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THE SYNTHESIS OF HEMILOLINE: 3-AZA-9-OXABRENDANE[1]

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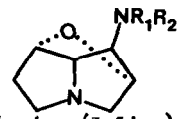
A novel synthetic approach[2] to the bridged ring system of the lolium alkaloids[3] 1a-d is now



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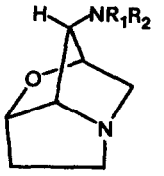


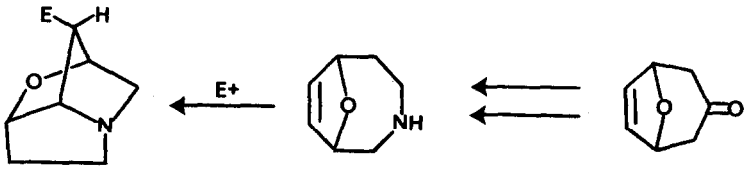
1a. Festucine (Loline) $R_1=CH_3, R_2=H$

1b. Norloline $R_1=R_2=H$

1c. Lolinine $R_1=CH_3, R_2=COCH_3$

1d. Decorticasine $R_1=H, R_2=COCH_2CH_3$

reported. The synthetic strategy outlined in Scheme I involves transannular addition of a suitable electrophile to an unsaturated amine, leading to the bridged skeleton. This tricyclic intermediate

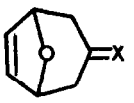


SCHEME I

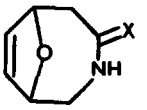
contains a leaving group E which in principal could be displaced by an appropriate nitrogen nucleophile leading to the members of the loline class.

The starting point for this synthesis is the ketone 2[10] which can be prepared by the method of Hoffmann[11] of Noyori.[12] Formation of the oxime 3[13,14], (mp 111-112°) proceeds in 81% yield. Reaction of oxime 3 with p-toluenesulfonyl chloride in pyridine gives tosyl oxime 4[15] (mp 98-99°) in 92% yield. Compound 4 is remarkably stable compared to closely related tosyl oximes lacking the

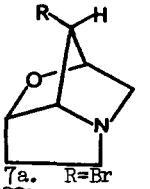
oxygen bridge[16], and can be stored for long periods of time without decomposition. However, 4 undergoes a facile Beckmann rearrangement under mild conditions (K_2CO_3, H_2O, THF) affording lactam 5[17] (mp 133-134°) in 79% yield. Reduction of 5 with lithium aluminum hydride gives the desired



2. X=O
3. X=NOH
4. X=NOpTs



5. X=O
6. X=H_2



7a. R=Br
7b. R=H
7c. R=I
7d. R=HgCl

unsaturated amine 6[18] as a clear liquid (65%, bp 95-105° at 20 mm, picrate mp 172-174°C). Treatment of 6 with bromine in methylene chloride[19] results in the transannular cyclization yielding the bromoalkaloid 7a[20] (99%, HBr salt, mp 162-164°C) which was converted to the free base with sodium hydroxide (84% yield). The proposed structure was confirmed by a single crystal X-ray diffraction experiment on the picrate salt.[21] Reduction of 7a with lithium aluminum hydride gave hemiloline 7b[22,23], the bridged pyrrolizidine skeleton of the loline group of alkaloids.

The use of other electrophiles[19] has demonstrated selectivity in ring closure. Treatment of 6 with iodine in methylene chloride yields the cyclized product 7c[24] in good yield (85%, HI salt, mp 135-140°C, picrate mp 166-169°C). However, reaction of 6 with mercuric chloride in tetrahydrofuran yields a salt (99%, mp 157-160°d, $C_7H_{11}NOHgCl_2$) of the starting unsaturated amine 6 and not cyclized product 7d.

Attempts to prepare loline itself by direct displacement of the bromine of 7a with methylamine (CH_3CN, 100°) proved very difficult. The reaction is analogous to displacement at C-7 in the norbornane system which have also proved difficult if not impossible.[25] In addition, electron-electron repulsion between the lone pair electrons on the bridgehead nitrogen and incoming nucleophile may make displacement electronically unfavorable as well.

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Indiana University, for carrying out the X-ray structure determination.

REFERENCES AND NOTES

1. Contribution No. 3096 from the Department of Chemistry, Indiana University. This work has been presented orally: S. R. Wilson and R. A. Sawicki, 172nd ACS meeting, San Francisco, California Aug. 29 - Sept. 3, 1976, ORGN 76.

2. For a related synthetic approach see: R. S. Glass, D. R. Deardorff and L. H. Gains, Tetrahedron Lett., 000 (1978), accompanying communication.

