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Dedicated to the Corresponding Member of the Russian Academy of Sciences B. V. Gidaspov on occasion of his 70th anniversary

Synthesis of 3-Azido-5-amino-1,2,4-triazole

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Abstract—3-Azido-5-amino-1,2,4-triazole was obtained from 3,5-diamino-1,2,4-triazole in two ways: by partial diazotization-substitution directly in the substrate or at its primarily nitrosation, and also with the use of direct or indirect protection of an amino group with subsequent conversion into azido compound followed by deprotection.

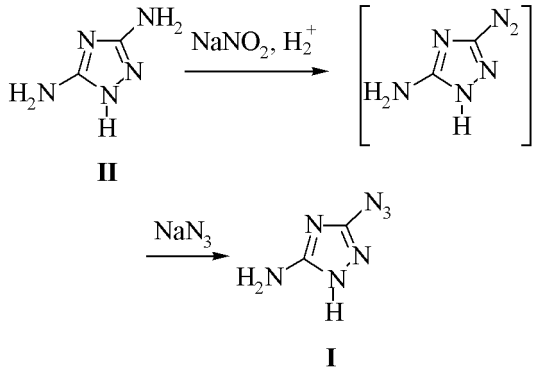
3-R-5-Amino-1,2,4-triazoles are the main group among compounds of this class that are subjected to purposeful modification through reactions of amino group (diazotization-substitution, diazotization-azo-coupling, oxidation, nitration, nitrosation, Schiff's reaction, various cyclocondensations etc.). Therefore the synthesis of new representatives of 3-R-5-amino-1,2,4-triazoles series, e.g., 3-azido-5-amino-1,2,4-triazole, can provide new possibilities.

The 3-R-5-amino-1,2,4-triazoles are commonly prepared by condensation-cyclization of appropriated reagents. However this synthesis occurs sufficiently cleanly mainly for C-alkyl, C-aryl, C-carboxy, C-carboxyalkyl derivatives and for 3,5-diamino-1,2,4-triazole (guanazole) [1–3]. The transformations at both substituents in the ring of 3-R-5-amino-1,2,4-triazoles are possible only in the group of carboxy derivatives with R = $(CH_2)_nCOOH$ and in the guanazole. Therefore just these compounds are especially valuable for they provide a possibility to synthesize a large group of versatile 3,5-disubstituted 1,2,4-triazoles [1–6].

The reactions of guanazole are a special case for the synthesis of new compounds: It may be a precursor of symmetrically disubstituted 1,2,4-triazoles [2,5], and if the reaction would proceed by a single amino group it may serve as initial product of new unsymmetrically substituted 1,2,4-triazoles [3, 4, 6]. However since both amino groups in the guanazole are virtually equivalent the reaction with electrophylic agents occurs as a rule at both functional groups; in particular, on diazotization-substitution arises usually symmetrically disubstituted 1,2,4-tetrazole, for instance, 3,5-dihalo or 3,5-dinitro derivatives [3, 5]. Nevertheless, a direct partial diazotization followed by substitution of the diazo group in the monodiazotized compound by an appropriate nucleophilic agent is also possible, as has been, for example, demonstrated in the synthesis of 5-amino-3-chloro-1,2,4-triazole [4, 6]. We attempted similar process for preparation of 3-azido-5-amino-1,2,4-triazole (**I**), using a diazotization-azidation procedure applied formerly to preparation of a large group of 3-azido-5-R-1,2,4-triazoles from the corresponding amino compounds [7].

The monodiazotization of the guanazole was carried out at low temperature (−4 ÷ −2°C) by adding equimolar amount of sodium nitrite to a solution of guanazole (**II**) in 20% sulfuric acid with subsequent addition to the reaction mixture where already existed diazonium salt of a solution of an equimolar amount of sodium azide (Scheme 1).

