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Directed Synthesis of Alkyl-Substitued Pyrrolo[*3,4-c*]pyrrole-1,3,4,6-tetraones

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Abstract—Reactions of 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles with aqueous hydrohalic acid led to the formation of alkyl-substituted pyrrolo[3,4-*c*]-pyrrole-1,3,4,6-tetraones.

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Five-membered nitrogen heterocyclic compounds are widely spread among natural substances of important biological action. For instance, pyrrolidine-2,5-dione fragment was found in the compositions of inhibitors of aldose reductase enzyme [1] and in agonists of the cannabinoid receptors CB1 [2].

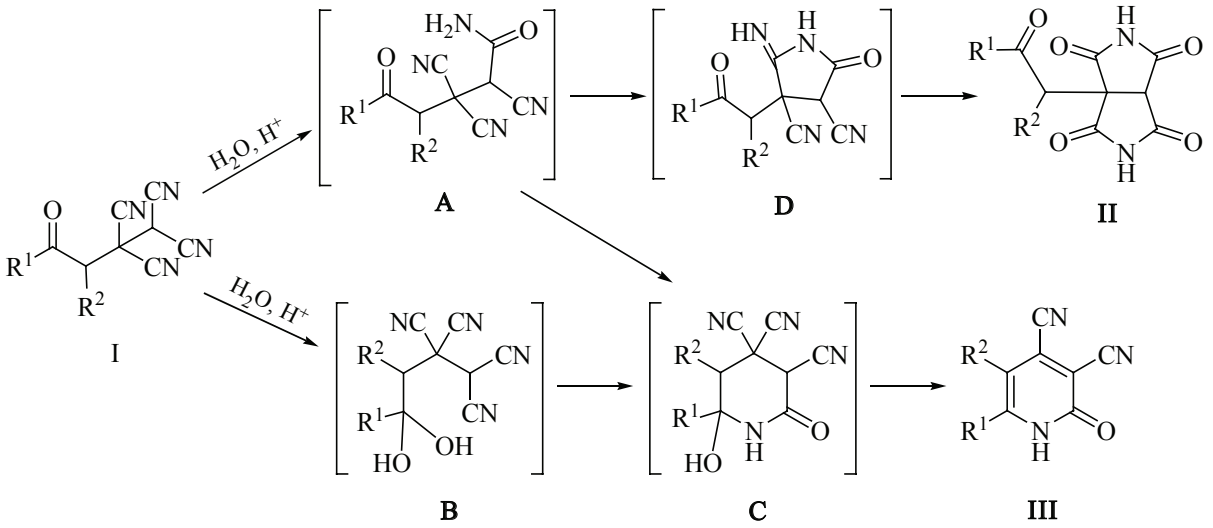
Compounds with two fused pyrrolidine-2,5-dione fragments are poorly studied, for the methods of their preparation mainly consist in the heterocyclization of difficultly available derivatives of tetracarboxylic acids which either are already contained in the structure of the initial compound or result from the hydrolysis of cyano groups [3–5]. These reactions proceed in stringent conditions and provide low yields.

We formerly demonstrated that the reaction with water solutions of acids of 4-oxoalkane-1,1,2,2-tetracarbonitriles (tetracyanoalkanones) (**I**) where R^1 was a bulky substituent or a phenyl with electron-donor groups led to the formation of pyrrolo[*3,4-c*]-pyrrole-1,3,4,6-tetraones (pyrrolopyrroles, diimides) **II** [6–8]. At the same time tetracyanoalkanones **I** with alkyl substituent R^1 under the same conditions converted into 2-oxo-1,2-dihydropyridine-3,4-dicarbonitriles **III** [7, 9] (Scheme 1). Apparently the formation of diimides **II** started with the hydrolysis of the terminal cyano group of tetracyanoalkanone **I** activated because of the nitrile-ketenimine tautomerism leading to intermediate **A**. Further stabilization of the formed carboxamide may occur as a cyclization into tetrahydropyridine **C** [9], but this process does not proceed with compounds possessing a bulky substituent or a phenyl with electron-donor groups. Just this reason causes the primary addition of water to the cyano group and not to a carbonyl group providing diol **B** [10]. Therefore the most probable stabilization path of intermediate **A** is the formation of pyrrole **D** with its subsequent conversion into pyrrolopyrrole **II**.

