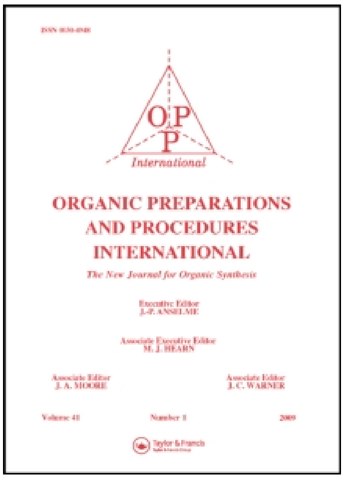

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USE OF SODIUM CYANOBOROHYDRIDE IN THE SYNTHESIS OF BIRADICAL NITROXIDES

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USE OF SODIUM CYANOBOROHYDRIDE IN THE SYNTHESIS OF BIRADICAL NITROXIDES

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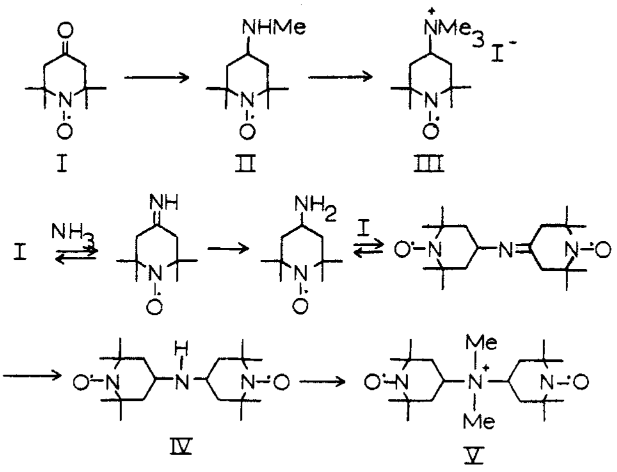
As a part of our continuing study of acetylcholinesterase,[1-3] it was advantageous to prepare spin labeled analogs of cholinesterase inhibitors for the purpose of mapping the anionic site of acetylcholinesterase. This communication describes the synthesis of spin labeled analogues of tetramethylammonium iodide, 4-(N-trimethylamino)-2,2,6,6-tetramethylpiperidinoxyl iodide(III) and 4-dimethyl-4-di(2,2,6,6-tetramethylpiperidinoxyl)ammonium iodide(V). We have previously discussed the preparation of 4-(N-methylamino)-2,2,6,6-tetramethylpiperidinoxyl(II) by reductive amination of 4-oxo-2,2,6,6-tetramethylpiperidinoxyl(I) using methylamine and sodium cyanoborohydride. As noted earlier,[4,5] reductive aminations are generally run using a large excess of the amine in order to shift the ketone-imine equilibrium in the direction of the imine and to minimize the formation of dialkylated amines. By varying the ratio of ketone to amine, it is possible to obtain predominately the dialkylated amines. For example, reaction of the ketone I with ammonium acetate in a ratio of 2:1 (ketone:amine) provides a good yield of the desired product IV. It is interesting to note that if the ratio of ketone to amine was reduced to 1:1 or even 1:2, formation of the trisubstituted amine was not observed, but the yield of IV was decreased.

Nitroxide biradicals may be characterized by the appearance of their electron paramagentic resonance (epr) spectrum in which the close spatial



relationship of the two unparied electrons results in a five line spectrum as depicted in Fig. 1. A mononitroxide gives an epr spectrum composed of three lines because the nitrogen nucleus has a spin of 1. Since line widths of the biradical spectrum are affected by the spatial relationship between the nitroxides, they are especially useful probes for investigating enzyme interactions.

