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SYNTHESIS AND BIOLOGICAL ACTIVITY OF DERIVATIVES OF 4,8-DIOXO-3,4,5,6,7,8-HEXAHYDROBENZOTHIENO[2,3-d]PYRIMIDINE

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We communicated earlier on derivatives of 4,5,6,7-tetrahydrobenzo[b]thiophene and 4-oxo-3,4-dihydrobenzothieno[2,3-d]pyrimidine possessing antiviral [1] and antitubercular [2] activity. In a continuing search for biologically active compounds among the thiophenes, we undertook the synthesis of derivatives of 4,8-dioxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]-pyrimidine containing fragments of the above compounds. However, the synthesis of the 4,8-dioxo-derivatives (IV-VI) from 2-amino-3-ethoxycarbonyl-7-oxo-4,5,6,7-tetrahydrobenzo(b)thiophene [4] by addition of the pyrimidine ring by our described method [5] was accompanied by tarring of the reaction mixture and failure to isolate the final product.

We therefore oxidized the known 4-oxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidines (I-III) [5, 6] by the method of [4] and obtained compounds IV-VI in yields of 25.3-83.3%. In the IR spectra of the dioxo derivatives IV-VI are bands for the CO-group occurring as wide bands at 1710 (IV) and 1660 (V, VI) cm^{-1}. The ^1H NMR spectra showed the following signals (ppm) for IV: 2.15 2 (H-6), 2.61 t (H-5), 3.18 t (H-7), 8.23 s (H-2), and for V: 2.13 q (H-6), 2.60 t (H-5), 3.16 t (H-7), 7.76 m [2,3-$(CH_2)_5$].

The bromination of compound V with 2 moles of bromine gave the 7.7-dibromo derivative VII. The dehydrobromination of compound VII resulted in the formation of monobromide VIII, the constants of which agreed with those of the earlier-prepared 2,3-pentamethylene-4-oxo-7-bromo-8-hydroxy-3,4-dihydrobenzothieno[2,3-d]pyrimidine [2].

The synthesis of the known bromide VIII proves the structures of compounds V and VII. Usage of one mole of bromine gave the monobromo derivative (IX). Nucleophilic substitution of the bromine by the thiocyanoto group by the action of KSCN gave the thiocyanate (X) in a yield of 65.3%.

The IR spectrum of compound X shows an absorption band for the thiocyanate group at 2160 cm^{-1}, and an absorption band for the CO groups at 1650 and 1675 cm^{-1}. Boiling the 4,8-dioxo derivative V with formamide gave the 8-formylaminobenzothienopyrimidine (XI), the structure of which was verified by IR spectroscopy; 3300 (NH) and 1660 cm^{-1} (CO).

EXPERIMENTAL (CHEMICAL)

The IR spectra were obtained with a Perkin-Elmer instrument (Great Britain) in vaseline oil. The molecular weights of the synthesized compounds were measured by the mass-spectrometric method using a Varian MAT-112 instrument (FRG) with direct injection of the sample into the ion source. The energy of the ionizing electrons was 70 eV. The ^1H NMR spectra were determined with a Varian XL-200 spectrometer (Switzerland), with TMS as internal standard. The characteristics of the compounds obtained are presented in Table 1. The found values for the elemental analyses agreed with the calculated ones.

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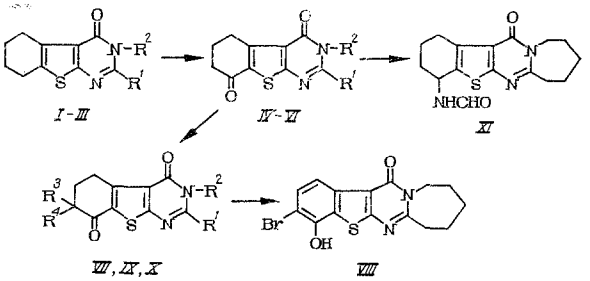
TABLE 1. Characteristics of the Synthesized Compounds

Compound	Yield, %	Mp, °C	Empirical formula
IV	31,6	321 dec.	$C_{10}H_8N_2O_2S$
V	66,6	199—200	$C_{15}H_{16}N_2O_2S$
VI	25,3	200—1	$C_{13}H_{12}N_2O_2S$
VII	84,7	185—6	$C_{15}H_{14}Br_2N_2O_2S$
VIII	87,9	243—4,5	$C_{15}H_{13}N_2O_2SBr$
IX	77,2	204—5	$C_{15}H_{15}BrN_2O_2S$
X	65,3	207—8	$C_{15}H_{15}N_3O_2S_2$
XI	13,0	199—200	$C_{15}H_{16}N_2O_2S$

Note: Recrystallization solvents: V-VIII, alcohol; X and XI, mixture of alcohol and dioxane; IV, dioxane.



$R^1=R^2=H$(I, IV); $R^1+R^2=(CH_2)_5$(II, V, VII, IX, X), $(CH_2)_3$(III, VI); $R^3=H$(IX, X), Br(VII); $R^4=Br$(VII, IX), SCN (X).

