OPENING OF THE THREE-MEMBERED RING IN 1,1-DISUBSTITUTED CYCLOPROPANES AS A METHOD FOR THE SYNTHESIS OF FUNCTIONAL DERIVATIVES OF PYRAZOLE AND ISOXAZOLE

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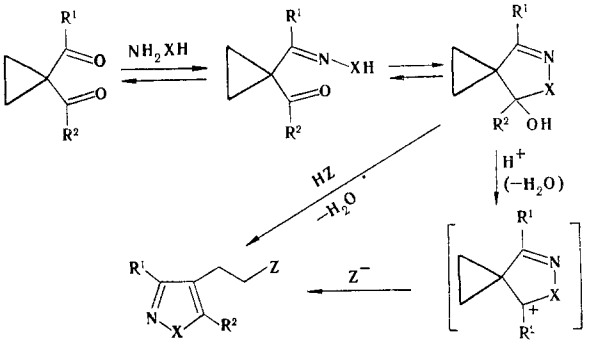
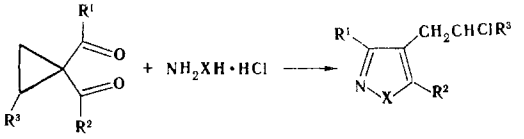
The reaction of 1,1-diacylcyclopropanes with hydrazine and hydroxylamine derivatives, which leads to nucleophilic opening of the three-membered ring and the formation of pyrazole and isoxazole derivatives, was studied. The dependence of the occurrence of this reaction on the structure of the diketo derivatives of the cyclopropane series was investigated.

We have previously shown [1, 2] that the reaction of 1,1-diacetylcyclopropane with hydrazine and hydroxylamine derivatives proceeds with exceptionally facile opening of the three-membered ring and leads to pyrazole and isoxazole derivatives. A peculiarity of this reaction is the fact that an external nucleophile, including a nucleophilic solvent, is included in the structure of the recyclization product. We explained the unusual ease of occurrence of the reaction from the point of view of the concept of "spiro activation" [3], introducing the idea of "dynamic spiro activation": in the course of a multistep process one of the intermediates has the geometry and electron-density distribution that are characteristic for spiro-activated structures, and this promotes nucleophilic opening of the cyclopropane ring.



X=NH, O, NTs, NPh, $NCONH_2$; Z=Cl, Br, I, SCN, OMe, OEt, OPh, OAc

In order to make a further study of the limits of the applicability of this reaction, in the present research we investigated in detail the dependence of its occurrence on the structure of the 1,1-diacyl derivative of the cyclopropane series:



I-VI VIII-XV

I $R^1=CH_3$, $R^2=Ph$, $R^3=H$; II $R^1=R^2=Ph$, $R^3=H$; III $R^1=CH_3$, $R^2=$ cyclopropyl, $R^3=H$; IV $R^1=CH_3$, $R^2=$2-pyridyl, $R^3=H$; V $R^1=R^2=R^3=CH_3$; VI $R^1=CH_3$, $R^2=OEt$, $R^3=H$; VIII $R^1=CH_3$, $R^2=Ph$, $R^3=H$, X=NH; IX $R^1=CH_3$, $R^2=Ph$, $R^3=H$, X=O; X $R^1=CH_3$, $R^2=$ cyclopropyl, $R^3=H$, X=NH; XI $R^1=CH_3$, $R^2=$ cyclopropyl $R^3=H$, X=O; XII $R^1=CH_3$, $R^2=$2-pyridyl, $R^3=H$, X=O; XIII $R^1=CH_3$, $R^2=$2-pyridyl $R^3=H$, X=NH; XIV $R^1=R^2=R^3=CH_3$, X=NH; XV $R^1=CH_3$, $R^2=OEt$, $R^3=H$, X=NH

We found that the reaction is extremely sensitive to the character of the substituents conjugated with the carbonyl group. Thus the introduction of phenyl substituents hinders

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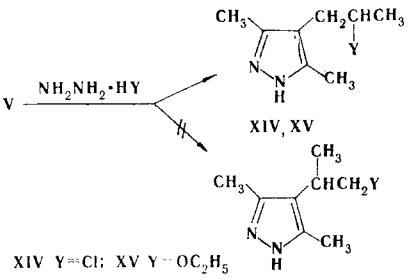
the reaction: whereas 1,1-diacetylcyclopropane reacts with hydrazine hydrochloride at room temperature in ethanol, refluxing is required for 1-acetyl-1-benzoylcyclopropane, while 1,1-dibenzoylcyclopropane does not react under these conditions (80% of the starting diketone was isolated after refluxing in ethanol for 20 h). The decrease in the activity of the carbonyl group due to its conjugation with the aromatic ring is quite obvious.