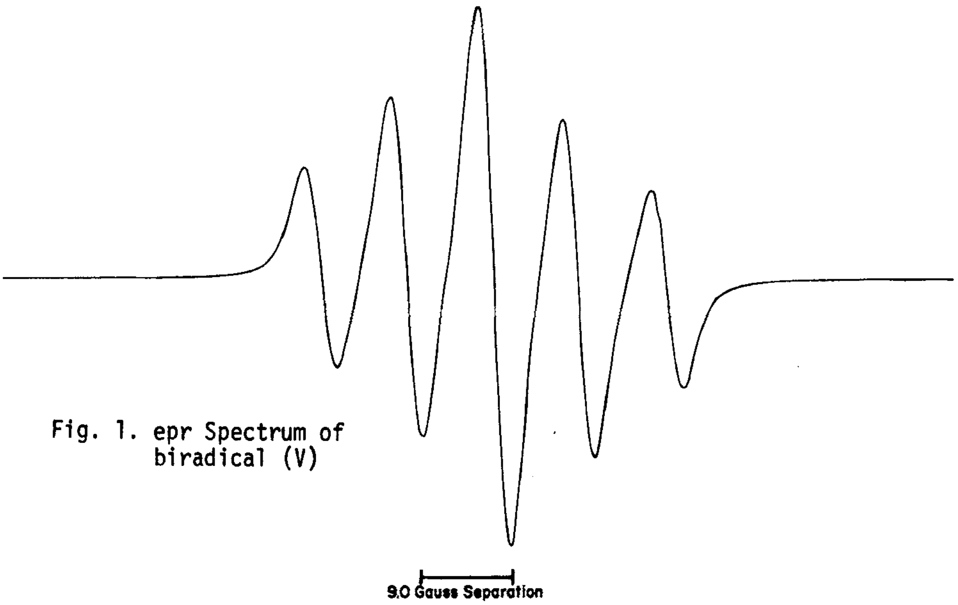


Fig. 1. epr Spectrum of biradical (V)

EXPERIMENTAL

Sodium cyanoborohydride was obtained from Aldrich. Mps were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Elemental analyses were performed by M-H-W Laboratories of Garden City, Mich. The electronparamagnetic resonance (epr) spectra were obtained on the Varian Associates E-9 spectrometer.

4-(N-Trimethylamino)-2,2,6,6-tetramethylpiperidinoxyl Iodide(III).-To a solution of 2.38g (352 mmoles) of methylamine hydrochloride in 150 ml of absolute methanol adjusted to pH 7-8 was added 1 g (58.8 mmoles) of 4-oxo-2,2,6,6-tetramethylpiperidinoxyl(I) and 0.22g (35.2 mmoles) of sodium cyanoborohydride. The reaction was stirred at ambient temperature for 24 hrs, filtered and the solvent removed *in vacuo*. The remaining oil was taken up in water, saturated with sodium chloride, extracted with ether, dried over anhydrous magnesium sulfate and distilled giving 0.82g (75%) of 4-(N-methylamino)-2,2,6,6-tetramethylpiperidinoxyl(II), bp. 56-59°/0.07 mm[5], as a red oil.

The methiodide salt was prepared by dissolving some of the red oil in an ether solution of methyl iodide at ambient temperature, overnight. The product III was filtered and was recrystallized from absolute ethanol, mp. 210-214°.

Anal. Calcd for $C_{12}H_{26}N_2OI$: C, 42.24; H, 7.67; N, 8.21. Found: C, 42.18; H, 7.52; N, 8.31.

4-Dimethyl-4-di(2,2,6,6-tetramethylpiperidinoxyl)ammonium Iodide(V).- To a solution of 1g (12.9 mmoles) of ammonium acetate in 150 ml of absolute methanol adjusted to pH 7-8 was added 4.39g (25.8 mmoles) of 4-oxo-2,2,6,6-tetramethylpiperidinoxyl(I) and 2.94g (46.7 mmoles) of sodium cyanoborohydride. The reaction mixture was stirred at ambient temperature for 24 hrs, filtered and the solvent was removed under vacuum. The remaining red oil was taken up in water, the pH lowered to 3-4 with 10% hydrochloric acid and extracted with ether. The remaining aqueous solution was made basic with 10% sodium hydroxide, saturated with sodium chloride and extracted with ether. The organic solution was dried over anhydrous magnesium sulfate, evaporated to dryness and chromatographed using neutral alumina (grade I) and chloroform to give 7.6g (60%) of 4-di(2,2,6,6-tetramethylpiperidinoxyl)amine(IV), mp. 155-156°.

Anal. Calcd. for $C_{18}H_{35}N_3O_2$: C, 66.42; H, 10.84; N, 12.91. Found: C, 66.43 H, 10.70; N, 12.80.

The methiodide salt was prepared as described above giving the product V, mp. 218-220° (from absolute ethanol).

Anal. Calcd. for $C_{20}H_{40}N_3O_2I$: C, 49.89; H, 8.37; N, 8.73. Found: C, 50.02; H, 8.18; N, 8.92.

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