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Condensation of Thiourea with Uracyl Derivatives Containing Ketone and Ketoester Fragments, Alkylation and Macrocyclization of the Condensation Products

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Abstract—By condensation of thiourea with 6-methyluracyl derivatives containing ketone and ketoester fragmenst in the alkyl chains attached to the nitrogen atoms of the pyrimidine ring the products containing 6-methyl- or 3,6-dimethyluracyl fragment and one or two 6-methyl-4-oxo-2-thio-1,2,3,4-tetrahydropyrimidin-5-yl fragments were synthesized. These compounds can be alkylated with alkyl bromides.

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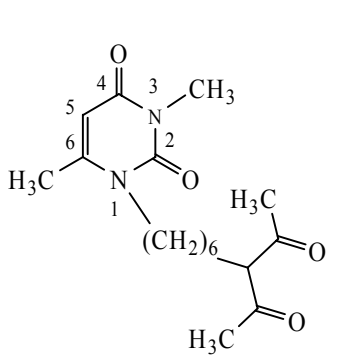
Nucleotide bases and their derivatives bound together by the hydrocarbon bridge are interesting as non-glycoside synthetic analogs of natural oligonucleotides. These compounds are used as ligands forming complexes with the complementary nucleotide bases [1, 2], and the models for investigation the non-covalent interactions between the nucleotide bases and the UV-initiated reactions between the nucleotide bases [2–6].

Non-glycoside analogs of dinucleotides with two uracyl fragments, α,ω-bis(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)alkanes [2–4, 7, 8] containing N^3 atoms substituted with CH_3-group as well as the unsubstituted N^3H groups were synthesized and described. The analogs of trinucleotides, 1,3-bis[ω-(uracyl-1-yl)alkyl]thymines with the terminal uracyl fragments containing N^3H as well as N^3–CH_3 groups are also known. They were synthesized by the reactions of sodium or potassium salts of uracyl derivatives or 2,4-bis(trimethylsiloxy)uracyls with 1- or 1,3-bis(ω-bromoalkyl)uracyls [9, 10].

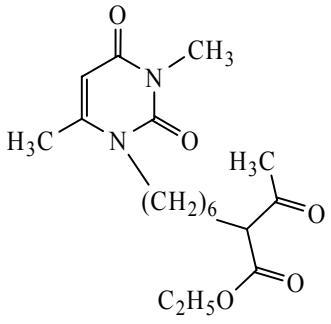
Synthetic analogs of oligonucleotides with uracyl fragments where both N^1 and N^3 atoms of pyrimidine rings carry the imide functions are practically unknown. Only one work describing the synthesis of 1-[ω-(uracyl-5-yl)alkyl]thimines in 28-73% yield by the reaction of 5-(ω-bromoalkyl)uracyls with thimine in the presence of K_2CO_3 was found [4]. 5-(ω-Bromoalkyl)uracyls were synthesized by the sufficiently complex sequence of reactions including the formylation of the corresponding lactone, its metallation with sodium, reaction of sodium salt of the lactone derivative with thiourea, and substitution of S-atom and OH-group in the obtained 5-(ω-hydroxyalkyl)-2-thiouracyl with the oxygen and bromine respectively.

We have prepared 6-methyluracyl derivatives **I–III** with the alkyl chains on N^1 and N^3 atoms containing ketone and ketoester fragments [11]. In this work the possibility is studied of using these compounds as starting substances for preparing the non-glycoside analogs of di- and trinucleotides where the uracyl derivatives are bound with one another with the polymethylene chains through the N^1, N^3, and C^5 atoms of pyrimidine rings. As a result the compounds can be prepared with one or two uracyl fragments containing the unsubstituted N^1H and N^3H groups. These substances are interesting as complexones which are capable of formation of various supramolecular structures with the complementary nucleotide bases by the multiple hydrogen bonds [12, 13].

