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Acyl Iodides in Organic Synthesis: VIII. Reactions with Amino Acids

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Abstract—Reactions of acyl iodides RCOI (R=Me, Ph) with glycine, β-alanine, and γ-aminobutyric acid were investigated. The reaction proceeded easily at room temperature without solvent involving both functional groups H_2N and COOH. The prevalence of one of the reaction directions depends on the acidity of the amino acid. The more acidic glycine (pK_a 2.4) reacts with RCOI affording mainly N-acylated product, whereas β-alanine (pK_a 3.60) and especially γ-aminobutyric acid (pK_a 4.06) are predominantly involved into exchange iodination furnishing the corresponding aminoacyl iodides.

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We formerly established by examples of simple acyl iodides reactions with alcohols [1, 2], acyclic and cyclic ethers [3], esters [4] and vinyl alkyl ethers [5], and also with carboxylic acids [6] that acyl iodides RCOI (R = Me, Ph) are efficient iodinating, acylating, and deoxygenating agent. For instance, the reaction of acetyl iodide with carboxylic acids occurred exclusively as an exchange process resulting in the corresponding acyl iodides and acetic acid [6]. Here we report on the study of acyl iodides RCOI (R = Me, Ph) reactions with α-, β-, and γ-amino acids. The reaction of α-amino acids with acyl chlorides $C1CH_2COC1$, $C1_3CCOC1$, and PhCOCl at heating in solution without bases proceeded with formation of the corresponding N-acylated derivatives and with HCl liberation. This process occurred easily only with α-amino acids [7, 8]. The attempts to bring into this reaction, e.g., β-alanine and some other β-amino acids failed [8].

Unlike that the reactions we studied of acetyl iodide with glycine (**I**), β-alanine (**II**), and γ-aminobutyric acid (**III**) occurred without solvent at room temperature without HI liberation. The process with amino acids **I** and **II** proceeded with heat evolution. In all cases the products were crystalline compounds virtually insoluble in organic solvents corresponding to an empirical formula $C_{3+n}H_{6+2n}NO_3I$ [n = 1 (**IV**), 2 (**V**), 3 (**VI**)]. According to the IR spectra the reaction products **IV** and **V** obtained from amino acids **I** and **II** are mixtures of an N-acetyl derivative hydroiodide $I^- MeCON^+H_2(CH_2)_nCOOH$ (A, n = 1, 2) and an acetate of the acyl iodide of the initial amino acid $MeCOO^- N^+ H_3 (CH_2)_nCOI$ (B, n = 1, 2). The formation of compounds A and B occurred along the equations:

$$MeCOI + NH_2(CH_2)_nCOOH$$

$$\longrightarrow I^- MeCON^+H_2(CH_2)_nCOOH$$

$$MeCOI + NH_2(CH_2)_nCOOH \qquad (1)$$

A

$$\longrightarrow MeCOO^- N^+H_3(CH_2)_nCOI \qquad (2)$$

B

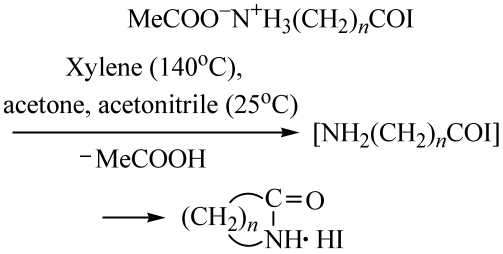
At n = 1 prevailed reaction (1), at n = 2, reaction (2). For instance, with glycine (**I**) the main component of the product is aceturic acid hydroiodide $I^-MeCON^+ H_2CH_2COOH$ (**IVA**). Salt B, $MeCOO^-N^+H_3CH_2COI$ (**IVB**), formed in small amount. In the IR spectrum of the crystalline compound **IV** a strong absorption band at 1750 cm^{-1} is present corresponding to the CO group in the fragment $C(=O)N^+H_2$- of salt **IVA**. The presence in the adduct **IV** of the salt structure **IVB** is confirmed by the presence in the IR spectrum of absorption bands at 1790 and 1640 cm^{-1}, characteristic of the stretching vibrations of a carbonyl group in the acyl iodide moiety COI and carboxylate anion COO^- respectively. However these bands are very weak.

The product of β-alanine (**II**) reaction with acetyl iodide **V** is also a mixture of two salts **VA** and **VB** with the latter $MeCOO^- N^+ H_3 (CH_2)_2COI$ prevailing. In this case dominated the exchange reaction between the amino acid **II** and MeCOI (2).

The only direction of reaction between the γ-aminobutyric acid (**III**) with acetyl iodid was the exchange iodination process affording the acetate of γ-butyryl iodide $MeCOO^- N^+ H_3 (CH_2)_3COI$ (**VIB**) (3).

