

INVESTIGATION OF THE FORMATION OF N—SUBSTITUTED CARBOXYLIC ESTERS WITH THE USE OF VARIOUS HALOID CARBOXYLIC ESTERS

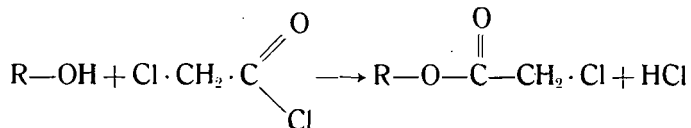
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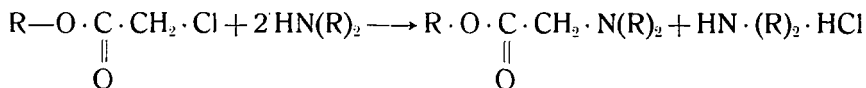
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On preparing, under identical conditions, by condensation with various haloid acetic esters, the ethylates of N-piperidine-, morpholine- and pyrrolidine-acetic acid, the highest yields were observed in the cases when bromo-acetic ethylate as a tertiarizing agent was applied. In the group of cyclic secondary amines, the order of reactivity proved to be piperidine > pyrrolidine > morpholine.

A great number of methods are known in literature for the synthesis of aminoacetic esters, a group of compounds of great interest, due to their valuable pharmacological properties. Aminoacetic esters were synthesized by REMIZOV and co-workers [1] with the use of the general method:



The second step of preparing esters consisted in a condensation with secondary amine:



It can be seen from the above equation that, in addition to N-tertiary carboxylic ester, also the haloid hydrogen salt of the secondary amine forms.

N-piperidine-acetic ethylate was first prepared by WEDEKIND [2] in 1902, from piperidine and chloroacetic ethylate.

In the course of our researches of pharmacological nature, we set us the aim of preparing the N-carboxylic esters of pyrrolidine, piperidine and morpholine. In this connection we investigated what haloid carboxylic ester should be used to obtain the tertiary carboxylic ester in the highest yield, and which conditions affect the formation of the desired end product.

The applied various haloid carboxylic esters were prepared from chloroacetic acid [3], bromoacetic acid [4] by subjecting them to esterification, or

from chloroacetic ethylate. [5], by subjecting this latter to a halogen exchange, with the use of potassium iodide.

For this purpose, one mole of the haloid acetic ester was reacted in a benzene solution with 2 moles of the adequate base. The haloid salt of secondary amine obtained as a by-product was removed by filtering the tertiary N-carboxylic ester isolated and converted into hydrochloride.

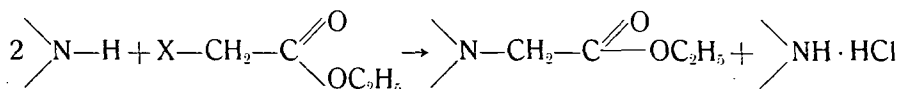
No essential differences exist between the nucleophilic activity of various amines, and their dissociation constants disclose values adjacent to each other (e. g. $k = 1,3 \cdot 10^{-3}$ in the case of pyrrolidine whilst $k = 1,28 \cdot 10^{-3}$ in the case of piperidine). Accordingly, when differences are observed in the reaction rates and in the ratios of end products, respectively, of the reactions with different haloid esters, obviously the different reactivities of the various haloid compounds are responsible for these differences.

On examining the refraction constants and the values of bond energies of the various haloid derivatives [6]:

Type of haloid C—X	Bond energy Kcal	Refraction constant
C—Cl	66,5	5,933
C—Br	54,0	8,803
C—I	45,5	13,757

we find that, on applying the same base, reaction rates should increase in the order $\text{Cl} < \text{Br} < \text{I}$. Thus, if no side reaction would occur, under identical experimental conditions, the percentage ratio of the obtained product should follow the same order.

The obtained experimental results are summarized on the basis of the equation



in the following table.

N—H	Percentage of yield with haloid X		
	Cl	Br	I
Pyrrolidine	52	77	57
Piperidine	84	85	78
Morpholine	42	71	68

The values of the table prove that in the case of the chloro- and bromo-acetic esters, changes in yields correspond to changes of polarizability. In the reaction with iodo-acetic ester, the amount of formed product decreased with each compound tested. This may be interpreted by the observation that always iodine precipitated when derivatives of iodoesters entered reactions.

Experimental

The ethylates of N-piperidino-, morpholino- and pyrrolidino-acetic acids were prepared and identified as picrates. Also the hydrochlorides and quaternary iodine salts of tertiary bases were produced. In order to make possible the comparison of reaction rates and yields, reactions were carried out with all three cyclic amines identical conditions, as follows.