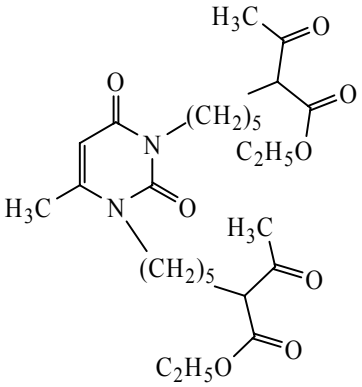
The reaction of β-diketones and β-ketoesters with ureas, guanidines, and amidines is the classical method for preparing the pyrimidine derivatives [14]. Compounds **I–III** we regarded as precursors whose condensation with ureas would lead to the analogs of dinucleotides, α-(3,6-dimethyluracyl-1-yl)-ω-(pyrimidin-



I



II



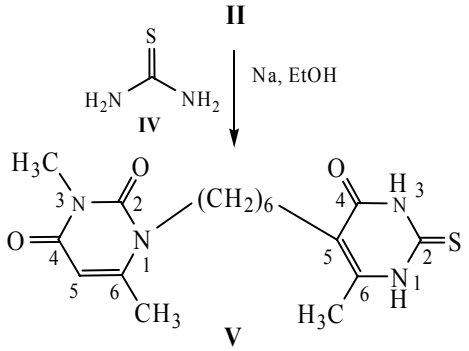
III

5-yl)alkanes, and trinucleotides, 1,3-bis[ω-(uracyl-5-yl)alkyl]-6-methyluracyls. In this work the synthesis and some chemical properties of such compounds are described.

The reaction of diketone **I** with thiourea **IV** in ethanol in the presence of HCl [14] did not lead to the expected condensation product, 1-(3,6-dimethyl-2,4-dioxo-1,2,3,5-tetrahydropyrimidin-1-yl)-6-(4,6-dimethyl-2-thio-1,2-dihydropyrimidin-5-yl)hexane. Its formation was not registered even in the trace amounts in the mass spectra of the reaction mixture. Note that the information on synthesis of 5-substituted pyrimidines by the reaction of 3-substituted acetylacetone with ureas is absent. Only scarce reports concerning the synthesis of 5-substituted pyrimidines by this approach [15,16] were found. Evidently the presence of alkyl substituent on C^3 carbon atom of acetylacetone prevents the condensation of diketone with ureas.

Unlike compound **I** ketoesters **II**, **III** react with compound **IV** to form the expected condensation products. Hence, the condensation of ketoester **II** with compound **IV** in anhydrous ethanol in the presence of sodium ethylate leads to the formation of compound **V** in 42% yield (Scheme 1).

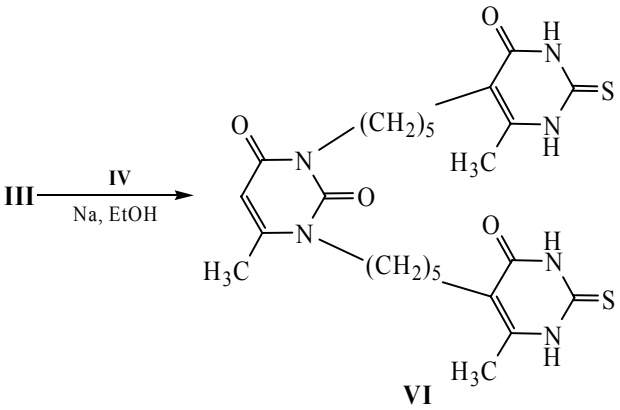
Scheme 1.



V

Under the analogous conditions bis-ketoester **III** gives the analog of trinucleotide **VI** in small yield (9%) (Scheme 2) which is evidently connected with the side reactions.

Scheme 2.



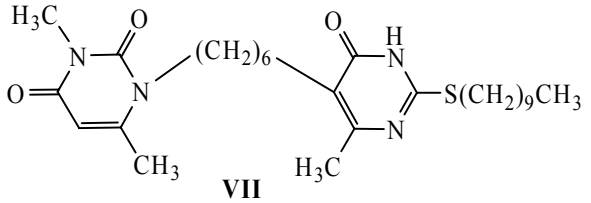
VI

Using anhydrous ethanol as a solvent is fundamentally important. Performing the reactions of compounds **II**, **III** with substance **IV** in non-anhydrous ethanol gives the products of ketonic cleavage, 1-(8-oxononyl)-3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine and 1,3-bis(7-oxooctyl)-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine respectively [11] in almost quantitative yields.

