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STRUCTURE OF CYANOETHYLATION PRODUCTS OF 1,2,3-TRIAZOLECARBOXYLIC ACID DERIVATIVES

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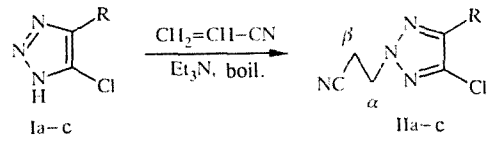
The cyanoethylation of derivatives of 5-chloro-1,2,3-triazolecarboxylic acids was studied, and it was shown by mass spectrometry and ^1H NMR spectroscopy that the only products of this reaction are 2-N-cyanoethyl derivatives.

It is known that 1,2,3-triazole derivatives are capable of engaging in addition reactions with such unsaturated compounds as acrylonitrile, acrylic acid and its esters, acetylene and its derivatives, as well as with benzalacetone and benzalacetophenone [1]. In this case, as a rule, depending on the nature of the initial reagents and the reaction conditions, isomeric $N_{(1)}$, $N_{(2)}$, $N_{(3)}$ derivatives of triazole are formed [1-3]. Alkylation or arylation of compounds of the 1,2,3-triazole series also proceeds ambiguously [2-4]. On the basis of these facts, the result of the cyanoethylation of derivatives of 5-chloro-1,2,3-triazolecarboxylic acid, for which we had previously developed a preparatively convenient method of synthesis [5], did not seem obvious.

As a rule, establishing the structure of products of N-substitution of 1,2,3-triazoles is a complex problem, and its solution requires the enlistment of various physicochemical methods, including the most modern. Thus, for example, in a study of the glycosylation of 1,2,3-triazole derivatives Ia, b, only with the aid of high-resolution mass spectrometry were the reaction products assigned the structure of $N_{(2)}$ derivatives, and not $N_{(1)}$ derivatives, as had been erroneously established earlier [6, 7].

The production of N-cyanoethyl derivatives of 1,2,3-triazoles Ia-c may be of practical interest, since it is known that 1-alkyl(aryl)-5-chloro-1,2,3-triazoles, in contrast to the N–H, $N_{(2)}$, and $N_{(3)}$ derivatives, are capable of entering into a nucleophilic substitution of the chlorine atom [6, 8, 9]. On the other hand, transformation of the substituent in the 4-position of the triazole ring cannot be accomplished for N–H derivatives in a number of cases [6, 8-11]. Thus, the introduction of a cyanoethyl group into the triazole ring permits us to hope for obtaining a broad spectrum of 4,5-derivatives of this heterocyclic system by transformation of substituents already in these positions.

In a study of the cyanoethylation of derivatives of 5-chloro-1,2,3-triazolecarboxylic acids (Ia-c), we found that the best yields of the cyanoethyl derivatives IIa-c are observed when compounds Ia-c are heated in an excess of acrylonitrile without an organic solvent in the presence of triethylamine.



I, II a R = COOMe, b R = CN, c R = $CONH_2$

According to the data of thin-layer chromatography and PMR spectroscopy it was established that as a result of the cyanoethylation, individual substances are formed, and not a mixture of isomers, as might have been expected on the basis of the literature data mentioned above. The chromatograms of compounds IIa-c, obtained using chromatographic systems with various polarity, contain only one spot, and the PMR spectra contain only one set of signals.

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TABLE 1. Mass Spectra of Compounds Ia-c and IIa-c

