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# A Study of Alkylation Regioselectivity of 5-Substituted Tetrazoles with Chloroacetamides

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**Abstract**—Alkylation of 5-aryltetrazoles with *N*-arylchloroacetamides commonly proceeds regioselectively at 2 position of the tetrazole ring. The ratio of 1,5- and 2,5-regioisomers depends on the nature of a substituents in the benzene ring of the *N*-arylchloroacetamide and position of a substituent in the aryltetrazole aryl group. Features of $^1$H NMR spectra of the synthesized compounds are discussed.

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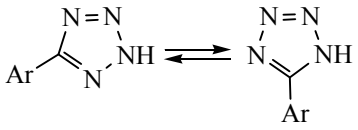
Tetrazole derivatives are used as drugs [1], are applied in biochemistry [2–4] and agriculture [5, 6], as well as in designing materials for the systems for the registration of information [7]. Many compounds of this class show biological activity of a wide range [8–15]. Recently methods were developed for the targeted synthesis of biologically active compounds containing tetrazol-5-ylalkyl fragment [16].

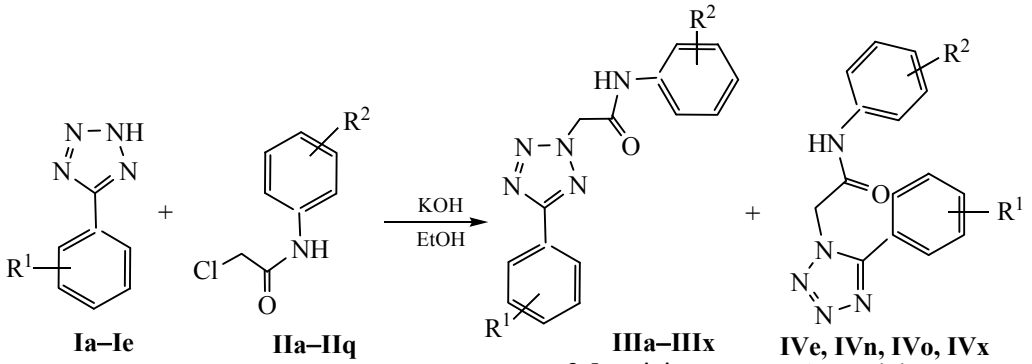
2-Substituted and 2,5-disubstituted tetrazoles remain poorly studied compounds because of the lack of available methods for their synthesis [17–19]. These compounds are prepared, in general, by alkylation of tetrazole or 5-substituted tetrazoles. Note however, that due to the prototropic tautomerism characteristic of C-substituted tetrazoles these reactions can proceed by two pathways leading to the formation of either 1,5- or 2,5-disubstituted regioisomers [12–15, 20–24]:



The dependence of the direction of the tetrazoles alkylation on the nature of the reagents and the environment was poorly described in the literature. In this work we investigated the regioselectivity of alkylation of 5-substituted tetrazoles with chloroacetamides. We studied a reaction of a series of aryltetrazoles **Ia–Ie** containing substituents of different nature in the *ortho*- and *para*-position of the aryl fragment, with *N*-arylchloroacetamides (**IIa–IIc**) in ethanol in the presence of KOH leading to the formation of compounds **III** and **IV**.

The reaction mixture was refluxed for 5 h, and the crude products were analyzed by $^1$H NMR spectroscopy. In most cases only 2,5-regioisomers **III** were formed. Their formation is associated probably with the steric hindrances to the alkylation of tetrazole ring at 1 position. This was confirmed, in particular, by the absence of 1,5-regioisomers at the use of *ortho*-methyl- and *ortho*-chloro-phenyltetrazoles **Ib** and **Id**, although in these cases the yield of 2,5-regioisomers was also reduced. Besides according to quantum-chemical calculations and mass spectra, 2-H tautomer of 5-substituted tetrazole is more stable than 1-H tautomer, at least in the gas phase [25–28]. In the case of chloroacetamides **IIk, IIl, IIn,** and **IIo** containing an electron-withdrawing substituent in the aromatic ring the regioselectivity decreased due to the increased reactivity of these compounds. The minor product, 1,5-regioisomer, was obtained with the highest yield at the alkylation of tetrazole **Ic** with chloroacetamide **IIo** containing two chlorine atoms in the ring. Tetrazoles **Ib** and **Id** owing to the steric hindrances caused by the substituent in the *ortho*-position to the tetrazole ring formed at the alkylation only the 2,5-disubstituted isomers regardless of the nature of $R^2$ in compounds **IIb, IId, IIh–IIj, IIm,** and **IIp** (Table 1).

