Reaction of 1-amino-2-phenylethynyl- and 2-acylethynyl-1-amino-9,10-anthraquinones with HNO_2. Synthesis of 1*H*-3-acylnaphtho[2,3-*g*]indazole-6,11-diones

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The reactions of 1-amino-2-phenylethynyl- and 2-acylethynyl-1-amino-9,10-anthraquinones with HNO_2 in a mixture of dioxane and a mineral acid at 20 °C were studied. Under these conditions, 2-alkynyl-1-amino-9,10-anthraquinones, irrespective of the structure of the C≡CR substituent, are cyclized into 3-substituted 1*H*-naphtho[2,3-*g*]indazole-6,11-diones. The nature of the acetylenic group in the initial compound and the choice of the mineral acid determine the structure of the substituent in position 3 of the product (1,1-dichloroalkyl or acyl) but have no effect on the regiospecificity of cyclization.

Key words: 1-amino-2-phenylethynyl-9,10-anthraquinones, 2-acylethynyl-1-amino-9,10-anthraquinones, nitrous acid, cyclization; 3-substituted 1*H*-naphtho[2,3-*g*]indazole-6,11-diones, *N*-methylation.

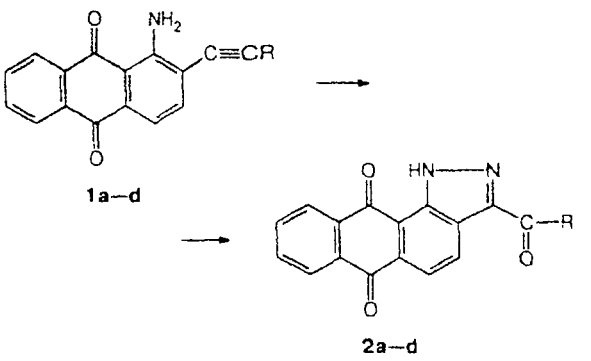
Previously we described the reaction of 2-alkynyl-1-amino-9,10-anthraquinones with HNO_2, involving closure of the pyrazole ring and yielding 1*H*-3-(1,1-dichloroalkyl)naphtho[2,3-*g*]indazole-6,11-diones.[1] It is of interest that the regiospecificity of this reaction differs substantially from that of the known cyclization of *ortho*-acetylenylarenediazonium salts, which yields a six-membered rather than a five-membered heterocyclic ring (Richter synthesis[2,3]).

In this work, we studied the characteristic features of new heterocyclization of 1-amino-2-phenylethynyl- and 2-acylethynyl-1-amino-9,10-anthraquinones **1a—d**. We suggested that an aromatic or electron-withdrawing group present in the C≡CR substituent in the initial compound could have an effect on the pathway of the process and even on the possibility of its occurrence. It would obviously be expedient to verify this suggestion in a study dealing with the common character, field of application, and mechanism of cyclization.

Under the conditions described previously[1] (dilute HCl—dioxane, 20 °C), amines **1a—d** react with HNO_2 much more slowly than the analogous alkynyl derivatives (1.0—7.5 h and 10—30 min, respectively) to give one product in each case. The reaction was found to follow the same pathway: the compounds obtained were 3-substituted 1*H*-naphtho[2,3-*g*]indazole-6,11-diones **2a—d** (Scheme 1). However, unlike the 2-(α-dichloroalkyl)naphthoindazolediones prepared from *vic*-alkynylaminoanthraquinones, these products contained no chlorine but contained a carbonyl group in the α-position of the side chain.

The structures of compounds **2a—d** were confirmed by analytical and spectral methods (Table 1) as well as by condensation with *o*-phenylenediamine to yield quinoxalines **3b—d**. The latter indicates that products **2b—d** incorporate two neighboring carbonyl groups in the side chain (Scheme 2), which would be impossible for their isomers containing six-membered pyridazine rings. In addition, 3-(1,2-dioxopentyl)-1*H*-naph-

Scheme 1



R = Ph (**a**), COPh (**b**), COPr (**c**), $COBu^t$ (**d**)

