A FORMAL SYNTHESIS OF ($\pm$)-LYCORINE

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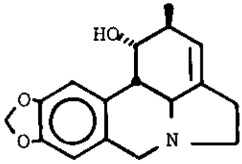
Abstract—— Since the title compound has been known to be derivable from ($\pm$)-α-Δ^2-lycorene-7-one (14), its alternative synthesis is described briefly.

Two recent publications[1,2] concerning the synthesis of ($\pm$)-lycorine (1), the main alkaloid of Lycoris radiata HERB (Amaryllidaceae), have prompted us to communicate our own results up to the present.

The ($\pm$)-*cis*-oxocyclohexanecarboxylic acid (2)[3], mp 188-189° (EtOH), was prepared in an acceptable yield by six steps[4] starting from piperonal. Esterification (MeOH, conc.H_2SO_4) of 2, followed by acetalization, epimerization (KOt-Bu, t-BuOH, reflux, 0.5 hr) and hydrolysis (20%aq. KOH-EtOH, reflux) gave ($\pm$)-*trans*-5,5-ethylenedioxy-2-(3',4'-methylenedioxyphenyl)cyclohexanecarboxylic acid (3), mp 208.5-209.5°(MeOH), in overall 92.3% yield.

Stereospecific conversion of the carboxyl group into an amino group was performed as follows. The Curtius rearrangement (benzene, reflux) of the acid azide derived from 3 by the conventional mixed anhydride method (1. ClCOOEt, Et_3N, acetone;2. NaN_3-H_2O) afforded the ($\pm$)-*trans*-cyclohexyl isocyanate (4), mp 88-88.5° (Et_2O-n-hexane, 73%), *trans*-diequatorial disposition of the phenyl and isocyanate groups in



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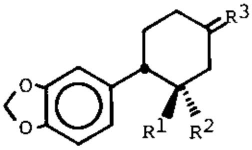
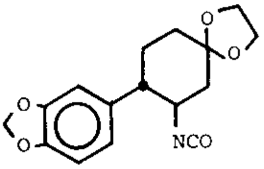


2 R^1 = H, R^2 = COOH
R^3 = O

3 R^1 = COOH, R^2 = H,
R^3 = OCH_2CH_2O



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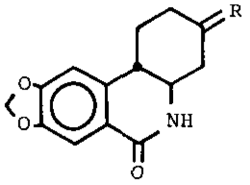
4 being explicitly indicated by the presence of one-proton double triplets centered at δ 3.73 (J=11 and 5 Hz).[5]

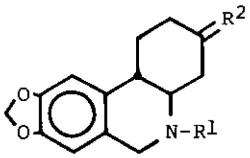
Cyclization of 4 with anhydrous phosphoric acid[6] furnished a mixture of the (±)-phenanthrid-6-one (5) and (6), re-acetalization of which gave (±)-3,3-ethylenedioxy-8,9-methylenedioxy-1,2,3,4,4aα,5,6,10bβ-octahydrophenanthrid-6-one (6), mp 288-289° (dec.)($CHCl_3$, 60%). The lactam carbonyl group of 6 was reduced with lithium aluminum hydride in boiling anhydrous dimethoxyethane leading to the (±)-acetal amine (7), mp 126-127° ($MeOH-H_2O$, 93.3%).

Deacetalization of 7 with 6N hydrochloric acid at room temperature produced the (±)-keto amine (8), mp 164-165.5° (EtOH, 73.5%)(lit.[7] 164-165.5°), which was converted into (±)-α-lycorane-3,5-dione (9), mp 196-199° (acetone, overall 31% yield from 8)[lit.[7] 195-197° (dec.)] according to Hamada's method.[7]



