SYNTHESIS OF ISOMERIC 1,1'-PHENYLENE-BIS(6-AZAURACIL-5--CARBONITRILES)*

Jan SLOUKA

Department of Analytical and Organic Chemistry,
Palacký University, 771 46 Olomouc

Dedicated to Professor O. Červinka on the occasion of his 65th birthday.

The described synthesis of all three isomeric 1,1'-phenylenebis(6-azauracil-5-carbonitriles) *IVa—IVc* starts from the respective 1-nitrophenyl-6-azauracil-5-carbonitriles *Ia—Ic* which were reduced to the corresponding amino derivatives *IIa—IIc*, diazotized, and coupled with ethyl cyanoacetylcarbamate to give the isomeric hydrazones *IIIa—IIIc* which were finally cyclized to the title compounds containing two 6-azauracil rings. A general formula is presented for calculation of mutual distance of arbitrary atoms in any planar molecules.

Hydrogen bonds play an extraordinarily important role in biological systems. Well--known interactions of this type include e.g. the intermolecular hydrogen bonds between purine and pyrimidine cycles in nucleic acids or interactions between various polar groups in proteins.

Substances which interfere with these interactions can affect functions of such biomolecules at molecular level. This way of action is exhibited e.g. by some anti-viral antibiotics as well as by some synthetical antivirotics[1].

Compounds which can be presumed to interact with biomolecules also include 6-azauracil derivatives, especially the 3-nonsubstituted ones. These intermolecular hydrogen bonds can still be stronger than their analogues formed by the less acidic N—H group in uracil ring (pK is 7·00 for 6-azauracil[2,3] and 9·43 for uracil[3]). Hence it can be anticipated that among 6-azauracil derivatives one can find such compounds which will be able to form intermolecular hydrogen bonds with e.g. nucleic acids and block some of their sections.

From this standpoint particularly interesting are the compounds containing two or more 6-azauracil rings in their molecule, which rings can interact with biomolecules at positions of various mutual distances whereby the spatial arrangement of the biomolecules can be affected. In this respect an important role is played by both

the distance of the respective bonding centres and their steric orientation. Syntheses of some compounds of this type were described earlier[4-11].

The syntheses of the title compounds started from the isomeric 1-(X-nitrophenyl)--6-azauracil-5-carbonitriles $Ia-Ic$ (Scheme 1) which were prepared earlier[12-14] by cyclization of the respective ethyl nitrophenylhydrazonocyanoacetylcarbamates.
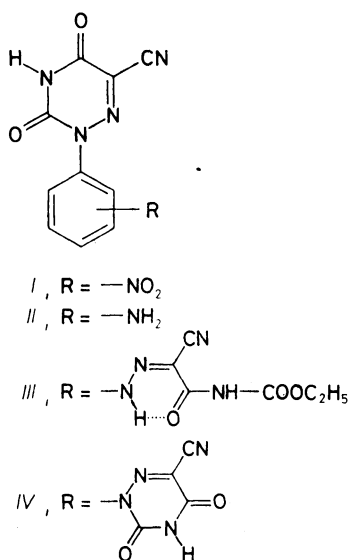

In formulae $I-IV$: a, o-isomers b, m-isomers c, p-isomers

SCHEME 1

The preparation of compounds Ia and Ib by thermal and alkaline cyclizations, respectively, has not yet been described, and therefore these cyclization procedures are given in the present communication. The nitro compounds $Ia-Ic$ were reduced to the corresponding isomeric 1-(X-aminophenyl)-6-azauracil-5-carbonitriles IIa to IIc. The best reducing agent for Ia and Ib was the ferrous hydroxide prepared from ferrous sulfate and barium hydroxide (the reducing solution contains no inorganic salts). The amino deriative IIa was obtained in this way with a higher yield as compared with the earlier reduction in ammoniacal medium[12]. The best way to IIc was the reduction of Ic with stannous chloride in ethanolic medium[15]. The diazotization of amino compounds $IIa-IIc$ and azo coupling of the diazonium salts obtained with ethyl cyanoacetylcarbamate in aqueous natrium acetate gave good yields of the respective ethyl (5-cyano-6-azauracil-1-yl)phenylhydrazonocyanoacetylcarbamates $IIIa-IIIc$. These compounds were cyclized by heating in slightly alkaline

medium to give the corresponding isomeric 1,1'-phenylene-bis(6-azauracil-5-carbo-nitriles) $IVa-IVc$. Compound IVc was identical with the product obtained earlier[6] by cyclization of p-phenylene-bis(hydrazonocyanoacetylcarbamate).

