Synthesis of 2,5-Dialkylpyrrolidines via Metallated Nitrosamines, A Constituent of Fire Ant Venom

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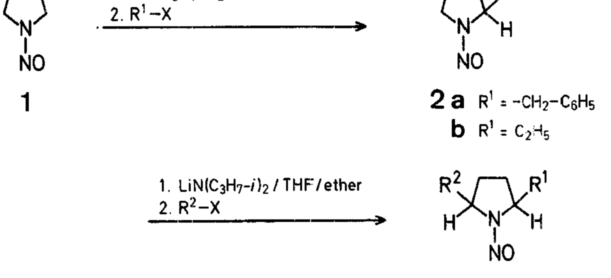
The standard method of synthesis of 2,5-dialkylpyrrolidines via reduction of the appropriate pyrroles is not well suited to the preparation of higher dialkyl derivatives as the immediate precursor, the 1,4-diketone, is not always readily available. In view of the recent interest in dialkylpyrrolidines as constituents of the venom of the South African fire ant, *Solinopsis Punctaticeps*[1], we have examined and achieved the synthesis of 2,5-dialkylpyrrolidines from pyrrolidine by stepwise alkylation of 2-lithio-1-nitrosopyrrolidines (see Scheme). We have also examined the stereochemistry of the dialkylation for comparison with that observed in the dialkylation of 1-nitrosopiperidines[2].



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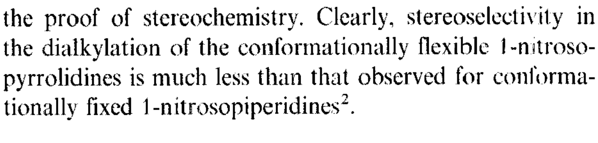
2 a R^1 = –CH$_2$–C$_6$H$_5$
b R^1 = C$_2$H$_5$

3 a R^1 = R^2 = –CH$_2$–C$_6$H$_5$
b R^1 = C$_2$H$_5$; R^2 = *n*-C$_7$H$_{15}$

Lithiation of 1-nitrosopyrrolidine (**1**) under standard conditions[3], followed by reaction with benzyl bromide gave 2-benzyl-1-nitrosopyrrolidine **2a** in 95% isolated yield. Repetition of the procedure gave 2,5-dibenzyl-1-nitrosopyrrolidine (**3a**) in 85% isolated yield. Removal of the nitroso group with hydrogen chloride in benzene gave a mixture of pure 2,5-dibenzylpyrrolidine hydrochlorides (**4a**) in overall 66% yield from 1-nitrosopyrrolidine (**1**).

The ^{13}C-N.M.R. spectrum of the hydrochlorides **4a** showed the presence of two isomers whose ratio varied from 85:15 to 62:38 depending, apparently, on the source of the alkyllithium used to generate lithium diisopropylamide. The major isomer was proven to be the *trans* isomer by Raban's method[4] which involved conversion to a mixture of trichloromethanesulfenamides whose 220 MHz ^{1}H-N.M.R. spectra provided the proof of stereochemistry. Clearly, stereoselectivity in the dialkylation of the conformationally flexible 1-nitrosopyrrolidines is much less than that observed for conformationally fixed 1-nitrosopiperidines[2].



3a,b **4a,b** (*cis* + *trans*)

Following the same approach, 1-nitrosopyrrolidine (**1**) was converted into the 2-ethyl derivative (**2b**) and thence into 2-ethyl-5-heptyl-1-nitrosopyrrolidine (**3b**). Removal of the nitroso function gave an overall 33% yield of a 50:50 mixture of isomeric hydrochlorides **4b**. A sample converted to the free base and submitted to mass-spectral analysis gave a spectrum identical to that obtained by Fales et al.[6] for 2-ethyl-5-heptylpyrrolidine, isolated from fire-ant venom. Obviously, this method will be applicable to the preparation of other 2,5-dialkylpyrrolidines identified as venom constituents[1], i.e. 2-ethyl-5-pentyl-[7] and 2-butyl-5-heptylpyrrolidine.

Some practical observations merit attention. Although benzylation was achieved in high yield without the use of hexamethylphosphoric triamide (HMPT), all alkylations with *n*-alkyl iodides were improved by its addition. For example, the yield of alkylation of 1-nitrosopyrrolidine (**1**) with 1-iodoheptane rose from 15% (no HMPT) to 67% upon addition of 2 ml HMPT to the solvent (140 ml). In this regard, none of the reported yields of alkylation have been maximized with respect to the amount of HMPT added. In several attempted alkylations of 2-heptyl-1-nitrosopyrrolidine with 1-iodoheptane, only trace amounts of dialkylated product could be discerned by T.L.C. Obviously, the size of the alkylating agent influences the yield in this reaction.

