QUATERNARY AMMONIUM SALTS OF POTENTIAL BIOLOGICAL ACTIVITY

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ABSTRACT

For possible antimicrobial activity, several quaternary ammonium salts were synthesised which were derived from 4-*N*-dimethylaminopyridine.

INTRODUCTION

Quarternary ammonium salts show a variety of pharmacological effects. Einham and Gottler[1] reported the antiseptic activity of quaternary compounds. Since then a considerable amount of work had been published on these compounds involving synthesis structural activity relationship, mode of action and different pharmacological effects such as germicidal[2], antibacterial[3], antifungal[4] and anticancer activities[5].

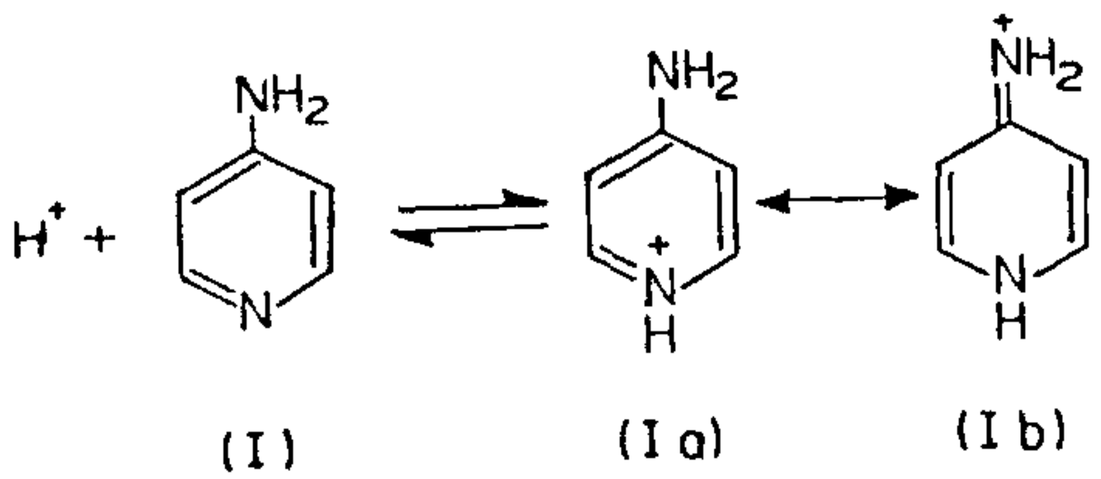
The author embarked on the synthesis of a new series of quaternary ammonium salts with the general formula:

$$[\dot{R}\,CH_2\text{-}\overset{+}{N}]\,X$$

Where the nitrogen atom was the hetero atom in an aromatic base which may be expected to enhance the biological action.

INVESTIGATIONS, RESULTS AND DISCUSSION

It is known that the addition of a proton to the 4-amino-pyridine I gives the mesomeric cation Ia, Ib and it is impossible to add a second proton to the mono cation because if this occurred, the additional ionic resonance would necessarily be lost[6].



(I) (I a) (I b)

Thus interaction of 4-*N*-dimethylaminopyridine with methyl-iodide in acetone gave the corresponding 1-methiodide derivative (IIa). The latter was characterised by its ready conversion to the corresponding pyridinium periodate (IIb) and perchlorate (IIc) derivatives.

Condensation of 4-dimethylaminopyridine with iodoacetamide and *n*-decyliodide furnished the corresponding normal quanternary ammonium derivates (IId) and (IIe) respectively.

