4. V. B. Prozorovskii, Farmakol. Toksikol., No. 1, 115-118 (1962).
5. N. P. Skakun and A. N. Oleinik, ibid., No. 3, 334 (1967).
6. I. D. Stal'naya and T. G. Garishvili, Current Methods in Biochemistry [in Russian], V. N. Orekhovich (ed.), Moscow (1977), pp. 44-46.
7. J. H. Bragdon, P. W. Sunderman, and F. W. Sunderman, Lipids and the Steroid Hormones in Clinical Medicine, Montreal (1960), pp. 6-8.
8. J. Gallastegui, J. M. Lago, and C. Palomo, J. Chem. Res., (S), No. 5, 170-171 (1984).
9. A. S. Gupta and J. R. Merchant, Indian J. Chem., 17, No. 4, 410-411 (1979).
10. B. S. Kirkiacharian and C. Mentzer, Bull. Soc. Chim. Fr., 2030-2033 (1968).
11. M. Lácova, J. J. Chovancová, and V. Konečny, Chem. Papers, No. 1, 121-126 (1968).
12. S. Larratini, R. Paoletti, and L. Bizzi, Drugs Affecting Lipid Metabolism, Amsterdam (1961), pp. 144-147.
13. J. R. Merchant and A. S. Gupta, Chem. and Ind. (London), No. 16, 628 (1978).
14. B. D. Mulay, L. K. Shriniwas, and M. S. Wadia, Synth. Commun., 17, No. 5, 535-541 (1987).
15. B. P. Neri and C. S. Frings, Clin. Chem., 19, No. 10, 1201 (1973).
16. A. Rabaron, J.-R. Didry, B. S. Kirkiacharian, and M. M. Plat, Org. Magn. Reson., 12, No. 5, 284-288 (1979).
17. S. Reitman and S. Frankel, Am. J. Clin. Path., 28, 56-59 (1957).

SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF BENZOTHIENO[2,3-d]PYRIMIDINES

M. V. Kapustina, O. Yu. Amel'kin, I. A. Kharizomenova, V. I. Shvedov, and L. N. Filitis

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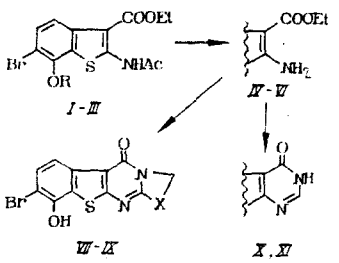
Thienopyrimidines, being thiophene isosteres of quinazolines, are used extensively as key compounds for the synthesis of polyfunctional derivatives with a wide spectrum of biological activity [2, 3]. Continuing these studies, we have now obtained some novel benzothienopyrimidines.

In order to obtain bifunctional benzothiophenes suitable for annelation of a pyrimidine ring, we have selectively hydrolyzed the amides (I-III) [1] with aqueous-alcoholic alkali. The IR spectrum of the amino-compound (IV) obtained in this way, in dilute solution in CCl_4, shows amino-group absorption at 3310-3490 cm^{-1}, and hydroxyl absorption at 3510 cm^{-1}, and the amino-group absorption for (V) and (VI) is seen at 3340-3500 cm^{-1}. Reaction of (I) with hydrazine hydrate in a mixture of alcohol and dioxane for 10 h also results in cleavage of the amide bond.

We have obtained the benzothieno[2,3-d]pyrimidines (VII-IX) by reacting the amino-compound (IV) with lactams in the presence of phosphoryl chloride, as in [2]. The benzothieno-[2,3-d]pyrimidines (X) and (XI) which are unsubstituted in the 2- and 3-positions were obtained by boiling (V) and (VI) with formamide.

The structures of (VII-XI) were confirmed by their IR spectra, which showed no absorption for the amino-group, but carbonyl absorption was present at 1640-1670 cm^{-1}. The molecu-



R=H (I, IV), Me (II, V, X), CH_2Ph (III, VI, XI); X=$(CH_2)_2$ (VII), $(CH_2)_4$ (VIII), CH_2OCH_2 (IX).

