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STUDIES ON PYRAZINE DERIVATIVES. 39*. SYNTHESIS, REACTIONS, AND TUBERCULOSTATIC ACTIVITY OF 3-PYRAZINYL-1,2,4-TRIAZOLO[4,3-*a*]-1,3-DIAZACYCLOALKANES

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In the reactions of S,S'-dimethyldithiocarbamate pyrazinoylhydrazone with diamines some 3-pyrazinyl-1,2,4-triazolo[4,3-a]-1,3-diazacycloalkanes were obtained, and the mechanism of their formation was proposed. The products were acylated, hydroxyalkylated, and aminomethylated. Their tuberculostatic activity was tested in vitro.

Keywords: S,S'-dimethyldithiocarbonates, pyrazines, 1,2,4-triazoles, 1,2,4-triazolo[4,3-*a*]-1,3-diazacycloalkanes, acylation, hydroxyalkylation, Mannich reaction, tuberculostatics.

The products of 1,2,4-triazole condensation with 1,3-diazacycloalkanes are scarce, their chemical properties being insufficiently recognized. The methods of 3-hydroxyhexahydro-1,2,4-triazolo[4,3-*a*]pyrimidine syntheses in the reactions of 1-ethoxycarbonyl-2-methylthiotetrahydropyrimidine with hydrazine and its derivatives were reported by Krezel, who described their reactions with acylating agents, isocyanates and isothiocyanates as well [2-6]. The action of some of these compounds on the CNS was investigated [7].

The preparation of 3-substituted (CF_3, Et, Ph, Bn, C_6H_4Me-*m*, C_6H_4Cl-*p*) 1,2,4-triazolo[4,3-*a*]-1,3-diazepines and 1,2,4-triazolo[4,3-*a*]pyrimidines upon treatment of 2-hydrazonohexahydropyrimidine and 2-hydrazonohexahydro-1H-1,3-diazepine hydroiodides with acid chlorides in pyridine medium was reported by Krezel [8, 9].

The preparation of an analogous derivative of dimethylthiomethylene-2-pyridinecarboxyimide with 2-pyridyl substituent and its crystal structure were described elsewhere [10].

In the present study new methods of syntheses of condensed 1,2,4-triazole systems with pyrazine-substituted 1,3-diazacycloalkanes and their chemical properties are reported (Scheme 1).

The preparation of S,S'-dimethyldithiocarbonate pyrazinoylhydrazone **1**, which was planned to be the starting material for the syntheses of compounds **2**-**6**, was reported elsewhere [11]. When heated with diamines in ethanol, the hydrazone **1** yielded N'-(1,3-diazacycloalkylidene-2)pyrazine hydrazides [11].

* Communication 38 see [1].

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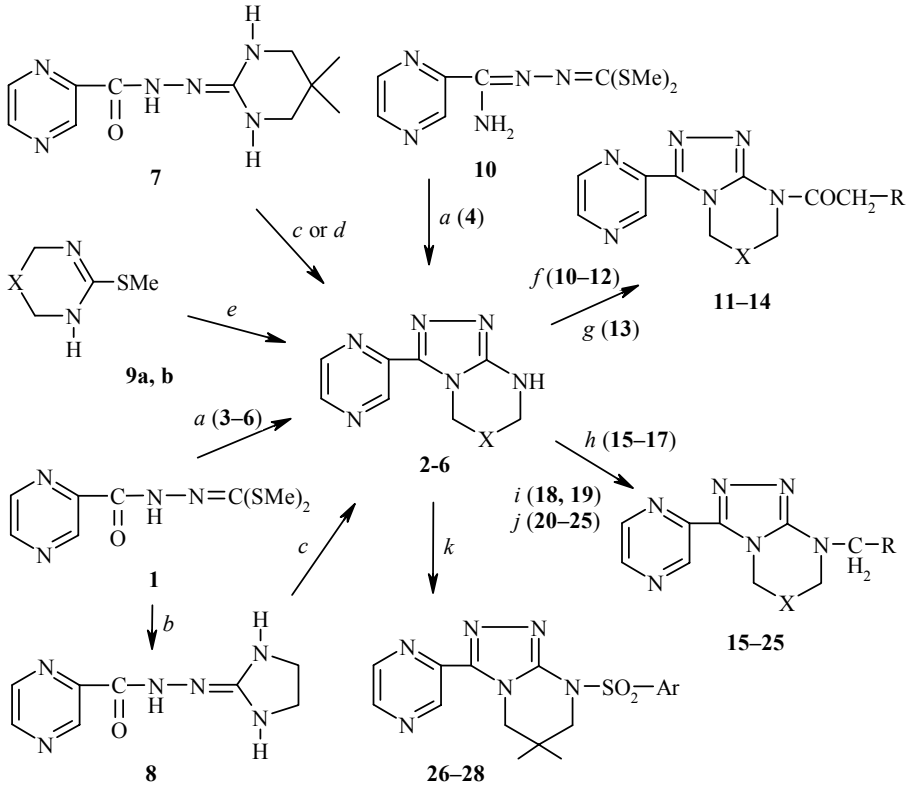
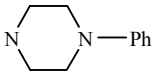
Scheme 1

