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Synthesis of 2-Aryl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrroles

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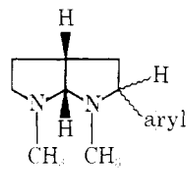
The synthesis of a series of 2-aryl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrroles (**1**) via the reductive cyclization of 3-(2-aryl-2-aminoethyl)-1-methyl-2-pyrrolidones (**4**) using diisobutylaluminum hydride is described. The diastereomers of **1** were separated and structures assigned on the basis of NMR spectra. The products resulting from the reductive trapping of the ring opened iminium species **7** with sodium cyanoborohydride generated from **1** in acid solution are also identified.

In our search for new bioactive structures, the octahydropyrrolo[2,3-*b*]pyrrole ring system bearing an aryl substituent in the 2 position (**1**) appeared as a promising candidate. This



1

relatively simple ring system has not previously been reported, although it does occur fused to an aromatic ring in the physostigmine-type alkaloids.

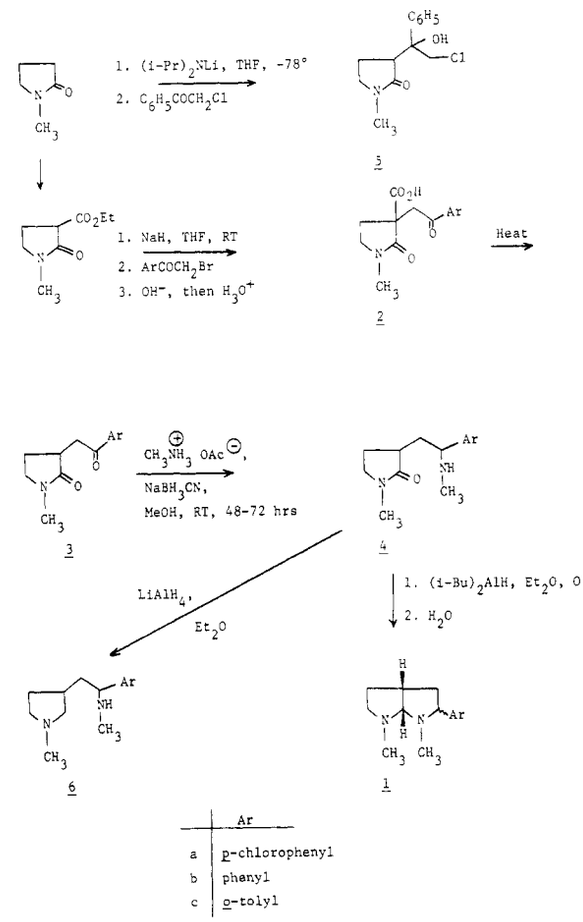
N-Methyl-2-pyrrolidone was chosen as the starting material for the synthesis of **1** since it was hoped that anion formation followed by alkylation with a phenacyl halide would lead to ketone **2**. Surprisingly, the only product which could be isolated from the alkylation reaction was the chloro alcohol **5** in 20–25% yield.

We then decided to alkylate the enolate of *N*-methyl-3-carbethoxy-2-pyrolidinone[1] since it was felt that this anion would be less reactive with respect to carbonyl addition. In the event, the desired alkylation proceeded cleanly and was followed by hydrolysis to afford the carboxylic acids **2**. Decarboxylation then gave the ketolactam **3**. The ketolactam **3** was then aminated using sodium cyanoborohydride[2] and methylammonium acetate to afford good yields of **4**.

Although the literature of the physostigmine alkaloids reports ring closures of the desired type (**4** to **1**) using lithium aluminum hydride,[3] in our hands this reagent gave only poor yields of **1**. The primary product from this reaction was the mixture of diastereomers **6**. Changing the order of addition, temperature, or using clarified solutions of lithium aluminum hydride in place of a suspension had little or no effect on the results. However, the use of diisobutylaluminum hydride, which has found utility in the generation of enamines from lactams,[4] afforded **1** in good yield accompanied by small amounts of **6** (Scheme I).

Chromatography of the reaction mixture on alumina cleanly separated the C-2 epimers of **1**. Table I lists examples of

Scheme I



compounds prepared by this route. The yields are believed to represent the distribution of products from the reaction mixture since the epimers of **1** were found to be stable to base and to rechromatography on alumina. However, the dissolution of either isomer in acid and reisolation gave the same mixture of isomers observed in the reaction before chromatography, determined in both cases by NMR spectrometry.

