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Dedicated to the Full Member of the Russian Academy of Sciences G.A. Tolstikov on occasion of his 75th anniversary

Stereochemical Features of Addition of O- and C-Nucleophiles to 5-(Het)aryl-2,3-dicyano-1-ethylpyrazinium Salts

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Abstract—Stable σ^H-adducts of O- and C-nucleophiles were obtained with cations of 5-(het)aryl-2,3-dicyano-1-ethylpyrazinium, and their structure was investigated by X-ray diffraction analysis. Analytical separation was performed of 1,2-dihydropyrazines into individual enantiomers by means of HPLC on columns with chiral sorbents.

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2,3-Dicyanopyrazines are known to be precursors in the synthesis of tetrapyrazinoporphyrazines, aza analogs of phthalocyanines that are of interest as dyes, optical sensors, and also as photosensitive compounds used in the photodynamic therapy of cancer [1–5]. One of the general methods of pyrazines modification is applying the reactions of nucleophilic substitution. For instance, in a series of publications a substitution of chlorine in 5,6-dichloro-2,3-dicyanopyrazine under stringent conditions was described [1, 6, 7].

At the same time published data exist [8, 9] on easy exchange of cyano groups of cyanopyrazines and their salts for nucleophiles residues; in the other cases the cyano groups in the dicyanopyrazines are transformed under the action of nucleophiles [10] yielding, for instance, cyclic products resulting from the attack of a dinucleophile on both cyano groups [10, 11].

We previously [12] reported on reactions of 2,3-dicyano-1-ethylpyrazinium tetrafluoroborate with C- and O-nucleophiles leading to the formation of cyclic and acyclic σ^H-diadducts at the unsubstituted positions of the pyrazine ring; the products were characterized by X-ray diffraction analysis. Published data exist [13–15] on equilibrium mixtures of mono- and diadducts of 1,4-diazinium salts with methoxide anion and water, but the stability of the monoadducts is not sufficient for their isolation in the crystalline state.

On the other hand, an interest grew recently to the synthesis of individual stereoisomers of biologically active aza heterocycles. In this connection much attention is given to the stereoselective reactions of nucleophilic addition to C=N and also C=C bonds of nitroalkenes and to the other multiple bonds [16, 17]. In particular, a diastereoselective synthesis was described [18] of σ^H-adducts in the series of 1,2,4-triazin-5(4*H*)-one, but no such studies were reported in the series of 1,4-diazines.

We report here on the investigation of reactions of 5-(het)aryl-2,3-dicyano-1-ethylpyrazinium salts with O- (water and alcohols) and C-nucleophiles (enolates of dicarbonyl compounds, indole etc.). It was presumed that the bulky aryl sybstituent would block the diadducts formation, and the presence of two cyano groups would provide for enhanced stability of the σ^H-adducts and would permit their characterization by the spectral and crystallographic methods.

In order to obtain 1-ethyl-5-(het)aryl-pyrazinium salts **IIa–IIc** 2,3-dicyanopyrazines **Ia–Ic** were subjected to the treatment of the Meerwein reagent, $Et_3O^+BF_4^-$, in $CHCl_3$ at 20°C (Scheme 1). The structure of compounds

IIa–IIc was confirmed by X-ray diffraction analysis by an example of **IIb** salt (Fig. 1). We did not observe a forma-tion of possible isomers, namely, other 6-(het)aryl-2,3-dicyano-1-ethylpyrazinium salts (^{1}H NMR data); they apparently did not form due to steric reasons.

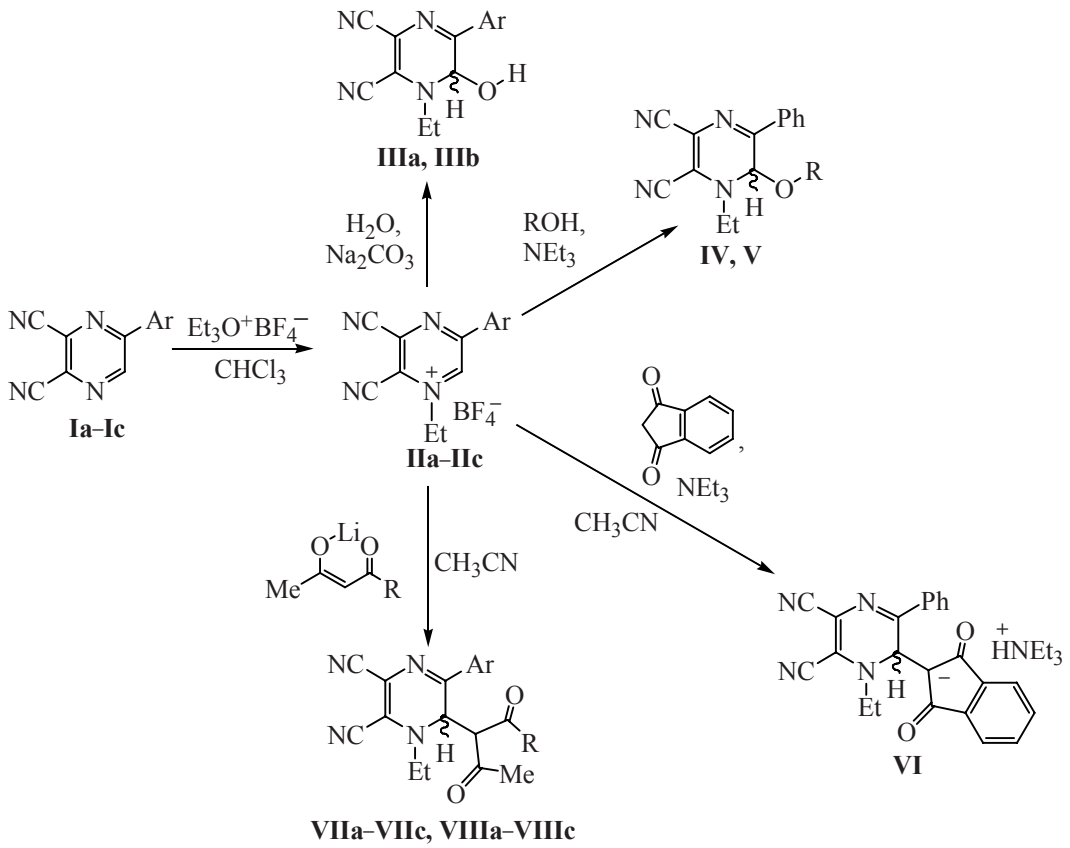
It was established that salts **IIa–IIc** readily reacted with C- and O-nucleophiles under mild conditions (CH_3CN, NEt_3, 20°C) giving σ^H-adducts at the position *6*. For instance, in the reaction of salts **IIa** and **IIb** with water in the presence of Na_2CO_3 formed stable 5-aryl-6-hydroxy-1-ethyl-1,6-dihydropyrazine-2,3-dicarbonitriles **IIIa** and **IIIb** (Scheme 1) as proved by the presence in the ^{1}H NMR spectra of a characteristic doublet due to the coupling of the proton at C^6 with the OH group with a constant ~8 Hz, and also by the X-ray diffraction data obtained for the first time for a monohydrated azinium cataion, namely for compound **IIIa** (Fig. 2).

