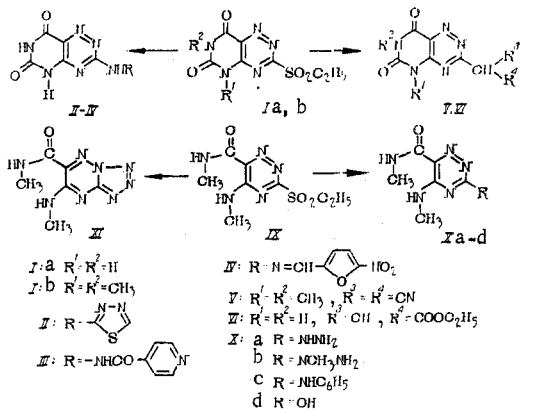
SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF DERIVATIVES OF PYRIMIDO[1,2,4]TRIAZINE AND OF THE METHYLAMIDE OF 5-METHYLAMINO-1,2,4-TRIAZINE-6-CARBOXYLIC ACID

Yu. A. Azev, N. N. Vereshchagina, I. Ya. Postovskii,* E. L. Pidémskii, and A. F. Goleneva

UDC 615.276:547.874].012.1

Among the 3-substituted pyrimido[4,5-e][1,2,4]triazine-6,8-diones that we have synthesized, compounds have been detected which possess an antiinflammatory activity [1]. In view of this, to elucidate the link between structure and antiinflammatory activity it appeared desirable to obtain new derivatives of this class. At the same time, to ascertain the role of the annellated pyridine ring it was of interest to study the biological properties of 3-substituted derivatives of the methylamide of 5-methylamino-1,2,4-triazine-6-carboxylic acid, all the more since some compounds of this series are readily obtained by the hydrolytic cleavage of the corresponding pyrimido[4,5-e][1,2,4]triazines [2].

In a preceding investigation [1] it was shown that 3-alkylsulfonyl groups in the pyrimido[4,5-e][1,2,4]triazine-6,8-diones (Ia, b) can be replaced under mild conditions by residues of amines and of hydrazine and also by anions such as N_3^-, SCN^-, OCN^-, and S^{2-}. In the present investigation it has been established that the alkylsulfonyl group can also be replaced by weaker nucleophiles – heterocyclic amines. Thus, the reaction of the sulfone (Ia) with 2-aminothiadiazole at room temperature gave 3-(thiadiazol-2'-ylamino)-5,6,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine-6,8-dione (II).



The reaction of (Ia) with a twofold molar excess of isonicotinic acid hydrazide takes place similarly with the formation of 3-isonicotinoylhydrazino-5,6,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine-6,8-dione (III). The reaction of the sulfone (Ia) with 5-nitrofurfurylidenehydrazine gave 3-(5'-nitrofurfur-2'-ylidenehydrazino)-5,6,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine-6,8-dione (IV).

A promising route to obtaining new derivatives of pyrimido[4,5-e][1,2,4]triazine-6,8-diones is opened up by the reaction of the sulfones (Ia and b) with C-nucleophiles. It is known that the replacement of a 3-alkylthio group in a 1,2,4-triazine by a malononitrile residue takes place only when the reactants are subjected to prolonged boiling in pyridine [3]. The sulfonyl derivatives (Ia and b) used in the present investigation proved to be extremely reactive even with respect to C-nucleophiles. In actual fact, the alkylsulfonyl groups in compounds (Ia and b) are displaced by residues of such CH acids as malononitrile and ethyl cyanoacetate even at room temperature. For the reaction to take place completely it is sufficient to stir compound (Ia) or (Ib) with the

*Deceased.

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 15, No. 11, pp. 50-53, November, 1981. Original article submitted December 22, 1980.

0091-150X/81/1511-0789$ 07.50 © 1982 Plenum Publishing Corporation

TABLE 1. Compounds (II-XI)