In the $^1$H NMR spectra of regioisomeric mixtures (Table 2, Fig. 1) the signals of compounds **IVe, IVn, IVo,** and **IVx** are shifted upfield as compared with the




**I**, $R^1$ = H (**a**), 2-Me (**b**), 4-Me (**c**), 2-Cl (**d**), 4-Cl (**e**); **II**, $R^2$ = H (**a**), 2-Me (**b**), 3-Me (**c**), 4-Me (**d**), 2,6-$Me_2$ (**e**), 3,4-$Me_2$ (**f**), 2-OMe (**g**), 3-OMe (**h**), 4-OMe (**i**), 2-Me-3-Cl (**j**), 2-Me-5-Cl (**k**), 2-Cl (**l**), 3-Cl (**m**), 4-Cl (**n**), 2,5-$Cl_2$ (**o**), 3-Ac (**p**), 4-NHAc (**q**); **III,** $R^1 = R^2$ = H (**a**); $R^1$ = H, $R^2$ = 3-Me (**b**) ; $R^1$ = H, $R^2$ = 3,4-$Me_2$ (**c**); $R^1$ = H, $R^2$ = 2-OMe (**d**); $R^1$ = H, $R^2$ = 2-Me-5-Cl (**e**); $R^1$ = 2-Me, $R^2$ = 4-Me (**f**); $R^1$ = 2-Me, $R^2$ = 3-OMe (**g**); $R^1$ = 2-Me, $R^2$ = 4-OMe (**h**); $R^1$ = 2-Me, $R^2$ = 2-Me-3-Cl (**i**); $R^1$ = 2-Me, $R^2$ = 3-Cl (**j**); $R^1$ = 4-Me, $R^2$ = H (**k**); $R^1$ = 4-Me, $R^2$ = 2-Me (**l**); $R^1$ = 4-Me, $R^2$ = 3-OMe (**m**); $R^1$ = 4-Me, $R^2$ = 4-Cl (**n**); $R^1$ = 4-Me, $R^2$ = 2,5-$Cl_2$ (**o**); $R^1$ = 4-Me, $R^2$ = 4-NHAc (**p**); $R^1$ = 2-Cl, $R^2$ = 2-Me (**q**); $R^1$ = 2-Cl, $R^2$ = 4-Me (**r**); $R^1$ = 2-Cl, $R^2$ = 3-Al (**s**); $R^1$ = 4-Cl, $R^2$ = 2-Me (**t**); $R^1$ = 4-Cl, $R^2$ = 3-Me (**u**); $R^1$ = 4-Cl, $R^2$ = 4-Me (**v**); $R^1$ = 4-Cl, $R^2$ = 2,6-Me (**w**); $R^1$ = 4-Cl, $R^2$ = 2-Cl (**x**). **IV**, $R^1$ = H, $R^2$ = 2-Me-5-Cl (**e**); $R^1$ = 4-Me, $R^2$ = 4-Cl (**n**); $R^1$ = 4-Me, $R^2$ = 2,5-$Cl_2$ (**o**); $R^1$ = 4-Cl, $R^2$ = 2-Cl (**x**).