4,8-dioxo-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidine (IV), 4,8-dioxo-2,3-pentamethylene-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyridine (V), and 4,8-dioxo-2,3-trimethylene-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidine (VI). To a solution of 0.007 mole of compounds I, II, or III in 15 ml of HOAc heated to 70-80°C was added with stirring at 70-80°C a solution of 2.5 g (0.008 mole) of potassium bichromate in 7.5 ml of water. The reaction mixture was heated to 105°C for 3 h, then was stirred for 2 h without heating. The precipitate was filtered off and washed with water and alcohol.

7,7-Dibromo-4,8-dioxo-2,3-pentamethylene-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidine (VII). A mixture of 1.55 g (0.0053 mole) of compound V, 0.62 ml (0.012 mole) of bromine and 25 ml of $CHCl_3$ was boiled for 1 h, cooled, and washed with water. The solution was concentrated and the residue was treated with alcohol and the precipitate was filtered off and washed with alcohol.

7-Bromo-8-hydroxy-4-oxo-2,3-pentamethylene-3,4-dihydrobenzothieno[2,3-d]pyrimidine (VIII). A mixture of 2.23 g (0.005 mole) of compound VII, 1.4 g (0.019 mole) of lithium carbonate and 10 ml of DMF was boiled for 15 min, cooled, poured into water, treated with 3 ml of AcOH, and the resulting precipitate was filtered off and washed with alcohol.

7-Bromo-4,8-dioxo-2,3-pentamethylene-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidine (IX). A mixture of 2.88 g (0.01 mole) of compound V, 0.52 ml (0.01 mole) of bromine, and 35 ml of $CHCl_3$ was boiled for 30 min, cooled, and the precipitate was filtered off and stirred with 20 ml of saturated aqueous sodium bicarbonate at 80-90°C for 10 min. The reaction mixture was cooled, filtered, and washed with water and alcohol.

4,8-Dioxo-7-thiocyanato-2,3-pentamethylene-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidine (X). To a solution of 2.8 g (0.0075 mole) of compound IX in 70 ml of alcohol and 90 ml of dioxane was added 1.06 g (0.011 mole) of KSCN. The reaction mixture was boiled for 2 h, cooled, and added to water. The resulting precipitate was filtered off, washed with water, and dried.

2,3-Pentamethylene-4-oxo-8-formylamino-3,4,5,6,7,8-hexahydrobenzothieno[2,3-d]pyrimidine (XI). A mixture of 14 g (0.049 mole) of compound V, 14 ml of AcOH, and 21 ml of H_2NCHO was boiled for 30 h and cooled. The precipitate was filtered off, washed with isopropyl alcohol, and dried.

EXPERIMENTAL (BIOLOGICAL)

The activity of compounds IX and VII was studied in vitro by the twofold serial dilution method on liquid nutritive medium according to the generally accepted procedure. Bacterial experiments used the Khottinger boullion and fungal experiments used the Saburo medium.

The bacterial activity was studied on the following reference strains: S. aureus 209-p, B. subtilis 6633 ATCC, E. coli 25922 ATCC, Pr. vulgaris 6896 ATCC, and also highly virulent strains used in animal experiments of Ps. aeruginosa 165, S. typhi 4446, and S. aureus 178 (polyresistant, in this case, to methicillin and to oxacillin). The experiments with fungi used M. canis 3/84, Tr. gypseum 5/85, and C. albicans 1755.

The microbial loading in experiments with bacteria was 1×10^5 KOE/ml, and in experiments with fungi 1×10^6 KOE/ml. The bacteria were incubated at 37°C for 18 h, and the fungi at 25°C for 24 h in experiments with Candida and 5 days in experiments with dermatophytes. The compounds were studied in concentrations of 250 μg/ml and lower.

The chemotherapeutic activity of compound IX was studied in vivo against 3 types of acute generalized bacterial infections. The experiments were carried out on non-hybrid white mice weighing 15-17 g. The S. typhi 4446 strain was used as representative of typhoid fever infection, the Ps. aeruginosa 165 strain for pyocyanaeus infection, and the polyresistant S. aureus 178 strain for staphylococcal infection. The infective dose was introduced intraperitoneally in a volume of 1 ml mixed with a 0.25% nutritional agar solution. The infective dose was sufficient to produce death in 80-100% of the nontreated animals.

The experiments showed that compounds IX and VII in vitro showed activity against S. aureus 209-p (susceptible strain) and B. subtilis [Minimum Inhibitory Concentration (MIC) = 3.9-7.8 μg/ml] and moderate activity against the pathogenic trichophytes and microspores (MIC = 15.6-31.2 μg/ml). The compounds did not suppress the growth of the polyresistant bacteria. In experiments with animals, compound IX showed a weak chemotherapeutic action for treatment of typhoid fever and pyocyanaeus infections (survival of 15 and 5% of the experimental animals) and was ineffective against staphylococcal sepsis.

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