SYNTHESIS OF MACROHETEROCYCLIC COMPOUNDS ON THE BASIS OF 3-CHLORO-2-HYDRAZINOQUINOXALINE

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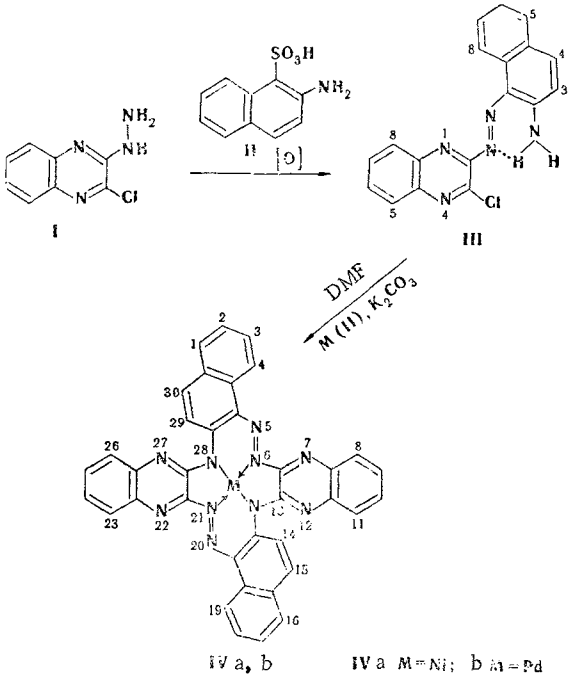
2-Amino-1-[(3-chloro-2-quinoxalinyl)azo]naphthalene was obtained by oxidative coupling of 3-chloro-2-hydrazinoquinoxaline with 2-aminonaphthalenesulfonic acid; cross self-cyclization of the product was used to synthesize macrocyclic compounds, viz., [1,2,5,8,9,12]hexaazacyclotetradecene derivatives. 4-[(3-Chloro-2-quinoxalinyl)azo]-5-chloro-3-methyl-1-phenylpyrazole was obtained by the reaction of the 4-(3-chloro-2-quinoxalinyl)hydrazone of 2,4-dihydro-5-methyl-2-phenyl-3H-pyrazole-3,4-dione with $POCl_3$. Reaction of this product with 2,2'-diaminoazobenzene under standard conditions gave [1,2,5,8,9,12]-hexaazacyclotetradecene derivatives.

The presence of a labile chlorine atom in o-chloroazo compounds obtained on the basis of 3-chloro-2-hydrazinoquinoxaline (I) [1-4] opens up possibilities for the synthesis of new macroheterocyclic compounds by cross self-cyclization with twofold nucleophilic replacement of the halogen atom by an arylamino group.

2-Amino-1-[(3-chloro-2-quinoxalinyl)azo]naphthalene (III) was obtained by oxidative coupling of I with 2-aminonaphthalene-1-sulfonic acid (II). Macrocyclic metal chelates IV were obtained via template self-cyclization via the scheme



IV a, b IV a M=Ni; b M=Pd

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TABLE 1. PMR Spectrum (δ, ppm) of I and III-VIII

Compound	Solvent	Quinoxaline	NH	NH_2	CH_3	Quinoxaline 5-H	Quinoxaline 6-H	Quinoxaline 7-H	Quinoxaline 8-H	Naphthalene 3-H	Naphthalene 4-H	Naphthalene 5-H	Naphthalene 6-H	Naphthalene 7-H	Naphthalene 8-H
III	$CDCl_3$	30	—	8,40	—	8,05	7,79	7,64	8,24	6,89	7,76	7,67	7,39	7,63	9,01
I	$CDCl_3$	30	6,77	4,15	—	7,78	7,45	7,62	7,85						

Compound	Solvent	Quinoxaline	NH	NH_2	CH_3	Quinoxaline 5-H	Quinoxaline 6-H	Quinoxaline 7-H	Quinoxaline 8-H	Phenyl 2,6-H	Phenyl 3,5-H	Phenyl 4-H
V	$CDCl_3$	60	14,20	—	2,48	7,99	7,66	7,76	8,08	7,97	7,45	7,22
VI	$CDCl_3$	30	—	—	2,67	8,08	7,80	7,77	8,22	7,44	÷	7,72

Compound	Solvent	NH	NH_2	CH_3	3-H	4-H	5-H	6-H
VII	$CDCl_3$	—	5,44	—	6,76	7,17	6,78	7,68