Similarly salts **IIa** and **IIb** reacted with alcohols yielding the corresponding 6-alkoxy-5-aryl-1-ethyl-1,6-dihydropyrazin-2,3-dicarbonitriles **IV** and **V** whose structure was proved by ^{1}H NMR spectrum and X-ray diffraction analysis by an example of compound **IV** (Fig. 3). Under similar conditions [12] unsubstituted 2,3-dicyanopyrazinium salt (**IX**) formed the product of cyano group substitution in the position *2*, namely pyrazinone **X**, or diadducts **XIa–XIc** (Scheme 2).

The formation of monoalkoxy adducts in reactions of N-alkylazinium salts with alcohols formerly was only detected in the NMR spectra [15].

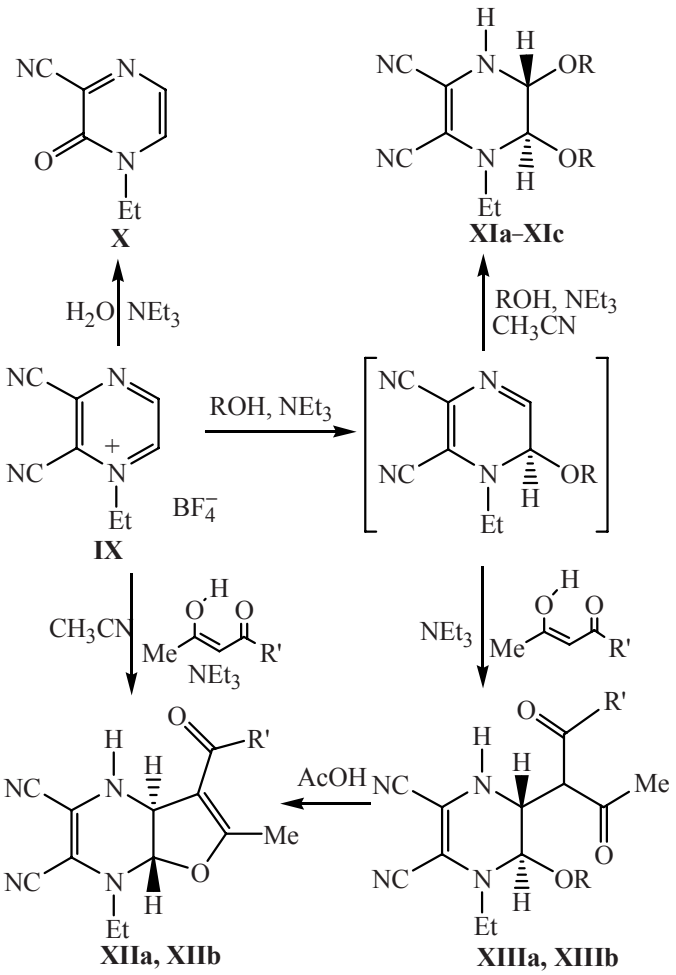
Reactions with C-nucleophiles also have specific features. In the reactions of 2,3-dicyano-1-ethyl-pyrazinium tetrafluoroborate with enolates of 1,3-dicarbonyl compounds it was observed formerly the fusion of a furan ring (Scheme 2): therewith the 1,3-dicarbonyl compounds behaved as O,C-dinucleophiles [12]. Naturally, the reaction of salts **IIa–IIc** with the enolates of 1,3-dicarbonyl compounds occurs at the unsubstituted C^6 position of the heterocycle providing stable C-adducts **VI–VIII**

Scheme 1.



R = Me (**IV, VII**), Et (**V**), OEt (**VIII**); Ar = Ph (**a**), *p*-FC_6H_4 (**b**), 3-thienyl (**c**).

Scheme 2.



R = Me (**a**), Et (**b**), *i*-Pr (**c**); R' = Me (**a**), OEt (**b**).

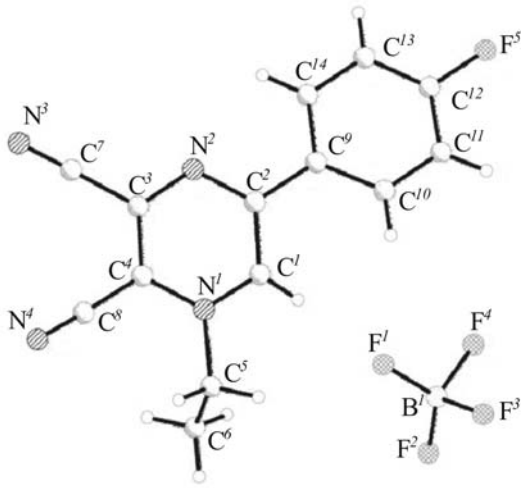


Fig. 1. Geometry of molecule **IIb** in a crystal.

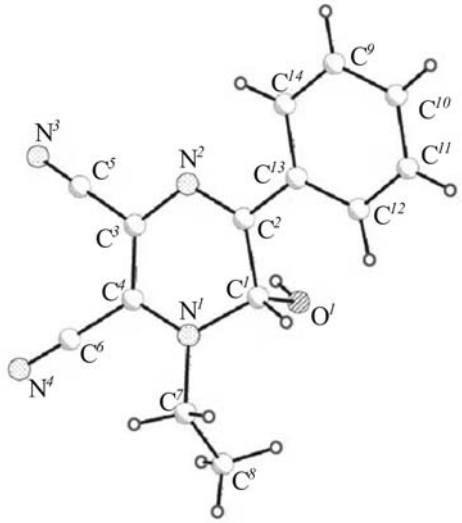


Fig. 2. Geometry of molecule **IIIa** in a crystal.