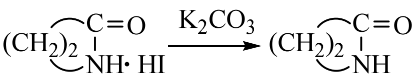
$$MeCOI + NH_2(CH_2)_3COOH \longrightarrow \underset{\mathbf{B}}{MeCOO^- N^+H_3(CH_2)_3COI} \qquad (3)$$

Treating of the salt adducts **IV**–**VI** with acetone and acetonitrile or subjecting salt **VI** to pyrolysis in xylene gave rise in the case of salt **IV** aceturic acid $MeCONHCH_2COOH$ (**VII**), and from salts **V** and **VI** formed in hydroiodides of β-propiolactam (**VIII**) and γ-butyrolactam (**IX**) respectively originating from the intramolecular cyclization of the the primarily formed aminoacyl iodides (4).



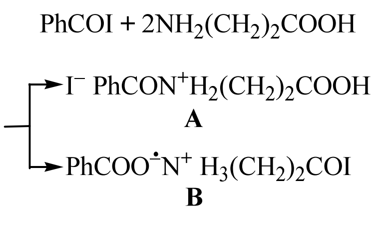
$$MeCOO^-N^+H_3(CH_2)_nCOI \xrightarrow[-MeCOOH]{\text{Xylene (140°C), acetone, acetonitrile (25°C)}} [NH_2(CH_2)_nCOI] \longrightarrow (CH_2)_n\,\mathrm{C{=}O \cdots NH \cdot HI} \qquad (4)$$

In the IR spectra of compounds **VIII** and **IX** the characteristic absorption bands of CO group in acyl iodides at 1790 cm^{-1} are lacking, but appear strong bands in the region 1730–1700 cm^{-1}, characteristic of stretching vibrations of a cabonyl in lactams. Besides we succeeded in separation of pure β-propiolactam (**XI**) by treating compound **IX** with potassium carbonate (5).



XI (5)

The benzyl iodide reacted with amino acids similarly to the acetyl iodide. Its reaction with β-alanine also afforded a product of salt character corresponding to an empirical formula $C_{10}H_{12}NO_3I$ and containing a mixture of salts originating from N-acylation A and from iodination B with considerable predominance of the latter (6).



$$PhCOI + 2NH_2(CH_2)_2COOH \rightarrow \begin{cases} \underset{\mathbf{A}}{I^- \, PhCON^+H_2(CH_2)_2COOH} \\ \underset{\mathbf{B}}{PhCOO^- N^+ H_3(CH_2)_2COI} \end{cases} \qquad (6)$$

However we failed to isolate from this adduct an individual substance by procedures used with the amino acids derivatives obtained by treating them with acetyl iodide apparently because of higher strength of formed salts owing to higher acidity of the benzoic acid compared to that of the acetic acid (pK_a 4.19 and 4.75 respectively).

Thus the reaction of amino acids with acyl iodides involves both functional groups, H_2N and COOH. The prevailing direction of the reaction depends on the acidity of the amino acid. With decreasing acidity the exchange iodination process becomes more pronounced than N-acyla-tion. For instance, when glycine (pK_a 2.4) treated with acyl iodides mainly underwent N-acylation, for β-alanine (pK_a 3.60), and especially for γ-aminobutyric acid (pK_a 4.06) the principal process was exchange iodination. These results are well consistent with our findings concerning reactions of acyl iodides with carboxylic acids where the exchange iodination process is the easier the weaker the acid [6].

EXPERIMENTAL

Initial acyl iodides were prepared from appropriate acyl chlorides by reaction with an anhydrous sodium iodide by the known procedure [9]. IR spectra were recorded on a spectrometer UR-20 from thin film or solutions in acetonitrile or pyridine.

Reaction of acetyl iodide with glycine. To 1.0 g (0.005 mol) of acetyl iodide was added an equivalent amount of glycine (0.4 g, 0.005 mol). The reaction mixture self-heated. The mixture was maintained without additional heating for 4–5 h. We obtained 1.2 g (86%) of crystalline compound with mp 75–76°C. IR spectrum, ν, cm^{-1}: 3011–2923, 2653, 1976 (NH); 1790 (CO in COI), 1750 [CO in C(=O)N$^+$H$_2$-], 1640 [ν_{as} (COO$^-$)], 1512 [δ(NH in RNH$_3^+$)], 1424 [ν_s (COO$^-$)]. Found, %: C 19.42; H 3.54; I 50.55; N 5.40. $C_4H_8INO_3$. Calculated, %: C 19.61; 3 3.29; I 51.79; N 5.71.

