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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Regioselective Synthesis of Alkyl Derivatives of 3,5-Diamino-1,2,4-triazole

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Abstract—New procedures were suggested for regioselective synthesis of alkyl derivatives of 3,5-diamino-1,2,4-triazole.

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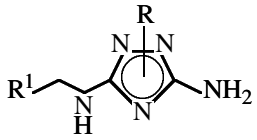
Alkyl derivatives of 3,5-diamino-1,2,4-triazole of general formula **I** are used in medicine as blockators of histamine [1, 2] and neurokinin [3] receptors, inhibitors of peroxide oxidation of lipids [4], and agents for treating diabetes and other diseases [5, 6].



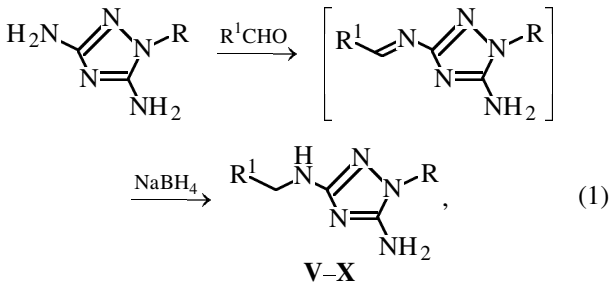
I

The most important synthetic routes to compounds **I** are based on condensation of hydrazines $RNHNH_2$ with *N*-alkyl-*N*'-cyano-*S*-methylisothioureas [2, 6, 7], 3-R^1-2-cyanoiminothiazolidines [4], or *N*-alkyl-*N*'-cyano-*O*-phenylisoureas [3, 8], or on base-catalyzed cyclization of 1-alkyl-3-isopropylidenaminoamidinothioureas [9] prepared by the reaction of isopropylidenaminoguanidine with alkyl isothiocyanates. The major drawbacks of methods [2, 4, 6–9] is the use of difficultly available expensive chemicals or low yield of the target products. Furthermore, the reactions of *N*-cyano compounds with substituted hydrazines ($R \neq H$) sometimes yield mixtures of regioisomers [8].

It seems more promising to prepare compounds **I** from readily accessible 3,5-diamino-1-R-1,2,4-triazoles (R = H, Alk, Ar). For example, by alkylation of 3,5-diamino-1-phenyl-1,2,4-triazole with 2-methoxybenzyl chloride under the conditions of deprotonation of the amino group (THF, *t*-BuOK), Dunstan et al. [3] prepared 3-amino-5-*o*-methoxybenzylamino-1-phenyl-1,2,4-triazole in 30% yield [3]. However, alkylation is not a versatile route to compounds **I**, because at R = H this reaction occurs at the 1-position of the triazole ring [7, 10].

The goal of this study was to develop new procedures for regioselective synthesis of alkyl derivatives of 3,5-diamino-1,2,4-triazole of general formula **I**. We found that an efficient route to 3-alkylamino-5-amino-1-R-1,2,4-triazoles (R = H, Bn, Ph) is hydrogenation of Schiff bases prepared by reactions of 3,5-diamino-1-R-1,2,4-triazoles **II**–**IV** with aldehydes.

Condensation of diamines **II** and **III** with aldehydes at eqimolar ratio of the reactants or at a small excess of diamine in ethanol occurs regioselectively at the 3-amino group [10]. Hydrogenation of Schiff bases with sodium borohydride was performed without their isolation from the reaction mixture [scheme (1)]; in the process, we obtained 5-amino-1-benzyl-3-benzylamino-1,2,4-triazole **V**, 5-amino-1-benzyl-3-*p*-methoxybenzylamino-1,2,4-triazole **VI**, 5-amino-3-*o*-methoxybenzylamino-1-phenyl-1,2,4-triazole **VII**, 5-amino-1-phenyl-3-(2-furylmethyl)amino-1,2,4-triazole **VIII**, 5-amino-3-(4-benzyloxybenzyl)amino-1-phenyl-1,2,4-triazole **IX**, and 5-amino-1-phenyl-3-(3-phenylpropyl)-amino-1,2,4-triazole **X**:



V–**X** (1)

where R = Bn (**II**, **V**, **VI**), Ph (**III**, **VII**–**X**), R^1 = Ph (**V**), *p*-$MeOC_6H_4$ (**VI**), *o*-$MeOC_6H_4$ (**VII**), 2-furyl (**VIII**), = *p*-$BnOC_6H_4$ (**IX**), $PhCH_2CH_2$ (**X**).