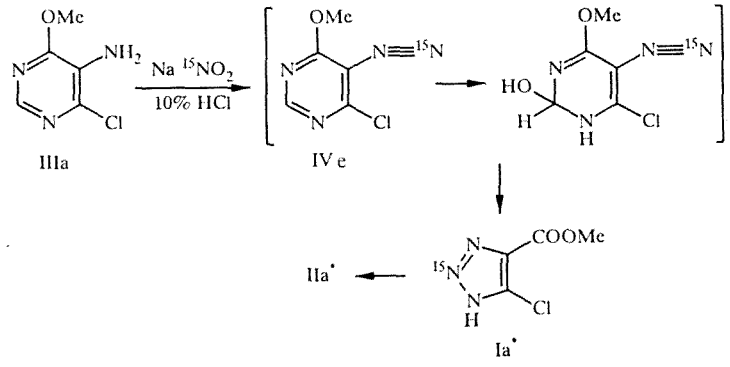
Compound	Value of *m/z* (intensity of the peaks of the ions in % of the maximum)*
Ia	163(7), 161(23), 133(18), 132(35), 131(59), 130(100), 105(4), 103(6), 102(3), 90(5), 78(2), 76(9), 74(12), 73(3), 63(3), 62(3), 59(6)
Ia*	164(8), 162(23), 134(12), 133(29), 132(41), 131(100), 105(7), 104(7), 102(3), 92(3), 90(11), 79(2), 77(5), 76(11), 75(5), 74(39), 63(6), 62(7), 59(25)
Ib	130(31), 128(100), 101(4), 100(3), 99(9), 78(8), 76(23), 75(8), 73(26), 67(8), 64(8), 62(3)
Ic	148(26), 146(80), 132(29), 130(100), 111(6), 91(3), 90(5), 77(10), 76(19), 75(35), 74(29), 63(16)
IIa	216(10), 215(4), 214(28), 186(6), 185(32), 184(19), 183(91), 176(33), 174(100), 156(6), 130(5), 116(5), 89(4), 74(5), 62(3), 59(10)
IIa*	217(8), 215(27), 187(5), 186(30), 185(17), 184(100), 177(34), 175(92), 157(5), 131(8), 117(5), 92(3), 90(10), 76(4), 74(12), 62(8), 59(25)
IIb	183(6), 181(20), 143(31), 141(100), 89(5), 88(4), 86(11), 73(3), 64(3), 62(6), 54(5)
IIc	201(16), 199(53), 185(21), 183(62), 161(33), 159(100), 130(6), 118(3), 116(11), 102(3), 89(7), 76(3), 74(5), 62(3), 54(4)

*Mass numbers of the ions whose $i_{rel} > 2$ are shown.

TABLE 2. PMR Spectra of Compounds Ia, IIa-c in $CDCl_3$

Compound	Chemical shift, δ (ppm), J (Hz)
Ia	4,06 (COOMe, s, 3H), 13,10 (NH, br. s, 1H)
IIa	3,98 (COOMe, s, 3H), 3,10 (β-CH_2, t, 2H), 4,73 (α-CH_2, t, 2H, $^3J_{\alpha\text{-}CH_2,\beta\text{-}CH_2} = 7,0$)
IIb	3,11 (β-CH_2, t, 2H, $^3J_{\alpha\text{-}CH_2,\beta\text{-}CH_2} = 6,7$), 4,75 ($\alpha$-$CH_2$, t, 2H)
IIc	3,08 (β-CH_2, t, 2H, $^3J_{\alpha\text{-}CH_2,\beta\text{-}CH_2} = 6,8$), 4,68 ($\alpha$-$CH_2$, t, 2H), 5,60, 6,72 ($NH_2$, br.s. 1H each)

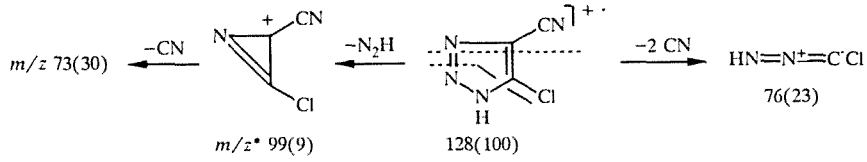
For a more reliable establishment of the structure of N-cyanoethyl derivatives IIa-c we synthesized model compounds Ia* and IIa*, containing the label (^{15}N) in the heterocyclic ring. In this case, in view of the terminal position of the labeled N atom in the intermediate diazopyrimidine IV, its recyclization product Ia should have contained the label in the 2-position of the thiazole ring.



*Here and below the mass numbers of the ions containing the ^{35}Cl isotope are indicated for the chlorine-containing fragments.

The structure of the synthesized cyanoethyl derivatives IIa-c was established by a combination of methods of mass spectrometry and PMR spectroscopy.

