Synthesis and intramolecular conversion of substituted 2-methyl-11-nitro-5,6-dihydro-2*H*-2,6-methanobenzo[*g*][1,3,5] oxadiazocin-4(3*H*)-ones in different solvents*

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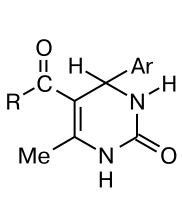
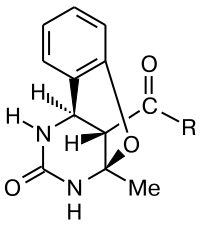
A Biginelli reaction of 5-R-salicylic aldehydes (R = H, Me, Br) with nitroacetone and urea in each case leads to a predominant formation of 2*R**,6*S**,11*S** diastereomers of 8-R-2-methyl-11-nitro-5,6-dihydro-2*H*-2,6-methanobenzo[*g*][1,3,5]oxadiazocin-4(3*H*)-one. In solutions in DMF and DMSO, these diastereomers undergo the oxadiazocine ring opening with setting a three-component equilibrium between predominant 4-(2-hydroxy-5-R-phenyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-ones and 2*R**,6*S**,11*S** and 2*R**,6*S**,11*R** diastereomers of methanobenzoxadiazocine as two minor components.

Key words: salicylic aldehydes, Biginelli reaction, nitrodihydro-2,6-methanobenzo-[1,3,5]oxadiazocin-4(3*H*)-ones, intramolecular transformations.

At the present time, a three-component Biginelli reaction involving a β-dicarbonyl compound, aromatic aldehyde, and urea constitutes a simple and available method for the preparation of various 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones **1** (see Refs 1—4), which possess a wide range of biological activity.[5—8] It is known that for salicylic aldehydes this reaction in most cases proceeds with the transformation of the structure of the intermediately formed pyrimidinones **1** to the corresponding 11-carbonyl derivatives of 5,6-dihydro-2*H*-2,6-methanobenzo[*g*]-[1,3,5]oxadiazocin-4(3*H*)-ones **2** as a single stable diastereomer.[9—15] It is believed that the formation of benzoxadiazocines **2** results from a tandem Biginelli reaction and intramolecular oxa-Michael reaction, an addition of the hydroxy group at the double bond of the dihydropyrimidine ring.



1



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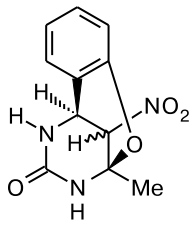

3

R = Alk, OAlk

In continuation of our studies on the use of nitro carbonyl compounds in the Biginelli reaction,[16,17] we carried out the condensation of nitroacetone, salicylic aldehyde, and urea with the isolation of 5,6-dihydro-2*H*-2,6-methanobenzo[*g*][1,3,5]oxadiazocin-4(3*H*)-one (**3a**) with the nitro group at the methylene bridge as the only reaction product, the structure of which was confirmed ^{1}H and ^{13}C NMR spectra. X-ray diffraction analysis showed that compound **3a** is a diastereomer with the framework configuration 2*R**,6*S**,11*S** (see Ref. 18).

Compound **3a** is stable upon storage in the solid state and in solution in ethanol. However, in solutions in highly polar aprotic solvents such as DMF and DMSO compound **3a** undergoes oxadiazocine ring opening with setting a three-component equilibrium between 4-(2-hydroxyphenyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-one (**4**) and two diastereomers of benzoxadiazocine **3a** (2*R**,6*S**,11*S** configuration) and **3b** (2*R**,6*S**,11*R** configuration). Such an equilibrium for substituted 2,6-methanobenzo[*g*][1,3,5]oxadiazocines was for the first time described in our short communication.[18]

The purpose of the present work is the confirmation of generality of the Biginelli reaction course leading to the formation of 11-nitromethanobenzoxadiazocines in the condensation of nitroacetone, substituted salicylic aldehydes (5-methyl- and 5-bromo substituted), and urea, as well as the evaluation of influence of structural modifications on the character of intramolecular conversions of methanobenzoxadiazocine nitro derivatives and a three-

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component equilibrium discovered by us in the media of different nature.

Results and Discussion

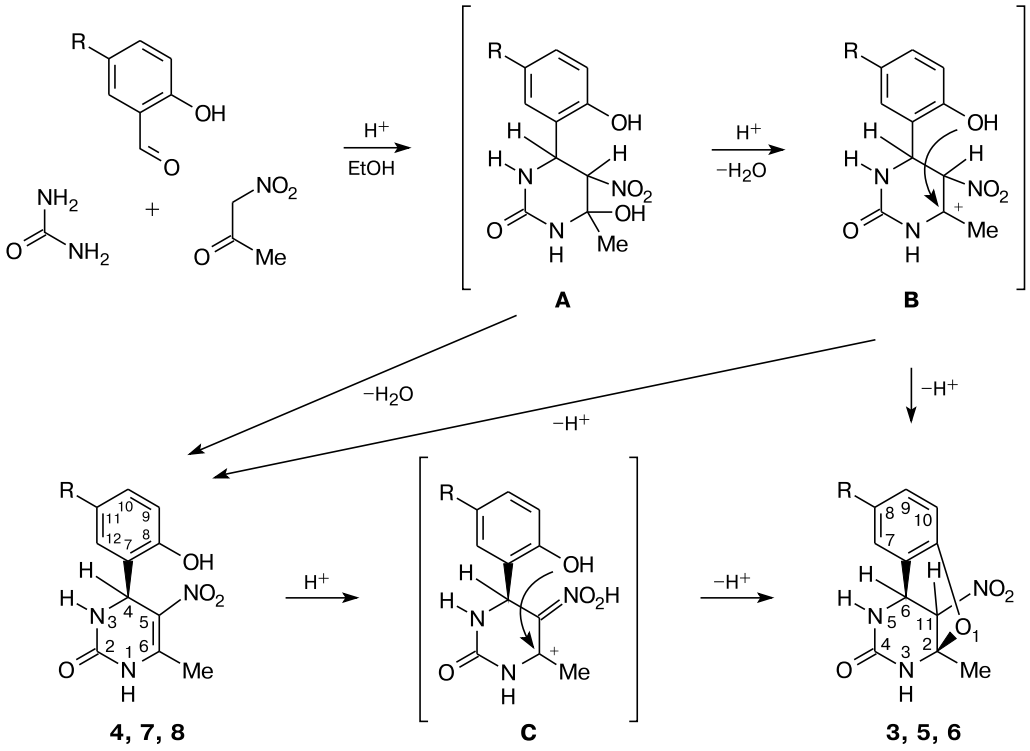
Heating a mixture of nitroacetone, the corresponding substituted salicylic aldehyde, and urea taken in the molar ratios 1 : 1.05 : 2 was carried out in refluxing ethanol in the presence of a catalytic amount of HCl (conc.). The reaction products **5** and **6** were isolated as snow-white solid compounds (like compound **3a**[18]). The IR spectra of these compounds exhibited absorption bands of stretching vibrations of the N—H, C=O, NO_2, and C—O—C groups, while no stretching vibrations band for the O—H group (in KBr and mineral oil) was observed. These data indicate the formation of *O*-cyclic compounds, namely, the corresponding 8-substituted 2-methyl-11-nitro-5,6-dihydro-2*H*-2,6-methanobenzo[*g*][1,3,5]oxadiazocin-4(3*H*)-ones (**5** and **6**) (Scheme 1).

