tion. The residue was treated with ether, and the ether solution was washed with water and dried with Na_2SO_4. Removal of the solvent gave V.

1-(4-Amino-3-methylphenyl)-1,3,3-triphenylthiophthalane (VI). This compound was obtained as in the preceding experiment, but the reaction mixture was heated for 1.5 h.

Hydrolysis of Arylaminothiophthalanes II-IV. A 0.5-ml sample of 57% $HClO_4$ was added to a hot solution of 0.5 mmole of the corresponding arylaminothiophthalane in 5 ml of acetic acid, after which the mixture was cooled and worked up to give perchlorate I (80-90%), which was crystallized from glacial acetic acid. No melting-point depression was observed for a mixture of this perchlorate with a genuine sample.

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SYNTHESIS AND PROPERTIES OF 9-THIA-1,4-DIAZASPIRO[5.5]UNDECANES

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4-Bromo-4-formyltetrahydrothiopyrans, which were used to develop a method for the synthesis of 8,8-dialkyl-9-thia-1,4-diazaspiro[5.5]undecanes, were synthesized from 4-formyltetrahydrothiopyrans. Alkylation of these products with ethyl bromoacetate and ethyl acrylate gave, respectively, their di- and monosubstituted derivatives.

Considering the ever increasing interest in recent years in methods for the synthesis and investigation of the biological properties of spiro biheterocyclic compounds [1-4], we have developed a method for the synthesis of a new spiro biheterocyclic system in which the tetrahydrothiopyran and piperazine rings are spiro-bonded; this method also makes it possible to obtain diverse derivatives of the indicated spiro biheterocycle. The synthesis was accomplished via the scheme at the top of the following page.

Aldehydes I [5] were converted to the corresponding α-bromo aldehydes (II) by bromination by means of dioxane dibromide. It should be noted that bromination in acetic acid does not give the desired result. α-Bromo aldehydes II are relatively unstable and undergo partial resinification upon vacuum distillation. However, they can be used in the next step for the preparation of spiro imines III without additional purification. The corresponding spiro amines IV were obtained in high yields by reduction of the spiro imines III with lithium aluminum hydride. The nitrogen atom in the 4 position of spirans IV is more nucleophilic than the nitrogen atom in the 1 position. Thus a product of monoaddition to the nitrogen atom in the 4 position (Va) is obtained in the reaction of spiro amine IVa with excess ethyl acrylate;

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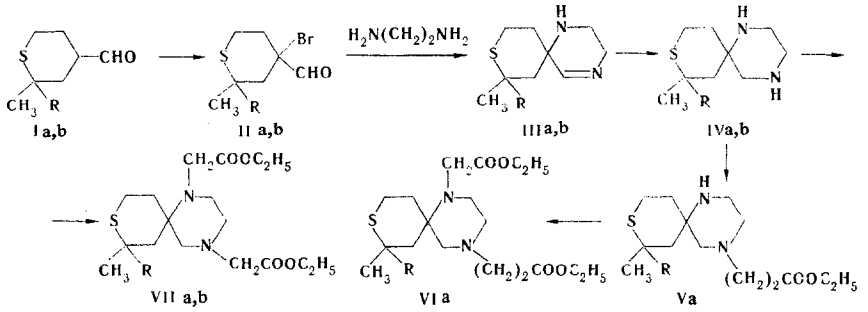

Ia–VIIa R=CH_3; Ib–IVb, VIIb R=C_2H_5

this is in agreement with the inertness of spiro imine IIIa under the same conditions. However, when ethyl bromoacetate is used as the reagent in the alkylation with spiro amines IV, exclusively disubstitution products are formed. Thus, using the different basicities of the nitrogen atoms in the 1 and 4 positions and the appropriate reagents one can selectively carry out mono- and disubstitution in the spiro tetrahydrothiopyranopiperazine series. Under the influence of ethyl bromoacetate the monoalkylation product (Va) was converted to a mixed diester (VIa). The structures of the synthesized compounds were proved by IR, PMR, and mass spectroscopy (see the Experimental section).

EXPERIMENTAL

The purity of the compounds was monitored by gas–liquid chroamtography (GLC) and thin-layer chromatography (TLC). Gas–liquid chromatography was carried out with a Khrom-4 chromatograph with a flame-ionization detector. The stationary phase was E-301 methylsilicone elastomer (6%) on Chromaton NAW (0.20-0.25 mm) treated with hexamethyldisiloxane, the column dimensions were 120 cm by 0.3 cm, the carrier gas was nitrogen, and the flow rate was 0.9 liter/h. Thin-layer chromatography was carried out on Silufol UV-254 plates in a water–dioxane system (1:1); the chromatograms were developed with iodine vapors. The IR spectra of thin layers of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in CCl_4 were recorded with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 spectrometer with direct introduction of the samples into the ion source.

