Tetrahedron Letters No. 12, pp 1031 - 1034.
0040-4039/79/0315-1031$02.00/0

SYNTHESIS OF UNSYMMETRICAL 2,5-DI-n-ALKYLPYRROLIDINES: 2-HEXYL-5-PENTYLPYRROLIDINE FROM THE THIEF ANTS Solenopsis molesta, S. texanas, AND ITS HOMOLOGUES.

Tappey H. Jones*
Department of Chemistry, Furman University, Greenville, SC 29613

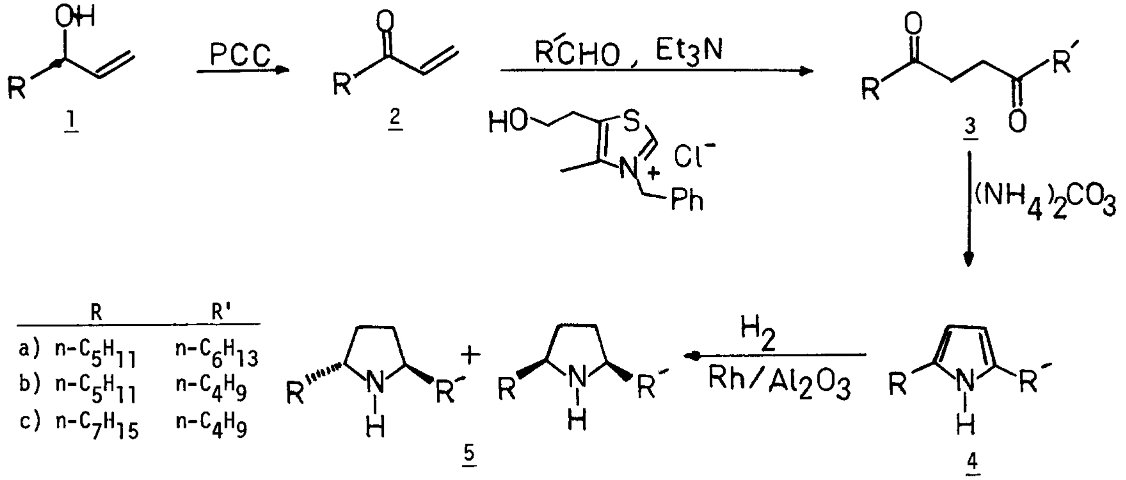
Murray S. Blum
Department of Entomology, University of Georgia, Athens, GA 30602

H. M. Fales
Laboratory of Chemistry, National Heart, Lung and Blood Institute
Bethesda, MD 20014

Unsymmetrical 2,5-di-n-alkylpyrrolidines have been identified as characteristic poison gland products of the South African ant Solenopsis punctaticeps; the stereochemistry of these compounds has not been assigned in previous syntheses.[1,2] We now wish to describe a convenient stereoselective synthesis of these 2,5-diakylpyrrolidines from the corresponding 1,4-diketones, which elucidates the geometry of the natural products. In addition, we report on the occurrence of a new venomous constituent, 2-hexyl-5-pentylpyrrolidine, as the major poison gland product of two species of thief ants, Solenopsis molesta and S. texanas.[3]

The buffered pyridinium chlorochromate oxidation[4] of 1-octen-3-ol (Aldrich) gave the unstable 1-octen-3-one (2a) in 43% isolated yield (b.p. 60-65°/13mm). The freshly prepared enone was immediately refluxed overnight under a nitrogen atmosphere with equivalent amounts of distilled heptanal, triethylamine, and 0.1 equivalent of 5-(2'-hydroxyethyl)-4-methyl-3-benzylthiazolium chloride.[5,6] After filtration, distillation gave 6,9-pentadecadione (3a) in 78% yield, b.p. 150-155° (0.5mm); m.p. 55-56°.[7]

The sequence was repeated using pentanal to give 5,8-tridecadione (3b) in 72% yield, b.p. 104° (0.4mm); m.p. 37-38°.[7] The preparation of 5,8-pentadecadione (3c) required the preparation of 1-decen-3-ol (1c) which was obtained in 65% yield by treatment of octanal with 1.5 equivalent of vinyl magnesium bromide: b.p. 53-54°(0.35mm); ir 3360, 3070, 3010, 995, 925 cm^{-1}; nmr (60MHz) δ 6.1 - 4.9 (3H, vinyl ABX multiplet identical to that shown by a commercial sample of 1-octen-3-ol), 4.0 (1H, m, CH-OH), 3.3 (1H,-OH by D_2O exchange), 1.35 (12H, br s, $(CH_2)_6$), 0.9 (3.H, br t, CH_3). Oxidation of enol 1c gave the unstable 1-decen-3-one (2c) in 59% yield (b.p. 107-108°/26mm), which was immediately condensed with pentanal in the manner described above to give the diketone 3c in 61% yield; b.p. 122° (0.35mm); m.p. 53-54°.[7]