Reaction of acetyl iodide with β-alanine. Under similar conditions from 3.3 g (0.02 mol) of β-alanine and 1.7 g (0.02 mol) of acetyl iodide we obtained 4.8 g (96%) of crystalline substance with mp 53–54°C. IR spectrum, cm^{-1}: 3136–2925, 2652–2545 (NH); 1750 [CO in C(=O)N$^+$H–], 1640 [ν_{as} (COO$^-$)], 1540 [δ(NH in RNH3+)], 1387 [ν_s (COO$^-$)], 540 (I in COI). Found, %: C 24.52; H 4.36; I 48.83; N 5.26. $C_5H_{10}INO_3$. Calculated, %: C 23.18; H 3.89; I 48.99; N 5.41.

Reaction of acetyl iodide with γ-aminoacetic acid. Under similar conditions from 1.5 g (0.02 mol) of γ-aminoacetic acid and 2.5 g (0.02 mol) of acetyliodide we obtained 3.5 g (89%) of crystalline substance with mp 112–113°C. IR spectrum, ν, cm^{-1}: 3000, 2600, 2000–1900 (NH in RNH_3^+), 1620 [ν_{as} (COO$^-$)], 1500 [δ(NH in RNH_3^+)], 1400 [ν_s (COO$^-$)]. Found, %: C 26.86; H 4.48; I 46.03; N 4.45. $C_6H_{12}INO_3$. Calculated, %: C 26.39; H 4.43; I 46.47; N 5.13.

Reaction of benzoyl iodide with β-alanine. To 2.5 g (0.007 mol) of benzoyl iodide was added 0.6 g (0.007 mol) of β-alanine. The mixture self-heated and then was maintained at room temperature for 4 h. We obtained 2.0 g (93%) of crystalline compound with mp 126–128°C. IR spectrum, ν, cm^{-1} : 3000, 2590, 1990 (NH in RNH_3^+), 1750 [CO in C(=O)N$^+$H–], 1625 [ν_{as} (COO$^-$)], 1580 [δ(NH in RNH_3^+)], 1390 [ν_s (COO$^-$)]. Found, %: C 36.95; H 3.67; I 40.92; N 3.88. $C_{10}H_{12}INO_3$. Calculated, %: C 37.40; H 3.76; I 39.52; N 3.46.

Preparation of aceturic acid. With 10 ml of anhydrous acetone was mixed 2 g of the crystalline product obtained from glycine and acetyl iodide. The mixture was stirred without heating for 1 h, the precipitate was filtered off and kept at reduced pressure to remove the residual acetone. We obtained 0.7 g (75%) of aceturic acid with the melting point in agreement with the published data [10]. IR spectrum, ν, cm^{-1}: 3350 (NH in –CONH–), 3300–2500 (OH in –COOH), 1710 (CO in –COOH), 1600 (I amide band), 1540 (II amide band). Found, %: C 40.59; H 6.02; N 12.11. $C_4H_7NO_3$. Calculated, %: C 41.03; 3 6.03; N 11.95.

Preparation of β-propiolactam hydroiodide. With 10 ml of anhydrous acetonitrile was mixed 2.5 g of the crystalline product obtained from β-alanine and acetyl iodide. The mixture was stirred for 1 h at room temperature, the precipitate was filtered off and kept at reduced pressure. We obtained 1.3 g (73%) of β-propiolactam hydroiodide, mp 70°C. IR spectrum, ν, cm^{-1}: 3200 (NH), 1720 (CO), 1650 [δ(NH)], 1220 (CN). Found, %: C 18.31; H 3.98; I 58.58; N 6.76. $C_3H_6INO_3$. Calculated, %: C 18.11; H 3.04; I 63.78; N 7.04.

Preparation of γ-butyrolactam hydroiodide. *a.* In anhydrous xylene was boiled for 4 h 2.9 g of the product obtained from γ-aminobutyric acid and acetyl iodide. Then the precipitate was filtered off . We obtained 2.1 g (93%) of γ-butyrolactam hydroiodide, mp 90°C. Found, %: C 22.73; H 4.03; I 58.39; N 6.68. $C_4H_8INO_3$. Calculated, %: C 22.55; H 3.79; I 59.58; N6.57.

b. With 10 ml of anhydrous acetonitrile was mixed 2 g of the product obtained from γ-aminobutyric acid and acetyl iodide. The mixture was stirred for 1 h at room temperature, the precipitate was filtered off and kept at reduced pressure. We obtained 1.4 g (87%) of γ-butyrolactam hydroiodide with mp 90°C. IR spectrum, ν, cm^{-1}: 3400 (NH), 1710 (CO), 1630 [δ(NH)], 1210 (CN). Found, %: I 61.03; N 6.86. $C_4H_8INO_3$. Calculated, %: I 59.58; N 6.57.

Preparation of β-propiolactam. To 0.5 g of β-propiolactam hydroiodide was added 5 ml of 10% solution of K_2CO_3. On completion of the gas liberation the solution was extracted with ether. On evaporating the ether from the extract we obtained 0.1 g of β-propiolactam with a melting point consistent with the published data [10].

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