Approximately 10—15 min after dissolution, the ^1H and ^{13}C NMR spectra (DMSO-d_6) of compounds **5** and **6** exhibit signals of only one diastereomer: for atoms H(6) and H(11) in the region δ 4.50—5.75 with the spin-spin coupling constants characteristic of 11-nitro-substituted 2,6-methanobenzoxadiazocines,[18] as well as for sp^3-hybridized atoms C(2) (82.32 and 82.91, C(N)O), C(6) (49.32 and 48.74), and C(11) (79.30 and 78.63, C(H)(NO_2)), respectively (for compound **5a** Fig. 1, *a* and 2, *a*).[18,19]

The steric structure of compound **5** established by X-ray diffraction analysis (Fig. 3) confirms the presence of a bridged framework with three stereogenic C atoms with configuration 2*R**,6*S**,11*S** (diastereomer **5a**) similarly to the structure of compound **3a** described earlier.[18] Because of the pseudoaxial position of the benzene ring, it is oriented approximately perpendicular (89.01(8)°) to the hexahydropyrimidine ring. Dihydropyran and tetrhydropyrimidine rings are each in the half-chair conformation with the deviation of atoms C(2), C(11) by –0.367(4), 0.515(4) Å and atoms C(6), C(11) by –0.417(4), 0.424(5) Å from the planes of the corresponding rings formed by the rest of the atoms. In crystal, the hydrogen bonds N(3)—H···O(2) (H···O 2.05(4) Å, N—H···O 170(3)°) and N(5)—H···O(2) (1.96(4) Å, 171(3)°) combine the molecules in the zigzag-like centrosymmetric chains oriented along the axis *a*. Similar chains were also observed in compound **3a** (see Ref. 18).

Steric configuration of compound **6** (R = Br) cannot be found by X-ray diffraction analysis because of the formation of twin crystals during its crystallization from ethanol. However, based on the similarities of the ^1H and ^{13}C NMR spectral characteristics of this compound and diastereomers **3a** and **5a** (Table 1), the 2*R**,6*S**,11*S** configuration was also assigned to its steric structure (diaste-

Scheme 1



R = H (**3**, **4**), Me (**5**, **7**), Br (**6**, **8**)

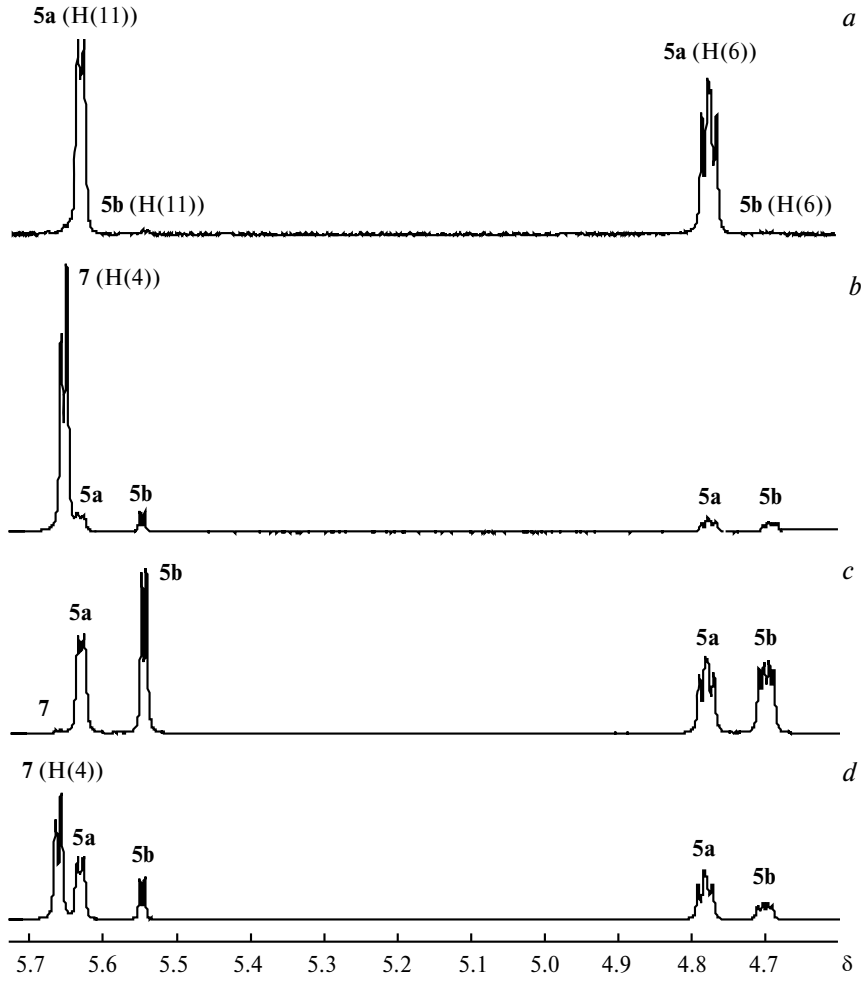


Fig. 1. Characteristic signals in the ^{1}H NMR spectra of compounds **5a**, **5b**, and **7** in DMSO-d_6: (*a*) immediately after dissolution of diastereomer **5a**; (*b*) the same solution 9 days later (an equilibrium mixture of compounds **5a** + **5b** + **7** with the ratio 7 : 6 : 87); (*c*) a solution of the precipitate formed from DMSO + H_2O (1 : 10) (a mixture of **5a** + **5b** + **7** with the ratio 48 : 50 : 2); (*d*) the same solution 15 days later for the mixture **5a** + **5b** + **7** with the ratio 37 : 19 : 44).

