HYDRAZINOPYRIMIDINE DERIVATIVES

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Hydrazine derivatives are widely used in the practice of medicine, as physiologically active preparations [1,2]. We have obtained hydrazinopyrimidines containing amino, nitro, and methyl groups in the pyrimidine nucleus and a number of other derivatives, and we have studied the biological activity of these compounds.

The hydrazinopyrimidines (I-VIII, Table 1) were synthesized from the corresponding chloropyrimidines and hydrazine hydrate according to the scheme,

$$R-Cl + NH_2-NH_2 \cdot H_2O \rightarrow R-NH-NH_2,$$

where R is the pyrimidyl substituent.

The reaction should be carried out in an excess of hydrazine hydrate in order to avoid the formation of polyalkylated hydrazine derivatives.

The hydrazinopyrimidines are colorless or slightly colored crystalline substances moderately soluble in water and alcohol and soluble in acids. The salts of the hydrazinopyrimidines are quite soluble in water.

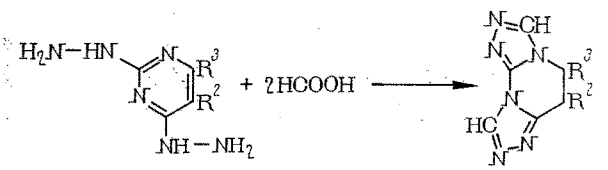
Starting from the literature data (according to which the sugar derivatives of the hydrazines are less toxic than the starting hydrazines [5]), we have obtained the products of condensation of 2,4-dihydrazino-5-methylpyrimidine (II) and 2,4-dihydrazino-6-methylpyrimidine (III) with glucose: 2,4-di(glucosyl-hydrazino)-5-methylpyrimidine (IX) and 2,4-di(glucosyl-hydrazino)-6-methylpyrimidine (X) (Table 2).

2,4-Di(isopropylidinehydrazino)-6-methylpyrimidine (X) was obtained from (III) and acetone. The hydrazinopyrimidines reacted with methylisothiourea to form the guanidinaminopyrimidine sulfates (XII, XIII, XIV, XV, see Table 2):

$$R-NH-NH_2 + [CH_3S-\overset{\overset{NH}{\|}}{C}-NH_2]\cdot H_2SO_4 \rightarrow [R-NH-NHC(=NH)NH_2]\cdot H_2SO_4,$$

where R is the pyrimidyl substituent. The starting hydrazinopyrimidines in this reaction were compounds (I), (II), (III), and (V). All the guanadinaminopyrimidines were isolated as sulfates. The guanadinaminopyrimidine bases could not be isolated since they are unstable.

The hydrazinopyrimidines on reaction with formic acid form triazolopyrimidines. Thus, di-triazolo-(1,5-a,1',5'-6)-5-methylpyrimidine (XVI) and di-triazolo(1,5-a,1',5'-6)-6-methylpyrimidine (XVII) are formed from (II) and (III) with formic acid,



II, III

XVI: $R^2=CH_3$, $R^3=H$,
XVII: $R^2=H$, $R^3=CH_3$

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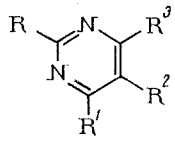
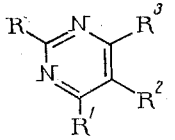
TABLE 1. Hydrazinopyrimidines



Compound	R	R^1	R^2	R^3	Yield, %	Mp, °C	N, found, %	Empirical formula	N, calc., %	Literature value
I	$-NH-NH_2$	$-NH-NH_2$	H	H	59	216	60,36, 60,45	$C_4H_8N_6$	59,94	[3]
II	$-NH-NH_2$	$-NH-NH_2$	CH_3	H	70	200—1	54,34, 54,19	$C_5H_{10}N_6$	54,54	
III	$-NH-NH_2$	$-NH-NH_2$	H	CH_3	80	208—10	54,14, 54,40	$C_5H_{10}N_6$	54,54	[4]
IV	$-NH-NH_2$	$-NH-NH_2$	H	$-NH-NH_2$	78	217—8	62,46, 62,61*	$C_4H_{10}N_8$	65,88	
V	NH_2	$-NH-NH_2$	H	CH_3	65	236—8	50,37, 50,08	$C_5H_9N_5$	50,36	[4]
VI	NH_2	$-NH-NH_2$	CH_3	H	55	230—4	50,02, 49,81	$C_5H_9N_5$	50,36	
VII	NH_2	$-NH-NH_2$	NO_2	CH_3	45	184—5	45,57, 45,78	$C_5H_8N_6O_2$	45,16	
VIII	NH_2	$-NH-NH_2$	CH_3	CH_3	60	220	45,60, 45,59	$C_6H_{11}N_5$	45,75	

