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REACTIONS OF 3,6-BIS-(3,5-DIMETHYL-4-R-PYRAZOL-1-YL)-1,2,4,5-TETRAZINES WITH INDOLE AND 1,3,3-TRIMETHYL-2-METHYLENEINDOLINE

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Dedicated to Professor Dr. V. N. Charushin on the occasion of his 60th birthday

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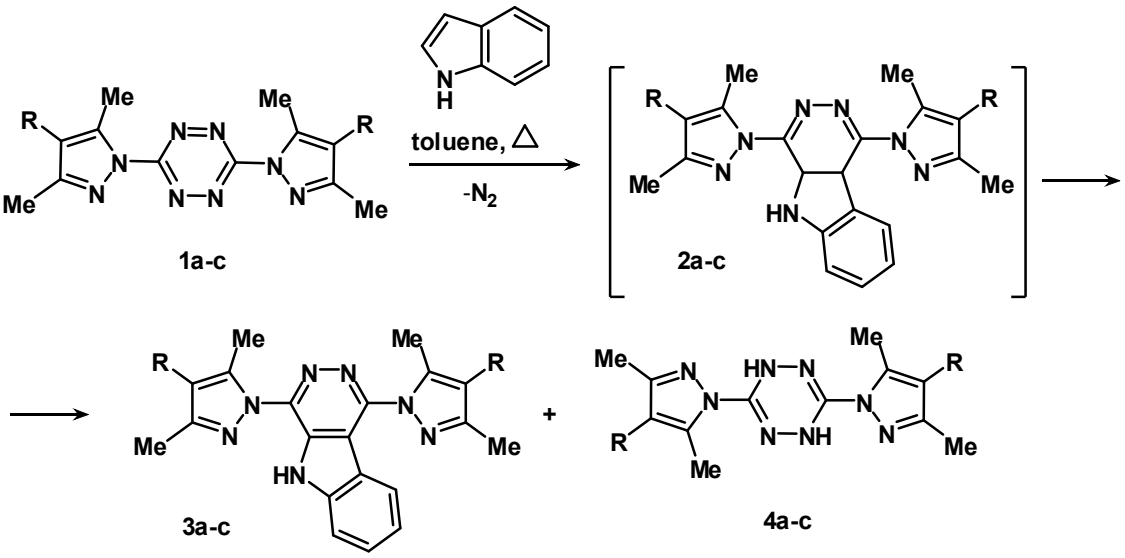
Abstract – It has been found that 3,6-bis-(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines react with indole and 1,3,3-trimethyl-2-methyleneindoline to give pyridazines as [4+2]cycloaddition products. 1,3,3-Trimethyl-2-methyleneindoline has been shown to act as C-nucleophile in the substitution of pyrazolyl group as well as in the reactions of tetrazine ring expansion in [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine derivatives.

Substituted indoles are the structural elements of a large number of natural alkaloids demonstrating various biological activities. Indole as would be expected is widely used as a building block in the design of potential biologically active compounds.[1] The ability of indole to act as nucleophile in the substitution reactions or as dienophile in [4+2]cycloaddition processes can be used for an attachment of the indole moiety to heterocyclic compounds. The reaction of 3,6-disubstituted *s*-tetrazines bearing electron-withdrawing substituents (2-Py, CO_2CH_3) with indole and its *N*-derivatives has been observed to give rise to 1,4-disubstituted 5*H*-pyridazino[4,5-*b*]indoles.[2,3] It has been established earlier that the reaction of indole or 5-bromoindole with 3,6-bis-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (**1a**) in acetonitrile in the presence of triethylamine results in the formation of mono- and disubstitution products.[4] 3,6-Bis-(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines (**1a-c**) (R=H, Br, Cl, respectively)

appear to undergo [4+2]cycloaddition reaction with enamines yielding 1,4-dihydropyridazines.[5] On the other hand the reactions of **1a-c** with anhydrobases formed *in situ* from *N*-methylquinaldinium iodide give give rise to the products of nucleophilic substitution of pyrazolyl group along with the products of cycloaddition reaction.[6]

