# STEREOSELECTIVE TRANSFORMATION OF LYCORINE TO DEMETHYLUNGIMINORINE AND HIPPAMINE (2-O-METHYLLYCORINE) TO UNGIMINORINE

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Ungiminorine, an alkaloid of Ungernia minor, was chemically synthesized from lycorine by the route similar to that suggested in the biosynthesis of narcissidine from galanthine. This transformation constitutes the total synthesis of ungiminorine in a formal sense.

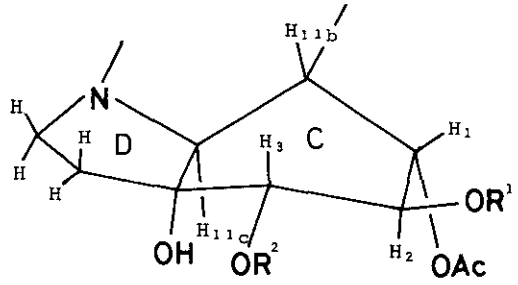
Ungiminorine, an alkaloid of Ungernia minor[1,2], is considered as IIIa[3] from the spectral analogy with narcissidine (IIIb). They and the related alkaloid, parkacine (IIIc), were suggested to be biosynthesized from the corresponding lycorine alkaloids (Ia-c), the widely occurring subgroup of skeletal variants found in Amaryllidaceae, via the α-epoxide (II) or its equivalent, since Sempre Avanti daffodil converted galanthine (Ib) into narcissidine (IIIb) with loss of pro-S hydrogen at $C_4$[4].

Lycorine is the alkaloid known to be vulnerable to various chemical oxidations. Usually the product is a mixture of fully aromatized compounds[5]. We found that a strictly controlled oxidation of diacetyllycorine proceeds as suggested in the above biosynthetic pathway . This finding made possible the chemical transformation of lycorine to ungiminorine alkaloids.

Very short oxidation (2.5 min.) of diacetyllycorine (Ie) with excess of potassium permanganate in acetone-water yielded a glycol-lactam (IVa), m.p. 232-237°, $\nu_{max}$(Nujol): 3400, 1740, and 1660 $cm^{-1}$, as a major product (18%) together with diacetyllycorine-lactam (V)[6] and C-aromatized compound (VIa)[7], m.p. 248-252°, $\lambda_{max}$(EtOH): 243 (ε=35,700) and 275 nm (ε=16,100). V was convertible in high yield to IVa by further oxidation in a similar condition and IVa was stable on treatment with 4% $H_2SO_4$-EtOH. The structure and stereochemistry of IVa were

established from the detailed analysis of its $^1$H-N.M.R. spectrum as shown in Fig. 1[8], showing α-orientation of the cis-glycol moiety and the distorted boat conformation of the ring C. Neither chair conformations nor β-orientation of the cis-glycol function would give the coupling constants shown in Fig. 1. This assignment was confirmed by conversion of IVa to demethylungiminorine (IIId).

Acetylation of IVa with acetic anhydride and pyridine gave the triacetate (IVb) (90%), gum, and a tetraacetate (IVc) (6%), m.p. 258-261°. On treatment with thionyl chloride and pyridine at room temperature, IVb gave the dehydrated compound (VIIa) in 91% yield. Appearence of an olefinic proton signal at δ6.06 ppm (1H, m.) in the N.M.R. spectrum of VIIa indicated the formation of double bond at $C_{3a}$-$C_4$. Lithium aluminum hydride reduction of VIIa in tetrahydrofuran afforded, in 86% yield, the base corresponding to demethylungiminorine (IIId), m.p. 210° (decomp.), which formed the triacetate (IIIe), m.p. 216-218° (decomp.). Its mass spectral fragmentation pattern was in agreement with that expected from the reported fragmentation of narcissidine[9].




IVa: $R^1$= Ac, $R^2$= H
IVe: $R^1$= Me, $R^2$= Ac

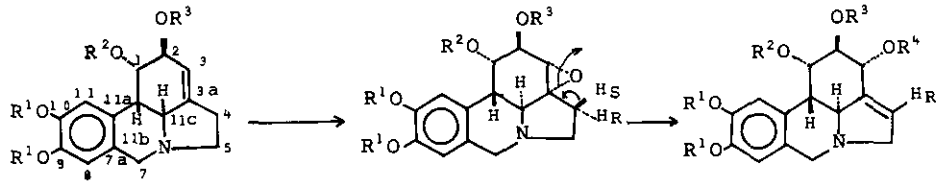
Chemical Shift (ppm)

| | $H_1$ | $H_2$ | $H_3$ | $H_{11b}$ | $H_{11c}$ |
|---|---|---|---|---|---|
| IVa | 5.58 (dd) | 5.12 (dd) | 3.88 (d) | 3.09 (dd) | 4.00 (d) |
| IVe | 5.72 (dd) | 3.61 (dd) | 5.22 (d) | 3.24 (dd) | 3.97 (d) |

First Order Coupling Constant (Hz)

| | $J_{1,2}$ | $J_{2,3}$ | $J_{1,11b}$ | $J_{11b,11c}$ |
|---|---|---|---|---|
| IVa | 2.5 | 10.0 | 3.5 | 14.0 |
| IVe | 2.0 | 8.3 | 3.0 | 14.0 |

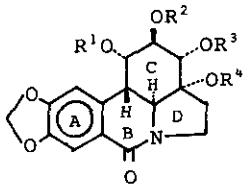
Fig. 1. Analyses of $^1$H-N.M.R. spectra (in $CDCl_3$, 100MHz) of IVa and IVe.