These alkylations of 1-nitrosopyrrolidine serve as further examples of the currently rapidly increasing utility of lithiated nitrosamines as synthetic intermediates[5].

Caution! In view of the known carcinogenicity of nitrosamines[3, 5] all reactions have to be carried out in a fume hood on as small a scale as practicable. Standard safety precautions have previously been outlined[3].

2-Benzyl-1-nitrosopyrrolidine (2a):

The reaction is carried out in a round-bottom flask equipped with a septum-covered side arm, under an atmosphere of nitrogen. To a solution of diisopropylamine (0.165 ml, 1.15 mmol) in dry tetrahydrofuran (35 ml) is injected a solution of butyllithium (1.15 mmol) in ether (Ventron Corp.). The mixture is stirred for 5 min at room temperature and the flask then immersed in a cooling bath (–95°). After 10 min, a solution of 1-nitrosopyrrolidine (**1**; 100 mg, 1.0 mmol) in tetrahydrofuran (1 ml) is injected and stirring is continued for 1 h. Then, benzyl bromide (0.85 g, 5 mmol) is added and the mixture stirred for another 30 min at –95° and for 5 h at –78°. Water (0.05 ml) is then added and the cooling bath removed. The contents of the flask are concentrated to a syrupy residue which is dissolved in dichloromethane (30 ml), washed with water, dried, and again concentrated. The crude product is purified by chromatography on silica (ratio 1:50) using hexane (to elute benzyl bromide) followed by hexane/ethyl acetate (3:1) as eluent; crude yield: 184 mg (97%). The product obtained is used directly in the next step.

^{1}H-N.M.R. (CDCl$_3$): δ = 1.9–2.1 (m, 4H, at C-3, C-4); 2.6–3.1 (1H, half of benzylic AB as two quartets; *syn*/*anti* ratio 3:1); 3.4–3.9 (3H, 1 benzylic + 2H at C-5); 4.7 ppm (m, 1H, methine).

2,5-Dibenzyl-1-nitrosopyrrolidine (3a):

The above procedure is repeated with **2a** on a 1 mmol scale, with identical work-up and purification; yield: 238 mg (85%, based on **1**).

^{1}H-N.M.R. (CDCl$_3$): δ = 1.6–1.9 (m, 4H, at C-3, C-4); 2.55–3.75 (complex m, CH$_2$); 4.5 (2H, br s, CH); 7.2 ppm (br s, 5H$_{\text{arom}}$).

2,5-Dibenzylpyrrolidine Hydrochloride (4a):

A solution of 2,5-dibenzyl-1-nitrosopyrrolidine (**3a**; 74 mg, 0.26 mmol) in dry benzene (30 ml) is saturated with dry hydrogen chloride. The solution is heated with stirring for 1 h while a stream of hydrogen chloride is continuously passed into the solution. Then, dry nitrogen, more hydrogen chloride, and again dry nitrogen are passed through for 30 min intervals. The solvent is removed in vacuo and the amorphous residue recrystallized from 99% ethanol/acetone mixture; yield: 61 mg (90%) of colorless crystals; m.p. 203–205°.

$C_{18}H_{22}ClN$	calc.	C 75.1	H 7.7
(287.8)	found	75.3	7.7

^{13}C-N.M.R. of free base ($CDCl_3$): (a) *trans* Isomer: $\delta = 31.2$ (C-3); 58.9 (C-2); 42.9 ($\underline{C}H_2—C_6H_5$); 126.0, 128.3, 128.9, 139.3 quaternary (phenyl); (b) *cis* Isomer 30.5 (C-3); 60.3 (C-3); 42.9 ($\underline{C}H_2—C_6H_5$); 126.0, 128.3, 128.9, 140.1_9 (phenyl).

2,5-Dibenzyl-1-trichloromethylthiopyrrolidine:

To a solution of 2,5-dibenzylpyrrolidine (**4a**; 125 mg, 0.5 mmol) in hexane (10 ml), trichloromethanesulfenyl chloride (102 mg, 0.55 mmol) and triethylamine (203 mg, 2 mmol) are added with stirring.