The IR spectra of the compounds prepared show characteristic bands of carbonyl groups of the 6-azauracil cycle (in compounds $IIa-IIc$ and $IVa-IVc$) beside the bands of amidic and carbamate carbonyl groups (in compounds $IIIa-IIIc$). Also typical are the bands of nitrile groups. The vibrations of nitrile groups bound to 6-azauracil ring are found at higher wavenumbers as compared with those of the nitrile groups in side chain of compounds $IIIa-IIIc$.

IVa - A

IVa - B

IVa - C
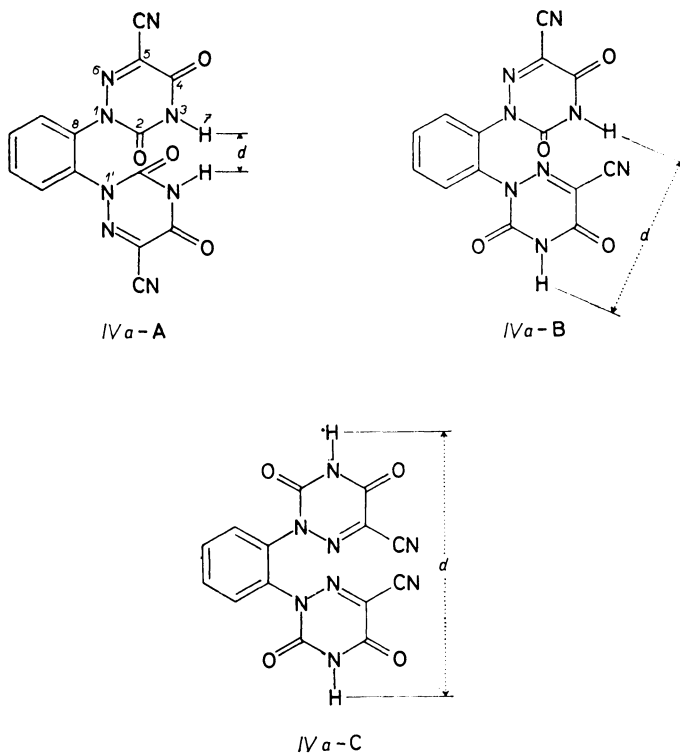
SCHEME 2

If free rotation around single bonds is presumed, then the 6-azauracil cycles of compounds $IVa-IVc$ can assume various spatial conformations. Three planar conformations (A, B, C) can exist with compounds IVa and IVb but only two con-formations (A, B) with compound IVc (Schemes 2 – 4).

For a preliminary estimation of interactions of these compounds with biomolecules at two positions it is important to know the possible mutual distances between the

