ANALOGS OF PYRIMIDINE NUCLEOSIDES.

13.* 1-SUBSTITUTED 4-THIOURACILS

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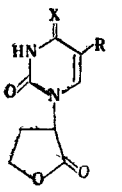
4-Thiouracil derivatives with various oxygen-containing groupings as substituents attached to the N_1 atom were obtained by thionation of 1-substituted uracils with phosphorus pentasulfide. It is demonstrated that the yield of the 4-thiouracil derivative depends on the strength of the C–N pseudoglycoside bond in the starting 1-substituted uracil.

4-Thiopyrimidine nucleosides, viz., 4-thiouridine, 2-thiocytidine, and their derivatives, are included in the composition of some t-RNA [2, 3] and also have antitumorigenic [4] and antivirus [5, 6] activity.

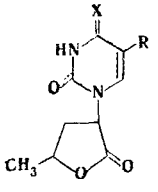
In the present research we accomplished the synthesis of 4-thiouracil derivatives with various oxygen-containing groupings attached to the N_1 atom.† These compounds can be regarded as distant analogs of 4-thiouridine. They are of interest in the search for new antitumorigenic preparations and for the synthesis of 1-substituted cytosines. In addition, these compounds can serve as markers in the study of the reaction of analogs of nucleosides with enzymes.

α-(4-Thio-5-substituted 1-uracilyl)-γ-butyrolactones (I-IVb), α-(4-thio-5-substituted 1-urcilyl)-γ-methyl-γ-butyrolactones (V-VIIIb), diethyl (4-thio-1-uracilyl)malonate (IXb), and 1-(3-halo-2-tetrahydrofuryl)-4-thio-5-substituted uracils (XI-XIVb) were obtained in 40-80% yields by thionation of the corresponding uracil derivatives in absolute dioxane with a twofold excess of phosphorus pentasulfide (Table 1). The carrying out of the reaction under consideration in dioxane [6] differs favorably from the carrying out of similar reactions in pyridine [8] in that it decreases the reaction time, simplifies the isolation and purification of the desired products, and raises the yields.

The thionation of 1-(2-tetrahydrofuryl)-5-fluorouracil (Xa) under the same conditions is complicated by the fact that, in addition to replacement of the oxo group by a thioxo group,



I-IV a, b



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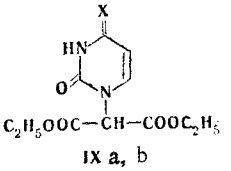
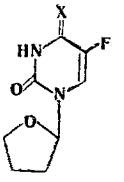
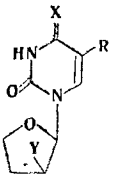


IX a, b



X a, b



XI-XIV a, b

I, V R=H; II, VI R=CH_3; III, VII R=F; IV, VIII R=Br; XI R=H, Y=Cl; XII R=F, Y=Cl; XIII R=H, Y=Br; XIV R=F, Y=Br; I–XIV a X=O; b X=S

*See [1] for communication 12.
†See [7] for a preliminary communication.

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TABLE 1. 1-Substituted 4-Thiouracils

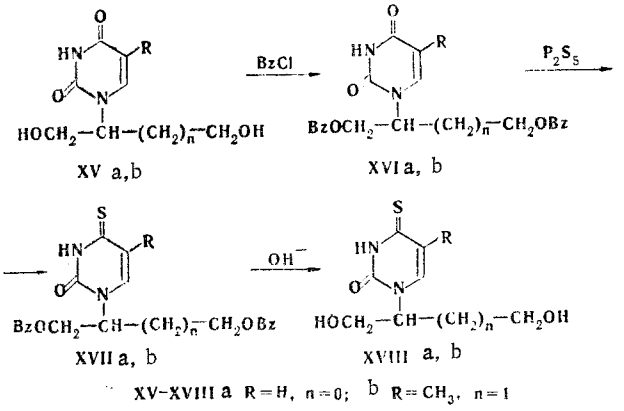
Compound	mp, °C	R_f	UV spectra, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)			Yield, %
			pH 2	pH 7	pH 11	
I b	229—230	0,88	287 (7,0), 335 (22,0)	287 (7,0), 335 (22,0)	320 (20,0)	65
II b	265—267	0,81	287 (4,8), 340 (15,5)	287 (4,8), 340 (14,5)	320 (15,5)	67
III b	238—240	0,80	287 (4,0), 342 (29,0)	286 (4,2), 335 (26,0)	330 (26,5)	55
IV b	263—265	0,88	255 (6,1), 345 (24,6)	250 (7,6), 340 (26,0)	335 (19,2)	95
V b	221—223	0,84	253 (4,0), 333 (19,4)	253 (5,0), 333 (18,4)	320 (17,8)	65
VI b	293—295	0,87	245 (4,0), 338 (19,2)	245 (3,6), 338 (19,2)	324 (17,5)	67
VII b	239—241	0,88	245 (3,2), 340 (20,0)	243 (3,6), 340 (18,4)	328 (19,2)	38
IX b	162—164	0,88	253 (3,8), 333 (20,8)	253 (3,8), 332 (18,2)	259 (24,0), 317 (15,2)	75
XI b	181—183	0,95	257 (6,0), 335 (26,0)	257 (1,5) 332 (25,0)	319 (22,0)	69
XII b	190—192	0,97	256 (4,0), 340 (14,0)	256 (3,8), 337 (14,0)	325 (13,0)	80
XIII b	192—194	0,94	255 (4,1), 335 (24,0)	255 (4,1), 335 (24,0)	317 (21,0)	80
XIV b	188—189	0,92	257 (1,5), 337 (17,0)	257 (1,5), 337 (17,0)	328 (17,0)	77
XVII a	174—176	0,98	235 (6,0), 330 (7,0)	235 (12,0) 332 (10,0)	318 (18,7)	84
XVII b	144—145	0,95	233 (26,0), 340 (17,0)	233 (22,0), 340 (17,0)	323 (17,0)	68
XVII a	165—166	0,52	247 (4,2), 335 (20,5)	247 (4,0), 335 (19,6)	318 (16,8)	53
XVIII b	163—165	0,82	240 (5,6), 342 (29,0)	240 (12,8) 342 (34,0)	325 (25,6)	47

