3-Methyl-4-isothioureido-3-thiolene 1,1-Dioxide Hydrochloride (IXb). A mixture of 0.76 g (0.01 mole) of thiourea, 1.67 g (0.01 mole) of sulfone IVb, and 40 ml of isopropyl alcohol was heated at 80°C for 16 h, after which it was cooled to 20°C. The resulting precipitate of salt IXb was removed by filtration, crystallized from water, and air dried to give 2.04 g of IXb.

3-Methyleneisothioureido-3-thiolene 1,1-Dioxide Hydrobromide (X). A mixture of 0.76 g (0.01 mole) of thiourea, 2.11 g (0.01 mole) of sulfone V, and 20 ml of isopropyl alcohol was heated at 80°C for 5 h, after which it was cooled, and the resulting precipitate of salt X was removed by filtration, crystallized from ethanol, and air dried to give 2.43 g of X.

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BROMINATION OF 1,3,5-TRIMETHYL-4-CHLOROPYRAZOLE

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The bromination of 1,3,5-trimethyl-4-chloropyrazole with N-bromosuccinimide (NBS) in the presence of benzoyl peroxide leads to 5-bromomethyl-1,3-dimethyl-4-chloropyrazole, whereas 3,5-bis(bromomethyl)-1-methyl-4-chloropyrazole predominates in the case of a twofold excess of NBS. Products of subsequent substitution in the 3- and 5-bromomethyl groups of the 3,5-bis(bromomethyl) compound in a ratio of 3:1 were detected in small amounts; this is evidently associated with the syn orientation of the bromine atom in the 5-bromomethyl group, which hinders attack by the bromine radical.

We have previously studied the peculiarities of the bromination of 1,3- and 1,5-dimethyl-4-chloropyrazoles with N-bromosuccinimide (NBS) in the presence of benzoyl peroxide [1]. In the present research we carried out the radical bromination of 1,3,5-trimethyl-4-chloropyrazole (I) to determine the relative reactivities of the methyl groups in the 3 and 5 positions of the pyrazole ring. In the case of an equimolar ratio of chloropyrazole I and NBS the principal reaction product is bromomethyl-substituted II, which was obtained in individual form after distillation in 60% yield based on the converted chloropyrazole I. Signals of protons of a 1-CH_3 group and of CH_3 and $BrCH_2$ groups in the 3 and 5 positions were identified

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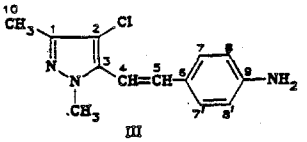
TABLE 1. Data from the PMR Spectra of 1,3,5-Trimethyl-4-chloropyrazole and the Products of Its Bromination [CCl_4, hexamethyldisiloxane (HMDS) internal standard], ppm

Compound	1-R (3H)	3-R	5-R
I	3,59	2,06 (3H)	2,11 (3H)
II	3,77	2,10 (3H)	4,34 (2H)
V	3,62	4,27 (2H)	2,14 (3H)
VI	3,84	4,28 (2H)	4,35 (2H)
VII	4,11	4,28 (2H)	6,72 (1H)
VIII	3,86	6,50 (1H)	4,35 (2H)

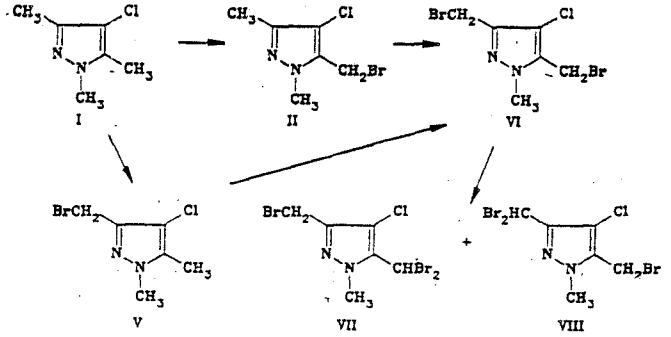
in the PMR spectrum of II (Table 1). However, the PMR spectrum does not make it possible to make an unequivocal choice between the two possible isomers. For this reason II was converted by known methods [2] to the corresponding trans-(4-aminostyryl)pyrazole III. A comparison of the PMR and UV spectra of III and trans-1-methyl-5-(4-aminostyryl)-4-chloropyrazole (IV) [2] makes it possible to assume that the 4-aminostyryl residue in the III molecule is in the 5 position of the pyrazole ring.



