We have thus discovered a novel macromolecular compound which effectively suppresses the silicotic processes in the living body, and which has no deleterious side effects.

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF ω-SUBSTITUTED 2-ALKYLTHIO-4,6-DIMETHYLPYRIMIDINES

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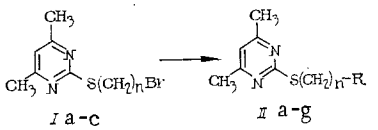
It has previously been shown that 2-(ω-bromoalkylthio)-4,6-dimethylpyrimidines (Ia-c) react with nucleophilic reagents such as the sodium salts of 4,6-dimetnyl-2-hydroxypyrimidine and 6-methyl-2-thiouracil to give the compounds (IIa-g), as follows [1]:



I a-c II a-g

Ia: $n = 4$; Ib: $n = 5$; Ic: $n = 6$; IIa: $n = 4$, R = pyridinium bromide; $n = 5$, R = pyridinium bromide; IIc: $n = 6$, R = pyridinium bromide; IId: $n = 5$, $R = \overset{+}{N}Et_3Br^-$; II e: $n = 6$, $R = NHC_6H_5$; IIf: $n = 6$, $R = NC_5H_{10}$; IIg: $n = 6$, $R = N(CH_2)_4O$.

Pyrimidines containing a variety of substituents in the alkyl chain (including the amino-function) are known to possess a wide range of biological activity [2].

In continuation of work on the reactions of (Ia-c) with nucleophiles, and in order to establish the dependence of bioloigcal activity on the structures of these compounds, we have examined the reactions of (Ia-c) with a variety of famines. It was found that, irrespective of the type of amine, only the compounds (IIa-g) were obtained, in high yields. Thus, reaction of (Ia-c) with pyridine, and of (Ib) with triethylamine in solution in methyl ethyl ketone afforded (IIa-d), and reaction of (Ic) with aniline, piperidine, and morphiline in solution in DMF in the presence of potassium carbonate gave (IIe-g).

The structures of the compounds obtained were confirmed by IR spectroscopy and elemental analysis.

The IR spectra of (IIa-g) showed no absorption at 650 cm^{-1} characteristic of νC—Br [3, pp. 470-471] such as is present in (Ia-c). In addition, (IIa-g) displayed absorption at 565-595 cm^{-1} assignable to νC—S [3, pp. 502-504] and at 1560-1590 cm^{-1} characteristic of stretching vibrations of the pyrimidine ring [4]. The IR spectrum of (IIe) contained a band of 3350

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cm^{-1} characteristic of νN–H [5]. The ionic structure of (IIa-d) was confirmed by their reaction with silver nitrate.

EXPERIMENTAL CHEMISTRY

Compounds (Ia-c) were obtained as described in [6]. IR spectra were obtained on a UR-20 spectrometer (East Germany), solids as a suspension in vaseline oil, and liquids as a film between KBr plates. Column chromatography was carried out with neutral alumina (grade II activity).

[(4,6-Dimethylpyrimidin-2-ylthio)butyl]pyridinium Bromide (IIa). A solution of 2.2 g (0.008 mole) of (Ia) and 1.2 g (0.016 mole) of pyridine in 150 ml of methyl ethyl ketone was boiled for 45 h, cooled, the solvent evaporated to 30 ml, ether (30 ml) added, and the solid filtered off and dried to give 2.4 g (85.7%) of (IIa), mp 85-86°C (methyl ethyl ketone). Found, %: C 50.51; H 5.39; N 11.72. $C_{15}H_{20}BrN_3S$. Calculated, %: C 50.84; H 5.64; N 11.86.

[(4,6-Dimethylpyrimidin-2-ylthio)pentyl]pyridinium Bromide (IIb). This was obtained similarly after 60 h, mp 98-99°C, (decomp.), yield 88.1%. Found, %: C 52.00; H 5.79; N 11.21. $C_{16}H_{22}BrN_3S$. Calculated, %: C 52.20; H 5.97; N 11.40.

[(4,6-Dimethylpyrimidin-2-ylthio)hexyl]pyridinium Bromide (IIc). This was obtained similarly after 65 h, mp 134-135°C, yield 82%. Found, %: C 53.51; H 6.19; N 10.76. $C_{17}H_{24}BrN_3S$. Calculated, %: C 53.41; H 6.27; N 10.86.

[(4,6-Dimethylpyrimidin-2-ylthio)pentyl]triethylammonium Bromide (IId). This was obtained similarly form (Ib) and triethylamine after 55 h, mp 78-79°C (decomp.), yield 87.2%. Found, %: C 52.10; H 8.24; N 10.94. $C_{17}H_{32}BrN_3S$. Calculated, %: C 52.32; H 8.20; N 10.76.

