Russian Journal of Organic Chemistry, Vol. 38, No. 5, 2002, pp. 738–743. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 5, 2002, pp. 775–779.

Five-Membered 2,3-Dioxo Heterocycles: XLIV.* Reaction of 3-Aroyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]-quinoxaline-1,2,4-triones with *o*-Phenylenediamines**

A. N. Maslivets[1], I. V. Mashevskaya[1], S. V. Kol'tsova[2], A. V. Duvalov[1], and V. P. Feshin[2]

[1] *Perm State University, ul. Bukireva 15, Perm, 614600 Russia*
e-mail: info@psu.ru

[2] *Institute of Technical Chemistry, Ural Division, Russian Academy of Sciences, Perm, Russia*

Received March 11, 2001

Abstract—The reaction of (*Z*)-3-phenacylidene-1,2,3,4-tetrahydroquinoxalin-2-ones with oxalyl chloride gives 3-aroyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinoxaline-1,2,4-triones which react with *o*-phenylenediamine to afford 8-aryl-6,7,9,14,15,16-hexahydroquinoxalino[1,2-*a*]pyrrolo[2,3-*b*][1,5]benzodiazepine-6,7,15-triones.

The structure of products formed by reaction of *o*-phenylenediamine with substituted 2,3-dihydropyrrole-2,3-diones fused to aza heterocycles through the *a* bond is determined mainly by the substituent in position *4* of the dihydropyrrole ring. Reactions of *o*-phenylenediamine with 4-unsubstituted, 4-dialkylcarbamoyl-, and 4-phenyl-2,3-dihydropyrrole-2,3-diones [2–4] fused to isoquinoline [2, 3], phenanthridine [3], or 1,3-oxazine ring [4] begin with nucleophilic attack on the carbonyl group in position *2* (path *a*) or *3* (path *b*) of the pyrrole ring with subsequent recyclization either to quinoxalin-2-ones and then to pyrroloquinoxalines (path *a*) or to pyrrolobenzimidazoles (path *b*) [2–4]. By contrast, 4-aroyl-2,3-dihydropyrrole-2,3-diones, fused through the *a* bond to 2-oxo-1,4-benzoxazine ring, react with *o*-phenylenediamine via primary nucleophilic addition at C^5 of the pyrrole ring, followed by recyclization with opening of the benzoxazine ring [5].

In continuation of our studies on nucleophilic transformations of 4-acyl-2,3-dihydropyrrole-2,3-diones, fused through the *a* bond to 2-oxoquinoxaline moiety, namely 3-aroyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinoxaline-1,2,4-triones **Ia**–**Ig** [6], the latter were brought into reaction with *o*-phenylenediamine. Taking into account our previous data on the direction of primary nucleophile addition to compounds **I** (at C^5 of the pyrrole ring) and on reactions of monocyclic substituted 4-acyl-2,3-dihydropyrrole-2,3-diones with the same nucleophile [7], we expected formation of different products. Therefore, we performed a detailed study of the reaction, and its results were interpreted with the aid of quantum-chemical methods.