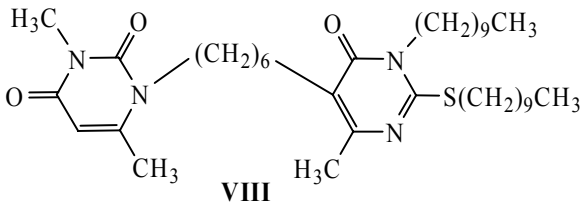
The presence of 1,2,3,4-tetrahydropyrimidine cycles in compounds **V**, **VI** permits regarding them as promising participants of the proton-donor and proton-acceptor pairs in the formation of hydrogen bonds. Compounds **V**, **VI** proper evidently form intermolecular hydrogen bonds in the individual state and solutions. It is confirmed by the location of ν_{NH} absorption bands in the range 3100–3200 cm^{-1} of the IR spectrum of compound **V** in KBr, and also the downfield position of signals of the NH-group protons at 12.0 ppm in the ^1H NMR spectra of the compounds

V, **VI** in the 2:1 $CDCl_3$–DMSO-d_6 mixture, at *c* 5 mM, that does not change at further dilution [2].

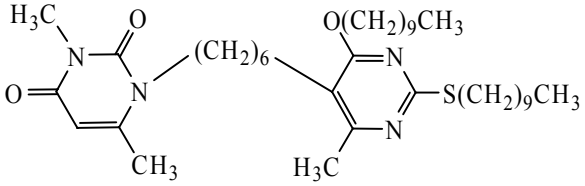
Compound **V** is alkylated cleanly at the sulfur atom with alkyl bromides, for example, with decyl bromide at room temperature in DMF in the presence of NaH to form the substance **VII** in 71% yield. Performing the reaction at 40°C gives evidently the mixture of products of S- N,S- and O,S-alkylation **VIII**–**IX**. It is confirmed by the presence of the peak $[M]^+$ 645 besides the peak of the molecular ion $[M]^+$ 504 in the mass spectrum of the reaction mixture. ^{1}H NMR spectrum of the reaction mixture in $CDCl_3$ besides the triplet at 3.14 ppm (SCH_2) contained the triplets at 3.41 ppm (N^3CH_2) and at 3.65 ppm (OCH_2) Compounds **VIII**, **IX** were not isolated in the pure state.



VII



VIII



IX

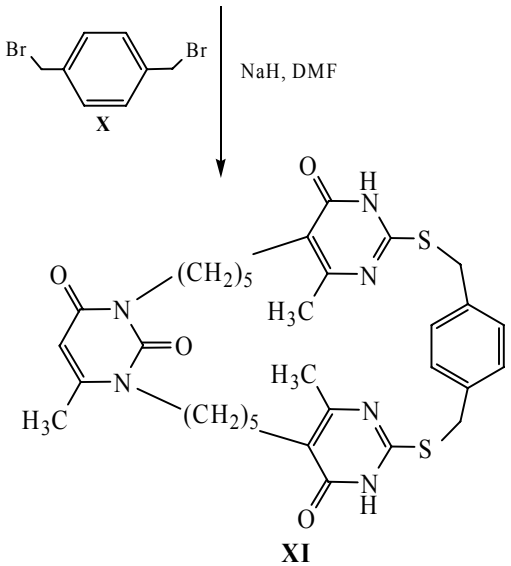
The reaction of compound **VI** with *para*-dibromoxylylene **X** was carried out analogously to give pyrimidinophane **XI** containing three 6-methyluracyl fragments in 12% yield (Scheme 3). Its formation was confirmed by mass spectrometry and ^{1}H NMR data. Note that the signal of NH-protons of the macroring **IX** (9.95 ppm) in ^{1}H NMR spectrum in $CDCl_3$ is significantly shifted upfield as compared to the compound **VI**. It is caused evidently by the rupture of the net of intermolecular hydrogen bonds formed by compound **VI** resulting from macrocyclization.

Hence, the condensation of thiourea with the derivatives of 6-methyluracyl carrying the ketone and ketoester fragments in the alkyl chains on nitrogen atoms of pyrimidine ring the non-glycoside analogs of di- and trinucleotides containing 6-methyl- or 3,6-dimethyluracyl fragment and one or two 6-methyl-4-oxo-2-thio-1,2,3,4-tetrahydropyrimidin-5-yl fragments were synthesized. The compounds obtained were alkylated at the sulfur atom with decyl bromide and *para*-dibromoxylylene. In the last case the pyrimidinophane consisting of three 6-methyluracyl fragments bound with one another through the N, C^5 atoms of pyrimidine rings and the sulfur atoms at the pyrimidine rings with the hydrocarbon bridges was isolated.

