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LETTERS TO THE EDITOR

The Reaction of *para*-Aminobenzoic Acid with 1-Iodopropan-2-one

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Derivatives of *p*-aminobenzoic acid are of practical interest due to their diverse biological activity [1–8], stimulating the search for the synthesis routes towards new representatives of this class of compounds and investigation of their properties.

In the literature, numerous methods for functionalization of *p*-aminobenzoic acid are described, based on the reactions with alkyl or acyl halides with the formation of the products of *N*-alkylation; the reactions are favored in alkaline media. Modification of the *N*-substituted derivatives of *p*-aminobenzoic acid proceeds in the presence of sodium hydride in DMF and gives the products of *O*- and *N*-alkylation [4, 5]. To our knowledge, the data on functionalization of aminobenzoic acids with α-iodoketones have been absent.

In this present work we studied for the first time the reaction of *p*-aminobenzoic acid **1** with 1-iodopropan-2-one **2** at different temperature, both in the presence and in the absence of solvent and bases. The reaction in an aqueous–acetone solution of Na_2CO_3 both at room temperature and on heating (50°C) results in the formation of exclusively 4-(2-oxopropyl)aminobenzoic acid **3** (Scheme 1).

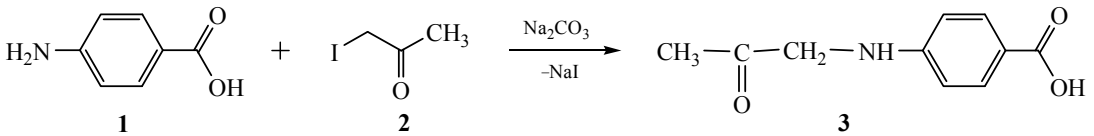
It turned out that in the absence of base the course of the reaction depended on temperature. On heating (50°C) in the absence of solvent, the alkylation also proceeded at the amino group, giving rise to monoiodide **A** (route *a*). However, *O*-alkylation with the formation of adduct **B** occurred at room temperature (route *b*). Further, iodide anions of the adducts **A** and **B** entered the reaction with molecular iodine formed due to the reduction of iodoketone **2** with hydrogen iodide, the latter being evolved during the alkylation; that process led to the earlier unknown triiodides of 4-carboxy-*N*-(2-oxopropyl)phenylammonium **4** or 4-[(2-oxopropoxy)carbonyl]phenylammonium **5** in 41 and 49% yield, respectively (Scheme 2).

Low yields of triiodides **4** and **5** were apparently due to the competing reaction of polycondensation of acid **1**, leading to a mixture of oligopeptides that we failed to separate.

Triiodides **4**, **5** were dense oils; upon formation, they act as a solvent affording the homogeneous reaction mixture.

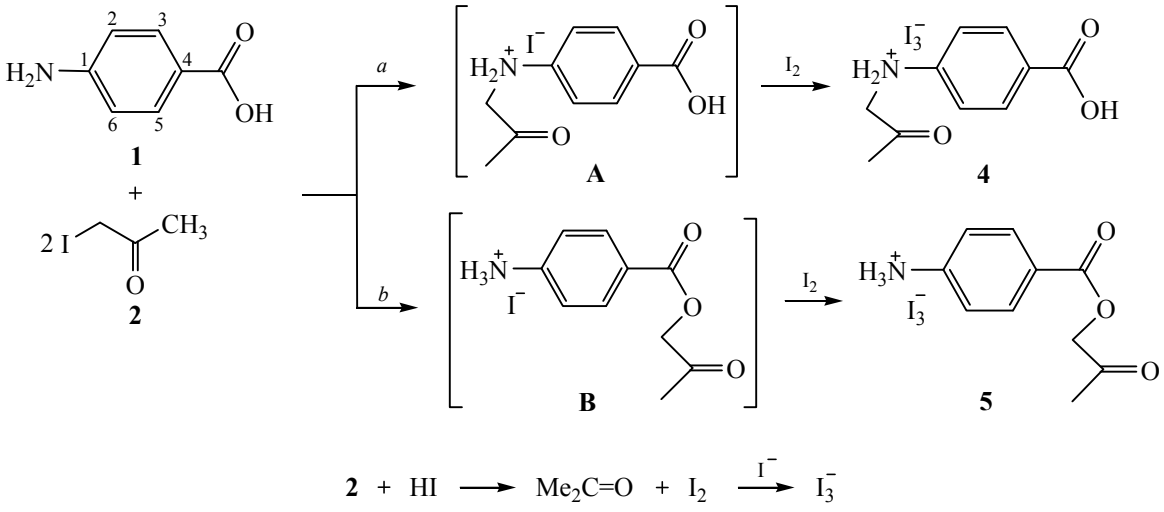
Structure and composition of compounds **3**–**5** were confirmed by the data of elemental analysis, ^{1}H, ^{13}C, and ^{15}N NMR and UV spectroscopy. The ^{15}N HMBC $\{^{1}H–^{15}N\}$ spectrum of 4-(2-oxopropyl)aminobenzoic acid **3** contained the cross peaks of the nitrogen atom at –304 ppm and the *ortho*-protons of the benzene ring

Scheme 1.



1 **2** **3**

Scheme 2.



and the CH_2 group. The same spectrum of compound **4** contained cross peaks of the nitrogen atom at –175.1 ppm and both the *ortho*-protons of the ring and the methylene protons, whereas the spectrum of compound **5** contained a cross peak of the nitrogen atom (–328 ppm) only with the *ortho*-protons of the aromatic ring.