S. Ordzhonikidze All-Union Research Institute for Pharmaceutical Chemistry, Moscow.
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TABLE 1. Constants of Compounds Obtained

Compound	Yield, %	Mp, °C	Empirical formula
IV	88,6	138—9	$C_{11}H_{10}BrNO_3S$
V	64,6	118—9	$C_{12}H_{12}BrNO_3S$
VI	80,0	136—7	$C_{18}H_{16}BrNO_3S$
VII	69,54	270—1	$C_{13}H_9BrN_2O_2S$
VIII	65,43	243—4,5	$C_{15}H_{13}BrN_2O_2S$
IX	73,65	257 (decomp.)	$C_{13}H_9BrN_2O_3S$
X	75,6	290—2	$C_{11}H_7BrN_2O_2S$
XI	72,1	265—6,5	$C_{17}H_{11}BrN_2O_2S$

Note. Compounds (IV-VIII) were recrystallized from alcohol, and (IX-XI) from alcohol–dioxane.

TABLE 2. Tuberculostatic Activity of (IV-XI) in vitro (minimum inhibitory concentration, μg/ml)

Compound	$H_{37}Rv$	Academia	Bavis 8	M. Kansasii	M. avium	M. fortuitum	ATCC607
IV	23	<0,08	3,5	3,5	>1000	<0,08	—
V	3,5	23	—	—	>1000	<0,08	—
VI	3,5	23	—	—	>1000	>1000	—
VII	<0,08	3,5	0,55	3,5	>3,5	<0,08	1000
VIII	>1000	—	>1000	>1000	—	>1000	—
IX	>1000	—	>1000	>1000	—	>1000	—
X	>1000	1000	>1000	>1000	—	>1000	—
XI	1000	—	>1000	>1000	>1000	>1000	—

lar masses, obtained for (VII-XI), were in agreement with the calculated values. The constants of the products are shown in Table 1.

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained in Vaseline grease on a Perkin-Elmer 599 (UK). The concentration and solvent are shown for IR spectra obtained in solution. The molecular masses of the products were determined by mass spectrometry on a Varian MAT-112 (West Germany) with direct introduction of the sample into the ion source. The ionizing electron energy was 70 eV.

The elemental analyses were in agreement with the calculated values.

2-Amino-3-ethoxycarbonyl-6-bromo-7-hydroxybenzo[b]thiophene (IV). A. To a suspension of 3.58 g (0.01 mole) of (I) in 75 ml of alcohol was added at 30-40°C a solution of 1.8 g (0.045 mole) of sodium hydroxide in 60 ml of water. The mixture was stirred for 1.5 h at room temperature, poured into water, and acidified with acetic acid until neutral. The solid which separated was filtered off and dried.

B. A mixture of 3.58 g (0.01 mole) of (I), 50 ml of alcohol, 35 ml of dioxane, and 4.5 ml of hydrazine hydrate was boiled for 10 h, poured into water, and the solid which separated was filtered off and dried to give 2.77 g (87.6%) of (IV), identical in its IR spectrum and melting point with the material obtained by method A.

2-Amino-3-ethoxycarbonyl-6-bromo-7-methoxybenzo[b]thiophene (VI). To a suspension of 0.03 mole of (II) or (III) in 200 ml of alcohol was added 1.6 g (0.04 mole) of sodium hydroxide in 10 ml of water. The mixture was heated with stirring to 60°C, heating withdrawn, and stirring continued for 30 min. The mixture was then poured into water, and the solid filtered off, recrystallized from aqueous alcohol, and dried.

7-Bromo-8-hydroxy-2,3-trimethylene-4-oxo-3,4-dihydrobenzothieno[2,3-d]pyrimidine (VII), 7-Bromo-8-hydroxy-2,3-pentamethylene-4-oxo-3,4-dihydrobenzothieno[2,3-d]pyrimidine (VIII), and 7-Bromo-8-hydroxy-2,3-(2-oxatetramethylene)-4-oxo-3,4-dihydrobenzothieno[2,3-d]pyrimidine (IX). A mixture of 0.07 mole of the amine (I), 0.08 mole of the lactam (2-pyrrolidone for (VII), caprolactam for (VIII), and morpholin-2-one for (IX)), 200 ml of dioxane, and 7 ml (0.078 mole) of phosphoryl chloride was boiled for 1 h, cooled, and the solid which separated filtered off. The solid was suspended in water, aqueous potassium hydroxide, added until basic, and acidified with KOH. The solid which separated was filtered off, washed with water and alcohol, and dried.

7-Bromo-8-methoxy-4-oxo-3,4-dihydrobenzothieno[2,3-d]pyrimidine (X) and 7-Bromo-8-benzyloxy-4-oxo-3,4-dihydrobenzothieno[2,3-d]pyrimidine (XI). A mixture of 0.014 mole of (V) or (VI) and 10 ml of formamide was boiled for 0.5 h, cooled, and the solid filtered off, washed with alcohol, and dried.