2,2-Dimethyl-4-bromo-4-formyltetrahydrothiopyran (IIa). A 12.4 g (50 mmole) sample of freshly prepared dry dioxane dibromide was added in small portions, as the mixture became colorless, to a solution of 6.3 g (40 mmole) of 2,2-dimethyl-4-formyltetrahydrothiopyran (Ia) in 50 ml of absolute ether, and the mixture was stirred for 10-15 min with blowing out of the liberated hydrogen bromide with a stream of nitrogen. At the end of the reaction, the ether layer was separated, washed with water until the wash water was neutral, and dried over anhydrous calcium chloride. The ether was removed by distillation, and the residue was distilled rapidly *in vacuo* to give 5.4 g (57%) of a product with bp 98-100°C (4 mm) and n_D^{20} 1.5410. The retention time was 2.9 min (156°C). IR spectrum: 1720 (C=O) and 2740 cm^{-1} (CHO). Found: C 40.4; H 5.6; Br 33.5; S 13.6%. $C_8H_{13}BrOS$. Calculated: C 40.5; H 5.5; Br 33.7; S 13.5%.

2-Methyl-2-ethyl-4-bromo-4-formyltetrahydropyran (IIb). This compound was obtained in 51% yield by a method similar to that used to prepare homolog IIa. The product had mp 120-123° (5 mm) and n_D^{20} 1.5385. The retention time was 5.7 min (154°C). IR spectrum: 1730 (C=O) and 2735 cm^{-1} (CHO). Found: C 42.8; H 5.9; Br 32.0; S 12.9%. $C_9H_{15}BrOS$. Calculated: C 43.0; H 6.0; Br 31.8; S 12.7%.

8,8-Dimethyl-9-thia-1,4-diazaspiro[5.5]-4-undecene (IIIa). A solution of 5.7 g (24 mmole) of bromo aldehyde IIa in 15 ml of acetonitrile was added dropwise with stirring, while maintaining the temperature at 15-20°C, to a mixture of 5 g (36 mmole) of potassium carbonate, 3 ml of water, 20 ml of acetonitrile, and 3 g (25 mmole) of a 50% solution of ethylenediamine, after which stirring was continued for 5-7 h, and the mixture was allowed to stand overnight. It was then extracted with ether, and the extract was dried over potassium hydroxide. The solvents were removed by distillation, and the residue was distilled *in vacuo* to give 2.9 g (61%) of a product with bp 145-147°C (4 mm). The product crystallized when it was triturated. It was sufficiently pure, but, when necessary, it could be recrystallized from hexane to give a product with mp 83-84°C. The retention time was 1.7 min (212°C). IR spectrum: 1660 (C=N)

and 3290 cm^{-1} (NH). PMR spectrum: 1.21 and 1.5 [6H, s, 8,8-$(CH_3)_2$]; 1.60 (2H, d, J = 3 Hz, 7,7-H_2); 2.7 (2H, t, J = 4 Hz, 2,2-H_2) 3.1-3.4 (2H, m, 3,3-H_2); 7.23 ppm (1H, t, J = 2.3 Hz, 5-H). Found: C 60.7; H 9.0; N 14.2; S 16.3%; $[M]^+$ 198. $C_{10}H_{18}N_2S$. Calculated: C 60.6; H 9.1; N 14.1; S 16.2%; M 198.

8-Methyl-8-ethyl-9-thia-1,4-diazaspiro[5.5]-4-undecene (IIIb). This compound was similarly obtained in 63% yield and had bp 150-152°C (4 mm) and n_D^{20} 1.5470. The retention time was 1.9 min (212°C). IR spectrum: 1680 (C=N) and 3300 cm^{-1} (NH). PMR spectrum: 1.1 and 1.46 (3H, s, 8-CH_3); 0.9 (3H, t, J = 6 Hz, 8-CH_2CH_3); 2.73 (2H, t, J = 5.0 Hz, 2,2-H_2); 3.1-3.45 (2H, m, 3,3-H_2); 7.26 ppm (1H, t, J = 2.5 Hz, 5-H). Found: C 62.4; H 9.6; N 12.9; S 15.2%; $[M]^+$ 212. $C_{11}H_{20}N_2S$. Calculated: C 62.2; H 9.5; N 13.2; S 15.1%; M 212. The dihydrochloride of IIIb had mp 124-125°C (from ethanol).