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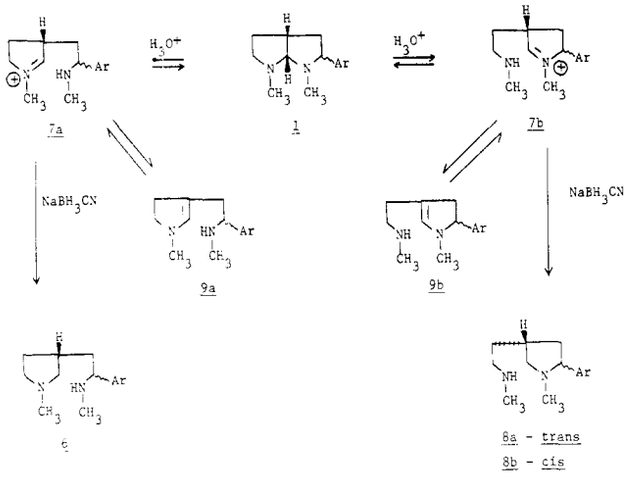
Table I. Product Distribution of 2-Aryl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrroles

compd 1, Ar =	isomer[a] A	registry no.	δ_{H6a}	B	registry no.	δ_{H6a}
a. *p*-chlorophenyl	mp 69–70 °C (27%)	67505-89-9	3.9, J = 7 Hz	mp 56–57 °C (36%)	67529-75-3	3.6, J = 7 Hz
b. phenyl	mp 46–47 °C (29%)	67505-90-2	3.9, J = 7 Hz	bp 74–77 °C (0.01 mm) (42%)	67529-76-4	3.6, J = 7 Hz
c. *o*-tolyl	bp 79–81 °C (0.02 mm) (19%)	67505-91-3	3.9, J = 7 Hz	mp 48–50 °C (42%)	67529-77-5	3.6, J = 7 Hz

[a] Isomer A is the compound which eluted first from the column and isomer B eluted second. Numbers in parentheses are yields after purification.

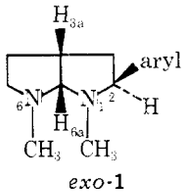
Scheme II



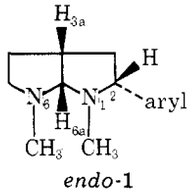
Because each of the epimers of 1 was readily equilibrated to the original mixture of diastereomers, we thought it would be desirable to determine how the ring system opened and reclosed. We also felt that this information could have biological significance. A priori, in acidic solution two modes of ring opening are possible to give the iminium species **7a** and **7b**. Both **7a** and **7b** could be trapped by sodium cyanoborohydride under the conditions of the reaction to give the amines **6** and/or **8**. Furthermore, both **6** and **8** could be produced as a mixture of diastereomers from a given epimer of **1** if equilibration through enamines **9a** and **9b** were to be faster than reduction. However, choice of a suitable pH for the trapping experiment could be expected to minimize enamine formation.

In the event, each epimer of **1b** gave rise to a single diastereomeric product when added to a solution of sodium cyanoborohydride initially at pH 4. If, however, each epimer of **1b** was first dissolved in acid (pH 4) and after several minutes treated with sodium cyanoborohydride, then a mixture of diastereomeric reduction products could be detected. Identification of the reduction product was straightforward since comparison of the NMR spectral data of the reduction product with that of the diastereomeric mixture **6** prepared by an independent route (vide supra) confirmed that **8** was indeed the compound isolated, no trace of **6** being detected (Scheme II). The stereochemistry of **8** will be commented on below.