one observes cleavage of the C—N pseudoglycoside bond to give 4-thio-5-fluorouracil. This is due to the fact that 1-(2-tetrahydrofuryl)-5-fluorouracil is readily hydrolyzed in acidic media to the pyrimidine base [9]. When we carried out the reaction in pyridine, we were able to obtain 1-(2-tetrahydrofuryl)-4-thio-5-fluorouracil (Xb) in 7% yield.

The introduction of halogen in the tetrahydrofuran ring increases the resistance of the C—N bond to hydrolysis as compared with the corresponding 1-(2-tetrahydrofuryl)uracils. 1-(3-Halo-2-tetrahydrofuryl)-4-thiouracils (XI-XIVb) were obtained in good yields (60-70%) in dioxane.

The corresponding 4-thiouracil derivatives XVII were obtained in high yields by thionation of the benzoyl derivatives of 1-(α,ω-dihydroxyalkyl)uracils (XVI) with phosphorus pentasulfide in dioxane, and diols XVIII were obtained after removal of the benzoyl protective groups.

Rapid splitting out of the protective groups and side reactions are observed in the thionation of 1-(1,3-dirityloxy-2-propyl)-5-substituted uracils. Similar splitting out of the protective groups was observed by Holy [10] in the thionation of 1-(2,3-isoproylidene-2,3-dihydroxy-1-propyl)uracil. Benzoyl protection of the hydroxy groups during thionation is therefore preferable.



XV-XVIII a R=H, n=0; b R=CH_3, n=1

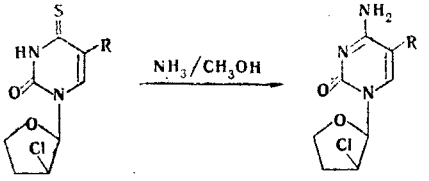
TABLE 2. PMR Spectra of α-(4-Thio-5-substituted-1-uracilyl)-γ-butyrolactones (Ib-IVb), α-(4-Thio-5-substituted-1-uracilyl)-γ-methyl-γ-butyrolactones (Vb-VIIb), and 1-(3-Halo-2-tetrahydrofuryl)-4-thio-5-substituted Uracils (XIb-XIVb)

Compound	Chemical shift, δ, ppm[a]							SSCC, Hz
	2'-H	3'-H	4'-H	5'-H	6-H	5-H (5-CH_3)	5-CH_3	$^3J_{6-H-5-H}$ ($^3J_{6-H-F}$)
Ib	—	5,03 b	2.29—2,96	4.07—4,50	7.47	6,16	—	8.0
IIb	—	5.07 b	2.29—2,65	4.11—4,50	7,60	(1,93)	—	—
IIIb	—	5,06 b	2.30—2,67	4.08—4.52	7.72	—	—	(5,0)
IVb	—	5,10 b	2,33—2,71	4,15—4,54	8,25	—	—	—
Vb	—	4,90—4,53	1,93—2,96	4,36—4,90	7,46; 7,25	6,17	1,33; 1,06	8,0
VIb	—	4,97—5,41	1,86—2,71	4,42—4,97	7,65; 7,85	(1,90)	1,39; 1,08	—
VIIb	—	4,65—5.07	1,98—2,85	4,43—4,65	7,83; 8,10	—	1,33; 1,04	(5,0)
XIb	5,93	4,85 c	1,97—2,85	3,83—4,23	7,51	6,51	—	8,0
XIIb	5,81	4,86 c	2,00—2,78	3,81—4,37	7,98	—	—	(5,0)
XIIIb	5,81	4,94 c	2,02—2,85	3,85—4,34	7,51	6,23	—	8,0
XIVb	5,82	4,91 c	2,00—2,87	3,82—4,37	7,90	—	—	(5,0)