Table 1. Chemical shifts of characteristic signals of diastereomers of compounds **3**, **5**, and **6** in the ^{1}H and ^{13}C NMR spectra in DMSO-d_6 (δ, *J*/Hz)

Compound	H(6)	H(11)	NH(3)	NH(5)	C(2)	C(6)	C(11)
3a	4.86 (dd, $J = 3.3$, $J = 4.6$)	5.67 (d, $J = 3.3$)	8.00 (br.s)	7.54 (d, $J = 4.6$)	82.48	49.27	79.13
3b	4.76 (dd, $J = 2.7$, $J = 5.2$)	5.58 (d, $J = 2.7$)	7.91 (d, $J = 2.1$)	7.68 (dd, $J = 2.1$, $J = 5.2$)	81.83	46.32	80.01
5a	4.77 (dd, $J = 3.3$, $J = 4.5$)	5.53 (d, $J = 3.3$)	7.96 (br.s)	7.50 (d, $J = 4.5$)	82.32	49.32	79.30
5b	4.70 (dd, $J = 2.4$, $J = 4.7$)	5.55 (d, $J = 2.4$)	7.87 (d, $J = 2.1$)	7.63 (dd, $J = 2.1$, $J = 4.7$)	81.75	46.36	80.07
6a	4.93 (dd, $J = 2.7$, $J = 3.7$)	5.70 (d, $J = 2.7$)	8.11 (br.s)	7.54 (d, $J = 3.7$)	83.96*	50.21*	79.77*
6b	4.82 (dd, $J = 2.5$, $J = 5.0$)	5.63 (d, $J = 2.5$)	8.0 (d, $J = 2.2$)	7.63 (dd, $J = 2.2$, $J = 5.0$)	83.88*	50.12*	79.94*

* The data extracted from the spectra of a mixture of diastereomers in DMF-d_7.

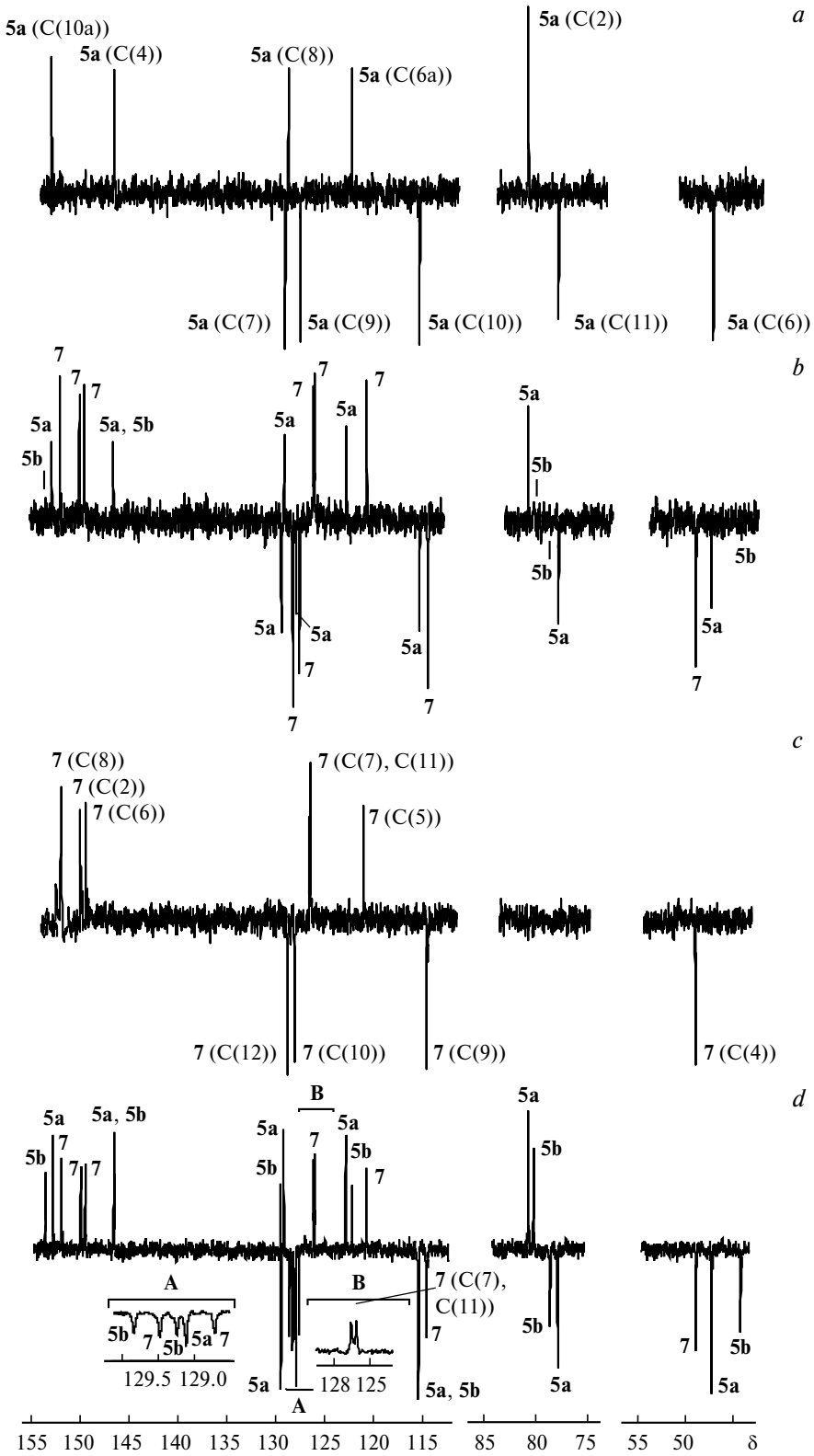


Fig. 2. The fragments the ^{13}C NMR spectra (JMOD) of compounds **5a**, **5b**, and **7** in DMSO-d_6: (*a*) 30 min after dissolution of diastereomer **5a**; (*b*) the same solution 2 days later (a mixture **5a** + **5b** + **7** with the ratio ~ 32 : 4 : 64); (*c*) the same solution 9 days later (a mixture **5a** + **5b** + **7** with the ratio 7 : 6 : 87); (*d*) a solution of the precipitate formed from DMSO + H_2O (1 : 10), for the mixture **5a** + **5b** + **7** with the ratio 40 : 25 : 35 (*d*).

