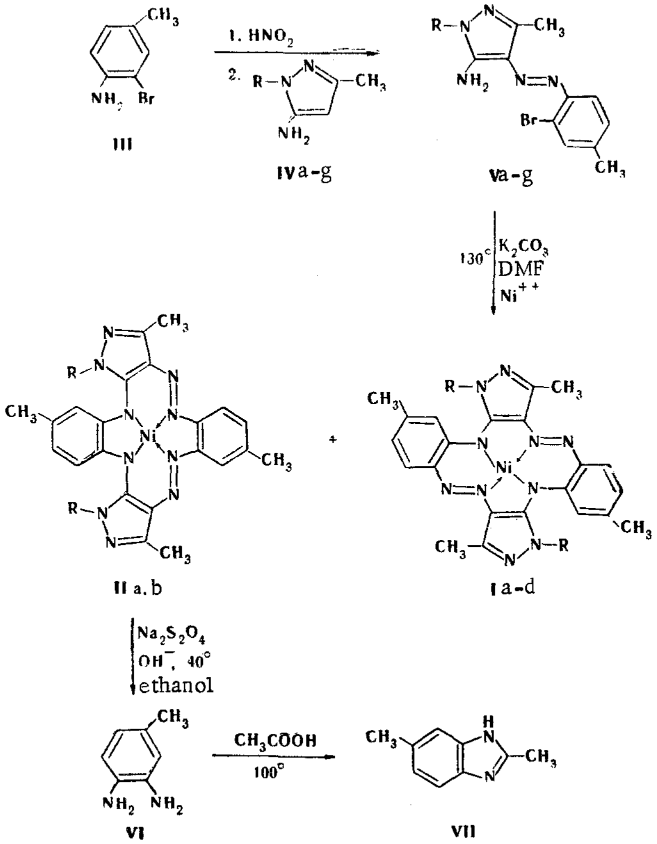
SYNTHESIS OF TETRAHYDRODIBENZODIPYRAZOLO-[1,2,5,8,9,12]- AND -[1,2,5,6,9,12]-HEXAAZACYCLOTETRADECINE DERIVATIVES

V. M. Dziomko, B. K. Berestevich,
A. V. Kessenikh, Yu. S. Ryabokobylko,
and R. S. Kuzanyan

UDC 541.572.54:547.779'863

The reaction of nickel(II) nitrate with 4-(2-bromo-4-methyl-1-phenylazo)-3-amino-5-methyl-2-alkylpyrazoles by refluxing in dimethylformamide in the presence of K_2CO_3 followed by purification with a column filled with Al_2O_3 gave [1,10,11,20-tetrahydro-1,11-dipropyl-3,8,13,18-tetramethyldibenzo[c,j]dipyrazolo[3,4-f:3',4'-m]-[1,2,5,8,9,12]hexaazacyclotetradecinato(2-)-4,10,14,20]nickel and [1,14,15,20-tetrahydro-1,14-dipropyl-3,7,12,17-tetramethyldibenzo[c,j]dipyrazolo[4,3-g:3',4'-m]-[1,2,5,6,9,12]hexaazacyclotetradecinato(2-)-5,10,15,20]nickel, which were characterized by the results of elementary analysis and the IR, UV, PMR, and mass spectra.

1,10,11,20-Tetrahydrodibenzo[c,j]dipyrazolo[3,4-f:3',4'-m][1,2,5,8,9,12]hexaazacyclotetradecine derivatives (I) were recently obtained [1-5] and little study has been devoted to them. In the present research, in addition to derivatives Ia-d, we synthesized and investigated 1,14,15,20-tetrahydrodibenzo[c,j]dipyrazolo[4,3-g:3',4'-m][1,2,5,6,9,12]hexaazacyclotetradecine derivatives IIa-b with azo groups in the ortho positions. The synthesis of the hexaazacyclotetradecines I and II was accomplished via the scheme



Ia R=CH_3; b R=Pr; c R=*i*-Pr; d R=Ph. IIa R=CH_3; b R=Pr. IV—Va R=H. b R=CH_3; c R=C_2H_5; d R=Pr; e R=*i*-Pr; f R=C_6H_5; g R=*p*-Tolyl

---

All-Union Scientific-Research Institute of Chemical Reagents and Ultrapure Chemical Substances, Moscow 107258. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1097-1103, August, 1978. Original article submitted September 20, 1977.