(Scheme 1) as proved by the presence in the ^{1}H NMR spectra of compounds **VIIa–VIIc** and **VIIIa–VIIIc** of doublets with vicinal coupling constants *J* 9.2–9.6 Hz, and also by the X-ray diffraction data for compound **VIIc** (Fig. 4).

In the ^{1}H NMR spectra of products **VIIIa–VIIIc** of ethyl acetoacetate addition to salts **II** signals were observed belonging to two diastereomers present in a ~ 1 : 1 ratio and distinguished by the configuration of chiral centers C_{exo} and C^6 (Scheme 1). The diastereomers formation originated from the appearance of a new chiral center, the carbon atom of the CH-active compound after the formation of its C–C bond with the pyrazine ring. The stereoisomers mixture was by means of flash chromatography first enriched to the ratio 9 : 1–11 : 1, and then the major (*S*,*R*/*R*,*S*) stereoisomers **VIIIa** and **VIIIb** were isolated in pure form and characterized by the X-ray diffraction analysis (Fig. 5).

Using arylamines and indoles as C-nucleophiles in reactions with salts **IIa** and **IIc** we also succeeded to obtain stable C-adducts **XIVa** and **XIVc**, and **XV** (Scheme 3).

Indol added to salts **IIa** and **IIc** by its $C^{3'}$ atom as confirmed by the existence of the vicinal coupling between protons $NH^{1'}$ and $H^{2'}$ of the indole fragment in the ^{1}H NMR spectra of compounds **XIVa** and **XIVc** registered in DMSO-d_6, and N,N-dimethylaniline formed a C-adduct **XV** at the *para*-position of the aryl substituent (Scheme 1).

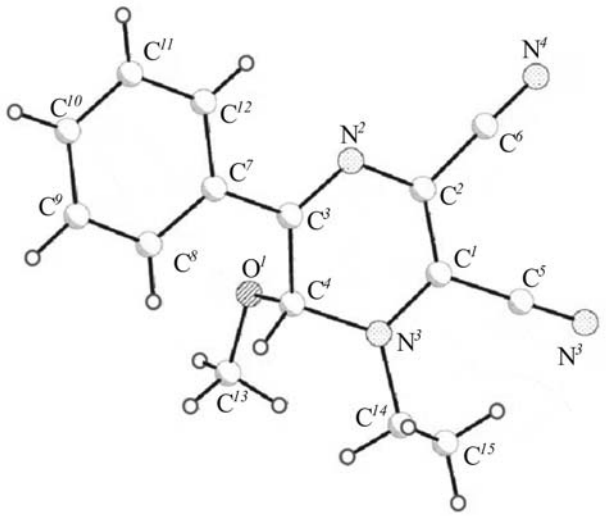


Fig. 3. Geometry of molecule **IV** in a crystal.

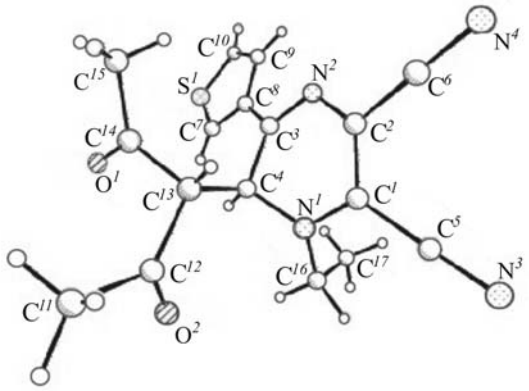


Fig. 4. Geometry of molecule **VIIc** in a crystal.

The structure of compound **XIVc** was confirmed by ^{1}H and ^{13}C NMR spectra. A complete assignment of proton and carbon signals was carried out with the use of a combination of 2D spectroscopy procedures HSQC/HMBC.

As already mentioned, the adducts obtained adduct **III–VIII**, **XIV**, and **XV** are mixtures of two enantiomers. In order to investigate the enantiomeric composition of the obtained 1,2-dihydropyrazines we attempted their separation into individual enantiomers by means of HPLC on chromatographic columns with chiral sorbents, Chiralcel OD-H and Chiralpak AD. We selected as objects of the chromatographic study compounds **VIIb** and **VIIc**, and also previously prepared 1-ethyl-6-(2,2,6,6-tetramethylpiperidin-1-oxyl-4-ylideneaminoxyl)-5-phenyl-1,6-dihydropyrazine-2,3-dicarbonitrile (**XVI**) [19]. The results of the study with the use of HPLC are presented in the table.

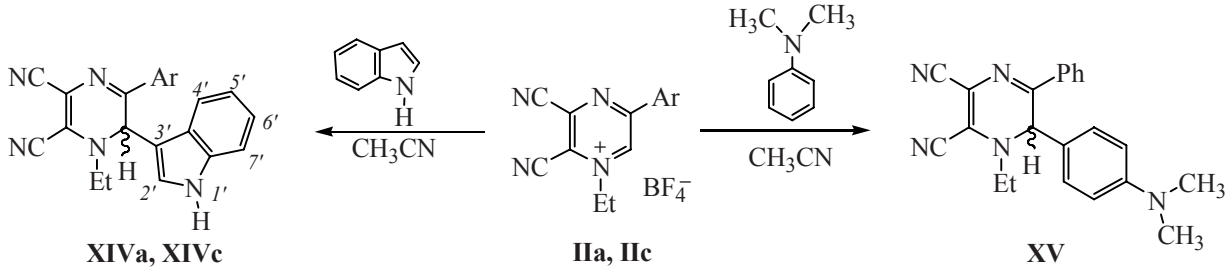
Thus we demonstrated that 5-(het)aryl-2,3-dicyano-1-ethylpyrazinium salts formed stable mono-σ^{H}-adducts with C- and O-nucleophiles. The analysis of the enantiomeric composition and analytical separation of adduct obtained into individual enantiomers by means of HPLC was performed.

EXPERIMENTAL

Compounds **Ia–Ic** were prepared by procedure from [20]. The solvents were dried and purified as described in [21].

NMR spectra were registered on a spectrometer Bruker DRX-400 [400 (^{1}H), 100 MHz (^{13}C)], internal reference TMS. Mass spectra were measured on a quadrupole liquid GC-MS instrument Shimadzu LCMS-2010 in acetonitrile at the scanning rate 0.25 ml/min on a column Supelco LC-18 (4.6×250 mm). Mass spectra were obtained in the mode of positive ions scanning using APCI, (atmospheric pressure chemical ionization), operating voltage 4.5 kV, tuning control by the autotuning file, carrier gas nitrogen, flow rate 2.5 l/min. Elemental analysis was carried out on an automatic analyzer Carlo Erba 1108. Melting points were measured on combined Boëtius heating blocks and are reported without correction. For the flash-chromatography silica gel Lancaster 0.040–0.063 mm (230–400 mesh) was used. The enantiomers mixtures were analyzed by HPLC

Scheme 3.



