REACTION OF 2-THIOURACIL WITH CARBOXYLIC ACID 1,2,2,2-TETRACHLOROETHYLAMIDES

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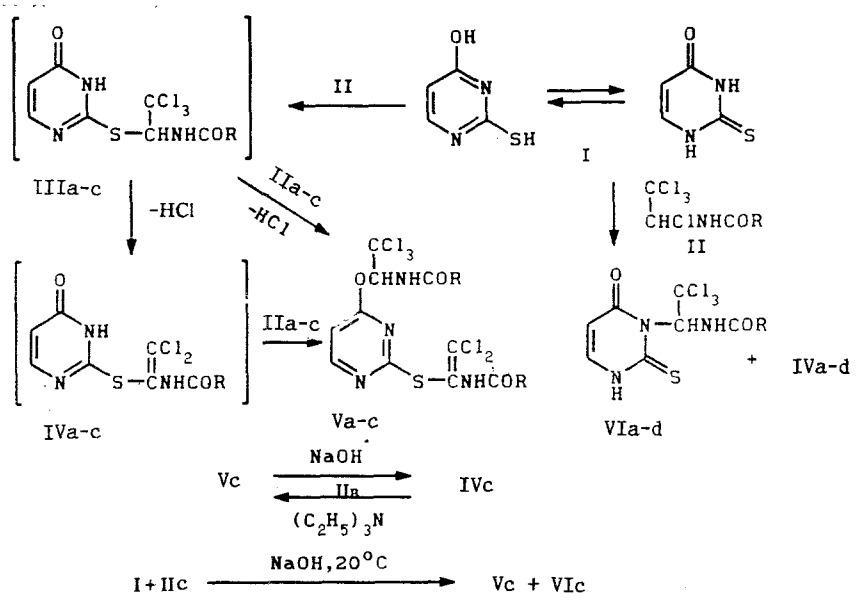
Amidoalkylation of 2-thiouracil with 1,2,2,2-tetrachloroethylamides in the presence of triethylamine or sodium hydroxide gives products of S-, O-, and N-substitution, depending on the reaction conditions.

Alkylation of 2-thiouracil is known to yield mainly S-alkyl derivatives [1]. Amidoalkylation of thiouracil has not been studied. Since thiouracil has several nucleophilic centers, its amidoalkylation may be expected to proceed in several ways.

The amidoalkylating agents used were carboxylic acid (IIa-c) and methylcarboxylic acid (IId) 1,2,2,2-tetrachloroethylamides. This choice of reagents was based on their availability and high reactivity. Reaction of 2-thiouracil with reagents IIa-d in the presence of triethylamine or sodium hydroxide involves various nucleophilic centers and affords compounds V and VI (see Table 1).



II—VI a R=C_6H_5, b R=C_6H_4Cl-4, c R=$C(CH_3)_3$, d R=OCH_3

Thus, in the presence of triethylamine in acetonitrile at 0° or 20°C, as well as in the presence of sodium hydroxide in water—acetone solution at 20°C, products of substitution on the sulfur and oxygen atoms, compounds V, are formed. The reaction probably proceeds through intermediates III, which may further react by two pathways: 1) first amidoalkylation at the oxygen atom with subsequent dehydrochlorination; 2) compounds III are dehydrochlorinated and then substituted vinylthiouracils IV are amidoalkylated at the oxygen atom. The transformation of Vc upon alkaline hydrolysis into IVc and the reverse transformation IVc—Vc on amidoalkylation support the second pathway.

Amidoalkylation of 2-thiouracil in the presence of sodium hydroxide in water—acetone solution at 0°C gave a mixture of products from which were isolated products of substitution on the nitrogen atom, compounds VI. This reaction probably also forms substituted vinylthiouracils IV. Thus, on chromatographic separation of compounds VIc from the reaction mixture we were able to detect the starting thiouracil and product IVc.

