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# INTERACTION OF 3-CHLORO-2-HALOPROPENYL KETONES WITH β-AMINOCROTONIC ACID ETHYL ESTER

**R. A. Gadzhili, A. G. Aliev, R. A. Nadzhafova, and R. I. Ibragimov**

*The reaction of 3-chloro-2-halo-1-propenyl ketones with β-aminocrotonic acid ethyl ester leads to the formation of ethyl esters of 6-alkyl(aryl, benzyl, cyclohexyl)-4-chloromethyl-2-methylnicotinic acids. It was established that at increased temperatures the compounds obtained are partially converted into the corresponding dihydrofuro[3,4-c]pyridines.*

**Keywords:** 3-chloro-2-halo-1-propenyl ketones, dihydrofuro[3,4-*c*]pyridines, β-aminocrotonic acid ethyl ester, 6-alkyl(aryl, benzyl, cyclohexyl)-4-chloromethyl-2-methylnicotinic acid ethyl esters.

The interaction of 2,3-dichloropropyl alkyl ketones with alkyl esters of aminoacetic acid leads to the preparation of 1-alkoxycarbonylmethyl-2-alkylpyrroles [1], but in the case of the interaction of β-chlorovinyl ketones with β-aminocrotonic acid ethyl ester it leads to nicotinic acid ethyl esters [2]. We have also established that the interaction of 2,3-dichloropropenyl alkyl ketones with β-aminocrotonic acid ethyl ester leads to the preparation of ethyl esters of 6-alkyl-4-chloromethyl-2-methylnicotinic acids [3].

However further investigations showed that during the vacuum distillation of the products of this reaction, together with the ethyl esters of 6-alkyl-4-chloromethyl-2-methylnicotinic acids **2a-e**, starting with $R \geq C_2H_5$, partial conversion of the latter into 6-alkyl-4-methyl-2-oxo-1,2-dihydrofuro[3,4-*c*]pyridines **3b-d** occurs. It was established that in a series of ethyl esters of 6-alkyl-4-chloromethyl-2-methylnicotinic acids the yield of lactones **3** increases sharply with an increase in radical R. For example, on distilling nicotinic acid derivatives **2a-e** lactones **3b** 8, **3c** 15, **3d** 24, and **3e** 36% were formed as by-products. An explanation of this might be the fact that depending on the increase in alkyl radical the boiling point of the compound being distilled increases and with it the probability of thermal intramolecular cyclization of compounds **2a-e** is increased. When distilling the ethyl esters of 6-benzyl(phenyl, *p*-tolyl, *p*-chlorophenyl, cyclohexyl)-4-chloromethyl-2-methylnicotinic acids **2f-j** complete lactonization was observed (Scheme 1).

With the aim of preventing intramolecular cyclization of compounds **2f-j** into lactones the appropriate 6-benzyl(phenyl, *p*-tolyl, *p*-chlorophenyl, cyclohexyl)-derivatives of nicotinic acid were isolated and identified as the hydrochlorides.

The reaction was carried out in ether or methanol in the presence of an equimolar quantity of triethylamine at 35-40°C for 5 h and the ethyl esters of 6-alkyl(aryl, benzyl, cyclohexyl)-4-chloromethyl-2-methylnicotinic acids **2a-j** or their hydrochlorides were obtained in 57-84% yield.

On distilling the nicotinic acid derivatives **2a-e** at a residual pressure of 20-30 mm Hg they were completely converted into the corresponding lactones **3a-e**.

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Institute of Polymer Materials, Azerbaijan National Academy of Sciences, Sumgait, Az5004; e-mail: ipoma@dcacs.ab.az. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1184-1188, August, 2005. Original article submitted December 2, 2003.