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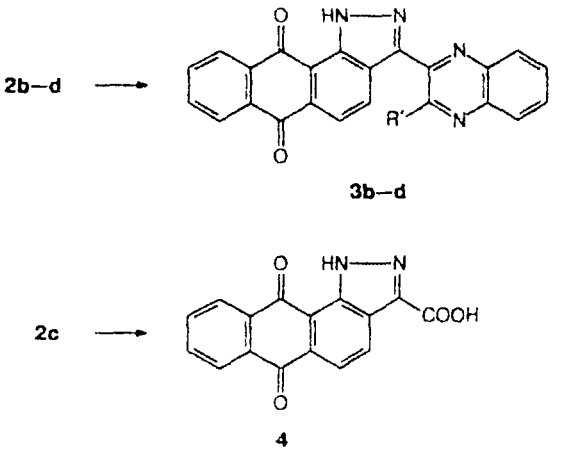
Table 1. Main characteristics of 3-substituted 1*H*-naphtho[2,3-g]indazole-6,11-diones

Compound	Yield (%)	M.p./°C (solvent)	Molecular formula	Found / Calculated (%)			^{1}H NMR ($CDCl_3$), δ
				C	H	N	
2a	78.0, 30.3[a]	302—303 (toluene)	$C_{22}H_{12}N_2O_3$	75.24 / 74.99	3.50 / 3.43	8.15 / 7.95	—
2b	62.5	305—306 (toluene)	$C_{23}H_{12}N_2O_4$	72.79 / 72.63	3.25 / 3.18	7.28 / 7.36	—
2c	62.4	252—253 (toluene)	$C_{20}H_{14}N_2O_4$	69.26 / 69.36	4.01 / 4.07	7.93 / 8.09	0.95 (t, 3 H, CH_3, J = 6.7 Hz); 1.70 (sext, 2 H, β-CH_2, J = 6.7 Hz); 2.93 (t, 2 H, α-CH_2, J = 6.7 Hz); 7.80—8.05 (m, 2 H, H(8), H(9)); 8.05—8.35 (m, 2 H, H(7), H(10)); 8.15 (d, 1 H, H(4)[H(5)], J = 9.0 Hz); 8.60 (d, 1 H, H(5)[H(4)], J = 9.0 Hz); 14.90 (br.s, 1 H, NH)[d]
2d	69.7	295—296 (toluene)	$C_{21}H_{16}N_2O_4$	70.02 / 69.99	4.67 / 4.48	7.85 / 7.77	1.35 (s, 9 H, CH_3); 7.80—7.95 (m, 2 H, H(8), H(9)); 8.20—8.40 (m, 2 H, H(7), H(10)); 8.30 (d, 1 H, H(4)[H(5)], J = 8.5 Hz); 8.72 (d, 1 H, H(5)[H(4)], J = 8.5 Hz); 12.35 (br.s, 1 H, NH)
2e	33.3, 72.5[b]	276—277 (dioxane)	$C_{22}H_{16}N_2O_3$	74.23 / 74.15	4.70 / 4.55	7.80 / 7.86	—
2f	68.4	207—208 (benzene—hexane)	$C_{22}H_{18}N_2O_4$	70.48 / 70.58	4.81 / 4.85	7.32 / 7.48	1.35—2.20 (m, 10 H, *cyclo*-C_6H_{10}); 7.65—7.95 (m, 2 H, H(8), H(9)); 8.10—8.45 (m, 2 H, H(7), H(10)); 8.23 (d, 1 H, H(4)[H(5)], J = 9.0 Hz); 8.70 (d, 1 H, H(5)[H(4)], J = 9.0 Hz); 13.65 (br.s, 1 H, NH)[d]
6f	83.3	247—248 (toluene)	$C_{22}H_{18}Cl_2N_2O_3$	61.78 / 61.35	3.94 / 4.23	16.44 / 16.52	1.35—2.00 (m, 10 H, *cyclo*-C_6H_{10}); 7.80—8.05 (m, 2 H, H(8), H(9)); 8.05—8.30 (m, 3 H, H(4)[H(5)], H(7), H(10)); 8.65 (d, 1 H, H(5)[H(4)], J = 8.3 Hz); 14.45 (br.s, 1 H, NH)[d]
3b	91.0	330—332 (dioxane—hexane)	$C_{29}H_{16}N_4O_2$	77.18 / 76.98	3.56 / 3.36	11.75 / 12.38	7.30—7.65 (m, 5 H, Ph); 7.80—8.00 (m, 4 H, H(8), H(9), H(6′), H(7′)); 8.05—8.35 (m, 5 H, H(4)[H(5)], H(7), H(10), H(5′), H(8′)); 8.65 (d, 1 H, H(5)[H(4)], J = 9.0 Hz); 14.18 (s, 1 H, NH)
3c	71.4	306—307 (toluene—hexane)	$C_{26}H_{18}N_4O_2$	74.71 / 74.63	4.36 / 4.34	13.23 / 13.39	1.00 (t, 3 H, CH_3, J = 6.8 Hz); 1.65—2.10 (m, 2 H, β-CH_2)[e]; 7.80—8.35 (m, 9 H, H arom.); 9.05 (d, 1 H, H(5)[H(4)], J = 9.0 Hz); 14.38 (br.s, 1 H, NH)
3d	83.3	292—293 (toluene—hexane)	$C_{27}H_{20}N_4O_2$	75.34 / 74.98	4.60 / 4.66	12.63 / 12.95	1.37 (s, 9 H, CH_3); 7.80—8.35 (m, 10 H, H arom.); 14.30 (br.s, 1 H, NH)
5a	88.2	223—224 (dioxane—hexane)	$C_{24}H_{18}N_2O_4$	72.29 / 72.35	4.73 / 4.55	6.90 / 7.03	3.30 (s, 6 H, OMe); 7.20—7.40 (m, 3 H, 3 HPh); 7.55—7.90 (m, 4 H, H(8), H(9), 2 HPh); 8.00 (d, 1 H, H(4)[H(5)], J = 8.5 Hz); 8.15—8.40 (m, 3 H, H(5)[H(4)], H(7), H(10)); 11.80 (br.s, 1 H, NH)
8a	86.0	171—172 (benzene—hexane)	$C_{25}H_{20}N_2O_4$	73.01 / 72.80	4.91 / 4.89	6.57 / 6.79	3.10 (s, 6 H, OMe); 3.90 (s, 3 H, NMe), 7.10—7.40 (m, 5 H, 5 HPh); 7.55—7.80 (m, 2 H, H(8), H(9)); 7.95 (d, 1 H, H(4)[H(5)], J = 9.0 Hz); 8.10—8.30 (m, 2 H, H(7), H(10)); 8.55 (d, 1 H, H(5)[H(4)], J = 9.0 Hz)
7a	88.9[c], 74.9	191—192 (dioxane—hexane)	$C_{23}H_{14}N_2O_3$	75.22 / 75.40	3.82 / 3.85	7.51 / 7.65	4.63 (s, 3 H, NMe); 7.35—7.90 (m, 8 H, H(4)[H(5)], H(8), H(9), 5 HPh); 8.05 (d, 1 H, H(5)[H(4)], J = 8.5 Hz); 8.20—8.45 (m, 2 H, H(7), H(10))