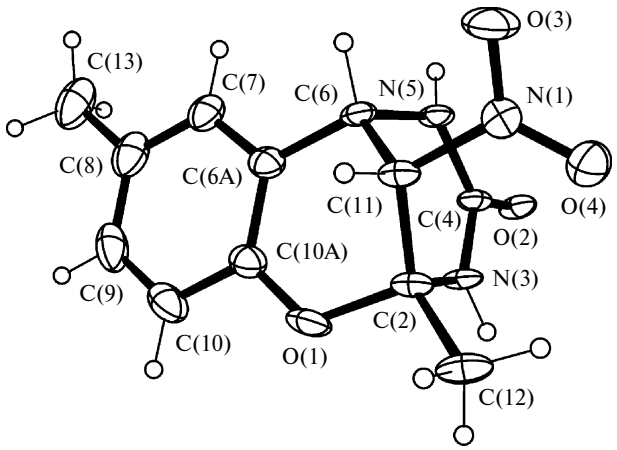


Fig. 3. Spatial structure of compounds **5a** (the ORTEP view).

reomer **6a**). Note that the steric structure of compounds **5a** and **6a** completely correspond to the described structures of 11-ethoxycarbonyl analogs of methanobenzoxadiazocine **2** obtained by the Biginelli reaction and isolated as individual diastereomers.[10,12,14]

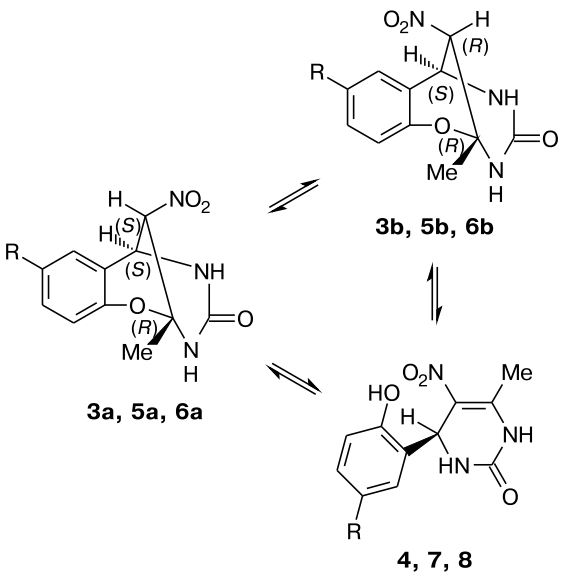
Diastereomers **5a** and **6a** are stable on recrystallization from ethanol, as well as upon storage in the solid state and as alcoholic solutions and solutions in CF_3COOH. Only one diastereomer is present in the last mentioned solvent, which remains unchanged for several days.

Upon recording NMR spectra of solutions of the nitro-substituted methanobenzoxadiazocines **5a** and **6a** in DMSO-d_6, a conversion of the starting individual diastereomers to the three-component mixtures of isomeric compounds was observed like it was described earlier for compound **3a** (see Ref. 18).

Some time later after dissolution of individual diastereomers **5a** and **6a**, the NMR spectra began to exhibit signals of two another compounds, whose intensities gradually grew at different rates, with simultaneous decrease in the intensities of the signals for the starting diastereomers until an equilibrium is set (see Fig. 1, *a*, *b* and 2, *a*, *b*, *c*). Some of the growing signals appear next to the signals of the starting diastereomers, whereas some signals completely collapse to one multiplet signals. Thus, for compound **5** (R = Me) the difference in chemical shifts of ^{1}H signals for diastereomer **5a** and a forming compound is 0.01—0.09 ppm (see Table 1), and only for the signal NH(5) it reaches 0.13 ppm. The differences in chemical shifts of ^{13}C signals for these compounds does not exceed 1 ppm, except for the signal of C(6) (~3 ppm) (see Table 1). The data obtained allow us to assign to the emerged compound **5b** the structure of 2*R**,6*S**,11*R** diastereomer (see Schemes 1 and 2). Similar picture with the appearance of diastereomer **6b** is observed for the solution of diastereomer **6a** in DMSO-d_6.

The NMR spectra show that yet another compounds formed upon standing of solutions of the individual diastereomers **5a** and **6a** in DMSO-d_6 are the corresponding 4-(5-R-2-hydroxyphenyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-ones **7** (R = Me) and **8** (R = Br), whose structural identification is obvious enough and confirmed by plenty of literature examples.[18]

Scheme 2



With time, solutions of the individual diastereomers in DMSO form an equilibrium mixture, consisting of the corresponding two diastereomers and dihydropyrimidinone. The ratios of isomers in the mixtures formed remain unchanged upon standing for a month and longer (Table 2).

Table 2. Isomerization of individual diastereomers **3a**, **5a**, and **6a**

Compound	Solvent	Isomers	*t**	Ratio of isomers (%)**
3a	DMF-d_7	**3a** : **3b** : **4**	10 min	99 : <1 : <1[18]
			24 h	16 : 10 : 74[18]
3a	DMSO-d_6	**3a** : **3b** : **4**	10 min	26 : 3 : 71
			30 min	5 : 4 : 91
5a	DMSO-d_6	**5a** : **5b** : **7**	12 min	96 : 1 : 3
			2 days	32 : 4 : 64
			5 days	10 : 6: 84
			9 days	7 : 6 : 87
6a	DMSO-d_6	**6a** : **6b** : **8**	10 min	94 : 4 : 2
			1 h	7 : 2 : 91
			3 h	2 : 2 : 96

* Time after dissolution.

** Ratio of isomers in the mixture was calculated based on the ^{1}H NMR spectra from relative intensities of the signals for atoms H(6)/H(11) of diastereomers **3**, **5**, **6** and the signals for atoms H(4) of compounds **4**, **7**, **8**, respectively.