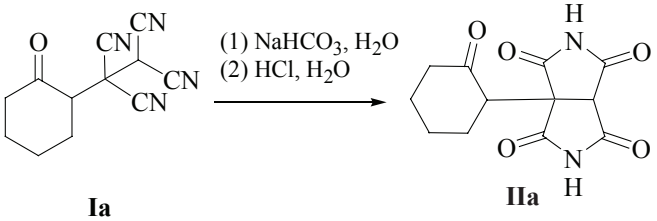
The analysis of published data and our experiment allow a conclusion that the formation of diimides **II** is governed by the presence of a bulky substituent [7, 8] or a phenyl substituent with electron-donor groups [6] that impede the nucleophile attack on the carbonyl group. In event of tetracyanoalkanones **I** with the alkyl substituent the carbonyl group is more active, and therefore pyridones are formed, presumably through intermediate **B** (Scheme 1) [10]. Consequently, synthesis of pyrrolopyrroles **II** with alkyl substituents cannot be performed by the above described procedure.

As known, in the reaction with amines of 4-oxoalkane-1,1,2,2-tetracarbonitriles **I**, also of those with alkyl substituents, β- and γ-cyano groups are involved affording as a result pyrrole derivatives [11, 12]. Testing the possibility to obtain diimides **II** from the alkyl-substituted tetracyanoalkanones in basic environment we found that in water in the presence of sodium hydrogen carbonate pyrrolopyrrole **IIa** formed in 56% yield (Scheme 2). The final product was isolated at acidifying the reaction mixture.

Scheme 1.



Scheme 2.



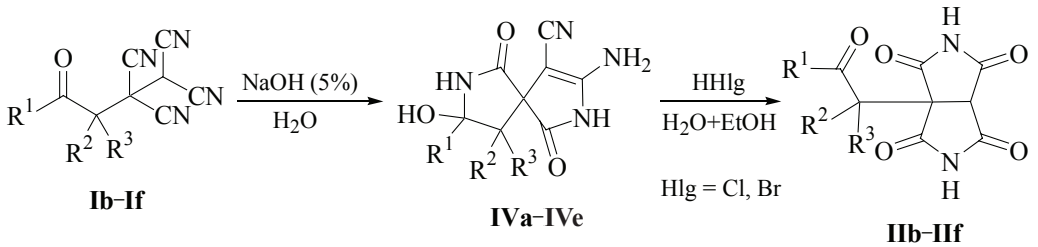
Ia **IIa**

The cyano groups are stable against the action of weak bases, therefore it is presumable that the formation of diimide **IIa** occurs involving the carbonyl group through intermediate **B** (Scheme 1). It is besides known that alkyl-substituted 4-oxoalkane-1,1,2,2-tetracarbonitriles **I** under similar conditions (5% aqueous NaOH) form spiranes **IV** (Scheme 3), whose preparation method we have described before [13]. However they form within 30–60 min, whereas the synthesis of diimide **IIa** requires 72 h. It is therefore presumable that spiranes of **IV** type may be intermediates in the formation of pyrrolopyrrole **IIa**. To prove this assumption we carried out the reaction of spiranes **IV** with water solutions of HCl and HBr and obtained alkyl-substituted diimides **IIb–IIf**.

The structure of compounds synthesized was confirmed by IR, ^{1}H NMR, and mass spectra, and also by XRD analysis of the single crystal of compound **IId** (see the figure).