0009-3122/78/1408-0885$07.50 © 1979 Plenum Publishing Corporation

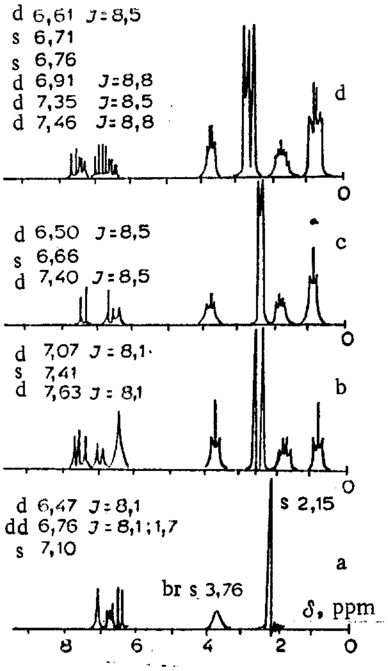


Fig. 1. PMR spectra: a) III (0.4 M in CCl_4); b) Vd; c) Ib; d) IIb.

Compounds Va-g were obtained by diazotization of III and coupling at pH 3-4 with pyrazoles IVa-g. A signal of an NH_2 group is observed in the PMR spectra of azo compounds Va-g at 6.14-6.59 ppm (Table 4). Bands of symmetrical and asymmetrical stretching vibrations of an NH_2 group are noted in the IR spectra at 3370-3475 cm^{-1}. According to these data, Va-g are o-aminoazo compounds, in contrast to the pyrazolone azo analogs, which exist in the hydrazone form [11]. The cyclization of o-amino-o-bromo azo compounds Va-g was carried out in dimethylformamide (DMF) in the presence of nickel(II) nitrate and potassium carbonate. Two isomers (Ib-IIb, Ic-IIc, and Id*) were isolated in 15 to 20% yields in the preparation of macrocyclic compounds from Vb-d. The IR spectra of I and II do not contain characteristic bands in the region of the vibrations of NH bonds.

We selected 1-amino-2-bromo-4-methylbenzene (III) as the amine for diazotization in order to facilitate the use of PMR spectroscopy to establish the structure of synthesized I and II. As a result, the PMR spectra of the aromatic protons in all of the intermediate and final products were of the ABX type (with J_{AX} and $J_{BX} \lesssim 2$ Hz), which is convenient for interpretation (Fig. 1). In particular, this made it possible to detect the isomerism of the macrocyclic compounds.

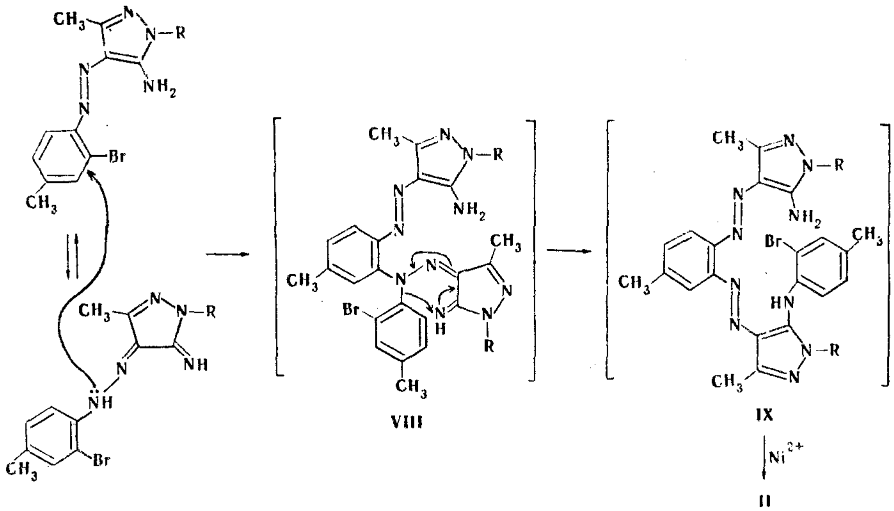
The PMR spectra of Ia, b and IIa, b contain (in a ratio of 12:12) signals of aromatic protons and methyl groups, as well as protons of the corresponding alkyl substituents attached to the nitrogen atom. Compounds Ia-d have a second-order axis of symmetry; this leads to equivalence of the two groups of pyrazole and phenyl protons. The absence of symmetry in IIa, b makes them nonequivalent.

