temperature and diluted with ether. The precipitated crystals were washed successively with glacial acetic acid and ether to give 5.2 g (53%) of snow-white crystals of II with mp 165°C (from glacial acetic acid). IR spectrum: 1830 (C=O); 1740 (O–C=O); 1610, 1530 ($O=\overset{+}{C}=N$); 1100 cm^{-1} (ClO_4^-). Found: C 40.6; H 5.7; Cl 11.0; N 4.3%. $C_{11}H_{18}ClNO_8$. Calculated: C 40.3; H 5.5; Cl 10.8; N 4.3%.

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RESEARCH ON AMINOMETHYLENE DERIVATIVES OF AZOLES.

24.* CYCLIZATION OF THIOHIPPURIC ACID IN THE PRESENCE OF THE VILSMEIER REAGENT

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UDC 547.787.2'789.5

It is shown that, in contrast to hippuric acid, thiohippuric acid reacts with dimethylformamide in the presence of phosphorus oxychloride to give three compounds, viz., 2-phenyl-4-dimethylaminomethylene-5-thiazolone, 2-phenyl-4-dimethylaminomethyleneoxazole-5-thione, and 2-phenyl-4-formyl-5-chlorothiazole. The pathways of their formation are discussed. The structures of the compounds obtained and some transformations of 2-phenyl-4-formyl-5-chlorothiazole were studied. 2-Phenyl-4-formyl-5-hydroxy(mercapto)thiazoles and their methyl derivatives, as well as 2-phenyl-4-dimethylaminomethylenethiazole-5-thione, were synthesized from the latter.

Hippuric acid readily undergoes cyclodehydration in the presence of N-methylformanilide and phosphorus oxychloride to 2-phenyl-5-oxazolone, which is then aminoformylated to give an aminomethylene derivative (I) [2]. The reaction of hippuric acid with the adduct from dimethylformamide (DMF) and phosphorus oxychloride proceeds similarly and leads to II.

We used thiohippuric acid to obtain 2-phenyl-4-dimethylaminomethylene-5-thiazolone (III) under the conditions of the formation of II. It was found that in this case one ob-

*See [1] for Communication 23.

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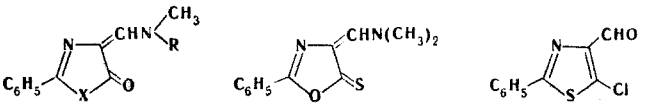
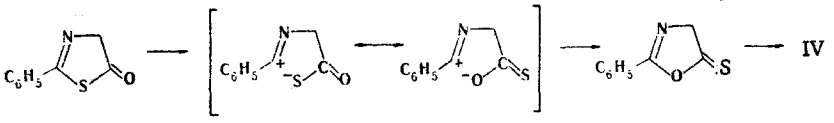


I-III IV V

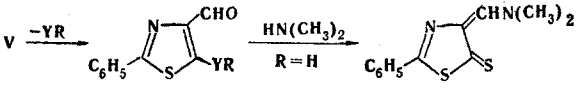
I R=C_6H_5, X=O; II R=CH_3, X=O; III R=CH_3, X=S

tains three products, the ratio of which changes only slightly as a function of the reaction conditions. Chromatographic separation and identification of the resulting compounds showed that, in addition to the expected III, 2-phenyl-4-dimethylaminomethyleneoxazole-5-thione (IV) and 2-phenyl-4-formyl-5-chlorothiazole (V) are obtained. With respect to its properties, IV is identical to the substance obtained from 2-phenyl-4-formyl-5-mercaptooxazole and dimethylamine [3], whereas III is identical to the product of the reaction of 2-phenyl-5-thiazolone with the Vilsmeier reagent from DMF and phosphorus oxychloride. The presence of V in the reaction products is explained by chlorination of 2-phenyl-4-dimethylaminomethylene-5-thiazolone (III) with phosphorus oxychloride, as in the case of other similar compounds [4], and is confirmed by a specially designed experiment.