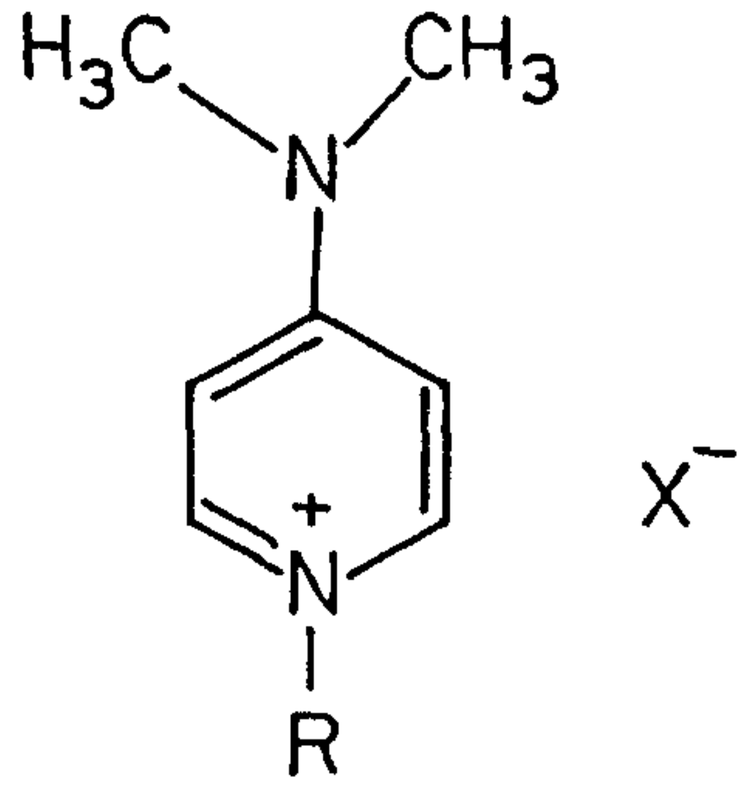
The reaction between phenacyl halide and pyridine to give quaternary ammouium salts was first described by Krohnke[7].

Thus, the reaction between 4-*N*-dimethylaminopyridine and phenacyl chloride, led to the formation of 1-phenacylpyridinium chloride. (IIf).

On similar lines, the interaction of 4-*N*-dimethylaminopyridine with *n*-butyl bromide, β-bromopropionic acid and benzyl bromide was successful and led to the formation of the pyridinium derivatives (IIj), and (IIh) and (IIi) respectively.

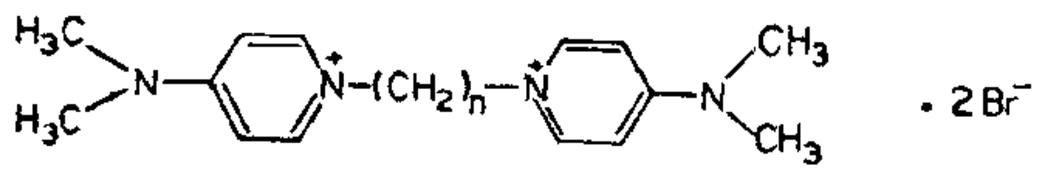
A range of *bis*-quaternary ammonium salts from various bases and γ-ω compounds was described by Libman *et al*[8] while the reaction of 4-aminoquinoline and similar dihalogen compounds has been studied by Austin *et al*[9].

In analogy with the above findings, condensation of 4-*N*-dimethylaminopyridine with one mole of 1,2-dibromoethane gave readily the corresponding 1-pyridinium derivative (IIj).



(II a-j)

When the reaction was carried out with one mole of 1,2-dibromopropane and two moles of the base the corresponding *bis*-quaternary ammonium salts (IIIa) and (IIIb) were isolated.



(III a-b)

IIIa $n=2$
b $n=3$

The structures of these compounds were established by elemental analysis corresponding to their molecular formula and by IR spectra which showed streaching frequences at 1575, 1640 and 1655 cm^{-1} (C=N) 3080-3040 cm^{-1} (C=H) and at 1700-1600 cm^{-1} (C=O).

U.V. showed λ MeOH max and ε as in table 1.

II	R	X
a	CH_3	I
b	CH_3	IO_4
c	CH_3	ClO_4
d	CH_2CONH_2	I
e	$CH_2(CH_2)_8CH_3$	I
f	$CH_2COC_6H_5$	Cl
g	$CH_2CH_2CH_2CH_3$	Br
h	CH_2CH_2COOH	Br
i	$C_6H_5CH_2$	Br
j	CH_2CH_2Br	Br

TABLE 1

U. V. spectra λ max, ε of some of the compounds:

Compound	λ max	ε	λ max	ε
II a	217	561×10^4	289	627×10^4
II f	205	252×10^4	238	179×10^4
	287	270×10^4		

The antibacterial activity of the prepared compounds was tested against 6 strains. The sensitivity of a microrganism to the test compounds was determined by the cup-plate method[10].

