Tetrahedron Letters,Vol.27,No.13,pp 1489-1492,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

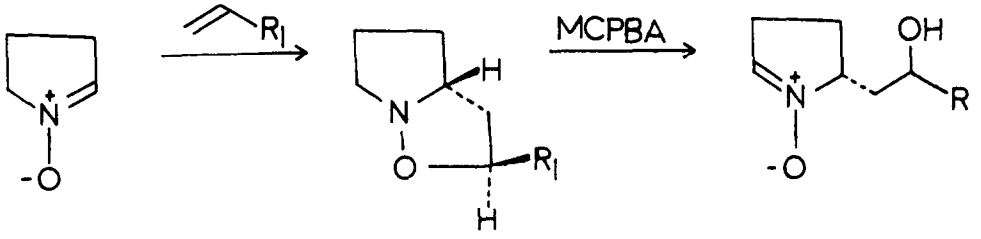
THE α,α'-DIALKYLATION OF CYCLIC AMINES. THE SYNTHESIS OF SOLENOPSIS ANT VENOMS.

J. J. Tufariello and J. M. Puglis
Department of Chemistry, State University of New York at Buffalo
Buffalo, New York 14214

Summary: A trans-α,α'-dialkylation of cyclic amines has been investigated through the use of nitrone methodology. This procedure has been utilized in the synthesis of Solenopsis ant venoms.

The α-alkylation of amines through the use of nitrone methodology has proven to be of considerable synthetic value.[1] The related α,α'-dialkylation sequence has also proven to be valuable.[2] Indeed, the α-alkylation and α,α'-dialkylation of amines has received considerable recent attention.[3]

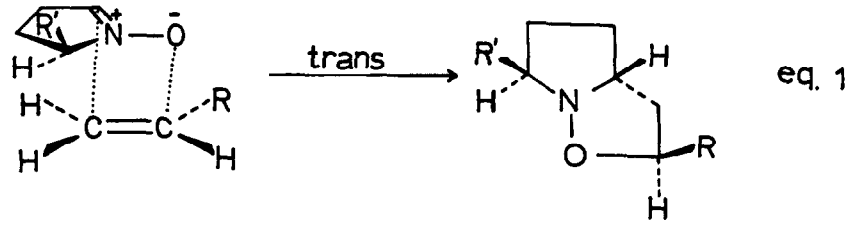
We have chosen to explore the α,α'-dialkylation of cyclic amines via nitrones from a stereochemical perspective. For example, whereas 5-alkyl-1-pyrroline 1-oxides (e.g., 3) can be readily and regiospecifically derived by the MCPBA induced oxidation[4,5] of the isoxazolidines



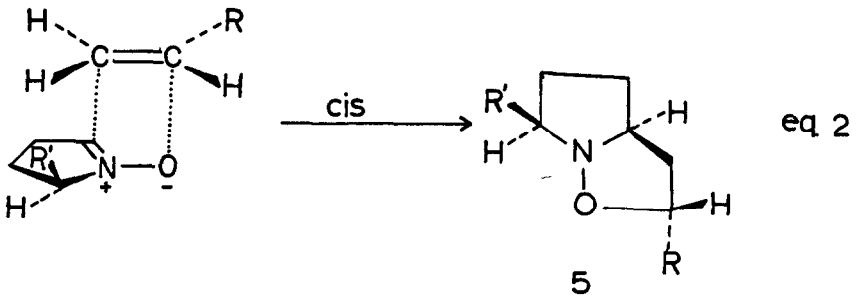
1 2 3

(e.g. 2) obtained from nitrone-alkene cycloaddition reactions, the stereochemical outcome of their subsequent cycloaddition reactions (i.e. of 3) was uncertain at the outset of this research.

We anticipated that the second cycloaddition would proceed preferentially from the trans-direction (i.e. away from the 5-alkyl substituent; eq. 1) rather than from the sterically more encumbered cis-direction (cf., eq. 2). We chose to confirm the stereochemical assignments of the resultant cycloadducts (i.e. 4 or 5) by conversion of certain of them to natural products of known configuration.