Thus cyclization of thiohippuric acid in the presence of DMF and phosphorus oxychloride leads to both thiazole and oxazole derivatives in an approximately equal ratio. The production of oxazole derivative IV under the conditions used is evidently associated with recyclization of 2-phenyl-5-thiazolone to 2-phenyloxazole-5-thione, which then undergoes aminoformylation:



It has been noted that if previously prepared 2-phenyl-5-thiazolone or its hydrobromide are subjected to aminoformylation [5], only a thiazole derivative (III) is obtained. Instead of the hydrobromide, it is more convenient to use the hydrochloride, which is obtained by cyclization of thiohippuric acid with phosphorus trichloride; in this case the reaction can be carried out either up to the formation of III or in one step to give 2-phenyl-4-formyl-5-chlorothiazole (V). The chlorine atom in the latter compound is easily replaced by hydroxy, methoxy, and mercapto groups to give the corresponding derivatives (VI-VIII). Compounds IX and X are obtained by reaction of VIII with methyl iodide and dimethylamine:



VI-IX X

VI YR=OH; VII YR=OCH_3; VIII YR=SH; IX YR=SCH_3

Two approximately equally intense absorption bands of C=O, C=N, and C=C bonds are observed in the IR spectrum of II, just as in the case of I [6], and this indicates the existence of Z and E stereoisomers. The conversion to the corresponding thione (IV) is accompanied by a change in the ratio of the intensities of the bands of the vibrations of these groups, evidently in the direction of the E isomer as a consequence of the large size of the sulfur atom as compared with the oxygen atom. The presence of two stereoisomers is also confirmed by the data from the electronic spectra of II and IV (Table 1), in which two maxima are observed for the closely located absorption bands. Judging from the data from the IR and electronic spectra, the thiazole derivatives (III, X) also exist in the form of two stereoisomers with, however, predominance of the E isomer.

The corresponding thiazole derivatives are more deeply colored than the oxazole derivatives, and replacement of the carbonyl oxygen atom by sulfur leads to 40-50 nm deepening of the color in ethanol and 50-70 nm deepening of the color in heptane (Table 1) as a consequence of the large contribution of the dipolar resonance hybrid for sulfur-containing compounds (IV, X).

EXPERIMENTAL

2-Phenyl-4-dimethylaminomethylene-5-oxazolone (II). A 1.8-g (10 mmole) sample of hippuric acid was added with stirring at −20°C to the adduct obtained from 4.4 g (60 mmole) of DMF

TABLE 1. Spectral Characteristics of II-IV and X

Compound	UV spectrum, λ_{max}, nm (log ε)		IR spectrum, cm^{-1} ($CHCl_3$)
	in ethanol	in heptane	
II	235 (4,1), 285 (3,7), 295 (3,7), 337 (4,4) sh 352 (3,6), 368 (4,4)	235 (3,8), 245 (3,8), 270—280 (3,8), 340 (4,0), 355 (4,2), 375 (4,1)	1750 s, 1730 s, 1660 s, 1645 s, 1608, 1580, 1500
IV	234 (4,2) sh 264 (4,2), 335 (4,1), 412 (4,3)	245 (3,7) sh 252 (3,7), 273 (3,9), 338 (3,7), 357 (3,6), 425 (3,8), 450 (3,6)	1645 s, 1630 s, 1615, 1580, 1495
III	255 (3,8), 330 (3,7) sh 374 (4,1), 384 (4,0) sh	245 (4,1), 250 (4,2) sh 264 (4,2), 273 (4,1) sh 305 (3,9) sh 315 (3,9), 386 (4,5), 395 (4,3) sh	1740 w, 1665 s, 1595 s, 1450 s
X	250 (4,1), 294 (4,3), 374 (4,2), 444 (4,1)	255 (3,6), 260 (3,6), 304 (4,1), 312 (4,0), 376 (3,5), 397 (3,5), 450—470 (3,5) sh	1625 s, 1615 s, 1580 m, 1495 s

and 4.6 g (30 mmole) of phosphorus oxychloride. After 30 min, the mixture was heated to 45-50°C and maintained at this temperature for 3 h. It was then cooled and poured over ice, and the aqueous mixture was neutralized to pH ∿ 4 with 20% NaOH. The precipitate was removed by filtration, washed with water, and dried to give 2 g (92.5%) with mp 166-167°C (from benzene). Found: C 66.5; H 5.5; N 13.0%. $C_{12}H_{12}N_2O_2$. Calculated: C 66.6; H 5.5; N 12.9%.

