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THE SELECTIVE DEMETHYLATION OF QUATERNARY AMMONIUM SALTS[1]

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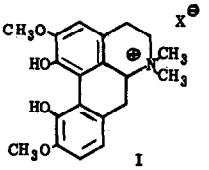
The problem of the N-demethylation of quaternary ammonium salts has bee a perennial one in organic chemistry. The classical method for demethylatio involves the pyrolysis of ammonium halides, which may however lead to extens decomposition.[2] Refluxing ethanolamine has also been used for purposes of demethylation,[3] but this reagent can lead to predominantly Hofmann eliminati and when methoxy groups are present, O-demethylation can also take place. T examples where these side reactions overshadow N-demethylation are the conversion of magnoflorine iodide (I) and isocorydine methiodide (II) to the diphenolic phenanthrene derivative III.[4]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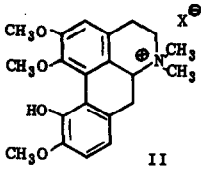
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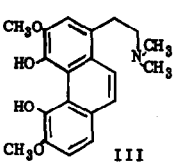
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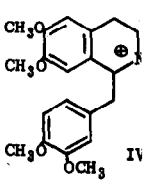
IV

Finally, N-demethylation conditions involving the use of $LiAlH_4$ in a refluxing high boiling solvent such as THF or dioxane usually fail whenever one or more phenolic group is present, so that salts I and II are recovered unchanged.[5]

We now wish to report that the ideal method of N-demethylation may turn out to involve the use of thiophenoxide anion in refluxing 2-butanone. The reaction is of the simple S_N2 type, and consists of attack by the thiophenoxide anion on the N-methyl group. In Table I it can be seen that the

thiophenoxide method is preferable to the use of ethanolamine because of the greater ratio of demethylation to deethylation. Of further interest is the fact that deethylation, like demethylation, occurred by S_N2 displacement so that $C_6H_5SCH_2CH_3$ was the product, not ethylene.

Table I[6]

Dealkylation of $(C_2H_5)_3\overset{\oplus}{N}-CH_3\ X^{\ominus}$

Nucleophile	Solvent	Temp.	Time	Overall Yield	$\frac{\%\ (C_2H_5)_3N}{\%\ (C_2H_5)_2N-CH_3}$
Thiophenoxide anion	2-Butanone	80°	19 hrs.	96 %	3.5
Ethanolamine	Ethanolamine	172°	5 hrs.	98 %	1.6[3]

The effect of solvent upon the thiophenoxide dealkylation of triethylamine methochloride is depicted in Table II, and it is evident that the reaction is more selective for demethylation when one operates at low temperature.

Table II[6]

Dealkylation of $(C_2H_5)_3\overset{\oplus}{N}-CH_3\ Cl^{\ominus}$ using $\phi S^{\ominus}$

Solvent	Temp.	Time	Overall Yield	$\frac{\%\ (C_2H_5)_3N}{\%\ (C_2H_5)_2N-CH_3}$
2-Butanone	80°	19 hrs.	96 %	3.5
Acetonitrile	82°	19 hrs.	95 %	3.5
DMF	154°	2 hrs.	96 %	2.2
Pyrolysis of dry thiophenoxide salt	130-140°	2 hrs.	78 %	2.1

In the case of N,N-dimethyl-β-phenethylamine methochloride which is susceptible to Hofmann elimination,[3] we have obtained by the thiophenoxide method an 85% yield of N,N-dimethyl-β-phenethylamine.

A variety of N-methyl quaternary alkaloids or alkaloidal derivatives have been demethylated in the present study, using the thiophenoxide anion (see Table III). The reactions were carried out in refluxing 2-butanone over a period of 24 to 36 hours.

Table III

N-Demethylation Using Thiophenoxide Anion

Alkaloid or Alkaloid Derivative	% Yield of Tertiary Amine
Canadine Methochloride	75
3-Ethylmorphine Methochloride	70
(±)-Laudanosine Methochloride (IV)	85
Yohimbyl Alcohol Methochloride	80
Bulbocapnine Methochloride[a)]	72
Tropine Methochloride	63
(+)-Tubocurarine Chloride[a) and b)]	70

a) Preparative TLC on silica gel was used for the purification of the product.

b) This is the first isolation of the free base from (+)-tubocurarine. The free base, tubocurine, analyzed correctly for $C_{36}H_{38}O_6N_2$, and melted 222.5-223.5°, $[\alpha]_D$ 221° (c 1.15 in 0.1 N HCl).

Typical experimental conditions for demethylation are given below. It will be noticed that the iodide anion was first exchanged for chloride, since NaCl is essentially insoluble in ethanol and could be filtered out.

(±)-Laudanosine methiodide (IV) (318 mg., 0.64 mmole) was dissolved in 50 ml. methanol and stirred with 500 mg. of freshly prepared AgCl for 5 hrs. The AgCl-AgI precipitate was filtered, and the methanolic filtrate evaporated to dryness under vacuo. The residue was dissolved in 20 ml.

of ethanol, and a solution of 235 mg. of sodium thiophenoxide[8] (1.78 mmoles) in 20 ml. of ethanol was added. After stirring for 20 min., the NaCl formed was filtered and washed with ethanol. The ethanolic filtrate and washings were combined, and the solvent evaporated under vacuo. To the residue was added 100 ml. of 2-butanone freshly distilled from zinc dust. The system was then heated to reflux under nitrogen for 36 hrs. Following removal of the solvent, 20 ml. of water and 50 ml. of chloroform were added. The chloroform layer was separated, and the aqueous layer extracted three times with more chloroform. Evaporation of the combined chloroform fractions under vacuo was followed by the addition of 10% hydrochloric acid. The aqueous acid solution was then repeatedly extracted with ether. Neutralization of the aqueous solution with sodium bicarbonate was followed by extraction into chloroform. After drying over sodium sulfate, and evaporation of the solvent, 205 mg. of light yellow crystals, m.p. 112-114° was obtained. Recrystallization from petroleum ether yielded 193 mg. (85%) of white crystals of laudanosine, m.p. 115-116°; literature m.p. 115°.[9]

One limitation of the present method is that ester groups are attacked by the thiophenoxide anion, with formation of derivatives of the corresponding carboxylic acid.[7]

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1. This research was supported by Grant GP-1941 from the National Science Foundation.

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6. The products were separated and identified by VPC. Column 12.5 ft. of 16% Carbowax 12M-16% KOH on Chromosorb W. Column temperature 84°. Flow rate 100 cc/min. Retention times: N-methyldiethylamine 328 sec., triethylamine 405 sec.

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