**Table 1.** The products yield and ratio of regioisomers **III** and **IV**

| Reagents | | $R^1$ | $R^2$ | Ratio of regioisomers in the products[a], % | | Total yield **III** + **IV**, % |
|---|---|---|---|---|---|---|
| tetrazole | chloroacetanilide | | | **III** | **IV** | |
| **Ia** | **IIa** | H | H | 100 | – | 74 |
| **Ia** | **IIc** | H | 3-Me | 100 | – | 70 |
| **Ia** | **IIf** | H | 3,4-$Me_2$ | 100 | – | 75 |
| **Ia** | **IIg** | H | 2-OMe | 100 | – | 56 |
| **Ia** | **IIk** | H | 2-Me-5-Cl | 93 | 7 | 71 |
| **Ib** | **IId** | 2-Me | 4-Me | 100 | – | 75 |
| **Ib** | **IIh** | 2-Me | 3-OMe | 100 | – | 68 |
| **Ib** | **IIi** | 2-Me | 4-OMe | 100 | – | 71 |
| **Ib** | **IIj** | 2-Me | 2-Me-3-Cl | 100 | – | 66 |
| **Ib** | **IIi** | 2-Me | 3-Cl | 100 | – | 45 |
| **Ic** | **IIa** | 4-Me | H | 100 | – | 78 |
| **Ic** | **IIb** | 4-Me | 2-Me | 100 | – | 61 |
| **Ic** | **IIh** | 4-Me | 3-OMe | 100 | – | 69 |
| **Ic** | **IIn** | 4-Me | 4-Cl | 92 | 8 | 77 |
| **Ic** | **IIo** | 4-Me | 2,5-$Cl_2$ | 84 | 16 | 72 |
| **Ic** | **IIq** | 4-Me | 4-NHAc | 100 | – | 81 |
| **Id** | **IIb** | 2-Cl | 2-Me | 100 | | 45 |
| **Id** | **IId** | 2-Cl | 4-Me | 100 | | 63 |
| **Id** | **IIp** | 2-Cl | 3-Ac | 100 | | 55 |
| **Ie** | **IIb** | 4-Cl | 2-Me | 100 | – | 63 |
| **Ie** | **IIc** | 4-Cl | 3-Me | 100 | – | 71 |
| **Ie** | **IId** | 4-Cl | 4-Me | 100 | – | 76 |
| **Ie** | **IIe** | 4-Cl | 2,6-$Me_2$ | 100 | – | 34 |
| **Ie** | **III** | 4-Cl | 2-Cl | 93 | 7 | 49 |

[a] Ratio of isomers is determined from the $^1$H NMR spectra of crude mixture.