[a] 2'-H—5'-H are the protons of the tetrahydrofuran ring, and 5-H and 6-H are protons in the pyrimidine ring. [b] $^3J_{3-H-4'-H}$ = 9.4 Hz. [c] $^3J_{2'-H-3'-H} = {}^3J_{3'-H-4'-H}$ = 4.6 Hz.

The ammonolysis of XI and XIIb with a methanol solution of ammonia at 120-125°C for 20-25 h leads to 1,5-disubstituted cytosines XIX and XX.

A halogen atom in the 3 position of the tetrahydrofuran ring is inactive and is not replaced by an amino group.



XI, XII b XIX, XX

XI, XIX R=H; XIIb, XX R=F

The UV spectra of 1-substituted 4-thiouracils contain characteristic intense absorption at 340 nm, while the IR spectra contain an intense band of deformation vibrations of the C=S bond at 1100-1140 cm^{-1}.

The PMR spectra of 1-substituted 4-thiouracils (Table 2) demonstrated that the configuration of the starting compounds is retained in the course of the thionation; thus, for example, α-(4-thio-1-uracilyl)-γ-methyl-γ-butyrolactones V-VIIb are mixtures of cis and trans isomers in the same ratio as in starting lactones V-VIIIa [11].

Thus, this study showed that compounds with a strong pseudoglycoside bond can be thionated in dioxane, whereas compounds with an acid-labile C—N bond can be thionated only in pyridine. The thionation of dihydroxyalkyluracils should be carried out with prior benzoyl protection of the hydroxy groups.

EXPERIMENTAL

The purity of the compounds obtained was monitored by chromatography on Whatman-1 paper in an n-butanol—water—acetic acid system (4:5:1) and by elementary analysis. The IR spectra of suspensions of the compounds in mineral oil or hexachlorobutadiene were obtained with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in d_6-DMSO were obtained with a Bruker WH90/DS spectrometer with hexamethyldisiloxane as the internal standard. The melting points were determined with a Boëtius microblock. The starting Ia-IVa, Va-VIIIa, IXa, and XV were obtained by the methods in [11-13, 15, 16].

General Method for the Thionation of Ia-IXa, XIa-XIVa, and XVI. A 4-mmole sample of phosphorus pentasulfide was added to a solution of 2 mmole of the starting compound in 50 ml of dry dioxane, and the mixture was refluxed for 2 h. The hot mixture was filtered, and the precipitate was washed with hot dioxane. The filtrate was concentrated to a volume of 5-10

ml, 10 ml of absolute ethanol was added, and the mixture was cooled. The resulting precipitate was removed by filtration and recrystallized from water, alcohol, or acetone (Table 1).

1-(2-Tetrahydrofuryl)-4-thio-5-fluorouracil (Xb). A 2.0-g (9 mmole) sample of phosphorus pentasulfide and a few drops of water were added to a solution of 0.4 g (2 mmole) of 1-(2-tetrahydrofuryl)-5-fluorouracil in 50 ml of dry pyridine, and the mixture was refluxed for 5 h. It was then allowed to stand overnight, after which it was filtered, and the filtrate was concentrated to a volume of 5-10 ml and treated with 10 ml of absolute ethanol. The resulting precipitate (0.28 g of the starting compound) was separated, and the filtrate was worked up to give 0.1 g of a substance with mp 170-175°C, which was recrystallized from alcohol to give 0.05 g of Xb with mp 173-175°C. Found: C 44.6; H 4.1; N 12.9%. $C_8H_9FN_2O_2S$. Calculated: C 44.4; H 4.2; N 13.0%.

1-(1,3-Dibenzoyl-1,3-dihydroxy-2-propyl)uracil and 1-(1,4-Dibenzoyl-1,4-dihydroxy-2-butyl)-5-methyluracil (XVIa, b). These compounds were obtained by acylation of the corresponding diols with benzoyl chloride [14].