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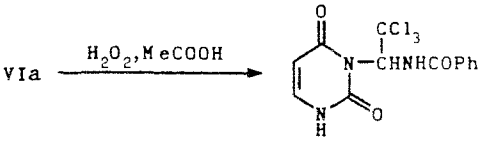
TABLE 1. Characteristics of Synthesized Compounds IVc, Va-c, VIa-d, VII, IX, and X

Compound	Elemental formula	T_{mp}, °C	Yield, %	Compound	Elemental formula	T_{mp}, °C	Yield, %
IVc	$C_{11}H_{13}Cl_2N_3O_3S$	156...158	52	VIc	$C_{11}H_{14}Cl_3N_3O_2S$	201...203	74
Va	$C_{22}H_{15}Cl_5N_4O_3S$	169...170	35	VId	$C_8H_8Cl_3N_3O_3S$	176...177	44
Vb	$C_{22}H_{13}Cl_7N_4O_3S$	168...170	26	VII	$C_{13}H_{10}Cl_3N_3O_3$	240...241	73,5
Vc	$C_{18}H_{23}Cl_5N_4O_3S$	167...168	60	IX	$C_{14}H_{12}Cl_3N_3O_2S$	146...147,5	36
VIa	$C_{13}H_{10}Cl_3N_3O_2S$	178...180	53	X	$C_{15}H_{12}Cl_3NO$	175...176	14,5
VIb	$C_{13}H_9Cl_4N_3O_2S$	190...192	44				

N-Substituted thiouracil VIc, along with compounds Vc, is also formed on amidoalkylation of thiouracil in the presence of sodium hydroxide at 20°C. The presence in compounds VI of a free thio group at the 2-position of the ring was confirmed by iodometric titration of VIa. The amidoalkyl group in N-substituted thiouracils VI is at the $N_{(3)}$ of the ring, as confirmed by UV spectra and by a chemical method. The UV spectra of compounds VI show a bathochromic shift of the long-wave absorption maximum upon addition of alkali, characteristic for $N_{(3)}$ substitution [2]. Oxidation of N-substituted thiouracil VIa by hydrogen peroxide in acetic acid at 0°C gave the $N_{(3)}$-amidoalkyl derivative of uracil VII, obtained by us previously using another method [3].



VII

We have established that the products of thiouracil amidoalkylation at the sulfur, oxygen, and nitrogen atoms respond differently to hydrolysis. The S-amidoalkylation derivatives show the greatest stability to hydrolysis while the O- and N-amidoalkyl derivatives of thiouracil are not stable in alkaline media. We have remarked above on the conversion of Vc to IVc by alkaline hydrolysis, while the products of $N_{(3)}$-substitution of VI hydrolyze to the starting thiouracil.

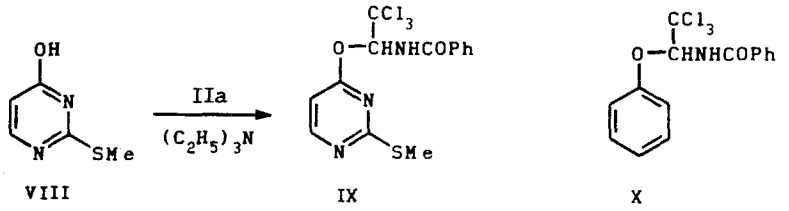
The structures of the synthesized compounds IVc, V, and VI were confirmed by ^{35}Cl NQR, PMR, ^{13}C NMR, and IR spectroscopy.