The rate of isomerization of compounds decreases in the order **3a** > **6a** > **5a**, that allows us to draw a conclusion on a sequential decrease in the effect of substituents R (H > Br > Me) (see Table 2).

It is seen from the data in Table 2 that during the process of isomerization of individual diastereomers **3a**, **5a**, and **6a** in aprotic dipolar solvents and setting the equilibrium, the amount of the starting diastereomers in the mixture decreases to 2—7%, whereas the amount of forming diastereomers **3b**, **5b**, and **6b** does not exceed 6% (in DMSO-d_6). Dihydropyrimidinones **4**, **7**, and **8** become the major components of the mixtures (up to 70—96%). The data obtained confirm the earlier observation[18] that in highly polar aprotic media the C(2)—O bond of the oxadiazocine ring in 11-nitro-2,6-methanobenzoxadiazocines is easily cleaved, whereas 4-(2-hydroxyaryl)dihydropyrimidinones formed in this case are stabilized due to the solvation of the aromatic hydroxy group by the dipolar molecules of solvents.

Attempted isolation of dihydropyrimidinones **4**, **7**, and **8** from the equilibrium mixtures by dilution of the solutions with water failed. After the yellow solutions of dihydropyrimidinones in DMSO were poured into a tenfold amount of water, the color of the solutions gradually became paler, which was accompanied by a slow formation of a white precipitate. According to the NMR spectra, this precipitate was a three-component mixture of the same isomers, but with another ratio. Since benzoxadiazocines and dihydropyrimidinones differ little in the solubility, it can be suggested that the composition of these precipitates characterizes the changes taking place in dilute aqueous DMSO solutions. For each mixture, the equilibrium was shifted to the side of *O*-cyclic compounds: 91% for **3a** + **3b**, 98% for **5a** + **5b**, 76% for **6a** + **6b**, with predominance in the mixtures of diastereomers **3a** and **6a** over diastereomers **3b** and **6b** and virtually equal amounts of diastereomers **5a** and **5b** (Table 3; see Fig. 1, *c*, *d*; 2, *d*). The DMSO molecules in aqueous media possess lower solvation affinity to the aromatic hydroxy group, that facilitates the oxa-Michael-type addition of the latter to the activated double bond of dihydropyrimidine framework. In this case, the ratio of diastereomers **a** and **b** considerably changes as compared to the products isolated from the Biginelli reaction formed during the acid-catalyzed cyclocondensation of salicylic aldehydes, nitroacetone, and urea.

The facts given above on the whole do not agree with the opinion suggested in the literature that the classic Biginelli reaction conditions involving substituted salicylic aldehydes lead to the initial formation of dihydropyrimidinone 4-(2-hydroxyaryl) derivatives with subsequent proceeding the oxa-Michael reaction.[10,11] At least, when nitroacetone is used in the reaction, the major products of the conversion of the intermediate carbocation **B** (see Scheme 1) are the corresponding dihydromethanobenzoxadiazocines **3**, **5**, and **6** predominantly as single diastereomers. Such an assumption on the step of the formation of the *O*-bridged structure as a single diastereomer of compound **2** (R = Me) was suggested earlier in the works.[9,10]

Table 3. Ratio of isomeric products of the Biginelli reaction and the products precipitated with water from the equilibrium mixtures in solutions in DMSO-d_6[a]

Mixture of isomers	Ratio of isomers		
	In the reaction products[b]	Upon standing in DMSO-d_6[c]	Upon precipitation with water[b]
3a : 3b : 4	99 : <1 : <1[d]	16 : 10 : 74[d]	71 : 20 : 9
5a : 5b : 7	96 : 1 : 3	7 : 6 : 87	48 : 50 : 2
6a : 6b : 8	94 : 4 : 2	2 : 2 : 96	51 : 25 : 24

[a] Ratios of isomers were calculated from the integral intensities of the signals for atoms H(6) or H(11) of diastereomers **3**, **5**, and **6** and the signals for atom H(4) of compounds **4**, **7**, and **8** in the ^{1}H NMR spectra.
[b] The spectra were recorded immediately after dissolution (10—12 min).
[c] For the time of standing, see Table 2.
[d] According to the ^{1}H NMR spectrum in DMF-d_7 (see Ref. 18).

It can be supposed that the selective formation of one diastereomer of nitromethanobenzoxadiazocinone occurs directly through the intermediate carbocation **B** and is kinetically controlled. The formation of the intermediate carbocation **C** on the way to the nitromethanobenzoxadiazocinone molecules can be also considered as a minor pathway (see Scheme 1).

In conclusion, the Biginelli condensation of substituted salicylic aldehydes, nitroacetone, and urea is of general character and leads to the formation of 8-substituted 2-methyl-11-nitro-5,6-dihydro-2*H*-methanobenzo[*g*]-[1,3,5]oxadiazocin-4(3*H*)-ones predominantly as a single diastereomer with configuration 2*R**,6*S**,11*S**.

The nitro group at the methylene bridge of methanobenzoxadiazocines promotes the formation of the equilibrium three-component mixtures in the aprotic dipolar solvents, *viz.*, two diastereomers (2*R**,6*S**,11*S** and 2*R**,6*S**,11*R**) of compounds **3**, **5**, and **6** and substituted dihydropyrimidinones **4**, **7**, and **8**, respectively with considerable predominance of the last mentioned compounds. The products isolated from the dilute aqueous DMSO (DMF) solution predominantly contain diastereomers of *O*-cyclic compounds **3**, **5**, and **6**.

Experimental

IR spectra were obtained on a Bruker Vector 22 spectrophotometer for samples in KBr and in perfluorinated mineral oil in the region 4000—2600 cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400.13 (^{1}H) and

100.61 (^{13}C) MHz) in DMSO-d_6 and DMF-d_7, using residual signals of DMSO (δ_H 2.50, δ_C 39.50) and DMF (δ_H 2.74, δ_C 30.10) as references. High resolution mass spectra were measured on a DFS Thermo Electron Corporation instrument (EI, 70 eV, direct injection of samples in source of ions). Electrospray ionization technique (ESI) was used for compound **3a** in solution in MeOH on a Bruker Daltonics micro TOF-Q instrument.

X-ray diffraction analysis of compound **5a** was performed on a Bruker Kappa Apex II CCD X-ray diffractometer using MoKα irradiation (0.71073 Å) with graphite monochromator. Single crystals were prepared by crystallization of compound from ethanol.

