

BIS-DEALKYLATION OF QUATERNARY AMMONIUM SALTS

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Several good methods are known for the monodealkylation of quaternary ammonium compounds employing non-reductive nucleophilic agents (1-5). We wish to report here a simple one-step method that leads directly from a quaternary ammonium salt to the acyl derivative of the corresponding secondary amine in fair yields.

The procedure involves the heating of a solution of the quaternary salt in a carboxylic anhydride at 200° for 24 hr. The acyl derivative of the secondary amine is isolated, after hydrolysis of the anhydride with aq.  $\text{Na}_2\text{CO}_3$ , by extraction with chloroform, removal of the solvent and distillation. The conditions of the procedure have not been optimized.

We have tested the reaction with mono-, di-, and trimethyl and with diethyl quaternary ammonium salts, with three different anhydrides and four different anions. The results are listed in Table 1.

The results reported show that when at least two alkyl groups are attached to the positive nitrogen atom, both are eliminated, but when only one alkyl group is linked to it, as in sparteine methiodide, there is no attack to the cyclic carbon atoms, the tertiary base being produced in high yield. The yield falls markedly in the case of the aromatic ammonium salt tried, possibly due to an unfavourable equilibrium in the acylammonium salt formation (v.i.), and to acyl substitution in the aromatic nucleus.

The different anhydrides used gave comparable yields. With acetic anhydride it was necessary to operate in a closed tube to attain the indicated temperature. When anions less nucleophilic than iodide were employed the yields fell markedly, as observed in the case of the methochloride, methobutyrate and methotosylate.

Table 1

Anhydride	Ammonium cation	Anion	Product <sup>1</sup>	Yield % <sup>2</sup>
butyric	N,N,N-trimethylcyclohexilium	I <sup>-</sup>	N-methylcyclohexylbutyramide	62
butyric	N,N,N-trimethylanilinium	I <sup>-</sup>	N-methyl butyranilide	22
butyric	N,N-dimethylpiperidinium	I <sup>-</sup>	N-butyroyl piperidine	58 <sup>3</sup>
butyric	N,N-dimethyl-1,2,3,4-tetrahydroquinolinium	I <sup>-</sup>	N-butyroyl-1,2,3,4-tetrahydroquinoline	20
butyric	N,N-diethylpiperidinium	I <sup>-</sup>	N-butyroyl piperidine	56
butyric	N,N-dimethylpiperidinium	Cl <sup>-</sup>	N-butyroyl piperidine	8 <sup>4</sup>
butyric	N,N-dimethylpiperidinium	But <sup>-</sup>	N-butyroyl piperidine	12 <sup>5</sup>
butyric	N,N-dimethylpiperidinium	Tos <sup>-</sup>		0 <sup>6</sup>
acetic	N,N-dimethylpiperidinium	I <sup>-</sup>	N-acetyl piperidine	47
benzoic	N,N-dimethylpiperidinium	I <sup>-</sup>	N-benzoyl piperidine	82
butyric	N-methylsparteinium	I <sup>-</sup>	sparteine	90
butyric	N-methylquinolinium	I <sup>-</sup>	quinoline	51

<sup>1</sup> The products gave correct analytical data and were identified by comparison with authentic samples.

<sup>2</sup> Yield of isolated amide in the conditions stated in the paper.

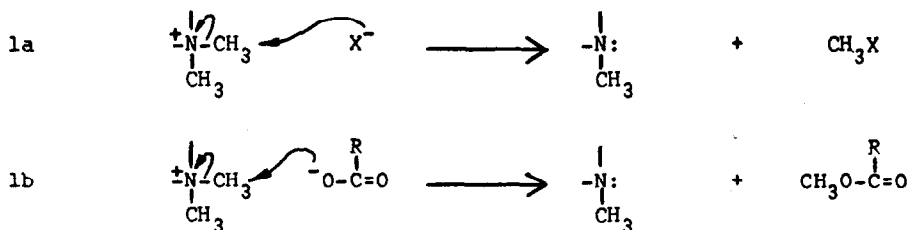
<sup>3</sup> Addition of 1 mol of NaI increases the yield to 83%.

<sup>4</sup> When the heating is prolonged to 70 hr the yield increases to 24%.