Assignment of Structures. The two possible cis diastereomers of **1** are shown below (only one component of each racemic mixture is shown for clarity):



exo-**1**



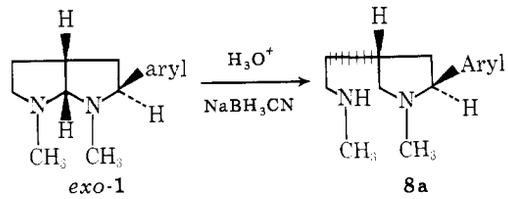
endo-**1**

The cis ring fusion is assigned on the basis of what is known concerning *cis*- and *trans*-bicyclo[3.3.0]octanes. On the basis of combustion data,[5,6] the cis hydrocarbon is ca. 6 kcal/mol more stable than the trans isomer. We expect that this preference should carry over to the octahydropyrrolo[2,3-*b*]pyrrole system. Further, our observed coupling constants for the bridgehead protons ($J_{3a,6a}$ = 7 Hz) are indicative of a cis ring fusion. A coupling constant of the same order (6.2 Hz) was reported[7] for the *cis*-tetrahydrofuro[2,3-*b*]furan[8] moiety present in clerodendrin A. Similar J values (6.0–6.7 Hz) have also been reported[9] for the bridgehead protons in *cis*-hexahydrofuro[2,3-*b*]imidazolones. Unfortunately, there do not appear to be any reports in the literature where the coupling constants between bridgehead protons in *trans*-[3.3.0]bicyclic systems have been observed, thus making a direct comparison impossible.

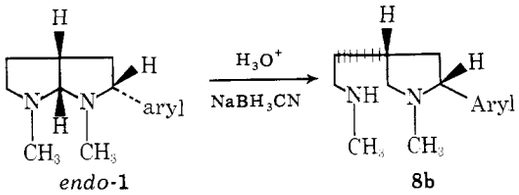
Examination of Dreiding models suggests that the N_1–CH_3 and the aryl substituent should prefer a trans relationship in both isomers. This observation is supported by recent NMR evidence[10] that the *N*-methyl group and pyridine ring of nicotine are trans in the most stable conformation. For both isomers examination of models predicts a pseudoequatorial assignment for N_6–CH_3. This leads to the conclusion that the 6a proton will be cis to N_6–CH_3 in both isomers. The 6a proton, however, is cis to N_1–CH_3 in the endo isomer and trans to N_1–CH_3 in the exo isomer when both isomers are in their most stable conformation.

Breuer and Melumad[11] have shown that protons attached to the α position of *N*-methylpyrrolidines are shielded when situated cis to the *N*-methyl group. Thus, for our case, the endo isomer should show more shielding of the 6a proton than the exo isomer due to the relationship between the 6a proton and N_1–CH_3. A distinct difference is observed, the 6a proton being more shielded in isomer B than in A (Table I). Therefore, on the basis of NMR data, isomer A can be assigned as *exo*-**1** and isomer B as *endo*-**1**.

Each epimer of **1** was shown to give a single diastereomeric product (**8**) upon reduction in acid solution. The structures of these products can now be assigned based on the structure of the starting epimer of **1** and are shown below (one component of the racemic mixture is shown for clarity):



exo-**1** **8a**



endo-**1** **8b**

Experimental Section

NMR spectra were run on a Varian T-60 spectrometer using $CDCl_3$ as solvent with tetramethylsilane as internal standard. All melting and boiling points are uncorrected. Elemental analyses were done by the analytical staff of MSDRL under the direction of Mr. Jack Gilbert. Tetrahydrofuran (THF) was distilled from sodium–benzophenone and ether was used from freshly opened cans.

Reaction between *N*-Methylpyrrolidone Anion and Phenacyl Chloride. To a cold (−60 °C) solution of lithium diisopropylamide (50 mmol) in THF–hexane (1:1, 50 mL) was added a solution of *N*-methyl-2-pyrrolidone (4.95 g, 50 mmol) in THF (25 mL) during 30 min followed by an additional 15 min of stirring. Phenacyl chloride (7.75 g, 50 mmol) in THF (125 mL) was added to the cold anion solution during 1 h followed by stirring at −60 °C for 4 h. The cooling bath was then removed and the reaction mixture allowed to reach room temperature after which it was poured into saturated sodium chloride solution (100 mL). The organic phase was separated, washed with brine, and dried over anhydrous Na_2SO_4. Filtration followed by concentration of the filtrate on the rotary evaporator left a yellow oil. Dissolution of the oil in ether followed by standing yielded a white crystalline solid (2.20 g). Recrystallization from CH_2Cl_2–ether gave white needles: mp 126–127 °C; NMR ($CDCl_3$) δ 7.30 (5 H), 4.56 (d, 1 H, J = 13 Hz), 4.47 (s, 1 H), 4.01 (d, 1 H, J = 13 Hz), 3.07 (m, 3 H), 2.73 (s, 3 H); MS, M^+, 235; base peak, 204.