It is known [4] that nucleophilic opening of three-membered rings is complicated when alkyl substituents are introduced into the cyclopropane ring; complex mixtures of products are generally formed in this case. Thus the reaction of 1,1-dicarbethoxycyclopropane with pyrrolidine leads to approximately equal amounts of products that are formed by attack on the unsubstituted and alkyl-substituted carbon atoms of the cyclopropane ring [4]. At the same time, spiro-activated cyclopropanes are much more sensitive to the fine differences in the electron-density distribution of the molecule, and ring opening in alkyl-substituted spiro-activated cyclopropanes proceeds via attack at the alkyl-substituted carbon atom [3]. We found that in the reaction of 1,1-diacetylcyclopropane in ethanol with hydrazine hydrate and hydrazine hydrochloride even though the introduction of a methyl group in the 2 position does hinder opening of the three-membered ring (the reaction is carried out by refluxing), the expected pyrazole derivatives are nevertheless obtained in 50% yield; in this case, in contrast to [4] and in complete agreement with [3], the reaction proceeds strictly regioselectively, leading only to one of the two possible pyrazole isomers; this is characteristic for spiro-activated cyclopropanes:



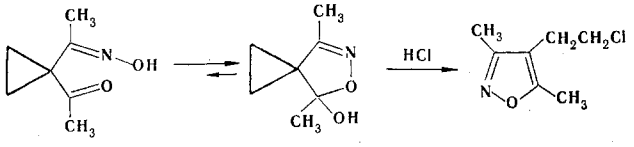
It should be noted that the thermal isomerization of diacetylcyclopropane V proceeds regioselectively, leading to 2,5-dimethyl-3-acetyl-4,5-dihydrofuran [5].

Previously [2], in a discussion of the probable reaction mechanism we proposed that the final step in the reaction scheme proceeds either synchronously or with the prior formation of a carbonium ion. In the latter case (when R^2 = cyclopropyl) a product of opening of the second cyclopropane ring could, in principle, also be formed, since it is known that cyclopropylmethyl carbonium ion systems undergo rearrangement to homoallylic systems via ring opening [6]. We established that opening of exclusively the spiro-activated ring occurs in the reaction of diketone III with hydrazine hydrochloride and hydroxylamine.

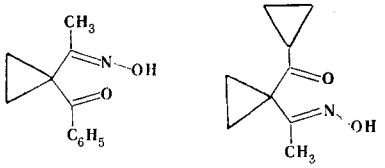
Another factor that promotes the facile occurrence of the investigated reaction may be the stability of the resulting azole of aromatic character. The literature contains data that indicate that 4,4-dialkylisopyrazoles upon reaction with concentrated hydrochloric acid under severe conditions may be converted to pyrazoles with the simultaneous formation of an alkyl halide (the isopyrazole–pyrazole rearrangement [7]). We therefore studied the behavior of 1,1-diacetylcyclopentane (VII) under the conditions of our reaction. We found that the only product formed when diketone VII is refluxed with hydrazine hydrochloride in ethanol for 20 h is 3,5-dimethylisopyrazole-4-spiropentane (XVII), the IR spectrum of which contains one intense absorption band at 1590 cm^{-1} (the disappearance of this band is a criterion for the occurrence of the isopyrazole–pyrazole rearrangement [7]). Thus, the energy gain due to the aromatic character of the reaction product is not a sufficient factor for cleavage of the ring C–C bond. Precisely the peculiarities of the electronic structure of the three-membered ring conjugated with electron-acceptor groups, as well as the configurational fixing of the conformation that ensures the most effective interaction of the activating groups with the cyclopropane ring in the case of dynamic spiro activation, make it possible to explain the relative ease of ring opening under the conditions of our reaction.