Cyclization of Thiohippuric Acid. The reaction with 1.95 g of thiohippuric acid was carried out similarly. The yield was 2.1 g. Separation with a chromatographic column (on L5R40μ silica gel by elution with chloroform) gave 2-phenyl-4-dimethylaminomethylene-5-thiazolone (III, R_f 0.28, 35% yield), 2-phenyl-4-dimethylaminomethyleneoxazole-5-thione (IV, R_f 0.58, 30% yield), and 2-phenyl-4-formyl-5-chlorothiazole (V, R_f 0.7, 5% yield). The products were identified from mixed-melting-point determinations, R_f values, and spectral characteristics.

2-Phenyl-4-dimethylaminomethylene-5-thiazolone (III). A) A 0.42-g (5.8 mmole) sample of DMF and 0.34 g (1.9 mmole) of 2-phenyl-5-thiazolone [5] were added at 0°C to 0.28 g (1.8 mmole) of phosphorus oxychloride. After 30 min, the mixture was heated to 50°C and maintained at this temperature for 2 h. It was then cooled and treated with ice water, and the aqueous mixture was neutralized to pH ∿ 4. The precipitate was removed by filtration, washed with water, and dried to give 0.37 g (84%) of a product with mp 153-154°C (from heptane). Found: N 11.9; S 13.8%. $C_{12}H_{12}N_2OS$. Calculated: N 12.0; S 13.8%.

B) A 0.6-g (3 mmole) sample of thiohippuric acid was dissolved in 100 ml of anhydrous diethyl ether, 1.65 g (6 mmole) of phosphorus tribromide was added, and the mixture was stirred for 30 min. The ether layer was decanted, and 1.9 g (2.6 mmole) of DMF was added to the precipitated 2-phenyl-5-thiazolone hydrobromide. The mixture was then treated at 0°C with 3.4 g (2.2 mmole) of phosphorus oxychloride, and the reaction was carried out as in method A. The product was obtained in 74% yield. Phosphorus trichloride can be used in place of phosphorus tribromide for the cyclization of thiohippuric acid; III was obtained in 86% yield in this case.

2-Phenyl-4-formyl-5-chlorothiazole (V). A) A 4.6-g (30 mmole) sample of phosphorus oxychloride was added to 2.3 g (10 mmole) of III, and the mixture was heated at 100°C for 5 h. It was then poured over ice, and the aqueous mixture was neutralized to pH ∿ 2 with aqueous alkali. The precipitate was removed by filtration, washed with water, and dried to give 1.9 g (85%) of a product with mp 91°C (from aqueous ethanol) (mp 91-93°C [7]). IR spectrum ($CHCl_3$): 1700 cm^{-1} (CHO). UV spectrum (in ethanol), λ_{max} (log ε): 236 (4.3) and 290 nm (4.2). Found: Cl 15.8; N 6.2; S 14.5%. $C_{10}H_6ClNOS$. Calculated: Cl 15.9; N 6.3; S 14.4%.

B) A 4.7-g (34 mmole) sample of phosphorus trichloride was added to a solution of 6 g (31 mmole) of thiohippuric acid in 100 ml of diethyl ether, and the mixture was stirred in an argon atmosphere at 20°C for 30 min. The ether layer was decanted from the precipitated 2-phenyl-5-thiazolone hydrochloride, 17 g (234 mmole) of DMF was added to the precipitate, and the resulting solution was cooled to −10°C. A 36-g (240 mmole) sample of phosphorus oxychloride was added with stirring at this temperature, after which the temperature was raised to 100°C, and the mixture was maintained at this temperature for 7 h. The mixture was then poured over ice, and the aqueous mixture was neutralized to pH 2 with aqueous alka-

li. The precipitate was removed by filtration, washed with water, and dried to give 6.2 g (90%) of a product with mp 90-91°C (from aqueous ethanol).