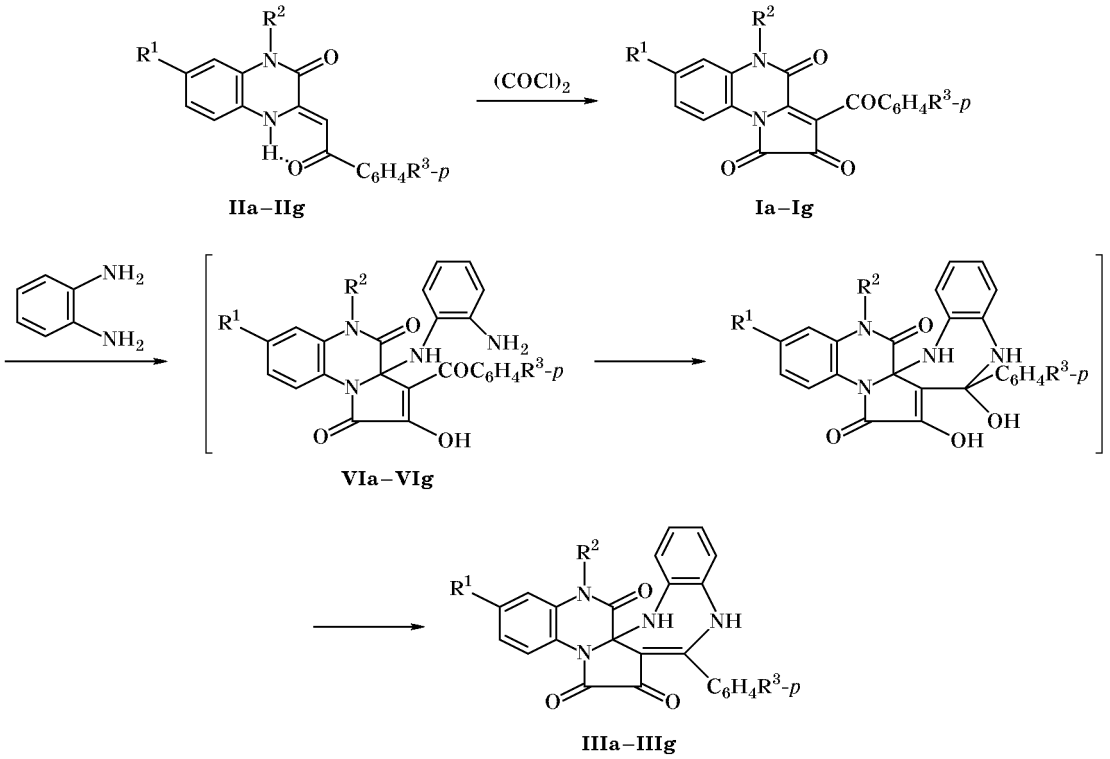
Compounds **Ic**, **Id**, and **Ig** were synthesized by the procedure described in [1] from (*Z*)-3-phenacylidene-1,2,3,4-tetrahydroquinoxalin-2-ones **IIc**, **IId**, and **IIg**, respectively, and oxalyl chloride. 3-Aroyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinoxaline-1,2,4-triones **Ia**–**Ig** reacted with *o*-phenylenediamine in anhydrous dioxane on heating for a short time (1–5 min) under reflux. The products were 8-aryl-6,7,9,14,15,16-hexahydroquinoxalino[1,2-*a*]pyrrolo[2,3-*b*][1,5]benzodiazepine-6,7,15-triones **IIIa**–**IIIg** (Scheme 1, Table 1) which were formed in almost quantitative yields via successive nucleophilic attack by the amino groups of the reagent on C^5 and carbonyl carbon atom of the aroyl fragment in position *4* of the pyrrole ring. The same ptoducts were also obtained when the reaction was carried out at 0°C, and their yield did not change to an appreciable extent.

Compounds **IIIa**–**IIIg** are dark red high-melting crystalline substances, which are almost insoluble in common organic solvents, poorly soluble in DMF and DMSO, and insoluble in water. They give a negative

* For communication XLIII, see [1].

** This study was financially supported by the Russian Foundation for Basic Research (projects nos. 01-03-32641 and 02-03-96411).

Scheme 1.



$R^1 = R^2 = R^3 = H$ (**a**); $R^1 = R^2 = H$, $R^3 = Me$ (**b**); $R^1 = R^2 = H$, $R^3 = OMe$ (**c**); $R^1 = R^2 = H$, $R^3 = NO_2$ (**d**); $R^1 = R^3 = H$, $R^2 = Ph$ (**e**); $R^1 = H$, $R^2 = Ph$, $R^3 = Me$ (**f**); $R^1 = NO_2$, $R^2 = R^3 = H$ (**g**).