UV spectra of triiodides **4** and **5** contained the absorption bands with maximums at 291–292 and 362–364 nm, typical of I_3^- anion [9].

N-Alkylation of acid **1** at room temperature in the presence of Na_2CO_3, unlike *O*-alkylation in the absence of the base, was apparently due to the formation of the salt and the increase in the basicity of the amino group owing to a weakened conjugation with the negatively charged substituent COO^-. The reasons of the temperature dependence of the course of the reaction require a separate investigation.

In summary, depending on the conditions of the reaction, alkylation of *p*-aminobenzoic acid with 1-iodopropan-2-one occurs either at the amino or the carboxyl group.

4-(2-Oxopropyl)aminobenzoic acid (3). 1 eq./L solution of Na_2CO_3 was added to a solution of 0.2 g (1.5 mmol) of *p*-aminobenzoic acid **1** in 2 mL of distilled water to pH 8. Then, a solution of 0.26 g (1.5 mmol) of iodoketone **2** in 1 mL of acetone was added dropwise at stirring. After completion of the reaction (2 h at 20°C or 20 min at 50°C), the precipitate was filtered off, washed with water, and dried in vacuum. Yield 0.25 g (85%), white powder, mp 191–193°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.10 s (3H, CH_3), 4.04 s (2H, CH_2), 6.57 d (2H, $H^{2,6}$ J = 8.8 Hz), 7.65 d (2H, $H^{3,5}$ J = 8.8 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 27.33 (CH_3), 52.79 (CH_2), 111.53 ($C^{2,6}$), 117.86 (C^4), 131.39 ($C^{3,5}$), 152.25 (C^1), 167.87 (COO), 206.03 (C=O). Found, %: C 62.57; H 5.43; N 7.31. $C_{10}H_{11}NO_3$. Calculated, %: C 62.17; H 5.74; N 7.25.

Reaction of *p*-aminobenzoic acid with 1-iodopropan-2-one. A suspension of 0.2 g (1.5 mmol) of *p*-aminobenzoic acid **1** and 0.55 g (3 mmol) of iodoketone **2** was stirred at 20°C for 72 h or at 45°C for 6 h. After the completion of the reaction, the dense oil was dissolved in 10 mL of acetonitrile, and 50 mL of diethyl ether was added. The formed precipitate of oligopeptides was separated by filtration. The filtrates containing triiodides **4** and **5** were evaporated and purified by column chromatography on a column with MN Kieselgel 60 silica (0.063–0.2 mm) using acetone as eluent.

4-Carboxy-*N*-(2-oxopropyl)phenylammonium (4). Yield 0.18 g (41%), R_f 0.87 (acetone). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.33 s (3H, CH_3), 4.28 s (2H, CH_2), 7.75 d (2H, $H^{3,5}$ J = 8.3 Hz), 8.19 d (2H, $H^{2,6}$ J = 8.3 Hz), 8.59 s (2H, NH_2). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 27.77 (CH_3), 65.83 (CH_2), 114.20 ($C^{2,6}$), 125.87 (C^4), 130.59 ($C^{3,5}$), 133.57 (C^1), 166.10 (COO), 197.60 (C=O). Found, %: C 20.54; H 1.92; N 2.18; I 66.08. $C_{10}H_{12}I_3NO_3$. Calculated, %: C 20.89; H 2.10; N 2.44; I 66.22.

4-[(2-Oxopropoxy)carbonyl]phenylammonium triiodide (5). Yield 0.21 g (49%), R_f 0.85 (acetone). ^{1}H

NMR spectrum (acetonitrile-d_3), δ, ppm: 2.31 s (3H, CH_3), 4.41 s (2H, CH_2), 7.50 d (2H, $H^{2,6}$ J = 8.6 Hz), 8.13 d (2H, $H^{3,5}$ J = 8.6 Hz), 8.52 s (2H, NH_2). ^{13}C NMR spectrum (acetonitrile-d_3), δ_C, ppm: 27.70 (CH_3), 30.86 (CH_2), 113.84 ($C^{2,6}$), 124.72 (C^4), 130.95 ($C^{3,5}$), 133.98 (C^1), 166.36 (COO), 201.78 (C=O). Found, %: C 20.24; H 1.89; N 2.20; I 65.98. $C_{10}H_{12}I_3NO_3$. Calculated, %: C 20.89; H 2.10; N 2.44; I 66.22.

^1H, ^{13}C, and ^{15}N NMR spectra were registered using DPX-400 and AV-400 [400.13 (^1H), 100.61 (^{13}C), 40.56 (^{15}N) MHz] spectrometers (Bruker) relative to TMS (^1H and ^{13}C) or nitromethane (^{15}N). Two-dimensional ^{15}N NMR spectra were recorded using the HMBC-gp ^1H–^{15}N correlation technique. UV spectra were recorded using a UV-Vis Lambda 35 spectrometer in CH_3CN. Elemental analysis was performed using an automated Flash 2000 CHNS-analyzer (Thermo scientific). Iodine content was determined by mercurimetry. The reactions were monitored by means of ^1H, ^{13}C, and ^{15}N NMR spectroscopy as well as TLC on Silufol UV-254 plates (eluent acetone, development with iodine vapors).

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