PYRIMIDINE DERIVATIVES.

XLIV. SOME 5,6-DIHYDROURACILS AND THIOURACILS AND AN INVESTIGATION OF THEIR ANTITUMORAL ACTIVITY

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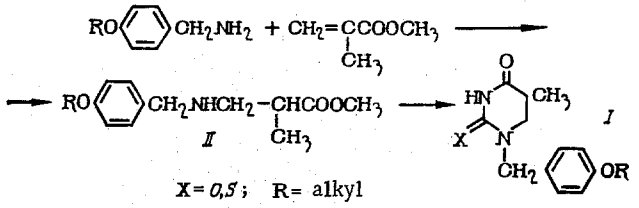
The synthesis of dihydrouracils and thiouracils (I) differing from those obtained previously [1] by the presence of methyl group in position 5 is described, which makes it possible to follow the change in their biological activity due to the introduction of the methyl group.

Compounds (I) were synthesized by the cyclization of methyl β-(4-alkoxybenzylamino)-α-methylpropionates (II) with urea or ammonium thiocyanate in an acid medium (Table 1). The initial methyl propionates (II) were obtained by heating 4-alkoxybenzylamines with methyl methacrylate (Table 2).



X = O, S; R = alkyl

The structures of the compounds obtained were shown by elementary analysis and also by mass spectrometry. The mass spectra of (I) have fairly strong peaks of the molecular ions and of a number of fragmentary ions the origin of which confirms the structures of the 5-methyl-5,6-dihydrouracils and thiouracils.

The toxicities and antitumoral properties of the 5,6-dihydrouracils and thiouracils [1] and their methyl analogs (I) were studied by the method described previously [2]. The results obtained (Table 3) show that these substances greatly resemble the alkoxybenzoylpyrimidine derivatives studied earlier [3-5].

The LD_{100} values for the N'-(4-alkoxybenzyl)-5,6-dihydrouracils averaged 1333 mg/kg. Compounds containing ethoxy-, propoxy-, and butoxybenzyl radicals inhibited the growth of sacrcoma 45 by 30-59%, and the isobutoxybenzyl derivatives by 75%. N'-(4-Propoxybenzyl)-5,6-dihydrouracil had a moderate action on sarcoma 180.

The introduction of a methyl group in position 5 of a dihydro uracil leads to an almost twofold increase in its toxicity. Simultaneously, a weakening of its antitumoral activity is observed. Of the 5-methyl-5,6-dihydrouracils only N'-(4-methoxybenzyl)- and N'-(4-isopropoxybenzyl)5,6-dihydrouracils suppressed the growth of sarcoma 45 to a moderate extent, and the propoxybenzyl derivative had a similar effect on sarcoma 180. The least toxic substances of those studied proved to be the 5,6-dihydrothiouracils. Their antitumoral activities on sarcoma 45 were almost identical with those of the 5,6-dihydrouracils, and were somewhat superior on sarcoma 180. The presence of a methyl group in position 5 of the 5,6-dihydrothiouracils leads to the almost complete loss of antitumoral activity.

All the compounds tested on Ehrlich's ascitic carcinoma proved to be ineffective.

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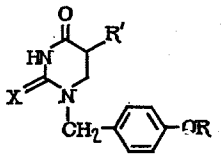
TABLE 1. Methyl β-(4-Alkoxybenzylamino)-α-methylpropionates (II)

R	Yield (in %)	bp (in °C/mm)	d_4^{20}	n_D^{20}	Found (in %)			Empirical formula	Calculated (in %)		
					C	H	N		C	H	N
CH_3	55,0	150—2/2	1,0720	1,5070	65,47	7,85	6,15	$C_{13}H_{19}NO_3$	65,79	8,07	5,90
C_2H_5	46,5	164—6/3	1,0451	1,5091	67,12	8,12	5,78	$C_{14}H_{21}NO_3$	66,90	8,42	5,57
C_3H_7	50,0	160—2/2	1,0286	1,5060	57,65	8,65	5,43	$C_{15}H_{23}NO_3$	67,89	8,74	5,27
iso C_3H_7	60,3	149—150/1	1,0217	1,5008	67,93	8,42	5,15	$C_{15}H_{23}NO_3$	67,89	8,74	5,27
C_4H_9	50,2	163—5/2	1,0152	1,5032	68,48	8,90	5,27	$C_{16}H_{25}NO_3$	69,78	9,01	5,01