Scheme 1



However this seemingly simple way of monodiazotization-substitution in guanazole turned out to be of low efficiency. It is presumable that this procedure may be relatively successful in these individual cases

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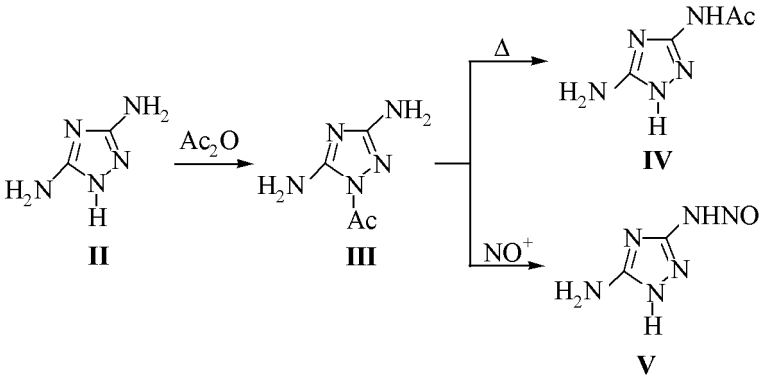
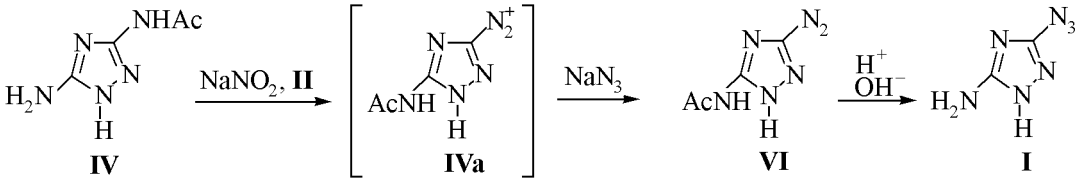
Scheme 2.



Scheme 3.



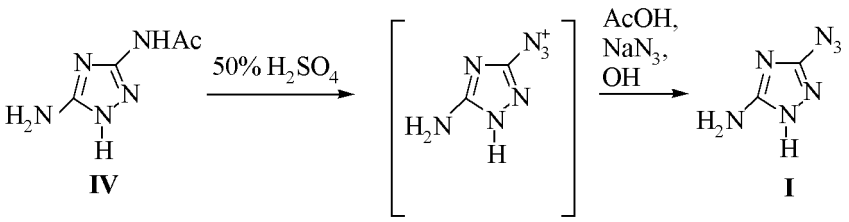
when both stages, diazotization and substitution, may be carried out in acid media, as has been performed in the synthesis of 5-amino-3-chloro-1,2,4-triazole where both reactions occur in hydrochloric acid [4]. In the synthesis of azido compound **I** along Scheme 1 where in the second stage as nucleophilic agent is used sodium azide the acidity of the medium is very important. If the acid excess used in the synthesis is small, then the acidity of the medium considerably decreases due to addition of alkaline reagents: first sodium nitrite, then sodium azide. Therefore arise mainly azocoupling products (triazenes). At the attempt to maintain the acidity of the medium on the sufficiently high level by using excess sulfuric acid the formation of side products was suppressed, but the target product was isolated only in a poor yield (5%) apparently due to the reduced activity of the protonated hydrazoic acid.

Therefore a preliminary protection of one of amino groups in the guanazole seemed more promising. The presumed protection might be performed directly by N-acylation at the heteroatom in the ring giving rise to 1-acyl-3,5-diamino-1,2,4-triazole (**III**) which at heating rearranges into 5-amino-3-acetamido-1,2,4-triazole (**IV**) (Scheme 2) [8]. Besides a partial nitrosation of one amino group may be performed affording 5-amino-3-nitrosamino-1,2,4-triazole (**V**) [6, 9] which is a cryptic form of monodiazo compound that in acid medium transforms into 5-amino-3-diazo-1,2,4-triazole [4, 6]. We tried to subject both compounds **IV** and **V** to azidation applying the experience gained in the synthesis of 5-amino-3-nitro- and 5-amino-3-chloro-1,2,4-triazoles [10, 4]. The synthesis of intermediate compounds is described in Scheme 2.