The positive antibacterial activity of the tested compounds are shown in table 2.

Among 12 water soluble derivatives of 4-*N*-dimethylaminopyridine only (IIe) and (IIIa) possess bacteriocidal effect. The derivative (IIe) is found to be the most active compound of this series.

TABLE 2

Antibacterial activity of quaternary ammonium salts.

Compound	B S	S A	S O	S T	E C
II e	+++	+++	+++	+++	+++
III a	++	++		+	+

B S. = *Bacillus Subtilis* (ice strain)
S A. = *Staphylococcus aureus* (NRRL B-313)
S O. = *Staphylococcus oyama*
S T. = *Salmonella typhimuium*
E C. = *Escherichia coli* (NRRL B-210)

The antifungal activity of the prepared compounds was tested against five organisms by the filter paper disc method[11].

The positive antifungal activity of the tested compounds is shown in table 3. From this table it is clear that quaternization of 4-*N*-dimethylpyridine generally induces antifungal activity.

TABLE 3

Antifungal activity of quaternary ammonium salts:

Compound	A S.	A N.	P T.	P C.	M R.
II b	++	++	++	++	++
II c	+	+	-	-	-
II d	+	+	-	-	-
II e	-	++	++	++	-
II f	++	++	++	++	++
II g	-	-	++	++	-
II h	++	-	-	++	-
II i	-	-	-	++	-
II j	-	+	+	+	-
III a	-	+	+	+	-
III b	-	-	+	+	-

A S. = *Asperigillus sulfures*, A N. = *Asperigillus niger* P T. = *Penicillium terrestra*, P C. = *Penicillium chrysogenum* M R. = *Mucor rouxii*

EXPERIMENTAL

All m.p. are uncorrected, IR. measurements were carried out on a Pye Unicam recording spectrometer in KBr. UV. spectra were carried on a UNICAM SP-800 ultraviolet recording spectrometer.

Quaternary ammonium salts of 4-N-dimethyl aminopyridine:

A solution of 4-N-dimethylaminopyridine (0.01 or 0.02 moles) in acetone (50 ml) was treated with the

TABLE 4

Quaternary Ammonium Salts of 4-N-dimethylamino-pyridine and their periodate and perchlorate derivates:

Compound	m.p.°C	
II a	246	(100%)
IIb	240	(64%)
IIc	270	(58%)
IId	275	(100%)
IIe	71	(85%)
IIf	120	(60%)
IIg	219	(65%)
IIh	86	(55%)
IIi	211	(100%)
IIj	188	(56%)
IIIa	212	(40%)
IIIb	125	(54%)

The yield percentage of each compound is shown in brackets.

required alkyl halide or alkyl dihalide (0.01 mole) in acetone (50 ml). The reaction mixture was heated under reflux for 3–5 hr, then allowed to stand until precipitation took places. The precipitated solid was collected, washed with benzene, recrystallised from ethanol and the m.p. shown in table 4.

Periodate and Perchlorate derivatives (IIb) and (IIc):

The methiodide derivative (IIa) about 1 g. was dissolved in cold water (20 ml) and an excess of cold saturated solution of potassium perchlorate or periodate was added and shaked for 15 min. The product formed was filtered off, recrystallised from ethanol and m.p. determined (table 4).

18 December 1982; Revised 5 March 1983

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MACROSCOPIC DESCRIPTION OF THE STRENGTH OF COMPOSITE LAMINATES

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ABSTRACT

The strength of laminated composites can be calculated by measuring the strength and elastic properties of the unidirectional lamina and by applying a failure criterion. The results obtained distinguish between the first ply failure and the ultimate failure of the laminate. Using the first ply failure as the design criterion, a simple method for laminate optimisation is suggested and used for a specific problem. The present approach which takes into account the anisotropic composite properties and their tensor transformations and simplifies them by using graphical methods, will lead to simple methods of optimal design with composite laminates.

INTRODUCTION

IN the laminated composites, the basic building block is the unidirectional lamina or the ply which contains continuous aligned fibres in a matrix. The structural elements are then made by stacking up the plies and each ply can be selected to have any given orientation. Such a material offers a remarkable oppor-