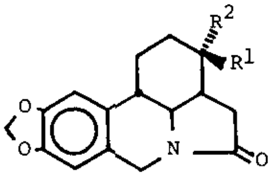
5 R = O

6 R = OCH_2CH_2O



7 R^1= H, R^2= OCH_2CH_2O

8 R^1= H, R^2= O



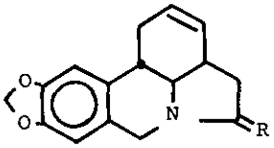
9 R^1+R^2 = O

10 R^1 = $N(CH_3)_2$,
R^2 = H

11 R^1 = $NO(CH_3)_2$,
R^2 = H

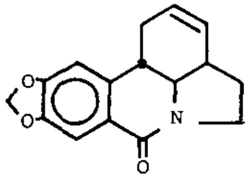
Regioselective transformation of the carbonyl group at 3-position to a 2,3-double bond was carried out by the Cope reaction. Reductive amination[8] of 9 with dimethylamine hydrochloride and sodium cyanoborohydride in anhydrous methanol afforded expectedly (±)-α-(3β-dimethylamino)lycorane-5-one (10), mp 204-205° (acetone, 43%), stereochemistry of which was ascertained by the presence of one-proton multiplet ($W_{1/2}$ 22 Hz) at δ 2.82 and one-proton double doublets (J=10 and 6 Hz) at δ 3.15 in the nuclear magnetic resonance (NMR) spectrum. N-Oxidation of 10 with m-chloroperbenzoic acid occurred under mild conditions (-18°, 1.5 hr) after column chromatographic purification on basic alumina to give the hygroscopic (±)-N-oxide (11), mp 175-176° (dec.)(AcOEt-n-hexane, 95%), thermolysis of which at 200° produced as expected (±)-α-Δ^2-lycorene-5-one (12), mp 148-150° (AcOEt-n-hexane, 57%);NMR δ :

3.41 (1H, dd, J=7.5 and 10 Hz, C_{11c}-H), 5.90 (4H, s, C_2- and C_3-H and OCH_2O), 6.59, 6.69 (each 1H, s, arom. H).



12 R = O

13 R = H_2



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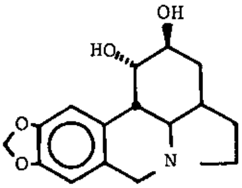

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A facile synthesis of the Torssell's intermediate (14) from 12 was achieved by transposition of the lactam carbonyl group at 5-position into that at 7-position. Reduction with lithium aluminum hydride in boiling dimethoxyethane of 12 produced (±)-α-Δ^2-lycorene (13), mp 93-95° (MeOH-H_2O, 96.5%);NMR δ :3.20 (1H, td, J=9.7, 8.6, and 6.3 Hz, C_{3a}-H), 5.83 (2H, bs, C_2- and C_3-H), 6.57, 6.69 (each 1H, s, arom. H).

Oxidation of 13 with active manganese dioxide in boiling chloroform and column chromatography on silica gel of the reaction mixture with chloroform afforded 14, mp 194.5-196° (EtOH, 69.7%)(lit.[2] 196-198°). Comparison of NMR signals[9] of 14 with those of authentic (±)-α-Δ^2-lycorene-7-one revealed their identity within experimental errors; 14, NMR δ : 4.18 (1H, dd, J=11 and 7 Hz, C_{11c}-H), 5.87 (2H, bs, C_2- and C_3-H), 6.66 (1H, s, C_{11}-H), 7.46 (1H, s, C_8-H).

Linked to Torssell's experimental data, preparation of 14 constituted a formal synthesis of 1.

Now that stereochemistry of 9 was confirmed as such, we are currently exploring another possible route to (±)-dihydrolycorine (15) and/or 1 starting from 9.

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REFERENCES AND FOOTNOTES

1 Y. Tsuda, T. Sano, J. Taga, K. Isobe, J. Toda, H. Irie, H. Tanaka, S. Takagi, M. Yamaki, and M. Murata, *J.C.S. Chem. Commun.*, **1975**, 933; Y. Tsuda, T. Sano, J. Taga, K. Isobe, J. Toda, S. Takagi, M. Yamaki, M. Murata, H. Irie, and H. Tanaka, *J. Chem. Soc. Perkin I*, **1979**, 1358.

2\. O. Mϕller, E. Steinberg, and K. Torssell, *Acta Chem. Scand.*, 1978, **B32**, 98.

3 All new compounds described gave satisfactory analytical (except *5*, *11*, and *13*) and spectral data.

4 *Cf*. F. E. Ziegler and M. E. Condon, *J. Org. Chem.*, 1971, **36**, 3707.

5 NMR spectra were measured on a JEOL FX 100 spectrometer (100 MHz) in $CDCl_3$ solution using $(CH_3)_4Si$ as the internal standard, unless otherwise noted.

6 L. F. Fieser and M. Fieser,"Reagents for Organic Synthesis", vol. 1, John Wiley & Sons, Inc., N.Y., 1967, p. 860.

7 Y. Hamada, Ph.D. Dissertation, Kyushu University.

8 R. F. Borch, M. Bernstein, and H. D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2893.

9 The NMR spectrum was measured on a Hitachi R-24B spectrometer (60 MHz) in $CDCl_3$ solution using $(CH_3)_4Si$ as the internal standard.

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