	R	R'
a)	n-C_5H_{11}	n-C_6H_{13}
b)	n-C_5H_{11}	n-C_4H_9
c)	n-C_7H_{15}	n-C_4H_9

The diketone 3a was heated under a nitrogen atmosphere at 120° (bath temperature) with an excess of ammonium carbonate for 18 hr. GLC analysis showed ca. 90% conversion to a single unstable product, 2-hexyl-5-pentylpyrrole (4a) whose nmr spectrum was quite characteristic, δ 5.50 (2H, d, J=2.5Hz).[8] The diketones 3b and 3c were also cyclized in this way to give 2-n-butyl-5-n-pentylpyrrole (4b), nmr δ 5.59 (2H, d, J=2.5Hz), and 2-n-butyl-5-n-heptylpyrrole (4c), nmr δ 5.46 (2H, d, J=2.5Hz), respectively.

Each of the unstable pyrroles was immediately taken up in five volumes of acetic acid and hydrogenated over a fourth of their weight of 5% Rh/Al$_2$O$_3$ at 3atm. pressure.[9] After neutralization of the solvent with aqueous sodium hydroxide, GLC analysis (OV-1, OV-17) indicated ca. 85% conversion of each pyrrole to a more volatile product which was isolated as a colorless liquid by preparative GLC (2m x 5 mm column packed with 10% OV-1 on Gaschrom Q).[10] The diketones 3 and pyrrolidines 5 are well characterized by their mass spectra (See Table).

TABLE. Mass spectral data for diketones (3) and pyrrolidines (5). (70 eV). MS: m/e (rel. %)

3a: 240(M$^+$, 9), 197(5), 184(24), 170(23), 169(23), 155(33), 141(21), 127(46), 114(46), 113(36), 99(33), 85(16), 71(41), 57(13), 55(30), 43(100).

3b: 212(M$^+$, 5), 197(2), 183(8), 170(31), 156(60), 155(50), 141(80), 127(56), 114(48), 113(40), 99(73), 95(15), 85(52), 73(32), 71(72), 57(100), 55(35), 43(93), 41(63).

3c: 240(M$^+$, 8), 198(24), 183(22), 169(8), 157(6), 156(56), 155(20), 141(55), 127(60), 114(44), 113(32), 99(8), 98(10), 95(10), 85(60), 73(23), 71(28), 69(12), 57(100), 55(27), 43(36).

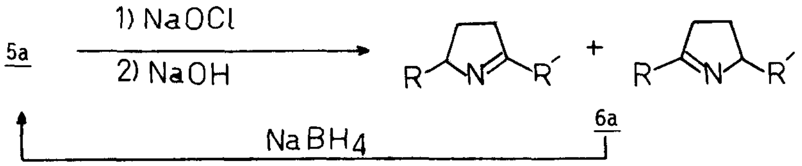
5a: 225(M$^+$, 2), 224(3), 155(13), 154(97), 141(13), 140(100), 97(1), 96(3), 95(4), 84(2), 83(4), 82(13), 81(7), 70(4), 69(16), 68(11), 67(7), 57(4), 56(9), 55(24), 44(7), 43(9), 42(4), 44(16).

5b: 197(M$^+$, 2), 196(5), 141(9), 140(88), 127(12), 126(100), 112(7), 98(1), 97(1), 96(2), 84(5), 83(7), 82(14), 81(5), 70(5), 69(7), 68(9), 67(7), 57(2), 56(9), 55(26), 44(5), 43(7), 42(2), 41(14).

5c: 225(M$^+$, 2) 224(3), 169(12), 168(84), 127(12), 128(100), 94(3), 93(3), 92(4), 85(3), 84(3), 83(9), 82(12), 69(6), 68(9), 67(5), 57(3), 56(6), 55(15), 44(6), 43(8), 42(2), 41(12).

Further examination by GC/MS using a column packed with 10% SP-1000 on Supelcoport showed that each pyrrolidine 5 was a mixture of two components, (ca. 85/15 ratio) which had identical mass spectra. The major component elutes first, and by analogy from dimethylpyrrole hydrogenation and GLC behavior has the cis configuration.[1,9] The cis isomer of the 2,5-dialkylpiperidines also elutes first on this liquid phase.[11]

The mass spectrum of 5a was identical to that of the product from both S. molesta and S. texanas, the mass spectrum of 5b was identical to that of 2-butyl-5-pentylpyrrolidine in S. punctaticeps, and the mass spectrum of 5c was identical to that of 2-butyl-5-heptylpyrrolidine in S. punctaticeps. In every case, comparison by retention times and coinjection showed that the naturally occuring pyrrolidine was of the trans configuration.