The yields and properties of **V**–**X** are given in the table.

To prepare 3-alkylamino-5-amino-1,2,4-triazoles (R = H), it is advisable to use instead of expensive 3,5-diamino-1,2,4-triazole **IV** its more available derivatives: nitrate **XI** [11, 12] or 1-acetyl-3,5-diamino-1,2,4-triazole **XII** [13]. To prepare alkyl derivatives from nitrate **XI**, it is necessary to add to the reaction

Yields and properties of the sompounds synthesized

Compound no.*	Yield, % (synthesis procedure)	mp, °C	Found, % / Calculated, %			Formula	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
			C	H	N		
V	61	173–175	68.5 / 68.8	6.0 / 6.1	25.2 / 25.0	$C_{16}H_{17}N_5$	4.16 d (2H, CH_2, *J* = 6.5), 4.86 s (2H, CH_2), 5.85 t (1H, NH, *J* = 6.5), 6.04 s (2H, NH_2), 7.11–7.30 m (10H, 2Ph)
VI	65	169–170	66.1 / 66.0	6.3 / 6.2	22.4 / 22.6	$C_{17}H_{19}N_5O$	3.70 s (3H, OMe), 4.08 d (2H, CH_2, *J* = 6.5), 4.86 s (2H, CH_2), 5.73 t 1H, NH, *J* = 6.5), 6.03 s (2H, NH_2), 6.80 m (2H, arom.), 7.11–7.31 m (7H, arom.)
VII	72	171–172	65.3 / 65.1	5.7 / 5.8	23.5 / 23.7	$C_{16}H_{17}N_5O$	3.79 s (3H, OMe), 4.24 d (2H, CH_2, *J* = 6.4), 5.63 t (1H, NH, *J* = 6.4), 6.22 s (2H, NH_2), 6.84–6.96 m (2H, arom.), 7.15–7.21 m (2H, arom.), 7.28 m (1H, arom.), 7.37–7.47 m (4H, arom.)
VIII	66	136–137	61.2 / 61.2	5.0 / 5.1	27.7 / 27.4	$C_{13}H_{13}N_5O$	4.22 d (2H, CH_2, *J* = 6.3), 6.12 t (1H, H, *J* = 6.3), 6.21 m (1H, CH of furan), 6.24 s (2H, NH_2), 6.35 m (1H, CH of furan) 7.20 m (1H, CH of furan), 7.39–7.52 m (5H, Ph)
IX	60	167–168	71.4 / 71.1	5.6 / 5.7	19.0 / 18.9	$C_{22}H_{21}N_5O$	4.17 d (2H, CH_2, *J* = 6.2), 5.05 s (2H, CH_2), 6.13 t (1H, NH, *J* = 6.2), 6.21 s (2H, NH_2), 6.92 m (2H, arom.), 7.17–7.48 m (12H, arom.)
X	70	114–115	70.0 / 69.6	6.4 / 6.5	23.8 / 23.9	$C_{17}H_{19}N_5$	1.80 m (2H, CH_2), 2.62 t (2H, CH_2, *J* = 7.6), 3.05 m (2H, CH_2), 5.67 br.s (1H, NH), 6.18 s (2H, NH_2), 7.15–7.28 m (6H, arom.), 7.38–7.49 m (4H, arom.)
XIII	40 (A)	147–148 148–149 [9]	57.3 / 57.1	6.1 / 5.9	36.9 / 37.0	$C_9H_{11}N_5$	4.20 d (2H, CH_2, *J* = 6.2), 5.32 br.s (2H, NH_2), 6.09 br.s (1H, NH), 7.17–7.28 m (5H, Ph), 10.72 s (1H, NH)
XIV	60 (A) 76 (B)	194–196	54.7 / 54.8	6.0 / 6.0	32.0 / 31.9	$C_{10}H_{13}N_5O$	3.69 s (3H, OMe), 4.11 d (2H, CH_2, *J* = 6.5), 5.37 br.s (2H, NH_2), 5.85 br.s (1H, NH), 6.82 d (2H, arom., *J* = 8.6), 7.21 d (2H, arom.), 10.68 s 1H, NH)
XV	60 (A)	193–194	48.1 / 48.3	4.6 / 4.5	31.5 / 31.3	$C_9H_{10}N_5Cl$	4.18 d (2H, CH_2, *J* = 6.3), 5.50 br.s (2H, NH_2), 6.0 br.s (1H, NH), 7.26–7.35 m (4H, arom.), 10.7 br.s (1H, NH)
XVI	62 (B)	178–180	46.2 / 46.1	4.3 / 4.3	36.0 / 35.9	$C_9H_{10}N_6O_2$	4.31 d (2H, CH_2, *J* = 5.9), 5.65 br.s (2H, NH_2), 6.16 br.s (1H, NH), 7.57 m (1H, arom.), 7.76 m (1H, arom.), 8.04 m (1H, arom.), 8.17 s (1H, arom.), 10.71 s (1H, NH)

