SYNTHESIS OF SOME PYRIDAZINO[4,5-b]QUINOXALINE DERIVATIVES

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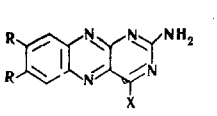
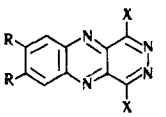
Several derivatives of the little-studied pyridazino[4,5-b]quinoxaline heterocyclic system, the structural isomer of benzopteridine, were synthesized in order to study their biological activity. 6,7-Dimethylquinoxaline-2,3-dicarboxylic acid and a number of its derivatives were also obtained.

In recent years, there has been intensive activity involving the synthesis and investigation of the biological (including antitumorigenic) activity in a number of vitamin antagonists. Benzopteridines (I), which can act as double antagonists (of either riboflavin or folic acid [1, 2]), are of great interest as antimetabolites of vitamins of the D group.

The present paper, which is a continuation of the research begun in [3], is devoted to the synthesis of derivatives of the pyridazino[4,5-b]quinoxaline heterocyclic system (II), which is the structural isomer of benzopteridine with a pyridazine ring in place of the pyrimidine ring. This method for the modification of the benzopteridine molecule was undertaken to compare the biological activity of the compounds obtained with the similarly constructed benzopteridine derivatives and also to search for new compounds with antivitamin and antitumorigenic activity.



I



II a-d

a X=OH, R=H; b X=OH, R=CH_3; c X=NH_2, R=H; d X=NH_2, R=CH_3

The first two pyridazino[4,5-b]quinoxaline derivatives – 1-phenylpyridazino[4,5-b]quinoxaline and 1,4-diphenylpyridazino[4,5-b]quinoxaline – were described in [4, 5]. We have synthesized some new derivatives of this heterocyclic system, primarily because of interest in the possibility of obtaining substances containing a 1,4-dihydroxypyridazine ring, since, according to the literature, many compounds of this type have biological activity.

In addition, it was of interest to obtain such structural isomers of benzopteridine as 1,4-dihydroxy-6,7-dimethylpyridazino[4,5-b]quinoxaline (IIb) and 1,4-diamino-6,7-dimethylpyridazino[4,5-b]quinoxaline (IId), since the biologically important benzopteridines contain methyl groups in the 6 and 7 positions, which is essential for the manifestation of physiological activity. However, the pyrimidine ring of compounds of this type contains amino or hydroxy groups.

The well-known ability of anhydrides or esters of o-dicarboxylic acids to form compounds with 1,4-dihydroxypyridazine rings by reaction with hydrazine hydrate or hydrazine salts was used in the syntheses of the compounds of general formula II. The starting materials in our case were quinoxaline-2,3-dicarboxylic acid (Va) [6] and 6,7-dimethylquinoxaline-2,3-dicarboxylic acid (Vb). The latter was obtained for the first time in analogy with the method in [6] via the scheme

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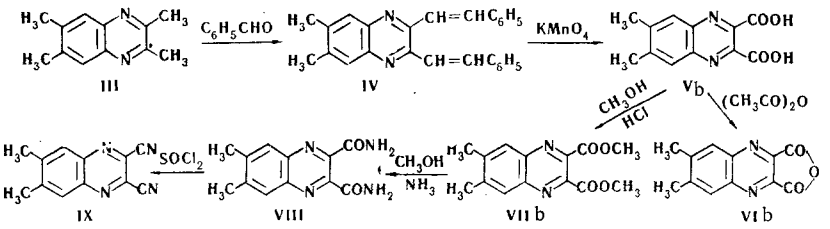
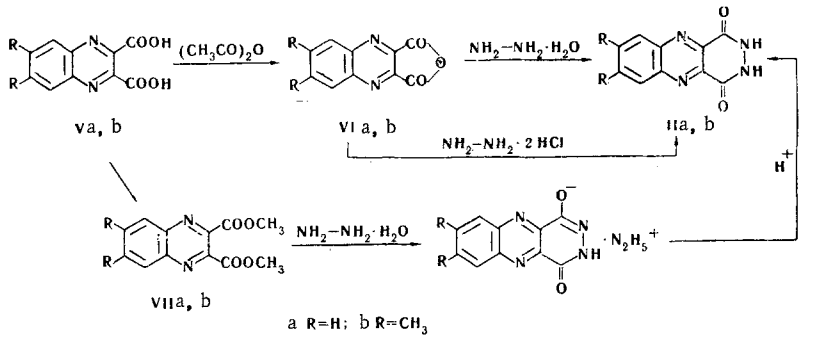