EXPERIMENTAL

^{1}H NMR spectra were taken on a Bruker Avance-400 spectrometer against internal TMS. MALDI-TOF mass spectra were obtained on a Bruker ULTRAFLEX mass spectrometer in *p*-nitroaniline matrix. IR

Scheme 3.



XI

spectrum of compound **V** was registered on a Bruker Vector 22 Fourier spectrometer under standard conditions in the range 4000-400 cm^{-1} at the resolution 1 cm^{-1} in KBr pellets.

The uncorrected melting points were measured on the Boetius apparatus. TLC was carried out on the Silufol-254 plates, development in the UV light. Column chromatography was carried out on SiO_2 (0.06–0.2 mm). All the solvents and reagents were dried before use.

1-(3,6-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-6-(6-methyl-4-oxo-2-thio-1,2,3,4-tetrahydropyrimidin-5-yl)hexane (V). To a solution of 0.07 g of sodium in 5 ml of anhydrous ethanol 0.18 g of thiourea **IV** and a solution of 0.56 g of compound **II** in 45 ml of anhydrous ethanol were added. The reaction mixture was refluxed with stirring for 9 h. After cooling the solvent was evaporated, 50 ml of water was added, the mixture obtained was acidified with hydrochloric acid to pH 6, and the precipitate formed was filtered off and dried in a vacuum to give 0.24 g of compound **V**, yield 42%, mp 270°C. IR spectrum, ν, cm^{-1}: 3209, 3136 [ν(NH)], 3060 [ν(C^5–H)], 2929, 2857, 1431, 1366 [ν, δ(CH_3, CH_2)], 1692, 1642 [ν(C^4=O), ν(C^2=O)], 1611, 1563, 1472 (uracyl ring), 1227, 1216, 1135 [ν(NCN), C–C, C–N, C^2=S]. ^{1}H NMR spectrum ($CDCl_3$ + DMSO-d_6 2:1, *c* 5 mM), δ, ppm (*J*, Hz): 1.30 m (4H, $2CH_2$), 1.54 m (2H, CH_2), 2.10 s (3H, C^6–CH_3), 2.24 br.s (5H, C^5–CH_2, C^6–CH_3), 3.31 s (3H, NCH_3), 3.74 (2H, N–CH_2, $^1J_{HH}$ 7.3), 5.61 s (1H, C^5H), 12.02 and 12.24 both s (1H, 2NH). MALDI–TOF mass spectrum: calculated for $C_{16}H_{24}N_4O_3S$ $[M]^+$ 364.2. Found 364.2. Found, %: C 56.05; H 6.58; N 15.31; S 8.67. $C_{17}H_{24}N_4O_3S$. Calculated, %: C 56.02, H 6.64; N 15.37; S 8.80.

1,3-Bis[5-(6-methyl-4-oxo-2-thio-1,2,3,4-tetrahydropyrimidin-5-yl)pentyl]-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine (VI). To a solution of 1.64 g of compound **III** in 50 ml of anhydrous ethanol 0.46 g of thiourea **IV** and a solution of 0.3 g of sodium in 10 ml of ethanol were added. The mixture obtained was refluxed for 12 h and then cooled. After that the solvent was evaporated, 50 ml of water was added, and the mixture obtained was acidified with hydrochloric acid to pH 6. The precipitate formed was filtered off, dissolved in 15 ml of methanol and subjected to column chromatography on SiO_2, elution with 40:1, 20:1, and 10:1 $CHCl_3$–CH_3OH mixtures. From the fractions eluted with 10:1 $CHCl_3$–CH_3OH mixture 0.15 g of compound **IX** were obtained. Yield 9%, mp 210°C. ^{1}H NMR spectrum ($CDCl_3$ + DMSO-d_6 2:1, *c* 5 mM), δ, ppm: 1.30–1.44 m (8H, $4CH_2$), 1.56–1.64 m (4H, $2CH_2$), 2.14, 2.15, 2.26 three sihglets (3×3H, $3C^6$–CH_3), 2.28–2.33 m (4H, $2C^5$–CH_2), 3.76–3.84 m (4H, $2NCH_2$), 5.52 s (1H, C^5–H), 11.91, 11.94, 11.99, 12.03 four s (4×1H, 4NH). MALDI-TOF mass spectrum: calculated for $C_{25}H_{34}N_6O_4S_2$ $[M]^+$, $[M + Na]^+$, and $[M + K]^+$ 546.2, 569.2, and 585.2 respectively. Found 546.3, 569.2, and 585.1. Found, %: C 54.99, H 6.19, N 15.31, S 11.72. $C_{25}H34N_6O_4S_2$. Calculated, %: C 54.92; H 6.27; N 15.37; S 11.73.