Table. (Contd.)

Compound no.*	Yield, % (sinthesis procedure)	mp, °C	Found, % / Calculated, %			Formula	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
			C	H	N		
XVII	78 (B)	207–208	40.3 / 40.3	3.9 / 3.8	26.0 / 26.1	$C_9H_{10}N_5Br$	4.19 d (2H, CH_2, *J* = 6.4), 5.42 br.s (2H, NH_2), 6.15 br.s (1H, NH), 7.25 m (2H, arom.), 7.37 m (1H, arom.), 7.47 s (1H, arom.), 10.73 br.s (1H, NH)
XVIII	70 (B)	238–240	53.1 / 53.0	6.2 / 6.1	28.0 / 28.1	$C_{11}H_{15}N_5O_2$	3.69 s (3H, OMe), 3.70 s (3H, OMe), 4.11 d (2H, CH_2, *J* = 6.4), 5.50 br.s (3H, NH + NH_2), 6.82 m (2H, arom.), 6.92 s (1H, arom.), 10.70 br.s (1H, NH)
XIX	50 (B)	138–139	43.1 / 43.0	4.6 / 4.7	36.0 / 35.9	$C_7H_9N_5S$	4.35 d (2H, CH_2, *J* = 5.8), 5.63 br.s (2H, NH_2), 5.81 br.s (1H, NH), 6.91 m (2H, 2CH of thiophene), 7.30 m (1H, CH of thiophene), 10.7 s (1H, NH)
XX	40	123–124	61.0 / 60.8	7.1 / 7.0	31.9 / 32.2	$C_{11}H_{15}N_5$	1.74 m (2H, CH_2), 2.58 t (2H, CH_2, *J* = 7.7), 2.98 m (2H, CH_2), 4.81 br.s (1H, NH), 5.40 br.s (2H, NH_2), 7.11–7.28 m (5H, Ph), 10.66 s (1H, NH)
XXI	34	170–171	71.3 / 71.6	7.6 / 7.5	20.7 / 20.9	$C_{20}H_{25}N_5$	1.75 m (4H, $2CH_2$), 2.58 t (4H, $2CH_2$, *J* = 7.7), 2.99 m (4H, $2CH_2$), 5.72 br.s (2H, 2NH), 7.12–7.28 m (10H, 2Ph), 10.76 s (1H, NH)
XXIV	72	181–182	64.3 / 64.5	5.2 / 5.1	20.9 / 20.9	$C_{18}H_{17}N_5O_2$	2.07 s (3H, Me), 3.94 s (3H, OMe), 7.09 m (1H, arom.), 7.21 m (1H, arom.), 7.42 m (1H, arom.), 7.56–7.65 m (3H, arom.), 7.79 m (2H, arom.), 7.98 m (1H, arom.), 9.58 s (1H, CH=N), 10.60 s (1H, NH)
XXV	78	194–195	64.0 / 64.1	5.9 / 5.7	20.5 / 20.8	$C_{18}H_{19}N_5O_2$	1.95 s (3H, Me), 3.79 s (3H, OMe), 4.40 d (2H, CH_2, *J* = 5.6), 6.86–6.96 m (2H, arom.), 7.06 t (1H, NH, *J* = 5.6), 7.18–7.23 m (2H, arom.), 7.38 m (1H, arom.), 7.50–7.57 m (4H, arom.), 10.18 br.s (1H, NH)
XXVI	73	114–115	68.1 / 68.0	6.2 / 6.3	20.7 / 20.9	$C_{19}H_{21}N_5O$	1.90 s (3H, Me), 2.25 s (3H, Me), 4.36 d (2H, CH_2, *J* = 5.5), 5.08 s (2H, CH_2), 7.07–7.35 m (10H, arom. NH), 10.0 br.s (1H, NH)
XXVII	68	128–129	67.3 / 67.3	5.9 / 6.0	21.7 / 21.8	$C_{18}H_{19}N_5O$	1.98 s (3H, Me), 2.25 s (3H, Me), 4.37 d (2H, CH_2, *J* = 5.8), 7.08–7.51 m (10H, arom. + NH), 10.13 s (1H, NH)
XXVIII	78	186–187	58.2 / 57.9	4.5 / 4.6	24.1 / 23.9	$C_{17}H_{16}N_6O_3$	1.96 s (3H, Me), 4.54 d (2H, CH_2, *J* = 5.6), 7.36–7.64 m (7H, arom. + NH), 7.81 m (1H, arom.), 8.04–8.19 m (2H, arom.), 10.15 s (1H, NH)
XXIX	74	121–123	57.5 / 57.5	5.0 / 4.9	22.6 / 22.4	$C_{15}H_{15}N_5OS$	2.00 s (3H, Me), 4.58 d (2H, CH_2, *J* = 5.9), 6.92–7.00 m (2H, CH of thiophene + NH), 7.34–7.54 m (7H, Ph + CH of thiophene), 10.18 s (1H, NH)