III

In the ^{13}C NMR spectra of III and IV the signals of all of the carbon atoms (except for the signal of the carbon atom in the 3 position) virtually coincide. The spectrum of III contains a signal of the carbon atom of the methyl group in the 3 position of the heteroring, and one observes a characteristic weak-field shift [3] of the signal of the carbon atom bonded to this methyl group relative to the same signal in the spectrum of IV. Thus primarily 5-bromomethyl-1,3-dimethyl-4-chloropyrazole (II) is formed initially in the bromination of 1,3,5-trimethyl-4-chloropyrazole. A similar principle was established in the monobromination of a number of 4-substituted 3,5-dimethylisoxazoles [4].

The determination of the structure of the principal reaction product and the difference in the chemical shifts of the protons of the $BrCH_2$ groups in the PMR spectra of 5-bromomethyl-1-methyl-4-chloropyrazole (4.35 ppm) and 3-bromomethyl-1-methyl-4,5-dichlorpyrazole (4.28 ppm) [1] made it possible to establish the peculiarities of the bromination of 1,3,5-trimethyl-4-chloropyrazole with an equimolar amount of NBS with the aid of the PMR spectrum of the reaction mass. According to these data, the ratio of I and II is 1:3. In addition to a signal of protons of the $BrCH_2$ group of 5-bromomethylpyrazole II (4.34 ppm) two low-intensity closely situated singlets at 4.27 and 4.28 ppm and corresponding signals of protons of methyl groups are present; this is associated with the presence in the reaction mixture of 3-bromomethyl-1,5-dimethyl-4-chloropyrazole (V) and 3,5-bis(bromomethyl)-1-methyl-4-chloropyrazole (VI) (Table 1). When a twofold amount of NBS is used the reaction products are the chromatographically isolated 5-bromomethylpyrazole II, 3,5-bis(bromomethyl)pyrazole VI (the principal product), 3-bromomethyl-5-dibromomethyl-1-methyl-4-chloropyrazole (VII), and 5-bromomethyl-3-dibromomethyl-1-methyl-4-chloropyrazole (VIII). The VII:VIII isomer ratio is 1:3 according to the PMR data. The characteristic weak-field shift of the signals of the protons of the $BrCH_2$ and Br_2CH groups in the 5 position relative to the signals of the same



groups in the 3 position of the pyrazole ring is a feature that makes it possible to assign the signals in the spectrum of the mixture to a definite isomer [1].

Isomers VII and VIII are evidently formed in the bromination of bis(bromomethyl)pyrazole VI, and, consequently, the bromomethyl group in the 3 position undergoes the reaction more easily that the bromomethyl group in the 5 position, as observed in the case of bromo-substituted 1,3- and 1,5-dimethyl-4-chloropyrazoles [1]. This is due to the fact that a syn orientation of the bromine atom relative to the $C_{(4)}$—$C_{(5)}$ bond of the heteroring is evidently realized in molecules of the 5-bromomethyl-1-methyl-4-chloropyrazole type; this syn orientation, on the one hand, determines minimal steric hindrance in the starting molecule and, on the other hand, hinders a linear (on the part of the N-methyl group) spin symmetry-allowed [6] approach of the bromine radical with respect to the C—H bond undergoing attack.