XIVa, XIVc **IIa, IIc** **XV**

Ar = Ph (**a**), 3-thienyl (**c**).

Results of chromatographic separation into enantiomers of compounds **VIIb, VIIc**, and **XVI** by HPLC on columns with chiral sorbents

Compound no.	Column type	Eluent	Retention time of first enantiomer (τ_1), min	Retention time of second enantiomer (τ_2), min	Enantiomers ratio
VIIb	Chiralcel OD-H	Hexane–2-propanol, 10:1	26.7	34.6	44.7:55.3
VIIb	Chiralpak AD	Hexane–2-propanol, 10:1	13.2	13.2	–
VIIc	Chiralcel OD-H	Hexane–2-propanol, 8:1	31.6	34.3	42.0:58.0
XVI	Chiralpak AD	Hexane–2-propanol, 20:1	158	17.0	48.2:51.8

on a chromatograph Merck-Hitachi (L-6200A Intelligent Pump, L-4000A UV Detector, D-2500A Chromato-Integrator) on columns Hibar Pre-packed Column RT250-4 250×4 mm with a sorbent LiChrosorb Si-60 5 μm, with chiral sorbents Chiralcel OD-H and Chiralpak AD 250×4.6 mm, produced by Daicel Chemical Industries Ltd (Japan), mobile phase hexane–2-propanol, 10:1 or 20:1, elution rate 1.0 ml/min, detecting on the wave length 230 nm. The monitoring of reactions progress and checking of the products purity was carried out by TLC on Silufol UV-254 plates, development under UV irradiation or by iodine vapor. X-ray diffraction analysis on single crystals was performed on an X-ray diffractometer Xcalibur-3 equipped with a CCD detector ($\lambda Mo K_\alpha$, graphite monochromator). The structure was solved by the direct method using SHELXS-97 program and refined applying SHELXL-97 program. The results of the X-ray structural data were deposited in the Cambridge Crystallographic Database under the numbers CCDC 652113 (compound **IIb**), CCDC 652114 (compound **IV**), CCDC 652115 (compound **IIIa**), CCDC 652116 (compound **VIIIb**), and CCDC 652118 (compound **VIIc**). The access to these data is free by the address www.ccdc.cam.ac.uk/data_request/cif.

2,3-Dicyano-5-phenyl-1-ethylpyrazinium tetrafluoroborate (IIa). To a solution of 1.0 g (14.6 mmol) of 2,3-dicyano-5-phenylpyrazine in 25 ml of $CHCl_3$ was added 5.52 g (29.1 mmol) of $Et_3O^+BF_4^-$. The reaction mixture obtained was left standing for 7 days without access of air. The separated precipitate was filtered off, washed with 20–30 ml of THF, and dried. Yield 3.55 g (76%), dark-yellow powder, mp 174–176°C (decomp.). ^{1}H NMR spectrum (CD_3CN), δ, ppm: 1.78 br.s (3H, CH_3), 5.00 br.s (2H, NCH_2), 7.72 br.m (3H, Ph), 8.30 br.s (2H, Ph), 9.75 br.s (1H, H^6). Found, %: C 52.20; H 3.26; N 17.35. $C_{14}H_{11}N_4 \cdot BF_4$. Calculated, %: C 52.21; H 3.44; N 17.40.

In the same way salts **IIb** and **IIc** were prepared.

2,3-Dicyano-5-(4-fluorophenyl)-1-ethylpyrazinium tetrafluoroborate (IIb). Yield 340 mg (45%), bright yellow crystalline powder, mp 180–182°C (decomp.). ^{1}H NMR spectrum (CD_3CN), δ, ppm: 1.79 t (3H, CH_3, *J* 7.4 Hz), 5.00 q (2H, NCH_2, *J* 7.4 Hz), 7.48 d.d (2H, H^m, *J* 9.1, 8.7 Hz), 8.39 d.d (2H, H^o, *J* 9.1, 5.2 Hz), 9.66 s (1H, H^6). Found, %: C 49.65; H 3.06; N 16.44. $C_{14}H_{10}FN_4 \cdot BF_4$. Calculated, %: C 49.45; H 2.96; N 16.48.

2,3-Dicyano-5-(3-thienyl)-1-ethylpyrazinium tetrafluoroborate (IIc) was obtained from 1.87 g (8.8 mmol) of 2,3-dicyano-5-(thiophen-3-yl)pyrazine and 8.35 g (44.00 mmol) of $Et_3O^+BF_4^-$, reaction time 48 h without access of air. Yield 2.07 g (72%), orange powder, mp 198–200°C (decomp.). ^{1}H NMR spectrum (CD_3CN), δ, ppm: 1.78 t (3H, CH_3, *J* 7.2 Hz), 4.00 q (2H, NCH_2, *J* 7.2 Hz), 7.77 d.d (1H, $H^{5'}$, *J* 5.2, 2.8 Hz), 7.89 d.d (1H,

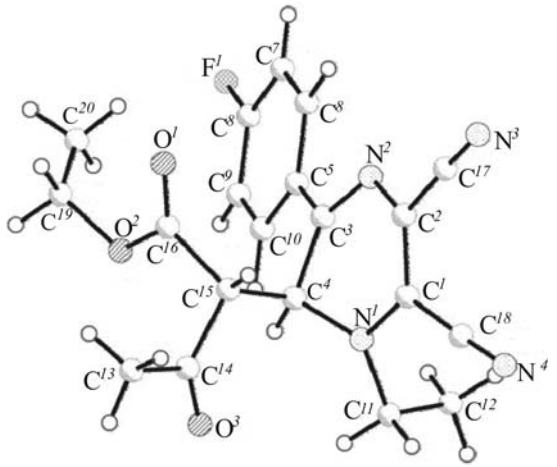


Fig. 5. Geometry of molecule **VIIIb** in a crystal.

$H^{4'}$, *J* 5.2, 1.2 Hz), 8.79 d.d (1H, $H^{2'}$, *J* 2.8, 1.2 Hz), 9.54 s (1H, H^{6}). Found, %: C 43.86; H 2.76; N 17.05. $C_{12}H_9N_4S\cdot BF_4$. Calculated, %: C 43.93; H 2.76; N 17.08.