EXPERIMENTAL (BIOLOGY)

The compounds were tested in vitro for tuberculostatic activity. The minimum inhibitory concentrations were found by serial dilution on Soton's medium. The test cultures used were Mycobacterium tuberculosis strains $H_{37}Rv$, Academia, and bovis 8, conditionally pathogenic mycobacteria (strains M. kansasii, M. avium, and M. fortuitum), and the saprophyte ATCC-

607. The test results are shown in Table 2, from which it will be seen that (VII) and (IV) show high tuberculostatic activity in vitro, while (VIII-XI) are inactive.

Also examined were the tolerance of white mice for (VII), and its therapeutic activity in experimental tuberculosis in white mice. The maximum tolerated dose following a single intragastric daily dose for five days was found to be greater than 2000 mg/kg. Treatment of mice with experimental tuberculosis for 39 days with a range of doses of the compound (from the MTD downwards) failed to influence the course of the disease.

LITERATURE CITED

1. A. N. Grinëv, I. A. Kharizomenova, M. V. Kapustina, et al., Khim. Geterotsikl. Soedin., No. 4, 460 (1987).
2. V. I. Shvedov, I. A. Kharizomenova, and A. N. Grinëv, ibid., No. 6, 765 (1975).
3. R. Pech and R. Böhm, Pharmazie, 39, No. 1, 8 (1984).

SYNTHESIS AND HEPATOPROTECTANT ACTIVITY OF 5-CARBAMOYL- AND 5-ACETYL-2-ALKYLTHIO-6-METHYL-4-ARYL-3-CYANO-1,4-DIHYDROPYRIDINES

A. A. Krauze, A. G. Odynets, A. A. Verreva, S. K. Germane, A. N. Kozhukhov, and G. Ya. Dubur

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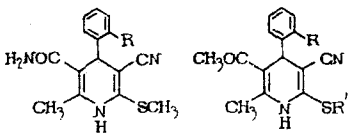
Continuing our work on the synthesis and biological activity of 2-alkylthio-1,4-dihydropyridines [1, 2], we have now obtained some 5-carbamoyl- and 5-acetyl-2-alkylthio-6-methyl-4-aryl-3-cyano-1,4-dihydropyridines (Ia-c) and (IIa-g), and examined their hepatoprotectant activity.



Ia-c IIa-g

Although hepatoprotectant activity in 1,4-dihydropyridines is well known and has been widely reported [3-5, 8-10, 13], we have found hepatoprotectant and antioxidant activity in related compounds, namely 1,4-dihydropyridine-2(3H)-thiones [6].

Alkylated derivatives of the latter (2-methylthio-6-methyl-4-aryl-5-carbamoyl-3-cyano-1,4-dihydropyridines (I)) have now been obtained for the first time. The 4-phenyl compound (Ia) was obtained in 81% yield by condensation of acetoacetamide, benzaldehyde, cyanothioacetamide and piperidine, followed by treatment with methyl iodide. The 4-(o-chlorophenyl)- and 4-(o-difluoromethoxyphenyl)-1,4-dihydropyridines (Ib) and (Ic) were prepared in 73 and 74% yields respectively by condensation of acetoacetamide with the appropriate 3-[o-chloro-(or o-difluoromethoxy)phenyl]-2-cyanoacrylthioamides in the presence of piperidine, followed by treatment with methyl iodide.

The 2-alkylthio-6-methyl-4-phenyl-5-acetyl-3-cyano-1,4-dihydropyridines (IIa-d) were obtained in 83-93% yields by alkylating piperidinium 6-methyl-4-phenyl-5-acetyl-3-cyano-1,4-dihydropyridine-2-thiolate [1]. The 2-alkylthio-6-methyl-4-o-chlorophenyl-5-acetyl-3-cyano-1,4-dihydropyridines (IIe-g) were obtained in 77-88% yields by condensing acetylacetone with 3-(o-chlorophenyl)-2-cyanothioacrylamide in the presence of piperidine, followed by treatment with the alkyl halide. Isolation of the 2-methylthio- compounds (Ia-c) and (IIe) was facilitated by acidifying the reaction mixtures.

The structures of (I) and (II) were confirmed spectroscopically. In the IR spectra of crystalline samples of the dihydropyridines (I) and (II), the most characteristic absorption

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Institute of Organic Synthesis, Latvian Academy of Sciences, Riga.

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