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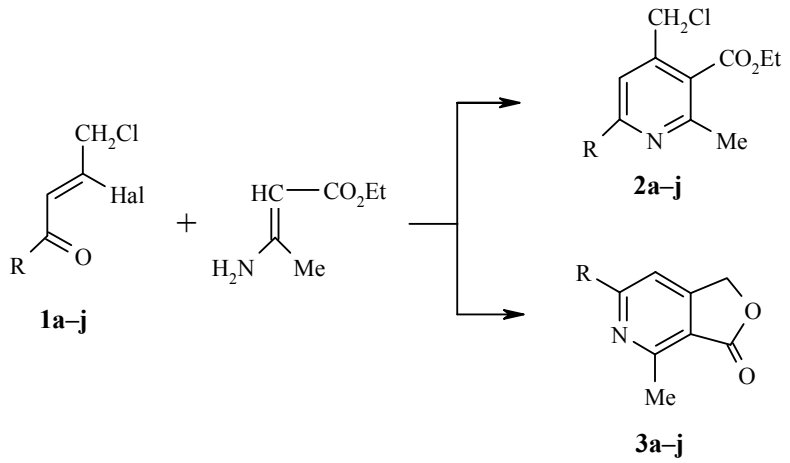
Scheme 1




**1-3 a** R = Me**, b** R = Et, **c** R = Pr, **d** R = Bu, **e** R = $C_5H_{11}$, **f** R = Bn, **g** R = Ph, **h** R = *m*-$C_6H_4Me$, **i** R = *m*-$C_6H_4Cl$, **j** R = *c*-$C_6H_{11}$; **1a-j** Hal = Cl, Br

The formation of lactones **3** is a successful confirmation of the structure of the nicotinic acid ethyl esters **2**. This is very important since, in principle, it is possible that the other regiodirected cyclocondensation of halo ketones **1** with the ethyl ester of β-aminocrotonic ester may occur, bringing about, as a result of the initial nucleophilic substitution of the amino group by the halogen atom in position 2 of ketones **1**, the formation of the isomeric ethyl esters of 4-alkyl(aryl, benzyl, cyclohexyl)-6-chloromethyl-2-methylnicotinic acids, which are not capable of intramolecular cyclization.

It may therefore be asserted that the reaction between 2,3-dihalo ketones **1** and the ethyl ester of β-aminocrotonic acid begins with the formation of a Schiff's base with its subsequent intramolecular cyclization with the elimination of a molecule of hydrogen halide and conversion into the ethyl ester of nicotinic acid **2** (Table 1).

Characteristic absorption bands were observed in the IR spectra of compounds **2** and **3** for the pyridine ring at 2995-3400 ($\gamma_{=C-H}$), 1510-1595 ($\gamma_{C=C}$), 1120-1200 ($\delta_{=C-H}$), 1716-1730 ($\gamma_{C=O}$), 1235-1282 ($\gamma_{C-O-C}$), 1755-1780 ($\gamma_{C=O}$ lactone), and 710-745 $cm^{-1}$ ($\gamma_{C-Cl}$), the positions of which are in agreement with the data of [4].

Characteristic singlet signals were present in the $^1H$ NMR spectra of compounds **2** and **3** for the protons of the pyridine ring, and of the $CH_2$ and $CH_3$ groups (Table 2). There were triplet and quadruplet signals for the protons of the $CO_2CH_2CH_3$ group and also signals for the protons of the R groups.

The described method enables the synthesis of the previously unknown ethyl esters of 4-chloromethylnicotinic acids selectively and in high yield. The products are possible starting materials for obtaining structural analogs of vitamin PP, cardiamine, etc.

## EXPERIMENTAL

The IR spectra were obtained on UR-20 and Specord M-80 spectrometers using a thin film for liquid compounds and nujol for crystalline substances. The $^1H$ NMR spectra were recorded on a Tesla BS-487B (80 MHz), internal standard was HMDS (δ 0.05 ppm) for 5-10% solutions of substances in $CCl_4$ or acetone-$d_6$. The purity of the synthesized compounds was checked by TLC on Silufol UV-254 plates.

