GUANIDINE DERIVATIVES OF NITROGEN HETEROCYCLES

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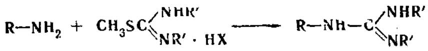
The synthesis of guanidine derivatives of nitrogen heterocycles was accomplished by means of the reactions of heterocyclic amines with S-methylisothiourea sulfate or N,N',S-trimethylisothiourea hydriodide. It is shown that the reaction depends on the basicity of the starting amine.

The goal of this study was the synthesis of guanidine derivatives of pyridine, piperidine, morpholine, and 2-(α-naphthylmethyl)imidazoline, which are potential cardiovascular preparations.

Guanidine and N,N'-dimethylguanidine derivatives of nitrogen heterocycles (Tables 1 and 2) were obtained by means of the reaction of heterocyclic amines with S-methylisothiourea sulfate or N,N',S-trimethylisothiourea hydriodide [1]:



$$R{-}NH_2 + CH_3SC\begin{matrix}\diagup NHR' \\ \diagdown\!\!\diagdown NR'\end{matrix}\cdot HX \longrightarrow R{-}NH{-}C\begin{matrix}\diagup NHR' \\ \diagdown\!\!\diagdown NR'\end{matrix}$$

The ease of the reaction with S-methylisothiourea depends on the basicity of the starting amines (see [2]).

TABLE 1. Synthesized Guanidines

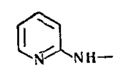
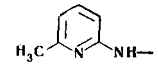
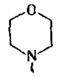
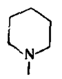
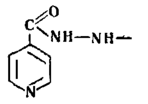
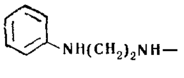
R	mp °C	λ_{max}, nm (lg ε)	Empirical formula	Found, %		Calculated, %		pK$_a$	Yield, %
				N	S	N	S		
	185	230 (4,07) 298 (3,76)	$C_6H_8N_4 \cdot H_2SO_4$	23,7	13,6	23,8	13,7	6,88±0,04	45
	215	—	$C_7H_{10}N_4 \cdot H_2SO_4$	22,6	13,0	22,6	12,9	7,39±0,04	40
	318	212 (3,88) 260 (2,25)	$C_{10}H_{22}N_6O_2 \cdot H_2SO_4$	23,5	9,3	23,6	9,0	9,52±0,1	66
	315	212 (3,90) 275 (2,77)	$C_{12}H_{26}N_6 \cdot H_2SO_4$	24,0	9,1	23,9	9,1	11,93±0,1	35
	224	213 (3,95) 270 (3,61)	$C_{14}H_{18}N_{10}O_2 \cdot H_2SO_4$	30,6	7,0	30,7	7,0	6,75±0,02	45
	Viscous oil	227 (3,95) 266 (3,16)	$C_8H_{13}N_5 \cdot H_2SO_4$	25,0	—	25,3	—	7,36±0,04	64

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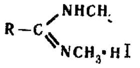
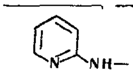
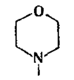
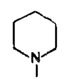
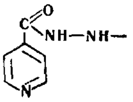
TABLE 2. Synthesized N,N'-Dimethylguanidines

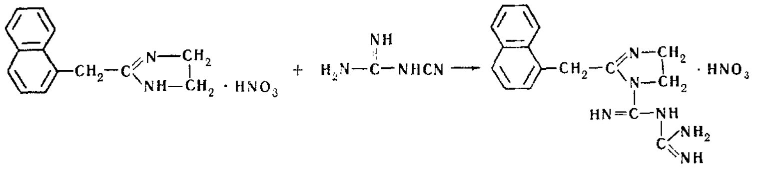


$$R-C\begin{matrix}\nearrow NHCH_3\\ \searrow\!\!\searrow NCH_3\cdot HI\end{matrix}$$

R	mp (dec.)	λ_{max}, nm (lg ε)	Empirical formula	Found, %		Calc., %		pK$_a$	Yield, %
				N	I	N	I		
	195	—	$C_8H_{12}N_4\cdot HI$	—	43,5	—	43,5	10,71±0,04	59
	270	225 (3,66) 265 (2,25)	$C_7H_{15}N_3O\cdot HI$	14,9	—	14,7	—	11,74±0,1	38
	335	225 (3,66)	$C_8H_{17}N_3\cdot HI$	14,8	—	14,8	—	12,33±0,1	23
	145	222 (3,65) 264 (2,86)	$C_8H_{13}N_5O\cdot HI$	21,3	—	21,7	—	10,33±0,06	30

We have found that heterocyclic amines with pK$_a$ values above 6.8 react with S-methylisothiourea sulfate to form the corresponding guanidine derivatives. Among such amines are 2-aminopyridine (pK$_a$ 6.86), 2-amino-6-methylpyridine (7.37), 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (9.46), 1-methyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (9.30), piperidine (11.22), and morpholine (8.70). Amines with lower basicities either do not react at all or only with difficulty with S-methylisothiourea. Compounds of this type include 5-methyl-7-hydroxytriazaindolicine (pK$_a$ 6.52 ± 0.11) and 2-aminobenzothiazole (pK$_a$ 4.20 ± 0.09).

We also accomplished the synthesis of a carbiminoguanidine derivative of 2-(α-naphthylmethyl)-imidazoline via the reaction



EXPERIMENTAL

Guanidine and Amidine Derivatives of Nitrogen Heterocycles (Table 1). The heterocyclic amine (0.1 mole) was dissolved in 100 ml of ethanol, and 13.9 g (0.05 mole) of S-methylisothiourea sulfate in 400 ml of water was added. The reaction mixture was refluxed for 8-10 h, cooled, and filtered; and the solvent was evaporated. The reaction product was crystallized from alcohol.

N,N'-Dimethylguanidine and Amidine Derivatives of Nitrogen Heterocycles (Table 2). The heterocyclic amine (0.05 mole) was dissolved in 60 ml of ethanol, and 12.4 g (0.05 mole) of N,N',S-trimethylisothiourea hydriodide in 80 ml of ethanol was added. The mixture was then treated as in the previous synthesis.

1-Carbiminoguanidino-2-(α-naphthylmethyl)imidazoline Nitrate. 2-(α-Naphthylmethyl)imidazoline nitrate [2.73 g (0.01 mole)] was dissolved in 25 ml of alcohol, and 0.84 g (0.01 mole) of dicyanodiamide in 20 ml of alcohol was added. The reaction mixture was refluxed for 10 h, the solvent was removed by distillation, and the residue was crystallized from benzene–alcohol to give 77% of a product with mp 120 deg. UV spectrum (alcohol), λ_{max}, nm (log ε): 222 (3.85) and 254 (2.43). pK$_a$ 10.29. Found %: C 52.2; H 5.4. $C_{16}H_{18}N_6\cdot HNO_3$. Calc. %: C 53.8; H 5.3.

LITERATURE CITED

1. Swiss Patent No. 890,602 (1960); Zbl., 4, 1597 (1964).
2. S. Angual and W. Warburton, J. Chem. Soc., 22, 492 (1951).