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A SYNTHESIS OF (±)-DIHYDRODEOXYEPIALLOCERNUINE BY APPLICATION OF A FACILE HOFMANN-LOEFFLER TYPE OF PHOTOCYCLIZATION

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Isopelletierine(3a) which is proved to be a precursor in the biosynthesis of cernuine(1), was converted into the quinolizidine(10a), whose N-chloro derivative(10b) was irradiated with a 300W high pressure mercury lamp in ether in the absence of strong acid to readily afford the entitled compound(2) as the free base with no base treatment.

Cernuine is an alkaloid isolated from *Lycopodium cernuum* L., whose structure was proposed by Ayer et al. to be (1=1a).[1] They also succeeded in the synthesis of (±)-dihydrodeoxyepiallocernuine(2=2a), providing the strong support for the stereochemistry assigned to these alkaloids.[1c]

We now report a new synthesis of the entitled compound(2) starting from isopelletierine(3a), an important precursor in the biosynthesis of these alkaloids,[2] which was prepared on condensation of the iminoether derived from α-piperidone with acetylacetone, followed by reduction and oxidation.[3]

N-Acetylisopelletierine(3b) which was obtained as an oil(M^+ 183, 80.7% yield) on treatment of isopelletierine(3a) with acetyl chloride in 10% NaOH solution, was refluxed with $Et_3O^+BF_4^-$ in methylene chloride at 45° for 2 hrs,[4] to which solution of (4) BF_3-etherate was added, and the whole mixture was refluxed for further 6 hrs to give (5)(m.p. 133°, M^+183) in 34.6% yield. The compound(5) was heated with t-BuOK in t-BuOH at 90° for 3 hrs to furnish (6) as an oil (M^+165, IR ν_{max}^{neat} 1680 and 1630 cm^{-1}; UV λ_{max}^{EtOH} 255 mμ) in 78.9% yield on purification by chromatography on alumina. A better yield (62% from 3b) of (6) was obtained when the crude product(4) which was prepared from (3b) according to the above procedure, was heated with t-BuOK in t-BuOH at 90° for 2.5 hrs without isolation of (5). Also, when heated with $Al(O\ t\text{-}Bu)_3$ in xylene at 150°, (3b) afforded (6a) as an oil[M^+ 165; IR ν_{max}^{neat} 1630 cm^{-1}; UV λ_{max}^{EtOH} 323 mμ; NMR δ4.75(1H, s, vinyl proton), 1.95(3H, s, $-CH_3$)], alternatively, instead of (6) or any other intermolecular aldol condensation product.[2]

The lactam(7) as an oil(M^+167, IR ν_{max}^{neat} 1630 cm^{-1}; ca. 100% yield) which was obtained by hydrogenation of (6) at 4 atm. pressure with Adams' catalyst in ethanol, was condensed with α-picolyl lithium in THF at −40° for 3 hrs to give the compound(8), colorless oil[M^+242; IR ν_{max}^{neat} 2800, 1610, 1592 and 1545 cm^{-1}; UV λ_{max}^{EtOH} 320 mμ(shifted to 265 mμ on addition of 1N-HCl); NMR δ0.95 (3H, d, $-CH_3$), 6.35(1H, s, vinyl proton), 7.0(3H, m, pyridyl protons) and 8.35(1H, d, pyridyl proton); 89.9% yield], which was submitted to hydrogenation with palladium charcoal in methanol to yield (9) as an oil[m/e 243(M-1), 152(base peak), 110; IR ν_{max}^{neat}

2800, 2750, 1590 and 1582 cm^{-1}; UV λ_{max}^{EtOH} 264 mμ; NMR δ0.8(3H, d, -C$\underline{H}_3$), 7.3(3H, m, pyridyl protons) and 8.48(1H, d, pyridyl proton), ca. 100% yield]. The pyridine part of (9) was hydrogenated at 4 atm. pressure with Adams' catalyst in acetic acid to afford the piperidylmethylquinolizidine(10) as an oil[m/e 250(M$^+$), 152(base peak), 110 and 84; IR ν_{max}^{neat} 3300, 2800 and 2750 cm^{-1}; 80% yield].