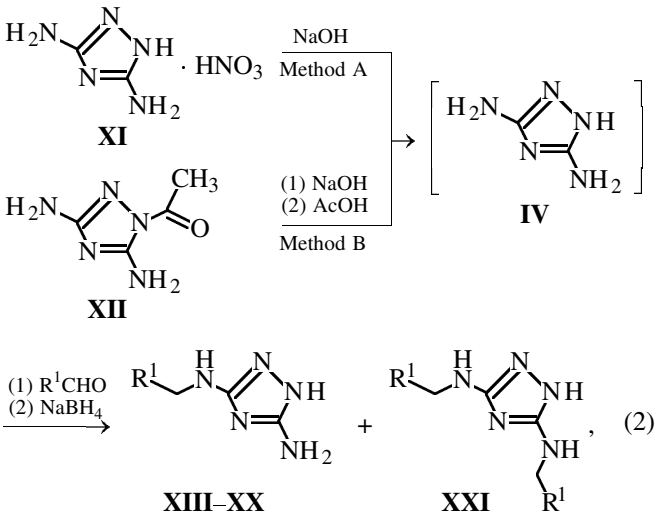
Table. (Contd.)

Compound no.*	Yield, % (sinthesis procedure)	mp, °C	Found, % / Calculated, %			Formula	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
			C	H	N		
XXX	70	125–126	65.3 / 65.1	5.8 / 5.8	23.6 / 23.7	$C_{16}H_{17}N_5O$	3.79 s (3H, OMe), 4.38 d (2H, CH_2, *J* = 5.8), 5.19 s (2H, NH_2), 6.74 t (1H, NH, *J* = 5.8), 6.86–6.96 m (2H, arom.), 7.17–7.26 m (3H, arom.), 7.43–7.52 m (4H, arom.)
XXXI	86	131–132	69.4 / 69.6	6.6 / 6.5	23.7 / 23.9	$C_{17}H_{19}N_5$	2.25 s (3H, Me), 4.33 d (2H, CH_2, *J* = 5.9), 4.84 s (2H, NH_2), 4.89 s (2H, CH_2), 6.88 t (1H, NH, *J* = 5.9), 7.06–7.32 m (9H, arom.)
XXXII	85	121–122	68.6 / 68.8	6.2 / 6.1	25.2 / 25.1	$C_{16}H_{17}N_5$	2.25 s (3H, Me), 4.35 d (2H, CH_2, *J* = 5.7), 5.17 s (2H, NH_2), 6.90 (1H, NH, *J* = 5.7), 7.09 m (2H, arom.), 7.19–7.24 m (3H, arom.), 7.40–7.48 m (4H, arom.)
XXXIII	83	137–138	58.3 / 58.1	4.7 / 4.6	27.3 / 27.1	$C_{15}H_{14}N_6O_2$	4.51 d (2H, CH_2, *J* = 5.7), 5.19 s (2H, NH_2), 7.16 t (1H, NH, *J* = 5.7), 7.22–7.28 m (1H, arom.), 7.43–7.48 m (4H, arom.), 7.58–7.63 m (1H, arom.), 7.77–7.81 m (1H, arom.), 8.06–8.18 m (2H, arom.)