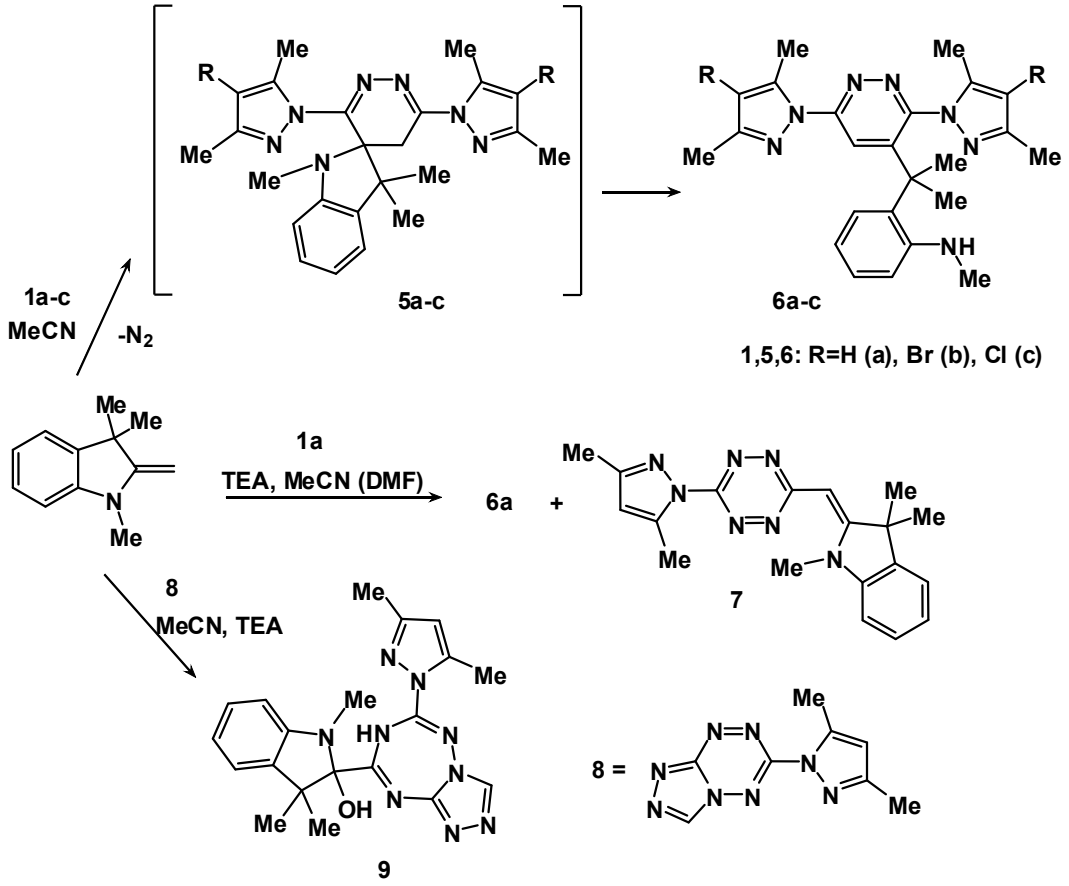
In the course of this study it has been established that 3,6-bis-(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines (**1a-c**) are able to react with indole and 1,3,3-trimethyl-2-methyleneindoline to give [4+2]cycloaddition products.

The interaction of tetrazines (**1a-c**) with indole proceeded in toluene at reflux (*method A*). The ^{1}H NMR spectra of the reaction mixtures exhibit the signals of the protons of pyridazines (**3a-c**) along with the chemical shifts of the protons of dihydrotetrazines (**4a-c**). Compounds (**4a-c**) derive from the reduction-oxidation reactions of the intermediates (**2a-c**) and tetrazines (**1a-c**) due to the high electrophilicity of latter.[6] [4+2]Cycloaddition reactions of indole with 3,6-bis-(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines also proceed upon melting (*method B*) giving rise to pyridazines (**3**) as exemplified by (**3a**) (Scheme 1). The structure of (**3a**) was established by X-ray analysis (Figure 1).