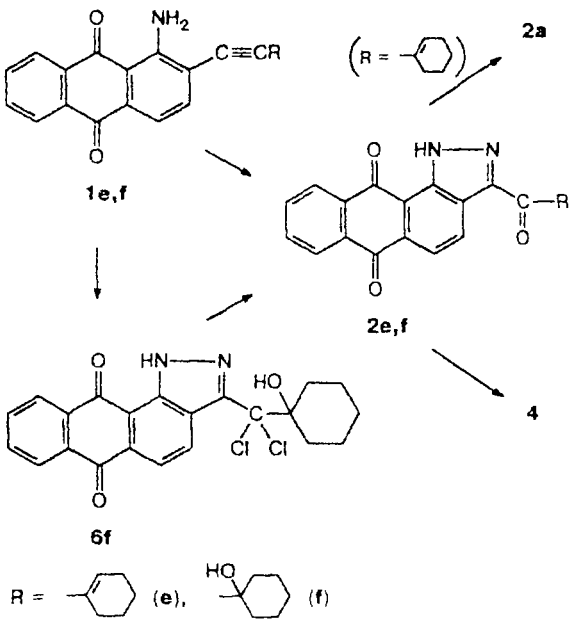
[a] Dehydrogenation of compound **2e**. [b] Dehydrochlorination of compound **6f**. [c] Hydrolysis of compound **8a**. [d] The spectrum was obtained in DMSO-d_6. [e] The signals of α-CH_2 and DMSO overlap.

tho[2,3-g]indazole-6,11-dione **2c** was oxidized to 6,11-dioxo-1*H*-naphtho[2,3-g]indazole-3-carboxylic acid **4** (see Scheme 2); this is direct evidence proving that ketones **2b—d** are naphthoindazole derivatives.

