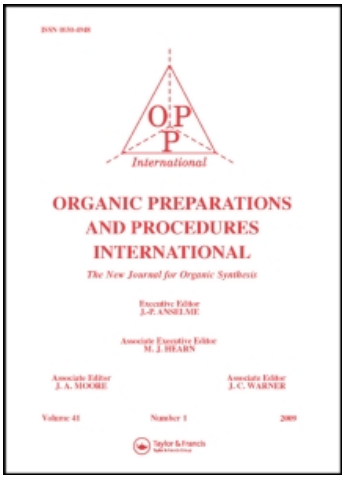

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THE USE OF TRIMETHYLSULFONIUM IODIDE IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE NITROXIDES

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THE USE OF TRIMETHYLSULFONIUM IODIDE IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE NITROXIDES

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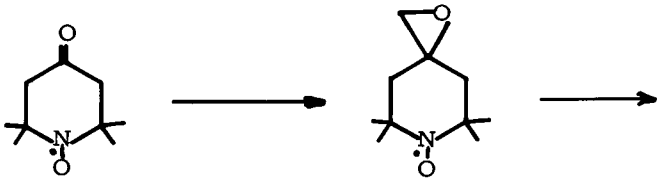
We have been engaged in the synthesis of several spin labeled acetylcholine analogs[1-3] and we now report the synthesis of the spin labeled acetylcholine analog, 4-trimethylaminomethyl-4-acetoxy-2,2,6,6-tetramethylpiperidinoxyl iodide (IV).



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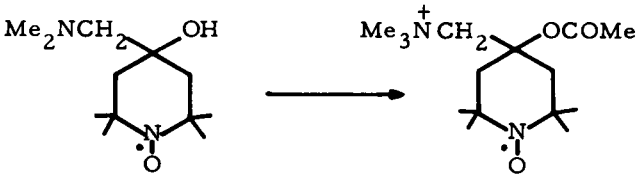

III IV

Our initial synthetic sequence used the original Corey[4] method in an attempt to obtain the desired oxirane intermediate (II) from the parent ketone. Unfortunately, this procedure failed to yield the desired product.

A modification of this procedure- namely adding the sodium hydride to a mixture of the ketone and trimethylsulfinium iodide in DMSO- however, resulted in a satisfactory yield of (II). Ring opening of the oxirane with dimethylamine proceeded readily to give the β-amino alcohol (III), which upon acetylation followed by methylation gave the desired acetylcholine analog (IV) in good yield. We have found this procedure to be applicable to all spin labeled ketones or aldehydes without fear of destruction of the nitroxide function.

EXPERIMENTAL

The elemental analysis was obtained from M-H-W- Laboratories of Garden City, Michigan.

5,5,7,7-Tetramethyl-1-oxa-6-azaspiro[2,5]oct-6-yloxy (II). To a cold solution of 6.5g (38 mmole) 2,2,6,6-tetramethyl-4-piperidone-1-oxyl(I) and 11.7g (57 mmole) of trimethylsulfonium iodide in 100 ml of DMSO was added 1.44g (60 mmole) of oil free sodium hydride over 1.5 hr. After the addition was completed, the mixture was stirred at room temperature for 18 hr. This mixture was then warmed at 60° for 1.5 hr and then poured into 500 ml of a cold buffer solution (NaH_2PO_4) at pH 5.8. This solution was extracted with chloroform. The chloroform solution was washed with water, dried over anhydrous magnesium sulfate and evaporated to dryness giving 4.0g (71%) of a red oil which solidified upon standing, mp 62-64°. The compound, mp 65°, has been obtained earlier in 38% yield by reaction of I with diazomethane[5].

4-Dimethylaminomethyl-4-ol-2,2,6,6-tetramethylpiperidinoxyl (III). A solution of 3.5g (19 mmole) of the oxirane (II) and 10 ml of dimethylamine

in 20 ml of methanol was heated in a sealed tube overnight at 60°. The solvent and excess dimethylamine were removed in vacuo, giving 4g (91%) of a red oil, ir, 3500-3400 cm^{-1}.

4-Trimethylaminomethyl-4-acetoxy-2,2,6,6-tetramethylpiperidinoxyl iodide IV

To a solution of 4g (17.5 mmole) of the alcohol (III) in 25 ml of methylene chloride was added 2.44g (17.5 mmole) of triethylamine. This mixture was cooled in an ice bath and to this mixture was added 1.25 ml (18.38 mmole) of acetyl chloride. The reaction was stirred overnight at room temperature and then washed with dilute sodium hydroxide. The organic solution was dried over anhydrous magnesium sulfate, evaporated to dryness and chromatographed using neutral alumina type I and methylene chloride giving 4g (84%) of red oil, ir 1750 cm^{-1}. The methyl iodide salt was recrystallized from absolute ethanol, mp. 203-204°. Anal. Calcd for $C_{15}H_{30}N_2O_3I$: C, 43.59; H, 7.32; N, 6.78. Found: C, 43.50; H, 7.59; N, 6.63.

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