Table 1. Yields, melting points, and elemental analyses of compounds **Ic**, **Id**, **Ig**, **IIc**, **IId**, **IIg**, and **IIIa**–**IIIj**

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
Ic	92	203–205 (dichloroethane)	65.69	3.41	7.99	$C_{19}H_{12}N_2O_5$	65.52	3.45	8.05
Id	87	290–292 (dichloroethane)	59.78	2.42	11.04	$C_{18}H_9N_3O_6$	59.50	2.48	11.57
Ig	83	267–269 (dichloroethane)	59.25	2.43	11.17	$C_{18}H_9N_3O_6$	59.50	2.48	11.57
IIc	84	238–240 (DMSO)	69.40	4.73	9.31	$C_{17}H_{14}N_2O_3$	69.45	4.80	9.53
IId	75	298–299 (DMSO)	62.04	3.37	13.41	$C_{16}H_{11}N_3O_4$	62.20	3.59	13.59
IIg	82	294–296 (DMSO)	62.97	3.48	13.04	$C_{16}H_{11}N_3O_4$	62.20	3.59	13.59
IIIa	95	385–387 (DMF)	70.76	3.90	13.62	$C_{24}H_{16}N_4O_3$	70.75	3.93	13.64
IIIb	89	369–370 (DMF)	71.27	4.24	13.17	$C_{25}H_{18}N_4O_3$	71.25	4.26	13.19
IIIc	92	312–314 (DMSO)	68.45	3.20	12.87	$C_{25}H_{18}N_4O_4$	68.02	3.23	12.90
IIId	85	328–330 (DMSO)	64.63	3.01	15.06	$C_{24}H_{15}N_5O_5$	64.66	3.02	15.09
IIIe	93	317–319 (DMF)	74.51	4.12	11.47	$C_{30}H_{20}N_4O_3$	74.53	4.14	11.49
IIIf	80	315–317 (DMSO)	74.67	4.40	11.23	$C_{31}H_{22}N_4O_3$	74.70	4.42	11.25
IIIg	90	338–340 (DMF)	64.64	2.99	15.07	$C_{25}H_{14}N_5O_5$	64.66	3.02	15.09
IIIh	87	302–304 (DMSO)	63.56	3.29	15.43	$C_{24}H_{15}N_5O_5$	63.58	3.31	15.45
IIIi	92	299–301 (DMSO)	69.12	2.95	13.00	$C_{31}H_{16}N_5O_5$	69.14	2.97	13.01
IIIj	79	305–307 (DMSO)	63.79	2.55	14.40	$C_{31}H_{15}N_6O_7$	63.81	2.57	14.41

Table 2. IR and ^{1}H NMR spectra of compounds **Ic**, **Id**, **Ig**, **IIc**, **IId**, **IIg**, and **IIIa**–**IIIg**

Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm
Ic	3080 (N^5–H), 1774 (C^1=O), 1742 (C^2=O), 1698 (C^4=O), 1636 (3-C=O)	
Id	3070 (N^5–H), 1783 (C^1=O), 1740 (C^2=O), 1699 (C^4=O), 1666 (3-C=O)	
Ig	3115 (N^5–H), 1789 (C^1=O), 1741 (C^2=O), 1660 (C^4=O), 1625 (3-C=O)	
IIc	3160 (N^1–H), 3040 br (N^4–H), 1687 (C^2=O), 1606 br (CH–C=O)	3.77 s (3H, CH_3O), 6.86 s (1H, CH=), 6.85–7.97 m (8H, H_{arom}), 11.81 s (1H, 1-H), 13.45 s (1H, 4-H)
IId	3200 (N^1–H), 3040 br (N^4–H), 1698 (C^2=O), 1608 br (CH–C=O)	6.86 s (1H, CH=), 7.10–7.50 m (4H, H_{arom}), 8.30 d (4H, H_{arom}, *AB* system), 12.10 s (1H, 1-H), 13.93 s (1H, 4-H)
IIg	3160 (N^1–H), 3020 br (N^4–H), 1701 (C^2=O), 1610 br (CH–C=O)	
IIIa	3050 br (N–H); 1685 (C^6=O); 1670, 1656 (C^7=O, C^{15}=O)	6.90 s (1H, 14-H), 7.15–7.80 m (11H, H_{arom}), 7.96 d (2H, *o*-H in Ph, *J* = 7.3 Hz), 12.58 br.s (2H, 9-H, 16-H)
IIIb	3110 br (N–H), 1680 (C^6=O), 1670 (C^7=O, C^{15}=O)	2.35 s (3H, CH_3), 6.87 s (1H, 14-H), 7.21–7.57 m (10H, H_{arom}), 7.85 d (2H, *o*-H in Tol, *J* = 8.2 Hz), 12.55 br.s (2H, 9-H, 16-H)
IIIc	3120 br (N–H), 1670 (C^6=O), 1660 (C^7=O, C^{15}=O)	3.65 s (3H, CH_3O), 6.92 s (1H, 14-H), 7.05–7.92 m (12H, H_{arom}), 12.11 br.s (2H, 9-H, 16-H)
IIId	3110 br (N–H), 1694 (C^6=O), 1671 (C^7=O, C^{15}=O)	
IIIe	3040 br (N–H); 1698 (C^6=O); 1686, 1670 (C^7=O, C^{15}=O)	
IIIf	3070 br (N–H), 1686 (C^6=O), 1665 (C^7=O, C^{15}=O)	2.36 s (3H, CH_3), 6.65 d (1H, *o*-H in Ph, *J* = 7.3 Hz), 6.90 s (1H, 14-H), 7.10–7.67 m (14H, H_{arom}), 7.90 d (2H, *o*-H in Tol, *J* = 8.2 Hz, 12.55 br.s (2H, 9-H, 16-H)
IIIg	3080 br (N–H), 1697 (C^6=O), 1680 (C^7=O, C^{15}=O)	