Because of the large percentage of the cis isomer in the pyrrolidine 5, we undertook the epimerization of 5a by stirring an 0.2M solution of 5a in methanol with a slight excess of 5% sodium hypochlorite solution under nitrogen for 1.5 hours. After refluxing for 3.5 hours with a ten-fold excess of sodium hydroxide,[12] GLC(OV-17) analysis indicated ca. 90% of an inseparable mixture of the isomeric 2-n-hexyl-5-n-pentyl-1-pyrrolines (6a), ir 1643, 725 cm^{-1}.[13] Reduction of the pyrroline mixture with sodium borohydride in methanol regenerated the pyrrolidines 5a in which the trans isomer predominated in a ratio of 3:2.

The chemistry of the venoms of the thief ants Solenopsis molesta and S. texanas contrasts considerably with that of the fire ants in this genus. The venoms of the latter species have been identified as unsymmetrical 2,5-di-n-alkylpiperidines[11,14] that are injected into either prey or predators. Thief ants, on the other hand, which are not reported to sting, utilize their pyrrolidine-rich venoms as repellents for other ant species,[15] especially those from which they steal larvae for food. It may be chemotaxonomically significant that while both thief ants and fire ants are placed in the genus Solenopsis, the former species are classified in the subgenus Diplorhoptrum whereas the latter are assigned to the subgenus Solenopsis.[16] That 2,5-dialkylpyrrolidines are not restricted in their distribution to thief ants is demonstrated by the report that two of these pyrrolidines, 5b and 2-(1-hex-5-enyl)-5-pentylpyrrolidine, are venomous constituents of Pharaoh's ant, Monomorium pharaonis.[17]

ACKNOWLEDGEMENTS. We thank Dr. A. C. Hung for collecting S. texanas, Dr. W. F. Buren for identifying the ants, and Dr. T. A. Bryson for part of the spectral data. Support of this work by Research Corporation is gratefully acknowledged.

REFERENCES AND NOTES

1. D. J. Pedder, H. M. Fales, T. Jaouni, M. Blum, J. MacConnell, and R. M. Crewe, *Tetrahedron*, *32*, 2275 (1976).
2. R. R. Fraser, S. Passannanti, *Synthesis*, 540 (1976).
3. Analyses were performed on methylene chloride extracts of excised poison glands of *S. molesta* and whole body extracts of *S. texanas*. We have since found that dialkylpyrrolidines are only produced in the poison glands of thief ants.
4. E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
5. K. Masuda, *Yakugaku Zasshi*, *81*, 536 (1961).
6. H. Stetter and H. Kuhlmann, *Tetrahedron Lett.*, 4505 (1974).
7. The 1,4-diketones *3a-c* had satisfactory elemental analyses and the following characteristic spectral data: ir 1715 cm^{-1}; nmr (60 MHz) δ 2.57 (4H,s, $CO\underline{CH_2}\underline{CH_2}CO$), 2.38 (4H b-t, $\underline{CH_2}COCH_2CH_2CO\underline{CH_2}$), 0.90 (6H, m, $\underline{CH_3}$).
8. D. M. Young and C. F. H. Allen, *Org. Syn., Coll. Vol. II*, 219 (1943). The nmr spectrum of 2,5-dimethylpyrrole prepared by this procedure showed a characteristic resonance at δ 5.55 (2H, d, J=2.5Hz), for the C-3 and C-4 pyrrole ring protons.
9. C. G. Overberger, L. C. Palmer, B. S. Marks, and N. R. Byrd, *J. Am. Chem. Soc.*, *77*, 4100 (1955).
10. The 2,5-di-n-alkylpyrrolidines *5a-c* gave satisfactory C, H, and N analyses and had nmr (60mHz) and ir spectra that were in accord with their structures.
11. J. G. MacConnell, M. S. Blum, and H. M. Fales, *Tetrahedron*, *26*, 1129 (1971).
12. A. Brossi, F. Schenker, and W. Leimgruber, *Helv. Chem. Acta*, *47*, 2089 (1964).
13. Homologues of these isomeric pyrrolines have been identified as major components of the venom of *S. punctaticeps*; this method constitutes their formal synthesis.
14. J. M. Brand, M. S. Blum, H. M. Fales, and J. G. MacConnell, *Toxicon*, *10*, 259 (1972).
15. B. Holldobler, *Oecologia* *11*, 371 (1973).
16. W. S. Creighton, *Bull. Mus. Comp. Zool.* *104*, 1 (1950).
17. F. G. Ritter and C. J. Persoons, *Neth. J. Zool.*, *25*, 261 (1975).

(Received in USA 18 December 1979)