Compounds **3b**, **4**, **5b**, **6b**, **7**, and **8** were not isolated in the pure form, their identification was inferred from ^{1}H and ^{13}C NMR spectra for the mixtures of different compositions. Nitroacetone was obtained according to the known procedures[20,21]. Description of the synthesis, analytical and spectral data for compound **3a** are given in the work.[18]

Condensation of nitroacetone, 5-R-salicylic aldehydes, and urea (general procedure). A mixture of nitroacetone (12.5 mmol), substituted salicylic aldehyde (12 mmol), urea (25 mmol), ethanol (25 mL), and concentrated HCl (1.25 mL) was heated in a water bath at 95 °C. Then, the mixture was cooled , a precipitate formed was filtered off, washed with water, dried, and recrystallized from ethanol.

2-Methyl-11-nitro-5,6-dihydro-2*H*-2,6-methanobenzo[*g*]-[1,3,5]oxadiazocin-4(3*H*)-one (3a)[18]. MS (ESI), *m/z*: 250.08 [M + H], 272.06 [M + Na]$^+$, 521.14 [2 M + Na]$^+$. $C_{11}H_{11}N_3O_4$. Calculated: 249.07 [M], 250.08 [M + H], 272.06 [M + Na], 521.13 [2 M + Na].

(2*R,6*S**,11*S**)-Diastereomer 3a.** ^{1}H NMR (DMSO-d_6), δ (the mixture was composed of **3a** (71%) + **3b** (20%) + **4** (9%)): 1.79 (s, 3 H, CH_3, **3a** + **3b**); 4.86 (dd, 1 H, H(6), $J_{H(6),H(11)}$ = 3.3 Hz, $J_{H(6),H(5)}$ = 4.6 Hz); 5.67 (d, 1 H, H(11), $J_{H(11),H(6)}$ = 3.3 Hz); 6.85 (d, 1 H, H(10), $J_{H(10),H(9)}$ = 8.1 Hz); 6.99 (t, 1 H, H(8), $J_{H(8),H(7)}$ = 7.8 Hz; $J_{H(8),H(9)}$ = 7.8 Hz); 7.24—7.28 (m, 2 H, H(7), H(9), **3a** + **3b**); 7.56 (d, 1 H, NH(5), $J_{H(5),H(6)}$ = 4.6 Hz); 8.02 (s, 1 H, NH(3)). ^{13}C NMR (DMSO-d_6), δ: 22.97 (Me), 49.27 (C(6)), 79.13 (C(11)), 82.48 (C(2)), 116.68 (C(10)), 121.43 (C(8)), 124.23 (C(6a)), 129.00 (C(9)), 130.03 (C(7)), 149.81 (C(4)), 153.78 (C(10a)).

(2*R,6*S**,11*R**)-Diastereomer 3b.** ^{1}H NMR (DMSO-d_6), δ (the mixture was composed of **3a** (71%) + **3b** (20%) + **4** (9%)): 1.79 (s, 3 H, Me, **3b** + **3a**); 4.76 (dd, 1 H, H(6), $J_{H(6),H(11)}$ = 2.7 Hz, $J_{H(6),H(5)}$ = 5.2 Hz); 5.58 (d, 1 H, H(11), $J_{H(11),H(6)}$ = 2.7 Hz); 6.82 (d, 1 H, H(10), $J_{H(10),H(9)}$ = 8.3 Hz); 7.01 (dt, 1 H, H(8), $J_{H(8),H(10)}$ = 1.0 Hz, $J_{H(8),H(7)}$ = 7.6 Hz, $J_{H(8),H(9)}$ = 7.6 Hz); 7.18—7.28 (m, 2 H, H(7), H(9), **3b** + **3a**); 7.68 (dd, 1 H, NH(5), $J_{H(5),H(6)}$ = 5.2 Hz, $J_{H(5),H(3)}$ = 2.1 Hz); 7.91 (d, 1 H, NH(3), $J_{H(3),H(5)}$ = 2.1 Hz). ^{13}C NMR (DMSO-d_6), δ: 24.06 (Me), 46.32 (C(6)), 80.01 (C(11)), 81.83 (C(2)), 115.75 (C(10)), 118.76 (C(8)), 123.61 (C(6a)), 128.37 (C(9)), 131.33 (C(7)), 147.63 (C(4)), 154.57 (C(10a)).

4-(2-Hydroxyphenyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-one (4). ^{1}H NMR (DMSO-d_6), δ (the content in the mixture 75%): 2.48 (s, 3 H, Me); 5.71 (d, 1 H, H(4), $J_{H(4),H(3)}$ 3.0 Hz); 6.74 (dt, 1 H, H (11), $J_{H(11),H(9)}$ = 1.0 Hz, $J_{H(11),H(10)}$ = = 7.5 Hz, $J_{H(11),H(12)}$ = 7.5 Hz); 6.81(d, 1 H, H(9), $J_{H(9),H(10)}$ = 7.5 Hz); 7.06 (dd, 1 H, H(12), $J_{H(12),H(10)}$ = 1.5 Hz, $J_{H(12),H(11)}$ = 7.5 Hz); 7.10 (dt, 1 H, H(10), $J_{H(10),H(12)}$ = 1.5 Hz, $J_{H(10),H(9)}$ = 7.5 Hz, $J_{H(10),H(11)}$ = 7.5 Hz); 7.84 (br.s, 1 H, NH(3)); 9.76 (s, 1 H, OH); 9.96 (s, 1 H, NH(1)). ^{13}C NMR (DMSO-d_6), δ: 19.45 (Me), 50.81 (C(4)), 115.77 (C(9)), 118.78 (C(11)), 121.91 (C(5)), 127.51 (C(7)), 128.33 (C(10)), 128.99 (C(12)), 150.59 (C(6)), 151.06 (C(2)), 155.21 (C(8)).