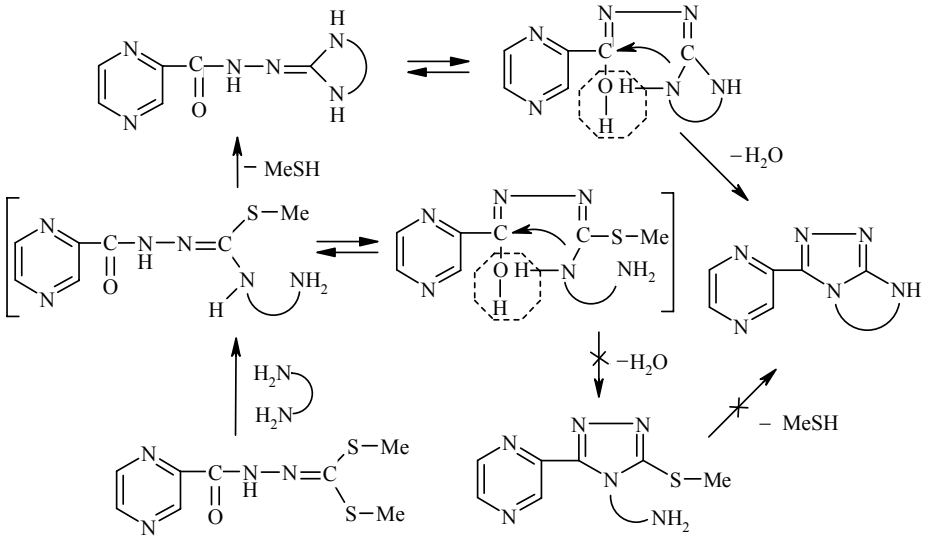


a $H_2N(CH_2)_2NH_2$, boiling; *b* $H_2N(CH_2)_2NH_2$, EtOH, boiling; *c* diglyme, DBU, EtOH, boiling; *d* Ph_2O, boiling; *e* pyrazinehydrazide, DBU; *f* Ac_2O, boiling; *g* $ClCH_2COCl$, dioxane; *h* CH_2O/H_2O; *i* propylene oxide; *j* CH_2O/H_2O, amines, MeOH; *k* $ArSO_2Cl$, pyridine
3, 9a, 11, 15, 18, 20-22 X = CH_2; **4, 9b, 12, 14, 16, 19, 23** X = CMe_2; **5, 17, 24, 25** X = CHOH; **6** X = CH_2CH_2; **13** X = CHOAc; **11-13** R= H, **14** R = Cl, **15-17** R= OH, **18, 19** R = CHOHMe;