XXXIV	68	144–146	57.3 / 57.5	4.7 / 4.8	26.0 / 25.8	$C_{13}H_{13}N_5S$	4.55 d (2H, CH_2, *J* = 5.9), 5.23 s (2H, NH_2), 6.91–6.98 m (2H, CH of thiophene), 7.04 t (1H, NH, *J* = 5.9), 7.23–7.44 m (6H, Ph + CH of thiophene)

* Compounds **V**, **VI**, **VIII**, **IX**, **XIV**–**XVIII**, **XXI**, **XXIV**–**XIX**, **XXXII**, and **XXXIII** were srystallized from EtOH; **VII**, **X**, and **XXX**, from MeCN; and **XIII**, **XIX**, **XIX**, **XX**, and **XXXIV**, from H_2O.

mixture an equivalent amount of NaOH to adjust the required pH 7–9.

With acetyl derivative **XII** used as the starting compound, the first step is base hydrolysis to diamine **IV**; this is followed by the reaction with an aldehyde and hydrogenation of the resulting Schiff base [scheme (2)]:



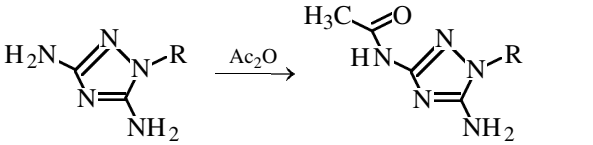
(2)

where R^1 = Ph (**XIII**), *p*-$MeOC_6H_4$ (**XIV**), *p*-ClC_6H_4 (**XV**), *m*-$NO_2C_6H_4$ (**XVI**), *m*-BrC_6H_4 (**XVII**), 3,4-$(MeO)_2C_6H_3$ (**XVIII**), 2-thienyl (**XIX**), $PhCH_2CH_2$ (**XX**, **XXI**).