6-Hydroxy-5-phenyl-1-ethyl-1,6-dihydropyrazine-2,3-dicarbonitrile (IIIa). To a solution of 164 mg (1.55 mmol) of Na_2CO_3 in 10 ml of H_2O was added 500 mg (1.55 mmol) of salt **IIa**. The reaction mixture was stirred for 30 min, the yellow precipitate was filtered off, washed with 20 ml of H_2O, and dried. Yield 365 mg (93%), mp 126–128°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.37 t (3H, CH_3, *J* 7.2 Hz), 3.72 d.q (1H, NCH^{B}, *J* 14.4, 7.2 Hz), 3.82 d.q (1H, NCH^{A}, *J* 14.4, 7.2 Hz), 6.24 d (1H, H^{6}, *J* 8.2 Hz), 7.13 d (1H, OH, *J* 8.2 Hz), 7.49–7.55 m (3H, Ph), 7.99 m (2H, Ph). Found, %: C 66.51; H 4.54; N 22.47. $C_{14}H_{12}N_4O$. Calculated, %: C 66.65; H 4.79; N 22.21.

6-Hydroxy-5-(4-fluorophenyl)-1-ethyl-1,6-dihydropyrazine-2,3-dicarbonitrile (IIIb). To a solution of 62 mg (0.59 mmol) of Na_2CO_3 in 5 ml of H_2O was added 200 mg (0.59 mmol) of salt **IIb**. The reaction mixture was stirred for 30 min, the yellow precipitate was filtered off, dried and separated on a column packed with silica gel, eluent acetone–hexane, 1:2. The oily substance obtained was ground with hexane till the formation of yellow powder. Yield 120 mg (75%), mp 110–112°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.37 t (3H, CH_3, *J* 7.2 Hz), 3.71 d.q (1H, NCH^{B}, *J* 14.4, 7.2 Hz), 3.82 d.q (1H, NCH^{A}, *J* 14.4, 7.2 Hz), 6.24 d (1H, H^{6}, *J* 8.1 Hz), 7.14 d (1H, OH, *J* 8.1 Hz), 7.36 t (2H, H^{m}, *J* 9.0 Hz), 8.04 d.d (2H, H°, *J* 9.0, 5.5 Hz). Mass spectrum, *m/z* (I_{rel}, %): 270 $[M]^+$ (22), 269 $[M-H]^+$ (100). Found, %: C 62.44; H 4.18; N 20.70. $C_{14}H_{11}FN_4O$. Calculated, %: C 62.22; H 4.10; N 20.73.

6-Methoxy-5-phenyl-1-ethyl-1,6-dihydropyrazine-2,3-dicarbonitrile (IV). To a solution of 210 mg (0.65 mmol) of salt **IIa** in 2 ml of MeOH was added 100 μl of NEt_3. The reaction mixture was stirred for 1 h, the residue was subjected to column chromatography on silica gel (eluent acetone–hexane, 1:2). The oily substance obtained was ground with hexane till the formation of bright yellow powder. Yield 116 mg (67%), mp 105–107°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 t (3H, CH_3, *J* 7.2 Hz), 3.28 s (3H, OCH_3), 3.85 d.q (1H, NCH^{B}, *J* 14.4, 7.2 Hz), 3.90 d.q (1H, NCH^{A}, *J* 14.4, 7.2 Hz) 6.41 s (1H, H^{6}), 7.51–7.57 m (3H, Ph), 8.02 m (2H, Ph). Mass spectrum, *m/z* (I_{rel}, %): 235 $[M-OMe]^+$ (100), 276 $[M-OMe+CH_3CN]^+$ (39). Found, %: C 67.58; H 5.36; N 21.07. $C_{15}H_{14}N_4O$. Calculated, %: C 67.65; H 5.30; N 21.04.

5-Phenyl-1-ethyl-6-ethoxy-1,6-dihydropyrazine-2,3-dicarbonitrile (V) was obtained similarly to compound **IV**. Yield 45%, yellow crystalline powder, mp 98–100°C (decomp.). ^{1}H NMR spectrum (CD_3CN), δ, ppm: 1.10 t [3H, CH_3(NEt), *J* 6.9 Hz], 1.29 t [3H, CH_3(OEt), *J* 7.3 Hz], 3.54 q (2H, OCH_2, *J* 6.9 Hz), 3.79 d.q (1H, NCH^{B}, *J* 14.6, 7.3 Hz), 3.86 d.q (1H, NCH^{A}, *J* 14.6, 7.3 Hz), 6.12 s (1H, H^{6}), 7.49–7.57 m (3H, $H^{m,p}$), 7.98 m (2H, H°). Mass spectrum, *m/z* (I_{rel}, %): 235 $[M-OEt]^+$ (100), 276 $[M-OEt+CH_3CN]^+$ (38). Found, %: C 68.61; H 5.65; N 20.02. $C_{16}H_{16}N_4O$. Calculated, %: C 68.55; H 5.75; N 19.99.

***N,N,N*-Triethyl-2-(5-phenyl-5,6-dicyano-1-ethyl-1,2-dihydropyrazin-2-yl)-1,3-dioxoindan-2-aminium (VI)**. To a solution of 259 mg (0.80 mmol) of salt **IIa** and 118 mg (0.80 mmol) 1,3-indandione in 5 ml of CH_3CN was added 123 μl of NEt_3, the mixture was stirred for 1.5 h, the separated precipitate was filtered off, washed with H_2O, and dried. Yield 95 mg (31%), orange powder, mp 167–169°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.19 m (12H, CH_3), 3.09 m (6H, NCH_2), 3.34 d.q (1H, NCH^{B}, *J* 14.2, 7.1 Hz), 3.41 d.q (1H, NCH^{A}, *J* 14.2, 7.1 Hz), 5.59 s (1H, H^{6}), 7.08–7.10 m (2H, indan), 7.23–7.25 m (2H, indan), 7.32–7.37 m (3H, Ph), 7.97 m (2H, Ph), 8.84 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 381 $[M-H-NEt_3]^+$ (6), 276 $[M-H-NEt_3-C_9H_4O_2+CH_3CN]^+$ (36), 235 $[M-H-NEt_3-C_9H_4O_2]^+$ (100), 102 $[NEt_3+H]^+$. Found, %: C 71.13; H 6.52; N 14.39. $C_{23}H_{16}N_4O_2\cdot N(C_2H_5)_3\cdot 0.5H_2O$. Calculated, %: C 71.00; H 6.57; N 14.28.