3,4-Diaminotoluene (VI) (with constants in agreement with the literature values [12]) was isolated in the reduction of Ib with sodium hydrosulfite. 2,5(or 6)-Dimethylbenzimidazole (VII), the melting point of which is in agreement with the data in [13], was obtained from it by heating with glacial acetic acid. This constitutes evidence that the two azo groups are in the ortho position in the benzene ring.

The formation of isomeric IIa, b seemed unexpected. If the normal trend of template cyclization assumes double nucleophilic attack by the o-amino group on the carbon atoms bonded to halogen, the imino-hydrazone and azo forms react during the formation of isomers IIa, b to give diarylhydrazone VIII. Template cyclization via the following scheme takes place after intramolecular migration, via a cyclic mechanism, of the o-bromo-p-tolyl residue to the imine nitrogen atom (VIII→IX):

---

*The second isomer was not isolated in pure form.



Compounds I and II did not undergo isomerization when they were heated in DMF in the presence of potassium carbonate. Only one isomer (Id) was obtained in the synthesis of a macrocyclic nickel chelate from Vf (R = Ph). We were unable to obtain a macrocyclic chelate from Va, and starting azo compound Va was recovered almost quantitatively. Macrocyclic derivatives were not obtained when the reaction was carried out with salts of other metals (Fe^{2+}, Co^{2+}, Mn^{2+}, Cd^{2+}, Pb^{2+}, La^{3+}, and Ce^{3+}). Macrocyclic chelates I and II are characterized by high stability: the nickel ion is not liberated under the influence of concentrated mineral acids.

An intense molecular-ion peak (m/e 566) is present in the mass spectrum of the macrocyclic compound (Fig. 2). Its intensity is 65%, which constitutes evidence for its exceptional stability with respect to electron impact. Peaks of fragment ions with m/e 524 and 482, which correspond to the detachment of propyl radicals, are also recorded.

EXPERIMENTAL

The IR spectra of $CHCl_3$ solutions were recorded with a UR-20 spectrometer. The UV spectra were obtained with Unicam-100A and SF-4a spectrophotometers. The PMR spectra were recorded with Varian XL-100-12 (100 MHz) and Tesla BS-487c (80 MHz) spectrometers with tetramethylsilane as the internal standard. The mass spectra were obtained with an MS-702 mass spectrometer with direct introduction of the samples into the ionization region; the temperature of the block for volatilization of the samples was 160-170°C at an ionizing voltage of 70 eV. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 plates in acetone—petroleum ether (5:1) and acetone—hexane (1:5) systems with development by iodine vapors.

5-Amino-3-methylpyrazoles (IVa-f). These compounds were obtained by the methods in [6-11]. The constants of the compounds obtained were in agreement with the literature data: IVa, mp 44-45°C (44°C [6]); IVb, mp 79-80°C (80-81°C [7]); IVc, mp 99-101°C (100-101°C [8]); IVe, mp 110-112°C (111-112°C [9]); IVf, mp 114-115°C (116°C [10]).

5-Amino-3-methyl-1-(p-tolyl)pyrazole (IVg). A solution of 82 g (1.0 mole) of diacetoacetonitrile in 200 ml of ethanol was added with stirring to 158.5 g (1.0 mole) of p-tolylhydrazine hydrochloride in 300 ml of water and 12 ml (0.12 mole) of concentrated HCl, and the

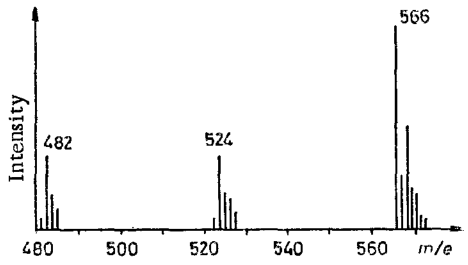


Fig. 2. Mass spectrum of Ib.