EXPERIMENTAL

The PMR and ^{13}C NMR spectra of solutions of the compounds in d_6-DMSO were measured with a Bruker CXP-100 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The electronic spectra of solutions in ethanol were recorded with a Specord spectrophotometer. Thin-layer chromatography was carried out on Silufol plates in benzene.

1,3,5-Trimethyl-4-chloropyrazole (I). Dry hydrogen chloride was passed through a solution of 14.1 g (130 mmole) of 1,3,5-trimethylpyrazole [7] in 150 ml of CCl_4, after which the precipitated hydrochloride was removed by filtration, washed with ether, and dissolved in 15 ml of acetic acid. The solution was heated to 80°C, 20 ml of 30% hydrogen peroxide was added dropwise, and the mixture was allowed to stand for 20 min. It was then neutralized with ammonium hydroxide and extracted with benzene (five 70-ml portions). The benzene was removed by distillation, and the residue was distilled to give 11.7 g (65%) of I with bp 79°C (13 mm) and n_D^{20} 1.4949 [bp 85°C (15 mm) and n_D^{23} 1.4923].

5-Bromomethyl-1,3-dimethyl-4-chloropyrazole (II). A 0.4-g sample of benzoyl peroxide and, in small portions in the course of 2 h, 6.16 g (35 mmole) of N-bromosuccinimide (NBS) were added to a refluxing solution of 5.0 g (35 mmole) of I in 80 ml of CCl_4, and the mixture was then refluxed for 2 h. It was then cooled, the precipitated succinimide was removed by filtration, and the filtrate was dried over sodium sulfate. According to the PMR spectral data, this solution contained the following compounds: I (20%), II (65%), V (10%), and VI (5%). The solvent was removed by distillation, and the residue was fractionated in vacuo to give the following products: 1.0 g (20%) of I with bp 67-75°C (8 mm) and n_D^{20} 1.4946; 4.6 g (60%) of II with bp 101-103°C (8 mm). Found: C 32.1; H 3.6%. $C_6H_8BrClN_2$. Calculated: C 32.2; H 3.6%.

3,5-Bis(bromomethyl)-1-methyl-4-chloropyrazole (VI). A 0.4-g sample of benzoyl peroxide and, in the course of 2 h with refluxing, 9.85 g (56 mmole) of NBS were added to a solution of 4.0 g (28 mmole) of I in 80 ml of CCl_4, after which the mixture was allowed to stand for 4 h. According to TLC data, II, VI, and VII + VIII were present in solution. The precipitate that formed when the mixture was cooled was removed by filtration, the solvent was removed by distillation, and the residue was fractionated in vacuo to give the following products: 1.6 g (25%) of II with bp 101-105°C (8 mm); 4.3 g (51%) of VI with mp 51-55°C. Found: C 23,5; H 2.2; N 9.3%. $C_6H_7Br_2ClN_2$. Calculated: C 23.8; H 2.3; N 9.2%. The still residue (1.2 g) was dissolved in 40 ml of benzene, and one fourth of the solution was chromatographed with a column (elution with benzene) with collection of the fraction that contained products with R_f 0.25 and 0.50. Removal of the solvent from the latter fraction by distillation gave 0.21 g of VII and VIII (1:3 according to PMR data) with mp 93-102°C. Found: C 18.7; H 1.7; N 7.4%. $C_6H_6Br_3ClN_2$. Calculated: C 18.9; H 1.6; N 7.3%.