20, 24 R =  , **21** R =  , **22, 23, 25** R = 

Upon direct heating with excess of diamines, S,S'-dithioester **1** yielded compounds **3-6**, the system of condensed rings. In the course of heating of dithioester **1** with 1,3-diamino-2,2-dimethylpropane, a precipitate appeared, which upon prolonged heating formed a cream-colored compound (end product of the reaction). When the reaction was stopped at the moment the precipitate appeared, the product was identified as compound **7**, identical with the one obtained previously [11]. This allowed us to suggest that the cyclization mechanism (Scheme 2) would be as follows: 1) two methyl mercaptan molecules are eliminated and compounds of type **7** are formed, 2) from their enolate forms, intramolecular elimination of the water molecule proceeds. This mechanism seems to be confirmed by the formation of compound **4** from **7** upon heating with diglyme in the presence of DBU or diphenyl ether. Another mechanism would be possible (Scheme 2): 1) 3-methylthio-1,2,4-triazole, substituted with the aminoalkyl group in position 4, is formed, 2) attack of the amino group results in elimination of the methyl thiol and ring closure. 4-Substituted triazole is formed similarly to 4-substituted 1,2,4-triazolo-3-thione (cf. the reaction of methyl 3-pyrazinodithiocarbazate with aminoethanol [11]).

Scheme 2



S,S'-Dithioester **1** when heated directly with ethylenediamine failed to yield the condensed system **2**, as the reaction stopped upon compound **8** formation. Compound **2** was obtained only upon heating of **8** in diglyme with DBU, though in low yield.

The reaction of pyrazine hydrazide with 2-methylthio-1,3-diazacycloalkanes appeared to be another way of obtaining the condensed systems, as proved by the synthesis of compounds **3** and **4** from derivatives **9a** and **9b** in the presence of DBU.

Compound **4** was obtained as well, though in rather poor yield, in accordance with the method given elsewhere, from dimethylthiomethylene-2-pyrazinecarboximide **10** [10, 12].

In the next step of this study some reactions with an imine group, present in the obtained condensed systems **3-5**, were investigated. The acetylation reactions gave compounds **11** and **12**. In compound **5** the hydroxyl group in position 6 was acetylated as well, which gave compound **13**. Compound **4** treated with chloroacetyl chloride in anhydrous dioxane gave hydrochloride **14**.

The reactions of triazoloperhydropyrimidines **3-5** with formalin and propylene oxide yielded the corresponding hydroxyalkyl derivatives **15-19**. Compounds **3-5** were also susceptible to aminomethylation reactions. They gave Mannich bases **20-25** upon heating with formalin and the corresponding amines in methanol.

Arylsulfonation reactions proceeded with very good yields. Compound **4** in anhydrous pyridine gave derivatives **26-28** with sulfonyl chlorides.

The structures of the compounds obtained were confirmed by the results of elemental analyses, IR, ^{1}H NMR, and mass spectra.

Compounds **3-5** and **17-24** were examined for their tuberculostatic activity towards *Myc. tbc*. $H_{37}Rv$ strain and two "wild" strains isolated from tuberculosis patients: one was resistant to *p*-aminosalicylic acid (PAS), isonicotinic acid hydrazide (INH), ethambutol (ETB), and rifampicin (RFP); another was fully susceptible to the drugs administered.

In vitro investigations were carried out by a classical test tube method of successive dilutions with Youman's fluid medium containing 10% of bovine serum.

The determined minimum concentrations inhibiting the growth of tuberculous strains (MIC) for most of the compounds examined were within the limits 50 - 100 μg/cm^3. The MIC of the most active compound **22** was 12.5 μg/cm^3 for $H_{37}Rv$ strain and 25 μg/cm^3 for other strains.

