SYNTHESIS OF BISURACIL SULFOLANE DERIVATIVES

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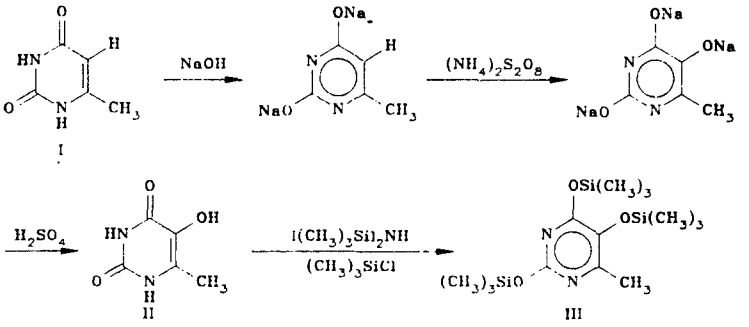
Bisuracil sulfolane derivatives have been synthesized using the silyl method of nucleoside synthesis in the presence of $SnCl_4$. The necessary starting materials were 5-hydroxy-6-methyluracil (prepared by oxidation of 6-methyluracil with ammonium persulfate in aqueous medium) and trans-3,4-diacetoxysulfolane (prepared from trans-3,4-dihydroxysulfolane). The structures of the bisuracil sulfolane derivatives were established based on their spectral data and elemental analysis.

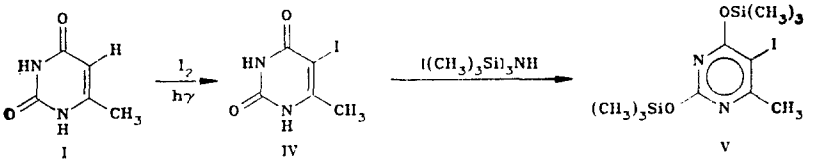
5-Hydroxy-6-methyluracil (II) is of interest in medicine as an immunomodulator and cardiostimulant [1-3]. In order to prepare transportable forms of this compound we have synthesized 6-methylpyrimidine nucleoside analogs, namely bisuracil sulfolane derivatives.

Oxidation of 6-methyluracil (I) with ammonium persulfate in basic medium gave methyluracil II.



Silylation of uracil II with excess hexamethyldisilazane in the presence of a catalytic amount of trimethylchlorosilane in dioxane led to the formation of its trimethylsilyl derivative III, whose IR spectrum contained absorption bands at 760, 850, and 1250 cm^{-1}, characteristic of $Si(CH_3)_3$ groups, as well as bands at 1045 (C–O–Si) and 1388, 1460, and 1580 cm^{-1} (aromatic pyrimidine ring). There was no OH absorption band present. The PMR spectrum contained three $Si(CH_3)_3$ group signals, at 0.26, 0.21, and 0.09 ppm, respectively, corresponding in intensity to 27 protons; the methyl group (in position 6) gave rise to a singlet signal at δ 2.14 ppm.

5-Iodo-6-methyluracil (IV) and its silyl derivative (V) were synthesized according to a published procedure [4].



Applying the silyl methyl for the synthesis of pyrimidine nucleoside analogs [5, 6], we added $SnCl_4$ as a catalyst to the reaction, making it possible to utilize stable and accessible 3,4-diacetoxy sulfolane derivatives VI. The trans-isomer VI, whose conformational equilibrium is shifted in favor of a pseudodiaxial orientation of CH_3COO groups [7], reacts with trimethylsilyl derivatives III and V in the presence of $SnCl_4$ in acetonitrile solution to give trans-3,4-disubstituted sulfolane derivatives VII and VIII, whose structures were confirmed based on their PMR spectra.

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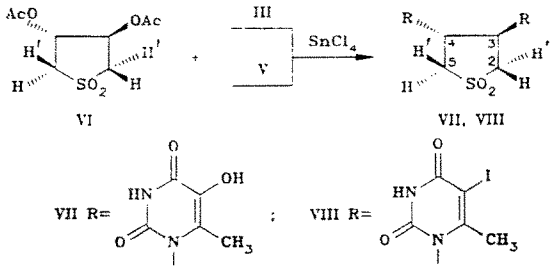