4

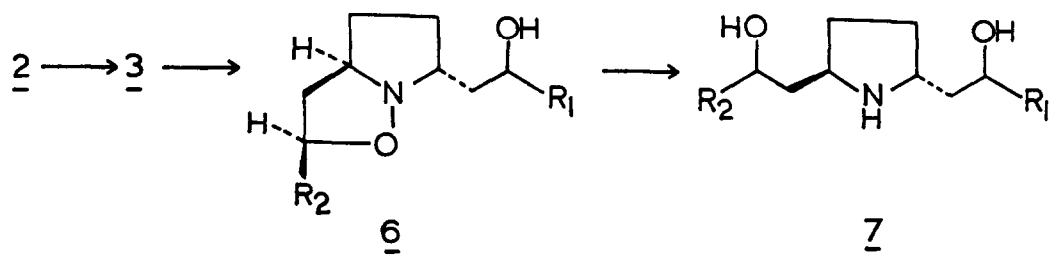


5

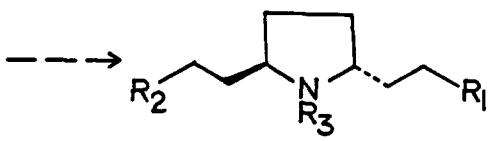
The major constituents of the poison gland secretions of several Solenopsis ants are dialkylpyrrolidine alkaloids.[6] For example, the venom of the European thief ant Solenopsis fugax consists of more than 90% trans-2-butyl-5-heptyl-pyrrolidine,[6b] while trans-2-hexyl-5-pentyl-pyrrolidine is the major venom constituent from Solenopsis molesta and Solenopsis texanas.[6c]

The early work in the synthesis of these venoms led to cis:trans isomeric mixtures.[3c,6a,6c,7] A more recent effort has resulted in greater stereoselectivity.[3d]

A nitrone-based synthesis for two of the ant venoms is outlined herein. The adduct 2a was prepared in 87% yield from 1-pyrroline 1-oxide (1) and 1-heptene. Oxidative cleavage of this isoxazolidine with m-chloroperbenzoic acid afforded the nitrone 3a in 94% yield. This reaction



6 7



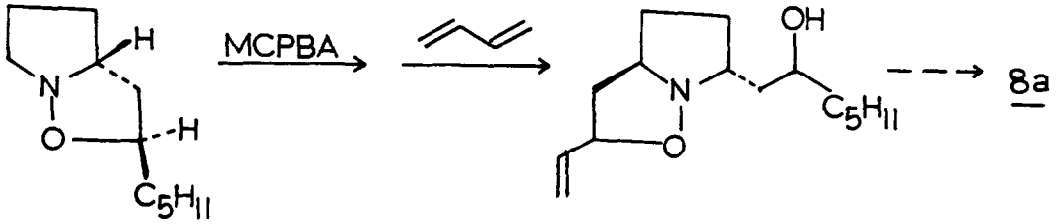
a, $R_1=C_5H_{11}$, $R_2=C_2H_5$, $R_3=H$
b, $R_1=C_4H_9$, $R_2=C_3H_7$, $R_3=H$
c, $R_1=C_5H_{11}$, $R_2=C_2H_5$, $R_3=CH_2Ph$
d, $R_1=C_4H_9$, $R_2=C_3H_7$, $R_3=CH_2Ph$

was, as anticipated,[5] regiospecific. The nitrone vinylic proton appears as a multiplet centered at δ 6.95 ppm in the nmr spectrum. The cycloaddition of 3 (R_1 = C_5H_{11}) with 1-butene in a sealed tube at 100° (toluene) provided the second adduct 6a in 66% yield. The amino diol 7a was obtained by reductive scission of the nitrogen-oxygen bond with lithium aluminum hydride in refluxing THF. The synthesis of the venom was completed by a dehydroxylation procedure initiated by an exhaustive mesylation (MsCl, Et_3N, CH_2Cl_2) of the amino diol to provide a trimesyl derivative from which the mesyloxy groups were removed (i.e. in 72% yield) with lithium triethylborohydride.[8] Cleavage of the resultant sulfonamide was accomplished with sodium bis-(2-methoxyethoxy)aluminum hydride.[9] The stereochemical relationship of the alkyl groups in the resultant 2,5-dialkylpyrrolidine was determined by method of Hill and Chan.[10] This method permits the configurational assignments to the corresponding N-benzyl amines on the basis of their distinguishable nmr behavior. The diastereotopic benzylic protons of the trans-isomer should appear as an AB pattern while the enantiotopic benzylic protons of the cis-isomer should result in a singlet at approximately the same chemical shift.

The requisite benzyl derivative 8c was prepared by the benzoylation of 8a (C_6H_5COCl, pyridine, benzene), followed by conversion of the resultant amide to the corresponding tertiary benzylic amine with lithium aluminum hydride. Gas chromatographic analysis revealed the presence of two isomers, 8a and its cis-counterpart in an 87:12 ratio. The nmr spectrum of the mixture revealed the expected benzylic methylene AB quartet (J=14 Hz) at δ 3.71 ppm, along with an overlapping singlet at approximately the same chemical shift for the cis-isomer. Careful integration clearly confirmed the predominance of the trans-isomer.

A second ant venom, trans-2-butyl-5-heptylpyrrolidine (8c) was prepared in analogous fashion. A similar analysis of the corresponding benzyl amines revealed the production of 8c and its cis-isomer in an 84:16 ratio, respectively.