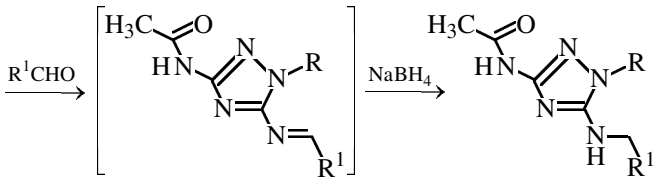
All the steps can be performed in the one-pot mode without isolation of the intermediates. By this scheme we prepared 5-amino-3-benzylamino-1,2,4-triazole **XIII**, 5-amino-3-*p*-methoxybenzylamino-1,2,4-triazole **XIV**, 5-amino-3-*p*-chlorobenzylamino-1,2,4-triazole **XV**, 5-amino-3-*m*-nitrobenzylamino-1,2,4-triazole **XVI**, 5-amino-3-*m*-bromobenzylamino-1,2,4-triazole **XVII**, 5-amino-3-(3,4-dimethoxybenzyl)amino-1,2,4-triazole **XVIII**, 5-amino-3-(2-thienylmethyl)amino-1,2,4-triazole **XIX**, and 5-amino-3-(3-phenylpropyl)-amino-1,2,4-triazole **XX**. It should be noted that in the synthesis of **XX** we obtained as the second product 3,5-bis(3-phenylpropyl)amino-1,2,4-triazole **XXI**. The yield of **XXI** decreased with a decrease in the temperature in the step of condensation of diamine **IV** with 3-phenylpropanal, with a simultaneous increase in the yield of **XX**. Thus, condensation of diamine **IV** with aliphatic aldehydes is less selective than the condensation with aromatic aldehydes.

The yields and properties of **XIII**–**XXI** are listed in the table.

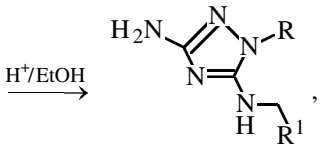
To prepare 5-alkylamino-3-imino-1-R-1,2,4-triazoles, we suggested a procedure based on the following reaction sequence:



II, **III** **XXII**, **XXIII**



XXV–**XXIX**



XXX–**XXXIV**

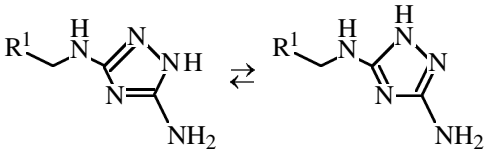
where R = Bn (**XXII**, **XXVI**, **XXXI**), Ph (**XXIII**, **XXV**, **XXVII**–**XXX**, **XXXII**–**XXXIV**); R^1 = *o*-$MeOC_6H_4$ (**XXV**, **XXX**), *p*-MeC_6H_4 (**XXVI**, **XXVII**, **XXXI**, **XXXII**), *m*-$NO_2C_6H_4$ (**XXVIII**, **XXXIII**), 2-thienyl (**XXIX**, **XXXIV**).

The synthesis of acetyl derivatives **XXII** and **XXIII** is described in [14]. The condensation of **XXII** and **XXIII** with aldehydes was performed in refluxing DMF, because under milder conditions the reaction is very slow. By so doing, we obtained 3-acetylamino-5-*o*-methoxybenzylidenamino-1-phenyl-1,2,4-triazole **XXIV** (see table) in 72% yield. To prepare the alkyl derivatives, the Schiff bases were hydrogenated without isolation; by so doing, we prepared 3-acetylamino-5-*o*-methoxybenzylamino-1-phenyl-1,2,4-triazole **XXV**, 3-acetylamino-1-benzyl-5-*p*-methylbenzylamino-1,2,4-triazole **XXVI**, 3-acetylamino-5-*p*-methylbenzylamino-1-phenyl-1,2,4-triazole **XXVII**, 3-acetylamino-5-*m*-nitrobenzylamino-1-phenyl-1,2,4-triazole **XXVIII**, and 3-acetylamino-5-(2-thienylmethyl)amino-1-phenyl-1,2,4-triazole **XXIX**. By hydrolysis of **XXV**–**XXIX**, we prepared 3-amino-5-*o*-methoxybenzylamino-1-phenyl-1,2,4-triazole **XXX**, 3-amino-1-benzyl-5-*p*-methylbenzylamino-1,2,4-triazole **XXXI**, 3-amino-5-*p*-methylbenzylamino-1-phenyl-1,2,4-triazole **XXXII**, 3-amino-5-*m*-nitrobenzylamino-1-phenyl-1,2,4-triazole **XXXIII**, and 3-amino-5-(2-thienylmethyl)amino-1-phenyl-1,2,4-triazole **XXXIV**. The yields and properties of **XXX**–**XXXIV** are given in the table.

The structures of the compounds were determined by elemental analysis and ^1H NMR spectroscopy, and their purity was confirmed by HPLC.