In the interpretation of the mass spectra of compounds IIa-c we used data on the mass spectrometric fragmentation of the original thiazoles Ia-c, as well as model compounds Ia* and IIa*, which contain the isotope ^{15}N in the 2-position of the ring. In the spectra of Ia and Ic, the most intense peaks belong to the ions whose formation involves a stepwise stripping of substituents in the 4-position of the triazole ring (Table 1). In the spectrum of Ib the maximum peak belong to the molecular ion. An important general feature of the spectra of these compounds is the presence of the peaks of chlorine-containing ions, the appearance of which is due to breaking of bonds in the triazole ring, as shown below on the example of compound Ib.



In the spectra of compounds Ia and Ic, instead of the ion with *m/z* 73 the ion 74, formed from the ion $[M-(X-H)]^+$, is observed. In the spectrum of compound Ia* there is no increase of the ion 74 by a unit mass number, which is evidence that it does not contain the $N_{(2)}$ nitrogen atom. Thus, this ion is formed as a result of stripping of $N_{(2)}$ from the triazole ring, and one of the nitrogen atoms eliminated is $N_{(2)}$. On the basis of the structure of the triazole ring, such elimination can occur in two ways: by cleavage of the bonds 2-3 and 5-1 or cleavage of the bonds 1-2 and 3-4, respectively. This indeterminacy hinders the use of this type of fragmentation in the determination of the site of cyanoethylation in the compounds IIa-c.

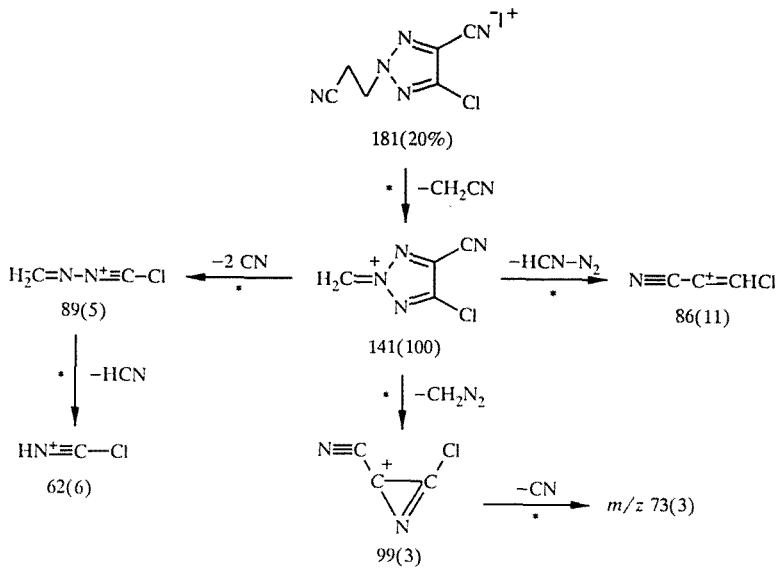
In contrast to the ion 74, the ion 76 contains the nitrogen atom $N_{(2)}$. This is indicated by the appearance of the peak of the chlorine-containing ion 77† in the spectrum of peak Ia*. From the intensity ratio of the isotopic peak it follows that the ion under consideration contains a Cl atom, and the mass number of this ion does not depend on the substituent R in the 4-position of the ring. This permits us to assert that the ion 76 is formed in cleavage of the 2-3 and 4-5 bonds, and it contains not only the $N_{(2)}$ atom but also the $N_{(1)}$ atom.

In the spectra of cyanoethyl derivatives IIa-c, a specific decay associated with the elimination of the CH_2CN group from the molecular ion is observed. The peak with maximum intensity belongs to the fragment formed in this case. Despite the fact that further breakdown of the ion $[M-CH_2CN]^+$ for each of the compounds under consideration is determined to a substantial degree by the nature of the substituent R in the 4-position of the ring, the directions of cleavage of the bonds of the 1,2,3-triazole ring indicated above are retained in the spectra of IIa-c, which permits us to draw a conclusion on the site of addition of the cyanoethyl substituent.