The ^{35}Cl NQR spectra of compounds Va show five signals of equal intensity at 37.581, 37.898, 38.798, 39.209, and 39.254 MHz. Investigation of the frequencies at various temperatures in the 77-294 K range showed that the three highest-frequency signals disappeared at 243 K. This indicates a reorientation about the axis of third-order symmetry [4] and permits assigning this group of signals to the trichloromethyl group. Consideration of the structure of compound Va must take into account the site of amidoalkyl addition since there are four possible addition centers: the O, S, $N_{(1)}$, and $N_{(3)}$ atoms. To this end we performed a correlation analysis of trichloromethyl-substituted compounds $CCl_3CR_1R_2R_3$, which produced the following dependence of the ^{35}Cl NQR frequency of CCl_3 on the sum of the modified Swain—Lupton F [5, 6] constants of substituents R_1, R_2, and R_3:

$$(CCl_3CR_1R_2R_3) = 38{,}06 + 2{,}26 \sum_{i}^{3} F(Ri),\ R\ 0{,}964;\ N\ 7$$

Substitution of the mean frequency of the CCl_3 group of compounds Va (39.09 MHz) in this equation gives an F value for the addition fragment of 0.37, which is very close to the F value for a phenoxy group (0.34) and permits assigning an O-amidoalkyl structure to Va. The remaining two signals at 37.581 and 37.898 MHz must be assigned, on account of their high frequencies [7], to the two geminal chlorine atoms of the vinyl group on the sulfur atom.

For comparison and exact assignment of the ^{13}C NMR signals we synthesized model compounds in which the amidoalkyl residue is on the oxygen atom. Reaction of 2-methylthiouracil with IIa in the presence of triethylamine gave O-amidoalkyl derivative IX.



Reaction of sodium phenolate and IIa in the presence of sodium hydroxide gave O-amidoalkyl derivative X. As model compounds both the starting 2-thiouracil (I) and 2-methylthiouracil (VIII) were used.

Analysis of the PMR spectra (see Table 2) of the synthesized compounds shows that amidoalkylation of 2-thiouracil on the nitrogen atom leads to an increased $^3J_{H5H6}$ (for compounds VIa, c, $^3J_{H5H6}$ = 8.2 Hz; for 2 thiouracil, $^3J_{H5H6}$ = 7.5 Hz), while amidoalkylation on the oxygen atom leads to a reduced $^3J_{H5H6}$ (for compounds Vc and IX, $^3J_{H5H6}$ = 5.7 Hz).

We confirmed the structures of compounds IVc, V, and VI by the ^{13}C NMR data (see Table 3). The main criterion for assigning a thionic structure of the I type or a thiol structure of the VIII type was the chemical shift of the $C_{(2)}$ atom (175-178 ppm for —C=S and 163-168 ppm for =C—SR). Besides this, the thionic structure of compounds I and VI is characterized by higher-field (by about 10 ppm) chemical shifts of the C_6 on the heteroxyclic ring and the CCl_3—C(—N)H—N substituent. The ^{13}C NMR spectra of model compound X showed a δ_C for the CCl_3—C(—O)H—NH of 85.4 ppm, corresponding to the δ in compounds Vc and IX of 81.1 and 81.4 ppm and confirming their O-amidoalkylation. The value of δ_C for the CCl_3—C(—H)H—N group in compounds VIa, c, 70.7 and 71.4 ppm, differs substantially from the value for model compound X and confirms their N-amidoalkylation.

The presence of the substituted vinyl group on the sulfur atom confirms the comparison of the ^{13}C NMR of IVc and Vc, which do not contain phenyl centers but display two pairs of signals at (126.78, 128.28) and (125.96, 127.76) ppm, respectively, which we assigned unambiguously to the C atoms of the C=C bond. The IR spectra furnished supplementary information about the structure of IVc. Amidoalkylation on the sulfur atom in IVc leads to a change in the frequency of the valence vibrations of the pyrimidine ring and also to the disappearance of the bands at 1216 and 454 cm^{-1}, assigned respectively to $\nu_{C=S}$ and $\delta_{C=S}$ in thiouracil [8].