8,8-Dimethyl-9-thia-1,4-diazaspiro[5.5]undecane (IVa). A solution of 4 g (20 mmole) of spiro imine IIIa in 10 ml of absolute tetrahydrofuran (THF) was added dropwise with stirring at −10°C in such a way that the temperature of the mixture did not exceed 0°C to a suspension of 1.5 g (39 mmole) of lithium aluminum hydride in 60 ml of absolute ether, after which the mixture was stirred at room temperature for 5-6 h and allowed to stand overnight. It was then cooled to ∿0°C, 6 ml of water and 1.5 ml of 15% sodium hydroxide solution were added cautiously, and the mixture was stirred at room temperature and filtered. The ether was removed by distillation, and the residue was distilled *in vacuo* to give 3.3 g (82%) of a product with bp 124-125°C (3 mm), n_D^{20} 1.5400, and d_4^{20} 1.0666. The retention time was 2.05 min (212°C). IR spectrum 3290 cm^{-1} (NH). PMR spectrum: 1.23 and 1.51 [6H, s, 8,8-$(CH_3)_2$]; 2.46 (2H, s, 5,5-H_2); 2.66 (4H, s, 2,2,3,3-H_4). Found: C 60.0; H 10.2; N 13.7; S 15.9%; $[M]^+$ 200. $C_{10}H_{20}N_2S$. Calculated: C 59.9; H 10.1; N 14.0; S 16.0%; M 200. The dihydrochloride of IVa had mp 230-231°C (from ethanol).

8-Methyl-8-ethyl-9-thia-1,4-diazaspiro[5.5]undecane (IVb). This compound was similarly obtained in 76% yield and had bp 140-142°C (3 mm), n_D^{20} 1.5370, and d_4^{20} 1.0538. The retention time was 3.3 min (212°C). IR spectrum: 3295 cm^{-1} (NH). PMR spectrum: 1.1 and 1.46 (3H, s, 8-CH_3); 2.45 (2H, d, J = 2.5 Hz, 5,5-H_2); 2.66 (4H, s, 2,2,3,3-H_4); 0.88 ppm (3H, t, J = 6.5 Hz, 8-CH_2CH_3). The dihydrochloride of IVb had mp 182-183°C (from ethanol). Found: C 61.4; H 10.1; N 13.0; S 14.8%; $[M]^+$ 214. $C_{11}H_{22}N_2S$. Calculated: C 61.6; H 10.3; N 13.1; S 15.0%; M 214.

8,8-Dimethyl-1,4-bis(ethoxycarbonylmethyl)-9-thia-1,4-diazaspiro[5.5]undecane (VIIa). A mixture of 4 g (20 mmole) of IVa, 20 ml of acetonitrile, 10 g (72 mmole) of potassium carbonate, 6 ml of water, and 6.68 g (40 mmole) of ethyl bromoacetate was refluxed for 18 h, after which 5 g of potassium carbonate was added, and the mixture was extracted with ether. The extract was dried over anhydrous magnesium sulfate, the solvents were removed by distillation, and the residue was distilled *in vacuo* to give 4.5 g (60%) of a viscous liquid with bp 198-200°C (2 mm) and R_f 0.74. IR spectrum: 1750 cm^{-1} (C=O). Found: C 58.3; H 8.6; N 7.6; S 8.5%. $C_{18}H_{32}N_2O_4S$. Calculated: C 58.0; H 8.7; N 7.5; S 8.6%. The dihydrochloride of VIIa had mp 105-106°C (from ethanol).

8-Methyl-8-ethyl-1,4-bis(ethoxycarbonylmethyl)-9-thia-1,4-diazaspiro[5.5]undecane (VIIb). This compound, with bp 226-229°C (5 mm), was obtained in 50% yield by a method similar to that used to prepare homolog VIIa. The viscous liquid had R_f 0.64. IR spectrum: 1750 cm^{-1} (C=O). Found: C 59.1; H 8.9; N 7.4; S 8.4%. $C_{19}H_{34}N_2O_4S$. Calculated: C 59.0; H 8.9; N 7.2; S 8.3%. The dihydrochloride of VIIb had mp 99-100°C (from ethanol).