The position of the R^1CH_2 group in **V**–**X** and **XXX**–**XXXIV** was determined from the ^1H NMR spectra taking into account the facts [7, 14] that the chemical shift of the protons of the unsubstituted amino group in 3-alkylamino-5-amino-1-R-1,2,4-triazoles is about 6 ppm, and in 5-alkylamino-3-amino-1-R-1,2,4-triazoles, about 5 ppm. Isomeric triazoles **VII** and **XXX** were described previously [3], and their structure was determined by single crystal X-ray diffraction. The ^1H NMR spectra of **VII** and **XXX** are similar to those given in [3].

Alkyl derivatives **XIII**–**XX** can exist in the form of tautomers **A** and **B**:



A **B**

The prototropy can lead to strong broadening of the signals of the amino and imino groups. According to the ^1H NMR spectra, in DMSO tautomer **B** prevails (the signal of amino group protons is observed at 4.8–5.6 ppm, see table).

EXPERIMENTAL

The ^1H NMR spectra were taken on a Varian Unity-300 spectrometer (300 MHz, DMSO-d_6, internal reference TMS). HPLC analysis was performed on a Milikhrom-5 chromatograph equipped with a UV detector. An 80 × 2-mm column was packed with Separon C18; eluent methanol, elution rate 80 μl min^{-1}, detection at 210 nm. The starting compounds **II** and **III** were prepared by procedures described in [10, 15].

3-Alkylamino-5-amino-1-R-1,2,4-triazoles V–IX. A solution of 0.06 mol of diamine **II** or **III** and 0.06 mol of appropriate aldehyde in 100 ml of ethanol was refluxed for 1 h, after which 3.42 g (0.09 mol) of $NaBH_4$ was added in small portions at a rate providing uniform boiling of the reaction mixture. The mixture was refluxed for an additional 30 min, after which the solvent was distilled off, and 40 ml of water was added to the residue. The resulting solution was cooled, and the precipitate was filtered off, washed with water, and recrystallized.

5-Amino-1-phenyl-3-(3-phenylpropyl)amino-1,2,4-triazole X. A solution of 0.74 g (0.0055 mol) of 3-phenylpropanal in 5 ml of ethanol was added dropwise over a period of 10 min with vigorous stirring at 0–5°C to a solution of 1.05 g (0.006 mol) of **III** in 10 ml of ethanol. The mixture was stirred for 2 h, after which 0.34 g (0.009 mol) of $NaBH_4$ was added in portions at 20–30°C. The mixture was stirred for 30 min, heated to boil, and refluxed for 30 min. The solvent was distilled off, 10 ml of water was added to the residue, the oil that separated out was extracted with chloroform (3 × 5 ml), and the extract was filtered through a bed of alumina (4 cm in diameter, 3 cm high). The solvent was distilled off, and compound **X** was crystallized from acetonitrile.

3-Alkylamino-5-amino-1,2,4-triazoles XIII–XIX. *a*. A solution of 2.9 g (0.072 mol) of NaOH in 2 ml of water was added to a suspension of 10 g (0.063 mol) of nitrate **XI** in 20 ml of ethanol. The mixture was refluxed for 5 min, after which a solution of 0.057 mol of appropriate aldehyde in 10 ml of ethanol was added, the mixture was refluxed for 1 h, and 3.3 g (0.086 mol) of $NaBH_4$ was added in portions. The mixture was refluxed for an additional 30 min, the solvent was evaporated to a small volume, and 40 ml of water was added to the residue. The resulting solution was cooled, and the precipitate thus formed was filtered off, washed with water, and crystallized.

b. A solution of 4.8 g (0.12 mol) of NaOH in 10 ml of H_2O was added with stirring to a suspension of 14.1 g (0.1 mol) of acetyl derivative **XII** in 50 ml of ethanol. The mixture was refluxed until it became fully homogeneous (10–15 min), after which it was neutralized with acetic acid to pH 7–9, and 10.1 g (0.09 mol) of appropriate aldehyde was added dropwise with stirring. The mixture was refluxed for 20 min, after which 5.13 g (0.135 mol) of $NaBH_4$ was added in portions over a period of 10 min. The mixture was refluxed for an additional 20 min and evaporated to a small volume. The residue was diluted with 100 ml of water, and the resulting solution was evaporated by half and cooled. The precipitate thus formed was filtered off, washed with water, and crystallized.

