SYNTHESIS AND SOME PHARMACOLOGICAL PROPERTIES OF ISOFERVENULIN DERIVATIVES

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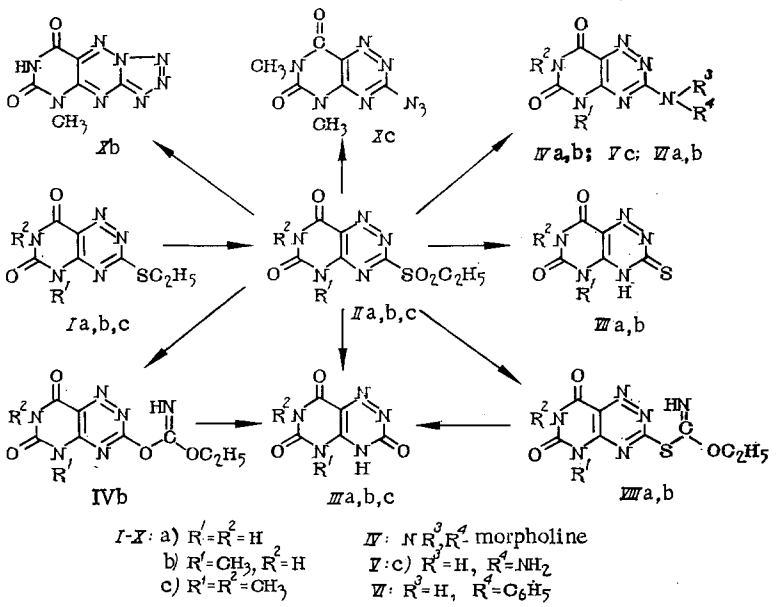
Compounds have been discovered among derivatives of pyrimido-as-triazines which have a varied spectrum of biological activity. Thus, 1,6-dimethyl-1,5,6,7-tetrahydropyrimido[5,4-e]-as-triazine-5,7-dione (xanthotricin) possesses marked activity against several tumors [1]. Antiinflammatory activity has been detected in 5-amino derivatives of pyrimido[5,4-e]-as-triazine [2].

The aim of the present work was the development of a practicable route for the synthesis of analogs of the natural antibiotic of the pyrimidotriazine series fervenulin, 6,8-dimethyl-5,6,7,8-tetrahydropyrimido[5,4-3]1,2,4-triazine-5,7-dione, and an investigation of some pharmacological properties of the obtained compounds.

Previously, derivatives of isofervenulin were obtained by nucleophilic substitution of a 3-alkylthio group in 5,6,7,8-tetrahydropyrimido[4,5-e]1,2,4-triazine-6,8-diones (Ia-c) by amine residues on extended heating of the reagents [3]. However, the possibilities of this method are limited as a result of the low reactivity of the alkylthio group. Furthermore, as a result of the use of drastic conditions destruction of the pyrimidine ring occurs in certain cases in addition to replacement of the alkylthio group [3].

In the present work oxidation of the alkylthio derivatives (Ia-c) gave the corresponding 3-alkylsulfonyl-5,6,7,8-tetrahydropyrimido[4, 5-e]1,2,4-triazine-6,8-diones (IIa-c) which, as we established, were distinguished by a high reactivity and may be widely used as starting materials for the synthesis of substituted isofervenulins (see Scheme). Thus, we investigated the reaction of sulfones (IIa-c) with water, morpholine, hydrazine, aniline, sodium sulfide, sodium azide, sodium cyanate, and potassium thiocyanate. On heating in boiling water for 3-5 min compounds (II) were converted quantitatively into the corresponding hydroxy derivatives (III),* while boiling for 3 h in 2 N hydrochloric acid is required to obtain these compounds starting from the alkylthio derivatives [3]. Reaction of sulfones (II) with morpholine and



*The trione structure is proposed for compounds (III) and was confirmed by the absence of characteristic OH-group absorption bands from the IR spectra.

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hydrazine proceeded at room temperature for several minutes. Thus on mixing compounds (IIa, c) with 1.5-2 molar excess of morpholine in ethanol for 3-5 min, 3-morpholino-5,6,7,8-tetrahydropyrimido[4, 5-e]1,2,4-triazine-6,8-diones (IVa, c) were obtained. The reaction of sulfone (IIc) with hydrazine also proceeded readily with the formation of 3-hydrazino-5,6,7,8-tetrahydropyrimido[4,5-e]1,2,4-triazine-6,8-dione (Vc). For complete conversion of sulfones (IIa, b) into 3-phenylamino-5,6,7,8-tetrahydropyrimido[4,5-e]1,2,4-triazine-6,8-diones (VIa, b) mixing them with a 1,5-2 molar excess of aniline in ethanol at room temperature for 10 min was sufficient. The reaction of sulfones (IIa, b) with sodium sulfide proceeded for 10-15 min on boiling the reagents in ethanol. As a result of the reaction 3,4,5,6,7,8-hexahydropyrimido[4,5-e]1,2,4-triazine-6,8-dione-3-thione (VIIa, b) were obtained in this case. The thione structure of compounds (VII) in the crystalline state followed from the absence of the characteristic SH-group absorption band from the IR spectra. In aqueous solution compounds (VIIa, b) also exist as the thione which was confirmed by the significant difference of the electronic spectra of these compounds from the spectra of the model alkylthio derivatives (Ia, b). Thus the UV spectrum of compound (VIIa) contains four absorption bands: λ_{max}, nm (log ε) 210 (4.040), 233 (4.115), 297 (4.343), 385 (3.301), while there are only 3 absorption bands in the spectrum of compound (Ia): 216 (3.380), 2.65 (4.176), 345 (4.040).