Compound	Solvent	Quinoxaline	N-phenyl	CH_3	17-H	18-H	19-H	20-H	5-H	6-H	7-H	8-H	11-H	12-H	13-H	14-H
VIIIa	$CDCl_3$	30	7,34	2,55	7,85	—	—	—	6,42	6,63	6,95	—	—	—	—	9,67
VIIIa	H_2SO_4	100	6,84—7,05	2,55	7,96	7,27	7,35	7,77	6,36	6,55	6,78	7,66	7,54	7,50	7,35	—
VIIIb	H_2SO_4	100	6,93—7,14	2,62	8,20	7,39	7,43	7,90	6,41	6,67	6,92	7,86	7,70	7,65	7,43	—

TABLE 2. Electronic Spectra of III-VIII

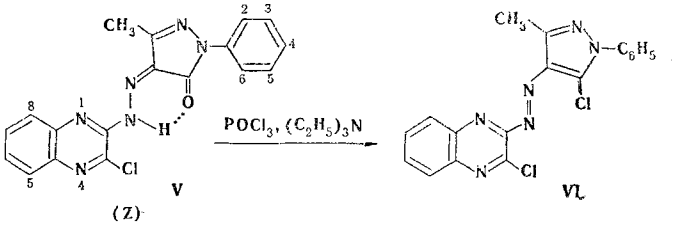
Compound	Solvent	λ_{max}, nm (log ε)
III	EtOH	233 i (4,58), 239 (4,59), 269_i (4,27), 318 (3,97), 395 (3,77), 542 (4,36)
IVa	20N. H_2SO_4	268 (4,68), 341 (4,44), 350 (4,46), 452_i (4,35), 482 (4,37), 540 sh (4,27), 713 (4,85)
IVb	20N. H_2SO_4	318 (4,40), 442 (4,37), 460 i (4,28), 525 (4,31), 710 (4,47)
V	EtOH	244 (4,40), 314 (3,90), 392 i (4,32), 403 (4,35), 495 (3,90)
VI	EtOH	236 (4,28), 256 i (4,18), 308 (4,16), 368 (4,35)
VIIIa	$CHCl_3$	265 (4,60), 281 i (4,54), 347 (4,35), 429 (4,16), 485 (4,58), 510 i (4,47), 565 i (3,85), 705 (3,80)
VIIIa	20 N H_2SO_4	283 (4,41), 410 (4,35), 543 (4,32), 685 (3,66),
VIIIb	$CHCl_3$	253 (4,47), 302 (4,30), 334 i (4,17), 445 (4,54), 480 i (4,36), 522 (4,46), 595 i (3,63), 635 (3,79)
VIIIb	20 N H_2SO_4	259 (4,49), 320 (4,60), 410 (4,36), 490 (4,54), 520 (4,57), 675 (3,96)
VIIIc	$CHCl_3$	280 (4,42), 300 sh (4,40), 337 (4,27), 432 (4,38), 532 (4,42), 640 i (3,47)
VIIIc	20 N H_2SO_4	256 (4,25), 318 (4,32), 474 (4,25), 490 i (4,23), 625 (3,87)

Bands of stretching vibrations of an NH_2 group at 3475 cm^{-1} (asymmetrical) (ε = 138 liters-mole^{-1}-cm^{-1}, $\Delta\nu_{1/2}$ = 30 cm^{-1}) and a weak band at 3400 cm^{-1} (symmetrical) are observed in the IR spectrum of III in CCl_4. In its PMR spectrum (Table 1) in $CDCl_3$ a broad NH_2 signal lies at 8.40 ppm. These data are in agreement with an aminoazo form in which the NH_2 group is bonded by a strong intramolecular hydrogen bond with the azo group [5].