2,3,6,7-Tetramethylquinoxaline (III) [7] reacts with benzaldehyde in the presence of boric acid to give 2,3-distyryl-6,7-dimethylquinoxaline (IV), which is oxidized by $KMnO_4$ in acetone to 6,7-dimethylquinoxaline-2,3-dicarboxylic acid (Vb).

A number of derivatives of Vb, which are necessary as intermediates in the synthesis of substances of the general formula II (Table 1), were obtained on the basis of its transformations.

Thus acid Vb is converted to anhydride VIb on heating in acetic anhydride. When it is heated in methanol saturated with dry hydrogen chloride, it forms dimethyl ester VIIb. The latter is converted to the diamide of 6,7-dimethylquinoxaline-2,3-dicarboxylic acid (VIII) when it is dissolved in methanol and the solution is saturated with dry ammonia. Amide VIII forms the dinitrile of 6,7-dimethylquinoxaline-2,3-dicarboxylic acid (IX) on brief heating with thionyl chloride in dimethylformamide.

The synthesis of IIa, b was accomplished via the scheme



a R=H; b R=CH_3

As seen from the above scheme, we obtained II by several methods. When acid Va is heated in acetic anhydride, it is converted to anhydride VIa [8], which reacts with hydrazine hydrate to give 1,4-dihydroxypyridazino[4,5-b]quinoxaline (IIa) in a yield of only 29%.

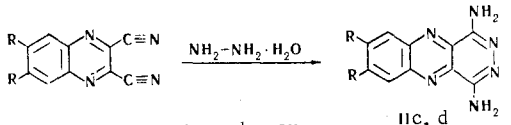
It is known [9] that side reactions are almost completely suppressed in strongly acidic aqueous solutions in the condensation of anhydrides of o-dicarboxylic acids with hydrazine. In fact, the yield of IIa was raised to 45% in the reaction of VIa with hydrazine hydrochloride.

Compound IIa was also synthesized from the dimethyl ester of quinoxaline-2,3-dicarboxylic acid (VIIa) [10] and hydrazine hydrate. The salt of IIa, initially formed with hydrazine, gives IIa in 66% yield on acidification with acetic or hydrochloric acids.

It is apparent from the above results that the best method for the synthesis of 1,4-dihydroxypyridazino[4,5-b]quinoxaline is the condensation of the dimethyl ester of quinoxaline-2,3-dicarboxylic acid with hydrazine hydrate. The identical character of the samples of IIa obtained by the various methods was confirmed by IR spectroscopy.

1,4-Dihydroxy-6,7-dimethylpyridazino[4,5-b]quinoxaline (IIb) was similarly synthesized from VIb and VIIb, respectively, and hydrazine hydrate. The identical character of the samples of IIb obtained by the two methods was also confirmed by IR spectroscopy.

1,4-Diaminopyridazino[4,5-b]quinoxaline (IIc) and 1,4-diamino-6,7-dimethylpyridazino[4,5-b]quinoxaline (IId) were obtained by the reaction of the dinitrile of quinoxaline-2,3-dicarboxylic acid [11] and the dinitrile of 6,7-dimethylquinoxaline-2,3-dicarboxylic acid (IX), respectively, with hydrazine hydrate in methanol at room temperature:



c R=H; d R=CH$_3$ IIc, d

The physical constants, yields, and results of elementary analysis of the pyridazino[4,5-b]quinoxaline derivatives obtained are presented in Table 2.