Anal. Calcd for $C_{13}H_{16}ClNO_2$: C, 61.54; H, 6.32; N, 5.52. Found: C, 61.63; H, 6.18; N, 5.43.

1-Methyl-3-phenacyl-2-pyrrolidone-3-carboxylic Acid (2b). In a 1 L three-neck flask equipped with a dropping funnel, nitrogen bubbler, and an efficient mechanical stirrer was placed sodium hydride (2.75 g, 57% mineral oil dispersion, 65 mmol) which was then washed several times with pentane to remove oil and finally was suspended in THF (200 mL). 1-Methyl-3-carbethoxy-2-pyrrolidone[1] (10.0 g, 58.5 mmol) in THF (200 mL) was added during 1 h and the mixture stirred an additional 1.5 h, all at room temperature. Phenacyl bromide (11.7 g, 58.5 mmol) in THF (100 mL) was added during 1 h at room temperature and the resulting mixture stirred for 18–20 h. Water (10 mL) was then added and the mixture filtered. The filtrate was dried over $MgSO_4$ and concentrated to give the ketoester as a thick oil which was hydrolyzed directly to the ketoacid.

The crude ketoester (50 mmol) was dissolved in methanol (50 mL) and treated with a solution of sodium hydroxide (4.2 g) in water (100 mL). The mixture was kept at 60 °C for 30 min, then cooled to room temperature, diluted with water (150 mL), and washed with CH_2Cl_2. The aqueous phase was acidified with concentrated hydrochloric acid and the precipitated carboxylic acid was filtered and dried. The dried acid was triturated with pentane to remove yellow impurities. The acid was recrystallized from pentane–CH_2Cl_2: yield 9.53 g, 73%; mp 158–159 °C dec.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.39; H, 5.74; N, 5.36. Found: C, 64.50; H, 5.96; N, 5.24.

1-Methyl-3-(*p*-chlorophenacyl)-2-pyrrolidone-3-carboxylic Acid (2a): 90% yield; mp 154–155 °C dec.

Anal. Calcd for $C_{14}H_{14}ClNO_4$: C, 56.88; H, 4.73; N, 4.73. Found: C, 56.99; H, 4.76; N, 4.67.

1-Methyl-3-(*o*-methylphenacyl)-2-pyrrolidone-3-carboxylic acid (2c): 86% yield; mp 143–144 °C.

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.47; H, 6.18; N, 5.09. Found: C, 65.47; H, 6.18; N, 4.99.

1-Methyl-3-phenacyl-2-pyrrolidone (3b). The acid **2b** (8.00 g, 30.6 mmol) was placed in a round-bottom flask and heated at 165 °C until CO_2 evolution ceased. The reaction mixture was cooled and the ketolactam **3b** purified by bulb-to-bulb distillation: bp 150 °C (50 μm); 5.78 g, 87%; NMR δ 8.0 (m, 2 H), 7.45 (m, 3 H), 3.0–4.0 (m, 5 H), 2.85 (s, 3 H), 1.5–2.9 (m, 2 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.90; H, 6.90; N, 6.45. Found: C, 71.63; H, 6.92; N, 6.53.

1-Methyl-3-(*p*-chlorophenacyl)-2-pyrrolidone (3a): 88% yield; mp 76–77 °C (ether–pentane); NMR δ 7.7 (4 H), 3.0–4.0 (m, 5 H), 2.85 (s, 3 H), 1.5–2.9 (m, 2 H).

Anal. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.06; H, 5.56; N, 5.56. Found: C, 62.00; H, 5.25; N, 5.16.

1-Methyl-3-(*o*-methylphenacyl)-2-pyrrolidone (3c): 96% yield; isolated as a thick oil after chromatography on silica gel with 95:5 $CHCl_3$–2-propanol; NMR δ 7.2–7.8 (4 H), 3.0–4.0 (m, 5 H), 2.85 (s, 3 H), 2.50 (s, 3 H), 1.5–2.9 (m, 2 H).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.55; H, 7.41; N, 5.97.