TABLE 2. Dihydrouracils and Dihydrothiouracils (I)

R	X	Yield (in %)	mp (in °C)	R_f	Found (in %)				Empirical formula	Calculated (in %)			
					C	H	N	S		C	H	N	S
CH_3	O	52,6	110—1	0,62	63,00	6,72	11,45	—	$C_{13}H_{14}N_2O_3$	61,88	6,49	11,28	—
C_2H_5	O	66,5	98—9	0,69	64,37	7,12	10,35	—	$C_{14}H_{16}N_2O_3$	64,11	6,91	10,68	—
C_3H_7	O	50,0	81—2	0,42	64,98	7,64	10,00	—	$C_{15}H_{18}N_2O_3$	65,19	7,29	10,13	—
iso-C_3H_7	O	65,6	131—2	0,40	65,32	7,47	10,25	—	$C_{15}H_{18}N_2O_3$	65,19	7,29	10,13	—
C_4H_9	O	41,0	97—8	0,40	66,32	7,45	9,72	—	$C_{16}H_{20}N_2O_3$	66,18	7,63	9,64	—
CH_3	S	40,0	124—5	0,38	—	—	10,21	12,35	$C_{13}H_{14}N_2O_2S$	—	—	10,59	12,13
C_2H_5	S	50,1	121—2	0,45	—	—	10,27	11,33	$C_{14}H_{16}N_2O_2S$	—	—	10,06	11,51
C_3H_7	S	30,1	130—1	0,49	—	—	9,96	10,63	$C_{15}H_{18}N_2O_2S$	—	—	9,58	10,96
iso-C_3H_7	S	35,2	119—120	0,50	—	—	9,76	10,81	$C_{15}H_{18}N_2O_2S$	—	—	9,58	10,96
C_4H_9	S	25,0	124—5	0,51	—	—	8,85	10,21	$C_{16}H_{20}N_2O_2S$	—	—	9,14	10,46

TABLE 3. Summarized Information on the Toxicity and Antitumoral Activity of the Compounds



R	R′	X	LD_{100} (in mg/kg) for mice	Sarcoma 45	Sarcoma 100
				inhibition of the growth of the tumor*	
CH_3	H	O	1100	0	0
C_2H_5	H	O	1155	+	0
C_3H_7	H	O	1590	+	+
iso-C_3H_7	H	O	636	0	0
C_4H_9	H	O	2200	+	0
iso-C_4H_9	H	O	1320	++	0
CH_3	CH_3	O	880	+	0
C_2H_5	CH_3	O	800	0	0
C_3H_7	CH_3	O	432	0	+
iso-C_3H_7	CH_3	O	400	+	0
C_4H_9	CH_3	O	864	0	0
CH_3	H	S	2000	0	+
C_2H_5	H	S	2000	0	+
C_3H_7	H	S	2000	0	+
iso-C_3H_7	H	S	2000	+	0
C_4H_9	H	S	2000	0	+
iso-C_4H_9	H	S	2000	+	+
CH_3	CH_3	S	2000	+	0
CH_3	CH_3	S	2000	+	0
C_2H_5	CH_3	S	2000	0	0
C_3H_7	CH_3	S	2000	0	0
iso-C_3H_7	CH_3	S	1750	0	0

Symbols: 0) absence of an effect; +) inhibition of the growth of the tumor by 30-59%; ++) the same by 60-79%.
*In the chemotherapeutic experiments, the preparations were tested at the maximum doses tolerated by the animals with the tumors.

EXPERIMENTAL

Thin-layer chromatography was performed on Silufol in the diethyl ether–petroleum ether (4:1) system. The spots were revealed in UV light.

The mass spectra were taken on an MKh-1303 instrument with the direct introduction of the sample into the region of ionization by 30 eV electrons at a temperature of 60-70°C.

