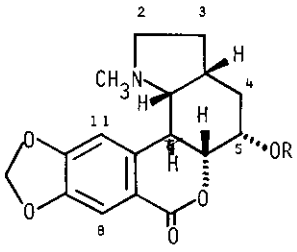
Abstract —— The structures of clivacetine (1) and clivatine (4) were confirmed by the partial synthesis of clivacetine (1) from clivonine (2). Clivimine (3) was obtained by biogenetic-type synthesis from clivacetine (1), which seems to be a biosynthetic precursor of clivimine (3).

Recently we reported[1] the isolation of a novel alkaloid clivacetine (1), having an acetoacetyl function, from Clivia miniata Regel.[2] (Amaryllidaceae), and proposed structure 1 for clivacetine on the basis of its physical and spectral data. This paper describes the partial synthesis of clivacetine (1) from clivonine (2) and the biogenetic-type synthesis of clivimine (3) from clivacetine (1), which seems to be a biosynthetic precursor of 3.

In order to confirm the structure of clivacetine (1), the partial synthesis of 1 from 2 was carried out as follows: heating a mixture of diketene (0.76 ml), 2 (90 mg), and chloroform (20 ml) in the presence of triethylamine (0.08 ml) (at 80° for 30 min.) gave O-acetoacetylclivonine (1) (55 mg, 48.2%) [mp 153-155° (lit.[1] mp 152-155°); $[\alpha]_D^{24}$ + 51.9° ($CHCl_3$) (lit.[1] $[\alpha]_D^{24}$ + 53.8° ($CHCl_3$); Found: C, 62.65; H, 5.81; N, 3.73%. Calcd. for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49%]. The spectral data and the melting point of O-acetoacetylclivonine were fully consistent with those of clivacetine (1)[1] from the natural source. Moreover, the partial synthesis of 1 presented the final proof of the structure (4) for clivatine,[3] since we have already reported[1] that O-acetylclivatine (5) derived from 4 is the same compound as that prepared by reduction of 1 with sodium borohydride, followed by O-acetylation of the resultant product.

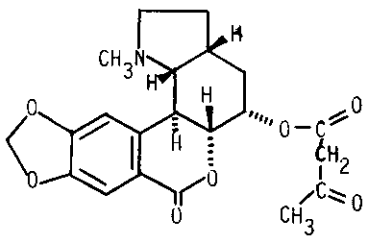


1 : R=$COCH_2COCH_3$

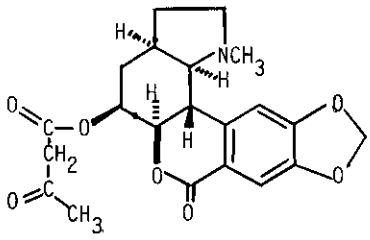
2 : R=H

4 : R=$COCH_2CH(OH)CH_3$

5 : R=$COCH_2CH(OAc)CH_3$



1



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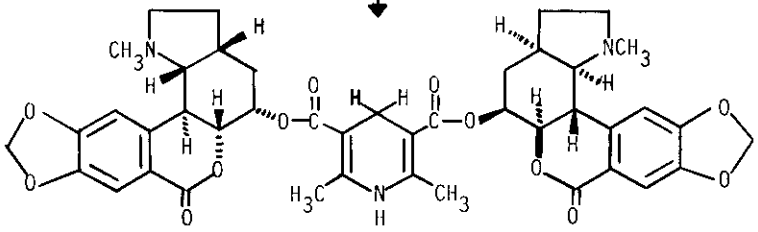

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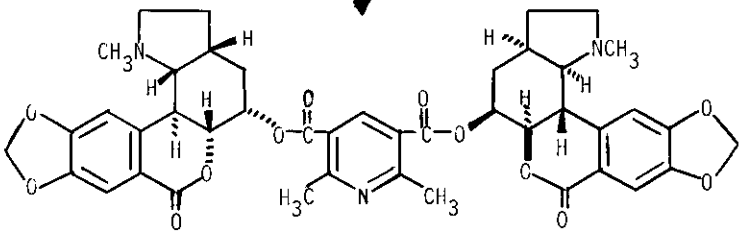
$NaNO_2$-AcOH



3

Clivacetine (1) has an interesting structure from a biogenetic viewpoint, since it seems to be a possible biosynthetic precursor of a unique Amaryllidaceae alkaloid clivimine (3)[4] having a 2,6-dimethyl-pyridine-3,5-dicarboxyl function. The biogenetic-type synthesis of 3 has been realized by the Hantzsch pyridine synthesis[5] of 1. Treatment of 1 (30 mg) in ethanol with 35% formalin (0.07 ml) and 25% ammonium hydroxide (0.26 ml) (at 100° for 30 min.) gave dihydroclivimine (6) (17 mg, 57.2%) as pale yellow needles, mp 233-237° (dec.)[IR (KBr) 1720 cm^{-1}; Mass m/e 795 (M^+)]. The NMR spectrum of 6 in $CDCl_3$ exhibited a characteristic pair of signals at δ 2.18 and 2.15 (total 6H) due to 2,6-dimethyl protons in the dihydropyridine ring, and other pairs of singals at δ 7.74 and 7.67 (total 2H, each s, 2 X C-11-H), 7.47 and 7.40 (total 2H, each s, 2 X C-8-H), and 2.52 and 2.48 (total 6H, each s, 2 X NCH_3). In this NMR spectrum the pairs of signals[6] of the aromatic protons at C-11 and C-8, C-, and N-methyl protons suggest that dihydroclivimine (6) may have two conformational isomers with respect to its dihydropyridine ring.

Dehydrogenation[5d] of 6 (8 mg) with sodium nitrite (20 mg) and acetic acid (0.5 ml) gave clivimine[1] (3.5 mg, 43.9%) [mp 254-256°(dec.)(lit.[1] mp 258-259° (dec.); IR (KBr) 1720 cm^{-1}; ORD $[M]^{21}$ (nm) (MeOH) 0° (342), -8821°(325)(trough), 0°(311), +17643° (296), +16761° (291), +28670° (278)(peak), +8821° (261) (trough), +105858° (241)(peak); NMR δ ($CDCl_3$) 8.52 (1H, s, γ-H in the pyridine ring), 7.48 (2H, s, 2 X C-11-H), 7.44 (2H, s, 2 X C-8-H), 6.06 and 6.03 (each 2H, d, J=2 Hz, 2 X AB type of OCH_2O), 5.54 (2H, m, 2 X C-5-H), 4.18 (2H, dd, J_{5a-11b}=12, J_{5a-5}=3 Hz, 2 X C-5a-H), 2.87 (6H, s, 2- and 6-CH_3 in the pyridine ring), and 2.34 (6H, s, 2 X NCH_3)]. This compound appeared identical with clivimine (3) from the natural source on direct comparison of their IR, ORD, and NMR spectra and in the mixed melting point test.

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3. In Heterocycles (1977, 6, 551), W. Döpke proposed that the structure of clivatine was 4, but gave no details about the presence of the β-hydroxybutyryl group in 4.

4. W. Döpke, M. Bienert, A.L. Burlingame, H.K. Schnoes, P.W. Jeffs, and D.S. Farrier, Tetrahedron Letters, 1967, 451.

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6. Similar pairs of signals were observed in the NMR spectrum of an ester of lycoramine and 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid : δ ($CDCl_3$) 2.16 and 2.12 (total 6H, each s, 2- and 6-CH_3 in the dihydropyridine ring), 3.82 and 3.80 (total 6H, each s, 2 X OCH_3) (unpublished result).

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