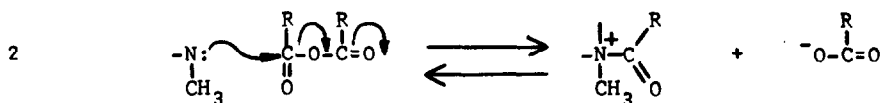
<sup>5</sup> Besides, a 13% yield of the tertiary base was isolated.

<sup>6</sup> 84% recovery of the ammonium salt.

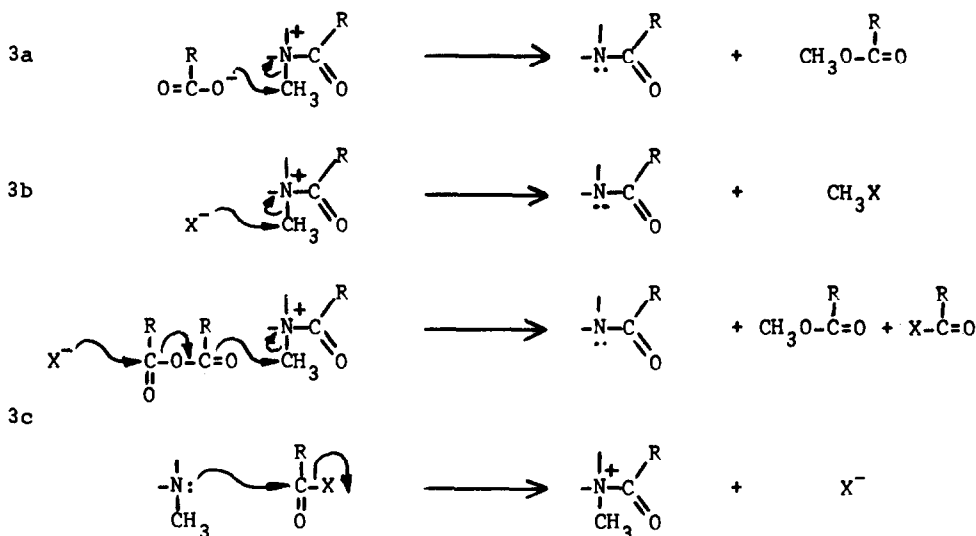
The first step in the reaction involves the nucleophilic attack of the anion on the  $\alpha$ -carbon of an alkyl group, the anhydride acting only as a dipolar aprotic solvent (1a). This was confirmed by the detection of methyl iodide in the reaction of quinoline methiodide, where only this first dealkylation step takes place. However, the moderate yield obtained in the reaction with a methoxybutyrate shows that the anion produced in step 2 may also act as a nucleophilic agent (1b).



The second step is an equilibrium between the tertiary amine produced in the first step and its acylammonium salt.



This acylammonium cation undergoes then a nucleophilic attack on the  $\alpha$ -carbon of an alkyl group through three possible reactions: 3a, 3b and 3c.



The operation of these three reactions was established by the results obtained in reacting tertiary amines with carboxylic acid anhydrides in the same conditions stated above. As previously found by Le Men and coworkers (6), the yields obtained were low. However, the addition of NaI markedly improved the yields (thus resulting in a simple method for the dealkylation of tertiary amines)(Table 2).

Table 2

Anhydride	Amine	NaI moles	Product <sup>1</sup>	Yield %
butyric	N,N-dimethylcyclohexylamine	0	N-methylcyclohexylbutyramide	18 <sup>2</sup>
butyric	N,N-dimethylcyclohexylamine	1	N-methylcyclohexylbutyramide	38
butyric	N-methylpiperidine	0	N-butyroyl piperidine	14
butyric	N-methylpiperidine	0.1	N-butyroyl piperidine	43
butyric	N-methylpiperidine	1	N-butyroyl piperidine	49 <sup>3</sup>
butyric	N-methylpiperidine	2	N-butyroyl piperidine	57 <sup>4</sup>
acetic	N-methyldioctylamine	1	N-acetyl dioctylamine	62

<sup>1</sup> The products gave satisfactory elemental analyses and were identified by comparison with authentic samples.

<sup>2</sup> Reaction time 3 hr: 13% yield.

<sup>3</sup> Added salt NaCN: 12% yield.

<sup>4</sup> Reaction time 6 hr: 56% yield.

The fact that the reaction occurs-though in small yield-in the absence of NaI, shows that reaction 3a is possible; when a molar amount of salt is added, methyl iodide is detected as a reaction product (reaction 3b); catalytic amounts of NaI suffice for markedly increasing the yield (reaction 3c).

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