Scheme 1

It has been found that the interaction of tetrazines (**1a-c**) with 1,3,3-trimethyl-2-methyleneindoline in acetonitrile proceeds in mild conditions resulting in formation of unstable spiro intermediates (**5a-c**) followed by the pyrrole ring opening to yield pyridazines (**6a-c**) (Scheme 2).



Scheme 2

The structural data for compounds (**6a-c**) were obtained by NMR ^{1}H spectroscopy and X-ray analysis (Figure 2).

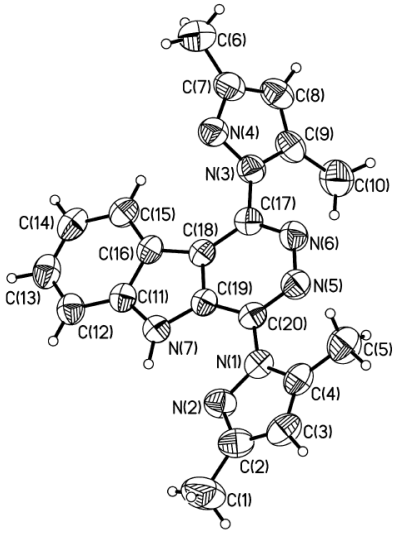


Figure 1. The X-ray structure of compound **3a** (50% probability thermal ellipsoids)

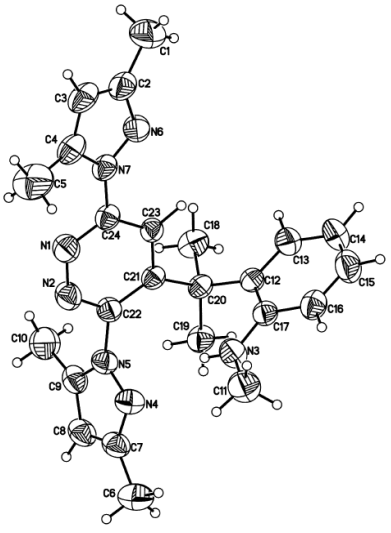


Figure 2. The X-ray structure of compound **6a** (50% probability thermal ellipsoids)

In the ^{1}H NMR spectra of (**6a-c**) the signals of aromatic protons of pyridazine ring appear as singlets at δ 8.37-8.25 ppm. The signals of methyl protons of the amino substitutents are observed as doublets at δ 2.64-2.72 ppm.

The substitution of the pyrazolyl group in tetrazine (**1a**) by 1,3,4-trimethyl-2-methyleneindoline proceeds upon the addition of triethylamine (Scheme 2), although the major compound is (**6a**). Evidence for the formation of (**7**) in reaction mixture was obtained by LC/MS data. Yield of (**7**) increased to 11% on transfer from acetonitrile to DMF. The structure of (**7**) was established by X-ray analysis (Figure 3).

Substituted [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines being the structural derivatives of aromatic tetrazines (**1a-c**) keep the lability of heterocyclic moiety in the position 6 and react with nucleophiles of different types.[6,10,11] Specific allocation of the electron density prevents triazolotetrazines from [4+2]cycloaddition processes. In our previous studies we have found that cyclic enamines are prone to demonstrate both dienophilic and *C*-nucleophilic properties reacting in extraordinary manner with 3,6-disubstituted *s*-tetrazines[12] and [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines.[6,13]

