6:6g, (85%), mp 266-268°C (from aqueous alcohol). Found, %: C 64.91; H 4.73; N 6.77. $C_{22}H_{18}N_2O_6$. Calculated, %: C 65.24; H 4.43; N 6.89. IR spectrum, cm^{-1}: ν_{NH} 3420, 3380; $\lambda C=O$ 1725, 1680. UV spectrum, λ_{max}, nm (log ε): 204 (4.09), 236 (4.29), 305 (4.07). The same method was used to prepare methyl 2,2'-dicarboxy-[3,5'-bi-1H-indole]-3-acetate from (XI) (22 g, 0.056 mole), methanol (180 ml), and alcohol (2 ml) saturated with hydrogen chloride. The yield was 20.1 g (89%), mp 198-200°C (with decomposition; from alcohol). Found, %: C 64.51; H 4.58; N 6.75. $C_{21}H_{16}N_2O_6$. Calculated, %: C 64.28; H 4.08; N 7.14. IR spectrum, cm^{-1}: ν_{NH} 3340, 3220: $\lambda_{C=O}$ 1700. UV spectrum, λ_{max}, nm (log ε): 204 (4.00), 236 (4.22), 300 (4.00).

[3,5'-Bi-1H-indole]-3-acetic Acid (XIV). Compound (XIII) (1 g, 0.0025 mole) was heated to 270-280°C in a stream of argon or carbon dioxide for 5 min. After cooling, an ethereal solution of the product was chromatographed on a column packed with neutral aluminum oxide (Brockmann grade II). It was eluted with ether–pentane. The solvent was stripped off and after some time the resulting oil crystallized. The synthetic product (0.2 g) was dissolved in 10% aqueous alcoholic potassium hydroxide. The solution was diluted with a threefold excess of water at room temperature over a period of 30 min and filtered through a small quantity of activated carbon. The filtrate was cooled to 0°C and acidified to pH 4.0 with 18% hydrochloric acid. The white precipitate acid was filtered off, washed with water until neutral, and dried. The operation was repeated several times. The yield was 0.13 g (68%), mp 127-129°C (with decomposition). Found, %: C 74.67; H 4.84; N 9.45. $C_{18}H_{14}N_2O_2$. Calculated, %: C 74.48; H 4.82; N 9.65. IR spectrum, cm^{-1}: ν_{NH} 3220, 3340, $\lambda C=O$ 1700. UV spectrum, λ_{max}, nm (log ε): 206 (4.05), 232 (4.18), 258 (4.05), 303 (3.65). PMR spectrum (in deuteroacetone): 3.80 (s, 2H, $-CH_2-$); 6.13 (br. s, acidic protons interacting with water); 10.06 (br. s, 1H, =NH); and 10.15 (br.s, 1H, =N'H).

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SYNTHESIS AND PROPERTIES OF PYRIDO[2,3-e]-1,2,4-THIADIAZINE 1,1-DIOXIDES

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Substituted benzo-1,2,4-thiadiazine 1,1-dioxides have a broad spectrum of biological activity. Many compounds of this group display diuretic, antibacterial, or hypotensive action [1-4]. The literature has little information on the corresponding pyridothiadiazine 1,1-dioxides. Pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxides substituted in the pyridine ring are known to have diuretic, hypotensive, and antiinflammatory activity [5, 6].

We have sought new and potentially biologically active compounds by preparing pyridothiadiazine 1,1-dioxides without substituents in the pyridine ring. We examined the susceptibility of o-aminopyridinesulfonamides to cyclization under conditions equivalent to those for the benzo derivatives (see scheme, next page.) We used ethyl orthoformate, acetic anhydride, urea, thiourea, and guanidine for cyclization, finding a marked difference between the reactivity of the benzene- and pyridinesulfonamides.