3-(2-Phenyl-2-*N*-methylaminoethyl)-1-methyl-2-pyrrolidone (4b). To a solution of methylammonium acetate, prepared by mixing ice cold solutions of 6 M methanolic methylamine (45 mL, 0.27 mol) and acetic acid (16.2 g, 0.27 mol) in methanol (25 mL), was added **3b** (8.68 g, 40 mmol) and sodium cyanoborohydride (1.70 g, 27 mmol). The solution was stirred at room temperature for 48 h after which it was reduced in volume by ca. 50% on the rotary evaporator. Water (150 mL) was added and the pH adjusted to 1 by the addition of concentrated hydrochloric acid (**Caution:** HCN). After the evolution of gas ceased, the reaction mixture was washed with CH_2Cl_2. The aqueous layer was made basic and extracted with CH_2Cl_2. Drying (K_2CO_3) and concentration of the organic extracts afforded **4b** as a pale yellow oil: 8.16 g, 94%; NMR δ 7.3 (s, 5 H), 3.6 (m, 1 H), 3.2 (m, 2 H), 2.8 (s, 3 H), 2.25 (s, 3 H), 1.3–2.4 (m, 6 H).

3-(2-*p*-Chlorophenyl-2-*N*-methylaminoethyl)-1-methyl-2-pyrrolidone (4a): 87% yield; NMR δ 7.2 (s, 4 H), 3.7 (m, 1 H), 3.2 (m, 2 H), 2.8 (s, 3 H), 2.2 (s, 3 H), 1.2–2.5 (m, 6 H).

3-(2-*o*-Tolyl-2-*N*-methylaminoethyl)-1-methyl-2-pyrrolidone (4c): 75% yield; NMR δ 7.3 (m, 4 H), 4.1 (t, 1 H), 3.2 (q, 2 H), 2.8 (s, 3 H), 2.4 (s, 3 H), 2.25 (s, 3 H), 1.2–2.4 (m, 6 H).

1,6-Dimethyl-2-phenyl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]-pyrrole (1b). To a 1 L three-neck flask equipped with a dropping funnel, thermometer, and a reflux condenser carrying a nitrogen bubbler was added a solution of **4b** (7.74 g, 33 mmol) in anhydrous ether (300 mL) which was then cooled to 0 °C with an ice–salt bath. The dropping funnel was charged with a heptane solution of diisobutylaluminum hydride (56 mL, 1.26 M, 70 mmol) diluted with ether (200 mL) which was added dropwise over a period of 3 h. After the addition was complete, the cooling bath was removed and the reaction mixture stirred an additional 20 h. The reaction was quenched by the very cautious addition of water (5 mL) during 20 min followed by 15% sodium hydroxide solution (5 mL). After a few minutes of additional stirring the mixture was filtered, the filter cake was washed with ether, and the combined filtrate and washings were concentrated. The crude product was chromatographed on neutral activity III Woelm alumina using 7:3 hexane–ether as eluent. Fractions were collected and examined by TLC for products. See Table I for mp/bp's and yields.

1,6-Dimethyl-2-phenyl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]-pyrrole (1b). Isomer A (exo): NMR δ 7.3 (s, 5 H), 3.9 (d, 1 H), 3.7 (q, 1 H), 2.9 (m, 2 H), 2.5 (s, 3 H), 2.2 (s, 3 H), 1.4–2.2 (m, 5 H).

Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.79; H, 9.25; N, 12.95. Found: C, 78.00; H, 9.50; N, 12.93.

Isomer B (endo): NMR δ 7.3 (m, 5 H), 3.6 (d, 1 H), 3.4 (q, 1 H), 2.8 (m, 2 H), 2.5 (s, 3 H), 2.2 (s, 3 H), 1.2–2.4 (m, 5 H).

Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.79; H, 9.25; N, 12.95. Found: C, 78.04; H, 9.28; N, 12.86.

1,6-Dimethyl-2-*p*-chlorophenyl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]pyrrole (1a). Isomer A (exo): NMR δ 7.2 (s, 4 H), 3.9 (d, 1 H), 3.6 (q, 1 H), 2.9 (m, 2 H), 2.45 (s, 3 H), 2.2 (s, 3 H), 1.3–2.4 (m, 5 H).

Anal. Calcd for $C_{14}H_{19}ClN_2$: C, 67.09; H, 7.58; N, 11.17. Found: C, 66.97; H, 7.75; N, 11.01.