6-(1-Acetyl-2-oxoprop-1-yl)-5-phenyl-1-ethyl-1,6-dihydropyrazine-2,3-dicarbonitrile (VIIa). A mixture of 1.29 g (4 mmol) of salt **IIa** and 0.42 g (4 mmol) of lithium acetylacetonate was dissolved in 25 ml of CH_3CN. The reaction mixture obtained was stirred for 1 h, evaporated, and the residue was subjected to chromatography on silica gel (eluent acetone–hexane, 1:2). The reaction product was recrystallized from MeOH. Yield 1.17 g (87%), bright yellow crystalline powder, mp 137–139°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.01 t (3H, CH_3, *J* 7.1 Hz), 2.03 s (3H, $COCH_3$), 2.22 s (3H, $COCH_3$), 3.59 q (2H, NCH_2, *J* 7.1 Hz), 4.52 d (1H, $H^{1'}$, *J* 9.2 Hz), 5.85 d (1H, H^{6}, *J* 9.2 Hz), 7.45–7.53 m (3H, Ph), 7.99 m (2H, H°). Mass spectrum, *m/z* (I_{rel}, %): 235 $[M+H-CH(COMe)_2]^+$ (100), 335 $[M+H]^+$ (90), 376 $[M+H+CH_3CN]^+$ (39). Found, %: C 68.51; H 5.40; N 16.85. $C_{19}H_{18}N_4O_2$. Calculated, %: C 68.25; H 5.43; N 16.76.

Compounds **VIIb** and **VIIc**, **VIIIa–VIIIc** were similarly obtained.

6-(1-Acetyl-2-oxoprop-1-yl)-5-(4-fluorophenyl)-1-ethyl-1,6-dihydropyrazine-2,3-dicarbonitrile (VIIb). Yield 83%, yellow crystalline powder, mp 142–144°C (decomp.). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.05 t (3H, CH_3, *J* 7.2 Hz), 2.11 s (3H, $COCH_3$), 2.26 s (3H, $COCH_3$), 3.53 d.q (1H, NCH^B, *J* 14.4, 7.2 Hz), 3.70 d.q (1H, NCH^A, *J* 14.4, 7.2 Hz), 4.13 d (1H, H$^{1'}$, *J* 9.2 Hz), 5.76 d (1H, H^6, *J* 9.2 Hz), 7.13 d.d (2H, H^m, *J* 9.2, 8.2 Hz), 7.97 d.d (2H, H°, *J* 9.2, 5.3 Hz). Found, %: C 64.53; H 4.88; N 16.05. $C_{19}H_{17}FN_4O_2$. Calculated, %: C 64.77; H 4.86; N 15.90.

6-(1-Acetyl-2-oxopropyl)-5-(3-thienyl)-1-ethyl-1,6-dihydropyrazine-2,3-dicarbonitrile (VIIc). Yield 52%, yellow crystalline powder, mp 151–153°C (decomp.). ^{1}H NMR spectrum (CD_3CN), δ, ppm: 1.01 t (3H, CH_3, *J* 7.2 Hz), 2.04 s (3H, $COCH_3$), 2.18 s (3H, $COCH_3$), 3.51 d.q (1H, NCH^B, *J* 14.4, 7.2 Hz), 3.62 d.q (1H, NCH^A, *J* 14.4, 7.2 Hz), 4.36 d (1H, H$^{1'}$, *J* 9.3 Hz), 5.65 d (1H, H^6, *J* 9.3 Hz), 7.46 d.d (1H, H$^{5''}$, *J* 5.2, 2.8 Hz), 7.58 d.d (1H, H$^{4''}$, *J* 5.2, 1.3 Hz), 8.04 d.d (1H, H$^{2''}$, *J* 2.8, 1.3 Hz). Mass spectrum, *m/z* (I_{rel}, %): 339 [*M* – H]$^+$ (100). Found, %: C 60.10; H 4.68; N 16.40. $C_{17}H_{16}N_4O_2S$. Calculated, %: C 59.98; H 4.74; N 16.46.

Ethyl 2-(3-phenyl-5,6-dicyano-1-ethyl-1,2-dihydropyrazin-2-yl)-3-oxobutanoate (VIIIa) was obtained analogously to compound **VIIa**. Yellow crystalline powder. Yield 90%, mp 170–172°C (decomp.). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, isomer *A* (*RS*/*SR*): 0.94 t (3H, CH_3, *J* 7.2 Hz), 1.07 t (3H, CH_3, *J* 7.2 Hz), 2.26 s (3H, $COCH_3$), 3.62 d.q (1H, NCH^B, *J* 14.5, 7.2 Hz), 3.73 d.q (1H, NCH^A, *J* 14.5, 7.2 Hz), 3.74 d (1H, H$^{1'}$, *J* 9.5 Hz), 3.77 m (2H, *AB*-system OCH_2), 5.78 d (1H, H^6, *J* 9.5 Hz), 7.42–7.50 m (3H, Ph), 7.96 m (2H, H°); isomer *B* (*RR*/*SS*): 1.08 t [3H, CH_3(NEt), *J* 7.2 Hz], 1.34 t [3H, CH_3(OEt), *J* 7.1 Hz], 2.10 s (3H, $COCH_3$), 3.56 d.q (1H, NCH^B, *J* 14.4, 7.2 Hz), 3.73 d (1H, H$^{1'}$, *J* 8.9 Hz), 3.74 d.q (1H, NCH^A, *J* 14.4, 7.2 Hz), 4.25 d.q and 4.29 d.q (2H, *AB*-system OCH_2, *J* 11.0, 7.1 Hz), 5.76 d (1H, H^6, *J* 8.9 Hz), 7.42–7.50 m (3H, Ph), 7.99 m (2H, H°). *A*:*B* ratio 9:1 (after flash-chromatography). Found, %: C 66.05; H 5.49; N 15.66. $C_{20}H_{20}N_4O_3$. Calculated, %: C 65.92; H 5.53; N 15.38.