test for enolic hydroxy group with an alcoholic solution of iron(III) chloride.

The IR spectra of compounds **IIIa**–**IIIg** (Table 2) contain absorption bands due to stretching vibrations of the NH groups (a broad band in the region 3040–3110 cm^{-1}) lactam C^6=O carbonyl group (1680–1698 cm^{-1}), and ketone C^7=O and amide carbonyl C^{15}=O groups (1656–1686 cm^{-1}). In the ^{1}H NMR spectra of **IIIa**–**IIIg** (Table 2) we observed signals from protons in the aromatic rings and CH_3 and CH_3O groups attahced thereto, a singlet from the secondary amino group proton $N^{14}H$ at δ 6.87–6.92 ppm, and a downfield broadened signal from protons of the amide group $N^{16}H$ (in **IIIa**–**IIIc**) and enamino group N^9 at δ 12.11–12.58 ppm. The position of the $N^{14}H$ signal is very consistent with our previous data for substituted 4-aroyl-5-arylaminopyrrol-2-ones, products of arylamine addition at C^5 of 4-aroyl-2,3-dihydropyrrole-2,3-diones [8].

The IR and ^{1}H NMR parameters of compounds **IIIa**–**IIIg** agree well with those reported for substituted 1-aryl-1,2,3,5,10,10a-hexahydropyrrolo[2,3-*b*]-[1,5]benzodiazepine-2,3-diones [7], which were obtained by reaction of *o*-phenylenediamine with monocyclic 4-acyl-1-aryl-2,3-dihydropyrrole-2,3-diones via successive nucleophilic attack first at C^5 and then at the acyl carbonyl carbon atom of the substituent in position *4*.

The UV spectra of 0.0003 M solutions of **IIIa**, **IIIb**, and **IIIe** in dioxane (see Experimental) are characterized by the presence of two absorption bands above 300 nm, λ_{max}, nm (log ε): **IIIa**: 341 (3.83), 432