2,8-Dimethyl-11-nitro-5,6-dihydro-2*H*-2,6-methanobenzo-[*g*][1,3,5]oxadiazocin-4(3*H*)-one (5). The yield was 71%, m.p. 241—243 °C (EtOH). IR (KBr), ν/cm^{-1}: 3334, 3232 (NH), 1697 (C=O), 1555, 1371 (NO_2), 1249 (C—O—C). MS, *m/z* ($I_{rel.}$ (%)): 263 [M$^+$] (89), 246 [M$^+$ – OH] (64), 217 [M$^+$ – NO_2] (55), 216 [M$^+$ – HNO_2] (61), 203 (38), 174 (73), 162 (78), 156 (19), 147 (84), 133 (100), 111 (51), 105 (41). Found (%): C, 54.76; H, 4.91; N, 15.86. $C_{12}H_{13}N_3O_4$. Calculated (%): C, 54.75; H, 4.98; N, 15.96. HRMS. Found: *m/z* 263.0903. $C_{12}H_{13}N_3O_4$. Calculated: M = 263.0901.

(2*R,6*S**,11*S**)-Diastereomer 5a.** ^{1}H NMR (DMSO-d_6), δ (10 min after dissolution, 100%): 1.76 (s, 3 H, Me(2)); 2.23 (s, 3 H, Me(8)); 4.77 (dd, 1 H, H(6), $J_{H(6),H(11)}$ = 3.3 Hz, $J_{H(6),H(5)}$ = 4.5 Hz); 5.53 (d, 1 H, H(11), $J_{H(11),H(6)}$ = 3.3 Hz); 6.74 (d, 1H, H(10), $J_{H(10),H(9)}$ = 8.0 Hz); 6.98—7.04 (br.s, 1 H, H(7)); 7.06 (dd, 1 H, H(9), $J_{H(9),H(10)}$ = 8.0 Hz, $J_{H(9),H(7)}$ = 1.9 Hz); 7.50 (d, 1 H, NH(5), $J_{H(5),H(6)}$ = 4.5 Hz), 7.96 (s, 1 H, NH(3)). ^{13}C NMR (DMSO-d_6), δ: 20.08 (Me(2)), 22.95 (Me(8)), 49.32 (C(6)), 79.30 (C(11)), 82.32 (C(2)), 116.48 (C(10)), 123.93 (C(6a)), 129.02 (C(9)), 130.22 (C(8)), 130.53 (C(7)), 147.55 (C(4)), 153.79 (C(10a)).

(2*R,6*S**,11*R**)-Diastereomer 5b.** ^{1}H NMR (DMSO-d_6), δ (the content of the diastereomer in the mixture 50%): 1.77 (s, 3 H, Me(2)); 2.25 (s, 3 H, Me(8)); 4.70 (dd, 1 H, H(6), $J_{H(6),H(11)}$ = 2.4 Hz, $J_{H(6),H(5)}$ = 4,7 Hz); 5.55 (d, 1 H, H(11), $J_{H(11),H(6)}$ = 2.4 Hz); 6.71 (d, 1 H, H(10), $J_{H(10),H(9)}$ = 8.1 Hz); 6.98—7.04 (m, 1 H, H(9)); 7.04—7.10 (m, 1 H, H(7)); 7.63 (dd, 1 H, NH(5), $J_{H(5),H(6)}$ = 4.7 Hz, $J_{H(5),H(3)}$ = 2.1 Hz); 7.87 (d, 1 H, NH(3), $J_{H(3),H(5)}$ = 2.1 Hz). ^{13}C NMR (DMSO-d_6,), δ: 20.19 (Me(2)), 22.95 (Me(8)), 46.36 (C(6)), 80.07 (C(11)), 81.75 (C(2)), 116.51 (C(10)), 123.93 (C(6a)), 129.14 (C(9)), 129.67 (C(7)), 130.61 (C(8)), 147.63 (C(4)), 154.61 (C(10a)).

8-Bromo-2-methyl-11-nitro-2*H*-2,6-methanobenzo[*g*]-[1,3,5]oxadiazocin-4(3*H*)-one (6). The reaction time was 2 h, the yield was 48%, m.p. 244—246 °C (EtOH). IR (KBr), ν/cm^{-1}: 3419, 3238 (NH); 1699 (C=O); 1556, 1367 (NO_2); 1246 (C—O—C). IR (Nujol), ν/cm^{-1}: 3334, 3196 (NH); 3072 (CH_{arom}). MS, *m/z* ($I_{rel.}$ (%)): 329, 327 [M$^+$] (57, 59); 312, 310 [M$^+$ – OH] (34, 36); 283, 281 [M$^+$ – NO_2] (30, 36); 282, 280 [M$^+$ – HNO_2] (31, 32); 269, 267 [M$^+$ – 60] (24, 25); 240, 238 [M$^+$ – 89] (47, 47); 228, 226 [M$^+$ – 101] (39, 41); 156 (26); 132 (80); 111 (38); 102 (28); 42 (100). Found (%): C, 39.84; H, 2.69; Br, 24.56; N, 12.76. $C_{11}H_{10}BrN_3O_4$. Calculated (%): C, 40.26; H, 3.07; Br, 24.36; N, 12.81. HRMS. Found: *m/z* 326.9855. $C_{11}H_{10}BrN_3O_4$. Calculated: M = 326.9849.

(2*R,6*S**,11*S**)-Diastereomer 6a.** ^{1}H NMR (DMSO-d_6), δ: (the content of the isomer 93%): 1.78 (s, 3 H, Me); 4.93 (dd, 1 H, H(6), $J_{H(6),H(11)}$ = 2.7 Hz, $J_{H(6),H(5)}$ = 3.7 Hz); 5.70 (d, 1 H, H(11), $J_{H(11),H(6)}$ = 2.7 Hz); 6.85 (d, 1 H, H(10), $J_{H(10),H(9)}$ = 8.6 Hz); 7.38–7.47 (m, 2 H, H(9), H(7)); 7.54 (d, 1 H, NH(5), $J_{H(5),H(6)}$ = 3.7 Hz); 8.11 (s, 1 H, NH(3)). ^{13}C NMR (DMSO-d_6), δ: 22.87 (Me); 48.74 (C(6)); 78.63 (C(11)); 82.91 (C(2)); 112.51 (C(8)); 119.14 (C(10)); 126.66 (C(6a)); 131.38, 132.63 (C(7), C(9)); 149.27 (C(4)); 153.67 (C(10a)). ^{13}C NMR (DMF-d_7), δ (the content was 83% in the mixture of three isomers): 23.42 (Me); 50.21 (C(6)); 79.77 (C(11)); 83.96 (C(2)); 113.40 (C(8)); 119.87 (C(10)); 127.59 (C(6a)); 132.12, 133.44 (C(7), C(9)); 150.37 (C(4)); 154.46 (C(10a)).