IR spectra of pyrrolo[3,4-*c*]pyrrole-1,3,4,6-tetraones **II** contain absorption bands of C=O groups at 1664–1773 cm^{-1} and of stretching vibrations of NH groups in the region 3070–3238 cm^{-1}. In the ^{1}H NMR spectra of compounds **II** the signals of the protons of NH groups of the tetrahydropyrrole rings appear at 11.67–12.04 ppm. The ^{1}H NMR spectra contain also the proton signals of alkyl substituents (1.23–2.71 ppm). The mass spectra are characterized by the presence of the molecular ion peaks of the intensity 7–41%.

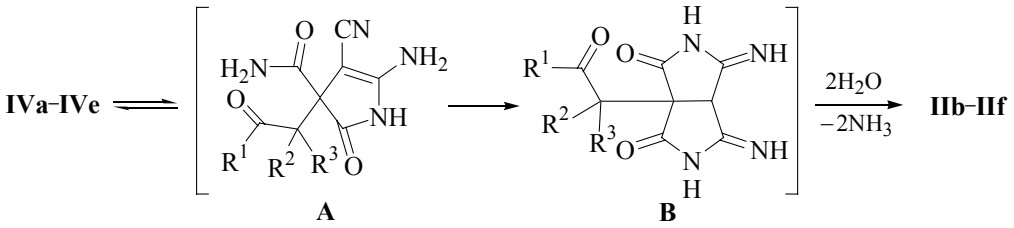
Scheme 3.



Ib–If **IVa–IVe** **IIb–IIf**

$R^1 = R^2 = CH_3$, $R^3 = H$ (**Ib, IIb, IVa**); $R^1 = CH_3$, $R^2 = C_2H_5$, $R^3 = H$ (**Ic, IIc, IVb**); $R^1 = R^2 = R^3 = CH_3$ (**Id, IId, IVc**); $R^1+R^2 = (CH_2)_4$, $R^3 = CH_3$ (**Ie, IIe, IVd**); $R^1 = Ph$, $R^2 = CH_3$, $R^3 = H$ (**If, IIf, IVe**).

Scheme 4.



The probable mechanism of tetraones **II** formation from 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]-non-3-ene-4-carbonitriles **IV** is presented in Scheme 4. The acid catalyzed decyclization of the hydroxylactam ring of spiranes **IVa–IVe** leads to the formation of carboxamide **A**. Further the intramolecular heterocyclization of carboxamide and cyano groups results in intermediate **B** whose hydrolysis completes the formation process of final diimides **IIb–IIf**.

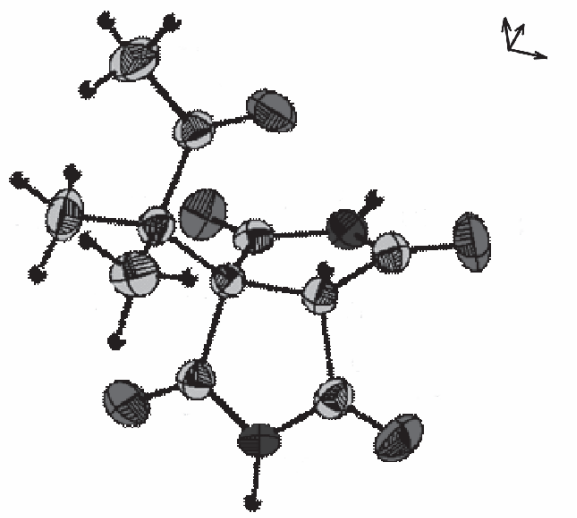
Hence in the course of investigation we developed a preparation method of alkyl-substituted pyrrolo[3,4-*c*] pyrrole-1,3,4,6-tetraones **IIa–IIf**. It was proved that their formation from 4-oxoalkane-1,1,2,2-tetracarbonitriles **I** in the presence of bases proceeded through the intermediate formation of 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles **IV**.

EXPERIMENTAL

The purity of compounds obtained was checked by TLC on Silufol UV-254 plates, development under UV irradiation, in iodine vapor, by thermal decomposition. IR spectra were recorded on an IR Fourier spectrometer FSM-1202 from thin film (mull in mineral oil). ^{1}H NMR spectra were registered on a spectrometer Bruker DRX-500, operating frequency 500.13 MHz, solvent DMSO-d_6, internal reference TMS. Mass spectra were taken on an instrument Finnigan MAT INCOS-50 (EI, 70 eV).