In the case of the synthesis of isoxazoles IX, XI, and XII we observed that initial attack takes place at the acetyl carbonyl group, and the reaction terminates with the formation of one of the two possible isoxazole isomers. We have previously reported [2] that in the reaction of 1,1-diacetylcyclopropane with hydroxylamine we were able, under special

conditions, to isolate a monooxime that exists exclusively in the cyclic tautomeric form and is readily converted to the corresponding isoxazole when HCl is added:

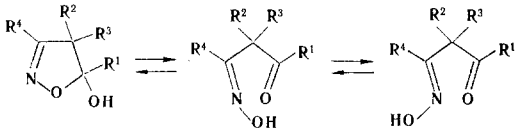


The analogous monooximes of diketones I and III are much less reactive and can be readily isolated (IXa and XIa). As we have already mentioned, hydroxylamine reacts at the acetyl carbonyl group (a shift of the signals of the protons of the methyl group to strong field is observed in the PMR spectra on passing from the diketone to the oxime). We determined the configurations of the oximes by means of a method based on the difference in the chemical shifts of the protons of the methyl group in benzene in the presence or absence of traces of HCl [8]. We found that oxime IXa has a Z configuration (a 3-Hz shift of the signal to weak field upon passage of 10 ml of HCl vapors [8]), whereas oxime XIa has the E configuration (a 2-Hz shift of the signal to strong field):



IX a XI a

In a study of the effect of substituents on the position of the A ⇄ B ⇄ C equilibrium Escale and co-workers [9, 10] demonstrated that oxime IXa, which they synthesized by the action of phenylmagnesium bromide on 3-methyl-4,4-ethylene-5-isoxazolone, exists in the form of cyclic tautomer A.

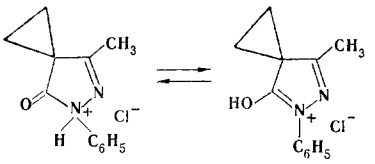


A B C

Our data contradict the data in [9, 10]: the oxime that we obtained gives in its PMR spectrum a signal of a hydroxy proton at 8.74 ppm rather than a signal at 4.25 ppm, and an absorption band of a carbonyl group (1680 cm^{-1}) is present in the IR spectrum. In addition, the compound that we obtained has mp 74°C rather than 57°C. This contradiction can be explained only by assuming that for this case the energy of activation of the A ⇄ B transition is sufficiently high and makes it possible for these tautomers to exist in the form of individual compounds. However, both oxime IXa and oxime XIa are readily converted to the corresponding isoxazoles IX and XI by the action of hydrochloric acid, i.e., the configuration of the oxime and the position of the tautomeric equilibrium do not play a substantial role.

To expand the synthetic possibilities of the reaction that we investigated and to extend it to cyclopropane compounds with substituents other than the keto group we investigated the behavior under these conditions of 1-acetyl-1-carbethoxycyclopropane (VI). It is evident that the decreased activity of the carbethoxy group as compared with the carbonyl group should hinder cyclization significantly. The literature contains information that indicates that oxime VIa is formed in the reaction of keto ester VI with hydroxylamine [11]. In reproducing this reaction we also obtained a substance, the constants of which are in agreement with the constants of VIa and the PMR spectrum of which confirms the oxime structure. However, keto ester VI reacts with hydrazine hydrochloride in ethanol with opening of the three-membered ring to give a pyrazole derivative. One may a priori assume the formation of a 5-pyrazolone derivative; however, only 3-methyl-5-ethoxy-4-(2-chloroethyl)pyrazole (XV) is formed (see the scheme presented above).

The results make it possible to have a critical attitude toward the literature data that indicate that a pyrazole derivative, to which Küster [11] assigned the following structure, is formed by the action of concentrated hydrochloric acid on 1-acetylcyclopropane-1-carboxamide phenylhydrazone:



The results of our research make it possible to assume that the cyclopropane ring actually is not retained under the described conditions and that the substance obtained is evidently 1-phenyl-3-methyl-4-(2-chloroethyl)-5-pyrazolone. This is also indicated by a number of physicochemical properties of the substance, viz., its low melting point (72°C) and solubility in benzene and chloroform.