TABLE 1. H^1 NMR Spectra of Compounds **2-6**, **11-27**

Com-pound*	^{1}H NMR spetrum, δ, ppm*
2	4.00-4.16 and 4.28-4.45 (4H, 2t, $2CH_2$); 6.72 (1H, s, NH); 8.57-8.75 (2H, m, pyrazine); 9.21(1H, s, pyrazine)
3	2.00-2.35 (2H, m, $2CH_2$); 3.45-3.65 (2H, m, CH_2); 4.45 (2H, t, CH_2); 6.60 (1H, br. s, NH); 7.35-8.60 (3H, 2s, pyrazine)
4	1.1 (6H, s, $2CH_3$); 3.2 (2H, s, CH_2); 4.15 (2H, s, CH_2); 7.0 (1H, br. s, NH); 8.55 and 9.5 (3H, 2s, pyrazine)
5	3.6 (2H, br.s, CH_2); 4.52 (2H, br. s, CH_2); 4.71 (1H, m, CH); 9.0 and 9.48 (3H, 2s, pyrazine)
6	2.0, 3.3 and 4.65 (8H, 3s, $4CH_2$); 6.15 (1H, s, NH); 8.7 and 9.55 (3H, 2s, pyrazine)
11	1.95-2.30 (2H, m, CH_2); 2.75 (3H, s, $COCH_3$); 3.95 and 4.55 (4H, 2t, $2CH_2$); 8.55 and 9.45 (3H, 2s, pyrazine)
12	1.1 (6H, s, $2CH_3$); 2.8 (3H, s, $COCH_3$); 3.7 and 4.15 (4H, 2s, $2CH_2$); 8.5 and 9.5 (3H, 2s, pyrazine)
13	2.00-2.80 (6H, 2s, $2CH_3$); 3.30-3.60 (2H, m, CH_2); 4.50-5.10 (3H, m, CH_2CH); 8.60-9.50 (3H, 2s, pyrazine)
14	1.2 (6H, s, $2CH_3$); 3.3 (2H, s, CH_2); 4.55 (2H, s, CH_2); 4.9 (2H, s, CH_2Cl); 8.8 and 9.3 (3H, 2s, pyrazine)
15	1.94-2.08 (2H, m, CH_2); 3.30-3.40 (2H, m, CH_2); 4.28-4.36 (2H, m, CH_2); 5.84-5.93 (2H, m, CH_2); 8.54-8.70 and 9.16-9.26 (3H, 2m, pyrazine)
16	1.15 (6H, s, $2CH_3$); 3.3 and 4.05 (4H, 2s, $2CH_2$); 5.2 (2H, s, $\underline{CH_2}OH$); 8.4 and 9.35 (3H, 2s, pyrazine)
17	2.50 (2H, s, CH_2); 3.40 (2H, s, CH_2); 4.40 (2H, s, CH_2); 4.55-4.95 (1H, m, CH); 7.20 (1H, br. s, OH)
18	1.20 (3H, d, CH_3); 1.70-2.10 (2H, m, CH_2); 3.50 (2H, t, CH_2); 3.70-4.50 (5H, m, CH_2 and CH_3); 8.50-8.70 and 9.20-9.40 (3H, 2m, pyrazine)
19	0.85-1.30 (9H, m, $3CH_3$); 3.15 (2H, s, CH_2); 3.85-4.15 (3H, m, CH_2OH); 8.50 and 9.50 (3H, 2s, pyrazine)
20	2.2, 2.7, 3.5, 3.7 and 4.7 (16H, 5br. s, $8CH_2$); 8.55 and 9.55 (3H, 2s, pyrazine)
21	1.65, 2.15, 2.85, 3.5 and 4.5 (20H, 5s, $10CH_2$); 8.55 and 9.6 (3H, 2s, pyrazine)
22	1.90-2.35 (2H, m, CH_2); 2.50-3.00 and 3.00-3.35 (8H, 2m, piperazine); 3.35-3.65 (2H, t, CH_2); 4.23-4.63 (4H, m, $2CH_2$); 6.62-7.05 and 7.05-7.42 (5H, 2m, Ph); 8.50-9.50 (3H, 2s, pyrazine)
23	1.1 (6H, s, $2CH_3$); 2.7-3.3 (8H, m, $4CH_2$); 4.15 and 4.45 (4H, 2s, $2CH_2$); 6.8-7.3 (5H, m, C_6H_5); 8.5 and 9.5 (3H, 2s, pyrazine)
24	2.45-2.90 (6H, m, $3CH_2$); 3.3-3.7 (6H, m, $3CH_2$); 4.15-4.50 (3H, m, CH_2CH); 8.65 and 9.3 (3H, 2s, pyrazine)
25	1.18 (6H, s, $2CH_3$); 3.7 (2H, s, CH_2); 4.15 (2H, s, CH_2); 7.48-7.66 (3H, m, 3CH); 8.20-8.28 (2H, m, 2CH); 8.48-8.58 (2H, m, 2CH pyrazine); 9.5 (1H, s, CH pyrazine)
26	1.17 (6H, s, $2CH_3$); 2.4 (3H, s, CH_3); 3.7 and 4.13 (4H, 2s, $2CH_2$); 7.28-7.36 (2H, m, 2CH); 8.07-8.15 (2H, m, 2CH); 8.48-8.56 (2H, m, 2CH pyrazine); 9.5 (1H, s, CH pyrazine)
27	1.19 (6H, s, $2CH_3$); 3.7 and 4.15 (4H, 2s, $2CH_2$); 7.46-7.55 (2H, m, 2CH); 8.15-8.24 (2H, m, 2CH); 8.49-8.58 (2H, m, 2CH pyrazine); 9.5 (1H, s, CH pyrazine)