It has previously been shown that the difference in the chemical shift values for the geminal protons and in the chemical shifts for the protons at the substituents is a reliable criterion for assigning the configuration of 3,4-disubstituted sulfolanes. The PMR spectra of compounds VII and VIII contain four groups of signals, three of which correspond to protons in the five-membered ring: in the region 4.5-5.8 ppm two protons at the $C_{(3)}$ and $C_{(4)}$ substituent positions, in the region 2.8-3.8 ppm two groups of signals for the geminal protons at $C_{(2)}$ and $C_{(5)}$. As can be seen from the available data, the difference in the chemical shift values of these protons is 0.3-0.4 ppm, which is characteristic of a trans-configuration for the substituents attached to $C_{(3)}$ and $C_{(4)}$ in the sulfolane ring (in this case the substituents are uracil rings). The nucleoside analogs VII and VIII could be isolated from the reaction mixtures, which contained unreacted 3,4-diacetoxysulfolane as an impurity, by fine crystallization from ethanol. The purities of compounds VII and VIII were monitored by TLC.

The $N_{(1)}$-nucleoside structure was confirmed by the IR spectra of compounds VII and VIII, which exhibited strong carbonyl absorption (ν_{CO}) for the uracil ring in the range 1630-1680 and 1710 cm^{-1}; this rules out the possibility of an O-nucleoside structure. The UV spectra of these pyrimidine sulfolane derivatives VII and VIII did not display shifting of the absorption bands in the transition from acidic to basic media, which is characteristic of $N_{(1)}$-pyrimidine nucleosides and their analogs [4].

EXPERIMENTAL

The purity of newly synthesized compounds was monitored by TLC on Silufol UV 254 plates using chloroform–methanol, 4:1, solvent system. The spots for these substances were visualized in UV light and with iodine vapor. Melting point temperatures were determined on a Boetius microblock apparatus. Ultra-violet spectra were recorded on a Specord M-40 spectrophotometer, IR spectra on a UR-10 spectrophotometer using Vaseline mull samples. Proton magnetic resonance spectra were measured on a Tesla BS-567 (100 MHz) spectrometer versus TMS as internal standard. Acetonitrile was distilled twice from P_2O_5. Dioxane was stored for 24 h over KOH then distilled from metallic sodium.

trans-3,4-Diacetoxysulfolane (VI) was prepared according to [8], mp 154-155°C.

The results of C, H, N, S, Si, and I elemental analysis for compounds II, III, VII, and VIII agreed with calculations.

5-Hydroxy-6-methyluracil (II, $C_5H_6N_2O_3$). To a suspension of 5 g (39.7 mmoles) 6-methyluracil I in 340 ml water was added sequentially a solution of 9.4 g (235 mmoles) NaOH in 35 ml water followed by 10.7 g (47 mmoles) $(NH_4)_2S_2O_8$ in 200 ml water. The temperature of the reaction mixture increased to 50-55°C, and the solution turned from light yellow to light green. The mixture was stirred for 5 h at 20°C, 18.9 ml H_2SO_4 was added, and the mixture was heated to 85°C and stirred at this temperature for 2 h. After cooling the resulting precipitate was removed by filtration and dried under vacuum. Yield 5.3 g (95%) of compound II, which was recrystallized from 50% ethanol, mp 320°C. According to [9], mp > 310°C. R_f 0.69. IR spectrum, ν: 3200 (OH); 3300 (NH), 1660, 1710 (CO); 1260 (CONH); 1380 cm^{-1} (CH_3). UV spectrum, λ_{max} (H_2O): 276 nm (ε 4785); λ_{min} (H_2O) 244 nm (ε 496).

2,4,5-Tris(trimethylsiloxy)-6-methyluracil (III, $C_{14}H_{27}N_2O_3Si_3$). A mixture of 14.2 g (100 mmoles) methyluracil II, 60 ml hexamethyldisilazane, and 1.2 ml trimethylchlorosilane in 50 ml dry dioxane was refluxed with the exclusion of moisture until the precipitate had dissolved. The solvent was evaporated along with excess silylating agent, and the resulting viscous oil which remained was distilled at 134-135°C (1 mm Hg). A colorless oil was obtained, which crystallized on standing. The yield of the silylated base III was 31.0 g (84%). IR spectrum (liquid film), ν: 760, 850, 1250 [$Si(CH_3)_3$]; 1035 (C–O–Si); 1387, 1460, 1580 cm^{-1} (pyrimidine ring). PMR spectrum, δ, relative to $CDCl_3$: 0.087, 0.21, 0.26 [s, 3 $Si(CH_3)_3$, 27H]; 2.14 ppm (s, CH_3, 3H); relative to TMS: 0.23, 0.35, 0.40 [s, $3Si(CH_3)_3$, 27H]; 2.28 ppm (s, CH_3, 3H).