IV b − A   IV b − B

SCHEME 3   IV b − C

IV c − A

IV c − B
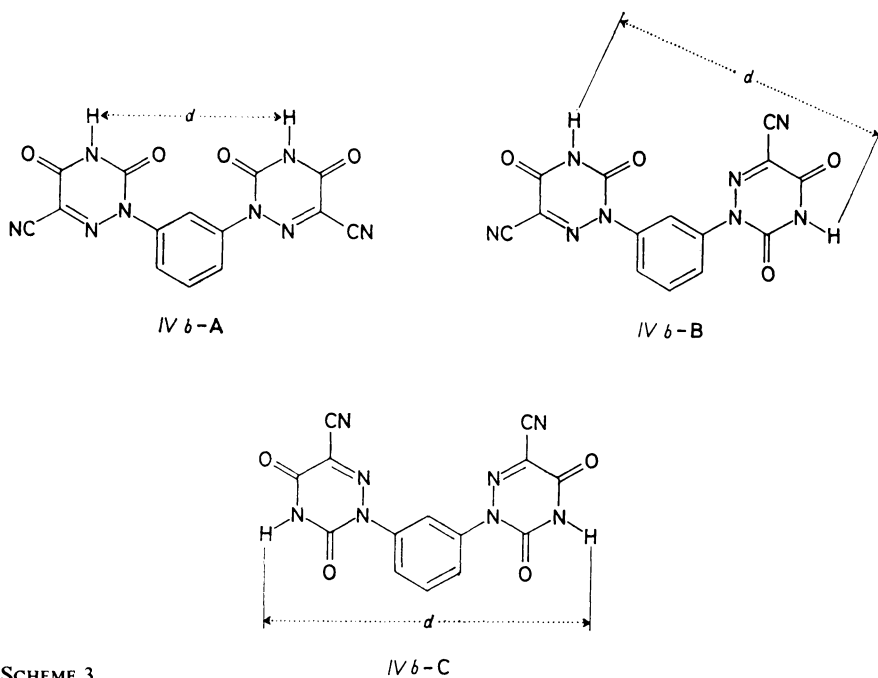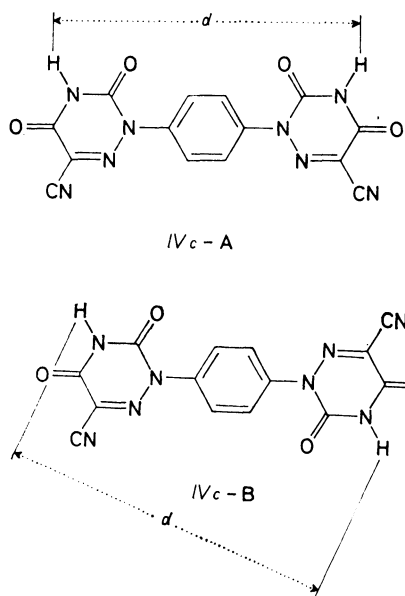
SCHEME 4

H atoms which tend to form the intermolecular hydrogen bonds. The limiting values of these distances are those given in the schemes between the H atoms in the planar conformations A, B, C. The distances between H atoms in other conformations lie between these limiting values.

The distance between any two atoms in a planar molecule (or planar conformation of nonplanar molecule) can easily be calculated if one knows all necessary bond lengths and bond angles between the two atoms. Such data are usually available and often tabulated. Trigonometry provides the general formula (1) for the distance d between two atoms (X, Y) in a planar molecule (see Scheme 5).

$$d^2 = \sum_{i=1}^{n} a_i^2 - 2 \sum_{i=1}^{n-1} a_i a_{i+1} \cos \alpha_i + 2 \sum_{i=1}^{n-2} a_i a_{i+2} \cos \left(\alpha_i - \alpha_{i+1} \right) +$$

$$- 2 \sum_{i=1}^{n-3} a_i a_{i+3} \cos \left(\alpha_i - \alpha_{i+1} + \alpha_{i+2} \right) + \ldots +$$

$$+ 2 \left(-1 \right)^k \sum_{i=1}^{n-k} a_i a_{i+k} \cos \left(\alpha_i - \alpha_{i+1} + \ldots + \left(-1 \right)^{k+1} \alpha_{i+k-1} \right) + \ldots$$

$$+ 2 \left(-1 \right)^{n+1} a_1 a_n \cos \sum_{i=1}^{n-1} \left(-1 \right)^{i+1} \alpha_i , \tag{1}$$

where $a_1, \ldots, a_n$ are the bond lengths between pairs of adjacent atoms and $\alpha_1, \ldots, \alpha_{n-1}$ are alternating angles included by two adjacent bonds, i.e. etiher bond angles or
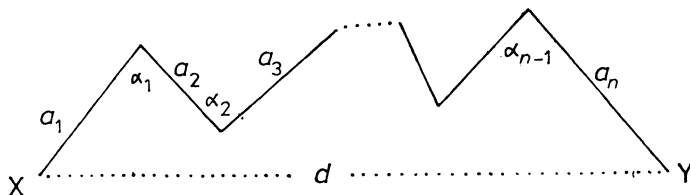
SCHEME 5

their complements to 360° depending on the shape of molecule. The formula given represents a generalization of the law of cosines which is obtained for $n = 2$. The formula can be applied not only to the above-mentioned purpose but also to evaluation of other sterical problems such as e.g. atropoisomerism.

