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Reaction of Tetracyanoethylene with Aldehydes. Synthesis of 6-Imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles

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Abstract—It was discovered by means of dynamic NMR that the 1-(*cis*-1-methylprop-1-en-1-yl)-1,2-dimethylacenaphthylenonium ion generated under conditions of "long life" for carbocations underwent fast ($\Delta G^{\#}$ 35.8 kJ mol^{-1} at –103°C) degenerate 1,2-shift of the *cis*-dimethylvinyl group. Quantum-chemical calculations by DFT method predict lower rate of 1,2-shift for the *trans*-dimethylvinyl group compared to *cis*-dimethylvinyl group and dependence on the cations conformation of the rates of these processes and of the rearrangement mechanism into the ions of phenalenyl type.

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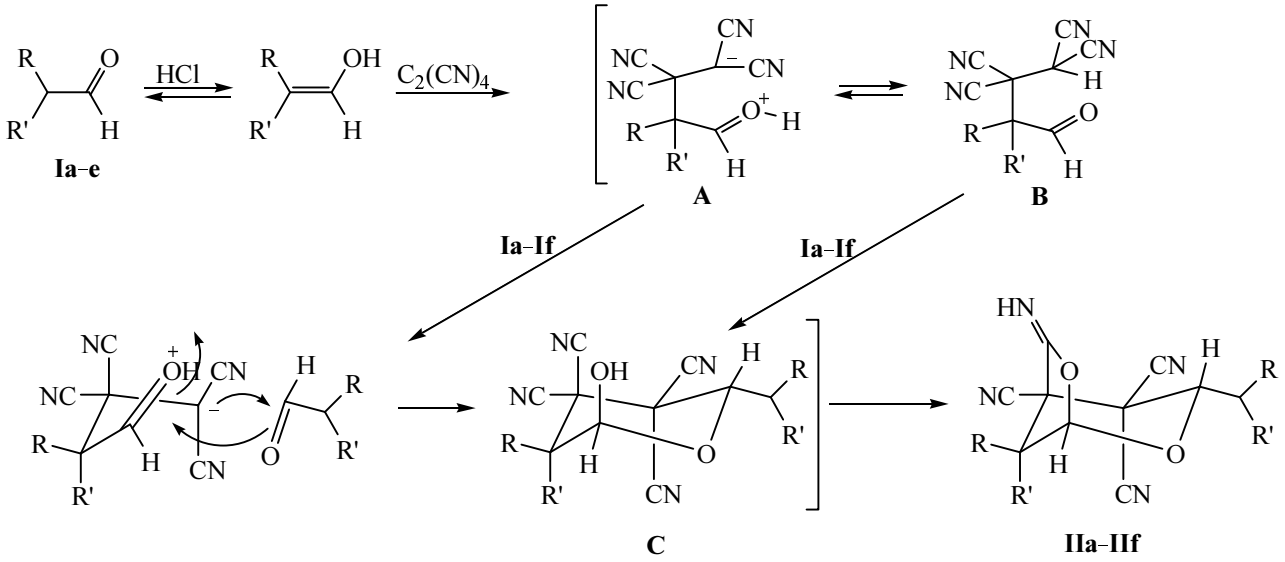
4-Oxoalkane-1,1,2,2-tetracarbonitriles were prepared for the first time by reaction of tetracyanoethylene with ketones in the presence of a specific catalyst, "molecular silver" [1]. It was found later that the tetracyanoethylation of ketones proceeded with high yields and regioselectively (with methyl alkyl ketones) in the presence of hydrohalic acids [2], that resulted in a greater availability of 4-oxoalkane-1,1,2,2-tetracarbonitriles. In a series of subsequent studies the extensive synthetic opportunities were demonstrated of these unique substances combining in their structure a C–H acid site, carbonyl, and cyano groups. The compounds were used in the syntheses of versatile heterocyclic structures by reactions with aldehydes [3, 4], hydrohalic acids [5, 6, 7], ammonia [8, 9], sodium borohydride [10], hydrogen peroxide [11], acrolein [12, 13], aryl isocyanates [14, 15], alcohols [14, 15], and hydrobenzamide [16, 17].