Ethyl 2-[3-(4-fluorophenyl)-5,6-dicyano-1-ethyl-1,2-dihydropyrazin-2-yl]-3-oxobutanoate (VIIIb). Yield 76%, yellow crystalline powder, mp 178–180°C (decomp.). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, isomer *A* (*RS*/*SR*): 1.00 t [3H, CH_3(OEt), *J* 7.1 Hz], 1.06 t [3H, CH_3(NEt), *J* 7.2 Hz], 2.27 s (3H, $COCH_3$), 3.59 d.q (1H, NCH^B, *J* 14.4, 7.2 Hz), 3.71 d.q (1H, NCH^A, *J* 14.4, 7.2 Hz), 3.75 d (1H, H$^{1'}$, *J* 9.6 Hz), 3.83 d.q, 3.86 d.q (2H, *AB*-system OCH_2, *J* 10.9, 7.1 Hz), 5.74 d (1H, H^6, *J* 9.6 Hz), 7.13 d.d (2H, H^m, *J* 9.0, 8.2 Hz), 8.00 d.d (2H, H°, *J* 9.0, 5.2 Hz); isomer *B* (*RR*/*SS*): 1.00 t [3H, CH_3(OEt), *J* 7.1 Hz], 1.07 t [3H, CH_3(NEt), *J* 7.2 Hz], 2.12 C (3H, $COCH_3$), 3.55 d.q (1H, NCH^B, *J* 14.4, 7.2 Hz), 3.73 d.q (1H, NCH^A, *J* 14.4, 7.2 Hz), 3.74 d (1H, H$^{1'}$, *J* 9.2 Hz), 4.26 d.q, 4.29 d.q (2H, *AB*-system OCH_2, *J* 10.9, 7.1 Hz), 5.71 d (1H, H^6, *J* 9.2 Hz), 7.14 d.d (2H, H^m, *J* 8.9, 8.3 Hz), 8.03 d.d (2H, H°, *J* 8.9, 5.3 Hz). *A*:*B* ratio 9:1 (after flash-chromatography). Mass spectrum, *m/z* (I_{rel}, %): 381 [*M* – H]$^+$ (100), 383 [*M* + H]$^+$ (27), 424 [*M* + H + CH_3CN]$^+$ (32). Found, %: C 62.86; H 4.97; N 14.95. $C_{20}H_{19}FN_4O_3$. Calculated, %: C 62.82; H 5.01; N 14.65.

Ethyl 2-[3-(3-thienyl)-5,6-dicyano-1-ethyl-1,2-dihydropyrazin-2-yl]-3-oxobutanoate (VIIIc). Yield 78%, yellow powder, mp 131–133°C (decomp.). ^{1}H NMR spectrum (CD_3CN), δ, ppm, isomer *A* (*RS*/*SR*): 0.95 t (3H, CH_3, *J* 7.2 Hz), 1.04 t (3H, CH_3, *J* 7.2 Hz), 2.17 s (3H, $COCH_3$), 3.62 d.q, 3.66 d.q (2H, *AB*-system NCH_2, *J* 14.4, 7.2 Hz), 3.74 d.q, 3.78 d.q (2H, *AB*-system OCH_2, *J* 10.9, 7.2 Hz), 3.87 d (1H, H$^{1'}$, *J* 9.6 Hz), 5.66 d (1H, H^6, *J* 9.6 Hz), 7.46 d.d (1H, H$^{5''}$, *J* 5.2, 2.8 Hz), 7.59 d.d (1H, H$^{4''}$, *J* 5.2, 1.3 Hz), 8.03 d.d (1H, H$^{2''}$, *J* 2.8, 1.3 Hz); isomer *B* (*RR*/*SS*): 1.04 t (3H, CH_3, *J* 7.2 Hz), 1.29 t (3H, CH_3, *J* 7.2), 2.06 s (3H, $COCH_3$), 3.52 d.q (1H, NCH^B, *J* 14.4, 7.2 Hz), 3.66 d.q (1H, NCH^A, *J* 14.4, 7.2 Hz), 3.85 d (1H, H$^{1'}$, *J* 9.1 Hz), 4.20 d.q, 4.24 d.q (2H, *AB*-system OCH_2, *J* 10.9, 7.2 Hz), 5.63 d (1H, H^6, *J* 9.1 Hz), 7.46 d.d (1H, H$^{5''}$, *J* 5.2, 2.8 Hz), 7.61 d.d (1H, H$^{4''}$, *J* 5.2, 1.3 Hz), 8.15 d.d (1H, H$^{2''}$, *J* 2.8, 1.3 Hz); *A*:*B* ratio 11:1 (after flash-chromatography). Found, %: C 58.51; H 4.89; N 14.98. $C_{18}H_{18}N_4O_3S$. Calculated, %: C 58.36; H 4.90; N 15.12.

6-(1*H*-Indol-3-yl)-5-phenyl-1-ethyl-1,6-dihydropyrazine-2,3-dicarbonitrile (XIVa). To a solution of 117 mg (1 mmol) of indole in 2 ml of CH_3CN was added at stirring 322 mg (1 mmol) of salt **IIa** in 5 ml of CH_3CN. The reaction mixture was stirred for 50 min, evaporated, and the residue was subjected to chromatography on silica gel (eluent acetone–hexane, 1:2). The dark-yellow resinous substance obtained was reprecipitated with H_2O from MeOH. Yield 212 mg (61%), bright yellow powder, mp 67–69°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.19 t (3H, CH_3, *J* 7.2 Hz), 3.72 d.q (1H, NCH^B, *J* 14.4, 7.2 Hz), 3.81 d.q (1H, NCH^A, *J* 14.4, 7.2 Hz), 6.59 s (1H, H^6), 7.11–7.17 m (2H, H$^{5'}$, H$^{6'}$), 7.24 d (1H, H$^{2'}$, *J* 2.7 Hz), 7.38–7.49 m (4H, H$^{7'}$, Ph), 7.84 m (1H, H$^{4'}$), 7.96 m (2H, H°), 11.31 br.d (1H, NH, *J* 2.7 Hz). Mass spectrum, *m/z* (I_{rel}, %): 352 [*M* + H]$^+$ (100), 393

$[M + H + CH_3CN]^+$ (45). Found, %: C 74.99; H 5.12; N 19.87. $C_{22}H_{17}N_5$. Calculated, %: C 75.19; H 4.88; N 19.93.