Bisuracil Sulfolane Derivatives (VII, VIII). General Procedure. Silylated base III or V (4.16 mmoles) in 20 ml acetonitrile was mixed with 5 mmoles $SnCl_4$, and under an Ar atmosphere at 0°C 5 mmoles of VI in 10 ml dichloroethane was added over the course of 45 min with vigorous stirring. The mixture was kept at 4-5°C for 2 h, then stirred an additional 48 h at 20°C. The reaction course was followed by TLC. The solution was diluted with 150 ml

dichloroethane and treated with 50 ml saturated $NaHCO_3$ solution. The organic phase was separated, washed with water, and dried over $MgSO_4$. The solvent was evaporated under vacuum at 50°C. Fine crystallization from ethanol gave 0.49 g (60%) VII and 0.83 g (65%) VIII.

3,4-Bis($N_{(1)}$-5-hydroxy-6-methyluracil)sulfolane (VII, $C_{14}H_{16}N_4O_8S$). mp 129-130°C, R_f 0.79. IR spectrum, ν: 1130, 1300 (SO_2); 1450, 1640, 1670, 1710 (pyrimidine ring), 3400-3500 cm^{-1} (OH). UV spectrum, λ_{max} (H_2O): 259 nm (ε 7680); λ_{min} (0.1 N NaOH): 257 nm (ε 7600). PMR spectrum, δ (acetone-D_6): 2.12, 2.18 (6H, S, S, $2CH_3$); 2.88-3.12 (2H, m, $C_{(2)}$-H, $C_{(5)}$H); 3.18-3.48 (2H, m, $C_{(2)}$-H^1, $C_{(5)}$-H^1); 4.53 ppm (2H, m, $C_{(3)}$-H, $C_{(4)}$-H).

3,4-Bis($N_{(1)}$-5-iodo-6-methyluracil)sulfolane (VIII, $C_{14}H_{14}I_2N_4O_6S$). mp 152-153°C, R_f 0.82. IR spectrum, ν: 1170, 1310 (SO_2); 1630, 1680, 1710 cm^{-1} (pyrimidine ring). UV spectrum, λ_{max} (0.1 N HCl): 220 (ε 17,505), 285 nm (ε 10,941); λ_{max} (0.1 N NaOH): 221 (ε 17,131), 289 nm (ε 10,115). PMR spectrum, δ (pyridine-D_5): 1.96, 197 (6H, s.s, $2CH_3$); 3.40-3.55 (2H, m, $C_{(2)}$–H, $C_{(5)}$–H); 3.70-3.90 (2H, m, $C_{(2)}$–H^1, $C_{(5)}$–H^1); 5.79 ppm (2H, m, $C_{(3)}$–H, $C_{(4)}$–H).

LITERATURE CITED

1. N. V. Yafarova and V. A. Davydova, *Problems in Organism Reactivity, Normal and in Pathology* [in Russian], Materials Scientific Conference, Ufa (1974), p. 138.
2. N. V. Yafarova, *Problems in Human and Animal Biochemistry and Immunology* [in Russian], Ufa (1974), p. 103.
3. V. V. Plechev, *Problems in Human and Animal Biochemistry and Immunology* [in Russian], Ufa (1974), p. 101.
4. E. Wittenberg, *Coll. Czech. Chem. Commun.*, **36**, 246 (1971).
5. É. Ya. Lukevits and A. É. Zablotskaya, *Silyl Method for Nucleoside Synthesis* [in Russian], Zinatne, Riga (1985), p. 438.
6. U. Niedballa and H. Vorbruggen, *J. Org. Chem.*, **39**, 3660 (1974).
7. L. V. Spirikhin, R. A. Sadykov, B. V. Flekhter, N. N. Novitskaya, A. A. Panasenko, and G. A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 5, 1029 (1980).
8. O. E. Lohuizen and H. J. Backer, *Rec. Trav. Chim.*, **68**, 1137 (1949).
9. H. R. Henze and E. N. Kahlenberg, *J. Am. Chem. Soc.*, **80**, 1664 (1958).