Reaction of sulfones (II) with salts of cyanic and thiocyanic acids was of interest not only as an independent investigation but as a way to obtain a series of new derivatives of isofervenulin. By boiling sulfones (IIa, b) with potassium thiocyanate in alcohol for 10-15 min the iminoesters (VIIIa, b) were obtained in 35-40% yield. The reaction of compound (IIb) with sodium cyanate proceeded similarly with the formation of iminoester (IXb). Evidently iminoesters (VIII) and (IX) are formed from the corresponding thiocyanates and cyanates by addition of a molecule of alcohol onto the C=N bond. The comparatively low yield of products (VIII) and (IX) is probably linked with the presence of competing reactions forming isocyanates and products of their decomposition. On boiling iminoesters (VIII) and (IX) in 18% hydrochloric acid solution they were converted into the corresponding hydroxy derivatives (III). The structures of iminoesters (VIII) and (IX) were confirmed by PMR spectral data in which there were multiplet methyl (1.39 and 1.29 ppm) and methylene (4.60 and 4.22 ppm) groups and also signals for NH groups (for VIIIb 13.13 and 12.63 ppm, and for IXb 11.46 and 12.06 ppm). The signals for the N—CH_3 groups of compounds (VIIIb and IXb) were observed at 3.41 and 3.38 ppm, respectively.

Interesting results were obtained on studying the interaction of sulfones (II) with sodium azide. It was discovered that 5-methyl-5,6,7,8-tetrahydropyrimido[4,5-e]tetrazolo[5,1-b]-as-triazine-6,8-dione (Xb) was formed by this reaction from the monomethyl derivative (IIb) while 3-azido-5,6-dimethyl-5,6,7,8-tetrahydropyrimido[4,5-e]1,2,4-triazine-6,8-dione (Xc) was obtained from the dimethyl derivative (IIc). The structures of compounds (Xa, b) were confirmed by IR spectral data where there was an absorption band at 2156 cm^{-1} for azide (Xc) while there was no absorption in this region for compound (Xb).

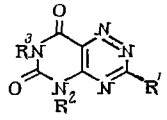
The pharmacological investigation was directed towards the antiinflammatory, analgesic, and antimicrobial properties of the synthesized derivatives of pyrimido[4,5-e]1,2,4-triazine-6,8-diones. The investigation was carried out on Wister rats and white mice (tetrahybrid) by intraperitoneal injection. For the assessment of antiinflammatory action the formalin inflammation model was used. The size of the edema of the rear paw was determined by an oncometric method [4] 3 and 6 h after injection of formalin. Phenylbutazone (butadione: 30 mg/kg) served as a standard for comparison. The hot plate method was used for the assessment of analgesic action [5]. Amidopyrine (100 mg/kg) was taken as the standard for comparison of analgesic activity. The investigations showed that only compounds (Ia, IIIa, and IVc) showed weak analgesic action. Among the tested compounds (IIIa) developed marked phlogolytic activity at the level of the standard, weaker activity was detected for (IVa). These same compounds showed weak antimicrobial (bacteriostatic) action in relation to cultures of *Escherichia coli* and *Staphylococcus aureus*. The tested compounds had low toxicity, their LD_{50} exceeded 200-500 mg/kg.

The low toxicity of the investigated pyrimido-as-triazines and the sufficiently high phlogolytic activity of some of them (IIIa) made it possible to consider further research expedient in this series of effective antiinflammatory agents.

EXPERIMENTAL

Electronic spectra of compounds were obtained on a Specord spectrometer. IR spectra were drawn on a UR-20 spectrometer. Samples were prepared as Nujol mulls. PMR spectra were drawn