The sequence of breakdown of compounds IIa-c was established by methods of direct analysis of the daughter ions (DADI) and metastable defocusing in the first field-free space, as well as in a comparison of the spectra of compound IIa and its labeled analog IIa*. It was established in this case that in all the spectra the peak of the chlorine-containing fragment *m/z* 89 $[CH_2{=}N{-}N{\equiv}C{-}Cl]^+$, which is formed directly in the breakdown of the ion $[M-CH_2CN]^+$, is observed. (In the case of compounds IIa and IIc, in addition to the pathway examined, the ion 89 is also formed by the elimination of HCN from the ion $[M-CH_2CN-(X-H)]^+$). The nitrogen atom $N_{(2)}$ is contained in the ion 89, since the ion 90 appears instead of the ion 89 in the spectrum of IIa* (see Table 1). Consequently, the formation of the ion 89 is due to cleavage of the 2-3 and 4-5 bonds of the triazole ring, which is analogous to the formation of the ion 76 in the spectra of the original compounds Ia-c. Such fragmentation unambiguously rules out the presence of a cyanoethyl substituent at the nitrogen atom $N_{(3)}$.

Further breakdown of the ion 89, according to the DADI spectra, proceeds with elimination of HCN ($HC^{15}N$ in the case of IIa*), on the basis of which the presence of a cyanoethyl substituent at the $N_{(1)}$ atom may be considered relatively improbable. Thus, it is evident that cyanoethylation proceeded at the 2-position of the thiazole ring. A scheme of the basic pathways of fragmentation of compounds IIa-c, examined on the example of IIb, is presented below:

†The ion 76 observed in the spectrum of Ia* is isotopic to the ion 74 and contains the isotope ^{37}Cl.



The structure of the cyanoethyl derivatives of 1,2,3-triazole IIa-c was confirmed by the data of PMR spectroscopy.

In the PMR spectra of compounds Ia and Ia*, taken in $CDCl_3$, the NH proton is represented by a greatly broadened signal at 13.10 ppm. The broadening of the signal may be due both to intramolecular (of the type of $NH_{(1)} \rightleftarrows NH_{(2)} \rightleftarrows N_{(3)}$), and to intermolecular exchange processes.

For cyanoethyl derivatives IIa-c, the PMR spectra are characterized by the presence of two triplets in the region of 4.68-4.75 and 3.08-3.11 ppm, belonging to the α- and β-protons of the cyanoethyl fragment, respectively ($^3J_{\alpha\text{-}CH_2}$, $\beta\text{-}_{CH_2}$ ~6.7-7.0 Hz).

A confirmation of the conclusion on the position of the cyanoethyl fragment in compounds IIa-c at $N_{(2)}$ of the triazole ring, drawn on the basis of the data of mass spectrometry, was obtained in an examination of the PMR spectrum of the labeled compound IIa*, for which both triplets, corresponding to the protons of the cyanoethyl fragment, are additionally broadened on account of spin-spin coupling with the heteroatom $^{15}N_{(2)}$ with $^2J_{^{15}NH}$ = 2.1 Hz for the α-CH_2 protons (4.73 ppm) and $^3J_{^{15}NH}$ = 3.0 Hz for the β-CH_2 protons (3.10 ppm). The observed values of the heteroconstants $^2J_{^{15}NH}$ and $^3J_{^{15}NH}$ are typical of aliphatic compounds [12]. In the case of a different arrangement of the cyanoethyl fragment in compounds IIa-c (namely, at the $N_{(1)}$ or $N_{(2)}$ atoms), spin-spin coupling between $^{15}N_{(2)}$ and the β-CH_2 protons should have been extremely negligible ($^4J_{^{15}NH\text{-}\beta\text{-}CH2}$ ~0) [12].

Thus, the cyanoethylation of derivatives of 5-chloro-1,2,3-thiazolecarboxylic acids was studied, and it was shown by mass spectrometry and PMR spectroscopy that the only products of this reaction are 2-N-cyanoethyl derivatives.