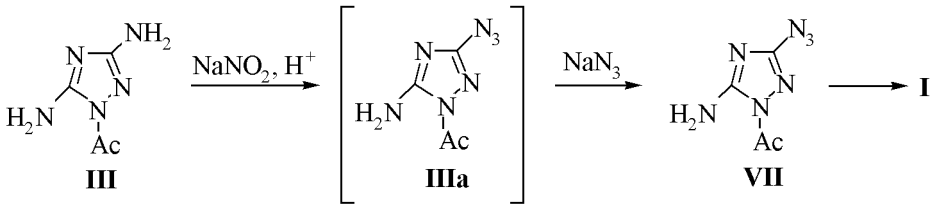
It should be noted that diazotization-substitution of monoacylated guanazole (**IV**) was performed under significantly different conditions than those used in the synthesis of the corresponding nitro derivatives [10]: The diazotization-azidation occurred only at cooling and in acid medium; therewith the intermediate diazo compound at the beginning was accumulated in the system and only afterwards was consumed as the second reagent was gradually added. This procedure is dictated by the specific features of sodium azide application at the substitution stage.

Carrying out this procedure we found that both yields of the intermediate 3-azido-5-acetamido-1,2,4-triazole (**VI**) and of the target azido compound **I** were not high (25–30 and 40% in the corresponding stages respectively) resulting in a poor overall yield (10% with respect to the initial guanazole). Besides although the method is quite reliable it is not free from other disadvantages. The method is complicated and multistage, it includes two labor-consuming long operations: the rearrangement of 1-acyl-3,5-diamino-1,2,4-triazole (**III**) into acetamide **IV** by heating in decalin, and hydrolysis of 3-azido-5-acetamido-1,2,4-triazole (**VI**) into the target product by boiling in hydrochloric acid. The synthesis is also dangerous due to the possibility of accumulation in the reaction mixture at the diazotization stage of the intermediate

Scheme 4.



Scheme 5.



diazo compound **IVa** that is virtually insoluble in the reaction mixture.

We regarded as simpler procedure that with application of 5-amino-3-nitrosamino-1,2,4-triasole (**V**) which is available and formed virtually in quantitative yield at equimolar nitrosation of guanazole with sodium nitrite in the acid medium [9]. Nitrosamine **V** was successfully used formerly in the synthesis of unsymmetrically substituted 1,2,4-triazoles [6], among them also azido derivatives. In particular, it was reduced to 5-amino-3-hydrazino-1,2,4-triazole that by treating with sodium nitrite [6] afforded not 3-azido-5-amino-1,2,4-triazole but 5-azido-1,2,4-triazole-3-diazonium chloride and 3-nitrosamino-5-azido-1,2,4-triazole. The structure of both compounds was confirmed by reduction into 5-amino-3-hydrazino-1,2,4-triazole. At the same time we used formerly nitrosamine **V** for partial conversion of one of its amino groups in the preparation of 5-amino-3-chloro-1,2,4-triazole. Therewith the procedure was simple: its heating in the concn. hydrochloric acid (80–100°C ensured both its conversion into the diazo form and subsequent substitution of the diazo group by chlorine [4]. In azidation the hydrochloric acid and stringent conditions are out of question. But at relatively low temperature (10°C and lower) and at the use of sulfuric acid that is common for preparation of azidothiazoles nitroguanazole **V** is nearly insoluble in the reaction mixture. It turned into diazo form in amounts sufficient for the synthesis only at the acid concentration no less than 50%. In a medium of this high acidity the hydrazoic acid arising on addition of sodium azide would be protonated, and that would be unfeasible for the azidation stage. The yield of 5-amino-3-azido-1,2,4-triazole along Scheme 4 was really no better than 10–12%. But it notably grew when the acidity of the medium was reduced by diluting the obtained diazo solution with equal volume of cooled glacial acetic acid. Certain difficulties arise in this procedure at isolation of the target product from the reaction mixture.