* Solvents: DMSO-d_6 (**2**, **17**, **24**), DMSO-d_6 + TFA (**5**), DMSO-d_6 + D_2O (**15**), $CDCl_3$ (all other compounds).

EXPERIMENTAL

Melting points were determined with a Boetius apparatus and are uncorrected. The IR spectra were taken with a Specord IR-75 spectrophotometer. The ^{1}H NMR spectra were taken with a Tesla Spectrometer BS-487 c, 80 MHz (Table 1), and the mass spectra – with a Varian MAT 711 apparatus, at electron beam energy

TABLE 2. Characteristics of the Newly Synthesized Compounds

Compound*	mp, °C (solvent for crystallisation)	Empirical formula	Found, % / Calculated, %			IR spectrum, ν, cm^{-1}	Yield, % (method)
			C	H	N		
1	2	3	4	5	6	7	8
2	276-278 (EtOH)	$C_8H_8N_6$	51.20 / 51.06	4.32 / 4.28	44.73 / 44.66	992, 1152, 1392, 1520, 1580, 3163	10
3	242-243 (MeOH)	$C_9H_{10}N_6$	53.57 / 53.46	5.11 / 4.98	41.78 / 41.56	1060, 1150, 1390, 1440, 1520, 1600, 2860, 2930, 2970, 3000, 3120, 3740	37 (C)
4	240-241 (H_2O)	$C_{11}H_{14}N_6$	57.44 / 57.38	6.17 / 6.13	36.63 / 36.50	992, 1024, 1520, 1640, 2960	68 (general); 63 (A), 55 (B), 56 (C)
5	272-273 (H_2O)	$C_9H_{10}N_6O$	49.46 / 49.54	4.71 / 4.62	38.76 / 38.51	1024, 1156, 1456, 1523, 1616, 3040, 3120, 3243	34
6	194-195 ($MeOH–C_6H_6$)	$C_{10}H_{12}N_6$	55.61 / 55.54	5.68 / 5.59	38.99 / 38.86	672, 1003, 1056, 1136, 1323, 1440, 1563, 3216, 3432, 3643	10
11	191-192 (H_2O)	$C_{11}H_{12}N_6O$	54.21 / 54.09	5.12 / 4.95	34.58 / 34.40	1024, 1243, 1376, 1532, 1680	44
12	200-201 ($EtOH–H_2O$)	$C_{13}H_{16}N_6O$	57.44 / 57.34	6.07 / 5.92	31.10 / 30.86	723, 1243, 1295, 1520, 1680	54
13	204-205 (H_2O)	$C_{13}H_{14}N_6O_3$	51.83 / 51.65	4.70 / 4.67	27.93 / 27.80	1244, 1363, 1523, 1696, 1723	67
14	226-228 ($MeOH–H_2O$)	$C_{13}H_{15}ClN_6O$	51.11 / 50.90	5.07 / 4.93	27.55 / 27.40	720, 1024, 1152, 1683	72
15	232-235 (EtOH)	$C_{10}H_{12}N_6O$	51.93 / 51.72	5.48 / 5.20	36.31 / 36.18	880, 1024, 1076, 1163, 1323, 1403, 1504, 1536, 1572	82
16	153-155 (Dioxane)	$C_{12}H_{16}N_6O$	55.43 / 55.37	6.42 / 6.20	32.18 / 32.29	1016, 1076, 1163, 1312, 1392, 1472, 1504, 1536, 1563, 1615, 2960, 3123	95