In the course of the study of the interaction of *C*-nucleophiles with substituted triazolo[4,3-*b*]-*s*-tetrazines we have investigated the reactions of 6-(3,5-dimethylpyrazol-1-yl)[1,2,4]triazolo[4,3-*b*]-*s*-tetrazine (**8**) with indole and 1,3,3-trimethyl-2-indoline. It has been found that indole doesn't react with (**8**) at room temperature in acetonitrile, whereas hardly separating complex mixture was obtained in the presence of triethylamine. The interaction of triazolotetrazine (**8**) with 1,3,3-trimethyl-2-methyleneindoline resulted in the formation of tetrazine ring expansion product – 2-(6-(3,5-dimethylpyrazol-1-yl)-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine-8-yl)-1,3,3-trimethylindoline-2-ol (**9**) in 19% yield (Scheme 2). Expansion of the tetrazine ring has first been found to occur when [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines were allowed to react with *CH*-active compounds in the presence of triethylamine.[13] The structure of **9** was strictly proved by ^{1}H NMR spectroscopy and X-ray analysis (Figure 4).

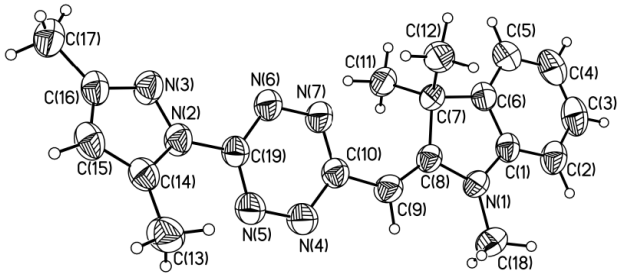


Figure 3. The X-ray structure of compound **7** (50% probability thermal ellipsoids)

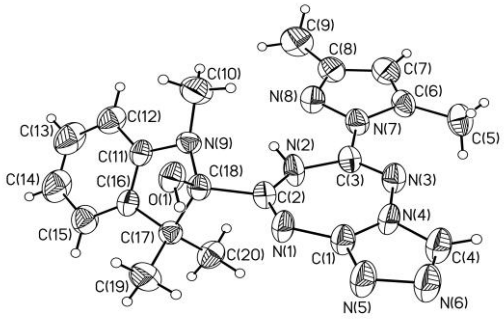


Figure 4. The X-ray structure of compound **9** (50% probability thermal ellipsoids)

In summary, it has been shown that 3,6-bis-(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines (**1a-c**) are able to react with indole and 1,3,3-trimethyl-2-methyleneindoline to give [4+2]cycloaddition products. Reaction of 6-(3,5-dimethylpyrazol-1-yl)[1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine with 2-methyleneindoline results in the formation of novel (7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepine-8-yl)-1,3,3-trimethylindoline-2-ol (**9**).

EXPERIMENTAL

General: Starting 3,6-bis-(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazines (**1a-c**) were synthesized according to known procedures.[5,7] 6-(3,5-Dimethylpyrazol-1-yl)[1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine (**8**) was obtained as described in the literature.[8] ^{1}H NMR spectra were recorded in $CDCl_3$ using Bruker Avance DRX-400 spectrometer operating at 400 MHz frequency with TMS as internal standard. Mass spectral data were obtained on a Shimadzu LCMS-2010 instrument operating in APCI mode. Melting points were determined on Boëtius apparatus. Elemental analyses were performed with an automatic analyzer Carlo Erba 1108. The Sorbfil ® TLC plates were used to control the reaction progress and the purity of the obtained compounds with 1:1 benzene/acetonitile mixture as eluent. X-Ray crystallography analyses were performed on a diffractometer "Xcalibur-3" (Oxford-Diffraction) equipped with CCD detector at 295(2)^o K, (λMoK_α, graphite monochromator, ω-scan). Corrections on absorbance were not used. The structures for all compounds were solved by direct method and refined using SHELX program package with anisotropic approximation (isotropic for hydrogen atoms). Hydrogen atoms of OH- and NH- groups were refined independently; other hydrogen atoms were included into the adjustment in the rider model with dependent heat parameters.[9]

CCDC 816604 (**3a**), 816605 (**6a**), 816606 (**7**), 816607 (**9**), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

1,4-Di-(3,5-dimethyl-4-R-pyrazol-1-yl)-5*H*-pyridazino[4,5-*b*]indoles (3a-c). *Method A*: A mixture of 0.001 mol of the starting tetrazine (**1**) and 0.001 mol of indole in 15 mL of toluene was refluxed for 3 h. During the reaction the color of the reaction mixture changed from bright red to light yellow. Toluene was removed, and the residue was triturated with MeOH and filtered off. The formed precipitate was suspended in a mixture of 10 mL of MeCN and 0.5 mL of AcOH. A solution of 50 mg of sodium nitrite in 2 mL of water was added to the precipitate. Partial dissolvation of the precipitate was observed, and the solution became red. A colorless residue was filtered off, recrystallized from MeOH, and then dried in vacuum for 6 h.