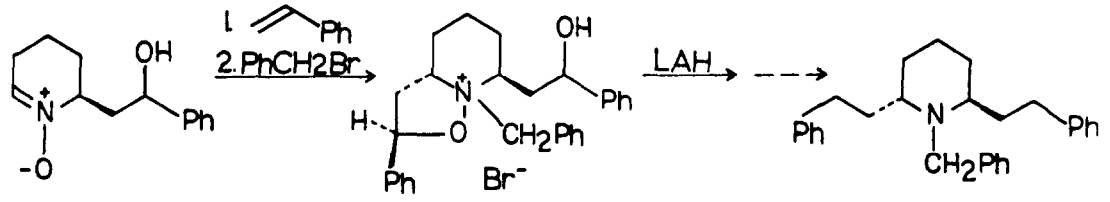
Interestingly, when a diene (i.e. 1,3-butadiene) was substituted for the alkene in the



2a 9

second cycloaddition step (i.e. to afford 9), a modest increase in stereoselectivity was observed. Thus, when the vinyl adduct 9 was transformed into 8a, after hydrogenation of the double bond, it was determined by glpc and nmr analysis (vide supra) that the trans:cis ratio is 93:7, respectively.[11,12]

The tendency for trans-dialkylation by the corresponding six-membered ring nitrone 10, prepared by oxidative cleavage (MCPBA, CH_2Cl_2) of the cycloadduct derived from 3,4,5,6-tetrahydro-



10 11 12

pyrridine 1-oxide and styrene, was also explored. Addition of a second equivalent of styrene affords an isoxazolidine which upon benzylation ($PhCH_2Br$, CH_2Cl_2) gives 11 in 80% yield. Reductive cleavage of the nitrogen-oxygen bond (LAH/THF) gives an amino diol which is readily dehydroxylated by the mesylate-lithium triethylborohydride method described above. The resultant benzylamine 12 displays a clean quartet at δ 3.75 (J=14 Hz) ppm, indicating that the nitrone-based alkylation sequence provides the predominant, if not exclusive, formation of the trans-2,6-substituted piperidine.

Thus, both five-membered and six-membered alkylated nitrones (i.e. 3 and 10) show a preference for trans-cycloaddition, with the latter nitrone exhibiting a somewhat greater selectivity in this regard.

References and Notes

1. Tufariello, J. J. Acct. Chem. Res. 1979 , 11, 396.
2. Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, Sk. A. J. Am. Chem. Soc. 1979, 101, 2435.
3. For example, see (a) Meyers, A. I.; Reiker, W. F.; Fuentes, L. M. J. Am. Chem. Soc. 1983, 105, 2082; (b) Meyers, A. I.; Fuentes, L. M. ibid, 1983, 105, 117; (c) Fraser, R.; Passannanti, S. Synthesis, 1976, 540; (d) MacDonald, T. J. J. Org. Chem. 1980, 45, 193; (e) Bonin, M.; Romero, T. R.; Grierson, D. S.; Huison, H.-P. Tetrahedron Lett. 1982, 23, 3369; (f) Matsumura, Y.; Maruoka, K.; Yamamoto, H. Tetrahedron Lett. 1982, 23, 1929.
4. (a) LeBel, N. A.; Spurlock, L. A. J. Org. Chem. 1964, 29, 1337; (b) LeBel; N. A.; Post, M. E.; Huang, D. J. Org. Chem. 1979, 44, 1819.
5. Tufariello, J. J.; Mullen, G. B. J. Am. Chem. Soc. 1978, 100, 3638.
6. (a) Pedder, D.; Fales, H.; Jaouni, T.; Blum, M.; MacConnell, J.; Crewe, R. Tetrahedron 1976, 2275; (b) Blum, M.; Jones, T.; Holldobler, B.; Fales, H.; Jaouni, T. Naturwiss. 1980, 67, 144; (c) Jones, T.; Blum, M.; Fales, H. Tetrahedron Lett. 1979, 1031.
7. Jones, T.; Franko, T.; Blum, M.; Fales, H. Tetrahedron Lett. 1980, 789.
8. Brown, H. C.; Krishnamarthy, S. J. Org. Chem. 1976, 41, 3064.
9. Gold, E.; Babod, E. J. Org. Chem. 1972, 37, 2208.
10. Hill, R.; Chan, T. Tetrahedron 1965, 21, 2015.
11. We thank Professor T. L. Macdonald (Vanderbilt University) for comparison samples of dialkylpyrrolidine precursors. We also thank Professor T. H. Jones (University of Georgia) for helpful information relative to the dialkylpyrrolidine project.
12. During the course of our work, the preferential trans-dialkylation of piperidines was described in a related procedure using nitrones. Gossinger, E. Tetrahedron Lett. 1980, 2229; Monatsh. Chem. 1980, 111, 143, 783.

(Received in USA 19 November 1985)