EXPERIMENTAL

The purity of the compounds was monitored by thin-layer chromatography on Silufol UV-254 plates (Czechoslovakia), eluent chloroform–methanol, 10:1. The mass spectra were obtained on a Varian MAT-112 mass spectrometer with direct introduction of the sample into the ion source. The energy of the ionizing electrons was 70 eV. Temperature of the ionization chamber 180°C. The PMR spectra were recorded on a Varian XL-200 spectrometer, internal standard TMS. The IR spectra were taken on a Perkin–Elmer spectrophotometer in suspension in liquid petrolatum.

The data of elementary analysis of compounds Ic, IIa-c for C, H, and N correspond to the calculated values.

The initial compounds Ia,b were synthesized according to the procedure of [5].

4-Carbamoyl-5-chloro-1,2,3-triazole (Ic, $C_3H_3ClN_4O$). To a solution of 0.5 g (3.89 mmoles) 4-cyano-5-chloro-1,2,3-triazole (Ib) in aqueous alkali, obtained by dissolving 0.42 g (7.5 mmoles) KOH in 30 ml of water, we added 7 ml of 30% hydrogen peroxide. The reaction mixture was left at room temperature for 48 h, shaking periodically, then acidified with conc. HCl to pH 1. The precipitate formed was filtered off and washed with ice water. After evaporation of the reaction mass and

treatment of the solid residue with boiling acetone, an additional amount of the product was obtained. The total yield was 0.54 g (95%) Ic in the form of a white crystalline substance. mp (dec.) 198-202°C (from acetone with hexane, 3:1). Literature mp 198-200°C [13]. M^+· 146. M 146. IR spectrum: 3480, 3280, 3220, 3120 (NH_2, NH); 1694 (amide); 1600 cm^{-1}.

2-(2-Cyanoethyl)-4-methoxycarbonyl-5-chloro-1,2,3-triazole (IIa, $C_7H_7ClN_4O_2$). A mixture of 1 g (6 mmoles) of 4-methoxycarbonyl-5-chloro-1,2,3-triazole (Ia), 10 ml acrylonitrile, and three drops of triethylamine was boiled on a water bath for 40 min, the reaction mass was evaporated, the oily residue was treated with boiling hexane, and we obtained 1.4 g (97.8%) of a white crystalline product IIa. mp 84-86°C (from methanol). M^+· 214. M 214. IR spectrum: 2250 (CN), 1730 (COOMe) cm^{-1}.

2-(2-Cyanoethyl)-4-cyano-5-chloro-1,2,3-triazole (IIb, $C_6H_4ClN_5$). A mixture of 1 g (6.8 mmoles) 4-cyano-5-chloro-1,2,3-triazole (Ib), 10 ml acrylonitrile, and three drops of triethylamine was heated on a boiling water bath for 3 h, monitoring the decrease in the content of Ic by thin-layer chromatography. Then the reaction mass was evaporated, the oily residue was dissolved in 20 ml of ethyl acetate, and it was washed with a 10% solution of $NaHCO_3$. After the ethyl acetate solution was dried with $MgSO_4$, it was evaporated, and 1.3 g (92%) of compound IIb was obtained in the form of a yellowish, strongly light-refracting oil, which was purified by column chromatography on SiO_2 (column diameter 30 mm, 30 g of silica gel, fraction 40-100 μk), eluent chloroform–methanol, 10:1. n_D^{20} 1.5128. M^+ 181. M 181. IR spectrum: 2272 (CN) cm^{-1}.

2-(2-Cyanoethyl)-4-carbamoyl-5-chloro-1,2,3-triazole (IIc, $C_6H_6ClN_5O$). A mixture of 0.9 g (7 mmoles) 4-carbamoyl-5-chloro-1,2,3-triazole (Ic), 15 ml acrylonitrile, and three drops of triethylamine was heated on a boiling water bath for 2.5 h. After the reaction mass was cooled to +5°C, a precipitate formed. Yield 1.0 g (81.6%) of the white crystalline compound IIc. mp 159-160°C (from methanol). M^+· 199. M 199. IR spectrum: 3450, 3340, 3284, 3160 (NH_2), 2248 (CN), 1675, 1612 ($CONH_2$) cm^{-1}.

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