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Telesubstitutions in reactions of 2-alkoxy-6-bromopyridines with nucleophiles possibly via <u>meta</u>-dehydropyridines as intermediates

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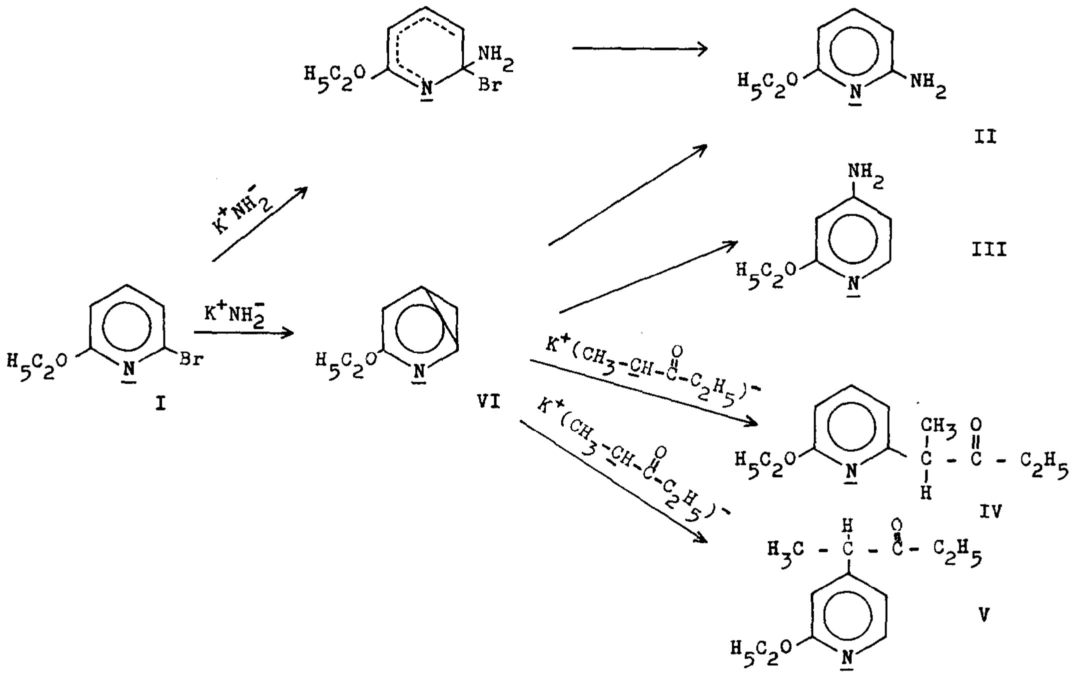
In a study on the aminations of isomeric bromoethoxypyridines with potassium amide in liquid ammonia a remarkable telesubstitution has been observed: 2-bromo-6-ethoxypyridine is converted not only into 2-amino-6-ethoxypyridine, but also into 4-amino-6-ethoxypyridine (ratio of amino compounds = 6 : 1)(2). Continuing this investigation we found that 2-bromo-6-methoxy- and 2-bromo-6-propoxypyridine react analogously. 2-Bromo-6-phenoxypyridine changes into a mixture of the 2- and 4-amino compounds too, but also undergoes ring transformation yielding 2-methyl-4-phenoxypyrimidine (3). Thus far no mechanism for the telesubstitutions described has been proposed.

We now reacted 2-bromo-6-ethoxypyridine (I, 25 millimoles) in a solution of the potassium compound of pentanone-3 (100 millimoles) in 200 ml of liquid ammonia at -33°C by adding a potassium amide solution (50 millimoles in 100 ml of liquid ammonia) in 2 h and allowing the reaction to proceed for 0.5 h. Analysis by G.L.C. using a column filled with polyphenyl ether at 180°C, showed the reaction mixture to consist of 2-[2'-(6'-ethoxypyridyl)]-pentanone-3 (IV) and 2-[4'-(6'-ethoxypyridyl)]-pentanone-3 (V)(ratio 5 : 1; total yield ~15%) together with 2- and 4-amino-6-ethoxypyridine (II and III; total yield~55%) and unchanged I. When no potassium amide solution was added to the mixture of I and the pentanone-3 compound, only a small amount of IV and no V was obtained. When 3-bromopyridine was reacted with potassium amide in the presence of the potassium compound of pentanone-3, together with 3- and 4-aminopyridine,2-(3'-pyridyl)- and 2-(4'-pyridyl)-pentanone-3 were formed. It is likely that in this reaction all four products are formed from primarily generated 3,4-dehydropyridine.

We wonder whether also in the reaction of 2-bromo-6-ethoxypyridine (I) the amino compounds II and III and the pentanone derivatives IV and V originate from a common intermediate. Certainly further investigation is necessary to verify the hypothesis that a <u>meta</u>-dehydro compound, i.e. 2,4-dehydro-6-ethoxypyridine (VI) or a more stable derivative of this species is the intermediate involved in this process.



Meta-dehydroaromatics are mentioned only once or twice in the literature. In carbocyclic chemistry the generation of 1,3-dehydrobenzene (4) and 1,8-dehydro-naphtalene (5) has been observed; in heterocyclic chemistry the possibility of the existence of 2,6-dehydropyridine has been discussed (6).

2-[2'-(6'-Ethoxypyridyl)]-pentanone-3 (IV) was prepared by reacting 2-bromo-6-ethoxypyridine with the potassium compound of pentanone-3 for 3 days. It is a liquid distilling at 126-127°C/10 mm; n_D^{20}= 1,496.

2-[4'-(6'-Ethoxypyridyl)]-pentanone-3 (V) was prepared by reacting 2-ethoxy-4-ethylpyridine with methyl propionate and sodium amide. It distilled at 139°C/10 mm; n_D^{20}= 1,503. The structures of these specimin of IV and V resulted from microanalysis and NMR-spectrometry. The identity of the samples of IV and V isolated by G.L.C. from the mixture obtained from the reaction of 2-bromo-6-ethoxypyridine (I) with the potassium compound of pentanone-3 and potassium amide was established by comparing their physical properties with those of the preparations described in this paragraph.

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