Method B: 0.001 mol of the starting tetrazine (**1**) and 0.001 mol of indole were mixed together. This mixture in a round-bottom flask was held at 140-150 °C until no nitrogen liberation observed (15-20 min). After cooling the mixture was crystallized from MeOH, filtered off and then isolated as described in the *method A*.

1,4-Di-(3,5-dimethylpyrazol-1-yl)-5*H*-pyridazino[4,5-*b*]indole (3a). Yield 56%. Mp. 158-159 ºC (from MeOH). Anal. Calcd for $C_{20}H_{19}N_7$: C 67.21; H 5.36; N 27.43. Found: C 67.38; H 5.39; N 27.75. ^{1}H NMR (δ, ppm): 2.43, 2.45, 2.48, 2.92 (all s, 4x3H, $4CH_3$); 6.15, 6.18 (both s, H(C4) in *pyrazole* ring); 7.88-7.90; 7.68-7.70; 7.59-7.64; 7.30-7.34 (all m, 4H in *benzene* ring); 11.03 (br.s., 1H, NH in *pyrrole* ring).

1,4-Di-(4-bromo-3,5-dimethylpyrazol-1-yl)-5*H*-pyridazino[4,5-*b*]indole (3b). Yield 74%. Mp 256-257 ºC (from MeOH). Anal. Calcd for $C_{20}H_{17}Br_2N_7$: C 46.62; H 3.33; N 19.03. Found: C 46.36; H 3.60; N 19.10. ^{1}H NMR, δ, ppm: 2.94, 2.51, 2.48, 2.44 (all s, 3H x $4CH_3$); 7.71-7.62; 7.64-7.59; 7.37-7.33 (all m, 4H in *benzene* ring); 10.88 (br. s., 1H, NH in *pyrrole* ring).

1,4-Di-(4-chloro-3,5-dimethylpyrazol-1-yl)-5*H*-pyridazino[4,5-*b*]indole (3c). Yield 71%. Mp 240-242 ºC (from MeOH). Anal. Calcd for $C_{20}H_{17}Cl_2N_7$: C 56.34; H 4.02; N 23.00. Found: C 56.38; H 3.97; N 23.03. ^{1}H NMR, δ, ppm: 2.93, 2.51, 2.47, 2.44 (all s, 4x3H, $4CH_3$); 7.96-7.94; 7.72-7.66; 7.65-7.62; 7.37-7.33 (all m, 4H in *benzene* ring); 10.89 (br. s., 1H, NH in *pyrrole* ring).

Typical procedure for the synthesis of **(2-{1[3,6-Bis-(3,5-dimethyl-4-R-pyrazol-1-yl)pyridazin-4-yl]-1-ethylmethyl}phenyl)methylamines (6a-c)**. To a suspension of 0.001 mol of 3,6-bis(3,5-dimethyl-4-R-pyrazol-1-yl)-1,2,4,5-tetrazine (**1a-c**) in 15 mL of MeCN 0.25 mL (0.002 mol) of 1,3,3-trimethyl-2-methyleneindoline was added. Reaction mixture was heated for 3-5 min until nitrogen liberation started. During this process the reaction color changed from bright red to brown-red. TLC was used to check the reaction completion. After 5-10 min the reaction mixture was filtered, and the filtrate was chilled using ice bath. The precipitated in few minutes colorless crystals were filtered off, washed by MeOH and recrystallized from MeCN. Yield 63-85%.