The cyclization of III takes place at 130-135°C, whereas more severe conditions (150-155°C) are required for the self-cyclization of a similar sort of azo compound on the basis of 3-amino-2-chloropyridine [5]. Compounds IVa, b are deeply colored (Table 2) and are only slightly soluble in most organic solvents but somewhat more soluble in DMF and DMSO. Characteristic bands of stretching vibrations of NH and NH_2 groups are not observed in the IR spectra of chelates IVa, b in mineral oil. Intense isotope peaks of molecular ions are recorded in their mass spectra. The absence of fragment ions is characteristic for compounds of this sort [6]. Broad signals of aromatic protons at 8.62 ppm (d, $J_{ortho} \sim 8$ Hz) and 7.35-7.90 ppm (m) with an intensity ratio of 1:9 are observed in the PMR spectrum of IVa in concentrated H_2SO_4. The weak-field part of the AB spectrum of the 14- and 15-H protons of the naphthalene ring is evidently associated with 14-H. The deshielding of this proton may be due to steric interaction with the unshared electron pair of the quinoxaline nitrogen atom. The magnetic equivalence of the 14- and 29-H protons indicates retention of the C_{2v} symmetry in the case of protonation in concentrated H_2SO_4.

Another method for the synthesis of macroheterocyclic compounds on the basis of 3-chloro-2-hydrazinoquinoxaline is the preparation of o,o'-dihalo azo compounds and cyclization of them with o,o'-diamino azo compounds. As the latter we used 2,2'-aaminoazobenzene [5, 7]. Hydrazones that are capable, after treatment with phosphorus oxychloride, of undergoing conversion to o,o'-dihalo azo compounds were necessary for the synthesis of o,o-dihalo azo compounds of the heteroaromatic series in which the halogen atoms are additionally activated due to the appropriate orientation in the heterocyclic rings. As a hydrazone of this sort we selected 2,4-dihydro-5-methyl-2-phenyl-3H-pyrazole-3,4-dione 4-(3-chloro-2-quinoxalinyl)hydrazone (V) [2, 8]. An intense absorption band of stretching vibrations of a carbonyl group at 1668 cm^{-1} is observed in the IR spectrum of hydrazone V in KBr, while a signal of the proton of an NH group that is tied up in an intramolecular hydrogen bond is found at 14.29 ppm in the PMR spectrum in $CDCl_3$. It follows from these data that V exists in the Z-hydrazone form, similar to 2,4-dihydro-5-methyl-2-phenyl-3H-pyrazole-3,4-dione 3-(2-chloropyridyl)- and o-halophenylhydrazones.

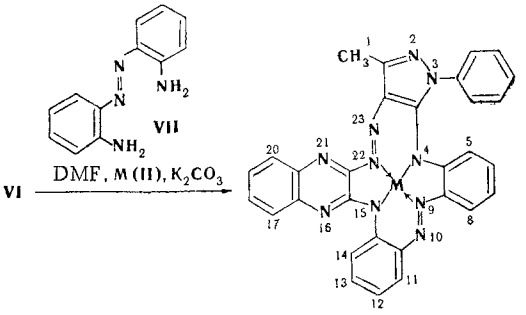
Replacement of the potential hydroxy group by chlorine is realized by the standard procedure via the scheme



V (Z) VI

The IR spectrum of dichloro azo compound VI does not contain the absorption band of stretching vibrations of a C=O group, and the ratio of the intensities of the isotope peaks in its mass spectrum is in agreement with the presence of two chlorine atoms. Because of the absence of an effect of magnetic anisotropy of the C=O group. the signals of the protons of N-phenyl ring merge to give a multiplet at 7.44-7.72 ppm in the spectrum of a solution of VI in $CDCl_3$ as compared with the spectrum of V.

The template cyclization of dichloro azo compound VI with 2,2'-diaminoazobenzene (VII) was carried out via the standard procedure in the presence of Ni(II), Pd(II), and Cu(II) salts via the scheme



VIII a M=Ni; b M=Pd; c M=Cu VIII a-c

Compounds VIII have limited solubility in organic solvents, which decreases in the order Cu > Ni > Pd. The IR spectra of chelates VIIIa-c in mineral oil and of their saturated solutions in chloroform do not contain bands of stretching vibrations of NH and NH_2 groups. Intense isotope peaks of molecular ions are observed in the mass spectra of metal chelates VIIIa-c, whereas fragment ions are virtually absent.