The initial 2,3-dichloropropenyl ketones were obtained by the procedure of [5].

TABLE 1. Characteristics of Compounds **2** and **3**

| Compound* | Empirical formula | Found, % / Calculated, % | | | T, °C*[2] | Yield, % |
|---|---|---|---|---|---|---|
| | | C | H | N | | |
| **2a** | $C_{11}H_{14}ClNO_2$ | 58.59 / 58.02 | 6.37 / 6.15 | 6.42 / 6.15 | 121-123 (2) | 84 |
| **2b** | $C_{12}H_{16}ClNO_2$ | 59.96 / 59.62 | 6.81 / 6.62 | 6.14 / 5.80 | 128-130 (2) | 76 |
| **2c** | $C_{13}H_{18}ClNO_2$ | 61.42 / 61.06 | 7.29 / 7.05 | 5.31 / 5.48 | 134-136 (1) | 71 |
| **2d** | $C_{14}H_{20}ClNO_2$ | 62.73 / 62.34 | 7.58 / 7.42 | 5.02 / 5.19 | 148-149 (2) | 64 |
| **2e** | $C_{15}H_{22}ClNO_2$ | 64.01 / 63.49 | 7.63 / 7.76 | 4.86 / 4.94 | 156-158 (2) | 57 |
| **2f** | $C_{17}H_{18}ClNO_2 \cdot HCl$ | 60.55 / 60.00 | 5.67 / 5.59 | 4.45 / 4.12 | 124-125 | 75 |
| **2g** | $C_{16}H_{16}ClNO_2 \cdot HCl$ | 59.46 / 58.88 | 5.33 / 5.21 | 4.50 / 4.29 | 137-139 | 80 |
| **2h** | $C_{17}H_{18}ClNO_2 \cdot HCl$ | 60.39 / 60.00 | 5.72 / 5.59 | 4.37 / 4.12 | 132-133 | 72 |
| **2i** | $C_{16}H_{15}Cl_2NO_2 \cdot HCl$ | 53.47 / 53.93 | 4.63 / 4.87 | 3.88 / 3.75 | 157-158 | 65 |
| **2j** | $C_{16}H_{22}ClNO_2 \cdot HCl$ | 57.19 / 57.83 | 6.71 / 6.93 | 4.37 / 4.22 | 190-192 | 68 |
| **3a** | $C_9H_9NO_2$ | 66.85 / 66.26 | 5.49 / 5.52 | 9.18 / 8.59 | 109-110 | 75 |
| **3b** | $C_{10}H_{11}NO_2$ | 68.23 / 67.80 | 6.47 / 6.21 | 7.69 / 7.91 | 85-86 | 77 |
| **3c** | $C_{11}H_{13}NO_2$ | 68.67 / 69.11 | 6.98 / 6.81 | 7.86 / 7.33 | 72-74 | 73 |
| **3d** | $C_{12}H_{15}NO_2$ | 69.59 / 70.24 | 7.11 / 7.32 | 6.43 / 6.86 | 65-66 | 67 |
| **3e** | $C_{13}H_{17}NO_2$ | 71.84 / 71.23 | 7.93 / 7.76 | 6.39 / 6.28 | 59-60 | 69 |
| **3f** | $C_{15}H_{13}NO_2$ | 75.91 / 75.31 | 5.67 / 5.44 | 6.01 / 5.86 | 54-56 | 72 |
| **3g** | $C_{14}H_{11}NO_2$ | 74.20 / 74.67 | 4.58 / 4.90 | 6.47 / 6.22 | 50-51 | 71 |
| **3h** | $C_{15}H_{13}NO_2$ | 75.77 / 75.31 | 5.32 / 5.44 | 5.73 / 5.86 | 47-48 | 73 |
| **3i** | $C_{14}H_{10}ClNO_2$ | 64.42 / 64.74 | 3.68 / 3.85 | 5.67 / 5.39 | 61-63 | 68 |
| **3j** | $C_{14}H_{17}NO_2$ | 72.18 / 72.72 | 7.09 / 7.36 | 6.17 / 6.06 | 87-89 | 70 |