TABLE 1. Physicochemical Constants, Results of Elementary Analysis, and Yields of the Compounds Obtained

Compound	mp, °C	m/e	Found, %					Empirical formula	Calc., %					M	Yield, %
			C	H	Br	N	Ni		C	H	Br	N	Ni		
IVd	150 (27nm)*	139	60,4	9,5	—	30,3	—	$C_7H_{13}N_3$	60,4	9,4	—	30,2	—	139,2	78
IVg	116	187	70,7	6,9	—	22,4	—	$C_{11}H_{13}N_3$	70,6	7,0	—	22,4	—	187,3	89
Va	189—190	293	44,7	4,2	27,4	23,8	—	$C_{11}H_{12}N_5Br$	44,9	4,1	27,2	23,8	—	294,2	80
Vb	229—230	307	46,7	4,5	26,0	22,8	—	$C_{12}H_{14}N_5Br$	46,8	4,6	25,9	22,7	—	308,2	60
Vc	159—160	321	48,6	5,1	24,6	21,6	—	$C_{13}H_{16}N_5Br$	48,5	5,0	24,8	21,7	—	322,2	55
Vd	135—136	335	50,1	5,5	23,5	21,0	—	$C_{14}H_{18}N_5Br$	50,8	5,4	23,8	20,8	—	336,3	60
Ve	173—175	335	50,0	5,5	23,6	20,7	—	$C_{14}H_{18}N_5Br$	50,8	5,4	23,8	20,8	—	336,3	72
Vf	113—115 (dec.)	369	55,0	4,4	21,8	18,7	—	$C_{17}H_{16}N_5Br$	55,1	4,4	21,6	18,9	—	370,3	90
Vg	146—147	383	56,4	4,7	20,9	18,1	—	$C_{18}H_{18}N_5Br$	56,3	4,7	20,8	18,2	—	384,3	95
Ia	248—249	510	56,3	4,8	—	27,5	11,3	$C_{24}H_{24}N_{10}Ni$	56,4	4,7	—	27,4	11,5	511,2	18
Ib	204—206	566	59,2	5,7	—	24,8	10,2	$C_{28}H_{32}N_{10}Ni$	59,3	5,7	—	24,7	10,4	567,3	20
Ic	305—307	566	59,3	5,6	—	24,7	10,2	$C_{28}H_{32}N_{10}Ni$	59,3	5,7	—	24,7	10,4	567,3	20
Id	Above 353	633	64,3	4,3	—	22,1	9,3	$C_{34}H_{28}N_{10}Ni$	64,3	4,4	—	22,0	9,2	635,4	55
IIa	120—121	510	56,4	4,8	—	27,4	11,3	$C_{24}H_{24}N_{10}Ni$	56,4	4,7	—	27,4	11,5	511,2	15
IIb	78—80	566	59,1	5,6	—	24,8	10,3	$C_{28}H_{32}N_{10}Ni$	59,3	5,7	—	24,7	10,4	567,3	20

*Boiling point.