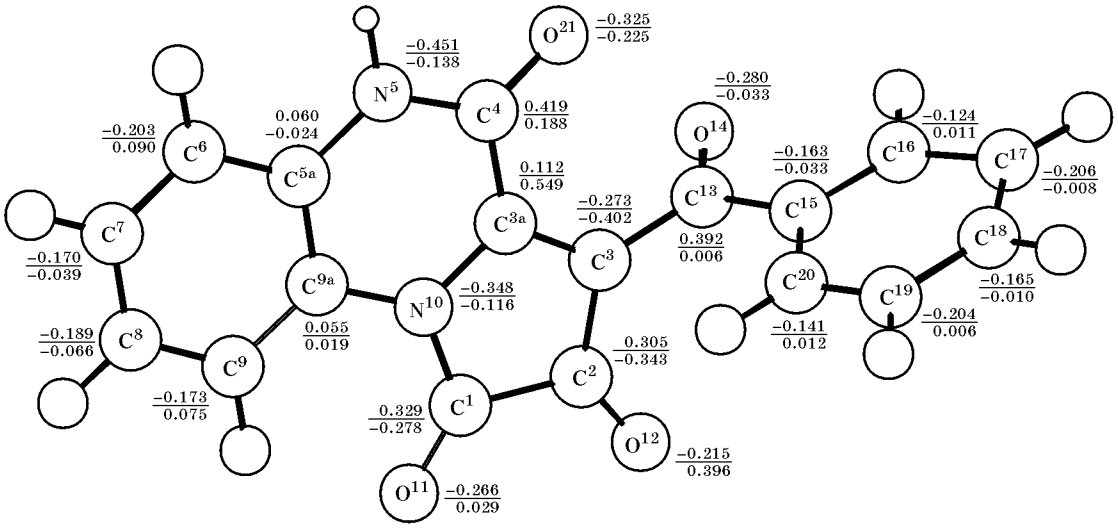
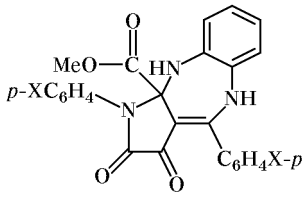
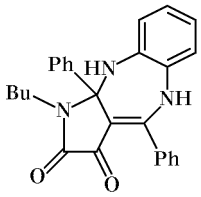


Fig. 1. Charges on atoms (in the numerator) and coefficients of $2p_z$-AO in the LUMO (in the denominator) of molecule **Ia**.

(3.81); **IIIb**: 348 (3.81), 428 (3.80); **IIIe**: 340 (3.78), 427 (3.77). The UV spectra of **IIIa**, **IIIb**, and **IIIe** are very similar to each other and also to those of model compounds, substituted 1,4-diaryl-10a-methoxycarbonyl-1,2,3,5,10,10a-hexahydropyrrolo[2,3-*b*][1,5]-benzodiazepine-2,3-diones **IVa**–**IVe** [6] and 1-butyl-4,10-diphenyl-1,2,3,5,10,10a-hexahydropyrrolo[2,3-*b*]-[1,5]benzodiazepine-2,3-dione (**V**). The structure of compound **V** was proved by the X-ray diffraction data [8]. Compounds **IVa**–**IVe** and **V** display two absorption bands in the UV spectra, λ_{max} 348–355 nm ($\log\varepsilon$ 3.85–3.88) and 417–418 nm ($\log\varepsilon$ 3.83–3.93) (**IVa**–**IVe**) [7]; 351 ($\log\varepsilon$ 3.76) and 460 nm ($\log\varepsilon$ 3.83) (**V**) [9].



IVa–IVe



V

IV, X = Y = H (**a**); X = H, Y = Me (**b**); X = Cl, Y = H (**c**); X = Br, Y = H (**d**); X = NO_2, Y = H (**e**).

In order to explain the direction of primary nucleophilic attack on compounds **Ia**–**Ig** we performed AM1 semiempirical quantum-chemical calculations of molecule **Ia** with full geometry optimization using GAUSSIAN-94W software [10]. The results are shown in Fig. 1. According to the calculations, the most electron-deficient atoms are C^1, C^2, C^4, and C^{13}, and the greatest contribution to the lowest unoccupied molecular orbital (LUMO) is that from $2p_z$-AO of C^{3a}. This means that just the latter atom should be attacked by nucleophile under conditions of orbital control.

Presumably, in the first reaction stage *o*-phenylenediamine adds at C^{3a} of pyrroloquinoxalinetriones **I** to give 3a-(*o*-aminophenylamino)-3-benzoyl-2-hydroxy-1,3a,4,5-tetrahydropyrrolo[1,2-*a*]quinoxaline-1,4-diones **VI**, as was reported in [1] for reactions of **I** with monofunctional nucleophiles. The subsequent nucleophilic attack by the second amino group can be directed at the carbonyl carbon atom of the heteroring (C^4) or aroyl fragment (C^{13}). Figure 2 shows the results of calculation of charges on atoms in molecule **VIa**, performed by the above procedure with full geometry optimization. It is seen that the C^{13} atom is the most electron-deficient; moreover, the contribution of its $2p_z$-AO to the LUMO is the largest. Obviously, these factors are responsible for the attack of C^{13} by the second amino group of *o*-phenylenediamine, which leads to closure of benzodiazepine ring.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in mineral oil. The ^{1}H NMR spectra were obtained on RYa-2310 (60 MHz), Bruker WP-80-54 (80 MHz), and Bruker AM-300 (400 MHz) spectrometers using DMSO-d_6 as solvent and HMDS or TMS as internal reference. The UV spectra were measured on a Specord UV-Vis instrument in dioxane. The mass spectrum was run on an MKh-1320 spectrometer