Isomer B (endo): NMR δ 7.3 (s, 4 H), 3.6 (d, 1 H), 3.4 (q, 1 H), 2.8 (m, 2 H), 2.5 (s, 3 H), 2.2 (s, 3 H), 1.1–2.4 (m, 5 H).

Anal. Calcd for $C_{14}H_{19}ClN_2$: C, 67.09; H, 7.58; N, 11.17. Found: C, 67.12; H, 7.77; N, 11.11.

1,6-Dimethyl-2-*o*-tolyl-*cis*-3a,6a-octahydropyrrolo[2,3-*b*]-pyrrole (1c). Isomer A (exo): NMR δ 7.3 (m, 4 H), 3.9 (d, 1 H), 3.8–4.2 (m, 1 H), 3.0 (m, 2 H), 2.5 (s, 3 H), 2.4 (s, 3 H), 2.3 (s, 3 H), 1.2–2.3 (m, 5 H).

Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.28; H, 9.56; N, 12.16. Found: C, 78.58; H, 9.74; N, 12.16.

Isomer B (endo): NMR δ 7.7 (m, 1 H), 7.2 (m, 3 H), 3.6 (d, 1 H), 3.5–3.9 (m, 1 H), 2.8 (m, 2 H), 2.5 (s, 3 H), 2.3 (s, 3 H), 2.2 (s, 3 H), 1.0–2.5 (m, 5 H).

Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.28; H, 9.56; N, 12.16. Found: C, 78.36; H, 9.28; N, 12.00.

Attempted Ring Closure of 4b with Lithium Aluminum Hydride. A solution of **4b** (1.15 g, 4.9 mmol) in ether (25 mL) was added to a cold (5 °C) solution of lithium aluminum hydride (10.5 mmol) in ether (25 mL) during 15 min. The reaction was brought to room temperature and stirred an additional 20 h, then quenched, filtered, and concentrated to a clear gum (0.95 g). Chromatography on alumina prep plates (8:2 ether–hexane) afforded 3 identifiable products, **1b** (isomer A), 85 mg, 8% yield; **1b** (isomer B), 119 mg, 11% yield; 1-methyl-3-(2-phenyl-2-methylaminoethyl)pyrrolidine (**6**), 570 mg, 54% yield, as a mixture of diastereomers. NMR ($CDCl_3$, diastereomeric mixture): N–CH_3 signals, δ 2.21, 2.24, 2.28.

Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.16; H, 10.03; N, 13.05.

Reductive Ring Opening of 1b (Isomer A, exo) and 1b (Isomer B, endo) with Sodium Cyanoborohydride. Sodium cyanoborohydride (50 mg, 0.8 mmol) was dissolved in aqueous acetic acid (2.0 mL),

prepared by adding sodium acetate (1.50 g) to 1 M acetic acid (100 mL). The substrate (50 mg, 0.23 mmol) was then added followed by methanol (10 drops) to give a homogeneous mixture. After 3 h at room temperature, 15% sodium hydroxide (1 mL) was added followed by extraction with CH_2Cl_2 (2 × 3 mL) after which the extracts were dried and concentrated. The products were isolated as oils.

***trans*-1-Methyl-2-phenyl-4-(2-methylaminoethyl)pyrrolidine (8a):** bp 58–60 °C (0.005 mm) (bulb to bulb); NMR δ 7.2 (s, 5 H), 3.3 (d of d, 1 H), 3.1 (t, 1 H), 2.4 (s, 3 H), 2.2 (s, 3 H), 1.4–2.8 (m, 8 H), 1.1 (s, 1 H). Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.12; H, 10.42; N, 12.80.

***cis*-1-Methyl-2-phenyl-4-(2-*N*-methylaminoethyl)pyrrolidine (8b):** bp 55 °C (0.005 mm) (bulb to bulb); NMR δ 7.1 (s, 5 H), 2.8–3.3 (m, 2 H), 2.4 (s, 3 H), 2.1 (s, 3 H), 1.2–2.8 (m, 9 H). Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 76.88; H, 10.38; N, 12.87.