We prepared the starting o-aminopyridinesulfonamides (IIIa) and (IIIb) by reaction of 2-chloropyridine-3-sulfonyl chloride (I) [7] with the appropriate amine. Fusion of 2-aminopyridine-3-sulfonamide (IIIa) with urea gave the ammonium salt, which we converted by acidifying the reaction mixture to 3-oxo-pyrido[2,3-e]1,2,4-thiadiazine 1,1-dioxide (IV). 2-Methylaminopyridine-3-sulfonamide (IIIb) differs markedly from its benzo

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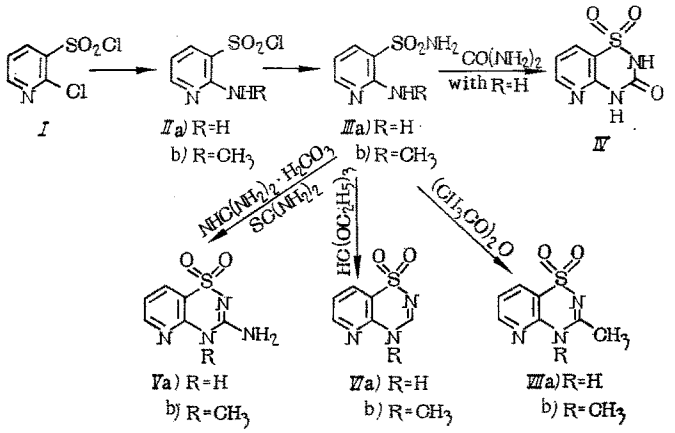

analog in its susceptibility to cyclization. Thus condensation of 2-methylaminopyridine-3-sulfonamide (IIIb) with urea under conditions equivalent to those for the benzo analog gave only the starting compound.

Condensation of pyridinesulfonamides (IIIa) and (IIIb) with guanidine carbonate formed the corresponding amino derivatives (Va) and (Vb). In contrast to o-aminobenzenesulfonamide, which does not cyclize with guanidine [8], cyclization of the pyrido analog (IIIb) proceeds readily, forming the 3-amino derivative (Vb) in high yield.

Fusion of o-aminopyridinesulfonamides (IIIa) and (IIIb) with thiourea gave not the expected 3-thio substituted pyrido[2,3-e]-1,2,4-thiadiazone 1,1-dioxide but the 3-amino derivatives (Va) and (Vb) in good yield, whereas cyclization of o-substituted benzenesulfonamides with thiourea is known to form the thio derivatives, accompanied by the 3-amino derivatives in 10% yield [9].

The reaction of sulfonamides (IIIa) and (IIIb) with ethyl orthoformate under conditions equivalent to those for the benzo derivatives [10] gave compounds (VIa) and (VIb). Condensation of o-aminosulfonamides (IIIa) and (IIIb) with acetic anhydride gave the 3-methylpyridothiadiazine 1,1-dioxides (VIIa) and (VIIb) in high yield.

EXPERIMENTAL BIOLOGY

We tested compounds (IV)-(VII) for analgesic and antiinflammatory activity. All the test compounds were relatively nontoxic (LD_{50} > 500 mg/kg). Their biological activity was evaluated in randomly bred white mice and Wistar white rats by intraperitoneal administration. We assayed their antiinflammatory activity against formalin inflammation. The degree of edema of the rear paw of rats was measured by L. S. Salyamon's on-

TABLE 1. Biological Evaluation of Compounds (IV)-(VII)

Compound	LD_{50}, mg/kg	Dose, mg/kg	% Increase in paw size (formalin inflammation)		Time of defensive reflex (hot plate procedure), sec (M ± m)
			after 3 h	after 6 h	
IV	>500	50	81	98	22,3±2,1; P_1<0,001
Va	>500	50	77	110	18,8±4,3; P_1>0,05
Vb	>500	50	76	90	24,8±3,9; P_1<0,01
VIa	>500	50	53 P_1<0,05; P_2>0,5	68 P_1>0,1; P_2<0,01	20,0±3,1; P_1<0,02
VIb	>500	50	41 P_1<0,001; P_2>0,25	51 P_1<0,001; P_2<0,02	55,8±3,5; P_1<0,001; P_2>0,1
VIIa	>500	50	80 P_1>0,5	101 P_1<0,25	20,2±2,7; P_1<0,05
VIIb	>250	40	33 P_1<0,002	60 P_1<0,001	25,8±6,7; P_1<0,05
Control and standard:					
Formalin (control), 2.5% solution			80	77	
Phenylbutazone (standard), 30% solution			48	32	
Starch slurry (control), 2% solution					12,1±0,8
Amidopyrine (standard)					50,4±2,8

Note: Here P_1 refers to comparison with the control and P_2 to comparison with the standard.