In a series of guanazole derivatives presented on Scheme 2 appears one more compound that might be interesting for the synthesis of azido compound **I**, namely, 1-acylguanazole (**III**). It is available and forms in quantitative yield at guanazole acylation [8]. Therewith the introduction of the substituent into position *1* of the guanazole ring should result in spatial nonequivalence of the amino groups. This factor may favor a partial reaction at the distal amino group (in position *3*). For instance, it was demonstrated by an example of oxidation of the N-substituted guanazoles with sodium pertungstate that the only products of these reactions were the corresponding derivatives of 5-amino-3-nitro-1,2,3-triazole [11]. Besides in the 1-acylguanazole the activity of amino group in the *5* position should be sharply decreased due to the basicity reduction caused by introduction of an acceptor substituent into position *1*. Introduction of such substituent into the *1* position of the guanazole may serve as indirect protection of the amino group in position *5*, and the structural factors of compound **III** suggest its monoazidation in position *3*. The only problem is to conserve the N-acyl protection till the moment of diazotization-

azidation, i.e. the acylguanazole should be stable in an environment of sufficiently high acidity characteristic of this process. It turned out that acylguanazole was easily hydrolyzed both in alkaline and acidic media, and we failed to obtain 3-amino-5-nitro-1,2,4-triazole from this compound by oxidation or diazotization: the acyl derivative lost the acyl group before the target process happened.

In azidation of 1-acylguanazole the intermediate compounds **IIIa, VII** turned out to be sufficiently stable, and 1-acyl-3-azido-5-amino-1,2,4-triazole (**VII**) was isolated in satisfactory yield.

Azido compound **VII** in contrast to its isomeric analog **VI** is very easily hydrolyzed in alkaline medium furnishing the target product in 70% yield. We believe that just this version of reaction is the simplest and safest procedure for preparation of 3-azido-5-amino-1,2,4-triazole.

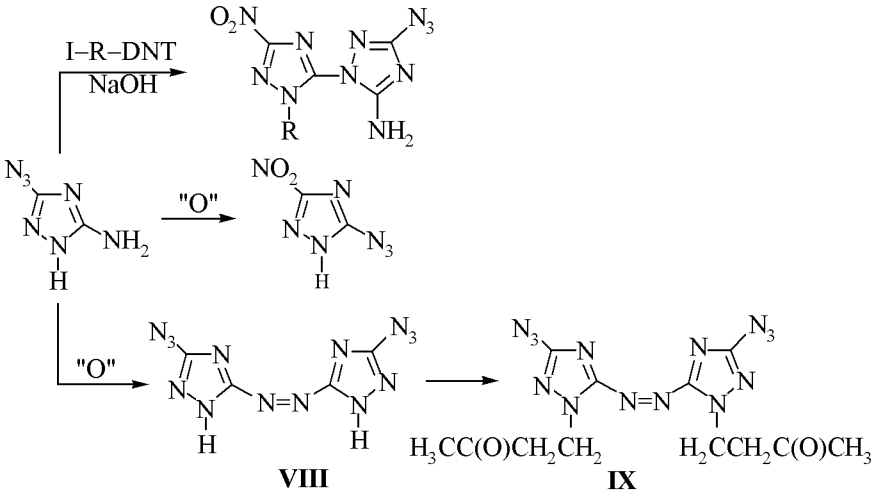
3-Azido-5-amino-1,2,4-triazole is an NH-acid of triazole series, pK_a 9.60 (potentiometric measurement). The compound is capable of reactions both at imine nitrogen and amino group. To the first type of reactions belongs heterylation of 3,5-dinitro-1,2,4-triazole derivatives(1-R-DNT, R = $CH_2CH_2COCH_3$) with nitro group replacement and formation of the corresponding N-C-bitriazoles [12]. As the second type reactions can be regarded oxidation of the amino compound **I** with various oxidants. For instance, its treatment with sodium pertungstate along procedure from [11] afforded in 50% yield 5-azido-3-nitro-1,2,4-triazole formerly synthesized by M.S.Pevzner from 5-amino-3-nitro-1,2,4-triazole [13] with the use of diazotization-substitution by method [7]. Oxidation with potassium permanganate in alkaline medium resulted in a previously unknown azobis(3-azido-1,2,4-triazol-5-yl) (**VIII**).