Thus the described reaction, in conjunction with our proposed method for the preparation of activated cyclopropanes, is a preparatively simple and convenient method for the preparation of diverse 3,5-dialkyl-4-(β-X-ethyl)pyrazoles and isoxazoles.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil were recorded with a UR-20 spectrometer. The PMR spectra were recorded with Varian T-60 and Tesla BS-497 spectrometers (60 and 100 MHz) with tetramethylsilane as the internal standard. The course of the reactions and the individualities of the substances were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates. Preparative TLC was accomplished on Silpearl UV-254 silica gel.

General Method for the Preparation of 1,1-Diketo Derivatives of the Cyclopropane Series. A mixture of 0.1 mole of the β-dicarbonyl compound, 0.2 mole of 1,2-dibromoethane, and 0.4 mole of freshly calcined potassium carbonate was stirred vigorously in 100 ml of DMSO for 8 h, after which it was diluted with an equal volume of water, and the mixture was extracted thoroughly with ether. The ether extract was washed with water and dried with magnesium sulfate. The ether was removed by distillation, and the residue was distilled in vacuo. This procedure was used to obtain the compounds listed below.

1-Acetyl-1-benzoylcyclopropane (I). This compound was obtained in 54% yield and had bp 108-110°C (3 mm) and n_D^{20} 1.5485 [12].

1,1-Dibenzoylcyclopropane (II). This compound was obtained in 62% yield and had mp 91-92°C (from hexane) and bp 185-190°C (3.5 mm). PMR spectrum ($CDCl_3$): 1.75 (4H, s) and 7.63 ppm (10H, m). Found: C 81.8; H 5.8%. $C_{17}H_{14}O_2$. Calculated: C 81.6; H 5.6%.

1-Acetyl-1-(cyclopropanylcarbonyl)cyclopropane (III).* This compound was obtained in 60% yield and had bp 71°C (2 mm) and n_D^{20} 1.4835. PMR spectrum (CCl_4): 0.97 (4H, m), 1.37 (4H, s), 1.98 (1H, m), and 2.23 ppm (3H, s). Found: C 70.8; H 7.7%. $C_9H_{12}O_2$. Calculated: C 71.0; H 8.0%.

1-Acetyl-1-(2-pyridylcarbonyl)cyclopropane (IV).† This compound was obtained in 45% yield and had bp 112-115°C (0.5 mm) and mp 33°C (from pentane). PMR spectrum (CCl_4): 1.40 (4H, m), 2.0 (3H, s), and 7.40-8.13 ppm (4H, m). Found: C 69.0; H 5.9; N 7.3%. $C_{11}H_{11}NO_2$. Calculated: C 69.8; H 5.9; N 7.4%.

1,1-Diacetyl-2-methylcyclopropane (V).‡ This compound was obtained in 16% yield and had bp 44-46°C (2 mm) and n_D^{20} 1.4653 [12].

1-Acetyl-1-carbethoxycyclopropane (VI). This compound was obtained in 80% yield and had bp 44°C (1 mm) and n_D^{20} 1.4420 [13].

1,1-Diacetylcyclopentane (VII).** This compound was obtained in 68% yield and had bp 47-48°C (1.5 mm) and n_D^{20} 1.4640. PMR spectrum (CCl_4): 1.37-1.73 (8H, m) and 2.0 ppm (6H, s). Found: C 70.1; H 9.2%. $C_9H_{14}O_2$. Calculated: C 70.0; H 9.1%.

*Obtained from acetonyl cyclopropyl ketone.

†The starting 1-(2-pyridyl)butane-1,3-dione was obtained by the method in [14]. The ether extract in the synthesis of diketone IV was not washed with water; it was dried with calcined potassium carbonate.

‡Obtained from acetylacetone and 1,2-dibromopropane.