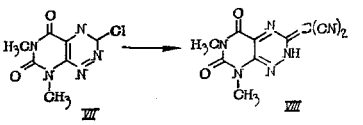
Compound	mp, °C (solvent)	Yield, %	Found, %			Empirical formula	Calculated, %		
			C	H	N		C	H	N
II	>300(a)	75—80	29,9	2,3	39,6	$C_7H_4N_8O_2S$	29,8	2,1	39,7
III	>300(a)	75—80	39,4	3,3	33,3	$C_{11}H_8N_8O_3 \cdot 2H_2O$	39,8	3,6	33,3
IV	>300(a)	85—90	37,6	2,0	35,2	$C_{10}H_6N_6O_5$	37,7	1,9	35,0
V	275—6(b)	75—80	46,9	3,1	37,9	$C_{10}H_7N_7O_2$	46,7	2,7	38,1
VI	>300(a)	65—70	43,3	3,2	30,0	$C_{10}H_8N_6O_4$	43,5	2,9	30,4
VIII	>240 (dec.)	65—70	47,1	2,9	38,0	$C_{10}H_7N_7O_2$	46,7	2,7	38,1
IX	163—4(b)	85—90	37,5	5,4	27,5	$C_8H_{13}N_5O_3$	37,1	5,1	27,1
Xa	215—6(d)	75—80	36,3	5,7	50,0	$C_6H_{11}N_7O$	36,5	5,6	49,7
Xb	155—6(d)	75—80	39,9	6,5	46,5	$C_{12}H_{13}N_7O$	39,8	6,2	46,4
Xc	252—3(e)	85—90	56,2	5,8	32,1	$C_{12}H_{14}N_6O_4$	55,8	5,5	32,5
Xd	300(d)	90—95	36,0	5,4	35,1	$C_6H_8N_5O_2 \cdot H_2O$	35,8	5,4	35,0
XI	182—3(d)	85—90	34,7	3,9	54,1	$C_6H_8N_8O$	34,6	3,9	53,8

Note: (a) DMFA; (b) ethanol; (c) pyridine; (d) water; (e) DMFA—water (1:1).

appropriate CH acid in the presence of triethylamine for 1-1.5 h. Thus, the reaction of the sulfone (Ib) with malononitrile gave 3-dicyanomethyl-5,7-dimethyl-5,6,8-tetrahydropyridimido[4,5-e][1,2,4]triazine-6,8-dione (V), and the reaction of sulfone (Ia) with ethyl cyanoacetate gave 3-(1'-cyano-1'-ethoxycarbonylmethyl)-5,6,7,8-tetrahydropyridimido[4,5-e][1,2,4]triazine-6,8-dione (VI).

The IR spectra of crystals of compounds (V) and (VI) have the absorption bands of nitrile groups at 2218 and 2230 cm^{-1}, respectively. The vibrations of associated amide amino groups for compound (VI) are observed in the spectrum in the form of broad bands at 3100 and 3180 cm^{-1}. For compound (V) there is no absorption in the 3000-3500 cm^{-1} region.

The derivatives (V) and (VI) obtained consist of red (V) and orange (VI) substances. At the same time, the reaction of 3-chloro-6,8-dimethyl-5,6,7,8-tetrahydropyrimido[5,4-e][1,2,4]triazine-5,7-dione (VII) [4] with malononitrile in the presence of triethylamine gave a dark brown dinitrile derivative isomeric with compound (V).



VII VIII

The IR spectrum of this compound has the absorption bands of nitrile groups at 2193 and 2211 cm^{-1}. However, in contrast to the isomer (V), the IR spectrum has a broad band at 3000-3200 cm^{-1}, which indicates the presence in this compound of an associated NH group and permits the assumption for it of the methylene structure (VIII).

We synthesized methylamides of 3-substituted 5-methylamino-1,2,4-triazine-6-carboxylic acids from the 3-ethylsulfonyl derivative (IX), obtained by the oxidation of the methylamide of 3-ethylthio-5-methylamino-1,2,4-triazine-6-carboxylic acid [2]. The sulfone (IX) reacts with hydrazine, methylhydrazine, aniline, water, and sodium azide somewhat more slowly than the sulfones (Ia and b). Consequently, more severe conditions are necessary for the completion of reactions. Thus, when the sulfone (IX) was boiled with a twofold molar excess of hydrazine in ethanol for 25-30 min, the methylamide of 3-hydrazino-5-methylamino-1,2,4-triazine-6-carboxylic acid (Xa) was obtained and the reaction with methylhydrazine the methylamide gave 3-α-methylhydrazino-5-methylamino-1,2,4-triazine-6-carboxylic acid (Xb). Under similar conditions, with aniline the sulfone (IX) gave the phenylamino derivative (Xc). Boiling the sulfone (IX) in water for 1 h led to the hydroxy derivative (Xd). The reaction with sodium amide yielded the methylamide of 5-methylaminotetrazolo[2,3-e]-[1,2,4]triazine-6-carboxylic acid (XI). The tetrazole structure of the crystals of (XI) follows from the absence of an absorption in the IR spectrum of this compound in the 2100-2200 cm^{-1} region. The opening of the tetrazole ring of compound (XI) to give the azide isomer does not take place even in trifluoroacetic acid solution.

The pharmacological investigation was directed to the search for antiinflammatory and analgesic properties in the compounds synthesized. The evaluation of the antiinflammatory and analgesic action of the compounds was carried out as described previously [1].