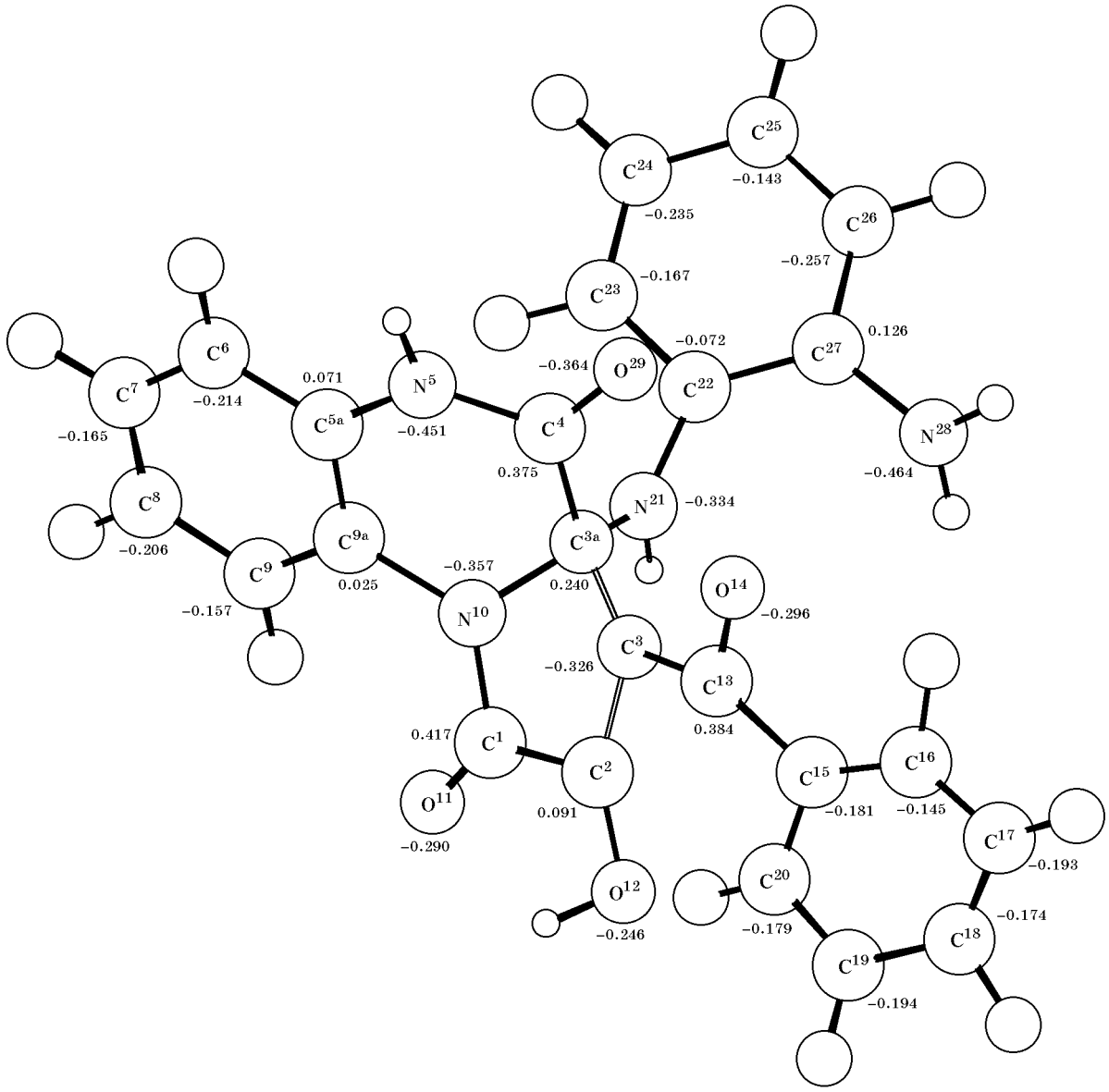


Fig. 2. Charges on atoms in molecule **VIa**.