TABLE 1. Substituted Pyrimido[4,5-e]1,2,4-triazine-6,8-diones



Compound	R^1	R^2	R^3	Mp °C	Yield, %	Found, %			Empirical formula	Calculated, %		
						C	H	N		C	H	N
IIa	$SO_2C_2H_5$	H	H	220—221 (with decomposition)	80—85	29,0	2,5	24,3	$C_7H_7N_5O_4 \cdot HCl$	28,6	2,7	23,9
IIb	$SO_2C_2H_5$	CH_3	H	162—3	75—80	35,8	3,3	26,0	$C_8H_9N_5O_4$	35,4	3,3	25,8
IIc	$SO_2C_2H_5$	CH_3	CH_3	155—6	75—80	38,2	3,8	24,8	$C_9H_{11}N_5O_4$	37,9	3,9	24,6
VIa	NHC_6H_5	H	H	>300	85—90	51,2	3,7	32,5	$C_{11}H_8N_6O_2$	51,6	3,5	32,8
VIb	NHC_6H_5	CH_3	H	>300	85—90	53,7	4,0	30,7	$C_{12}H_{10}N_6O_2$	53,3	3,7	31,1
VIIa	S	H	H	>300	75—80	27,5	2,4	32,2	$C_5H_2N_5O_2S \cdot H_2O$	27,9	2,3	32,6
VIIb	S	CH_3	H	269—70	70—75	34,4	2,5	33,6	$C_6H_4N_5O_2S$	34,1	2,4	33,2
VIIIa	$SC(NH)OC_2H_5$	H	H	265—6	35—40	36,2	3,3	31,7	$C_6H_8N_6O_2S$	35,8	3,0	31,3
VIIIb	$SC(NH)OC_2H_5$	CH_3	H	217—8	35—40	38,5	4,0	30,2	$C_9H_{10}N_6O_2S$	38,3	3,6	29,8
IXb	$OC(NH)OC_2H_5$	CH_3	H	261—2	30—35	40,6	4,0	32,0	$C_6H_{10}N_6O_4$	40,6	3,8	31,6
Xb	N_3	CH_3	H	189—90	50—55	32,8	1,9	51,2	$C_6H_4N_6O_2$	32,7	1,8	50,9
Xc	N_3	CH_3	H	178—9	50—55	35,6	3,0	48,3	$C_7H_6N_6O_2$	35,9	2,6	47,9

in deuterodimethyl solfoxide in a Perkin Elmer R-12B instrument with an operating frequency of 60 MHz. Chemical shifts are shown in a δ ppm scale and are given relative to tetramethylsilane.

3-Ethylsulfonyl-5,6,7,8-tetrahydropyrimido[4,5-e]1,2,4-triazine-6,8-diones (IIa, b, c). Compound (I) (6 mmole) was stirred at 10-15°C in water (30 ml) while passing gaseous chlorine simultaneously for 20-25 min. The solid hydrochloride of sulfone (II) was filtered off. Hydrochlorides (II) were unstable and readily split off HCl. Recrystallization of hydrochlorides (II) from absolute ethanol gave sulfones (II) in the free state (see Table 1). It is possible to use the hydrochlorides of sulfones (II) for reactions without further purification.

Hydrolysis of Sulfones (II). Method A. Sulfone (II) (6 mmole) was boiled in water (30 ml) for 5 min, cooled, and the hydroxy derivative (III) filtered off. The yields of compounds (IIIa, b, c) were 90-95%. Method B. Compounds (VIII) and (IX) were boiled in 18% hydrochloric acid solution (5 ml) for 1 h. The solution was evaporated to dryness and compound (III) obtained. The hydroxy derivatives (IIIa, b) obtained by methods A and B were identical to the product obtained by the method in [3, 6].

Reaction of Compounds (II) with Amines. Sulfone (II) (6.6 mmole) was stirred in ethanol (20 ml) with a 1.5-2-fold molar excess of amine for 5-10 min. Yields of (IVa, c) were 80-95%. The obtained compounds (IVa, c) were identical to those described in study [6].

The hydrazine (Vb), which was identical with that known in [7], was obtained in 60-65% yield.

The 3-phenylamino derivatives (VIa, b) were purified by reprecipitation from dimethylformamide with water.

Reaction of Sulfones (II) with Sodium Sulfide. Sulfone (II) (8 mmole) and sodium sulfide nonahydrate (6 g) in ethanol (30 ml) was boiled for 10 min (or stirred at 20°C for 30 min). The precipitate of (VII) was filtered off and recrystallized from water (pH 4.0-5.0).

Reaction of Compounds (II) with Potassium Thiocyanate. Sulfone (II) (4.8 mmole) was boiled with potassium thiocyanate (0.92 g) in ethanol (20 ml) (or stirred at 20°C for 30 min). The obtained suspension was cooled and filtered. The ethyl ester of (6,8-dioxo-5,6,7,8-tetrahydropyrimido[4,5-e]1,2,4-triazine-3-thio)carbamic acid (VIIIa) was extracted from the solid phase with hot ethanol. The ethanolic extract was evaporated. Iminoester (VIIIa) was recrystallized from water or ethanol. Iminoester (VIIIb) was isolated by recrystallization of the precipitate obtained in the reaction from 50% aqueous acetic acid.

Reaction of Compounds (II) with Sodium Cyanate. Sulfone (II) (1.4 g: 5.1 mmole) was added to a suspension of sodium cyanate (0.87 g) in ethanol (10 ml) and the mixture was stirred at 20°C for 30 min.

The precipitate of (5-methyl-6,8-dioxo-5,6,7,8-tetrahydropyrimido[4,5-e]1,2,4-triazine-3-hydroxy)carbamic acid ethyl ester (IX) was filtered off and recrystallized from water (pH 3.0-4.0).

Reaction of Sulfones (II) with Sodium Azide. The appropriate compound (II) (6 mmole) was stirred for 25-30 min in a solution of sodium azide (0.7 g) in water (30 ml). The precipitate of (Xb) or (Xc) was filtered off and recrystallized from water.

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