2-(ω-Anilinohexylthio)-4,6-dimethylpyrimidine (IIe). A mixture of 10.0 g (0.033 mole) of (If), 3.1 g (0.033 mole) of aniline and 4.6 g (0.033 mole) of calcined, finely ground potassium carbonate in 100 ml of DMF was stirred at 110°C for 65 h. The solid was filtered off, the DMF evaporated *in vacuo*, and the residue chromatographed on a column with alumina. The column was washed with light petroleum to give 8.3 g (80.5%) of (IIe), mp 64-65°C (light petroleum, bp 40-70°C). Found, %: C 68.65; H 7.75; N 13.59. $C_{18}H_{25}N_3S$. Calculated, %: C 68.57; H 7.93; N 13.32.

2-(ω-Piperidinohexylthio)-4,6-dimethylpyrimidine (IIf). This was obtained similarly after 65 h; d_4^{20} 1.0248; n_D^{20} 1.5318; yield 85%. Found, %: C 66.64; H 9.59; N 13.81. $C_{17}H_{29}N_3S$. Calculated, %: C 66.40; H 9.43; N 13.67.

2-(ω-Morpholinohexylthio)-4,6-dimethylpyrimidine (IIg). This was obtained similarly after 70 h; d_4^{20} 1.0678; n_D^{20} 1.5303; yield 84%. Found, %: C 62.32; H 8.58; N 13.42. $C_{16}H_{27}N_3SO$. Calculated, %: C 62.14; H 8.73; N 13.58.

EXPERIMENTAL PHARMACOLOGY

Analgesic activity was determined in white laboratory mice weighing 19-23 g using the spasm induced by intraperitoneal administration of an 0.75% solution of acetic acid [7].

Antiinflammatory activity was studied in agar inflammation of the rat paw. The tests were carried out with white male Wistar rats weighing 160-180 g [8]. Two screening tests were used to determine the local anesthetic activity of the compounds, namely their ability to induce anesthesia in the rabbit eye cornea, and their ability to reduce the amplitude of the action potential in the isolated sciatic nerve of the frog. The spikes were recorded on a data-storing C8-13 oscillograph and an H-3021 automatic pan recorder following preliminary amplification of the biosignal with a UBF-4-03 amplifier. Acute toxicities were determined by the intragastric route in mice, the results being recorded after 5 days.

The test compounds in all cases were introduced into the stomach via a metal probe, either in solution of suspended in 1% aqueous soidium carboxymethylcellulose.

The statistical treatment was carried out by variational statistics [9].

The results of the tests are shown in Table 1.

As will be seen from the table, (IIa, b, e, and g) significantly reduce rat paw edema in doses of $^1/_5$-$^1/_{25}$ of the LD_{50}

The highest analgesic activity in compounds (Ia-c) (approximating to that of amidopyrine and acetylsalicylic acid) was shown by (IIb). However, replacement of the pyridine moiety in (IIb) by the triethylamine moiety (IId) increased the toxicity.

TABLE 1. Pharmacological Activity and Toxicity of the Test Compounds

Compound	Antiinflammatory activity			Analgesic activity (dose required to reduce the No. of spasms by 25% in half the animals, LD_{50}, mg/kg)	Local anesthetic activity		LD_{50}, mg/kg
	dose, mg/kg	size of edema, g	%inhibition of edema		concentration, %	effect	
II a	50	0,45±0,1	17	>100	0,5—5	—	800
	100	0,37±0,1	31				
II b	50	0,35±0,02	35	50	0,5—2	—	850
II c	100	0,49±0,06	9	100	0,5—5	—	850
II d	50	0,30±0,04	44	...	0,5—2	—	60
II e	50	0,45±0,1	17	120	>2	+	2000
	100	0,38±0,03	30				
II f	...	...	...	...	0,5—1	+	40
II g	50	0,37±0,1	31	50	0,5—2	—	250
Amidopyrine	75	0,29±0,3	46	50			350
	100	0,14±0,02	74				
Acetylsalicyclic acid				~35—40			500

In the series (IIe-g), (IIg) has the same analgesic activity as (IIb).

Local anesthetic activity was found in (IIe and f), (IIf) being the most active but also the most toxic. The remaining compounds did not possess this type of activity.

This investigation has therefore shown that all the compounds tested display biological activity. For this reason, a more extensive search for biologically active compounds should be carried out amongst pyrimidine derivatives of this type.

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