*Compound decomposed on recrystallization.

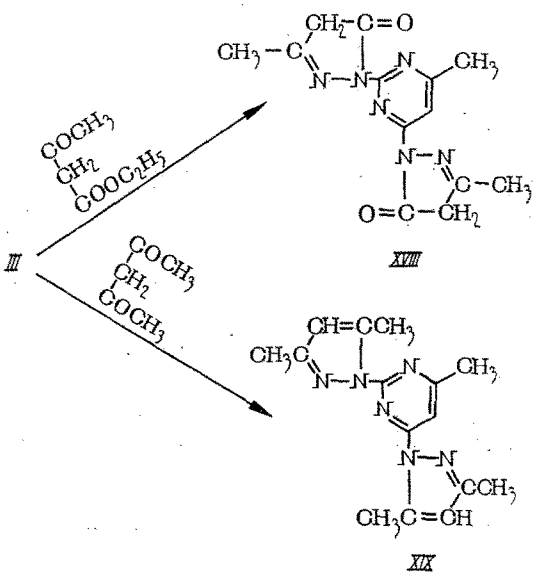
TABLE 2. Hydrazinopyrimidine Derivatives*



Compound	R	R^1	R^2	R^3	Yield, %	Mp, °C	Found %				Empirical formula	Calculated %			
							C	H	N	S		C	H	N	L
IX	$-NH-NH-C_6H_{11}O_5$	$-NH-NH-C_6H_{11}O_5$	CH_3	H	80	100—3	42,54 42,31	6,54 6,86	17,05	—	$C_{17}H_{30}N_6O_{10}$	42,68	6,25	17,55	—
X	$-NH-NH-C_6H_{11}O_5$	$-NH-NH-C_6H_{11}O_5$	H	CH_3	96	92—5	42,04 42,05	6,96 6,97	17,60 17,80	—	$C_{17}H_{30}N_6O_{10}$	42,68	6,25	17,55	—
XI	$-NH=N=C(CH_3)_2$	$-NH-N=C(CH_3)_2$	H	CH_3	98	170—1	—	—	35,42 35,72	—	$C_{11}H_{18}N_6$	—	—	35,85	—
XII	$-NH-NHC(=NH)NH_2$	$-NH-NHC(=NH)NH_2$	H	CH_3	92	235	25,26 25,95	5,74 5,49	—	9,17 9,28	$C_7H_{14}N_{10}\cdot H_2SO_4$	24,97	4,76	—	9,52
XIII	$-NH-NHC(=NH)NH_2$	$-NH-NHC(=NH)NH_2$	CH_3	H	80	220	25,09 25,21	5,11 5,30	—	9,14 9,24	$C_7H_{14}N_{10}\cdot H_2SO_4$	24,97	4,76	—	9,52
XIV	$-NH-NHC(=NH)NH_2$	$-NH-NHC(=NH)NH_2$	H	H	75	192	22,43 22,73	4,93 4,81	—	9,36 9,34	$C_6H_{12}N_{10}\cdot H_2SO_4$	22,34	4,34	—	9,8
XV	NH_2	$-NH-NHC(=NH)NH_2$	H	CH_3	85	250	31,06 30,82	5,68 5,8	—	7,21 7,47	$C_6H_{11}N_7\cdot 1/2\,H_2SO_4$	31,27	5,21	—	6,98

*Compounds (XII-XV) were characterized as the sulfates.