**Obtained from acetylacetone and 1,4-dibromobutane.

General Method for the Preparation of Pyrazole and Isoxazole Derivatives. A) A mixture of 1 mole of the diketo derivative of cyclopropane and 1 mole of NH_2XH hydrochloride (X = O, NH) was refluxed in ethanol. The solvent was removed by distillation, and the residue was distilled or recrystallized.

B) In contrast to method A, the solvent was partially removed by distillation, and the residue was diluted with water and made alkaline to pH 8 by the action of 10% KOH. This mixture was extracted with chloroform, and the extract was dried with magnesium sulfate. The chloroform was removed by distillation, and the residue was distilled or recrystallized.

C) Water was used as the solvent. The reaction mixture was then treated as in method B.

3-Methyl-5-phenyl-4-(2-chloroethyl)pyrazole (VIII). This compound was obtained by method B. The reaction of 3.76 g (0.02 mole) of diketone I and 1.4 g of hydrazine hydrochloride in 150 ml of ethanol for 8 h gave 3 g (70%) of pyrazole VIII with mp 97-98°C (from hexane). PMR spectrum ($CDCl_3$): 2.17 (3H, s), 3.28 (2H, t, J = 8 Hz), 3.83 (2H, t, J = 8 Hz), 8.20 (5H, m), and 13.7 ppm (1H, s). Found: C 65.2; H 5.9; N 12.5%. $C_{12}H_{13}ClN_2$. Calculated: C 65.3; H 5.9; N 12.7%. The hydrochloride (VIIIa) had mp 198-201°C (from acetonitrile). PMR spectrum ($CDCl_3$): 2.40 (3H, s), 3.10 (2H, t, J = 6.5 Hz), 3.58 (2H, t, J = 6.5 Hz), 7.63 (5H, m), and 15.1 ppm (2H, s).

3-Methyl-5-phenyl-4-(2-chloroethyl)isoxazole (IX) and Z-1-(1-Oximinoethyl)1-benzoylcyclopropane (IXa). The reaction (by method B) of 3.15 g (0.017 mole) of diketone I and 1.4 g of hydroxylamine hydrochloride in 150 ml of ethanol for 12 h gave 3.1 g of a fraction with bp 117-120°C (1.5 mm), which, according to TLC data, was a mixture of IX and IXa [R_f values, respectively, 0.73 and 0.58; methyl acetate–chloroform (1:3)]. The substances were separated by means of preparative TLC to give 1.8 g (48%) of isoxazole IX and 1.06 g (31%) of oxime IXa. Compound IX had mp 45-46°C (from hexane); PMR spectrum ($CDCl_3$): 2.30 (3H, s), 3.03 (2H, t, J = 7.5 Hz), 3.58 (2H, t, J = 7.5 Hz), and 7.48 ppm (5H, m). Found: C 65.1; H 5.8; N 6.1%. $C_{12}H_{12}ClNO$. Calculated: C 65.0; H 5.4; N 6.3%. Compound IXa had mp 74-75°C (from hexane); IR spectrum: 1650 (C=N), 1680 (C=O), and 3300 cm^{-1} (OH); PMR spectrum ($CDCl_3$): 1.43 (4H, m), 1.75 (3H, s), 7.76 (5H, m), and 8.74 ppm (1H, s). Found: C 70.8; H 6.3; N 7.0%. $C_{12}H_{13}NO_2$. Calculated: C 70.9; H 6.4; N 6.9%. A drop of concentrated HCl was added to an ampul containing a sample of oxime IXa, and the ampul was shaken several times. Repeated recording of the PMR spectrum established the formation of 75% isoxazole IX and 25% hydrolysis to the starting diketone I.

3-Cyclopropyl-5-methyl-4-(2-chloroethyl)pyrazole (X). This compound was obtained by method C. The reaction of 1 g (6.6 mmole) of diketone III and 0.45 g of hydrazine hydrochloride in 50 ml of water for 8 h gave 0.97 g (80%) of pyrazole X with mp 83-84°C (from hexane). PMR spectrum ($CDCl_3$): 0.87 (4H, m), 1.73 (1H, m), 2.16 (3H, s), 2.90 (2H, t, J = 7.5 Hz), 3.57 (2H, t, J = 7.5 Hz), and 11.35 ppm (1H, s). Found: C 58.6; H 7.2; N 15.4%. $C_9H_{13}ClN_2$. Calculated: C 58.5; H 7.1; N 15.2%.