6-(1*H*-Indol-3-yl)-5-(3-thienyl)-1-ethyl-1,6-dihydropyrazine-2,3-dicarbonitrile (XIVc). A solution of 54 mg (0.46 mmol) of indole and 150 mg (0.46 mmol) of salt **IIc** in 5 ml of CH_3CN was stirred for 55 min, evaporated, and the residue was subjected to chromatography on silica gel (eluent ethyl acetate–hexane, 1:3). The dark-yellow resinous substance obtained was ground. Yield 92 mg (66%), yellow powder, mp 84–86°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.19 t (3H, CH_3, *J* 7.2 Hz), 3.66 d.q (1H, NCH^B, *J* 14.3, 7.2 Hz), 3.73 d.q (1H, NCH^A, *J* 14.3, 7.2 Hz), 6.46 s (1H, H^6), 7.10–7.17 m (2H, $H^{5'}$, $H^{6'}$), 7.31 d (1H, $H^{2'}$, *J* 2.7 Hz), 7.41 m (1H, $H^{7'}$), 7.59 d.d (1H, $H^{5''}$, *J* 5.1, 2.5 Hz), 7.61 d.d (1H, $H^{4''}$, *J* 5.1, 1.6 Hz), 8.24 d.d (1H, $H^{2''}$, *J* 2.5, 1.6 Hz), 11.32 br.d (1H, NH, *J* 2.7 Hz). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.74 (CH_3), 47.92 (NCH_2), 50.64 (C^6), 107.02, 111.84, 117.40 [C^3, CN(C^2), CN(C^3)], 110.52 ($C^{3'}$), 112.11 ($C^{7'}$), 118.62 ($C^{4'}$), 118.96 (C^2), 119.86, 121.80 ($C^{5'}$, $C^{6'}$), 124.91 ($C^{3,a}$), 125.99 ($C^{2'}$), 126.69 ($C^{4''}$), 127.71 ($C^{5''}$), 129.55 ($C^{2''}$), 136.42 ($C^{7,a}$), 137.79 ($C^{3''}$), 145.67 (C^5). Mass spectrum, *m/z* (I_{rel}, %): 358 $[M + H]^+$ (59), 399 $[M + H + CH_3CN]^+$ (100). Found, %: C 67.55; H 4.28; N 19.34. $C_{20}H_{15}N_5S$. Calculated, %: C 67.21; H 4.23; N 19.59.

5-Phenyl-6-(4-dimethylaminophenyl)-1-ethyl-1,6-dihydropyrazine-2,3-dicarbonitrile (XV). To a solution of 381 mg (1.18 mmol) of salt **IIa** in 5 ml of CH_3CN was added dropwise at stirring a solution of 150 μl (1.18 mmol) of *N,N*-dimethylaniline in 1 ml of CH_3CN. The reaction mixture was stirred for 50 min, evaporated, and the residue was subjected to chromatography on silica gel (eluent acetone–hexane, 1:2). Yield 138 mg (33%), yellow-orange powder, mp 109–111°C (decomp.). ^{1}H NMR spectrum (CD_3CN), δ, ppm: 1.22 t (3H, CH_3, *J* 7.2 Hz), 2.90 s [6H, $N(CH_3)_2$], 3.65 d.q (1H, NCH^B, *J* 14.5, 7.2 Hz), 3.71 d.q (1H, NCH^A, *J* 14.5, 7.2 Hz), 5.90 s (1H, H^6), 6.71 d (2H, C_6H_4, *J* 8.9 Hz), 7.16 d (2H, C_6H_4, *J* 8.9 Hz), 7.40–7.49 m (3H, Ph), 7.92 m (2H, H^o). Mass spectrum, *m/z* (I_{rel}, %): 356 $[M + H]^+$ (100), 397 $[M + H + CH_3CN]^+$ (64). Found, %: C 74.41; H 6.08; N 19.51. $C_{22}H_{21}N_5$. Calculated, %: C 74.34; H 5.96; N 19.70.

Crystallographic data. Compound IIb. Crystals were obtained from chloroform, monoclinic, space group $P2_1/n$. Cell parameters at 295 K: *a* 11.6511(16), *b* 7.2872(9), *C* 18.8694(19) E, α 90.00, β 97.859(10), γ 90.00°, *V* 1587.0(3) E^3, *Z* 4, щ- and ц-scanning, $31.68 \geq \theta \geq 3.00$. Intensities were measured of 5012 reflections, 2390 of which with $I > 2\sigma$. Final values of divergence factors *R* 0.0687, R_w 0.1965.

Compound IIIa. Crystals were obtained from hot MeOH, monoclinic, space group *C*2/*C*. Cell parameters at 295 K: *a* 15.400(3), *b* 14.2785(9), *c* 13.545(3) E, α 90.00, β 119.549(19), γ 90.00°, *V* 2590.9(7) E^3, *Z* 8, ω- and ц-scanning, $31.75 \geq \theta \geq 2.85$. Intensities were measured of 3983 reflections, 1593 of which with $I > 2\sigma$. Final values of divergence factors *R* 0.0398, R_w 0.0602.

Compound IV. Crystals were obtained from hot MeOH, monoclinic, space group $P2_1/n$. Cell parameters at 295 K: *a* 10.0707(5), *b* 8.3387(11), *c* 17.0619(15) E, α 90.00, β 98.276(6), γ 90.00°, *V* 1417.9(2) E^3, *Z* 4, ω-scanning, $29.69 \geq \theta \geq 2.72$. Intensities were measured of 3687 reflections, 1468 of which with $I > 2\sigma$. Final values of divergence factors *R* 0.0418, R_w 0.0749.

Compound VIIc. Crystals were obtained from a mixture ethyl acetate–hexane, 1:2, monoclinic, space group $P2_1/n$. Cell parameters at 295 K: *a* 9.296(3), *b* 19.292(3), *c* 11.395(4) E, α 90.00, β 112.34(3), γ 90.00°, *V* 1890.2(9) E^3, *Z* 4. Intensities were measured of 3725 reflections, 1338 of which with $I > 2\sigma$, φ- and ω-scanning, $26.47 \geq \theta \geq 2.64$. Final values of divergence factors *R* 0.0465, R_w 0.0641.

Compound VIIIb. Crystals were obtained from CH_2Cl_2, triclinic, space group *P*-1. Cell parameters at 295 K: *a* 8.9118(7), *b* 11.5423(9), *c* 11.9106(9) E, α 61.282(8), β 68.366(7), γ 84.162(6)°, *V* 994.48(13) E^3, *Z* 2. Intensities were measured of 6578 reflections, 3620 of which with $I > 2\sigma$, ω-scanning, $33.98 \geq \theta \geq 2.77$. Final values of divergence factors *R* 0.0471, R_w 0.1394.

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