Registry No.—**2a,** 67505-92-4; **2b,** 67505-93-5; **2c,** 67505-94-6; **3a,** 67505-95-7; **3b,** 67505-96-8; **3c,** 67505-97-9; **4a,** 67505-98-0; **4b,** 67505-99-1; **4c,** 67506-00-7; **6b** isomer 1, 67506-01-8; **6b** isomer 2, 67506-02-9; **8a** (Ar = Ph), 67506-03-0; **8b** (Ar = Ph), 67506-04-1; 1-methyl-3-(2-chloro-1-hydroxy-1-phenylethyl)-2-pyrrolidone, 67506-05-2; *N*-methylpyrrolidone anion, 67506-06-3; *N*-methyl-2-pyrrolidone, 872-50-4; phenacyl chloride, 532-27-4; phenacyl bromide, 70-11-1; 1-methyl-3-carbethoxy-2-pyrrolidone, 30932-85-5; *p*-chlorophenacyl bromide, 536-38-9; *o*-methylphenacyl bromide, 51012-65-8; methylammonium acetate, 6998-30-7.

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2,2,6,6-Tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine: Synthesis and Thermal Stability[1]

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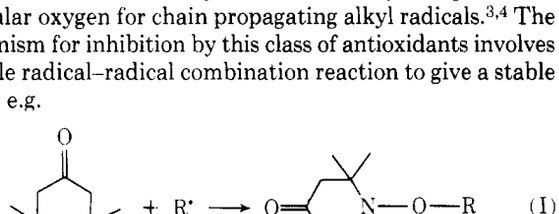
2,2,6,6-Tetramethyl-4-oxopiperidinyl-1-oxy reacts with the 1,1-diphenylethyl radical to give 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine. In solution this ether appears to exist in equilibrium with the parent radicals with $\Delta H°_2 \sim -21.4$ kcal mol^{-1} and $\Delta S°_2 \sim -36$ cal deg^{-1} mol^{-1}. In degassed solution there is an irreversible first-order decay of this *O*-alkyl hydroxylamine to give 1,1-diphenylethylene and 1-hydroxy-2,2,6,6-tetramethylpiperidin-4-one with $\log (k_3/s^{-1}) = 14.8 - 6425/T$. Decomposition is significantly faster when the solution contains dissolved oxygen because 1,1-diphenylethyl radicals are rapidly converted to 1,1-diphenylethylperoxy radicals and $\log (k_{-2}/s^{-1}) = 14.8 - 5354/T$. The strength of the O–C bond in 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine must be ~21 kcal mol^{-1}. 2,2,6,6-Tetramethyl-4-oxo-1-cumyloxypiperidine can be prepared from 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy and cumyl radicals and it is significantly more stable in degassed and oxygen-containing solutions than the *O*-1,1-diphenylethyl analogue.

Introduction

Cyclic di-*tert*-alkylnitroxides such as 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy, TMPO·, are efficient inhibitors for autoxidation because they can successfully compete with molecular oxygen for chain propagating alkyl radicals.[3,4] The mechanism for inhibition by this class of antioxidants involves a simple radical–radical combination reaction to give a stable ether,[3] e.g.



(I)

The stability of these ethers is pertinent to the use of nitroxides as antioxidants[3,4] and as radical scavengers in the determination of rates of initiation for homolytic reactions.[5] In this context we have recently discovered that several of these ethers, e.g., 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine, are thermally unstable. This discovery prompted us to embark on a kinetic and product study of the decomposition of this *O*-alkyl hydroxylamine and the closely related *O*-cumyl derivative and the results of this work are reported here.

Results and Discussion

During an attempt to measure the rate of production of 1,1-diphenylethyl from thermolysis of 2,2,3,3-tetraphenylbutane (3.3 mM) in oxygen-free *tert*-butylbenzene at 50 °C by monitoring the disappearance of 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy, TMPO· (initial concentration = 0.031 mM), we found (i) that the rate of nitroxide disappearance did not follow the expected zero-order kinetics, (ii) that the initial rate of nitroxide disappearance was about one-half the expected rate based on the known rate constant for decomposition of TPB[6] and the efficiency of radical production,[7] and (iii) that the nitroxide reached an apparent steady-state concentration of 0.002 mM (see Figure 1).

Now it is generally accepted that reactive alkyl radicals add rapidly to nitroxides to give *O*-alkyl hydroxylamines.[3,9–12] The reaction of 1,1-diphenylethyl with TMPO· would, therefore, be expected to give 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine, $TMPOR_1$, and in the presence of excess TPB all the nitroxide should have been consumed.

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