The investigations showed that compound (I) exhibits a moderate analgesic action. The same compound exhibited an antiinflammatory action comparable with the effect of the clinically used phenylbutazone. The hydrazide (III) showed a weak antiinflammatory action. The compounds tested had a low toxicity, their LD_{50} values amounted to 200-500 mg/kg.

Thus, as a result of the pharmacological investigations performed it has been found that in the series of 3-substituted pyrimido[4,5-e][1,2,4]triazine-6,8-diones studied the hydroxy and hydrazino derivatives possess an antiinflammatory activity. At the same time, similar derivatives of the methylamide of 5-methylamino-1,2,4-triazine-6-carboxylic acid exhibited no such action.

EXPERIMENTAL

The IR spectra of the compounds were taken on a UR-20 spectrometer (GDR). The samples were prepared in the form of mulls with paraffin oil.

3-(Thiadiazo-2'-ylamino)-5,6,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine-6,8-dione (II) was obtained by stirring the solvent (Ia) with a twofold molar excess of 2-aminothiadiazole for 20-25 min at 20-25°C. The colorless precipitate of (II) was filtered off (see Table I).

3-Isonicotinoylhydrazino-5,6,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine-6,8-dione (III) and 3-(5'-nitrofurfur-2'-ylidenehydrazino)-5,6,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine-6,8-dione (IV) were obtained similarly to compound (II) by the reaction of the sulfone (Ia) with isonicotinic acid hydrazide and 5-nitrofurfur-2-ylidinehydrazine, respectively. Compound (III) formed a colorless precipitate while (IV) was yellow.

3-Dicyanomethyl-5,7-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine-6,8-dione (V) was obtained by stirring equimolar amounts of the sulfone (Ib), malononitrile, and triethylamine in dry ethanol at 20-25°C for 1 h, dissolving the precipitate formed in a small amount of water, filtering the solution, and acidifying it with concentrated hydrochloric acid to pH 3.0-4.0. This gave a red precipitate of (V).

3-(1'-Cyano-1'-ethoxycarbonylmethyl)-5,6,7,8-tetrahydropyrimido[4,5-e][1,2,4]triazine-6,8-dione (VI) was obtained in a similar manner to compound (V).

3-Dicyanomethylene-6,8-dimethyl-2,3,5,6,7,8-hexahydropyrimido[4,5-e][1,2,4]triazine-5,7-dione (VIII) was obtained by boiling equimolar amounts of 3-chloro-6,8-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-e][1,2,4]-triazine-5,7-dione (VII), malononitrile, and triethylamine in dry ethanol for 2 h. The reaction mixture was diluted with water (1:1) and acidified with concentrated hydrochloric acid to pH 3.0-4.0. This gave a dark brown precipitate of (VIII).

The Methylamide of 3-Ethylsulfonyl-5-methylamino-1,2,4-triazine-6-carboxylic Acid (IX) was obtained as described previously [1] in a similar manner to compound (Ia) from the methylamide of 3-ethylthio-5-methylamino-1,2,4-triazine-6-carboxylic acid [2].

The methylamide of hydrazino-5-methylamino-1,2,4-triazine-6-carboxylic Acid (Xa) was obtained by boiling in ethanol equimolar amounts of the sulfone (IX) and hydrazine hydrate for 20-25 min. The solvent was distilled off, giving a colorless residue of (Xa).

The methylamides of 5-methylamino-3-α-methylhydrazino-1,2,4-triazine-6-carboxylic Acid and 5-methylamino-3-phenylamino-1,2,4-triazine-6-carboxylic acid (Xb and c) were obtained in a similar manner to compound (Xa) by the reaction of the sulfone (IX) with methylhydrazine and with aniline, respectively.

The Methylamide of 3-Hydroxy-5- methylamino-1,2,4-triazine-6-carboxylic Acid (Xd) was obtained by boiling the sulfone (IX) in a small amount of water for 1 h. When the reaction mixture was cooled, the colorless product (Xd) precipitated.

The Methylamide of 5-Methylaminotetrazolo[2, 3-e][1,2,4]triazine-6-carboxylic Acid (XI) was obtained by boiling equimolar amounts of the sulfone (IX) and sodium azide in ethanol for 25-30 min. Then the solvent was distilled off and the residue was treated with water, giving a colorless precipitate of (XI).

LITERATURE CITED

1. Yu. A. Azev, I. Ya. Postovskii, E. L. Pidémskii, et al., Khim. Farm. Zh., No. 4, 39 (1980).
2. L. Neinisch, W. Ozegowski, and M. Muhlstadt, Chem. Ber., 97, 5 (1964).
3. A. Dornow and H. Pietsch, Chem. Ber., 100, 2585 (1967).
4. M. Ichiba, S. Nishigaki, and K. Senga, J. Org. Chem., 43, 469 (1978).