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REARRANGEMENT OF TERTIARY AMINE N-OXIDES-XVII*

THE REACTION OF LEPIDINE N-OXIDE WITH BENZOYL CHLORIDE

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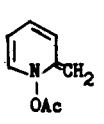
The anhydrobase (I, II, IV), which has been accepted as the key incipient intermediate of the reactions of 2- or 4-alkylpyridine N-oxides with acylating agent to give the corresponding 2- or



I

II

4-acyloxyalkylpyridines (1)~(7) was first postulated by Pachter for the reaction of quinaldine N-oxide with benzoyl chloride to give 2-benzoyloxymethylquinoline (8).

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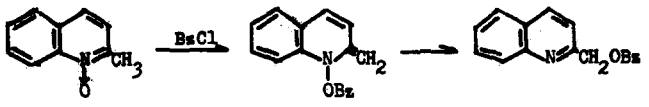
* Part XVI, S. Oae, S. Kozuka, Y. Sakaguchi and K. Hiramatsu, Tetrahedron. Part XV, S. Oae and K. Ikura, Bull. Chem. Soc. Japan, in press.



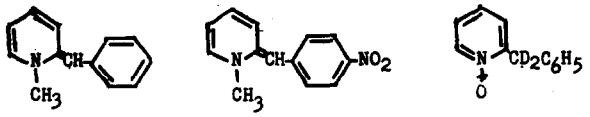
III IV V

Although the suggested mechanism of the reaction leading to the ester (V) from the anhydrobase (IV), namely the cyclic process was corrected to a radical cage process by our recent oxygen-18 tracer experiments, here again the anhydrobase (IV) was accepted as a probable intermediate of this reaction (9).

Thus, the formation of the anhydrobase has been well accepted by many workers inspite of the lack of any significant supporting evidence for the existence of the intermediate.

Very recently, Traynelis and Pacini (10) have made an interesting attempt to prove the anhydrobase intermediate in the reaction of 2-picoline N-oxide or homologaus N-oxide with acetic anhydride by following the UV spectra of the reacting mixture in comparison with that of the model anhydrobase (VI), (VII) and also by the measurement of the deuterium loss of the recovered N-oxide in the reaction of 2-α-dideuteratedbenzylpyridine N-oxide (VIII) with acetic anhydride at half completion of the reaction (10).

Although no concrete supporting evidence was obtained in these experiments, the total lack of proton loss in the recovered N-oxide

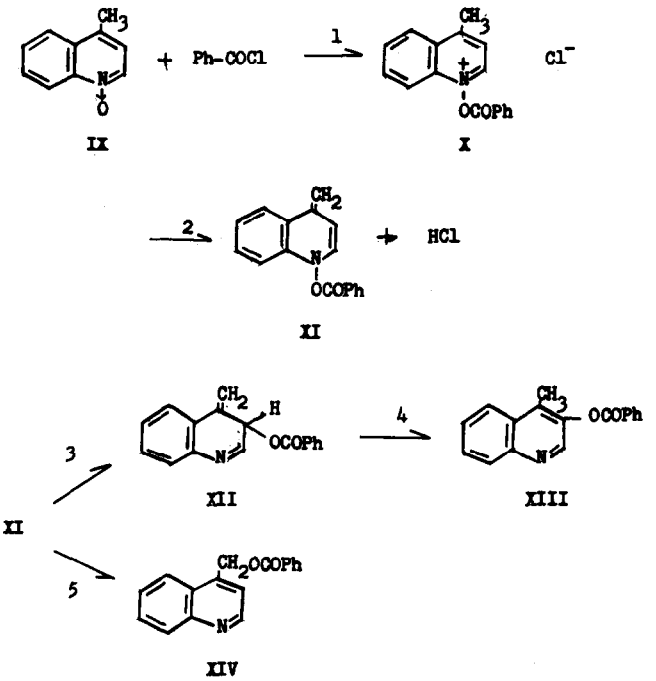


VI VII VIII

seems to favour the rate determining formation of the anhydrobase.

In this communication we wish to report a preliminary study to confirm the intermediate, anhydrobase in the similar reaction of lepidine N-oxide with benzoyl chloride using deuterium as a tracer.