(2-{1[3,6-Bis-(3,5-dimethylpyrazol-1-yl)pyridazin-4-yl]-1-ethylmethyl}phenyl)methylamine (6a). Yield 68%. Mp 133-135 ºC (from MeOH). Anal. Calcd for $C_{24}H_{29}N_7$: C 69.36; H 7.03; N 23.60. Found: C 69.20; H 7.09; N 23.98. ^{1}H NMR, δ, ppm: 2.00, 2.21, 2.30, 2.21, (all s,4x3H, 4CH3); 2.72 (d, 3H, $-NHCH_3$); 1.74 (s, 6H, 2 CH_3 in $-C(CH_3)_2$); 3.70 (m,1H, $-NHCH_3$); 5.68, 6.05 (both s, 2H, in *pyrazole* rings); 6.52-6.59, 7.10-7.20 (both m, 4H, in *benzene* ring); 8.25 (s, 1H, in *pyridazine* ring).

(2-{1[3,6-Bis-(4-bromo-3,5-dimethylpyrazol-1-yl)pyridazine-4-yl]-1-ethylmethyl}phenyl)methylamine (6b). Yield 63%. Mp 115-117 ºC (from MeOH). Anal. Calcd for $C_{24}H_{27}Br_2N_7$: C 49.84; H 5.02; N 18.60. Found: C 50.09; H 5.00; N 18.57. ^{1}H NMR, δ, ppm: 2.00, 2.18, 2.35, 2.60, 2.78 (all s, 5x3H, 5 CH_3, in *pyrazole* rings, HN-CH_3); (all s, 4x3H, $4CH_3$); 1.87 (s, 6H, 2 CH_3 in $-C(CH_3)_2$); 3.25 (m,1H,

-$NHCH_3$); 6.42-6.44, 6.55-6.59, 7.02-7.04, 7.07-7.11 (all m, 4H, in *benzene* ring); 8.37 (s, 1H, in *pyridazine* ring).

(2-{1[3,6-Bis-(4-chloro-3,5-dimethylpyrazol-1-yl)pyridazine-4-yl]-1-ethylmethyl}phenyl)methyl-amine (6c). Yield 85%. Mp 105-108 ºC (from MeOH). Anal. Calcd for $C_{24}H_{27}Cl_2N_7$: C 59.50; H 5.62; N 20.25. Found: C 59.37; H 5.70; N 20.06. ^{1}H NMR, δ, ppm: 2.00, 2.17, 2.34 (all s, of 3H, 3 CH_3, in *pyrazole* ring), 2.72-2.76 (m, 6H, CH_3 in *pyrazole* ring, -NH-CH_3), (all s, of 3H, 4CH_3); 1.84, 1.89 (both s, 6H, 2 CH_3 in -$C(CH_3)_2$); 3.20-3.25 (m,1H, -$NHCH_3$); 7.30-7.34, 7.59-7.64, 7.68-7.70, 7.88-7.90 (all m, 4H in *benzene* ring); 8.36 (s, 1H in *pyridazine* ring).

2-((6-(3,5-Dimethylpyrazol-1-yl)-1,2,4,5-tetrazin-3-yl)methylene)-1,3,3-trimethylindoline (7). Yield 11% Mp 198-201 ºC (from MeOH). MS (APCI): m/z (%) = 348 (100) $[M+1]^+$. Anal. Calcd for $C_{19}H_{21}N_7$: C 65.68; H 6.09; N 28.23. Found: C 65.46; H 6.32; N 27.95. ^{1}H NMR, δ, ppm: 1.60 (s, 6H, 2 CH_3 in *indoline*), 2.37, 2.67 (all s, 2x3H, 2CH_3 in *pyrazole* ring); 3.36 (s, 3H, in -NCH_3); 5.92 (s, 1H, *methylene*); 6.14 (s, 1H, in *pyrazole* ring); 6.81, 7.01, 7.21 (all m, 4H, in *benzene* ring).