A reflux condenser with a calcium chloride tube and a dropping funnel were attached to a ground threeneck flask equipped with stirrer. The flask was placed ice-water. On transferring 2 moles of freshly distilled anhydrous amine into the flask, together with 2,5 moles of anhydrous benzene, the solution of one mole of chloro-, bromo- or iodo-acetic ethylate in 2,5 moles of anhydrous benzene was dropwise added from the dropping funnel, under continuous stirring, at a slow rate. When the addition of the haloid ester was completed, stirring was continued for 15 minutes, and the solution was heated on the water bath. On cooling, the precipitate was filtered and repeatedly washed with some benzene. If further precipitate appeared during standing, it was similarly filtered and washed. The combined and dried benzene solutions were distilled under a pressure of 40 mm Hg. The appearing small amount of precipitate was filtered and the oily residue subjected to fractionation under a pressure of 2—5 mm Hg.

The hydrochlorides of the amine esters were prepared by treating the ethereal solution of the obtained tertiary amine esters with the calculated amount of ethereal hydrochloric acid, whilst the quaternary salts were precipitated from the solutions in anhydrous ethanol by methyl iodide.

The physical constants of the initial substances are as follows.

	b. p.	n_D^{20}	mol. weight
Piperidine	106,3°C	1,4534	85,15
Morpholine	128°C	1,4540	87,12
Pyrrolidine	88,5°C	—	71,12
Chloro-acetic ethylate	144—146°C	1,42274	122,51
Bromo-acetic ethylate	159°C	n_D^{15} : 1,45420	166,97
Iodo-acetic ethylate	178—180°C	n_D^{25} : 1,50789	203,92

N-piperidino-acetic ethylate

Prepared from piperidine and haloid acetic ethylate by the previously described method.

$C_9H_{15}O_2N$ (171,18) b. p, 68°C; n_D^{25} : 1,4525.

Picrate $C_9H_{15}O_2N \cdot C_6H_3O_7N_3$ m. p. 122°C.

Calcd.: C 44,99% H 5,04% N 13,99%.

Found: C 44,70% H 4,86% N 14,3%.

45,00% 4,80%

Hydrochloride: $C_9H_{17}O_2N \cdot HCl$ (mol. wt. 208,07) m. p. $117^\circ C$ N-methyl, N-(acetic ethylate)-piperidinium iodide $C_{10}H_{20}O_2NI$ (mol. wt. 160—160,3°C.
 Calcd.: C 38,35% H 6,44% I 40,53%.
 Found: C 38,22% H 6,82% I 40,70%.

N-(morpholino)-acetic ethylate

Prepared from morpholine and haloid acetic ethylate by the method given previously (an oily liquid).

$C_8H_{15}O_3N$ (mol. wt. 173,12) b. p. $81^\circ n_D^{25}$ 1,4531.

Picrate: $C_8H_{15}O_3N \cdot C_6H_3O_7N_3$ (mol. wt. 402,14) m. p. $136^\circ C$.

Calcd.: C 41,79% H 4,48% N 13,93%.

Found: C 41,82% H 4,50% N 14,29%.

Hydrochloride: $C_8H_{15}O_3N \cdot HCl$ (mol. wt. 209,68) decomp. at 176° N-methyl, N-morpholinium iodide-acetic ethylate.

$C_9H_{18}O_3NI$ (mol. wt. 315,05) m. p. $132,5^\circ C$.

Calcd.: C 34,28% H 5,71% I 40,32%.

Found: C 34,47% H 5,19% I 40,50%.

N-(pyrrolidino)-acetic ethylate

Prepared from pyrrolidine and haloid acetic ethylate by the previously described method (oily liquid).

$C_8H_{15}O_2N$ (mol. wt. 157,12) b. p.: $59-59,5^\circ n_D^{25}$ 1,4460.

Picrate $C_8H_{15}N \cdot C_6H_3O_7N_3$ (mol. wt. 386,14) m. p. $118,5^\circ C$.

Calcd.: C 43,52% H 4,66% N 14,50%.

Found: C 43,23% H 4,37% N 14,65%.

Hydrochloride $C_8H_{15}O_2N \cdot HCl$ (mol. wt.: 193,59) m. p. $133,5^\circ C$.

Attempts to isolate the methiodide quaternary salt of the pyrrolidine derivative so far failed.

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Tanks are expressed to the workers of the Analytical Laboratory of this Institute for carrying out the required analyses.

References

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