EXPERIMENTAL

2,3-Distyryl-6,7-dimethylquinoxaline (IV). A mixture of 5.2 g (2.8 mmole) of 2,2,6,7-tetramethylquinoxaline, 30 ml (280 mmole) of benzaldehyde, and 0.6 g of boric acid was heated at 200-210°C for 30 min with removal of the liberated water by distillation. At the end of the reaction, the melt was poured into cold alcohol, and the mixture was refluxed for 15-20 min and cooled to precipitate a yellow substance. This substance was removed by filtration and washed with alcohol. The compound thus obtained was sufficiently pure for use in the subsequent reactions without additional purification.

6,7-Dimethylquinoxaline-2,3-dicarboxylic Acid (Vb). A 1.2 g (80 mmole) sample of finely pulverized $KMnO_4$ was added in small portions with stirring to an ice-cooled suspension of 0.36 g (1 mmole) of IV in 20 ml of acetone. After all of the $KMnO_4$ had been added, the reaction mass was stirred with ice cooling for 2 h and filtered. The solid on the filter was treated with hot water and filtered. The filtrate was cooled and acidified with concentrated hydrochloric acid to pH 1-2 to give an abundant precipitate of a mixture of acid Vb and benzoic acid. The MnO_2 was treated several times until only slight turbidity appeared on acidification. After the acids were isolated, they were removed by filtration and washed with ether to remove benzoic acid. The residue (acid Vb) was obtained as slightly yellow needles, which were crystallized from water and dried in vacuo over P_2O_5 at 144°.

6,7-Dimethylquinoxaline-2,3-dicarboxylic Acid Anhydride (VIb). A 0.5 g (2 mmole) sample of Vb was added to 10 ml of refluxing acetic anhydride, and the mixture was refluxed until the solid had dissolved completely. The solution was cooled to precipitate light-brown needles of VIb.

Dimethyl 6,7-Dimethylquinoxaline-2,3-dicarboxylate (VIIb). Dry hydrogen chloride was passed in the course of 3 min into 50 ml of methanol, 2 g (8 mmole) of Vb was added, and the mixture was heated for 2 h. The methanol was evaporated to two-thirds of the original volume, and the mixture was neutralized with saturated sodium bicarbonate solution. The resulting precipitate was removed by filtration.

6,7-Dimethylquinoxaline-2,3-dicarboxamide (VIII). Dry ammonia was passed in the course of 2 h into a solution of 2.1 g (77 mmole) of VIIb in 200 ml of methanol. The resulting precipitate was removed by filtration to give the colorless, crystalline diamide.

2,3-Dicyano-6,7-dimethylquinoxaline (IX). A 2.7 ml sample of thionyl chloride was added to a suspension of 1.3 g (53 mmole) of VIII in 24 ml of dimethylformamide, and the mixture was heated for 1 h. The reaction mass was poured over ice, and the aqueous mixture was neutralized with sodium bicarbonate and extracted repeatedly with ether. The ether extracts were dried with calcium chloride, and the ether was removed by distillation.

1,4-Dihydroxypyridazino[4,5-b]quinoxaline (IIa). A) A mixture of 0.7 g (4 mmole) of VIa, 0.32 ml of hydrazine hydrate, and 2.1 ml of glacial acetic acid was heated for 30 min on a water bath and cooled. The resulting IIa was removed by filtration and washed with water and alcohol to give 29% of a light-yellow crystalline substance that was insoluble in water and most organic solvents but soluble in dilute alkali.

B) A solution of 0.25 ml of hydrazine hydrate in 1 ml of water was cooled in an ice bath, and 1 ml of concentrated hydrochloric acid was added. The solution was heated to the boiling point with stirring, and 1 g (5 mmole) of VIa was added. The mixture was refluxed for 2 h, cooled, and filtered. The solid was washed with water and alcohol to give IIa in 45% yield.