Azido compound **VIII** is very sensitive and unstable, it melts with ignition. Therefore we were not able to perform analysis and proved its structure only by spectral data and by synthesis of its derivative, azobis(3-azido-1-methylcarbonylethylyl-1,2,4-triazol-5-yl) (**IX**) by condensation of azotriazole **VIII** with methyl vinyl ketone in the presence of triethylamine.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometer Perkin Elmer R-12 (60 MHz) in $(CD_3)_2CO$, internal reference HMDS. IR spectra were measured on spectrophotometer Specord 75IR from thin films.

3-Azido-5-amino-1,2,4-triazole (I). (a) To a solution of 3 g (0.03 mol) of guanazole in 15 ml of 20% sulfuric acid (0.06 mol) cooled to –4°C was added at stirring a solution of 2.07 g (0.03 mol) of sodium nitrite in 20 ml of water maintaining the temperature below 0–2°C. the mixture was kept at this temperature for 1 h, and on cooling urea was added till the end of foam formation. Then at 0°C was added by portions a solution of 1.98 g (0.03 mol) of sodium azide in 20 ml of water, the reaction mixture was warmed to room temperature and kept for 30 min. If in the reaction mixture a diazo compound was present (tested azo coupling with β-naphthol) the reaction mixture was left standing for a longer time. The reaction mixture was neutralized with a solution of sodium hydrogen carbonate, the separated precipitate of triazenes was filtered off, the filtrate was extracted with ethyl acetate (3 × 30 ml), the solution was evaporated, the residue was crystallized from dioxane.



Yield 0.2 g (5.3%), mp 153–154°C. IR spectrum, cm^{-1}: 1510, 1570 (cycle), 1630, 1670,1690 (NH_2), 2175 (N_3). ^1H NMR spectrum, δ, ppm: 7.10 (NH_2, exchange in D_2O). Found, %: C 19.42, 19.13; H 2.04, 2.19; N 78.35, 78.64. $C_2H_3N_7$. Calculated, %: C 19.20; H 2.40; N 78.60.

(b) To 20 ml of 10% HCl was added 1 g (0.006 mol) of 3-azido-5-acetamido-1,2,4-triazole (**VI**), and the mixture was at stirring heated on a boiling water bath for 5 h. Then the solution was evaporated to residual volume of 3–5 ml, 5 ml of ethanol was added, carefully was added sodium hydrogen carbonate solution till pH 8, and the mixture was transferred into a Petri dish for evaporation of the solvents, The residue was crystallized from dioxane. Yield 40%, mp 153–154°C.

(c) To 10 ml of ethanol was added 1 g (0.006 mol) of 3-azido-5-amino-1-acyl-1,2,4-triazole (**VII**), a solution of sodium hydrogen carbonate was added till pH 10, the mixture was heated to 50°C and kept at that temperature for 10 min, then it was cooled to 0–5°C, acidified to pH 6–7, the separated precipitate was filtered off and recrystallized. Yield 70%, mp 153–154°C.