TABLE 2. Physicochemical Properties of the Synthetic Compounds

Compound	Yield, %	Melting point (from water), °C	Found, %			Formula	Calculated, %			UV spectra, nm (log ε)	R_f
			C	H	N		C	H	N		
II	85	184–5	31,5	2,69	14,5	$C_5H_5N_2O_2SCl$	31,3	2,60	14,6		0,63
IIIa	80	165–7	34,9	4,14	24,2	$C_5H_7N_3O_2S$	34,7	4,05	24,2	239 (4,09), 308 (3,78)	0,23*
IIIb	75	164–6	38,4	4,92	22,4	$C_6H_9N_3O_2S$	38,5	4,80	22,5	248 (4,15), 322 (3,66)	0,83*
IV	65	300–2	36,3	2,76	20,9	$C_6H_5N_3O_3S$	36,2	2,52	21,1	241 (4,03), 290 (3,66)	0,63
Va	60	325–9	36,0	3,21	28,6	$C_6H_6N_4O_2S$	36,4	3,03	28,3	292 (3,98), 287 (3,72)	0,68
Vb	60	315–20	39,5	3,84	26,4	$C_7H_8N_4O_2S$	39,6	3,77	26,4	247 (3,97), 285 (3,75)	0,60
VIa	70	294–5	39,1	2,50	23,0	$C_6H_5N_3O_2S$	39,3	2,80	22,9	263 (3,82), 286 (3,15)	0,71
VIb	60	241–2	42,7	3,67	21,3	$C_7H_7N_3O_2S$	42,6	3,60	21,3	268 (3,70), 289 (3,90)	0,62
VIIa	60	275–7	42,8	3,76	21,4	$C_7H_7N_3O_2S$	42,6	3,60	21,3	263 (3,82), 286 (3,15)	0,78
VIIb	60	165–6	45,5	4,56	19,5	$C_8H_9N_3O_2S$	45,5	4,30	19,9	268 (3,70), 286 (3,15)	0,61

*In the system chloroform–petroleum ether–ethanol (4:4:1); all others refer to the system butanol–water–acetic acid (4:1:1).

cometric method [11]; the standard was phenylbutazone. We assayed the analgesic effect by the hot plate procedure [12]; the standard was amidopyrine.

The results of our tests, which confirm the existence of anti-inflammatory and analgesic activity, are summarized in Table 1. We found that 4-methylpyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (VIb) has marked anti-inflammatory and analgesic activity, comparable with that of phenylbutazone and amidopyrine, whereas the activity of pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide (VIa) is only moderate. The 3-substituted pyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxides (Vb) and (IV) have analgesic activity only.

EXPERIMENTAL CHEMISTRY

Electronic spectra were recorded in water with a Specord UV-VIS recording spectrophotometer. Thin-layer chromatography was carried out on Silufol UV-254 (Czechoslovakia) in the systems butanol–water–acetic acid (4:1:1) and chloroform–petroleum ether–ethanol (4:4:1).

2-Aminopyridine-3-sulfonamide (IIIa). Compound (I) (3 g, 0.17 mmole) [7] was heated in a sealed ampul at 150°C for 4 h in concentrated aqueous ammonia (40 ml). The ampul was opened and the colorless precipitate was filtered off.

2-Methylaminopyridine-3-sulfonamide (IIIb). This was prepared in the same way from 2-chloropyridine-3-sulfonamide and methylamine.

2-Chloropyridine-3-sulfonamide (IIa). 2-Chloropyridine-3-sulfonyl chloride (3 g, 0.17 mmole) was kept at room temperature for 2 h in concentrated aqueous ammonia (40 ml). Evaporation of the ammonia solution gave a white crystalline precipitate.

