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SYNTHESIS OF THE BASIC STRUCTURE OF CORYNOLINE ALKALOID

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Abstract ——— Synthesis of the compound having the basic structure of corynoline from homophthalimide derivative is described.

Corynoline (I) and related alkaloids, which are representatives of the hydrobenzo[c]phenanthridine alkaloids. Onda and his co-workers who succeeded in a conversion of a protoberberine alkaloid into an analogue of corynoline.[1)]

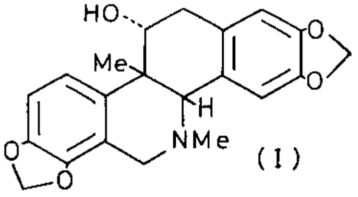
Ninomiya and his co-workers reported the first total synthesis of corynoline and 12-hydroxycorynoline by enamide photocyclisation.[2)]

In the connection with our synthetic studies on benzo[c]phenanthridine alkaloids from homophthalimide derivatives, we have investigsted the synthesis of the basic structure of corynoline, which involves synthesis of 4,4-disubstituted iscarbostyril derivative (IV) from 4-substituted homophthalimide derivative (II).[3)]

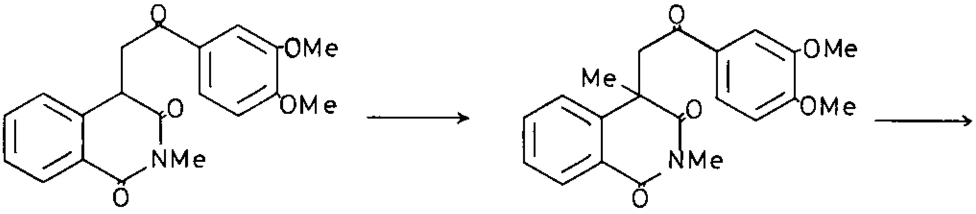
Methylation of 4-(3,4-dimethoxyphenacyl)-2-methylhomophthalimide (II) with methyl iodide in the presence of NaH gave 4-(3,4-dimethoxyphenacyl)-2,4-dimethylhomophthalimide (III) in 90% yield, mp 167-168°; ν_{max} ($CHCl_3$) 1700 and 1650 cm^{-1}; δ ($CDCl_3$) 1.60 (3H, s, C-CH_3), 3.44 (3H, s, N-CH_3), 3.82, 3.92 (3H each, s, O-CH_3x2); m/e 367 (M^+).

Treatment of the imide (III) with sodium borohydride afforded the 4,4-disubstituted 3-hydroxyisocarbostyril derivative (IV) in 90% yield; mp 149-151°; ν_{max} (nujol) 3400 and 1640 cm^{-1}; δ ($CDCl_3$) 1.52 (3H, s, C-CH_3), 3.30 (3H, s, N-CH_3), 3.58, 3.80 (3H each, s, O-CH_3x2); m/e 353 ($M-18^+$).

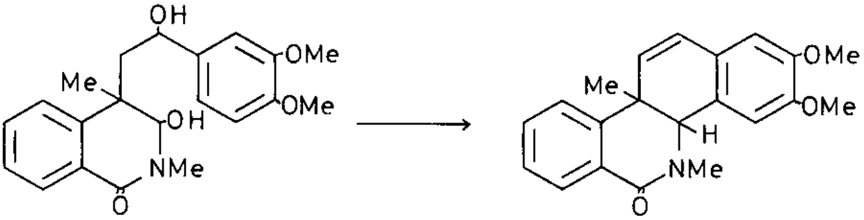
The isocarbostyril derivative (IV) was stereoselectively converted with p-toluensulfonic acid or hydrochloric acid in refluxing benzene into the 11,12-didehydrolactam (V) in 90% yield; mp 229-230°; ν_{max} (nujol) 1640 cm^{-1}; δ ($CDCl_3$) 1.51 (3H, s, C-CH_3), 3.42 (3H, bs, N-CH_3), 3.75, 3.78 (3H each, s, O-CH_3x2), 6.12



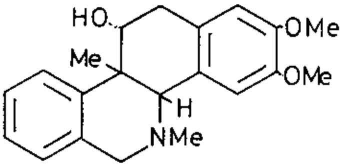
(I)



(II)　　(III)



(IV)　　(V)



(VI)

and 6.48 (2H, ABq, J=10Hz, 11- and 12-H); m/e 335 (M^+).

Assignment of the cis B/C ring fusion in the 11,12-didehydrolactam (V) is confirmed by Nuclear Overhauser effect (NOE)$^{1)}$ (8%) between the 4b-H (δ4.42) and the 10b-Me group (δ1.51) in the NMR spectrum (CF_3CO_2D) of the 11,12-didehydrolactam (V).

This stereoselective formation of the 11,12-didehydrolactam (V) suggested that this reaction occurs from the less steric hindrance, the anti side to the methyl group at C-4.

Thus, the 11,12-didehydrolactam (V) possesses the same B/C ring fusion as that of corynoline and also the C-11 and C-12 double bond which is useful for the hydroxy group to be introduced at C-11.$^{1,2)}$

The 11,12-didehydrolactam (V) was converted into the same basic structure of the corynoline group of alkaloid (VI) by Ninomiya *et al.*$^{2)}$

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