TABLE 2. Electronic Spectra of I, II, and V

Compound	Solvent	λ_{max}, nm (lg ε)				
		1	2	3	4	5
Ia	Methanol	295 (3,60)	340 (3,17)	sh 400 (3,36)	455 (3,57)	615 (3,20)
Ib	Hexane	256 (3,53) 280 (3,56)	i 292 (3,52) 390 (4,11)	410 (4,16)	455 (4,40)	628 (3,62)
Ib	CHCl₃	266 (3,59) 294 (3,54)	370 (4,11)	sh 425 (4,08)	460 (4,36)	610 (3,64)
Ic	Methanol	—	385 (3,90)	sh 400 (4,00)	460 (4,25)	615 (3,45)
Id	CHCl₃	312 (4,49)	395 (4,29)	sh 428 (4,39)	460 (4,62)	628 (3,80)
IIa	Methanol	295 (3,90)	340 (3,57)	420 (3,71)	450 (3,84)	615 (3,20)
IIb	Hexane	242 (3,50) 272 (3,48)	390 (4,00)	sh 420 (4,04)	455 (4,23)	610 (3,50)
IIb	CHCl₃	264 (3,50) i 286 (3,47)	sh 395 (4,00)	sh 420 (4,04)	460 (4,23)	610 (3,50)
Va	CHCl₃	—	375 (4,06)	383 (4,03)	—	—
Vb	„ „	—	385 (4,11)	sh 415 (3,91)	—	—
Vc	„ „	—	385 (4,18)	420 (4,02)	—	—
Vd	„ „	—	385 (4,46)			
Ve	Methanol	240 (4,02) 318 (3,91)	385 (4,26)	sh 410 (4,20)	—	—
Vf	CHCl₃	—	390 (4,36)	sh 405 (4,28)	—	—
Vg	CHCl₃	—	390 (4,78)	—	—	—

mixture was heated at 70°C for 3 h. Concentrated HCl [400 ml (4.0 moles)] was added, and the mixture was stirred at 90°C for 2 h. A total of 200 ml of ethanol and 500 ml of water were removed by distillation, and the residual mass was made alkaline to pH 10 with 40% KOH. The supernatant layer (the pyrazole) was separated and recrystallized from benzene to give 365 g of IVg with mp 116°C.

4-(2-Bromo-4-methyl-1-phenylazo)-3-amino-2-isopropyl-5-methylpyrazole (Ve). A solution of 7.0 g (0.1 mole) of sodium nitrite in 20 ml of water was added with stirring and cooling to 0°C to a solution of 18.6 g (0.1 mole) of III in 100 ml of water and 25 ml of concentrated HCl, and the resulting solution was maintained at the same temperature for 30 min (the presence of nitrous acid was monitored by means of starch-iodide paper). The diazonium solution was poured into a solution of 13.9 g (0.1 mole) of IVe in 200 ml of water and 25 ml of acetic acid, and the mixture was maintained at room temperature and pH 3-4 for 24 h. The yellow precipitate was removed by filtration, washed with 200 ml of water, and recrystallized from isopropyl alcohol to give 24.3 g of Ve. The shiny yellow plates were quite soluble in trichloromethane, acetic acid, DMF, and dimethyl sulfoxide (DMSO).

Compounds Va-d, f, g were similarly obtained. The physicochemical and spectral data are presented in Tables 1 and 4.

TABLE 3. PMR Spectra of IVa, c, e-g

Compound	Solvent (concn. in M)	δ, ppm, J, Hz			
		CH_3	CH	NH_2	R
IVa	Acetone-d_6 (0,15)	2,31 s	5,48 s	4,93 br s	
IVa	DMSO (0,2)	—	5,27 s	—	6,09 br s (NH; NH_2)
IVa	$CDCl_3$ (0,4)	2,03 s	5,26 s	—	6,26 br s (NH; NH_2)
IVc	$CDCl_3$ (0,05)	2,12 s	5,30 s	3,40 br s	1,34 t, J=7,3 (CH_3); 3,88 q J=7,3 (—CH_2—)
IVe	$CDCl_3$ (0,1)	2,15 s	5,32 s	3,40 br s	1,43 d J=6,6 (2CH_3); 4,24 m J=6,6 (CH)
IVf	$CDCl_3$ (0,4)	2,14 s	5,30 s	3,79 br s	7,18—7,48 m (Ph)
IVg	$CDCl_3$ (0,4)	2,18 s	5,33 s	3,80 br s	2,35 s (CH_3); 7,23* d J=8,5 (3,5-H); 7,37* d J=8,5 (2,6-H)

---

*Centers of multiplets.

