Hindered Amines[1]. 4-Hydroxy-1,3,3,5,5-pentasubstituted-2-piperazinones

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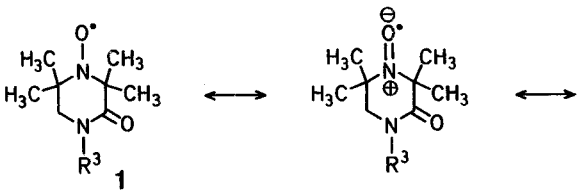
N-Hydroxy derivatives of hindered amines have been the topic of a number of articles[2] and were mentioned often in biological spin label studies[3]. They are generally sensitive to air oxidation and sometimes to hydrolysis[4], and are in all cases prepared, and often studied, *in situ* by the reduction of the corresponding nitroxyl radicals[2a,3]. Although the *N*-hydroxy derivatives are very similar to the nitroxyl radicals in structure, the two have distinctly different physical properties. For example, the *N*-hydroxy derivatives of certain cyclic hindered amines have wide melting points[2b] even when the four substituents on the two adjacent carbons to the amino group are symmetrical to the C—N—C plane, are diamagnetic, and colorless, while the nitroxyl radicals have sharp melting points, are paramagnetic, and highly colored.

The *N*-hydroxy groups of hindered amines (e.g. **3**) are rigid, therefore producing conformational isomers from the OH and R^3 groups. However, the nitroxyl radicals (e.g. **1**) are probably flexible due to the following contributing resonance forms:



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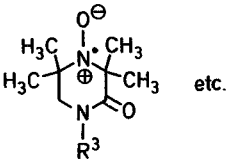


etc.

In the study of the oxidation of 1,3,3,5,5-pentasubstituted-2-piperazinones **(2)**, we found that increasing crowdedness around the amino nitrogen atom renders more stability to their N^4-hydroxy derivatives **(3)** towards further oxidation[5]. Therefore, although 3,3,5,5-tetramethylated compounds **2** (e.g. **2f**) cannot be oxidized cleanly to its *N*-hydroxy derivative **3** without heavy contamination from the nitroxyl radical **1** (the presence of **1** was indicated by peak broadening in the ^{1}H-N.M.R. spectra and by the unsatisfactory microanalysis values), compounds **3** with more crowded surroundings around the amino group (e.g. **3a–e**) can be isolated in pure form when one equivalent of *m*-chloroperbenzoic acid is used as the oxidant (Table 1). All compounds **2** are oxidized smoothly to **1** when two equivalents of *m*-chloroperbenzoic acid are employed[6].

Table 1. N^4-Hydroxy-1,3,3,5,5-pentaalkyl-2-piperazinones **3** prepared by Oxidation of **2**

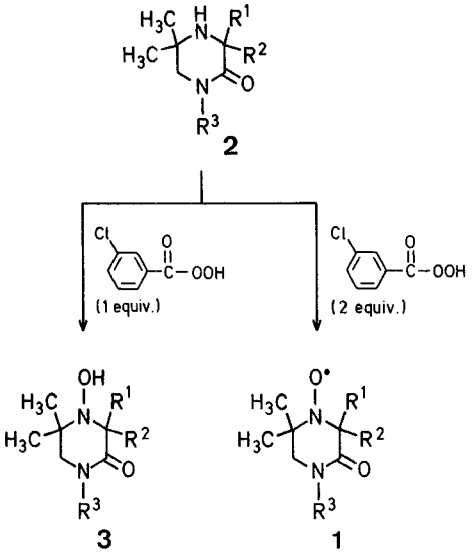
Product No.	R^1	R^2	R^3	Yield [%][a]	m.p. [°C]	Molecular Formula[b]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
3a	CH_3	C_2H_5	i-C_3H_7	75	142–153°	$C_{12}H_{24}N_2O_2$ (228.3)	0.81 (t, 3H, J=7.2 Hz); 1.12 (d, 6H, J=6.7 Hz); 1.13 (s, 6H); 1.42 (s, 3H); 1.68 (q, 2H, J=7.2 Hz); 2.91 (AB-q, 2H); 4.86 (hept, 1H, J=6.7 Hz); 5.8 (br. s, 1H)
3b	CH_3	i-C_4H_9	i-C_3H_7	72	122–129°	$C_{14}H_{28}N_2O_2$ (256.4)	0.79 (d, 3H, J=5.3 Hz); 0.92 (d, 3H, J=5.3 Hz); 1.07 (d, 6H, J=6.6 Hz); 1.18 (s, 3H); 1.26 (s, 3H); 1.36 (s, 3H); 1.6–1.8 (m, 3H); 2.94 (AB-q, 2H); 4.87 (hept, 1H, J=6.6 Hz); 4.9 (br. s, 1H)
3c	—$(CH_2)_5$—		i-C_3H_7	70	140–162°	$C_{14}H_{26}N_2O_2$ (254.4)	1.06 (d, 6H, J=6.7 Hz); 1.16 (s, 6H); 2.3–3.2 (m, 12H); 2.93 (s, 2H); 4.3 (br. s, 1H); 4.78 (hept, 1H, J=7.1 Hz)
3d	CH_3	C_2H_5	t-C_4H_9	71	126–132°	$C_{13}H_{26}N_2O_2$ (242.4)	0.82 (t, 3H, J=7.1 Hz); 1.14 (s, 3H); 1.22 (s, 3H); 1.40 (s, 3H); 1.41 (s, 9H); 1.5–1.8 (m, 2H); 3.0–3.1 (AB-q, 2H); 4.6 (br. s, 1H)
3e	CH_3	n-C_4H_9	C_6H_5	63	123–126°	$C_{17}H_{26}N_2O_2$ (290.4)	0.90 (t, 3H, J=6.9 Hz); 1.26 (s, 3H); 1.33 (s, 3H); 1.52 (s, 3H); 1.5–1.9 (m, 6H); 3.1–3.7 (AB-q, 2H); 4.5 (br. s, 1H); 7.2–7.4 (m, 5H)