It is apparent from a comparison of the PMR spectra of VIIIa and starting azo compounds VI and VII in $CDCl_3$ that in the case of the formation of a macrocycle all of the protons of the starting azo compounds, except for the 14-H atom of the benzene ring that is closest to the quinoxaline nitrogen atom, experience additional shielding. The 14-H signal lies at unusually weak field (9.67 ppm), evidently as a consequence of coupling with the unshared pair of the electrons of the nitrogen atom of the quinoxaline ring. The transition from solution in $CDCl_3$ to solution in concentrated H_2SO_4 has little effect on the chemical shifts of the aromatic protons in the spectrum of VIIIa. The better solubility made it possible to

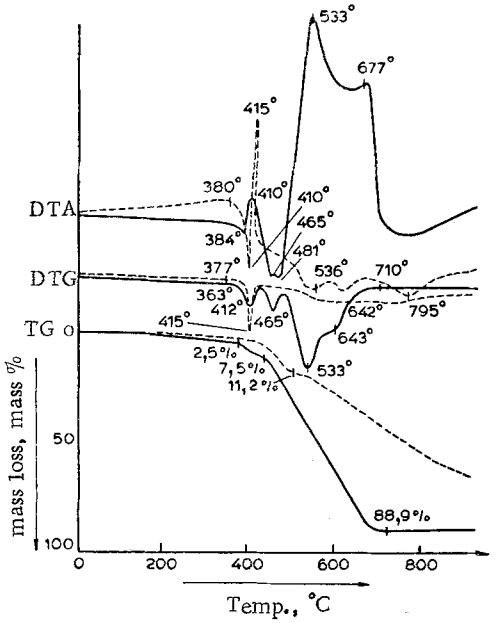


Fig. 1. Thermogravigram of VIIIa: ——) in air; ---) in nitrogen (TG is the mass-loss curve, DTG is the curve of the rate of mass loss, and DTA is the differential thermal analysis curve).

make a complete assignment of the PMR spectra of chelates VIIIa, b in H_2SO_4. A comparison of them with data from the PMR spectra of solutions of the starting azo compounds in $CDCl_3$ reveals, in addition to appreciable strong-field shifts of the signals of the 5- and 6-H protons of the benzene ring, of the 17-, 18-, and 19-H protons of the quinoxaline ring, and of the N-phenyl ring of pyrazole, considerable weak-field shifts of the 12- and 14-H protons of the benzene ring. It is known that the protonation of nitrogen heterocycles leads to considerable deshielding of the aromatic protons [9]. The fact that deshielding on passing to the macrocycle is observed only for the protons of the benzene ring in the ortho and para positions relative to the N_{15} atom indicates protonation of this sp^3-hybridized nitrogen atom.

The position of the long-wave bands in the electronic absorption spectra for chelates VIIIa-c forms the same sequence, viz., VIIIb < VIIIc < VIIIa, as for the previously obtained Pd, Cu, and Ni metal chelates, in which a benzene ring was present instead of a quinoxaline ring [5]. The longest-wave transitions vanish on passing from solutions in $CHCl_3$ to solutions in 20 N H_2SO_4 in the spectra of VIIIa-c; this is in agreement with disruption of the conjugation in the macrocyclic system in the case of protonation of the N_{15} atom.

Compounds IV and VIII have high thermal stability (the thermogravigrams of VIIIa in air and in a nitrogen atmosphere are depicted in Fig. 1). Melting is observed in the case of chelates VIIIa, b; in air it takes place simultaneously with decomposition of the compounds, whereas in nitrogen, decomposition begins immediately after melting. The mass spectrum of VIIIa heated to the point at which melting begins corresponds to the starting compound. This indicates that the smallest amount of mass loss prior to the start of melting (2.5 and 2.1% in nitrogen at 410 and 400°C for VIIIa and VIIIb, respectively) may be associated with sublimation. In air the total mass loss of VIIIa, b corresponds very precisely to decomposition to PdO and NiO. Decomposition in nitrogen proceeds relatively slowly (only 30-35% mass loss occurs at up to 800°C).

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The electronic spectra were obtained with a Unicam-100A spectrophotometer. The PMR spectra were recorded with a Varian XL-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MS-702 mass spectrometer with direct introduction of the samples into the

ionization region. The purity of the compounds obtained was monitored on Silufol UV-254 plates. The thermogravigrams were recorded with an OD-102 derivatograph in air and in an inert atmosphere (nitrogen). The temperature-rise rate was 10 deg/min in a nitrogen atmosphere and 20 deg/min in air. The samples (30-40 mg) were placed in thin layers in quartz or platinum crucibles.