Thus by ^{35}Cl NQR, PMR, ^{13}C NMR, UV, and IR spectroscopy the structures of the synthesized amidoalkyl derivatives IVc, V, and VI have been confirmed.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Varian VXP-300 spectrometer under standard conditions; temperature 295 K, solvent DMSO-d_6, internal standard TMS. The assignment of signals was checked by the APT method [9]. UV spectra were taken on a Specord spectrometer. IR spectra were taken on a Specord M 80 spectrophotometer with KBr disks. ^{35}Cl NQR spectra were recorded on a ISShI-13M impulse spectrometer at 77 K. TLC was done on Silufol UV-254 plates with benzene—methanol, 5:1, with UV visualization.

TABLE 2. PMR Spectra of Compounds I, IVc, Vc, VIa, c, VIII, and IX

Compound	Chemical shift, δ, ppm						SSCC, J, Hz	
	H_5, d	H_6, d	NH, br.s	NHCH, d	CHNH, d	other signals	$^3J_{H_5H_6}$	$^3J_{CHNH}$
I	5,83	7,42	12,27 12,43	—	—	—	7,5	—
IVc	6,29	8,00	—*	9,56	—	1,09 (9H, s, $C(CH_3)$)	6,3	—
Vc	6,93	8,56	—	8,99 9,06	7,50	1,16, 1,18 (9H, s $C(CH_3)_3$)	5,7	9,0
VIa	6,21	8,45	13,01	9,67	8,89	7,54...7,89 (5H, m., C_6H_5)	8,2	10,0
VIc	6,17	8,43	12,93	8,69	8,44	1,17 (9H, s, $C(CH_3)_3$)	8,2	10,2
VIII	6,06	7,81	12,70	—	—	2,45 (3H, s, S-CH_3)	6,6	—
IX	6,83	8,48	—	9,70	7,62	2,45 (3H, s, S-CH_3)	5,7	8,5

*No signal was detected.

TABLE 3. ^{13}C NMR Spectra of Compounds I, IVc, Vc, VIa, c, VIII, and IX

Compound	Chemical shift, δ, ppm							
	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	CHN	CCl_3	CO	other signals
I	176,01	161,04	105,28	142,09	—	—	—	—
IVc	164,80	161,60	109,23	155,40	—	—	176,78	26,78 ($C(CH_3)_3$); 38,65 ($\underline{C}(CH_3)_3$); 125,96 ($\underline{C}Cl_2$=C); 127,76 (N-$\underline{C}$(-N)=C)
Vc	167,97	165,50	104,75	160,31	81,36	98,42	176,47 179,05	26,69; 30,60 ($C(\underline{C}H_3)_3$); 38,52; 38,75 ($\underline{C}(CH_3)_3$); 126,78 ($\underline{C}Cl_2$=C); 128,28 (N-$\underline{C}$(-N)=CCl_2)
VIa	178,08	158,84	106,76	141,21	71,09	98,80	167,13	128,07; 128,42; 132,42; 132,54 ($\underline{C}_6H_5$)
VIc	177,98	158,78	106,61	141,24	70,71	98,91	177,29	26,57 ($C(\underline{C}H_3)_3$); 38,49 ($\underline{C}(CH_3)_3$)
VIII	163,20	162,70	106,67	151,80	—	—	—	12,76 (S-$\underline{C}H_3$)
IX	163,40	162,80	109,69	153,50	81,27	102,56	166,77	12,82 (S-$\underline{C}H_3$); 127,82; 128,18; 131,78; 133,36 ($\underline{C}_6H_5$)

Data from elemental analysis of C, H, N, S, and Cl corresponded to the calculated values.

2-(1′-Acylamino-2′,2′-dichlorovinyl)thio-4-(1′-acylamino-2′,2′,2′-trichloroethoxy)pyrimidines (Va-c). To a suspension of 10 mmoles of I and 20 mmoles triethylamine in 25 ml absolute acetonitrile at room temperature was added slowly, with stirring, a solution of 20 mmoles of the corresponding reagent IIa-c in 35 ml absolute acetonitrile. The reaction mixture was stirred at room temperature for 15 h. The precipitate was filtered off, washed with water (3 × 20 ml), and air-dried. The product compounds were crystallized from tetrachloromethane.