TABLE 2 (continued)

1	2	3	4	5	6	7	8
17	257-260 (MeOH)	$C_{10}H_{12}N_6O_2$	48.46 / 48.38	4.97 / 4.87	33.71 / 33.85	640, 960, 1016, 1056, 1104, 1316, 1392, 1456, 1504, 1603, 3256	51
18	139-140 (Cyclohexane)	$C_{12}H_{16}N_6O$	55.45 / 55.37	6.36 / 6.20	32.43 / 32.29	752, 1136, 1163, 1312, 1372, 1483, 1644, 2923	20
20	134-135 (C_6H_6)	$C_{14}H_{19}N_7O$	55.76 / 55.80	6.51 / 6.35	32.63 / 32.54	912, 1072, 1152, 1296, 1340, 1376, 1472, 1584, 2912, 3424	76
21	123-124 (C_6H_6)	$C_{16}H_{23}N_7$	61.46 / 61.32	7.62 / 7.40	31.37 / 31.28	960, 1003, 1056, 1136, 1376, 1456, 1504, 1596	35
22	193-196 (C_6H_6)	$C_{20}H_{24}N_8$	63.94 / 63.81	6.60 / 6.43	29.82 / 29.76	1003, 1072, 1152, 1232, 1376, 1504, 1584, 2843, 3403	80
23	155-156 ($MeOH–H_2O$)	$C_{22}H_{28}N_8$	65.48 / 65.32	6.86 / 6.98	27.54 / 27.70	683, 1003, 1152, 1243, 1376, 1456, 1504, 1536, 1600, 2816, 3403	81
24	190-192 ($MeOH–Et_2O$)	$C_{14}H_{18}N_7O_2$	51.28 / 51.16	5.91 / 5.73	31.12 / 30.99	1104, 1144, 1340, 1460, 1536, 1592, 2843, 3283	63
25	207-208 (MeOH)	$C_{17}H_{18}N_6O_2S$	55.40 / 55.12	5.08 / 4.90	22.78 / 22.69	576, 603, 683, 896, 992, 1024, 1083, 1184, 1376, 1532	70
26	264-266 (MeOH)	$C_{18}H_{20}N_6S$	61.51 / 61.34	5.93 / 5.72	23.80 / 23.84	543, 672, 880, 1083, 1163, 1360, 1456, 1500, 1536	15
27	233-236 (MeOH)	$C_{17}H_{17}N_6O_2SCl$	50.56 / 50.43	4.30 / 4.23	30.92 / 20.76	480, 656, 896, 992, 1083, 1176, 1376, 1480, 1523	41

* MS, *m/z* (*I*, %): **2** – 188 (100), 187 (27.4), 106 (7.3), 105 (20.2); **6** – 216 (100), 215 (12.6), 188 (26.5), 187 (28.1), 175 (48.6), 162 (10), 134 (5.4), 106 (5.8).

of 70 eV. The results of elemental analyses (% C, H, N) for all the compounds obtained were in good agreement with the data calculated. Reaction yields and physical constants of the obtained compounds are given in Table 2.

3-Pyrazinyl-4,5-dihydro-1,2,4-triazolo[4,3-*a*]imidazole (2). Compound **8** (1 g, 5 mmol) was refluxed in a solution of 3 ml diglyme and 0.5 ml DBU for 7 h [11]. On cooling, 20 ml of benzene was added and the mixture evaporated under reduced pressure. The residue was treated with 2 ml of water and cooled. The precipitate was collected and recrystallized.