2-Amino-1-[(3-chloro-2-quinoxalinyl)azo]naphthalene (III). A 19.4 g (0.1 mole) sample of I [1] and 22.3 g (0.1 mole) of 2-aminonaphthalene-1-sulfonic acid (II) were triturated thoroughly and suspended in a solution of 600 ml of glacial CH_3COOH and 10 ml of concentrated H_2SO_4. The mixture was then stirred and treated dropwise at room temperature in the course of 30 min with a solution of 57 g (0.25 mole) of $K_2S_2O_8$ in 200 ml of water. The mixture was stirred at room temperature for 2 h, 500 ml of water was added, and the mixture was neutralized to pH 6-7 with 40% NaOH. The precipitate was removed by filtration, washed with hot water, and dried. Recrystallization from benzene gave 15 g (45%) of III as shiny brown crystals with mp 194-195°C that were soluble in many organic solvents but insoluble in water. Found: C 65.0; H 3.7; Cl 10.2; N 20.8%; M^+ 333. $C_{18}H_{12}ClN_5$. Calculated: C 64.8; H 3.6; Cl 10.6; N 21.0%; M 333.8.

[13,28-Dihydrodinaptho[2,1-f:2',1'-m]diquinoxalino[2,3-c:2',3'j]1,2,5,8,9,12]hexaazacyclotetradecenato(2-)-N^5,N^{13},N^{20},N^{28}]nickel (IVa). A mixture of 9 g (0.027 mole) of III, 3.5 g (0.014 mole) of $Ni(CH_3COO)_2 \cdot H_2O$, 13.8 g (0.1 mole) of K_2CO_3, and 350 ml of DMF was heated with stirring to 130-135°C and maintained at that temperature for 7-8 h. A total of 150 ml of DMF was then removed by vacuum distillation, and the residue was cooled. The precipitate was removed by filtration, washed with water, dried, and suspended in 200 ml of ethanol. The suspension was refluxed for 30 min, and the precipitate was removed by filtration, dried, and dissolved in 50 ml of concentrated H_2SO_4. The acidic mixture was poured over ice, and the precipitate was removed by filtration, washed with water, and dried to give 4.3 g (49%) of a dark-violet finely crystalline substance that melted above 380°C and was only slightly soluble in most organic solvents; it dissolved in concentrated H_2SO_4 to give a bright dark-green solution. Found: C 66.1; H 3.0; N 21.1; Ni 9.3%; M^+ 650 (with respect to the I isotope peak). $C_{36}H_{20}N_{10}Ni$. Calculated: C 66.4; H 3.1; N 21.5; Ni 9.0%; M 651.3.

[13,28-Dihydrodinaphtho[2,1-f:2',1'-m]diquinoxalino[2,3-c:2',3'-j][1,2,5,8,9,12]hexaazacyclotetradecenato(2-)-N^5,N^{13},N^{20},N^{28}]palladium (IVb). This compound was similarly obtained in 37% yield; its solubility was similar to that of IVa, and it melted above 380°C. Found: C 61.5; H 2.7; N 19.9; Pd 15.4%; M^+ 694. $C_{36}H_{20}N_{10}Pd$. Calculated: C 61.8; H 2.9; N 20.0; Pd 15.2%; M 699.0.

4-[(3-Chloro-2-quinoxalinyl)azo]-5-chloro-3-methyl-1-phenylpyrazole (VI). A 20-ml [33.5 g (0.02 mole)] sample of $POCl_3$ was added to 3.64 g (0.01 mole) of V [8], and 1.4 ml (1 mmole) of triethylamine was added with stirring at room temperature. The mixture was refluxed for 8 h, after which 10 ml of $POCl_3$ was removed by distillation in vacuo, and the residue was poured with stirring over 200 g of ground ice. The mixture was neutralized with cooling to pH 6-7 with 40% NaOH. The precipitate was removed by filtration, washed with water, dried, and recrystallized from acetone to give 3.1 g (81%) of light-orange needles of dichloro azo compound VI with mp 177-178°C that were quite soluble in many organic solvents but insoluble in water. Found: C 56.6; H 3.1; Cl 18.3; N 21.7%; M^+ 382. $C_{18}H_{12}Cl_2N_6$. Calculated: C 56.4; H 3.2; Cl 18.5; N 21.9%; M 383.2.