C) A 1.5 g (6.4 mmole) sample of VIa was dissolved with stirring and heating in 50 ml of methanol, and 3 ml of hydrazine hydrate was added in portions. The reaction mass was then heated and stirred for 1 h to give a red-brown precipitate of the salt of IIa and hydrazine. The mixture was cooled, and the salt was removed by filtration and dissolved in hot water. The solution was acidified with acetic or hydrochloric acid, and the precipitate was removed by filtration and washed with water to give IIa in 66% yield.

TABLE 1. Derivatives of 6,7-Dimethylquinoxaline-2,3-dicarboxylic Acid

Compound	Mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
IV	211—213[a]	$C_{26}H_{22}N_2$	86,0	6,2	7,7	86,2	6,1	7,7	70
V[b]	180—182[b,c]	$C_{12}H_{10}N_2O_4$	58,8	4,5	10,9	58,5	4,1	11,4	88
VI[b]	248—250[d]	$C_{12}H_8N_2O_3$	63,4	3,7	12,7	63,2	3,5	12,3	61
VII[b]	118—120[e]	$C_{14}H_{14}N_2O_4$	61,4	5,4	10,5	61,7	5,3	10,2	44
VIII	286—288[c]	$C_{12}H_{12}N_4O_2$	59,3	5,4	23,2	59,0	5,0	22,9	65
IX	192—194[e]	$C_{12}H_8N_4$	69,2	3,6	27,0	69,2	3,9	26,9	66

[a]From ethanol. [b]With decomposition. [c]From water. [d]From acetic anhydride. [e]From methanol.

TABLE 2. Pyridazino[4,5-b]quinoxaline Derivatives (II)

Compound	R	X	Mp, °C	Empirical formula	Found, %			Calc, %			Yield, %
					C	H	N	C	H	N	
II[a]	H	OH	>300[a]	$C_{10}H_6N_4O_2$	55,9	2,9	26,2	56,1	2,8	26,1	66
II[b]	CH_3	OH	>300[b]	$C_{12}H_{10}N_4O_2$	59,3	4,1	23,3	59,1	4,1	23,1	67
II[c]	H	NH_2	280—282[c]	$C_{10}H_8N_6$	57,1	3,6	—	56,6	3,7	—	20
II[d]	CH_3	NH_2	>300[c]	$C_{12}H_{12}N_6$	59,7	5,2	—	59,9	5,0	—	45

[a]From dimethylformamide. [b]From aqueous dimethylformamide. [c]From water.

1,4-Dihydroxy-6,7-dimethylpyridazino[4,5-b]quinoxaline (IIb). A) A mixture of 0.4 g (1.75 mmole) of VIb, 7 ml of hydrazine hydrate, and 13 ml of glacial acetic acid was heated on a water bath for 40 min and cooled. The resulting precipitate was removed by filtration and washed with water and alcohol to give 50% of IIb as a light-yellow, crystalline substance that was insoluble in water and most organic solvents.

B) A 0.51 g (1.85 mmole) sample of VIIb was dissolved with stirring and heating in 20 ml of methanol, and 1 ml of hydrazine hydrate was added in portions. The reaction mass was stirred and heated for 2 h to give a red-brown precipitate of the salt of IIb and hydrazine. The mixture was cooled, and the salt was removed by filtration and dissolved in hot water. The solution was acidified with acetic or hydrochloric acid, and the resulting precipitate was removed by filtration and washed with water to give IIb in 65% yield.

1,4-Diamino-6,7-dimethylpyridazino[4,5-b]quinoxaline (IId). An 11 ml sample of hydrazine hydrate was added with stirring at room temperature to a solution of 0.3 g (1.4 mmole) of IX in 80 ml of methanol. A precipitate appeared in a short time. The reaction mixture was stirred for 24 h, and the precipitate was removed by filtration.

1,4-Diaminopyridazino[4,5-b]quinoxaline (IIc). This compound was similarly obtained by the method used to prepare IId.

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