XRD analysis of the single crystal of compound **IId** was carried out on a diffractometer StadiVari Pilatus 100K of STOE Co, MoK_α radiation. The data collection, the determination and refinement of unit cell parameters, the processing of the diffraction data was performed using the program package STOE X-Area. The structure was solved by the direct method in the framework of SHELXS-97 software [14]. The graphic imaging of the molecule in the crystal was done with the use of DIAMOND software [15]. XRD experiment was carried out on the equipment of the Chair of the general Chemistry of the Chemical Department of Lomonosov Moscow State University.

3a-(2-Oxocyclohexyl)pyrrolo[3,4-*c*]pyrrole-1,3,4,6(2*H*,3a*H*,5*H*,6a*H*)-tetraone (IIa). To a solution of 0.226 g (1 mmol) of nitrile **Ia** in 2 mL of acetone was added 2 mL of 10% solution of sodium hydrogen carbonate, and the mixture was stirred for 24 h. Then 1 mL of conc. HCl was added, and the solution was left standing for 40–48 h. The formed precipitate was filtered off, washed with water and 2-propanol, and dried in a vacuum-desiccator over $CaCl_2$. Yield 0.148 g (56%), mp 280–281°C. IR spectrum, ν, cm^{-1}: 3185, 3070 (NH), 1760–1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.59–1.77 m [6H, $(CH_2)_3$], 1.91–1.95 m (1H, CH_2), 2.18 d (1H, CH_2, *J* 13.9 Hz), 3.50 d.d (1H, CH, *J* 12.8, 5.4 Hz), 4.27 s (1H, CH), 11.70 s (1H, NH), 11.95 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 264 (33) $[M]^+$. Found, %: C 54.50; H 4.59; N 10.62. $C_{12}H_{12}N_2O_5$. Calculated, %: C 54.55; H 4.58; N 10.60. *M* 264.23.



Molecular structure of 3a-(2-metyl-3-oxobutan-2-yl)pyrrolo-[3,4-*c*] pyrrole-1,3,4,6(2*H*,3a*H*,5*H*,6a*H*)tetraone (**IId**) according to XRD data.

3a-(3-Oxobutan-2-yl)pyrrolo[*3,4-c*]pyrrole-1,3,4,6(2*H*,3a*H*,5*H*,6a*H*)-tetraone (IIb). To a slurry of 0.238 g (1 mmol) of spirane **IVa** in 1 mL of ethanol was added 3 mL of conc. HCl (HBr), and the mixture was boiled for 1 h. The reaction mixture was evaporated, the formed precipitate was filtered off, washed with water and 2-propanol, and dried in a vacuum-desiccator over $CaCl_2$. Yield 0.086 g (36%), mp 256–257°C. IR spectrum, ν, cm^{-1}: 3238–3150 (NH), 1773–1664 (C=O). ^1H NMR spectrum, δ, ppm: 1.19 d (3H, CH_3, *J* 7.6 Hz), 2.15 s (3H, CH_3), 3.61 q (1H, CH, *J* 7.6 Hz), 4.19 s (1H, CH), 11.70 s (1H, NH), 11.95 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 238 (7) $[M]^+$. Found, %: C 50.40; H 4.22; N 11.78. $C_{10}H_{10}N_2O_5$. Calculated, %: C 50.42; H 4.23; N 11.76. *M* 238.20.

Compounds **IIc–IIf** were obtained analogously.