3-Oxopyrido[2,3-e]-1,2,4-thiadiazine 1,1-Dioxide (IV). Compound (IIIa) (0.7 g, 0.04 mmole) and urea (0.6 g, 0.13 mmole) were fused at 190-200°C until the melt solidified, and kept at this temperature for a further 30 min. The resulting mass was dissolved with heating in water and the precipitate was filtered off. On cooling, colorless crystals of the ammonia salt of 3-oxopyrido[2,3-e]-1,2,4-thiadiazine 1,1-dioxide precipitated from the solution. Acidification of an aqueous solution of this to pH 2.0 gave (IV).

3-Aminopyrido[2,3-e]-1,2,4-thiadiazine 1,1-Dioxide (Va). Compound (IIIa) (0.85 g, 0.05 mmole) and guanidine carbonate (1.2 g, 0.1 mmole) were fused until the melt solidified and heated at 220°C for a further 30 min. The melt was then dissolved in water with heating and sodium bicarbonate was added to pH 8.0. The precipitate was filtered off; acidification of the cooled solution to pH 2.0 precipitated colorless crystals.

3-Amino-4-methylpyrido[2,3-e]-1,2,4-thiadiazine 1,1-Dioxide (Vb). This compound was prepared in the same way as compound (Va) from 2-methylaminopyridine-3-sulfonamide and guanidine carbonate.

Pyrido[2,3-e]-1,2,4-thiadiazine 1,1-Dioxide (VIa). Compound (IIIa) (2.7 g, 0.15 mmole) was refluxed for 1 h with ethyl orthoformate (30 ml). A colorless precipitate of (VIa) formed slowly.

4-Methylpyrido[2,3-e]-1,2,4-thiadiazine 1,1-Dioxide (VIb). This compound was prepared in the same way as compound (VIa) from 2-methylaminopyridine-3-sulfonamide (IIIb).

3-Methylpyrido[2,3-e]-1,2,4-thiadiazine 1,1-Dioxide (VIIa). A mixture of compound (IIIa) (2.5 g, 0.15 mmole) and acetic anhydride (6 ml, 0.6 mmole) was refluxed for 1 h. On cooling, colorless crystals precipitated from the reaction mixture.

3,4-Dimethylpyrido[2,3-e]-1,2,4-thiadiazine 1,1-Dioxide (VIIIb). This was prepared in the same way as compound (VIIa).

Table 2 summarizes the physicochemical properties of the synthetic compounds.

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SOLUBILITY PREDICTION UNDER THE SCREENING CONDITIONS OF BIOLOGICALLY ACTIVE COMPOUNDS. II. THE ADDITIVE AND SEMI-EMPIRICAL APPROACHES

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Solubility prediction on the basis of data on the chemical structure of compounds is advisable for use in a system of biological action tests of a large number of chemicals. Some routes for solving this problem were proposed in the preceding communication [1]. Below we examine the result of using the principle of additivity of substituent contributions or contributions of definite structure fragments to the solubility value, and also the use of semi-empirical relationships for this purpose. Considering that the process of solution in a standard solvent (with the exception of cases of "specific solvation") is determined exclusively by the physico-chemical properties of their molecules, most of which are additive, it may be assumed to a first approximation that solubility can be expressed as the sum of the contributions of individual atoms, groups of atoms, and bonds. The method of determining the contributions of substituents or other structure elements (Δ_R):

$$\Delta_R = \lg 1/N_{S,R} - \lg 1/N_{S,0} \quad (1)$$

and of calculating solubility on the basis of these data from additive components:

$$\lg 1/N_{S,x} = \lg 1/N_{S,i} + \sum_R \Delta_R \quad (2)$$

is a consequence of the applicability of the principle of free energy linearity to solution processes [1]. In Eqs. (1) and (2), solubilities are expressed in mole fractions; the subscripts R and O refer to the substances selected for calculation of Δ_R, that is, of substances which differ from one another by the element R; and i refers to the structure selected as the starting one for calculation of $N_{S,X}$.

Considering that the greatest amount of data on solubility pertain to water [2-5], it was selected as the standard solvent. Data obtained at 25 ± 5°C were used.

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