3-Methyl-5-cyclopropyl-4-(2-chloroethyl)isoxazole (XI). This compound was obtained by method C. The reaction of 1 g (6.6 mmole) of diketone III and 0.45 g of hydroxylamine hydrochloride in 50 ml of water for 15 h gave 0.77 g (63%) of isoxazole XI with bp 105°C (2 mm) and n_D^{20} 1.5070. PMR spectrum ($CDCl_3$): 1.07 (4H, m), 1.90 (1H, m), 2.30 (3H, s), 2.88 (2H, t, J = 7.5 Hz), and 3.65 ppm (2H, t, J = 7.5 Hz). Found: C 58.2; H 6.8%. $C_9H_{12}ClNO$. Calculated: C 58.2; H 7.5%.

E-1-(1-Oximinoethyl)-1-(cyclopropanylcarbonyl)cyclopropane (XIa). This compound was obtained by a method similar to that used to prepare isoxazole XI, but the reaction was stopped after 5 h, and the reaction product was isolated by means of preparative TLC [R_f 0.68; acetone–chloroform (1:3)]. From the same amounts of starting substances we obtained 0.6 g (55%) of oxime XIa with mp 71-72°C (from hexane). IR spectrum: 1650 (C=N), 1670 (C=O), and 3420 cm^{-1} (OH). PMR spectrum (CCl_4): 1.0 (4H, m), 1.30 (4H, m), 1.90 (1H, m), 2.04 (3H, s), and 9.60 ppm (1H, s). Found C 64.4; H 7.8; N 8.4%. $C_9H_{13}NO_2$. Calculated C 64.6; H 7.8; N 8.4%. A drop of concentrated HCl was added to an ampul containing a sample of oxime XIa, and the ampul was shaken several times. Repeated recording of the MPR spectrum established the quantitative formation of isoxazole XI.

3-Methyl-5-(2-pyridylcarbonyl)-4-(2-chloroethyl)isoxazole (XII). This compound was obtained by method C, but the reaction mixture was made alkaline with a saturated solution of potassium carbonate. The reaction of 3 g (0.016 mole) of diketone IV and 1.1 g of hydroxylamine hydrochloride in 100 ml of water for 8 h gave 2.3 g (64%) of isoxazole XII with mp 57-

58°C (from hexane). PMR spectrum ($CDCl_3$): 2.33 (3H, s), 3.23 (2H, t, J = 6.5 Hz), 3.80 (2H, t, J = 6.5 Hz), and 7.07-7.93 ppm (4H, m). Found: C 58.9; H 5.0; N 12.5%. $C_{11}H_{11}ClN_2O$. Calculated: C 59.3; H 5.0; N 12.6%.

3-Methyl-5-(2-pyridyl)-4-(2-chloroethyl)pyrazole Hydrochloride (XIIIa). A mixture of 3 g (0.016 mole) of diketone IV, 1.08 g (0.016 mole) of hydrazine hydrochloride, and 1.68 ml of 30% hydrochloric acid in 100 ml of ethanol was stirred for 8 h, after which the bulk of the solvent was removed by distillation, and the residue was treated with hexane to precipitate 2.4 g (58%) of salt XIIIa with mp 235-238°C (dec.). PMR spectrum (CD_3OD): 2.38 (3H, s), 3.06 (2H, t, J = 6.5 Hz), 4.96 (2H, t, J = 6.5 Hz), and 7.93-8.60 ppm (4H, m). Found: C 51.6; H 4.7% $C_{11}H_{12}ClN_3 \cdot HCl$. Calculated: C 51.2; H 5.1%. Free base XIII was obtained in 80% yield by treatment of salt XIIIa with a 10% solution of KOH in ethanol; the base had mp 42-43°C (from hexane). PMR spectrum ($CDCl_3$) 1.86 (3H, s), 3.27 (2H, t, J = 9.5 Hz), 4.50 (2H, t, J = 9.5 Hz), 7.20-7.80 (4H, m), and 12.40 ppm (1H, s).