The calculation of the distances d between H atoms of planar conformations (A, B, C) of compounds IV was carried out with application of the data from Cambridge Structural Database (Table I). The individual bond lengths and angles are specified by the corresponding atoms. All atoms of 6-azauracil ring are numbered in usual way, the H atom in 6-azauracil cycle is denoted as 7, and the C atom of

benzene ring to which 6-azauracil ring is attached is denoted as 8 (Scheme 2). The distances d between the H atoms in all the planar conformations of compounds IVa and IVb were calculated from Eq. (1) for $n = 8$, the following bond lengths being used with respect to symmetry: $a_1 = a_8 = 0.0924$ nm, $a_2 = a_7 = 0.1376$ nm,

TABLE I

Bond lengths and bond angles in compounds IV

Atoms	Bond lengths, nm	Atoms	Bond angles, °
H_7-N_3	0.0924	$H_7N_3C_2$	118.440
N_3-C_2	0.1376	$N_3C_2N_1$	114.721
C_2-N_1	0.1363	$C_2N_1C_8$	117.274
N_1-C_8	0.1419		
$C-C_{arom}$	0.1395		

TABLE II

Values of the bond angles α (°) introduced into Eq. (1) and the therefrom calculated distances d (nm) between the H atoms in planar conformations of compounds IV

Compound and con-formation	α_1	α_2	α_3	α_4	α_5	α_6	α_7	d
IVa-A	118.440	114.721	117.274	300	$=\alpha_3$	$=\alpha_2$	$=\alpha_1$	0.1925
IVa-B	118.440	114.721	117.274	60	$360 -$ $\alpha_3 =$ 242.726	$360 -$ $\alpha_2 =$ 245.279	$360 -$ $\alpha_1 =$ 241.560	0.6019
IVa-C	118.440	114.731	117.274	60	$=\alpha_3$	$=\alpha_2$	$=\alpha_1$	0.8533
IVb-A	118.440	114.721	117.274	240	$=\alpha_3$	$=\alpha_2$	$=\alpha_1$	0.7197
IVb-B	118.440	114.721	117.274	120	$360 -$ $\alpha_3 =$ 242.726	$360 -$ $\alpha_2 =$ 245.279	$360 -$ $\alpha_1 =$ 241.560	0.9663
IVb-C	118.440	114.721	117.274	120	$=\alpha_3$	$=\alpha_2$	$=\alpha_1$	1.1103
IVc-A	118.440	114.721	117.274	$360 -$ $\alpha_3 =$ 242.726	$360 -$ $\alpha_2 =$ 245.279	$360 -$ $\alpha_1 =$ 241.560	—	1.0578
IVc-B	118.440	114.721	117.274	$=\alpha_3$	$=\alpha_2$	$=\alpha_t$	—	1.1269

$a_3 = a_6 = 0 \cdot 1363$ nm, and $a_4 = a_5 = a(N_1—C_8) + a(C—C_{arom}) = 0 \cdot 2814$ nm. The alternating angles to be introduced into Eq. (1) are presented in Table II. The α_4 angles in compounds IVa and IVb are those formed by the straight lines from the centre of benzene ring to the attached 6-azauracil cycles. The situation is simpler with compound IVc, since the atoms $N_1C_8N_1'$ lie on a straight line. Hence it is possible to use Eq. (1) for $n = 7$ using the following bond length values: $a_1 = a_7 = 0 \cdot 924$ nm, $a_2 = a_6 = 0 \cdot 1376$ nm, $a_3 = a_5 = 0 \cdot 1363$ nm, and $a_4 = 2a(C—C_{arom}) + 2a(N_1—C_8) = 0 \cdot 5628$ nm. The values of the angles $\alpha_1 - \alpha_6$ to be introduced into Eq. (1) are also given in Table II.

As it follows from the data of Table II, according to expectation the greatest distance between the H atoms $(d = 1 \cdot 1269$ nm) is found in conformation B of compound IVc and the shortest one $(d = 0 \cdot 1925$ nm) in conformation A of compound IVa. In reality, however, this value cannot be reached, since the carbonyl groups at 2-positions of the two 6-azauracil rings prevent the planar conformation presumed because of their close vicinity.