3a-(2-Oxopentan-3-yl)pyrrolo[3,4-*c*]pyrrole-1,3,4,6(2*H*,3a*H*,5*H*,6a*H*)-tetraone (IIc). Yield 0.101 g (40%), mp 264–265°C. IR spectrum, ν, cm^{-1}: 3170, 3078 (NH), 1746–1668 (C=O). ^1H NMR spectrum, δ, ppm: 0.93 t (3H, CH_3, *J* 7.5 Hz), 1.47–1.56 m (1H, CH_2), 1.65–1.73 m (1H, CH_2), 2.19 s (3H, CH_3), 3.58 d.d (1H, CH, *J* 6.9, 5.7 Hz), 4.16 s (1H, CH), 11.75 s (1H, NH), 11.97 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 252 (10) $[M]^+$. Found, %: C 52.39; H 4.81; N 11.08. $C_{11}H_{12}N_2O_5$. Calculated, %: C 52.38; H 4.80; N 11.11. *M* 252.22.

3a-(2-Methyl-3-oxobutan-2-yl)pyrrolo[*3,4-c*]-pyrrole-1,3,4,6(2*H*,3a*H*,5*H*,6a*H*)-tetraone (IId). Yield 0.103 g (41%), mp 335–336°C. IR spectrum ν, cm^{-1}: 3187, 3076 (NH), 1763–1702 (C=O). ^1H NMR spectrum, δ, ppm: 1.42 s (6H, $2CH_3$), 2.12 s (3H, CH_3), 4.19 s (1H, CH), 11.74 s (2H, 2NH). Mass spectrum, *m/z* (I_{rel}, %): 252 (18) $[M]^+$. Found, %: C 52.41; H 4.79; N 11.10. $C_{11}H_{12}N_2O_5$. Calculated, %: C 52.38; H 4.80; N 11.11. *M* 252.22.

Crystallographic parameters of compound **IId**: *a* 8.6964(6), *b* 12.5540(6), *c* 20.4979(10) Å, *V* 2237.9(2) $Å^3$, *Z* 8, space group *Pbca*. The calculation of positions and thermal parameters of nonhydrogen atoms was performed in the full-matrix anisotropic approximation. The positions of the hydrogen atoms were determined from the Fourier difference synthesis and refined freely and also calculated and refined in isotropic approximation in the *rider* model. The divergence factor *R* 0.044. CCDC 940654.

3a-(1-Methyl-2-oxocyclohexyl)pyrrolo[3,4-*c*]-pyrrole-1,3,4,6(2*H*,3a*H*,5*H*,6a*H*)-tetraone (IIe). Yield 0.097 g (35%), mp 312–313°C. IR spectrum ν, cm^{-1}: 3181, 3080 (NH), 1757–1708 (C=O). ^1H NMR spectrum, δ, ppm: 1.62 s (3H, CH_3), 1.75–1.90 m [6H, $(CH_2)_3$], 2.06 d (1H, CH_2, *J* 14.1 Hz), 2.64–2.71 m (1H, CH_2), 4.23 s (1H, CH), 11.67 s (1H, NH), 11.83 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 278 (27) $[M]^+$. Found, %: C 56.15; H 5.08; N 10.04. $C_{13}H_{14}N_2O_5$. Calculated, %: C 56.11; H 5.07; N 10.07. *M* 278.26.

3a-(1-Oxo-1-phenylpropan-2-yl)pyrrolo[*3,4-c*]-pyrrole-1,3,4,6(2*H*,3a*H*,5*H*,6a*H*)-tetraone (IIf). Yield 0.144 g (48%), mp 319–320°C (decomp.). IR spectrum, ν, cm^{-1}: 3221, 3085 (NH), 1749–1668 (C=O). ^1H NMR spectrum, δ, ppm: 1.23 d (3H, CH_3, *J* 7.5 Hz), 4.42 s (1H, CH), 4.51 q (1H, CH, *J* 7.5 Hz), 7.56 t (2H, C_6H_5, *J* 7.6 Hz), 7.70 t (1H, C_6H_5, *J* 7.4 Hz), 7.99 d (2H, C_6H_5, *J* 7.7 Hz), 11.80 s (1H, NH), 12.04 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 300 (41) $[M]^+$. Found, %: 59.97; H 4.02; N 9.36. $C_{15}H_{12}N_2O_5$. Calculated, %: C 60.00; H 4.03; N 9.33. *M* 300.27.

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