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LETTERS TO THE EDITOR

Ketoalkylation of Adenine with 1-Iodopropan-2-one

L. V. Zhilitskaya, N. O. Yarosh, L. G. Shagun, I. A. Dorofeev, L. I. Larina

A.E. Favorskii Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, ul. Favorskogo 1, Irkutsk, 664033 Russia
e-mail: lara_zhilitskaya@irioch.irk.ru

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Adenine (6-aminopurine) and its derivatives can serve as synthons in alkylation reactions for preparation of compounds with a wide spectrum of biologically activity [1–5].

Adenine shows the highest reactivity in the N^3-position, as proved by the reaction with benzyl chloride or propargyl bromide [5, 6]. The reaction of adenine with 2-[ω-(chloroheptanoyl)cyclohexanone], trimethylphosphate or epichlorohydrin results in a mixture of N^3- and N^9-derivatives [2, 7], with ethyl ester of 2-bromopent-4-enoic acid a mixture of N^7- and N^9-derivatives is formed [8]. In the presence of K_2CO_3, NaH or DBU the reaction is predominantly directed to the N^9-position [2, 5–8]. A mixture of N^3-, N^7-, and N^9-products is formed in the reaction of adenine with phenyl glycidyl ester in DMF or acetic acid [9].

Alkylation of N^3-substituted adenines with excess of benzyl halides occurs at the 3,7-positions. In the presence of K_2CO_3, the reaction leads to 3,6,7-tribenzyladenines [5]. At the same time, the alkylation of N^6-substituted adenine with chloroacetone in the presence of K_2CO_3 proceeds exclusively at the N^9-nitrogen atom [4]. On alkylation of N^3- or N^9-substituted adenines the second alkyl group is directed to the N^1- and N^7-positions, respectively [10]. $N^{6,9}$-Dimethyl-derivatives of adenine are methylated with methyl iodide with the formation of the corresponding N^1-, N^3-, and N^7-isomeric iodides [11].

It was of interest to study the reaction of adenine with 1-iodopropan-2-one having a labile C–I bond in order to clarify the possibility of its use for functionalization of adenine.

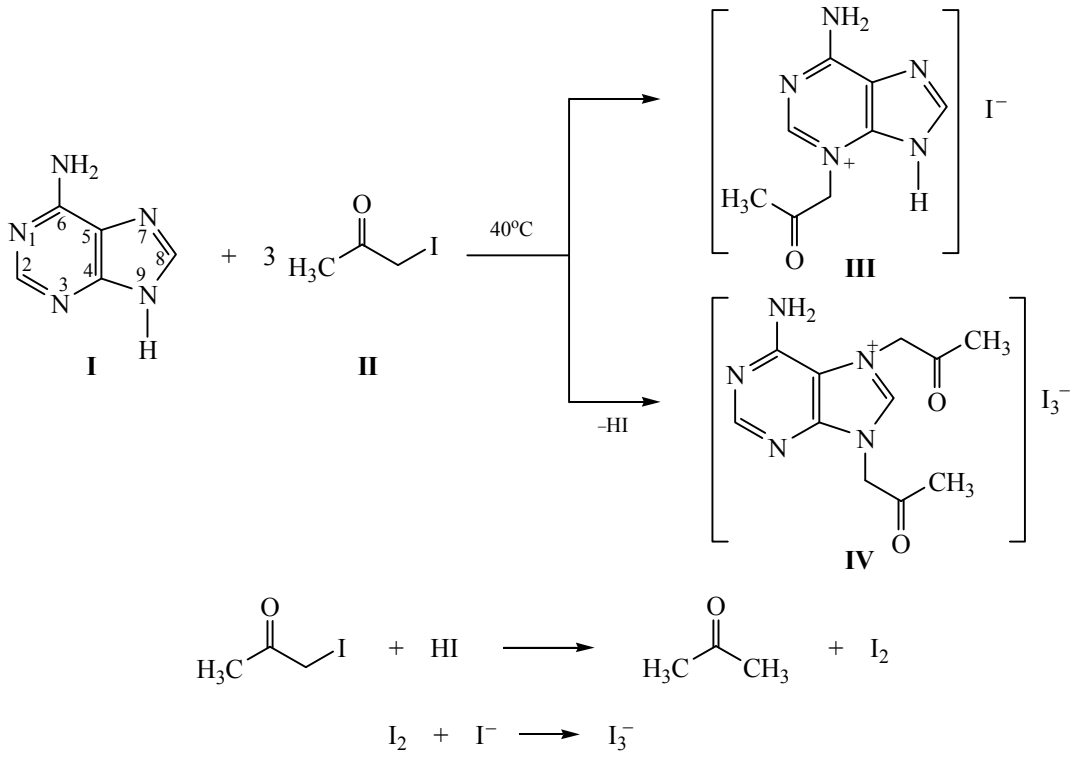
The reaction of adenine **I** with 1-iodopropan-2-one **II** in the molar ratio of 1:3 in the absence of bases or phase-transfer catalysts proceeds at the N^3 and $N^{7,9}$ nitrogen atoms with the formation of a mixture of 6-amino-3-(2-oxopropyl)-9*H*-purinium iodide **III** and 6-amino-7,9-bis(2-oxopropyl)-9*H*-purinium triiodide **IV** in the yield of 65 and 35 % respectively (Scheme 1).