After stirring for 3 h at room temperature, the solution was filtered, and washed in turn with water, 5% hydrochloric acid, saturated sodium hydrogen carbonate solution and water. The hexane solution was dried over magnesium sulfate, then filtered, and concentrated in vacuo to give a syrup; yield: 160 mg (80%). This material was then examined by 220 MHz ^{1}H-NM.R. spectroscopy. A portion of this crude was purified by chromatography on silica using benzene as eluent to yield a colorless oil, (for mass spectral analysis).

$C_{19}H_{20}Cl_3NS$ (399.2)

M.S.: $m/e = 399$. The isotopic cluster of M+2, M+4 and M+6 had relative intensities typical of a molecule containing three Cl atoms.

^{1}H-N.M.R. ($CDCl_3$, 220 MHz): $\delta = 1.7$–2.0 (br m, 4H, at C-3, C-4); 2.35 (2 overlapping q, J's = 11 and 13 Hz) and 2.66 (q, J's = 11 and 13 Hz) total of 2H, benzylic; 3.27, 3.50 and 3.58 (three equally intense q's, J's = 13 and 4 Hz) total of 2H benzylic); 4.15–4.35 (br m, 2H, at C-2, C-5); 7.1–7.3 ppm (m, $10H_{arom}$). Minor absorptions attributable to about 5% of a second *cis* isomer could be seen in the benzylic region.

The three different AB portions of ABX spectra are all of the same intensity, ±10%. Since the benzylic absorption for the major *N*-trichloromethylthio derivative (sulfenamide) of the *cis* amine must have twice the intensity of each non-equivalent benzyl group in the *trans* derivative, the major diastereomeric amine cannot be *cis*. Confirmatory evidence was seen in the presence of a minor benzylic AB (coupled with X) pattern of relative intensity 5% of total AB's. This is due to the minor *N*-trichloromethylthio derivative of the *cis* isomer, whose proportion of the total *cis* derivative is similar to that observed by Raban et al.[4] in the sulfenamides derived from *meso*-bis[1-phenylethyl]amine.

2-Ethyl-1-nitrosopyrrolidine (2b):

The procedure is analogous to that used for the preparation of **2a**, with the modification that hexamethylphosphoric triamide (1 ml) is added to the solvent. Ethyl iodide (172 mg, 1.1 mmol) is used as the alkylating agent. Work-up gives an oil which is purified by column chromatography on silica gel using hexane/ethyl acetate (4:1) as eluent; yield: 80 mg (64%) of **2b** as an oil. This material is used directly in the next step.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.7$–1.3 (two t, 6H, CH_3); 1.8–2.2 (br m, 8H, CH_2, s); 3.5 (m, 1H, CH); 4.2 ppm (m, 1H, CH).

2-Ethyl-5-heptyl-1-nitrosopyrrolidine (3b):

The reaction of 2-ethyl-1-nitrosopyrrolidine (**2b**; 80 mg, 0.6 mmol) with lithium diisopropylamide and the alkylation with 1-iodoheptane (268 mg, 1.1 mmol) is carried out under conditions identical to the above ethylation procedure. The oily product is purified by column chromatography as above; yield: 83 mg (65%).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.65$–1.05 (6H, 2 sharp t, $2CH_3$; equal intensities and 1 br. triplet, C-7, CH_3); 1.09–1.24 (br s, 2H, CH_2, s); 1.49–2.25 (br m, 6H, CH_2, s); 4.40–4.62 ppm (br s, 1H, methine).

2-Ethyl-5-heptylpyrrolidine Hydrochloride (4b):

2-Ethyl-5-heptyl-1-nitrosopyrrolidine (**3b**; 83 mg, 0.37 mmol) is treated with hydrogen chloride in benzene as described for **3a**; yield of *cis/trans* mixture **4b**: 69 mg (80%); m.p. 85–90°.

Analytical data of a sample converted to the free *2-ethyl-5-heptylpyrrolidine:*

$C_{13}H_{28}ClN$	calc.	C 67.0	H 12.1
(233.9)	found	67.1	12.5

M.S.: $m/e = 197$ ($M^{\oplus}$); 168 ($M^{\oplus} - C_2H_5$); 98 ($M^{\oplus} - C_7H_{15}$); and a whole fragmentation pattern identical to that measured by Fales et al.[6].

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[6] We are grateful to Dr. H. Fales, N.I.H., Bethesda Md., for providing us with a mass spectrum of this naturally occurring component of fire ant venom.

[7] The synthesis of 2-ethyl-5-pentylpyrrolidine has been accomplished using a Hoffmann-Löffler ring closure of the appropriate chloramine, H. Fales, Private communication.