The Hofmann-Loeffler type of photocyclization of (10) was attempted with expectation to obtain (2=2a) in preference to (11), because the easiness of hydrogen abstraction on the neighboring carbons to the nitrogen was anticipated,[5] although five-membered ring formation is favored in the usual Hofmann-Loeffler reaction.[6~8] Formation of (12) might be also excluded on account of difficult steric requirement, though the high selectivity for the tertiary hydrogen abstraction to form the radical at C-13 should be possible. Thus, the compound(10b) which was prepared from (10a) by action of N-chlorosuccinimide in ether,[6] was irradiated with a 300W high pressure mercury lamp in 95% sulfuric acid or in trifluoroacetic acid,[7] but any appreciable amount of product was not obtained. Therefore, the amine(10a) was mixed with N-chlorosuccinimide in ether *in situ*, and the mixture was immediately irradiated with the above mercury lamp in a current of nitrogen at room temperature for 5 hrs, during which time the colorless precipitate(10a-dihydrochloride) deposited. After the precipitate was filtered off and the solvent was removed from the filtrate, the residue was extracted with n-pentane to separate the insoluble succinimide, and n-pentane was evaporated from the extract to furnish the cyclized product(2=2a) as the free base, m.p. 63-64.5°(lit.[1c] m.p. 62-64°), picrate, m.p. 177-178°, in 30% yield, which was identified with the authentic specimen generously provided by Professor Ayer by mixed melting point determination and by direct comparison of the spectral data of both samples.

The features of the present photocyclization are remarkably different from those of the known Hofmann-Loeffler reaction in the following respects:

1. The 1,3-diaza six membered ring was exclusively generated instead of the five membered ring seen in (11), suggesting that the present cyclization did not involve the intramolecular 1,5-hydrogen shift.[6~8]
2. Any strong acid was absent, which means that the aminium radical as an key intermediate for the propagation sequence was not present in this reaction.[6]
3. Cyclization readily occurred with no base treatment to give the free base of the product.

These features suggest that the present reaction must not have proceeded via the mechanism for the usual Hofmann-Loeffler reaction proposed by Wawzonek[8] and scrutinized by Corey.[6] The availability of the present procedure should be limited to generation of 1,3-diaza, -oxaza and -thiaza cyclic derivatives, which will be published in the near future.

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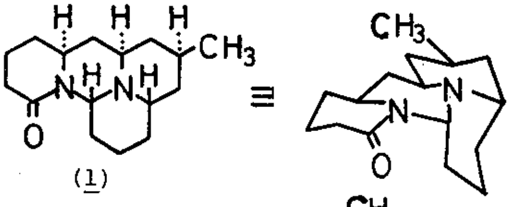
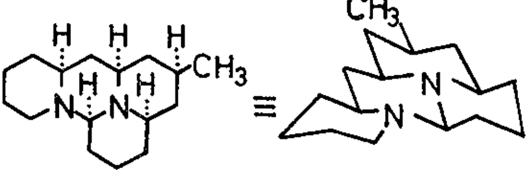
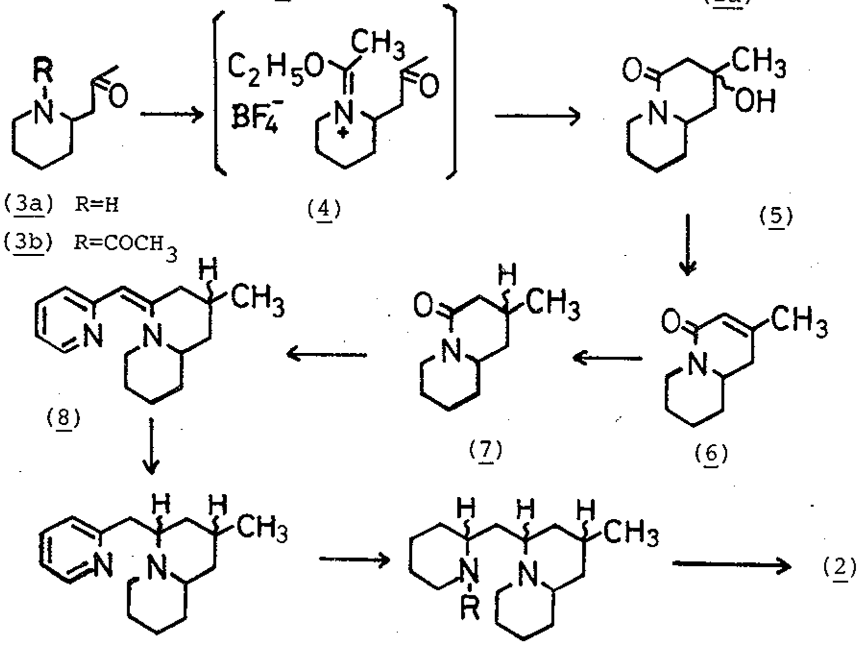


(1) (1a)



(2) (2a)



(3a) R=H

(3b) R=COCH$_3$

(4)

(5)

(6)

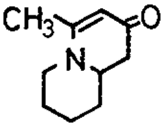
(7)

(8)

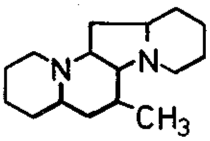
(9)

(10a) R=H

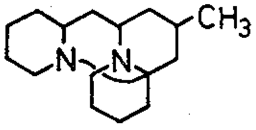
(10b) R=Cl



(6a)



(11)



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