* **2 a** $n_D^{20}$ = 1.5207, $d_4^{20}$ = 1.1558; **b** $n_D^{20}$ = 1.5175, $d_4^{20}$ = 1.1339; **c** $n_D^{20}$ = 1.5140, $d_4^{20}$ = 1.1123; **d** $n_D^{20}$ = 1.5108, $d_4^{20}$ = 1.0014, **e** $n_D^{20}$ = 1.5075, $d_4^{20}$ = 0.9918; **f-j** – hydrochlorides.

*[2] For compounds **2a-e** bp (mm Hg) are given, for compounds **2f-j** and **3a-j** mp are given.

TABLE 2. $^1$H NMR Spectra of Compounds **2** and **3**

| Compound | Chemical shifts, δ, ppm (*J*, Hz) | | | | |
|---|---|---|---|---|---|
| | =CH, s | $CH_2$, s | $CH_3$, s | $CH_2$–$CH_3$, q, t | R |
| **2a** | 6.90 | 4.49 | 2.46 | 4.26, 1.30 (*J* = 6.9) | 2.43, s |
| **2h** | 6.84 | 4.45 | 2.53 | 4.18, 1.27 (*J* = 6.8) | 3.20, s; 7.32-8.00, m |
| **2i** | 7.06 | 4.59 | 2.58 | 4.33, 1.35 (*J* = 7.0) | 7.16-7.65, m |
| **3a** | 7.00 | 5.01 | 2.72 | — | 2.45, s |
| **3b** | 7.02 | 5.05 | 2.70 | — | 1.23, t ; 2.87, q (*J* = 7.0) |
| **3i** | 7.04 | 5.03 | 2.73 | — | 7.30-7.88, m |

**Ethyl Esters of 6-Alkyl-4-chloromethyl-2-methylnicotinic Acids 2a-e.** Ethyl β-aminocrotonate (12.9 g, 0.1 mol) and triethylamine (14 ml, 0.1 mol) were added dropwise to a solution of 2-bromo-3-chloro- or 2,3-dichloropropenyl alkyl ketones **1a-e** (0.1 mol) in ether (100 ml) at 20-25°C, and the reaction mixture was boiled for 5 h. After cooling, it was washed with water, the aqueous layer was extracted with ether, the ether extracts were combined, and dried over $MgSO_4$. After distilling off the solvent the residue was fractionated in vacuum.

**Ethyl Ester Hydrochlorides of 6-Benzyl(phenyl, *p*-tolyl, *p*-chlorophenyl, cyclohexyl)-4-chloromethyl-6-methylnicotinic Acids 2a-j.** Analogously to the indicated method, an anhydrous ether solution of the ethyl esters of nicotinic acid **2a-j** was obtained from 2,3-dichloropropenyl benzyl(phenyl, *p*-tolyl, *p*-chlorophenyl, cyclohexyl) ketones **1a-j** (0.1 mol), ethyl β-aminocrotonate (12.9 g, 0.1 mol), and triethylamine (14 ml, 0.1 mol), after appropriate processing. A stream of dry hydrogen chloride was passed through this solution, the precipitated crystals were filtered off, and recrystallized from ethyl alcohol.

**6-Alkyl(benzyl, phenyl, *p*-tolyl, *p*-chlorophenyl, cyclohexyl)-4-methyl-3-oxo-dihydrofuro[3,4-*c*]-pyridines 3a-j.** The ether solution of ethyl esters of nicotinic acid **2a-j** was evaporated in vacuum and subjected to vacuum distillation at a residual pressure of 20-30 mm Hg. After recrystallization from hexane the dihydrofuro[3,4-*c*]pyridines were obtained.

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