Some of thus synthesized heterocycles, for instance, 1-R^1-3-R^2-8-R^3-6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles [3, 4] proved to be able to suppress the tumor cells growth, and for cells subgroups like those of rectal cancer, melanoma, and kidney cancer a cytotoxic activity was observed [18]. Therefore the studies directed to the synthesis of new dioxabicyclic derivatives are promising for the search of potential anticancer drugs.

It should be emphasized that although a significant success was reached in the study of 4-oxoalkane-1,1,2,2-tetracarbonitriles no analogous investigations were carried out with aldehyde derivatives, and publications lacked concerning their preparation and properties. In this connection we studied reactions of tetracyanoethylene with aliphatic enolizing aldehydes **Ia–If** in the presence of catalytic amounts of hydrochloric acid. We failed to isolate in the course of these experiments the expected analogs of 4-oxoalkane-1,1,2,2-tetracarbonitriles, tetracyanoalkanals **B**. On diluting the reaction mixture with water we obtained instead the corresponding 3,8-dialkyl-6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitriles **IIa–IIf** in 40–70% yields.

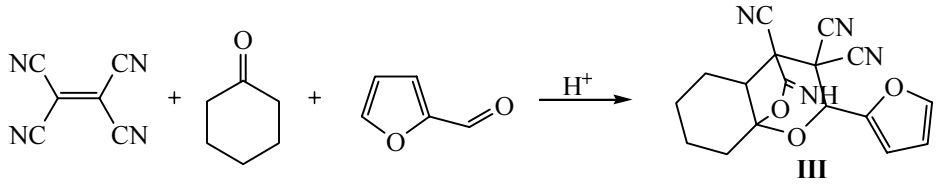
The building up of bicycles **IIa–IIf** apparently involved two successive reactions (Scheme 1). The first one, analogous to the tetracyanoethylation of ketones, started with the aldehyde enolization. Then the enols react wuth the tetracyanoethylene to yield the intermediate bipolar ion **A** that further transforms into tetracyanoalkanal **B**. The formation of bipolar ions in reaction of tetracyanoethylene with enol ethers was described in [19]. The second reaction is similar to that of 4-oxoalkane-1,1,2,2-tetracarbonitriles with aldehydes [3, 4]. Tetracyanoalkanal **B** probably quickly reacted with the second aldehyde molecule and did not accumulate in amounts sufficient for separation. This assumption is indirectly supported by the fact that the completion of reaction between 4-oxoalkane-1,1,2,2-tetracarbonitriles

Scheme 1.



R = Ph, R' =H (**a**); R = Me, R' = Me (**b**); R = Et, R' = H (**c**); R = Pr, R' = H (**d**); R = Me, R' = Ph (**e**); R = Et, R' = Et (**f**).

Scheme 2.



with aldehydes took considerably less time [3] than ketones tetracyanoethylation (except for cyclohexanone and cyclopentanone). It is also presumable that the bipolar ion **A** without isomerization into tetracyanoalkanal **B** directly reacted with the second aldehyde molecule forming a cyclic structure **C.** In intermediate **C** the optimum conditions exist for 1-3-diaxial interaction between the hydroxy and cyano groups resulting in the closure of the second ring in compounds **IIa–IIf**.

It should be noted that tetracyanoalkanal **B** added stereoslectively to the aldehyde furnishing only one of the possible diastereomers, namely, the one with the alkyl substituent on the C^3 atom in the *trans*-position to the carboxamide bridge. This reaction is apparently sensitive to steric hindrances: For instance, 4-oxoalkane-1,1,2,2-tetracarbonitriles do not react with ketones [20].