$N_{(3)}$-(1′-Acylamino-2′,2′,2′-trichloroethyl)-2-thiouracils (VIa-d). To a solution of 10 mmoles sodium hydroxide in 20 ml water at room temperature was added, with stirring, 10 mmoles of thiouracil I. The resulting solution of thiouracil I sodium salt was cooled in an ice bath and 10 mmoles of the corresponding reagent IIa-d in 20 ml acetone was added slowly with stirring. The reaction mixture was stirred for 6 h at 0°C and left overnight in the refrigerator. The precipitate was filtered off, washed with water (3 × 20 ml), and air-dried. Compounds VIa, b, d were crystallized from methanol and VIc from chloroform.

Reaction of 2-Thiouracil (I) with Pivalic Acid Tetrachloroethylamide (IIc) in the Presence of Sodium Hydroxide at 20°C. To a solution of 0.8 g (20 mmoles) of sodium hydroxide in 20 ml water was added at room temperature, with stirring, 1.28 g (10 mmoles) of uracil I. To the resulting solution of the sodium salt of compound I was slowly added a solution of 5.3 g (20 mmoles) of pivalic acid tetrachloroethylamide (IIc) in 20 ml acetone. The reaction mixture was stirred for 16 h at room temperature. The precipitate was filtered off, washed with water (3 × 20 ml), and air-dried. The residue was refluxed with tetrachloromethane and filtered. The residue insoluble in tetrachloromethane was the $N_{(3)}$-aminoalkyl derivative of VIc. Yield 0.9 g (25%). Compound Vc was separated from the tetrachloromethane solution on cooling, yield 0.65 g (12%).

2-(1′-Pivaloylamino-2′,2′-dichlorovinyl)thiouracil (IVc). To 1.1 g (2 mmoles) of Vc was added a solution of 0.08 g (2 mmoles) of sodium hydroxide. The suspension was stirred 0.5 h at room temperature. The precipitate was filtered off, neutralized with 2N HCl, and left to stand 12 h at room temperature. The precipitate was filtered off, washed with water (2 × 20 ml), and air-dried. Compound IVc was crystallized from ethyl acetate.

2-(1′-Pivaloylamino-2′,2′-dichlorovinyl)thio-4-(1′-pivaloylamino-2′,2′,2′-trichloroethoxy)pyrimidine (Vc) was obtained from IV and reagent IIc in the presence of triethylamine by the method described above for Va-c. Yield 55%.

$N_{(3)}$-(1′-Benzoylamino-2′,2′,2′-trichloroethyl)uracil (VII). To a mixture of 3 mmoles of VIa, 42 mmoles acetic anhydride, and 170 mmoles acetic acid was added at 0°C, with stirring, 10 ml of 30% hydrogen peroxide. The reaction mixture was stirred 5 h at this temperature and then 15 h at room temperature. The resulting solution was evaporated to dryness under vacuum. To the oily residue was added 5 ml methanol and it was cooled in an ice bath. The precipitate was filtered off and air-dried. Compound VII was crystallized from methanol.

2-Methylthio-4-(1′-benzoylamino-2′,2′,2′-trichloroethoxy)pyrimidine (IX) was obtained from 2-methylthiouracil and reagent IIa in the presence of triethylamine by the method described above for Va-c. Compound IX was crystallized from petroleum ether.

N-(2,2,2-Trichloro-1-phenoxyethyl)benzamide (X). To a suspension of 2.3 g (20 mmoles) of sodium phenolate in 25 ml absolute acetonitrile was added at room temperature, with stirring, a solution of 5.7 g (20 mmoles) of IIa. The reaction mixture was stirred for 3 h. The precipitate was filtered off, washed with water (2 × 20 ml), and air-dried. Compound X was crystallized from tetrachloromethane.

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