(d) To 10 ml of 50% sulfuric acid at 10°C was added at stirring 8.4 g (0.05 mol) of nitrosoguanazole (**V**), the mixture was kept for 1 h, 10 ml of cooled glacial acetic acid was added, and at 5–10°C was added a solution of 3.9 g (0.06 mol) of sodium azide in 5 ml of water. The reaction mixture was kept for 0.5 h, then it was transferred into a Petri dish and evaporated in the cold. Then a solution of sodium hydrogen carbonate was added till pH 6–7 and evaporated till dryness. The target product was extracted with ethanol, the solvent was evaporated, the residue was crystallized. Yield 40%, mp 153–154°C.

3-Azido-5-acetamido-1,2,4-triazole (VI). To a solution of 3 g (0.021 mol) of 3-amino-5-acetamido-1,2,4-triazole (**IV**) in 21.5 ml (0.05 mol) of sulfuric acid at cooling while stirring was added dropwise a solution of 1.5 g (0.021 mol) of sodium nitrate in 1.7 ml of water maintaining temperature below 0–2°C. The reaction mixture was kept at this temperature for 1 h, then a little urea was added, and at 0–2°C was added by portions a solution of 1.64 g (0.025 mol) of sodium azide in 13.5 ml of water. The reaction mixture was warmed to room temperature and stirred for 0.5 h. The separated precipitate was filtered off and washed with water on the filter. To the filtrate a solution of sodium hydrogen carbonate was added till pH 5, then the reaction product was extracted into ethyl acetate (2 × 20 ml). The residue after evaporation of the solvent was added to the main amount of the product, and the substance was crystallized from dioxane. Yield 25–30%, mp 210–212°C. IR spectrum, cm^{-1}: 1525 (cycle), 1640 (NH), 1720 (CO), 2170 (N_3). ^1H NMR spectrum, δ, ppm: 2.10 (CH_3), 11.82 (NH, exchange in D_2O). Found, %: C 29.07, 28.77; H 3.18, 2.95; N 58.68, 58.66. $C_4H_5N_7O$. Calculated, %: C 28.74; H 2.99; N 58.68.

3-Azido-5-amino-1-acetyl-1,2,4-triazole (VII). Azole **III** was treated at 0–2°C with a solution of sodium nitrite as described above, the reaction mixure at cooling was diluted with the same volume of glacial acetic acid and after addition of a small amount of urea azidation was carried out by adding portions of sodium azide solution in double excess maintaining temperature at 0–2°C. After keeping the reaction mixture for 0.5 h at this temperature it was warmed to room temperature, and filtered. The residue after evaporation of the filtrate was several times treated with hot ethanol, and the liquid was decanted through a folded paper filter into a Petri dish for evaporation. On removing ethanol the residue was crystallized from 2-propanol. Yield 35–40%, mp 155–156°C. IR spectrum, cm^{-1}: 1535 cycle), 1670 (NH_2), 1780 (CO), 2180 (N_3). ^1H NMR spectrum, δ, ppm: 2.50 (CH_3), 7.35 (NH_2, exchange in D_2O). Found, %: C 28.87, 28.64; H 3.04, 2.92; N 58.35, 58.44. $C_4H_5N_7O$. Calculated, %: C 28.74; H 2.99; N 58.68.

Azobis(3-azido-1,2,4-triazol-5-yl) (VIII). To a suspension of 4 g (0.032 mol) of 3-azido-5-amino-1,2,4-triazole in 25 ml of water was added a solution of 6 g (0.107 mol) of KOH in 25 ml of water. Then at stirring was added by portions 4 g (0.025 mol) of potassium permanganate maintaining the temperature below 50°C. The reaction mixture was cooled to room temperature, the separated manganese oxide was filtered off and washed on the filter with a small amount of water. The filtrate and washings were combined, the solution was heated to 70°C, cautiously acidified with glacial acetic acid (minimizing foaming) till pH 4, the solution was evaporated in a vacuum till residual volume of 50–60 ml, filtered, and this filtrate was left standing in a refrigerator for 24 h. The separated precipitate was filtered off and recrystallized from water. Yield 51%, mp about 180°C (with ignition). IR spectrum, cm^{-1}: 1490, 1570 (cycle), 2170 (N_3). ^1H NMR spectrum, δ, ppm: 10.10 (NH, exchange in D_2O).