The formation of dioxabicycles **IIa–IIf** in a single synthetic process suggested to try a similar procedure also for the system ketone–aldehyde–tetracyanoethylene (Scheme 2). Actually, in reaction of tetracyanoethylene, cyclohexanone, and furfural under conditions of acid catalysis we succeeded in one synthetic operation to obtain 12-imino-9-(furan-2-yl)-10,11-dioxatricyclo-[5.3.2.$0^{1,6}$]dodecane-7,8,8-tricarbonitrile (**III**) whose constants were published earlier [3].

The results of the study of the aldehyde structure effect on the dioxabicycles **IIa–IIf** formation are in complete agreement with the current concepts on the activity of the initial aldehydes. The fastest and the most complete reaction (within 1 h) was observed with the isobutyric aldehyde. Phenylacetaldehyde due to the stabilization of the enol form by the conjugation with the aromatic ring reacted in 1.5 h giving dioxabicycle **IIa**. The aliphatic aldehydes with no substituents in the α-position are less reactive: For instance, the butyric and caproic aldehydes react considerably slower and afford lower yields.

The structure of compounds **IIa** and **IIb** was established by the X-ray diffraction study on single crystals (Figs. 1 and 2). Within the limits of standard deviations the corresponding distances and angles in the molecules **IIa** and **IIb** are alike and are in the common

range for the respective bond types [21]. As seen from Figs. 1 and 2, in both molecules the hydrogen of the imino group is located in the plane HNCO and is directed to the oxygen atom being governed by the influence, on the one hand, of the electrophilic carbon atom of the contiguous cyano group, and on the other hand, by nucleophilicity of the neighboring oxygen atom. However the hydrogen of the imino group plays notably different part in the crystals of the molecules **IIa** and **IIb.** Only in the molecules **IIa** the imino group hydrogen is involved into an intramolecular hydrogen bond with a nitrogen of the neighboring nitrile group N–H···N* (1/2 – x, –1/2 – y, 1/2 + z) [H···N* 2.340 Å, angle NH···N* 157.1(2)°]. As a result of this interaction the molecules **IIa** form chains in the direction 001. For compound **IIb** the numerous intermolecular interactions between hydrogens of the methyl groups and nitrogens of the cyano groups govern the packing of **IIb** molecules in the crystal.

The structure of compounds **IIa–IIf** was confirmed by IR and ^{1}H NMR spectroscopy.

In the IR spectra of compounds **IIa–IIf** strong absorption bands were observed in the region 3280–3300 cm^{-1} characteristic of the N–H bond of imino group, and also bands of the stretching vibrations of the C=N group in the region 1685–1700 cm^{-1}. The vibrations of the non-conjugated cyano group appear as a weak band at 2260 cm^{-1}.

The ^{1}H NMR spectra of compounds **IIa–IIf** are characterized by the proton signal from the imine group appearing as a singlet in the region 9.8–9.6 ppm and by a singlet from the proton at acetal carbon in the region 6.6–5.8 ppm. In the spectra of compounds **IIc** and **IId** the proton signal at the acetal carbon is a singlet for the coupling constants between equatorial and axial protons in the oxacyclohexane ring are equal to zero. Each of the two other hydrogen atoms contiguous to CH_2 groups gives rise to two doublets of doublets at 4.28–4.3 (O–C<u>H</u>–CH_2) and 2.6–2.7 ppm (CH–C<u>H</u>–CH_2). This splitting is caused by the diastereotopicity of the CH_2 groups.

EXPERIMENTAL

The reactions progress was monitored and the purity of compounds synthesized was checked by TLC on Silufol UV-254 plates (development by UV irradiation, in iodine vapour, and by calcining). IR spectra were recorded in thin films from mulls in mineral oil on a spectrophotometer UR-20. The ^{1}H NMR spectra were registered on a spectrometer Bruker AM-500 in DMSO-d_6 at 500.13 MHz. X-ray diffraction study of single crystals of compounds **IIa** and **IIb** was performed on a four-circle automatic diffractometer Enraf Nonius CAD-4, CuK_α radiation, graphite monochromator, ω-scanning.