Scheme 2



Scheme 3



The structure of ketone **2a** should be confirmed separately. This was even more necessary since compound **2a** was found to undergo an unusual reaction with NaOMe in MeOH to give dimethylketal **5a**. Alkylketones, analogs of **2a**, for example, 1*H*-3-valeryl-naphtho[2,3-*g*]indazole-6,11-dione,[1] do not undergo this reaction.

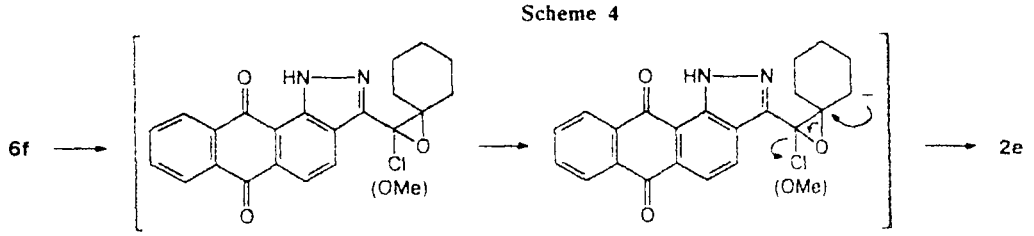
To determine the size of the ring in molecule **2a**, this compound was synthesized *via* an alternative pathway, namely, by dehydrogenation of 3-(3,4,5,6-tetrahydrobenzoyl)-1*H*-naphtho[2,3-*g*]indazole-6,11-dione **2e** carried out by prolonged boiling of this compound with active MnO_2 in toluene (Scheme 3). The aromatic product proved to be completely identical to compound **2a** obtained by cyclization of amine **1a**. Thus, compound **2a**, like α-diketones **2b–d**, contains a pyrazole rather than a pyridazine ring.

Aminoacetylene **1f** was cyclized in the reaction with HNO_2 under the conditions used to prepare ketones from 2-alkynyl-1-amino-9,10-anthraquinones.[1] The structure of product **2f** as a substituted naphthoindazole was additionally confirmed by its oxidation to acid **4** (see Scheme 3). However, the attempt to carry out dehydration of ketone **2f** to cyclohexenyl ketone **2e** by the action of $POCl_3$ in pyridine proved to be unsuccessful, and compound **2e** was obtained similarly to **2f**, *viz.*, by cyclization of cyclohexenylanthraquinone **1e**. Cyclization of amine **1e** occurred much more slowly than that of **1f** (19 and 3 h, respectively). It is apparently due to this reason and to the lability of vinylacetylene **1e** that the yield of product **2e** was only 33%. The best method for synthesis of ketone **2e** was found unexpectedly in a study of the reaction of dichloro(1-hydroxycyclohexyl)methyl-substituted naphthoindazoledione **6f** with MeONa in MeOH. Under these conditions, dione **6f** undergoes a sort of dehydrochlorination, accompanied by migration of an O atom, and is thus converted into cyclohexenyl ketone **2e** in a 72.5% yield; the overall yield of compound **2e** from acetylene **1f** is as high as 60%. The mechanism suggested for this reaction is presented in Scheme 4.

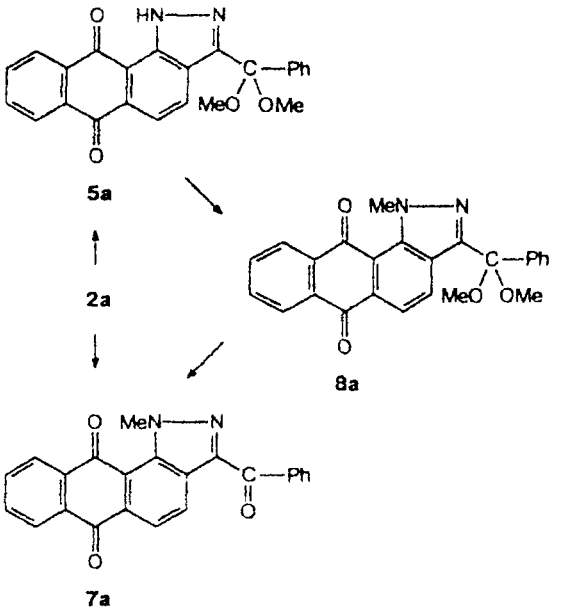
Ketone **2a**, like other 3-acylnaphthoindazolediones,[1] is methylated by Me_2SO_4 at the N atom of the ring, after preliminary conversion into the conjugated base by the action of butyllithium. The position of the methyl group in the product was confirmed by the fact that the same *N*-methyl derivative **7a** resulted from alkylation of dimethylketal **5a** followed by hydrolysis (Scheme 5).

