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UNSYMMETRICAL 2,5-DIALKYLPYRROLIDINES VIA REDUCTIVE AMINATION OF 1,4-DIKETONES

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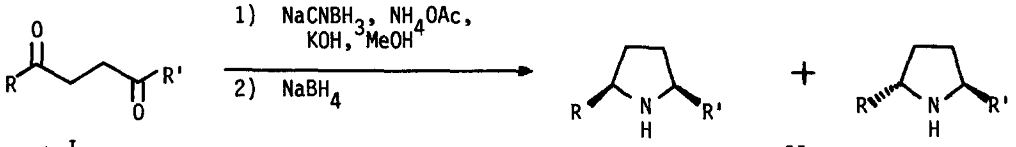
Summary. Reductive amination of 1,4-diketones with sodium cyanoborohydride and ammonium acetate produced 2,5-dialkylpyrrolidines in good yield and permitted inclusion of side chain unsaturation. The compounds were found in ants of the genus *Monomorium*.

Unsymmetrical 2,5-disubstituted pyrrolidines possessing unsaturated side chains have been identified as poison gland products of Pharaoh's ant, *Monomorium pharaonis*,[1] and we have observed them in other *Monomorium* species. We now wish to describe a convenient synthesis of these compounds directly from the appropriate 1,4-diketones, which permits the inclusion of the side chain unsaturation in the dione precursors. Additionally, we report on the occurrence of 2-(1-hex-5-enyl)-5-nonylpyrrolidine as a component of the poison gland secretions of *Monomorium minimum* and *M. viridum*, as well as the preparation of 2-ethyl-5-pentyl-1-pyrroline and 2-ethyl-5-pentyl-5-pyrroline, the most volatile alkaloid components in the venom of the fire ant *Solenopsis punctaticeps*.[2]

In an exploratory experiment, a methanolic solution of 2,5-hexanedione, 1.1 equivalents of NH_4OAc with 0.25 equivalents of KOH was treated with 1.0 equivalent of $NaCNBH_3$ and stirred overnight under anhydrous conditions.[3] Following acidification (conc. HCl) and solvent removal, the mixture was made basic (KOH) and extracted with ether. After drying, distillation gave 2,5-dimethylpyrrolidine (IIa) in 62% yield; bp 102-106^{0} (lit.[3] 104^{o}C). This reaction was not successful using either ammonium chloride or ammonium formate.

The long chain, 1,4-diketones Ib-e were prepared as described earlier.[5] Thus 1-octen-3-one was condensed with propanal in the presence of thiazolium salt catalyst and triethylamine[6]



I

II

a) $R = R' = CH_3$

b) $R = n\text{-}C_5H_{11}$
$R' = n\text{-}C_6H_{13}$

c) $R = -C_2H_5$
$R' = n\text{-}C_5H_{11}$

d) $R = n\text{-}C_5H_{11}$
$R' = -CH_2CH_2CH_2CH_2CH{=}CH_2$

e) $R = n\text{-}C_9H_{19}$
$R' = CH_2CH_2CH_2CH_2CH{=}CH_2$

to give 3,6-undecadione (Ic) in 50% yield.[7] The preparation of 1-pentadecen-7,10-dione (Id) and 1-nonadecen-7,10-dione (Ie) required 6-heptenal, obtained by the pyridinium chlorochromate oxidation of 6-hepten-1-ol[8,9] in 40% yield, bp 55-59° (26mm)[10], DNPH mp. 94°C (lit[11] 95-96°C). Condensation of 6-heptenal with 1-octen-3-one[5] and 1-dodecen-3-one (prepared from decanal by previously described methodology[5,12]) gave the diketones Id and Ie respectively in 50% yield.[7]

Reductive amination of the long chain diketones was found to give 20-30% of the 1-pyrrolines as well as the desired pyrrolidines. To obtain only the latter, the diketones were allowed to react with 1.25 equivalents of NH_4OAc, 0.3 equivalents of KOH, and 1.25 equivalents of $NaCNBH_3$ in methanol for 24 hrs. The mixture was then stirred an additional 2-3 hrs with a slight excess of $NaBH_4$. In this way, the pyrrolidines IIb-d were produced in 50-90% yield as the only volatile products by glc analysis (SE-30, SP-1000) and isolated as colorless liquids. In the case of diketone Ie, the pyrrolidine IIe was formed in 70% yield along with 15% of the corresponding pyrrole.[13] Gas chromatographic analysis using a 10% SP-1000 on Gaschrom Q column showed that each pyrrolidine was formed as an approximately 1:1 mixture of *cis* and *trans* isomers.[14] The diketones I and pyrrolidines II are well characterized by their mass spectra (see TABLE).