[4,15-Dihydro-1-methyl-3-phenyl-3H-dibenzo[c,m]pyrazolo[3,4-f]quinoxalino[2,3-j]1,2,-5,8,9,12]hexaazacyclotetradecenato(2-)-N^4,$N^{9(10)}$,N^{15},$N^{22(23)}$]nickel (VIIIa). A 3.83-g (0.01 mole) sample of VI and 2.12 g (0.01 mole) of 2,2'-diaminoazobenzene (VII) [7] were dissolved in 200 ml of DMF, 2.48 g (0.01 mole) of $Ni(CH_3COO)_2 \cdot 4H_2O$ and 5.5 g (0.04 mole) of finely ground K_2CO_3 were added, and the mixture was heated with stirring at 130-135°C for 7 h. It was then cooled, and the precipitate was removed by filtration, washed with water, and dried. Recrystallization from benzene gave 2.6 g (45%) of chelate VIIIa as dark-brown fine needles that were soluble in concentrated H_2SO_4, chloroform, DMSO, DMF, and (with heating) in benzene but insoluble in water; the product had mp 380°C (in air) and 410°C (in a nitrogen atmosphere). Found: C 62.5; H 3.4; N 24.0; Ni 10.3%; M^+ 578. $C_{20}H_{20}N_{10}Ni$. Calculated: C 62.2; H 3.5; N 24.2; Ni 10.1%; M 579.3.

[4,15-Dihydro-1-methyl-3-phenyl-3H-dibenzo[c,m]pyrazolo[3,4-f]quinoxalino[2,3-j][1,2,-5,8,9,12]hexaazacyclotetradecenato(2-)-N^4,$N^{9(10)}$, N^{15},$N^{(22)(23)}$]palladium (VIIIb). This com-

pound was similarly obtained, except that $PdCl_2$ was used as the metal salt. The product was purified by extraction and was obtained in 43% yield as fine needles that were soluble in concentrated H_2SO_4, chloroform (with heating), DMSO, and DMF, less soluble in benzene, and insoluble in water; the product had mp 384°C (in air) and 400°C (in a nitrogen atmosphere). Found: C 57.6; H 3.2; N 22.0; Pd 17.4%; M^+ 622. $C_{30}H_{20}N_{10}Pd$. Calculated: C 57.5; H 3.2; N 22.3; Pd 17.0%; M 626.9.

[4,15-Dihydro-1-methyl-3-phenyl-3H-dibenzo[c,m]pyrazolo[3,4-f]quinoxalino[2,3-j][1,2,-5,8,9,12]hexaazacyclotetradecenato(2-)-N^4,$N^{9(10)}$,N^{15},$N^{22(23)}$]copper (VIIIc). This compound was similarly obtained, except that $CuCl_2$ was used as the metal salt. The product was recrystallized from CCl_4 and was obtained in 25% yield; it melted above 300°C. Found: C 61.8; H 3.4; Cu 11.0; N 23.7%; M^+ 583. $C_{30}H_{20}CuN_{10}$. Calculated: C 61.7; H 3.4; Cu 10.9; N 24.0%; M 584.1.

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3-NITRO-1,2,4-TRIAZOL-5-ONE DERIVATIVES

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UDC 547.792.5

3-Nitro-1,2,4-triazol-5-one and its monomethyl derivatives react with methyl vinyl ketone to give products of addition to the ring N_1 and N_4 atoms. The reaction with formaldehyde and N-methylolacetamide proceeds only at the N_1 atom. The keto derivatives of 3-nitro-1,2,4-triazol-5-one undergo the Schmidt reaction to give the corresponding acetamides. A number of compounds that include functional groups in the N_1-alkyl substituent of the 3-nitro ring were obtained by treatment of the bases of N_1-substituted 3,5-dinitro-1,2,4-triazoles in aprotic media.

The biological activity of 1,2,4-triazol-5-one derivatives has been noted [1-3]. Modification of their properties can be achieved by varying the substituents attached to the ring carbon and nitrogen atoms. In particular, the nitration of 1,2,4-triazol-5-one leads to 3-nitro-1,2,4-triazol-5-one [4-6], while alkylation of the latter leads to its mono- or disubstituted derivatives [6-9]. In addition, 1-R-3-nitro-1,2,4-triazol-5-ones were obtained in the reaction of 1-R-3,5-dinitro-1,2,4-triazoles with hydroxylamine [10] or were isolated as side products in their reactions with other nucleophilic reagents [10, 11].

In the present research we used both variants, viz., the reaction of NH acids of the triazolone series with electrophilic reagents and substitution at the C_5 atom in 1-R-3,5-di-

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