3,5-Dimethyl-4-(2-ethoxypropyl)pyrazole (XVI). This compound was obtained by method A. The reaction of 5 g (0.036 mole) of diketone V and 1.75 g of hydrazine hydrate in 150 ml of ethanol for 7 h gave 3.2 g (49%) of pyrazole XIV with bp 128-130°C (2.5 mm) and n_D^{20} 1.4920. PMR spectrum ($CDCl_3$): 1.09 (3H, d, J = 6.2 Hz), 1.16 (3H, t, J = 7 Hz), 2.23 (6H, s), 2.30-2.80 (2H, m, ABX, ν_A = 2.38, ν_B = 2.66, J_{AB} = −14.25 Hz, J_{AX} = 7.07 Hz, and J_{BX} = 5.94 Hz), 3.46 (2H, q, J = 7 Hz), 3.40-3.66 (1H, m), and 10.77 ppm (1H, s). Found: C 65.8; H 9.8%. $C_{10}H_{18}N_2O$. Calculated: C 65.9; H 9.9%.

3.5-Dimethyl-4-(2-chloropropyl)pyrazole (XIV). This compound was obtained by method A. The reaction of 5 g (0.032 mole) of diketone V and 2.47 g of hydrazine hydrochloride in 150 ml of ethanol for 8 h gave 3.1 g (50%) of pyrazole XV with bp 123-125°C (3 mm) and n_D^{20} 1.5070. PMR spectrum ($CDCl_3$): 1.44 (3H, d, J = 7 Hz), 2.23 (6H, s), 2.70-2.95 (2H, m, ABX, ν_A = 2.88, ν_B = 2.92, J_{AB} = 0.5 Hz, J_{AX} = 7.6 Hz, and J_{BX} = 9.4 Hz), 3.90-4.23 (1H, m), and 12.43 ppm (1H, s). Found: C 55.5; H 7.8%. $C_8H_{12}ClN_2$. Calculated: C 55.6; H 7.5%.

1-Acetyl-1-carbethoxycyclopropane Oxime (VIa). This compound, with mp 76-77°C (from benzene), was obtained in 80% yield by method B. PMR spectrum ($CDCl_3$): 1.0-1.5 (7H, m from t, 3H, J = 7 Hz, and m, 4H), 2.0 (3H, s), 4.15 (2H, q, J = 7 Hz), and 8.73 ppm (1H, s) [11].

3-Ethoxy-5-methyl-4-(2-chloroethyl)pyrazole Hydrochloride (XVIa). This compound was obtained by method A. The reaction of 5 g (0.032 mole) of diketone VI, 2.19 g of hydrazine hydrochloride, and 3.36 ml of 30% hydrochloric acid in 150 ml of ethanol for 3 h gave 5 g (70%) of salt XVIa with mp 156-157°C (from acetone). PMR spectrum ($CDCl_3$): 1.50 (3H, t, J = 7 Hz), 2.48 (3H, s), 2.83 (2H, t, J = 6 Hz), 3.67 (2H, t, J = 6 Hz), 4.57 (2H, q, J = 7 Hz), and 12.35 ppm (2H, s). Found: C 42.6; H 6.3; N 12.4%. $C_8H_{13}ClN_2O \cdot HCl$. Calculated: C 42.7; H 6.2; N 12.4%. Free base XVI was obtained by treatment of XVIa with a 10% solution of KOH in ethanol; the base was obtained in 95% yield and had mp 94-96°C (from hexane). PMR spectrum (CCl_4): 1.37 (3H, t, J = 7.5 Hz), 2.13 (3H, s), 2.70 (2H, t, J = 7 Hz), 3.60 (2H, t, J = 7 Hz), 4.27 (2H, q, J = 7.5 Hz), and 11.65 ppm (1H, s). Found: 50.8; H 6.9; N 15.4%. $C_8H_{13}ClN_2O$. Calculated: C 50.8; H 6.9; N 14.8%.