5-(4-Aminostyryl)-1,3-dimethyl-4-chloropyrazole (III). This compound was obtained in 46% yield from II by the method in [1] and had mp 141-142°C (ethanol). UV spectrum (ethanol), λ_{max} (log ε): 342 nm (4.3). PMR spectrum: 2.0 (3H, s, 3-CH_3); 3.70 (3H, s, 1-CH_3); 5.42 (2H, s, NH_2); 6.71, 7.14 (2H, 2d, CH=CH, J = 16 Hz); 6.56, 7.30 ppm (two 2H, 2d, C_6H_4, J = 8 Hz). ^{13}C NMR spectrum: 8.8 [$C_{(10)}$], 102.5 [$C_{(2)}$], 106.0 [$C_{(4)}$], 111.9 [$C_{(8,8')}$], 121.6 [$C_{(6)}$], 126.1 [$C_{(7,7')}$], 131.6 [$C_{(5)}$], 134.2 [$C_{(3)}$], 141.4 [$C_{(1)}$], 147.6 ppm [$C_{(9)}$]. Found: C 62.5; H 5.8; N 16.5%. $C_{13}H_{14}ClN_3$. Calculated: C 62.5; H 5.7; N 17.0%.

5-(4-Aminostyryl)-1-methyl-4-chloropyrazole (IV) [1]. Electronic absorption spectrum (ethanol), λ_{max} (log ε): 338 nm (4.5). PMR spectrum: 3.86 (3H, s, 1-CH_3); 5.36 (2H, s, NH_2); 6.77, 7.20 (2H, 2d, CH=CH, J = 16 Hz); 6.60, 7.34 (two 2H, 2d, C_6H_4, J = 8 Hz); 7.44

ppm (1H, s, 3-H). ^{13}C NMR spectrum: 103.3 [$C_{(2)}$], 105.6 [$C_{(4)}$], 111.6 [$C_{(8,8')}$], 121.9 [$C_{(6)}$], 126.0 [$C_{(7,7')}$], 131.8 [$C_{(5)}$], 133.9 [$C_{(1)}$], 134.4 [$C_{(3)}$], 147.6 ppm [$C_{(9)}$].

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3-α-HALOCARBONYL DERIVATIVES OF PYRAZOLO[1,5-a] BENZIMIDAZOLE AND THEIR REACTIONS

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3-(α-haloacyl)-2,4-dialkylpyrazolo[1,5-a]benzimidazoles can be obtained either by brominating 3-acetylpyrazolo[1,5-a]benzimidazoles with bromine in acetic acid, or by acylating the 3-unsubstituted pyrazolobenzimidazoles with haloacetic halides. Halogenation of 3-acetylpyrazolo[1,5-a]benzimidazoles with bromine in acetic acid in the presence of sodium acetate, and bromination with N-bromosuccinimide or 1-chlorobenzotriazole, result in deacylation to give 3,6(7)-dibromo- and 3-chloropyrazolo[1,5-a]benzimidazoles. The mono- and trihaloketones obtained have been used to prepare the corresponding aminoketones, the 3-carboxylic acid, and its derivatives.

Derivatives of pyrazolo[1,5-a]benzimidazole, which is the closest structural analog of the biologically active imidazo[1,2-a]benzimidazole [1, 2], could be of interest for pharmacological study. However, the few investigations of methods of synthesizing functionally substituted derivatives of this heterocycle have mainly been concerned with the difficultly-accessible 4H-pyrazolo-[1,5-a]benzimidazoles [3, 4]. Making use of a simple method which we have developed for the preparation of 3-acyl-2,4-dialkylpyrazolo[1,5-a]benzimidazoles [5], we here examine possible approaches to 3-α-halocarbonyl derivatives of this series, and have obtained therefrom aminoketones, and the 3-carboxylic acid and its esters and hydrazide.

In the halogenation of 3-acetyl-2,4-dimethylpyrazolo[1,5-a]benzimidazole (I), the high electron density at the 3 position in the heterocycle has a marked deactivating effect on the reactivity of the methyl group attached to the carbonyl carbon, and creates a preference for facile ipso-substitution. For instance, the ketone (I) does not react with bromine in chloroform, alcohol, or carbon tetrachloride. The monoketone (II) can be obtained only in boiling acetic acid, in which case some of the dibromo compound (III) is formed together with the hydrobromide of the starting material, separation of which is possible only after

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