It can be suggested that the ability of compound **2a** to be converted into ketal **5a** in the reaction with MeONa in MeOH is due to the formation of an ex-

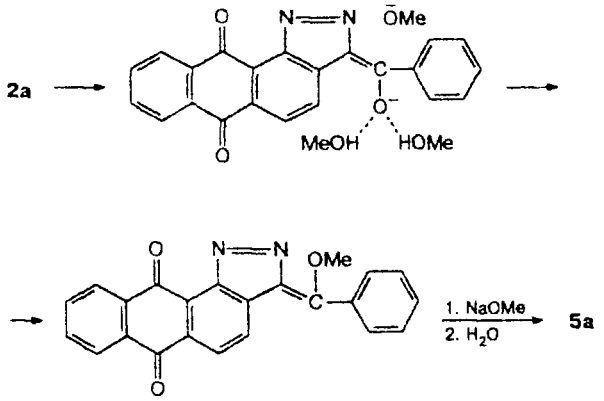
Scheme 4



Scheme 5



Scheme 6



tended conjugated system in the intermediate (Scheme 6).

Thus, the reaction of 2-alkynyl-1-amino-9,10-anthraquinones with HNO_2 in a mixture of dioxane and a mineral acid occurs as cyclization to give 3-substituted 1*H*-naphtho[2,3-*g*]indazole-6,11-diones, irrespective of the structure of the C≡CR substituent. The character of the acetylenic group in the starting compound and the nature of the acid affect only the structure of the side group (1,1-dichloroalkyl or acyl) of the naphthoindazole derivative formed. The reaction opens the pathway to previously unknown 1*H*-naphtho[2,3-*g*]indazole-6,11-diones.

Experimental

The NMR spectra were recorded on Jeol FX-90Q and Bruker 400 spectrometers in $CDCl_3$. The course of the reactions was monitored by TLC on Silufol UV 254 plates in $CHCl_3$. The initial acetylene derivatives **1a–f** were obtained by previously reported procedures.[4,5] The physicochemical characteristics of the 3-substituted 1*H*-naphtho[2,3-*g*]indazole-6,11-diones are listed in Table 1.

3-Benzoyl-1*H*-naphtho[2,3-*g*]indazole-6,11-dione (2a). Dilute (1 : 1) HCl (9 mL) and $NaNO_2$ (0.36 g, 5.2 mmol) in 4.5 mL of water were added successively to a solution of compound **1a** (0.96 g, 3.0 mmol) in 75 mL of dioxane; the mixture was stirred for 1 h at 20 °C, diluted with 500 mL of $CHCl_3$, and washed with water. Recrystallization from dioxane—hexane mixture gave 0.82 g (78.0%) of compound **2a**.

Compounds **2b–d** and **6f** were synthesized in a similar way.

3-(1-Hydroxyhexahydrobenzoyl)-1*H*-naphtho[2,3-*g*]indazole-6,11-dione (2f). A solution of compound **1f** (1.05 g, 3.0 mmol) in 75 mL of dioxane and 7.5 mL of 30% H_2SO_4 and a solution of $NaNO_2$ (0.40 g, 5.8 mmol) in 6 mL of water were stirred for 3 h at 20 °C. Chromatography on SiO_2 in $CHCl_3$ gave 0.78 g (68.4%) of compound **2f**.

3-(3-Propylquinoxalin-2-yl)-1*H*-naphtho[2,3-*g*]indazole-6,11-dione (3c). A mixture of compound **2c** (120 mg, 0.4 mmol), *o*-phenylenediamine (45 mg, 0.4 mmol), and 85% HCOOH (0.03 mL) in 15 mL of toluene was refluxed for 1.5 h and diluted with ~30 mL of hexane, and the precipitate that formed was filtered off. Chromatography on SiO_2 in $CHCl_3$ gave 100 mg (71.4%) of compound **3c**.