All the limiting values calculated for the distances between the H atoms in compounds IV, of course, can serve only for an approximative estimation of possible interactions between these molecules and suitable substrates by means of two simultaneous hydrogen bonds at two centres. A more precise description of such interactions would necessitate to take into account also the spatial orientation of the bonding centres involved.

EXPERIMENTAL

The melting points were determined by means of a Boetius apparatus and are not corrected. The IR spectra were measured with an IR-75 apparatus (Zeiss) using the KBr disc technique.

2-(2-Nitrophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*Ia*)

A mixture of $3 \cdot 10$ g ($10 \cdot 15$ mmol) ethyl 2-nitrophenylhydrazonocyanoacetylcarbamate[12] and 120 ml xylene was refluxed 60 h, concentrated to ca 30 ml, and cooled. The separated crystalline solid was collected by suction, washed with little benzene, and dried. Yield $2 \cdot 15$ g ($88 \cdot 2\%$), m.p. $229 - 231°C$ (toluene) in accordance with ref.[12].

2-(3-Nitrophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*Ib*)

A mixture of $6 \cdot 15$ g ($20 \cdot 15$ mmol) ethyl 3-nitrophenylhydrazonocyanoacetylcarbamate[13] and $2 \cdot 40$ g Na_2CO_3 was heated on a boiling water bath until a solution was formed and for another 20 min. After addition of a small amount of charcoal the reaction mixture was filtered and acidified to pH 1. The next day, the separated crystalline solid was collected by suction, washed with water, and dried. Yield $5 \cdot 05$ g ($96 \cdot 1\%$), m.p. $269 - 271°C$ (ethanol–water) in accordance with ref.[13]. For $C_{10}H_5N_5O_4$ ($259 \cdot 2$) calculated: $46 \cdot 34\%$ C, $1 \cdot 94\%$ H, $27 \cdot 02\%$ N; found: $46 \cdot 59\%$ C, $2 \cdot 05\%$ H, $27 \cdot 31\%$ N.

2-(2-Aminophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*IIa*)

A warm solution of 25·25 g (80·02 mmol) $Ba(OH)_2.8\ H_2O$ in 180 ml water was added to a solution of 22·25 g (80·03 mmol) $FeSO_4.7\ H_2O$ in 80 ml water with stirring. The suspension formed was then treated with a solution of 2·60 g (10·03 mmol) nitro compound *Ia* in a mixture of 40 ml water and 1·5 ml 25% NH_3 added portionwise. The reaction mixture was stirred at 60°C 5 min and heated on a boiling water bath with stirring for another 50 min. Then the precipitate was hot filtered, repeatedly washed with warm solution of 1% NH_3 in water, and the combined filtrates were concentrated to 30 ml in vacuum and acidified with acetic acid. On the next day the crystalline solid was collected by suction, washed with little water, and dried. Yield 1·78 g (71·8%), m.p. 221—223°C (water), the melt immediately solidifies with formation of 3-oxo-3,4--dihydro-1,2,4-triazino[2,3-*a*]benzimidazole-2-carbonitrile, which agrees with the data of ref.[12].

2-(3-Aminophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*IIb*)

The compound was prepared in analogy to *IIa* from 2·60 g (10·03 mmol) nitro compound *Ib* in the yield of 1·93 g (77·9% calculated on the monohydrate). After recrystallization from aqueous ethanol m.p. 251—253°C (decomposition). For $C_{10}H_9N_5O_3$ (247·2) calculated: 48·58% C, 3·65% H, 28·33% N; found: 48·76% C, 3·61% H, 28·56% N. IR spectrum (cm^{-1}): 1 707, 1 744 (ν(CO)); 2 246 (ν(CN)).