1-(1,3-Dihydroxy-2-propyl)-4-thiouracil (XVIIIa). A 3.2-g (7.6 mmole) sample of XVIIa was suspended in 50 ml of absolute methanol saturated at 0°C with dry ammonia, and the mixture was maintained at 4°C for 24 h. The methanol was evaporated, 52 ml of water was added to the residue, and the mixture was extracted with chloroform (two 25-ml portions) to remove the benzamide. The aqueous layer was evaporated, 15 ml of a mixture of alcohol with ethyl acetate (1:1) was added to the oily residue, and the precipitate was removed by filtration and recrystallized from absolute ethanol to give 0.97 g of XVIIIa (65% of the theoretical amount) with mp 165-166°C. PMR spectrum, δ: 3.65 (m, 2H, CH_2), 4.40 (m, 1H, CH), 6.16 (d, 1H, C_5H, $^3J_{5-H,6-H}$ = 6.40 Hz), 7.36 (d, 1H, C_6H, $^3J_{6-H,5-H}$ = 6.40 Hz), and 12.30 ppm (s, 1H, N_3H). Found: C 42.4; H 5.2; N 13.7%. $C_7H_{10}N_2O_3S$. Calculated: C 41.6; H 5.0; N 13.8%.

1-(1,4-Dihydroxy-2-butyl)-4-thio-5-methyluracil (XVIIIb). A 0.28-g (0.7 mmole) sample of XVIIb was suspended in 25 ml of absolute methanol saturated at 0°C with dry ammonia, and the mixture was worked up as in the method described above to give 0.1 g (66% of the theoretical value) of XVIIIb with mp 163-165°C. PMR spectrum, δ: 1.85 (s, 3H, CH_3), 3.45 (m, 2H, CH_2), 4.07-4.85 (m, 1H, CH), 7.38 (s, 1H, C_6H), and 12.2 ppm (s, 1H, N_3H). Found: C 47.2; H 6.2; N 12.3%. $C_9H_{14}N_2O_3S$. Calculated: C 47.0; H 6.1; N 12.2%.

1-(3-Chloro-2-tetrahydrofuryl)cytosine (XIX). A 1.0-g (4.3 mmole) sample of XIb was suspended in 70 ml of absolute methanol saturated at 0°C with dry ammonia, and the mixture was heated in a hermetic steel vessel at 125-130°C for 26 h. The solvent was evaporated with a rotary evaporator, and the precipitate was removed by filtration and recrystallized from ethanol to give 0.32 g (34% of the theoretical value) of XIX with mp 213-215°C. Found: C 44.0; H 4.5; N 19.9%. $C_8H_{10}ClN_3O_2$. Calculated: C 44.6; H 4.7; N 19.5%.

1-(3-Chloro-2-tetrahydrofuryl)-5-fluorouracil (XX). A 1.14-g (4.5 mmole) sample of XIIb was suspended in 70 ml of absolute methanol saturated at 0°C with dry ammonia, and the mixture was heated in a hermetic steel vessel at 110-120°C for 18 h. The solvent was evaporated, 5 ml of absolute ethanol was added to the residue, and the mixture was filtered. The product was recrystallized from absolute ethanol to give 0.05 g (4.7%) of XX with mp 215-217°C. Found: C 40.0; H 3.5; N 17.5%. $C_8H_9ClFN_3O_2$. Calculated: C 40.8; H 3.9; N 17.9%.

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PROTROPIC TAUTOMERISM AND CONFORMATIONAL ISOMERISM OF 4-(N-ARYLAMINO)-2-(1H-PYRAZOL-1-YL)PYRIMIDINES

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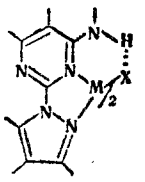
New 4-(N-arylamino)-2-(1H-pyrazol-1-yl)pyrimidine derivatives were synthesized, and the UV, IR, and PMR spectra of solutions of them in $CHCl_3$, CCl_4, and d_6-DMSO were studied. The questions of intermolecular association and conformational isomerism are discussed.

4-(N-Arylamino)-2-(1H-pyrazol-1-yl)pyrimidines are of interest as bidentate ligands that are potentially capable of reacting with transition metal salts to give complexes that are stabilized by metal chelates that include an intramolecular hydrogen bond (I) [1].



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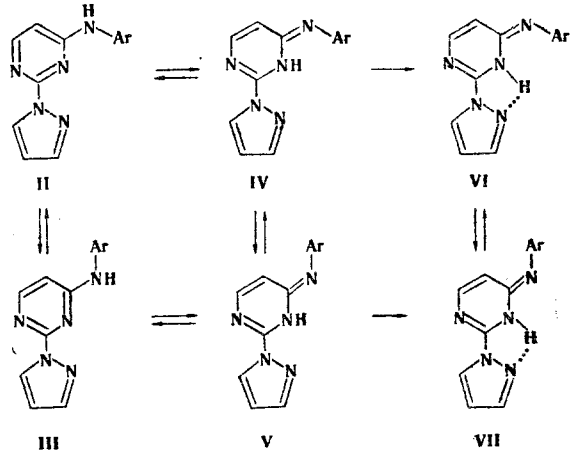
However, the structure of this series of compounds and their behavior in solutions have not been discussed. In addition, conformational isomerism and prototropic tautomerism (II-



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