Iodide **III** is easily precipitated when adding acetone to the reaction mixture. At the same time, salt **III**, which is poorly soluble in organic solvents, is readily soluble in the formed liquid salt **IV**. Therefore, the latter salt was successfully purified only by repeated reprecipitation. 6-Amino-7,9-bis(2-oxopropyl)-9*H*-purinium triiodide **IV** is a thick dark-red oil, which can be regarded as an ionic liquid of new type on the basis of adenine.

The structure and composition of iodides **III, IV** were proved by elemental analysis, ^1H, ^{13}C, ^{15}N NMR, IR, UV spectroscopy. In the 2D HMBC ^1H–^{15}N spectrum of salt **III** a cross peak appears between the signals of the methylene group protons and the nitrogen in the 3 position at –227.5 ppm. The absorption band at λ_{max} 275 nm in the UV spectrum corresponds to the model N^3-methyl-substituted adenine [16]. The UV spectrum of product **IV** contains the absorption band with maxima at λ_{max} 287 and 362 nm typical of triiodide anion (I_3^-) [17]. Its formation is consistent with the reaction occurring at the N^9-position since the molecular iodine required for the formation of triiodide anion is formed by the reduction of iodoacetone **II** with the evolved HI.

Therefore, we have shown that the high lability of the C–I bond in 1-iodopropan-2-one makes it possible

Scheme 1.



to perform alkylation of adenine in the absence of bases or phase transfer catalysts. The reaction of adenine with 1-iodopropan-2-one is the first example of formation of liquid salts of adenine with triiodide anion as a counterion.

IR spectra were recorded on a Vertex 70 spectrometer in KBr. ^{1}H, ^{13}C, ^{15}N NMR spectra were registered on a Bruker DPX-400 spectrometer [400.13 (^{1}H), 100.61 (^{13}C), 40.56 (^{15}N) MHz] in DMSO-d_6 or acetone-d_6. ^{1}H and ^{13}C chemical shifts are measured with respect to TMS, ^{15}N, to nitromethane. Elemental analysis was performed on an automated CHNS-analyzer Thermo scientific Flash 2000. Melting points were determined on a Micro-Hot-Stage PolyTherm A unit. UV spectra were taken on a UV–Vis Lambda 35 spectrometer (H_2O, pH 7; CH_3CN). The reactions were monitored and the purity of compounds controlled by TLC on Silufol UV-254 plates (eluent – acetone).

General procedure of alkylation of adenine. The suspension of 0.01 mol of adenine **I** and 0.03 mol of iodoketone **II** in 5 mL of DMSO or DMF was stirred at 25–40°C for 10–12 h until the starting ketone was consumed. Then 10 mL of acetone was added to the reaction mixture, the formed precipitate of **III** was separated by filtration, washed with acetone, and dried in a vacuum. The filtrate was added dropwise with stirring to 300 mL of ether, the precipitated thick oily compound **IV** was twice reprecipitated in the mixture acetone – ether, and dried in a vacuum.

6-Amino-3-(2-oxopropyl)-9*H*-purinium iodide (III) was obtained from 0.135 g of adenine **I** and 0.552 g of 1-iodopropan-2-one **II**. Yield 0.21 g (65%), yellow powder, mp 252–255ºC. IR spectrum, ν, cm^{-1}: 1727 (C=O), 2933 1411 (CH_2); 3261 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.38 s (3H, CH_3), 5.32 s (2H, CH_2), 8.35 s (2H, NH_2), 8.38 s (H, C^8), 8.50 s (H, C^2), 9.07 s (H, NH). ^{13}C (DMSO-d_6), δ_C, ppm: 27.87 (CH_3), 58.34 (CH_2), 110.34 (C^5), 145.97 (C^8), 148.38 (C^4), 149.37 (C^2), 154.29 (C^6), 201.57 (C=O). ^{15}N NMR spectrum (DMSO-d_6), δ_N, ppm: –227.5 ppm (N^3). Found, %: C 30.71; H 3.09; N 21.23; I 40.04. $C_8H_{10}N_5OI$. Calculated, %: C 30.11; H 3.15; N 21.95; I 39.77.

6-Amino-7,9-bis(2-oxopropyl)-9*H*-purinium triodide (IV) was obtained from 0.135 g of adenine **I** and 0.552 g of 1-iodopropan-2-one **II** as dark-brown oil, 0.22 g (35 %). IR spectrum, ν, cm^{-1}: 1720 (C=O), 2919, 1410 (CH_2); 3270 (NH). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.41 s (3H, CH_3), 2.64 s (3H, CH_3), 5.79 s (2H, CH_2), 6.21 s (2H, CH_2), 8.59 s (2H,

NH_2), 8.91 s (2H, C^8), 8.92 s (H, C^2), 9.2 (NH). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 26.86 and 27.94 (CH_3), 57.28 and 57.45 (CH_2), 111.76 (C^5), 144.18 (C^8), 148.24 (C^4), 149.43 (C^2), 152.97 (C^6), 199.09 and 209.67 (C=O). Found, %: C 21.82; H 2.66; N 11.62; I 60.07. $C_{11}H_{14}N_5O_2I_3$. Calculated, %: C 21.00; H 2.24; N 11.13; I 60.52.

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