TABLE 4. PMR Spectra of Va-g, IIb, and Ia-c

Compound	Concn. in M	δ, ppm, J, Hz (in $CDCl_3$ for II and V and in CCl_4 for I)						
		NH_2	CH_3	CH_3*	3-H	5-H	6-H	R
Va	0,5	6,59 br s	2,50 s	2,31 s	7,45 s	7,06 dd J=8,5; 1,5	7,56 d J=8,5	
Vb	0,3	6,14 br s	2,34 s	2,45 s	7,48 s	7,15 dd J=8,2; 2,0	7,62 d J=8,2	2,56 s (CH_3)
Vc	0,3	6,28 br s	2,31 s	2,44 s	7,45 s	7,13 d J=8,2	7,63 d J=8,2	1,38 t J=6,4 (CH_3); 3,83 q, J=6,4 (—CH_2—N)
Vd	0,5	6,38 br s	2,28 s	2,44 s	7,41 s	7,07 d J=8,1	7,63 d J=8,1	0,86 t, J=7,0 (CH_3); 1,78 m (—CH_2—); 3,70 t, J=7,0 (—CH_2—N)
Ve	0,4	6,26 br s	2,33 s	2,47 s	7,46 d J=1,6	7,14 dd J=8,2; 1,6	7,63 d J=8,2	1,44 d J=6,0 (2CH_3); 4,11 m (CH)
Vf	0,4	6,56 br s	2,35 s	2,54 s		7,18 dd J=8,0; 2,0	7,67 d J=8,0	7,39—7,55 m (Ph and 3-H)
Vg	0,1	6,54 br s	2,30 s	2,48 s	7,40 s	7,06 d J=8,5	7,64 d J=8,5	2,30 s (CH_3); 7,18 d, J=9,0 (3,5-H); 7,34 d., J=9,0 (2,6-H)
Ia	0,01	—	2,16 s 2,20 s		6,43 s	6,33 d J=8,2	7,20 d J=8,2	3,29 s (CH_3)
Ib	0,2	—	2,34 s	2,38 s	6,66 s	6,50 d J=8,5	7,40 d J=8,5	0,98 t, J=6,0 (—CH_3—C—C—); 1,83 m (—CH_2—); 3,80 t, J=6,0 (—CH_2—N)
Ic	0,01	—	2,18 s	2,25 s	6,55 s	6,33 d J=8,2	7,23 d J=8,2	1,44 d†, J=7,0 and 1,51 d† J=7,0 ($(CH_3)_2C$); 4,25 m (CH)
IIb	0,01	—	2,33 s (6H)	2,43 s 2,46 s	6,71 s 6,76 s	6,61 d J=8,5 7,35 d J=8,8	6,91 d J=8,5 7,46 d J=8,8	0,84 t J=7,0 (CH_3—C—C—); 0,86 t J=7,0 (CH_3—C—C—); 1,73 m (2-CH_2—); 3,83 t, J=7,0 (—CH_2—N); 3,91 t J=7,0 (—CH_2—N)

---

*Methyl group of pyrazole.

†Hindered rotation.

[1,10,11,20-Tetrahydro-1,11-dipropyl-3,8,13,18-tetramethyldibenzo[c,j]dipyrazolo[3,4-f:3',4'-m][1,2,5,8,9,12]hexaazacyclotetradecinato(2-)-4,10,14,20]nickel. A mixture of 4.04 g (0.012 mole) of Vd, 1.75 g (6 mmole) of nickel(II) nitrate hexahydrate, 9.67 g (70 mole) of potassium carbonate, and 500 ml of DMF was stirred at 120°C for 9 h. The course of the reaction was monitored by TLC [in an acetone—hexane system (1:5)]. The mixture was cooled and filtered, and the filtrate was diluted with 500 ml of water. The precipitate was washed successively with 500 ml of a mixture of DMF and water (1:1), dried, and purified by means of repeated column chromatography on activity II (Brockmann scale), neutral Al_2O_3 (elution with benzene). Two fractions were obtained, and the benzene was removed from them by evaporation.

The residue from the first fraction was recrystallized from methanol to give 0.68 g of Ib as fine green plates that were soluble in diethyl ether, DMF, DMSO, acetic acid, and concentrated inorganic acids, only slightly soluble in alcohols and acetic anhydride, and insoluble in water.