(70 eV). The purity of the products was checked by TLC on Silufol plates; spots were visualized with iodine vapor.

3-Aroyl-1,2,4,5-tetrahydropyrrolo[1,5-*a*]quinoxaline-1,2,4-triones Ic, Id, and Ig. To a solution of 0.01 mol of compound **II** in 50 ml of dry chloroform we added a solution of 0.01 mol of oxalyl chloride in 10 ml of dry chloroform. The mixture was refluxed for 2 h, cooled, and the precipitate was filtered off.

8-Aryl-6,7,9,14,15,16-hexahydroquinoxalino-[1,2-*a*]pyrrolo[2,3-*b*][1,5]benzodiazepine-6,7,15-triones IIIa–IIIg. To a solution of 0.01 mol of compound **I** in 50 ml of anhydrous dioxane we added a solution of 0.01 mol of *o*-phenylenediamine in 20 ml of anhydrous dioxane. The mixture was refluxed for 3 min, and the precipitate was filtered off.

REFERENCES

1. Pimenova, E.V., Maslivets, A.N., Khamatgaleev, R.A., and Andreichikov, Yu.S., *Russ. J. Org. Chem.*, 1996, vol. 32, no. 9, pp. 1357–1360.
2. Mikhailovskii, A.G., Shklyaev, V.S., and Aleksandrov, B.B., *Khim. Geterotsikl. Soedin.*, 1990, no. 6, pp. 808–810.
3. Mikhailovskii, A.G. and Shklyaev, V.S., *Khim. Geterotsikl. Soedin.*, 1994, no. 7, pp. 946–949.

4. Kollenz, G., Kriwets, G., Ott, W., and Ziegler, E., *Justus Liebigs Ann. Chem.*, 1977, nos. 11–12, pp. 1964–1968.
5. Maslivets, A.N., Mashevskaya, I.V., and Andreichikov, Yu.S., *Russ. J. Org. Chem.*, 1995, vol. 31, no. 4, pp. 569–572.
6. Mashevskaya, I.V., Makhmudov, R.R., Aleksandrova, G.A., Golovnina, O.V., Duvalov, A.V., and Maslivets, A.N., *Khim.-Farm. Zh.*, 2001, vol. 35, no. 4, pp. 20–21.
7. Maslivets, A.N., Smirnova, L.I., Ivanenko, O.I., and Andreichikov, Yu.S., *Russ. J. Org. Chem.*, 1995, vol. 31, no. 4, pp. 563–568.
8. Maslivets, A.N., Smirnova, L.I., and Andreichikov, Yu.S., *Zh. Org. Khim.*, 1989, vol. 25, no. 8, pp. 1748–1753.
9. Terpetschnig, E., Ott, W., Kollenz, G., Peters, K., Peters, E.-N., and von Schnering, H.G., *Monatsh. Chem.*, 1988, vol. 119, no. 3, pp. 367–378.
10. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Gill, P.M.W., Johnson, B.G., Robb, M.A., Cheeseman, J.R., Keith, T., Petersson, G.A., Montgomery, J.A., Raghavachari, K., Al-Laham, M.A., Zakrzewski, V.G., Ortiz, J.V., Foresman, J.B., Cioslowski, J., Stefanov, B.B., Nanayakkara, A., Challacombe, M., Peng, C.Y., Ayala, P.Y., Chen, W., Wong, M.W., Andres, J.L., Replogle, E.S., Gomperts, R., Martin, R.L., Fox, D.J., Binkley, J.S., Defrees, D.J., Baker, J., Stewart, J.P., Head-Gordon, M., Gonzalez, C., and Pople, J.A., *Gaussian 94, Revision E.3*, Pittsburgh: Gaussian, 1995.