2-(6-(3,5-Dimethylpyrazol-1-yl)-7*H*-[1,2,4]triazolo[4,3-*b*][1,2,4,6]tetrazepin-8-yl)-1,3,3-trimethyl-indolin-2-ol (9). To a suspension of 216 mg (1 mmol) of 6-(3,5-dimethylpyrazol-1-yl)-1,2,4-triazolo[4,3-*b*]-1,2,4,5-tetrazine (**7**) in 10 mL of MeCN 0.14 mL (1 mmol) of triethylamine was added with 200 mg (1.15 mmol) of indoline. The mixture was stirred at room temperature at the magnetic stirrer for 2 h. After cooling of a mixture by ice a precipitated product was filtered off and washed by MeCN. Yield 75 mg (19%). Mp 182 ºC (from EtOH). Anal. Calcd for $C_{20}H_{23}N_9O$: C 59.24; H 5.71; N 31.09. Found: C 59.28; H 5.89; N 30.54. ^{1}H NMR, δ, ppm: 1.30, 1.40, 2.15, 2.50, 2.76 (all s, 5x3H, 5CH_3); 6.27 (s, 1H, in *pyrazole* ring); 6.56 (s, 1H, OH), 6.70-6.74, 7.03-7.10 (all m, 4H, in *benzene* ring); 8.32 (s, 1H in *triazole* ring), 9.92 (s, 1H, NH in *tetrazepine* ring).

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REFERENCES

1. 'Izbrannye metody sinteza i modifikatsii geterotsiklov', (Selected Methods for Synthesis and Modification of Heterocycles. The Chemistry of Synthetic Indole Systems) ed. by V.G. Kartsev, Interbioscreen Monograph Series; IBS Press, Moscow, 2004, 3, 594 (in Russian).
2. S. C. Benson, C. A. Palabrica, and J. K. Snyder, *J. Org. Chem.*, 1987, **52**, 4610.

3. M. Giradot, R. Nomak, and J. K. Snyder, *J. Org. Chem.*, 1998, **63**, 10063.
4. G. L. Rusinov, N. I. Latosh, I. N. Ganebnykh, R. I. Ishmetova, N. K. Ignatenko, and O. N. Chupakhin, *Russ. J. Org. Chem.*, 2006, **42**, 757.
5. G. L. Rusinov, R. I. Ishmetova, N. I. Latosh, I. N. Ganebnych, O. N. Chupakhin, and V. A. Potemkin, *Russ. Chem. Bulletin*, 2000, **49**, 355.
6. I. N. Ganebnykh, Ph.D. thesis, I. Ya. Postovsky Institute of Organic Synthesis RAS, Yekaterinburg, 2003, 229 (in Russian).
7. M. D. Coburn, G. A. Buntain, B. W. Harris, M. A. Hiskey, K.-Y. Lee, and D. G. Ott, *J. Heterocycl. Chem.*, 1991, **28**, 2049.
8. G. L. Rusinov, I. N. Ganebnykh, and O. N. Chupakhin, *Russ. J. Org. Chem.*, 1999, **35**, 1350.
9. G. M. Sheldrick, *Acta Cryst.*, 2008, **A64**, 112.
10. G. L. Rusinov, I. N. Ganebnykh, R. I. Ishmetova, N. K. Ignatenko, M. V. Berezin, S. G. Tolshchina, and A. V. Zolotceva, *Vestnik UGTU-UPI Ser. Khim.*, 2005, **57**, 158.
11. D. E. Chavez and M. A. Hiskey, *J. Heterocycl. Chem.*, 1998, **35**, 1329.
12. G. L. Rusinov, R. I. Ishmetova, I. N. Ganebnykh, O. N. Chupakhin, G. G. Aleksandrov, I. A. Litvinov, and D. B. Krivolapov, *Heterocycl. Commun.*, 2003, **9**, 39.
13. I. N. Ganebnykh, S. G. Tolshchina, R. I. Ishmetova, N. K. Ignatenko, P. A. Slepukhin, G. L. Rusinov, and V. N. Charushin, *Eur. J. Org. Chem.*, 2011, 2309.