3-Phenyl- and 3-*tert*-butylquinoxalin-2-yl-substituted derivatives **3b,d** were obtained under the same conditions.

Oxidation of 3-(1,2-dioxopentyl)-1*H*-naphtho[2,3-*g*]indazole-6,11-dione (2c). Ketone **2c** (0.26 g, 0.8 mmol) was refluxed with a solution of potassium dichromate (1.10 g, 3.7 mmol) in 65 mL of AcOH and 15 mL of 30% H_2SO_4 for 2 h (see Ref. 1) to give 0.20 g (90.0%) of acid **4**.

Ketone **2f** was oxidized in a similar way.

Reaction of 3-[dichloro(1-hydroxycyclohexyl)methyl]-1*H*-naphtho[2,3-*g*]indazole-6,11-dione (6f) with MeONa. A solution of MeONa (1.50 g Na and 70 mL MeOH) was added to a suspension of 1.45 g (3.4 mmol) of compound **6f** in 70 mL of MeOH; the mixture was stirred for 15 min at 20 °C, diluted with 800 mL of $CHCl_3$, and washed with water. The crude **2e** thus obtained was heated at reflux in 30 mL of benzene for 5 min and cooled to give 0.87 g (72.5%) of compound **2e**.

Dehydrogenation of 3-(3,4,5,6-tetrahydrobenzoyl)-1*H*-naphtho[2,3-*g*]indazole-6,11-dione (2e). A mixture of compound **2e** (110 mg, 0.3 mmol) and active MnO_2 (2.20 g) in 140 mL of anhydrous toluene was heated at reflux for 45 h and filtered. The precipitate was thoroughly washed with $CHCl_3$. The combined filtrate was evaporated to dryness, and the residue was chromatographed on SiO_2 in $CHCl_3$ to give 33 mg (30.3%) of compound **2a**.

1*H*-3-[Dimethoxy(phenyl)methyl]naphtho[2,3-*g*]indazole-6,11-dione (5a). A mixture of compound **2a** (0.60 g, 1.7 mmol) and MeONa (obtained from 0.60 g of Na) in 45 mL of MeOH was stirred for 10 min at 20 °C; $CHCl_3$ (300 mL) was added, the mixture was stirred with water, and the solvent was removed *in vacuo*. The residue was crystallized in hexane to give 0.60 g (88.2%) of compound **5a**.

1-Methyl-3-benzoylnaphtho[2,3-*g*]indazole-6,11-dione (7a). *A.* A 1.45 *N* solution of BuLi in hexane (0.76 mL, 1.1 mmol) and then Me_2SO_4 (0.16 g, 1.3 mmol, 0.12 mL) were added in an Ar atmosphere to a solution of compound **2a** (0.18 g, 0.5 mmol) in 35 mL of anhydrous dioxane. The reaction mixture was stirred for 15 min at 50 °C and for 2 h at 20 °C. Product **7a** was extracted with $CHCl_3$ and purified by chromatography on SiO_2 in benzene to give 0.16 g (88.9%) of compound **7a**.

Ketal **8a** was obtained from compound **5a** in a similar way.

B. A solution of ketal **8a** (0.20 g, 0.5 mmol) in 20 mL of dioxane and 6 mL of 12% HCl was stirred for 30 min at 20 °C to give 0.16 g (88.9%) of compound **7a**.

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References

1. M. S. Shvartsberg, I. D. Ivanchikova, and L. G. Fedenok, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 1803 [*Russ. Chem. Bull.*, 1996, **45**, 1714 (Engl. Transl.)].
2. A. E. A. Porter, in *Comprehensive Organic Chemistry*, Eds. D. H. R. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, **4**.
3. S. F. Vasilevsky and E. V. Tretyakov, *Liebigs Ann.*, 1995, 775.
4. A. V. Piskunov, A. A. Moroz, and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 828 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 755 (Engl. Transl.)].
5. M. S. Shvartsberg, A. V. Piskunov, M. A. Mzhel'skaya, and A. A. Moroz, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1423 [*Russ. Chem. Bull.*, 1993, **42**, 1357 (Engl. Transl.)].

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