3,5-Dimethylisopyrazole-4-spirocyclopentane (XVIIa). This compound was obtained by method A. The reaction of 4.15 g (0.027 mole) of diketone VII and 1.85 g of hydrazine hydrochloride in 200 ml of ethanol for 20 h gave 3.73 g (74%) of salt XVIIa with mp 166-167°C (from acetonitrile). PMR spectrum (CD_3OD): 2.17 (8H, m) and 2.50 ppm (6H, s). Free base XVII was obtained by treatment of salt XVIIa with a10% solution of KOH in water with subsequent extraction with ether; the base was obtained in 93% yield. The base was also obtained by method A from 4.15 g (0.027 mole) of diketone VII and 1.36 g of hydrazine hydrate in 200 ml of ethanol after 10 h [3.48 g (86%)]. The base had mp 111-112°C (from hexane). PMR spectrum ($CHCl_3$) 1.87 (8H, m) and 2.13 ppm (6H, s). IR spectrum: 1590 cm^{-1} (C=N). Found: C 71.9; H 9.2; N 18.7%. $C_9H_{14}N_2$. Calculated: C 72.0; H 9.3; N 18.7%.

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REACTIONS OF 4,5-DINITROIMIDAZOLE AND 4(5)-NITROIMIDAZOLE-5(4)-SULFONIC ACID WITH NUCLEOPHILES

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The reactions of 4,5-dinitroimidazole and 5(4)-nitroimidazole-4(5)-sulfonic acid with nucleophilic agents were studied. Mercapto-, alkoxy-, and aminonitroimidazoles were synthesized. In the reaction of dinitroimidazole with sodium alkoxides 5(4)-nitroimidazole was obtained in addition to alkoxynitroimidazoles. It is shown that in the formation of salts of the starting imidazoles with bases nucleophilic-substitution reactions take place only with "soft" reagents.

The aim of the present research was to study the reactivities of 4,5-dinitroimidazole (I) and 4(5)-nitroimidazole-5(4)-sulfonic acid (II) in nucleophilic-substitution reactions.

As in the case of 4(5)-bromo-5(4) nitroimidazole (III) [1], 4(5)-mercapto-5(4)-nitroimidazole (IV) is formed in almost quantitative yield in the reaction of dinitroimidazole I with sodium sulfide at room temperature. At the same time, in contrast to imidazole III [2], I reacts with sodium sulfite even at room temperature to give sodium 4(5)-nitroimidazole-5(4)-sulfonate (II). Under the same conditions 4(5)-ethoxy- (VI) and 4(5)-methoxy-5(4)nitroimidazole (V) were obtained from imidazole I with sodium ethoxide and methoxide in the corresponding alcohol. It should be noted that, in addition to V and VI, we also isolated 4(5)-nitroimidazole (VII). By means of PMR spectroscopy we found that the ratio of imidazoles VI and VII in the reaction mixture prior to crystallization is 9:1. The formation of nitroimidazole VII constitutes indirect evidence for an anion-radical mechanism for this reaction. The reaction of dinitroimidazole I with aqueous alkali without heating leads to destruction of the imidazole ring. Compound I does not react with "harder" anionic nucleophiles such as sodium azide, acetate, and phenoxide in water, alcohol, and dimethylformamide (DMF) even at elevated temperatures. Attempts to carry out the reaction of the ammonium salt of imidazole I with potassium thiocyanate in water were also unsuccessful. However, bis[5(4)-nitro-4(5)-imidazolyl]disulfide (VIII) was obtained from dinitro compound I in the reaction with potassium thiocyanate in dilute sulfuric acid. The 4(5)-nitro-5(4)thiocyanatoimidazole formed under these conditions probably undergoes decomposition, since cyanogen is liberated during the process.

Methylamine and dimethylamine react with I in the same way as strong anionic nucleophiles and 4(5)-methylamino- (IX) and 4(5)-dimethylamino-5(4)-nitroimidazole (XII). The reaction of ammonia and aniline takes place only at 70-100°C to give 4(5)-amino- (XI) and 4(5)-phenylamino-5(4)-nitroimidazole (XII). The reaction of dinitroimidazole I with an equimolar amount of hydrazine hydrate in both water and alcohol proceeds very vigorously even with cooling. Four to five unidentified compounds with close chromatographic mobilities were detected in

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