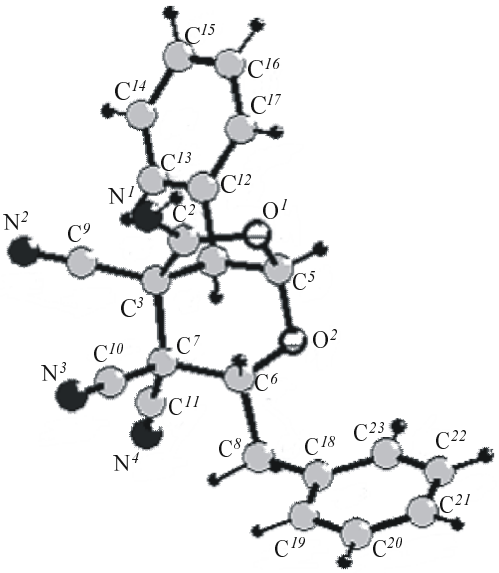


Fig. 1. Molecular structure of compound **IIa**.

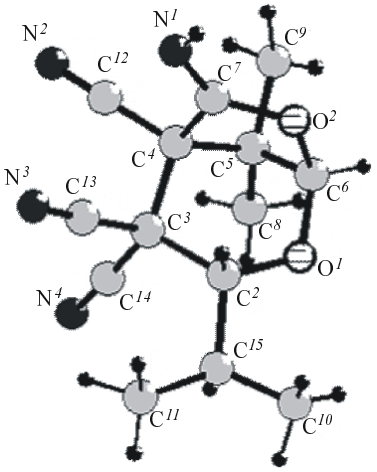


Fig. 2. Molecular structure of compound **IIb**.

3-Isopropyl-6-imino-8,8-dimethyl-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitrile (IIb). To a solution of 0.64 g (0.005 mol) of tetracyanoethylene in 10 ml of 1,4-dioxane was added 0.72 g (0.01 mol) of isobutyric alcohol and one drop of 10% solution of hydrochloric acid. On completion of the reaction (TLC monitoring, test with hydroquinone) the reaction mixture was diluted with water, the separated precipitate was filtered off, and washed with water. On recrystallization from 2-propanol we obtained 0.98 g (72%) of compound

IIb, mp 110–111°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 2260 (C≡N), 1690 (C=N). ^{1}H NMR spectrum, δ, ppm: 9.77 s (1H, NH), 5.81 s (1H, C<u>H</u>O$_2$), 4.03 d (1H, OC<u>H</u>CH), 2.17 m [1H, C<u>H</u>(CH$_3$)$_2$], 1.41 s (3H, CH$_3$C), 1.22 s (3H, CH$_3$C), 1.15 d (3H, C<u>H</u>$_3$CH), 1.09 d (3H, C<u>H</u>$_3$CH). Crystallographic parameters of compound **IIb**: *a* 8.6895(8), *b* 13.1698(10), *C* 13.276(1) Å, β 104.759(8)°, *Z* 4, space group *P*21/*n*. In the range 2θ < 144° 2711 reflections for **IIb** with the intensity >2σ(*I*) were used in the anisotropic full-matrix refinement for the nonhydrogen atoms. Hydrogen atoms were localized from the difference Fourier syntheses and were refined in isotropic approximation. Uncertainty factor *R* 0.057.

Compounds **IIa**, **IIc–IIf** were obtained by a similar procedure.

3-Benzyl-6-imino-8-phenyl-2,7-dioxabicyclo-[3.2.1]octane-4,4,5-tricarbonitrile (IIa). Yield 1.19 g (68%), mp 132–133°C. IR spectrum, ν, cm^{-1}: 3290 (NH), 2260 (C≡N), 1690 (C=N). Crystallographic parameters of compound **IIa**: *a* 23.308(2), *b* 12.4795(11), *c* 13.3482(12) Å, *Z* 8, space group *Pbcn*. In the range 2θ < 144° 2560 reflections with the intensity >2σ(*I*) were used in the anisotropic full-matrix refinement for the nonhydrogen atoms. Hydrogen atoms were localized from the difference Fourier syntheses and were refined in isotropic approximation. Uncertainty factor *R* 0.051.