Methyl β-(4-Alkoxybenzylamino)-α-methylpropionates (II). A mixture of 0.05 mole of a 4-alkoxybenzylamine, 5 g (0.05 mole) of methyl methacrylate, and 30 ml of absolute methanol was boiled for 48 h. The methanol was driven off and the residue was distilled in vacuum (see Table 1).

N′-(4-Alkoxybenzyl)-5-methyl-5,6-dihydrouracils (I). A mixture of 0.02 mole of a compound (II), 6 g (0.1 mole) of urea, and 8 ml of glacial acetic acid was boiled for 3 h, and then 4 ml of concentrated hydrochloric acid was gradually added and boiling was continued for another 2 h. The mixture was diluted with water (1:5) and cooled, and the precipitate that formed was filtered off, washed with water, and recrystallized from ethanol (see Table 2).

N′-(4-Alkoxybenzyl)-5-methyl-5,6-dihydrothiouracils (I). A mixture of 0.02 mole of a compound (II), 3.8 g (0.05 mole) of ammonium thiocyanate, and 8 ml of glacial acetic acid was heated at 100-105°C for 2 h, and then 5 ml of concentrated hydrochloric acid was added dropwise and heating was continued for another 3 h. The products were worked up as in the preceding case (see Table 2).

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SYNTHESIS AND STUDY OF THE BACTERICIDAL PROPERTIES OF N-CHLOROARENESULFONIMIDES

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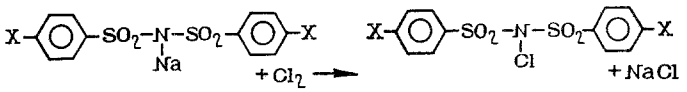
N-Chloro derivatives of arenesulfonamides (chloramines) are widely used in organic synthesis, analysis, and medical practice [1-4]. Until recently, N-chloroarenesulfonimides (I-VII) were unknown. We have obtained some of them (I, II, V) by the chlorination of aqeuous solutions of sodium salts of arenesulfonimides [5]:



I: X=H, *II*: X=CH_3, *III*: X=NO_2, *IV*: X=F, *V*: X=Cl, *VI*: X=Br, *VII*: X=I

The presence in these compounds of a chlorine atom attached to nitrogen permitted the expectation of bactericidal properties. To investigate the possibility of their practical use, in the present work we have synthesized a number of N-chloroarenesulfonimides (I-VII) with various substituents in the para position of the benzene nuclei, have recorded their IR spectra, and have studied their bacterial action.

The compounds that we obtained consist of colorless (with the exception of (III), which has a light cream shade) crystalline substances soluble in benzene, dioxane, and polychloroalkanes and isoluble in diethyl ether and petroleum ether. Their solubility in water at room temperature does not exceed 0.025%.

The IR spectra of all the substances, unlike that of the unsubstituted benzenesulfonimide, have strong absorption bands close to 800 cm^{-1}, which (together with the absence of bands of N—H vibrations) shows the replacement of the hydrogen of the imide group by chlorine.

The bactericidal action of the substances synthesized was studied* on test cultures of Staphylococcus, Streptococcus, Pneumococcus, *Bac. subtilis*, and *Ps. pyocyanea*. Compounds (I) and (III-VII) were active against all the bacteria mentioned in a dilution of 1:4000, and compound (II) in a dilution of 1:2000. For comparison, the bactericidal action of chloramines B and KhB was studied under similar conditions. It was found that they had the same effect only in a dilution of 1:20.

EXPERIMENTAL

N-Chloroarenesulfonimides (I-VII). At 20°C, a moderate current of chlorine was passed into an aqueous solution of 0.05 mole of the sodium salt of an arenesulfonimide obtained by dissolving the calculated amount of imide in an equivalent volume of a 1% solution of sodium carbonate. After 3-4 min, white flocs began to precipitate, and their amount rapidly increased. The passage of chlorine was continued until it appeared freely above the surface

*The bactericidal action of the N-chloroarenesulfonimides was studied by I. Yu. Kholupyak in the Department of Microbiology of Khar'kov Pharmaceutical Institute, for which the author expresses his deep gratitude.

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