1-(3,6-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1-yl)-6-(6-methyl-4-oxo-2-thiadecyl-1,2,3,4-tetrahydropyrimidin-5-yl)hexane (VII). To a solution of 0.2 g of compound **V** in 30 ml of DMF 0.012 g of NaH treated preliminary with hexane was added. The mixture obtained was stirred at room temperature (18–22°C) for 1 h, and the solution of 0.11 g of decyl bromide in 10 ml of DMF was added. Resulting mixture was stirred for 5 h at room temperature, the solvent was removed in a vacuum, the residue was treated with 30 ml of $CHCl_3$ and filtered. The filtrate was evaporated, the residue was treated with 50 ml of ether and decanted. After the second decantation of ether and drying of the residue 0.18 g (71%) of compound **VII** was obtained. ^{1}H NMR spectrum ($CDCl_3$, *c* 5mM), δ, ppm (*J*, Hz): 0.88 t (3H, CH_3, $^3J_{HH}$ 7.0), 1.26–1.64 m (22H, 11 CH_2), 2.15, 2.25 both s (6H, $2C^6$–CH_3), 2.33 t (2H, C^5–CH_3, $^3J_{HH}$ 7.7), 3.14 t (2H, SCH_2, $^3J_{HH}$ 7.4), 3.30 s (3H, NCH_3), 3.79 (2H, NCH_2, $^3J_{HH}$ 7.7), 5.58 s (1H, C^5H), 11.83 (1H, NH). MALDI–TOF mass spectrum: calculated for $C_{27}H_{44}N_4O_3S$ $[M]^+$ 504.3, found 504.4. Found, %: C 64.16, H 8.73, N 11.11, S 6.29. $C_{27}H_{44}N_4O_3S$. Calculated, %: C 64.25, H 8.79, N 11.10, S 6.35.

9,34-Dihydro-31,33,35-trimethyl-11,18-dithia-1,9,20,28,34-hexaazapentacyclo[26,3,1,$2^{13,16}$,$2^{19,22}$-[octatriaconta-7(8),9(10),13(14),15(16),37(38),-22(33),39(31)-heptaen-8,21,36-trione (XI). To a solution of 0.1 g of compound **VI** in 30 ml of DMF 0.01 g of sodium hydride treated preliminary with hexane was added. The reaction mixture was stirred for 0.5 h at room temperature, and a solution of 0.05 g of *p*-dibromoxylylene **X** in 10 ml of DMF was added. The resulting mixture was stirred at 30–35°C for 25 h, and the solvent was removed in a vacuum. The residue was treated with 30 ml of $CHCl_3$, filtered, and subjected to column chromatography on SiO_2. The elution was carried out with 80:1 and 60:1 $CHCl_3$–CH_3OH mix-

tures in succession. From the fractions eluted by the last mixture 0.013 g of pyrimidinophane **XI** was obtained, yield 12%, mp 194°C. ^{1}H NMR spectrum ($CDCl_3$, *c* 5 mM), δ, ppm: 1.34–1.75 m (12H, $6CH_2$), 2.18 s (6H, $2C^6$–CH_3), 2.24 s (3H, C^6–CH_3), 2.32-2.37 m (4H, $2C^5$–CH_2), 3.87–3.95 m (4H, $2NCH_2$), 4.32 br.s (4H, $2SCH_2Ph$), 5.60 s (1H, C^5H), 7.18–7.25 m (4H, ArH), 9.95 s (2H, NH). MALDI–TOF mass spectrum: calculated for $C_{33}H_{40}N_6O_4S_2$ $[M]^+$ and $[M + Na]^+$ 648.3 and 671.2. Found, %: C 61.09, H 6.25, N 12.91, S 9.96. $C_{33}H_{40}N_6O_4S_2$. Calculated, %: C 61.09, H 6.21, N 12.95, S 9.88.

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