6-Imino-3-propyl-8-ethyl-2,7-dioxabicyclo-[3.2.1]octane-4,4,5-tricarbonitrile (IIc). Yield 0.51 g (38%), mp 72–73°C. IR spectrum, ν, cm^{-1}: 3290 (NH), 2260 (C≡N), 1690 (C=N). ^{1}H NMR spectrum, δ, ppm: 9.8 s (1H, NH), 6.1 s (1H, C<u>H</u>O$_2$), 4.3 d.d (1H, OC<u>H</u>CH), 2.65 d.d (1H, C<u>H</u>CH$_2$), 1.25–1.75 m (6H, CH$_2$), 1.07 t (3H, C<u>H</u>$_3$CH$_2$), 0.92 t (3H, C<u>H</u>$_3$CH$_2$).

3-Butyl-6-imino-8-propyl-2,7-dioxabicyclo-[3.2.1]octane-4,4,5-tricarbonitrile (IId). Yield 0.61 g (40%), mp 70–71°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 2220 (C≡N), 1690 (C=N). ^{1}H NMR spectrum, δ, ppm: 9.77 s (1H, NH), 6.07 s (1H, C<u>H</u>O$_2$), 4.27 d.d (1H, OC<u>H</u>CH$_2$), 2.69 d.d (1H, C<u>H</u>CH$_2$), 1.3–1.9 m (6H, CH$_2$), 0.93 t (3H, C<u>H</u>$_3$CH$_2$), 0.89 t (3H, C<u>H</u>$_3$CH$_2$).

6-Imino-8-methyl-8-phenyl-3-(1-phenylethyl)-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitrile (IIe). Yield 1.28 g (65%), mp 162–163°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 2260 (C≡N), 1690 (C=N). ^{1}H NMR spectrum, δ, ppm: 9.6 s (1H, NH), 7.31–7.6 m (10H, 2Ph), 6.6 s (1H, C<u>H</u>O$_2$), 4.6 d (1H, OC<u>H</u>CH), 3.45 q (1H, PhC<u>H</u>CH$_3$), 1.88 s (3H, CC<u>H</u>$_3$), 1.47 d (3H, C<u>H</u>$_3$CH).

8,8-Diethyl-3-(1-ethylpropyl)-6-imino-2,7-dioxabicyclo[3.2.1]octane-4,4,5-tricarbonitrile (IIf). Yield 0.95 g (58%), mp 120–121°C. IR spectrum, ν, cm^{-1}: 3280 (NH), 2260 (C≡N), 1690 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 9.79 s (1H, NH), 5.82 s (1H, C<u>H</u>O$_2$), 4.1 d (1H, OC<u>H</u>), 2.00 m (1H, CHC<u>H</u>Et$_2$), 0.9–1.9 m (20H, 4Et).

12-Imino-9-(furan-2-yl)-10,11-dioxatricyclo-[5.3.2.0^{1,6}]dodecane-7,8,8-tricarbonitrile (III). To a solution of 0.64 g (0.005 mol) of tetracyanoethylene in 10 ml of 1,4-dioxane was added 0.49 g (0.005 mol) of cyclohexanone, 0.48 g (0.005 mol) of furfural, and one drop of 10% solution of hydrochloric acid. On completion of the reaction (TLC monitoring, test with hydroquinone) the reaction mixture was diluted with water, the separated precipitate was filtered off, and washed with water. On recrystallization from 2-propanol we obtained 1.23 g (78%) of compound **III**, mp 162–166°C (decomp.) (publ.: mp 163–166°C (decomp.) [3]).

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