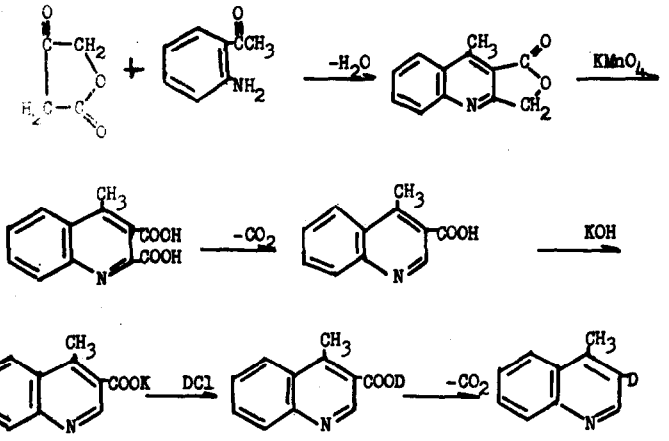
First, we have examined the product of the reaction of lepidine N-oxide with benzoyl chloride and found that 3-benzoyloxylepidine (XIII) was the main product (41%) while obtaining 4-benzoyloxymethylquinoline (XIV) and 4-chloromethylquinoline as the minor products. The ester product, i.e. 3-benzoyloxylepidine and 4-benzoyloxymethylquinoline would be considered to be formed via an anhydrobase (XI) like in the reaction of 4-picoline N-oxide with acetic anhydride giving 4-acetoxymethylpyridine and 3-acetoxy-4-methylpyridine, as follows:



If the reaction involves the anhydrobase intermediate, an introducing of deuterium at the C-3 position of the N-oxide, would result in the considerable incorporation of deuterium on the methyl group of 3-benzoyloxylepidine.

On the other hand, the direct migration of benzoyloxy group to the position 3 with no formation of the anhydrobase, would leave the methyl group of 3-benzyloxylepidine unaltered unless there would be some deuterium exchange with deuterium chloride formed during the reaction.

Thus, lepidine-3-d-N-oxide was prepared by the decarboxylation of deuterated-4-methylquinoline-3-carboxylic acid as follows: (11)



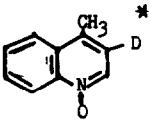
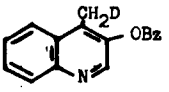
Unfortunately the deuterium labelling at the C-3 position of the lepidine skeleton was incomplete due probably to the prior rapid equilibration of the deuterated carboxylic acid with the medium during the formation. However the partially deuterated (containing 50% d at 3-position) N-oxide will serve as well for the same purpose. Thus, the

lepidine-3-d-N-oxide was treated with benzoyl chloride and the main product 3-benzolyloxylepidine was isolated.

The isotope contents of both the starting material and the ester product analysed by mass spectra are shown in Table 1.

TABLE 1

Deuterium Analytical Results

Compound	Deuterium Content Atom %	
	Run 1	Run 2
	55	45
	49	44

* Analysed in the state of free amine.

The results clearly indicate that the deuterium initially labelled at the C-3 position of lepidine N-oxide, migrated to the methyl group during the process.

Thus, both the existence of the anhydrobase intermediate and the succeeding, allylic shift of a proton of the addition intermediate (XII) leading to the product (XIII) are strongly supported by these deuterium tracer experiment.

Incidentally the rather small loss of deuterium during the allylic migration is not unusual when the deuteron migration occurs via an intimate ion pair process (12).

In order to shed a further light into the rearrangement mechanism of the step 3 and 5, the usual oxygen-18 tracer experiments were carried out.

An equimolar amount of lepidine N-oxide and O^{18}-labelled benzoyl chloride was allowed to react in benzene under refluxing, then the two esters were separated and subjected to the O^{18}-analyses as usual. These esters were hydrolyzed in the methanolic KOH solution, giving the corresponding alcohols, respectively. Oxygen-18 analyses were made for these esters and alcohols in order to determine the distribution of oxygen-18 incorporation in the esters.

The analytical results in these experiments are listed in Table 2.

TABLE 2

Oxygen-18 Analytical Results

Compound	Atom %
BzCl (used)	1.53
3-benzoyloxylepidine	0.83
4-benzoyloxymethylquinoline	0.81
3-hydroxylepidine	0.84
lepidylalcohol	0.75

These data show that both the carbonyl and ether oxygens of the esters were almost completely scrambled during the rearrangement and are quite similar to that of quinaldine N-oxide with benzoyl chloride to give 2-benzoyloxymethylquinoline in which the benzoyloxy group was suggested to migrate via a radical cage process (9).

Further extensive experiment to find out another supporting evidence for both the existence of the anhydrobase and the rearrangement mode of the benzoyloxy group is now undertaken in this laboratory.

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