The residue from the second fraction was recrystallized from methanol to give 0.695 g of brown-green crystals of [1,14,15,20-tetrahydro-1,14-dipropyl-3,7,12,17-tetramethyldibenzo[c,j]dipyrazolo[4,3-g:3',4'-m][1,2,5,6,9,12]hexaazacyclotetradecinato(2-)-5,10,15,20]-nickel (IIb). Compound IIb was satisfactorily soluble in acetone and hexane, quite soluble in trichloromethane, benzene, acetic acid, and concentrated inorganic acids, and insoluble in water.

Compounds Ia, c and IIa were similarly obtained. Their solubilities were similar to the solubilities of Ib and IIb.

[1,10,11,20-Tetrahydro-1,11-diphenyl-3,8,13,18-tetramethyldibenzo[c,j]dipyrazolo[3,4-f:3',4'-m][1,2,5,8,9,12 hexaazacyclotetradecinato(2-)-4,10,15,20]nickel (Id). A mixture of 1.11 g (3 mmole) of Vf, 0.5 g (1.5 mmole) of nickel(II) nitrate hexahydrate, 4.0 g of potassium carbonate, and 300 ml of DMF was stirred at 120°C for 5 h until the starting azo compound vanished (according to TLC). The mixture was then cooled, and the supernatant crystals of Id were separated, washed with water, dried, and recrystallized from trichloromethane to give 0.52 g of fine dark-green needles of Id.

Reduction of IIb with Sodium Hydrosulfite. A 2.08-g (12 mmole) sample of sodium hydrosulfite was added to 0.56 g (1 mmole) of IIb in 700 ml of ethanol and 4 ml of 5% NaOH, and the mixture was heated with stirring on a water bath until the green color changed to violet, after which it was filtered. The mother liquor was evaporated, and VI was separated by sublimation at 265°C and recrystallized from benzene to give 0.73 g (60%) of a product with mp 88-90°C (mp 89-90°C [12]). A 0.61-g sample of o-toluenediamine VI was heated in 20 ml of acetic acid at 100°C for 4 h, after which the acetic acid was removed by evaporation, and the residue was recrystallized from benzene to give 0.62 g of VI with mp 203°C (mp 203°C [13]). PMR spectrum (0.1 M, $CDCl_3$): 2.58 (3H, s, CH_3 attached to 2-C), 2.43 (3H, s, CH_3 attached to 5-C), 7.30 (1H, s, 4-H), 7.01 (1H, d, J = 8.0 Hz; 6-H), 7.40 (1H, d, J = 8.0 Hz, 7-H), and 9.44 (1H, broad s, NH).

LITERATURE CITED

1. V. M. Dziomko, L. G. Fedosyuk, and K. A. Dunaevskaya, Zh. Obshch. Khim., 45, 2488 (1975).
2. V. M. Dziomko and U. A. Tomsons, Khim. Geterotsikl. Soedin., No. 7, 968 (1976).
3. V. M. Dziomko and U. A. Tomsons, Khim. Geterotsikl. Soedin., No. 5, 669 (1976).
4. V. M. Dziomko and U. A. Tomsons, Tr. Vses. Nauchno-Issled. Inst. Khim. Reaktiv. Osobo Chistykh Khim. Veshchestv, No. 38, 248 (1976).
5. V. M. Dziomko, U. A. Thomsons, R. S. Kuzanyan, and Yu. S. Ryabokobylko, Zh. Vses. Khim. O-va., 22, 115 (1977).
6. E. Alcalde, J. Heterocycl. Chem., 11, 423 (1974).
7. E. Taylor and K. Hartke, J. Am. Chem. Soc., 81, 2456 (1959).
8. French Patent No. 1403372 (1965); Chem. Abstr., 63, 14871 (1965).
9. I. I. Grandberg, Din Wei-pi, and A. N. Kost, Zh. Obshch. Khim., 31, 2311 (1961).
10. E. Mohr, J. Prakt. Chem., 79, 1 (1909).
11. H. Dorn, J. Prakt. Chem., 315, 382 (1973).
12. The Chemist's Handbook [in Russian], Vol. 2, Goskhimizdat, Moscow (1963), p. 992.
13. O. Fischer and M. Rigaud, Ber., 35, 1259 (1902).