3. The most abundant alkaloid of Festuca sp., festucine 1a, was isolated by Yates[4] and the structure determined by X-ray crystallography.[5] Russian workers isolated the same alkaloid which they named loline from Lolium sp., (Rye grass) as well as two derivates, norloline 1b and lolinine 1c. Another alkaloid with the loline skeleton called decorticasine 1d was isolated by Spanish workers[7] from Adenocarpus decorticans, a member of the Leguminosae. The four known alkaloids of this class have been interconverted chemically and the identity of festucine and loline was shown by Culvenor[8] in 1969. The four alkaloids possess the absolute configuration depicted.

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10. Although theoretically interesting 4+3=7 Diels-Alder reaction of furan and cyclopropanone could in principal be employed here, unsubstituted cyclopropanone does not undergo this reaction: N. J. Turro, S. S. Edelson, J. R. Williams, T. R. Darling and W. B. Hammond, J. Amer. Chem. Soc., 91, 2283 (1969).

11. A. E. Hill, G. Greenwood and H. M. R. Hoffmann, J. Amer. Chem. Soc., 95, 1338 (1973).

12. R. Noyori, S. Makino, T. Okita and Y. Hayakawa, J. Org. Chem., 40, 806 (1975).

13. NMR spectra determined on a Varian HR-220 at 200 mHz. All new compounds possessed satisfactory combustion analysis.

14. IR: 3300 cm^{-1}, 1650 cm^{-1}; NMR ($CDCl_3$): δ 9.64(1H-bs), 6.16(2H-s), 4.84(2H-d,J-4Hz), 2.95(1H-d,J-16Hz), 2.57(1H-dd,J=4Hz,J=16Hz), 2.32(1H-dd,J=4Hz,J=16Hz), 2.20(1H-d,J=16Hz).

15. IR: 1650 cm^{-1}, 1610 cm^{-1}, NMR($CDCl_3$): δ 7.77(2H-d,J=8Hz), 7.27(2H-d,J=8Hz), 6.09(2H-s), 4.84(1H-d,J=4Hz), 4.80(1H-d,J=4Hz), 2.93(1H-d,J=16Hz), 2.57(1H-dd,J=4Hz,J=16Hz), 2.43(3H-s), 2.36(1H-dd, J=4Hz,J=16Hz), 2.27(1H-d,J=16Hz).

16. For our preliminary work in the unbridged pyrrolizidine series see: S. R. Wilson and R. A. Sawicki, J. C. S. Chem. Commun., 431 (1977).

17. IR: 1650 cm^{-1}; NMR($CDCl_3$): δ 7.30(1H-bs), 6.18(1H-d,J=6Hz), 5.93(1H-d,J=6Hz), 4.84(1H-s), 4.70(1H-s), 3.57(1H-d,J=14Hz), 3.0(1H-dd,J=3Hz,J=15Hz), 2.8-3.0(1H-m), 2.50(1H-d,J=15Hz).

18. NMR($CDCl_3$): δ 6.07(1H-dt,J=6Hz,J=1Hz), 5.91(1H-dt,J=6Hz,J=1Hz), 4.98(2H-m), 2.95(3H-m), 2.68(1H-d,J=14Hz), 1.95(1H-m), 1.59(1H-m), 1.48(1H-bs).

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20. NMR($CDCl_3$): δ 4.68(1H-d,J=4Hz), 4.41(1H-d,J=1Hz), 4.14(1H-s), 3.39(1H-t,J=1Hz), 3.30(1H-d,J=12Hz), 3.02(2H-t,J=7Hz), 2.45(1H-d,J=12Hz), 2.14(1H-m), 1.98(1H-m).

21. Compound 7a (picrate) crystallized in the space group Pbca with 8 molecules in the unit cell. Cell constants at -150°C are a=18.324, b=7.299 and c=23.62. Crystallographic data for this paper may be obtained in microfiche form for $2.50 from the Chemistry Library, Indiana University, Bloomington, Indiana 47401. Refer to J. C. Huffman, Indiana University, Molecular Structure Center Report No. 7604, 1976.

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23. NMR($CDCl_3$): δ 4.32(1H-m), 4.23(1H-bs), 3.36(1H-bs), 3.18(1H-d,J=11Hz), 2.98(2H-t,J=8Hz), 2.34(1H-d,J=11Hz), 1.8-2.2(4H-m).

24. Picrate NMR(acetone d_6): δ 8.68(2H-s), 4.91(1H-bs), 4.77(2H-s), 4.61(1H-s), 4.16(1H-d,J=13Hz), 3.95(2H-t,J=7Hz), 3.47(1H-d,J=13Hz), 3.0(1H-bs), 2.50(2H-m).

25. a) J. T. Lumb and G. H. Whitman, Chem. Commun., 400 (1966).
b) R. G. Weiss and E. I. Snyder, J. Org. Chem., 35, 1627 (1970).

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