Azobis(3-azido-1-methylcarbonylethylyl-1,2,4-triazol-5-yl) (IX). To a suspension of 3.45 g

(0.014 mol) of azotriazole **VIII** in 75 ml of ethanol was added 2.10 g (0.030 mol) of methyl vinyl ketone and 1.5 ml of triethylamine, the mixture was heated to 70°C and was stirred till the reaction mixture homogenized, and then the stirring was continued for 2 h at 60–70°C. Then the solution was cooled, acidified with diluted hydrochloric acid till pH 5–6, the separated unreacted azotriazole **VIII** was filtered off, the filtrate was evaporated, and the residue was crystallized from ethanol. Yield 30%, mp 165–166°C. IR spectrum, cm^{-1}: 1480, 1500, 1520, 1530 (cycle), 1740 (CO), 2140, 2180 (N_3). ^1H NMR spectrum, δ, ppm: 2.20 s (6H, CH_3), 4.30 t, 3.25 t (8H, CH_2). Found, %: C 37.10, 37.29; H 3.44, 3.33; N 50.75, 50.44. *M* 396. $C_{12}H_{14}N_{14}O_2$. Calculated, %: C 37.28; H 3.65; N 50.76. *M* 386.33.

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REFERENCES

1. Potts, K.T., *Chem. Revs.*, 1961, vol. 61, p. 119; Boier, J., *Heterocyclic Compounds*, Elderfield, R.C., Ed., New York: Wiley, 1957, vol. 6. Translated under the title *Geterotsiklicheskie soedineniya*, Moscow: Inostrannaya Literatura, 1960, vol. 6, pp. 268–309.
2. Kofman, T.P., Uvarova, T.A., and Kartseva, G.Yu., *Zh. Org. Khim.*, 1995, vol. 31, p. 270.
3. Stolle, R. and Krauch, K., *J. Prakt. Chem.* [2]., 1913, vol. 88, p. 306.
4. Kofman, T.P., Uspenskaya T.L., and Pevzner M.S., *Zh. Org. Khim.*, 1993, vol. 29, p. 2328.
5. Bagal, L.I., Pevzner, M.S., Frolov, A.N., and Sheludyakova, N.I., *Khim. Geterotsikl. Soed.*, 1970, p. 259.
6. Stolle, R. and Dietrich, W., *J. Prakt. Chem.*, 1934, vol. 139, p. 193.
7. Heitke, B.T. and McCarty, C.G., *J. Org. Chem.*, 1974, vol. 39, p. 1522.
8. Van den Bos, B.G., *Rec. Trav. Chim.*, 1960, vol. 79, p. 836.
9. Namestnikov, V.I., Kofman, T.P., and Pevzner, M.S., USSR Inventor's Certificate 1027159, 1982; *SSSR Byull. Izobr.*, 1983, no. 25.
10. Pevzner, M.S., Gladkova, N.V., and Kravchenko, T.A., *Zh. Org. Khim.*, 1996, vol. 32, p. 1230.
11. Kofman, T.P. and Paketina, E.A., *Zh. Org. Khim.*, 1997, vol. 33, p. 1201.
12. Kofman, T.P., Kartseva, G.Yu., Namestnikov, V.I., and Paketina, E.A., *Zh. Org. Khim.*, 1998, vol. 34, p. 1084.
13. Pevzner, M.S., *Ros. Khim. Zh.*, 1997, vol. 41, p. 73; Pevzner, M.S., Martynova, M.N., and Timofeeva, T.N., *Khim. Geterotsikl. Soed.*, 1974, 1288.