(2*R,6*S**,11*R**)-Diastereomer 6b.** ^{1}H NMR (DMSO-d_6), δ (the content in the mixture 25%): 1.77 (s, 3 H, Me); 4.82 (dd, 1 H,

H(6), $J_{H(6),H(11)}$ = 2.5 Hz, $J_{H(6),H(5)}$ = 5.0 Hz); 5.63 (d, 1 H, H(11), $J_{H(11),H(6)}$ = 2.5 Hz); 6.82 (d, 1 H, H(10), $J_{H(10),H(9)}$ = = 8.6 Hz); 7.38—7.47 (m, 2 H, H(7), H(9)); 7.63 (dd, 1 H, NH(5), $J_{H(5),H(6)}$ = 5.0 Hz, $J_{H(5),H(3)}$ = 2.2 Hz); 8.00 (d, 1 H, NH(3), $J_{H(3),H(5)}$ = 2.2 Hz). ^{13}C NMR (DMF-d_7), δ (the content 7% in the mixture of three isomers): 23.35 (CH_3); 50.12 (C(6)); 79.94 (C(11)); 83.88 (C(2)); 113.29 (C(8)); 119.92 (C(10)); 127.25 (C(6a)); 132.12, 133.44 (C(7), C(9)); 150.42 (C(4)); 154.39 (C(10a)).

4-(2-Hydroxy-5-methylphenyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-one (7). ^{1}H NMR (DMSO-d_6), δ (the content in the mixture 87%): 2.16 (s, 3 H, Me); 2.48 (s, 3 H, Me); 5.65 (d, 1 H, H(4), $J_{H(4),H(3)}$ = 3.0 Hz); 6.69 (d, 1 H, H(9), $J_{H(9),H(10)}$ = 8.1 Hz); 6.83 (d, 1 H, H(12), $J_{H(12),H(10)}$ = 2.0 Hz); 6.90 (dd, 1 H, H(10), $J_{H(10),H(12)}$ = 2.0 Hz, $J_{H(10),H(9)}$ = 8.1 Hz); 7.81 (s, 1 H, NH(3)); 9.51 (s, 1 H, OH); 9.95 (s, 1 H, NH(1)). ^{13}C NMR (DMSO-d_6), δ: 19.52 (Me); 20.18 (Me); 50.91(C(4)); 115.67 (C(9)); 121.85 (C(5)); 127.10, 127.23 (C(7), C(11)); 128.65 (C(10)); 129.34 (C(12)); 150.51 (C(6)); 150.99 (C(2)); 152.94 (C(8)).

4-(5-Bromo-2-hydroxyphenyl)-6-methyl-5-nitro-3,4-dihydropyrimidin-2(1*H*)-one (8). ^{1}H NMR (DMSO-d_6), δ (the content in the mixture 96%): 2.47 (s, 3 H, Me); 5.64 (d, 1 H, H(4), $J_{H(4),H(3)}$ = 2.7 Hz); 6.77 (d, 1 H, H(9), $J_{H(9),H(10)}$ = 8.6 Hz); 7.19 (d, 1 H, H(12), $J_{H(12),H(10)}$ = 2.0 Hz); 7.27 (dd, 1 H, H(10), $J_{H(10),H(12)}$ = 2.0 Hz, $J_{H(10),H(9)}$ = 8.6 Hz); 7.93 (d, 1 H, NH(3), $J_{H(3),H(4)}$ = 2.7 Hz); 10.04 (s, 1 H, OH); 10.14 (s, 1 H, NH(1)). ^{13}C NMR (DMSO-d_6), δ: 19.59 (CH_3), 51.25(C(4)), 109.72 (C(11)), 118.06 (C(9)), 121.20 (C(5)), 130.04 (C(7)), 131.20 (C(10)), 131.58 (C(12)), 150.38 (C(6)), 151.52 (C(2)), 154.82 (C(8)).

Isomerization of benzoxadiazocines in solutions (general procedure). Method A. A solution of benzoxadiazocine (30 mg) in DMSO-d_6 (or DMF-d_7) (0.5 mL), which was colorless at the moment of dissolution, upon standing at ~20 °C rapidly acquired yellow color of various intensity depending on compound taken. Registration of spectra began 10—12 min after dissolution of the sample. ^{1}H NMR spectra were regularly recorded while changes were observed in solutions until the spectra of the mixtures showed a constant ratio of isomers, indicating that an equilibrium was reached. Such a solution was poured into water (5 mL). A precipitate was slowly formed upon standing. Usually, a solution was allowed to stand for several days to maximize amount of isolated precipitate. The precipitate was filtered off, washed with water, and dried. The yield of the product was 80—85% based on the starting weight. Then, the precipitate was dissolved in DMSO-d_6 to record ^{1}H NMR spectrum.

Method B. A solution of benzoxadiazocine (100 mg) in DMSO (5 mL) was allowed to stand at ~20 °C. The changes of the solution color and further manipulations with it and precipitate formed upon pouring into water were similar to those described in method **A**.

Crystallographic data for compound 5a: at 150 K, $C_{12}H_{13}N_3O_4$, M = 263.25, monoclinic crystal system, space group $P2_1/n$, a = = 7.3919(7), b = 18.4971(17), c = 9.3583(9) Å, β = 108.531(3)°, V = 1213.2(2) Å^3, Z = 4, d_{calc} = 1.441 g cm^{-3}, μ = 0.110 mm^{-1}, region of scanning 2θ < 55°, number of measured reflections 20706, number of independent reflections 2749 (R_{int} = 0.0562), number of observed reflections 2126 with $I \geq 2\sigma(I)$, number of refined parameters 178, $R_1(I \geq 2\sigma(I))$ = 0.0621, wR_2 = 0.1678, S = 1.164 on all the reflections. Absorption was included using the SADABS program (T_{min}/T_{max} = 0.803/0.970). The structure was solved by direct method. Positional and temperature factors of nonhydrogen atoms were refined in anisotropic approximation using the full-matrix least squares method. Amine hydrogen atoms were localized from the differential syntheses and refined in isotropic approximation, other hydrogen atoms were refined using a riding model. All the calculations were performed using the SHELXTL software. Atomic coordinates and their temperature parameters were deposited with the Cambridge Structural Database (CCDC No. 949516).

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