2,4-Di(3'-methylpyrazolone-5')-6-methylpyrimidine (XVIII) and 2,4-di-(3',5'-dimethylpyrazole)-6-methylpyrimidine (XIX) are obtained from the reaction of (III) with acetoacetic ester or acetylacetone,



As a result of the biological investigation of the hydrazinopyrimidines it was found that they have an inhibitory action on MAO. The most active dihydrazinopyrimidines contain a methyl group in the 5- and 6-positions of the pyrimidine ring (II, III) [6]. The condensation product of (II) with glucose (IX) is 15 times more toxic than that of (II) and, in addition, has a clearly expressed hypotensive effect [7].

EXPERIMENTAL

2,4-Dihydrazino-5-methylpyrimidine (II). 2,4-Dichloro-5-methylpyrimidine (6 g) was added carefully in portions to 26.6 g of hydrazine hydrate heated to 95°. An immediate precipitate of hydrazine derivative was noted. The reaction mixture was heated to 95° for 20-30 min, after which 25 ml of water was added, the mixture was heated until the precipitate was dissolved, and the hot solution was filtered. After cooling, the crystalline substance was filtered, recrystallized from water and then from alcohol. Compounds (I) and (III)-(VIII) were similarly obtained.

2-Amino-4-hydrazino-5-methylpyrimidine (VI). A solution of 1.05 g of hydrazine hydrate, 50 ml of ethanol, and 2.3 g of 2-amino-4-chloro-5-methylpyrimidine was heated in a water bath for 3 h. After cooling, a crystalline substance (1.06 g) was isolated from the solution. It was filtered and recrystallized from water. Compound (V) was similarly obtained.

2,4-Di-(glucosylhydrazino)-5-methylpyrimidine (IX). A mixture of 0.5 g of (II) and 1.17 g of anhydrous d-glucose was refluxed in 20 ml of ethanol until a clear solution was obtained (ca. 30 min). The hot solution was filtered, the methanol was removed, and the viscous residue was dried in a vacuum dessicator. Compound (X) was similarly obtained.

2,4-Di-(isopropylidinehydrazino)-6-methylpyrimidine (XI). Compound (III) (1 g) in 20 ml of acetone was heated until complete dissolution. The acetone was removed and the crystalline residue was twice recrystallized from water.

2,4-Di-(guanadinamino)-6-methylpyrimidine Sulfate(XII). Compound (III) (1.54 g) and 2.78 g of S-methylthioronium sulfate in 30 ml of 50% alcohol were heated on a water bath for 6 h. The resulting methyl mercaptan was collected by passing it through a solution of lead acetate. After removal of the solvent, the residue was recrystallized several times from 50% alcohol and dried in a vacuum dessicator. Compounds (XIII, XIV, and XV) were similarly obtained.

Di-triazolo(1,5-a,1',5')-5-methylpyrimidine (XVI). A solution of 0.5 g of (II) in 3.5 ml of 85% formic acid was heated to 110° for 1 h. The solution obtained was neutralized with an ice-cooled 25% aqueous solution of ammonia. The precipitate obtained after neutralization was filtered and recrystallized from 50% alcohol to give 0.3 g (54%) of a compound with mp 296-298°. Found %: N 47.94, 48.02. $C_7H_6N_6$. Calculated %: N 48.22.

2,3-Di-(3'-methylpyrazolone-5'0-6-methylpyrimidine (XVIII). Compound (III) (1 g) was dissolved in 8 ml of 40% acetic acid. Acetcacetic ester (1.7 g) was added to this solution and the mixture was heated in a water bath for 1 h. The precipitate obtained after cooling was filtered and recrystallized from aqueous alcohol to give 0.9 g (42%) of a compound with mp 170°. Found %: N 29.49. $C_{13}H_{14}N_6O_2$. Calculated %: N 29.3.

2,4-Di-(3',5'-dimethylpyrazole)-6-methylpyrimidine (XIX). Compound (XVIII) was similarly obtained from (III) and acetyl acetone in 71% yield with mp 118°.

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