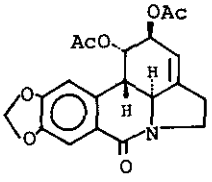
(I) (II) (III)

a:$R^1$-$R^1$= $CH_2$, $R^2$= H, $R^3$= Me
b:$R^1$,$R^3$= Me, $R^2$= H
c:$R^1$= Me, $R^2$= $R^3$= H
d:$R^1$-$R^1$= $CH_2$, $R^2$= $R^3$= H
e:$R^1$-$R^1$= $CH_2$, $R^2$=$R^3$= Ac
f:$R^1$-$R^1$= $CH_2$, $R^2$= Ac, $R^3$= Me

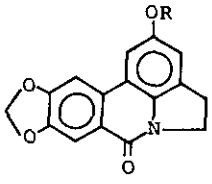
a:$R^1$-$R^1$= $CH_2$, $R^2$= $R^4$= H, $R^3$= Me
b:$R^1$= Me, $R^2$= $R^4$= H, $R^3$= Me
c:$R^1$= Me, $R^2$= $R^3$= $R^4$= H
d:$R^1$-$R^1$= $CH_2$, $R^2$= $R^3$= $R^4$= H
e:$R^1$-$R^1$= $CH_2$, $R^2$= $R^3$= $R^4$= Ac



(IV)



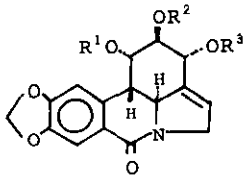
(V)



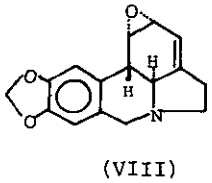
(VI)

a:$R^1$= $R^2$= Ac, $R^3$= $R^4$= H
b:$R^1$= $R^2$= $R^3$= Ac, $R^4$= H
c:$R^1$= $R^2$= $R^3$= $R^4$= Ac
d:$R^1$= Ac, $R^2$= Me, $R^3$= $R^4$= H
e:$R^1$= $R^3$= Ac, $R^2$= Me, $R^4$= H

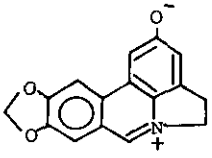
a:R = Ac
b:R = Me



(VII)



(VIII)



(IX)

a:$R^1$= $R^2$= $R^3$= Ac
b:$R^1$= $R^3$= Ac, $R^2$= Me

Similar permanganate oxidation (10 min.) of acetylhippamine (If), which is easily derivable from lycorine (Id) via lycorene-α-oxide(VIII)[10], gave the glycol-lactam (IVd)(27%), m.p. 276-280° (decomp.), $\nu_{max}$(Nujol): 3400, 1740, and 1640 $cm^{-1}$ and the C-aromatized compound (VIb)(trace), m.p. 278-279°, $\lambda_{max}$(EtOH): 242(ε= 48,400) and 282 nm (ε=23,400). Acetylation of IVd gave the diacetate (IVe), m.p. 230-231°, whose $^1$H-N.M.R. spectrum again confirmed its structure and conformation as those of IVa. Dehydration of IVe as described above gave, in good yield, di-acetylungiminorine-lactam (VIIb), m.p. 226-229°, δ 6.06 ppm (1H, m.), which on reduction with lithium aluminum hydride furnished ungiminorine (IIIa), m.p. 206-208° (decomp.). The identity of this with the natural ungiminorine [lit.[1] m.p. 206-208° (decomp.)] was confirmed by comparisons with the N.M.R. spectra of the diacetates[2,11].

As lycorine (Ib) was synthesized already[6] the above transformation constitutes a total synthesis of ungiminorine in a formal sense. This investigation also confirms the important role of oxidation step to the double bond of lycorine alkaloids in the (bio)synthesis of ungiminorine alkaloids and the C-aromatized alkaloids such as ungeremine (IX)[12], a minor constituent of Ungernia minor; α-face oxidation gives the former alkaloids and the latter alkaloids would be produced via β-face oxidation followed by subsequent dehydration.

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7. This would be a product from the β-glycol which will be dehydrated easily.
8. Details of signal assignment procedure will be published in a full paper.
9. T. H. Kinstle, W. C. Wildman, and S. L. Brown, Tetrahedron Lett., 1966, 4659.
10. a) W. C. Wildman and N. E. Heimer, J. Amer. Chem. Soc., 89, 5265 (1967).
    b) J. Toda, T. Sano, Y. Tsuda, M. Kaneda, and Y. Iitaka, Tetrahedron Lett., 1980, 369.
11. Direct comparison was not made since the authentic sample of ungiminorine was not available.
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