TABLE III

Characteristic data for compounds *IIIa—IIIc* and *IVa—IVc*

Com-pound	Formula (M.w.)	Calculated/Found			Yield, %	M.p., °C	IR spectrum, cm^{-1}	
		% C	% H	% N			ν(CN)	ν(CO)
IIIa	$C_{16}H_{12}N_8O_5$	48·49	3·05	28·27	91	165—167	2 219 2 227	1 773 1 769
	(396·3)	48·33	3·11	28·37				1 715
IIIb	$C_{16}H_{12}N_8O_5$	48·49	3·05	28·27	91	203—205	2 216 2 230	1 770 1 762
	(396·3)	48·27	3·10	28·01				1 715
IIIc	$C_{16}H_{12}N_8O_5$	48·49	3·05	28·27	93	213—215	2 218 2 233	1 770 1 764
	(396·3)	48·30	3·12	28·15				1 718
IVa	$C_{14}H_6N_8O_4$	48·01	1·73	31·99	72	335—337	2 247 2 253	1 755 1 719
	(350·3)	48·10	1·74	31·73				
IVb	$C_{14}H_6N_8O_4$	48·01	1·73	31·99	75	200—202	2 242 2 246	1 740 1 715
	(350·3)	47·83	1·86	31·80				
IVc	$C_{14}H_6N_8O_4$	48·01	1·73	31·99	74	over 350	2 253	1 745 1 711
	(350·3)	47·88	1·95	32·05				

2-(4-Aminophenyl)-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (*IIc*)

A solution of 8·00 g (35·46 mmol) $SnCl_2.2 H_2O$ in 80 ml ethanol was added to a boiling solution of 2·08 g (8·025 mmol) nitro compound *Ic* in 100 ml ethanol, and the reaction mixture was refluxed 2 h. Ethanol was evaporated, and the residue was mixed with 22 ml water and 9 ml 25% NH_3. The separated solid was filtered off and repeatedly washed with water, and the combined filtrates were evaporated in vacuum until dry. The residue was mixed with 20 ml water and 0·5 ml 25% NH_3 and, after several hours, the reaction mixture was filtered with charcoal and acidified with acetic acid. On the next day the precipitate was collected by suction, washed with little water, and dried in air. The yield of the monohydrate 1·44 g (72·6%), m.p. 190−192°C (aqueous ethanol). For $C_{10}H_9N_5O_3$ (247·2) calculated: 48·58% C, 3·65% H, 28·33% N; found: 48·69% C, 3·41% H, 28·47% N. IR spectrum (cm^{-1}): 1 700, 1 747 (ν(CO)); 2 240 (ν(CN)).

Ethyl X-(3,5-Dioxo-6-cyano-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)phenylhydrazonocyano-acetylcarbamates (*IIIa−IIIc*)

A solution of 1·70 g (7·42 mmol) of the respective anhydrous amino derivative *II* (or 1·84 g (7·44 mmol) monohydrate) in a mixture of 30−40 ml water and 4·0 ml 37% HCl was cooled in an ice bath and treated with a solution of 0·485 g (7·03 mmol) $NaNO_2$ in 10 ml ice water added with stirring. The solution was left to stand in the ice bath with intermittent stirring 75 min., whereupon it was added portionwise to a stirred mixture obtained by dissolving 1·40 g (8·97 mmol) ethyl cyanoacetylcarbamate in 300 ml warm water, cooling in ice bath, adding 5·20 g CH_3COONa and crushed ice. The reaction mixture was left at 0−5°C with intermittent stirring 24 h, acidified with 37% HCl to pH 1, and again left to stand at 0−5°C for several hours. The separated yellow crystalline solid of the corresponding hydrazone (*IIIa−IIIc*) was then collected by suction, washed with water, and dried in air. The hydrazones *IIIa*, *IIIb*, and *IIIc* thus obtained were in the form of dihydrate, anhydrous, and monohydrate, respectively. Recrystallization from ethanol and drying at 100°C in vacuum gave the anhydrous hydrazones (Table III).

1,X-Bis(3,5-dioxo-6-cyano-2,3,4,5-tetrahydro-1,2,4-triazin-2-yl)benzenes (*IVa−IVc*)

A mixture of 400 mg (1·01 mmol) of the respective anhydrous hydrazone *IIIa−IIIc* or 415 mg (1·00 mmol) corresponding monohydrate, 425 mg Na_2CO_3, and 20−30 ml water was heated on a boiling water bath until a solution was formed and then for another 15−20 min. Then the solution was cooled and acidified with 37% HCl to pH 1. After several hours the crystalline solid was collected by suction, washed with little water, and dried in air. The dinitriles *IVa* and *IVb* were obtained in the form of the corresponding monohydrates, dinitrile *IVc* in the form of dihydrate. The anhydrous products were obtained by drying in vacuum at 130−160°C (Table III).

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