The physical and spectral properties of pyrrolidine IIb were identical with those of an authentic sample.[5] A sample of IIc was converted by means of sodium hypochlorite followed by

TABLE. Mass spectral data for diketones (**I**) and pyrrolidines (**II**). MS: m/e (rel. %)

Ic:	184(M^+, 3), 155(16), 141(3), 128(64), 114(6), 113(67), 99(45), 95(16), 85(52), 71(83), 57(100), 55(22), 43(89), 41(19).
Id:	238 (M^+, 2), 183(14), 182(8), 170(39), 155(42), 154(16), 139(15), 136(8), 127(48), 114(34), 113(2), 111(30), 109(12), 107(26), 99(72), 95(20), 85(14), 83(40), 71(78), 69(16), 67(24), 57(16), 55(100), 43(88), 41(58).
Ie:	294(M^+, 3), 239(13), 226(18), 211(15), 183(28), 182(5), 168(2), 167(2), 155(28), 154(21), 139(20), 136(21), 128(28), 114(45), 111(38), 110(13), 109(15), 107(20), 99(13), 95(25), 85(28), 83(40), 81(18), 71(65), 69(30), 67(22), 57(40), 55(100), 43(62), 41(53).
IIc:	169(M^+, 2), 168(6), 141(13), 140(98), 99(17), 98(100), 97(8), 84(13), 83(4), 82(17), 81(17), 70(7), 69(8), 68(15), 67(11), 58(6), 56(26), 55(63), 54(8), 53(4).
IId:	223(M^+, 2), 222(1), 153(9), 152(100), 150(3), 141(5), 140(64), 122(2), 110(2), 109(3), 108(3), 96(4), 82(15), 81(5), 70(3), 69(5), 68(6), 67(10), 57(3), 56(8), 55(13), 44(3), 43(5), 41(13).
IIe:	279(M^+, 4), 278(3), 222(11), 197(20), 196(83), 178(10), 165(7), 153(2), 152(100), 150(5), 124(5), 110(5), 109(3), 108(3), 97(6), 96(10), 95(9), 94(4), 84(4), 83(13), 82(31), 81(10), 70(9), 69(18), 68(15), 67(23), 57(7), 56(14), 55(28), 54(6), 43(19), 41(29).

sodium hydroxide[5] to a mixture of the isomeric 2-ethyl-5-n-pentyl-1-pyrrolines, ir 1645 cm^{-1}, whose mass spectra were identical to those reported for these compounds from *S. punctaticeps*.[2] The *trans* isomer of **IId** has been reported as a major constituent of the venom of *M. pharaonis*.[15]

The mass spectrum of **IIe** was identical to that of the major product from *M. minimum* and *M.* species and a minor product from *M. viridum*. Comparison by retention time and coinjection showed that the naturally occuring pyrrolidine in *M. minimum* and *M.* species was of the *trans* configuration. In contrast, this compound was reported to be a trace constituent in the venom of *M. pharaonis*.[1]

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7. The 1,4-diketones Ic-e were purified by Kugelrohr distillation at $<$ 0.01 mm, had satisfactory elemental analyses, and had ir and nmr spectra in accord with their structures. All of the compounds containing a terminal double bond (Id, Ie, IId, IIe) had characteristic ir bands at 990 and 910 cm^{-1} and nmr (60MHz) signals at δ 5.9 (1H, d of d of t, J=18, 10, 6Hz), 5.0 (1H, br d, J=18Hz) and 4.9 (1H, br d, J=10Hz).
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12. 1-Dodecen-3-ol was prepared in 55% yield, bp 75-77^{o}C (0.4mm); ir 3360, 3080, 3005, 990 and 920 cm^{-1}; nmr comparable to that of a commercial sample of 1-octen-3-ol except for a larger aliphatic CH$_2$ signal. Oxidation gave the unstable 1-dodecen-3-one in 60% yield; bp 74^{o}C (0.4mm), which was used immediately.
13. 2-(1-Hex-5-enyl)-5-nonylpyrrole showed a characteristic resonance at δ 5.6(2H, d, J = 2.5Hz) (see ref. 5), and had MS; m/e, (rel. %), 275(M$^+$, 21), 232(11), 220(6), 207(17), 206(72), 196(29), 178(6), 176(8), 163(15), 162(100), 152(34), 106(26), 94(17), 93(17), 82(19), 80(15), 67(13), 65(17).
14. The 2,5-disubstituted pyrrolidines IIc, IId and IIe gave satisfactory C, H, and N analyses and had nmr (60MHz) and ir spectra that were in accord with their structures.
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