3-Pyrazinyl-1,2,4-triazolo[4,3-*a*]-1,3-diazacycloalkanes 3-6 (General method). Compound **1** (10 mmol) and the appropriate diamine (30 mmol) were refluxed for 3 h. On cooling, water (10 ml) was added and the mixture strongly cooled. The precipitate was collected and recrystallized.

Compound 4 was also obtained as follows:

A. Compound **7** (0.6 g, 2.5 mmol) in diglyme (2 ml) and DBU (0.5 ml) was refluxed for 2 h. On cooling, diethyl ether (5 ml) was added and the solution decanted from above the precipitate. The residue was treated with 5 ml of a mixture of MeOH–H_2O, 1:1. After cooling, compound **4** was filtered off and recrystallized; yield 0.35 g (63%).

B. Compound **7** (0.6 g, 2.5 mmol) in 2 ml of diphenyl ether was refluxed for 0.5 h [11]. On cooling, diethyl ether (20 ml) was added and the 0.3 g (55%) of precipitated compound **4** filtered off.

C (for compounds **3** and **4**). 2-Methylthiotetrahydropyrimidine hydroiodide **9a** or **9b** (0.78 g, 5 mmol) and pyrazine hydrazide (0.69 g, 5 mmol) were refluxed in EtOH (3 ml) or diglyme with DBU (0.9 ml) for 4 h. On cooling, the precipitates were collected.

D. Obtained as in the general method with compound **10** instead of compound **1**. Reaction yield 15% [11].

8-Acyl Derivatives of 3-Pyrazinyl-1,2,4-triazolo[4,3-*a*]-1,3-perhydropyrimidines 11-13. The appropriate compounds **3-5** (3 mmol) and 2 ml (20 mmol) Ac_2O were refluxed for 0.5 h. On cooling, ca. 10 g of ice was added. The precipitates were collected and recrystallized.

8-Chloroacetyl-3-pyrazinyl-1,2,4-triazolo[4,3-*a*]-6,6-dimethylperhydropyrimidine (14). Compound **4** (3 mmol) dissolved in anhydrous dioxane (30 ml) and 0.4 ml (5 mmol) of chloroacetyl chloride were refluxed for 15 min. On cooling, a crystalline product in the form of a hydrochloride was filtered off.

8-Hydroxymethyl-3-pyrazinyl-1,2,4-triazolo[4,3-*a*]perhydropyrimidines 15-17. These compounds were obtained by heating the appropriate compounds **3-5** (2 mmol) and formalin (0.5 ml) in 3 ml of dioxane, for 1 h. On cooling, benzene (50 ml) was added and the mixture evaporated under reduced pressure. The residues were recrystallized.

8-(2-Hydroxypropyl)-3-pyrazinyl-1,2,4-triazolo[4,3-*a*]perhydropyrimidines 18-19. Compounds **3** or **4** (5 mmol) dissolved in MeOH (20 ml) with 2 ml (30 mmol) of propylene oxide and 5 drops of pyridine were allowed to stand for 2 weeks at ambient temperature. Then the solutions were concentrated under reduced pressure. The oily residues on cooling and rubbing with a glass rod were crystallized.

8-Aminomethyl Derivatives of 3-Pyrazinyl-1,2,4-triazolo[4,3-*a*]perhydropyrimidines 20-24. The appropriate compounds **3-4** (2 mmol) dissolved in MeOH (10 ml), 0.5 ml of formalin, and 3 mmol of the appropriate amine were refluxed for 2 h. The mixtures were then concentrated under reduced pressure. The residues were treated with benzene (20 ml) and the mixtures evaporated under reduced pressure (this procedure was repeated 3 times). The residues were recrystallized.

8-Arylsulfonyl-3-pyrazinyl-1,2,4-triazolo[4,3-*a*]-6,6-dimethylperhydropyrimidines 25-27. Compound **4** (0.23 g, 10 mmol) in anhydrous pyrimidine (2 ml) was treated with 1.5 ml of the appropriate arylsulfonylchloride and refluxed for 20 min. On cooling, water (10 ml) was added and mixture cooled with ice. The precipitates were filtered off, washed with water and, after drying, recrystallized.

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