5-Amino-3-(3-phenylpropyl)amino-1,2,4-triazole XX and 3,5-di(3-phenylpropyl)amino-1,2,4-triazole XXI. A solution of 12.06 g (0.09 mol) of 3-phenylpropanal in 10 ml of ethanol was added with vigorous stirring over a period of 10 min at 0–5°C to the reaction mixture obtained as described above by hydrolysis of 14.1 g (0.1 mol) of acetyl derivative **XII.** The mixture was stirred for 2 h, after which 5.7 g (0.15 mol) of $NaBH_4$ was added in small portions at 20–30°C. The mixture was stirred for 30 min, heated to boil, and refluxed for 30 min. The solvent was distilled off, 300 ml of water was added to the residue, and the precipitate (compound **XXI**) was filtered off, washed with water, dried, and crystallized.

The filtrate and wash waters were evaporated to a volume of 50 ml; the precipitate that formed on cooling (compound **XX**) was filtered off and crystallized.

3-Acetylamino-5-*o*-methoxybenzylidenamino-1-phenyl-1,2,4-triazole XXIV. A mixture of 1 g (0.0046 mol) of **XXIII**, 0.75 g (0.0055 mol) of 2-methoxybenzaldehyde, and 1 ml of DMF was refluxed for 1 h, diluted with 10 ml of water, and extracted with chloroform (3 × 10 ml). The extract was dried over $CaCl_2$ and filtered through a bed of alumina (4 cm in diameter, 3 cm high); the solvent was distilled off, and the residue was crystallized.

5-Alkylamino-3-acetylamino-1-R-1,2,4-triazoles XXV–XXIX. A mixture of 0.01 mol of **XXII** or **XXIII** and 0.012 mol of appropriate aldehyde in 2 ml of DMF was refluxed for 1 h and diluted with 20 ml of ethanol. To the resulting solution, 0.68 g (0.018 mol) of $NaBH_4$ was added in small portions at 50–60°C, after which the mixture was refluxed for 30 min. The solvent was evaporated to a small volume, and 40 ml of water was added to the residue. The precipitate thus formed was filtered off, washed with water, and crystallized.

5-Alkylamino-3-amino-1-R-1,2,4-triazoles XXX–XXXIV. A mixture of 0.005 mol of **XXV–XXIX**, 10 ml of ethanol, and 3 ml of concentrated HCl was refluxed for 2 h and then neutralized with a 10% aqueous solution of sodium acetate. The precipitate thus formed was filtered off, washed with water, and crystallized.

CONCLUSIONS

(1) Condensation of 3,5-diamino-1-R-1,2,4-triazoles (R = Alk, Ar) with aldehydes at an equimolar ratio of the reactants, followed by hydrogenation of the resulting Schiff bases, is a one-pot method for regioselective synthesis of 3-alkylamino-5-amino-1-R-1,2,4-triazoles.

(2) 3,5-Diamino-1,2,4-triazole (R = H) reacts selectively only with aldehydes in which the carbonyl group is conjugated with the aromatic ring. Condensation with aliphatic aldehydes followed by hydrogenation yields a mixture of 3-alkylamino-5-amino-1,2,4-triazoles and 3,5-dialkylamino-1,2,4-triazoles.

(3) Condensation of 5-amino-3-acetylamino-1-R-1,2,4-triazoles with aldehydes in dimethylformamide, followed by hydrogenation of the resulting Schiff bases (without their isolation) with sodium borohydride and by acid hydrolysis of the reduction products, 5-alkylamino-3-acetylamino-1-R-1,2,4-triazoles, is a convenient method for regioselective synthesis of 5-alkylamino-3-amino-1-R-1,2,4-triazoles (R = Alk, Ar).

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