[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.13, N ±0.30; analyses performed by Huffman Labs., Inc., Wheatridge, Colorado.
[c] Bruker WH-200 spectrometer.

Table 2. N^4-Hydroxy-1,3,3,5,5-tetraalkyl-2-piperazinones **3** prepared by Reduction of **1**

Product No.	R^1	R^2	R^3	Method	Yield [%][a]	m.p. [°C]	Molecular Formula[b]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
3a	CH_3	C_2H_5	i-C_3H_7	B	82	142–148°	see Table 1	
				A	75	140–147°	see Table 1	
3f	CH_3	CH_3	i-C_3H_7	B	75	108–111°	$C_{11}H_{22}N_2O_2$	1.07 (d, 6H, J=6.7 Hz); 1.18 (s, 6H); 1.41 (s, 6H); 2.93 (s, 2H); 4.3 (br. s, 1H); 4.84 (hept, 1H, J=6.7 Hz)
				A	66	103–108°	(214.3)	
3g	—$(CH_2)_5$—		i-C_3H_7	A	62	137–147°	$C_{14}H_{26}N_2O_2$ (254.4)	1.07 (d, 6H, J=6.7 Hz); 1.21 (s, 6H); 1.3–2.1 (m, 10H); 3.05 (s, 2H); 4.86 (hept, 1H, J=6.7 Hz); 5.1 (br. s, 1H)

[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.36, H ±0.22, N ±0.14; analyses performed by Huffman Labs., Inc., Wheatridge, Colorado.
[c] Bruker WH-200 spectrometer.



The sensitivity of the oxidation from **3** to **1** as related to the sizes of the groups R^1, R^2, R^3 is illustrated by the examples of **3c** and **3g**. While **3c**, where R^2 and R^3 form a seven-membered ring can be prepared pure, **3g**, with a six-membered ring, cannot without being contaminated by **1g**. Compounds **3f** and **3g**, however, can be synthesized from the reductions of **1f** and **1g**, respectively, with phenylhydrazine[2a,b] or hydrogen[7].

N^4-Hydroxy-1,3,3,5,5-pentasubstituted-2-piperazinones (3a–e) from Oxidation of 1,3,3,5,5-Pentasubstituted-2-piperazinones (2); General Procedure:

Compound **2** (0.01 mol) is dissolved in dichloromethane (50 ml). *m*-Chloroperbenzoic acid (1.73 g, 0.01 mol) is added in small portions in 30 min. After 5 h, 5% aqueous sodium carbonate solution (50 ml) is added. The aqueous layer is further extracted with dichloromethane (3 × 50 ml). The combined organic solutions are dried with sodium sulfate and concentrated. The crude residue is washed with hexanes to afford product **3** as a white solid which can be further purified by recrystallization from hexanes or hexanes/toluene (Table 1).

N^4-Hydroxy-1,3,3,5,5-pentasubstituted-2-piperazinones 3 from Reduction of Nitroxyls 1:

Method A using phenylhydrazine: Crude nitroxyl **1a, f, g** (5.0 mmol) is dissolved in methanol (10 ml). Phenylhydrazine (0.27 g, 2.5 mmol) is added and the mixture is refluxed under argon for 8 h. Solvent is removed and the crude residue is recrystallized from heptane (Table 2).

Method B using hydrogen: Crude nitroxyl **1a, f** (1.0 g, obtained directly from the oxidation of **2**) is dissolved in tetrahydrofuran (20 ml). 10% Palladium on charcoal (0.05 g) is added, the mixture is hydrogenated at 3 atm until no further hydrogen uptake is observed (1–2 h), filtered, and concentrated to a solid which is recrystallized from heptane (Table 2).

Received: July 15, 1983

[1] Part 7 of a series. For part 6, see J. T. Lai, *Synthesis* **1984**, 122.
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[6] J. T. Lai, *Synthesis* **1981**, 40.
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