8,8-Dimethyl-4-(β-ethoxycarbonylethyl)-9-thia-1,4-diazaspiro[5.5]undecane (Va). A mixture of 4 g (20 mmole) of spiran IVa and 4 g (40 mmole) of ethyl acrylate was refluxed for 18 h, after which it was distilled *in vacuo* to give 4.5 g (75%) of a product with bp 180-183°C (3 mm), n_D^{20} 1.5110, and R_f 0.40. IR spectrum: 1740 (C=O) and 3290 cm^{-1} (NH). Found: C 59.8; H 9.5; N 9.4; S 10.7%. $C_{15}H_{28}N_2O_2S$. Calculated: C 60.0; H 9.4; N 9.3; S 10.7%. The dihydrochloride of Va had mp 128-130°C (from ethanol).

8,8-Dimethyl-1-ethoxycarbonylmethyl-4-(β-ethoxycarbonylethyl)-9-thia-1,4-diazaspiro[5.5]undecane (VIa). A mixture of 2.9 g (9.6 mmole) of spiran Va, 10 ml of acetonitrile, 1.7 g (10 mmole) of ethyl bromoacetate, 5 g (36 mmole) of potassium carbonate, and 3 ml of water was refluxed for 12 h, after which it was extracted with ether. The extract was dried over anhydrous magnesium sulfate, the ether was removed by distillation, and the residue was distilled *in vacuo* to give 2.4 g (65%) of a viscous liquid with bp 217-219°C (3 mm) and R_f 0.55. IR spectrum: 1730 cm^{-1} (C=O). Found: C 58.9; H 8.7; N 7.4; S 8.3%. $C_{19}H_{34}N_2O_4S$. Calculated: C 59.0; H 8.9; N 7.2; S 8.3%. The dihydrochloride of VIa had mp 93-94°C (from ethanol).

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5-ARYLIDENE DERIVATIVES OF 3-β-D-RIBOFURANOSYLTHIAZOLIDINE-2,4-DIONE

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The synthesis of modified nucleosides, viz., 5-arylidene derivatives of 3-β-D-ribofuranosyl-thiazolidine-2,4-dione, the structures of which were confirmed by data from the IR and PMR spectra, is described. The compounds have weak activity with respect to smallpox vaccine virus.

Thiazolidine derivatives are of interest both from the point of view of their ability to participate in diverse chemical transformations and owing to the broad spectrum of biological activity displayed by them, including bactericidal, pesticidal, anti-inflammatory, and antivirus activity [1].

Compounds with antivirus activity have also been detected among 2-thioxo-4-thiazolidinone (rhodanine) N-glycosides, viz., in a number of its 5-arylidene derivatives [2]. In this connection, it seemed of interest to synthesize and study the antivirus activity of N-glycosides of 5-arylidene derivatives of an oxygen-containing analog of rhodanine, viz., thiazolidine-2,4-dione. We selected β-D-ribofuranose, which is included in the composition of natural nucleosides, as the carbohydrate component.

We studied two approaches to the synthesis of such compounds. One of them was the synthesis of thiazolidine-2,4-dione N-ribosides [3] and their reaction with aromatic aldehydes through the reactive 5-methylene group of the thiazolidine ring, while the second approach was the synthesis of 5-arylidene derivatives of thiazolidine-2,4-dione itself with subsequent glycosylation of these compounds at the $N_{(3)}$ atom of the thiazolidine ring. We selected the conditions for glycosylation, condensation, and removal of the protective groups in such a way as to avoid anomerization of the glycoside bond and hydrolytic cleavage of the labile thiazolidine ring.

Thus in the first case 2',3',5'-tri-O-acetyl-3-β-D-ribofuranosylthiazolidine-2,4-dione (I), or directly, 3-β-D-ribofuranosylthiazolidine-2,4-dione (II) [3] was condensed with aromatic aldehydes IIIa-f in isopropyl alcohol in the presence of piperidine, and 5-arylidene derivatives IVa-f and Va-f, respectively, were obtained. The condensation products were isolated from the reaction mixture by column chromatography on silica gel. The yields of condensation products varied as a function of the aldehyde used in the reaction (but not as a function of the nucleoside) and ranged from 16% to 62% (see Table 1). (Scheme, following page.)

The traditional methods for removal of the acetyl protective groups by means of solutions of ammonia or sodium methoxide in methanol were unsuitable for IVa-f because of the instability of the thiazolidine ring under these conditions. We were able to realize the deacetylation of IVa-f to give the products in quantitative yields by means of a 5% solution of acetyl chloride in methanol at room temperature.

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