

TOTAL SYNTHESIS OF THE ALKALOID HOMOCHELIDONINE

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Homochelidonine (I) was synthesised for the first time by the route including enamide photocyclisation.

Homochelidonine (I), isolated from Chelidonium plants and shown to have the structure (I) by Späth¹ and Bersch², is one of the representative alkaloids of hexahydrobenzo[c]phenanthridine type along with chelidonine (II). Only a few synthetic achievements have been reported on chelidonine^{3a}, corynoline^{3b}, and its analog^{3c}. However, this alkaloid (I) remained hitherto untouched from attack of synthetic chemists.

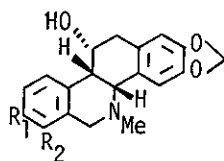
As an extension of our synthetic study on the hexahydrobenzo[c]phenanthridine alkaloids, we now report the first total synthesis of homochelidonine (I) by the route which we have just developed.⁴

The enamide (III), m.p. 140-141°, ir ν max 1635 cm^{-1} , was prepared quantitatively from 1-methylimino-6,7-methylenedioxy-tetralin by acylation with 1,2,6-trimethoxybenzoyl chloride.

Irradiation of a methanolic solution (0.02 M) of the enamide (III) with a high pressure mercury lamp at room temperature afforded a mixture of two photocyclised products (IV and V) in 18 and 19 % yields respectively due to non-selectivity on the direction of cyclisation⁵. Their spectral data [the methoxy-migrated lactam (IV)⁶, m.p. 165-167°, ir ν max 1640 cm^{-1} , nmr δ 2.90 (3H, s, 4b-OMe), and the didehydrolactam (V), m.p. 198.5-200°, ir ν max 1640 cm^{-1} , nmr δ 2.73 (4H, s, 11-H₂ and 12-H₂)] were enough to deduce their structures. The methoxy group of the lactam (IV) was readily eliminated under acidic condition and the structure of the didehydrolactam (V) was unambiguously established by the conversion into oxychelerythrine (VI)⁷ upon 2 hr's treatment with Pb(OAc)₄ (2 moles) in benzene under reflux.

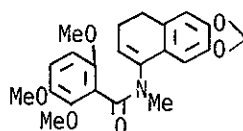
However, oxidation of V with Pb(OAc)₄ (4 moles) in benzene at refluxing temperature for 4 hrs brought about introduction of an acetoxy group⁸ into the 12-position, yielding the 12-acetoxylactam (VII) as glassy powder, ir ν max 1760 cm^{-1} , in 92 % yield. After hydrolysis of VII with KOH-MeOH, oxidation of the resulting 12-hydroxylactam (VIII) with CrO₃-H₂SO₄⁹ afforded the ortho-quinone (IX) as purple crystals, m.p. 222-225°, ir ν max 1690, 1670, 1640 cm^{-1} , in 53 % yield from VII.

Lithium aluminium hydride reduction of the quinone (IX) followed by catalytic hydrogenation of a double bond at the ring

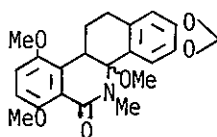


(I) $R_1 = R_2 = \text{OMe}$

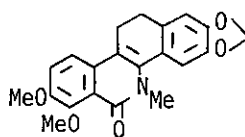
(II) $R_1 + R_2 = -\text{OCH}_2\text{O}-$



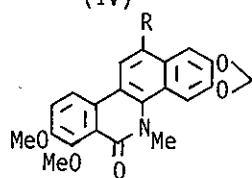
(III)



(IV)



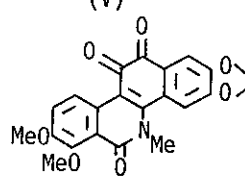
(V)



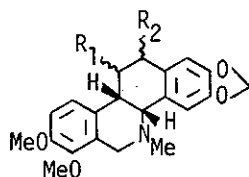
(VI) $R = \text{H}$

(VII) $R = \text{OAc}$

(VIII) $R = \text{OH}$



(IX)



(X) $R_1 = \text{OH}, R_2 = \text{OH}$

(XI) $R_1 = \text{OH}, R_2 = \text{OAc}$

(XII) $R_1 = \text{OMe}, R_2 = \text{OAc}$

(XIII) $R_1 = \text{OH}, R_2 = \text{OMe}$

junction with PtO_2 in EtOH afforded the BC-cis diol (X)⁴ as brown oil, ir ν max 3600 cm^{-1} , nmr δ 4.36 (2H, m, 11-H and 12-H), 3.38 (1H, d, $J=4\text{Hz}$, 4b-H), 2.98 (1H, t-like, $J=4\text{Hz}$, 10b-H), in 12 % yield.

Acetylation⁴ of the diol (X) with Ac_2O in CHCl_3 at room temperature afforded the 12-monoacetylated product (XI), m.p. $190-195^\circ$ (dec), ir ν max $3450, 1725\text{ cm}^{-1}$, nmr δ 6.00 (1H, d, $J=8\text{Hz}$, 12-H), 4.55 (1H, d-d, $J=10, 8\text{Hz}$, 11-H), 2.96 (1H, d-d, $J=10, 3\text{Hz}$, 10b-H), which was then mesylated to yield the corresponding 11-mesylate (XII), ir ν max $1730, 1360, 1180\text{ cm}^{-1}$.

Hydrolysis of the mesylate (XII) with 5% KOH-MeOH under reflux for 1 hr. afforded the 11-hydroxy-12-methoxyamine (XIII)⁴ in 94 % yield from the diol (X) [(XIII), m.p. $197-199^\circ$ (dec), ir ν max 3200 cm^{-1} (very broad), nmr δ 4.38-4.20 (2H, m, 11-H and 12-H), 3.89 (6H, s, $\text{OMe} \times 2$), 3.62 (3H, s, OMe), 3.53 (1H, d, $J=3\text{Hz}$, 4b-H), and 3.24 (1H, t-like, $J=3\text{Hz}$, 10b-H)], which was then subjected to hydrogenolysis using 40% Pd-C in 10% HCl solution in the presence of 70% HClO_4 under 5-6 atm. pressure. Upon chromatographic separation, the 11 α -alcohol as colourless cubes, m.p. $192-193.5^\circ$, was obtained. The identity of I with natural homochelidonine¹⁰ was provided by direct comparisons on both tlc and ir spectra.

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