2-Phenyl-4-formyl-5-hydroxythiazole (VI). A 1.1-g (5 mmole) sample of V was dissolved in an alcohol solution of potassium hydroxide (a tenfold excess), and the solution was allowed to stand for 24 h. It was then refluxed for 3 h, after which the solvent was removed by distillation, and the residue was dissolved in water. The aqueous solution was filtered, and the filtrate was acidified with 10% hydrochloric acid. The precipitate was removed by filtration, washed with water, and dried to give 0.7 g (70%) of a product with mp 173-175°C (from benzene with petroleum ether). IR spectrum ($CHCl_3$) 1665 (CHO); 3430, 3520 (br) cm^{-1} (OH). UV spectrum in ethanol, λ_{max} (log ε): 242 (4.1), 270 sh (4.3), and 342 nm (4.0); in heptane: 260 (4.4), 270 (4.4), and 325 nm (4.0). Found: N 7.0; S 15.7%. $C_{10}H_7NO_2S$. Calculated: N 6.8; S 15.6%.

2-Phenyl-4-formyl-5-methoxythiazole (VII). A 0.5-g (2.5 mmole) sample of V was dissolved in 15 ml of methanol containing 0.5 g (10 mmole) of sodium methoxide, and the solution was allowed to stand for 24 h. It was then refluxed for 2 h, after which the solvent was removed by distillation, and the residue was washed with water and removed by filtration to give 0.3 g (60%) of a product with mp 118-120°C (from aqueous ethanol). IR spectrum ($CHCl_3$): 1605 cm^{-1} (CHO). UV spectrum in ethanol, λ_{max} (log ε): 300 (4.3); in heptane: 225 (4.1) and 304 nm (4.3). Found: N 6.5; S 14.8%. $C_{11}H_9NO_2S$. Calculated: N 6.4; S 14.6%.

2-Phenyl-4-formyl-5-mercaptothiazole (VIII). A 2.2-g (10 mmole) sample of V was added to a solution of 5.2 ml of a 50% aqueous solution of potassium hydrosulfide (36 mmole) and 150 ml of methanol, and the mixture was refluxed for 2 h. The solvent was removed by distillation, the residue was treated with water and removed by filtration, and the filtrate was acidified. The resulting precipitate was removed by filtration, washed with water, and reprecipitated from sodium carbonate solution to give 2 g (90%) of VIII with mp 103-104°C. IR spectrum ($CHCl_3$): 1730 and 1680 cm^{-1} (CHO). UV spectrum (heptane), λ_{max} (log ε): 240 (4.2), 294 (3.7), and 340 nm (3.7). Found: N 6.1; S 28.7%. $C_{10}H_7NOS_2$. Calculated: N 6.3; S 29.0%.

2-Phenyl-4-formyl-5-methylmercaptothiazole (IX). A 0.4-g (2 mmole) sample of VIII and 0.34 g (2.5 mmole) of methyl iodide were added to a solution of 25 ml of methanol containing 0.5 g (10 mmole) of sodium methoxide, and the mixture was refluxed for 2 h. The solvent was removed by distillation, and the residue was washed with water and removed by filtration to give 0.27 g (64%) of a product with mp 102-103°C (from ethanol). IR spectrum ($CHCl_3$): 1700 cm^{-1} (CHO). UV spectrum (heptane), λ_{max} (log ε): 2.36 (4.3), 310 (4.2), and 322 nm (4.2). Found: N 5.8; S 27.6%. $C_{11}H_9NOS_2$. Calculated: N 5.9; S 27.2%.

2-Phenyl-4-dimethylaminomethylenethiazole-5-thione (X). A 0.5-g (2.5 mmole) sample of VIII was added to an aqueous solution of dimethylamine (a tenfold excess), and the mixture was refluxed for 30 min. It was then cooled, and the precipitate was removed by filtration, washed with water, and dried to give 0.45 g (80%) of a product with mp 236-238°C (from ethanol). Found: N 11.3; S 25.7%. $C_{12}H_{12}N_2S_2$. Calculated: N 11.3; S 25.8%.

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