**Table 2.** Data of $^1$H NMR spectra of compounds **III** and **IV**

| Comp. no. | $R^1$ | $R^2$ | $^1$H NMR chemical shifts, δ, ppm, $J$, Hz; solvent DMSO-$d_6$ | | | | |
|---|---|---|---|---|---|---|---|
| | | | $CH_3$ (s) | $CH_2$ (s) | Aryl fragment in chloroacetamide | Aryl fragment in tetrazole | NH (br.s) |
| **IIIa** | H | H | | 5.68 | 7.07 t (1H, 4-H, $^3J$ 7.8), 7.30 t (2H, 3,5-H, $^3J$ 7.8), 7.60 d (2H, 2,6-H, $^3J$ 7.8) | 7.48–7.56 m (3H, 3,4,5-H), 8.12 d.d (2H, 2,6-H, $^3J$ 7.8, $^4J$ 2.0) | 10.56 |
| **IIIb** | H | 3-Me | 2.33 | 5.66 | 6.88 d (1H, 4-H, $^3J$ 7.8), 7.17 t (1H, 5-H, $^3J$ 7.8), 7.41 d (1H, 6-H, $^3J$ 7.8), 7.43 s (1H, 2-H) | 7.48–7.56 m (3H, 3,4,5-H), 8.12 d.d (2H, 2,6-H, $^3J$ 7.8, $^4J$ 2.0) | 10.46 |
| **IIIc** | H | 3,4-$Me_2$ | 2.21, 2.23 | 5.64 | 7.03 d (1H, 5-H, $^3J$ 7.8), 7.30 d (1H, 6-H, $^3J$ 7.8), 7.36 s (1H, 2-H) | 7.46–7.56 m (3H, 3,4,5-H), 8.11 d (2H, 2,6-H, $^3J$ 7.8) | 10.37 |
| **IIId** | H | 2-OMe | 3.92 | 5.81 | 6.88 t (1H, 5-H, $^3J$ 7.8), 7.02 d (1H, 3-H, $^3J$ 7.8), 7.08 t (1H, 4-H, $^3J$ 7.8), 7.99 d (1H, 6-H, $^3J$ 7.8) | 7.46–7.56 m (3H, 3,4,5-H), 8.10 d.d (2H, 2,6-H, $^3J$ 7.8, $^4J$ 2.0) | 9.81 |
| **IIIe/ IVe** | H | 2-Me-5-Cl | 2.30/ 2.15 | 5.78/ 5.55 | 7.07 d (1H, 3-H, $^3J$ 7.8), 7.20 d (1H, 4-H, $^3J$ 7.8), 7.64 d (1H, 6-H, $^4J$ 1.6)/6.69 d (1H, 3-H, $^3J$ 7.8), 7.13 d (1H, 4-H, $^3J$ 7.8), 7.50 d (1H, 6-H, $^4J$ 1.6) | 7.48–7.56 m (3H, 3,4,5-H), 8.12 d.d (2H, 2,6-H, $^3J$ 7.8, $^4J$ 2.0)/ 7.48–7.56 m (3H, 3,4,5-H), 8.06 d.d (2H, 2,6-H, $^3J$ 7.8, $^4J$ 2.0) | 9.93/ 9.50 |
| **IIIf** | 2-Me | 4-Me | 2.31, 2.63 | 5.66 | 7.09 d (2H, 3,5-H, $^3J$ 7.8), 7.47 d (2H, 2,6-H, $^3J$ 7.8) | 7.30–7.40 m (3H, 3,4,5-H), 7.98 d (1H, 6-H) | 10.43 |
| **IIIg** | 2-Me | 3-OMe | 2.62, 3.74 | 5.68 | 6.61 d (1H, 4-H, $^3J$ 7.8), 7.09 d (1H, 6-H, $^3J$ 7.8), 7.18 t (1H, 5-H, $^3J$ 7.8), 7.29 s (1H, 2-H) | 7.31–7.40 m (3H, 3,4,5-H), 7.98 d (1H, 6-H) | 10.54 |
| **IIIh** | 2-Me | 4-OMe | 2.62, 3.64 | 5.64 | 6.83 d (2H, 3,5-H, $^3J$ 7.8), 7.50 d (2H, 2,6-H, $^3J$ 7.8) | 7.29–7.38 m (3H, 3,4,5-H), 7.96 d (1H, 6-H) | 10.42 |
| **IIIi** | 2-Me | 2-Me-3-Cl | 2.32, 2.63 | 5.74 | 7.16 t (1H, 5-H, $^3J$ 7.8), 7.24 d (1H, 4-H, $^3J$ 7.8), 7.41 d (1H, 6-H, $^3J$ 7.8) | 7.30–7.38 m (3H, 3,4,5-H), 7.98 d (1H, 6-H) | 10.10 |
| **IIIj** | 2-Me | 3-Cl | 2.62 | 5.71 | 7.07 d (1H, 4-H, $^3J$ 7.8), 7.30 t (1H, 5-H, $^3J$ 7.8), 7.47 d (1H, 6-H, $^3J$ 7.8), 7.77 s (1H, 2-H) | 7.32–7.40 m (3H, 3,4,5-H), 7.96 d (1H, 6-H) | 10.79 |
| **IIIk** | 4-Me | H | 2.43 | 5.65 | 7.06 t (1H, 4-H, $^3J$ 7.8), 7.31 t (2H, 3,5-H, $^3J$ 7.8), 7.29 d (2H, 2,6-H, $^3J$ 7.8) | 7.60 d (2H, 3,5-H, $^3J$ 7.8), 7.99 d (2H, 2,6-H, $^3J$ 7.8) | 10.52 |
| **IIIl** | 4-Me | 2-Me | 2.30, 2.42c | 5.69 | 7.07 t (1H, 4-H, $^3J$ 7.8), 7.13 t (1H, 5-H, $^3J$ 7.8), 7.19 d (1H, 3-H, $^3J$ 7.8), 7.48 d (1H, 6-H, $^3J$ 7.8) | 7.32 d (2H, 3,5-H, $^3J$ 7.8), 7.99 d (2H, 2,6-H, $^3J$ 7.8) | 9.83 |
| **IIIm** | 4-Me | 3-OMe | 2.41, 3.74 | 5.64 | 6.61 d.d (1H, 4-H, $^3J$ 7.8, $^4J$ 2.0), 7.08 d (1H, 6-H, $^3J$ 7.8), 7.18 t (1H, 5-H, $^3J$ 7.8), 7.28 s (1H, 2-H) | 7.32 d (2H, 3,5-H, $^3J$ 7.8), 7.97 d (2H, 2,6-H, $^3J$ 7.8) | 10.56 |
| **IIIn/ IVn** | 4-Me | 4-Cl | 2.41/ 2.37 | 5.67/ 5.05 | 7.29 d (2H, $^3J$ 7.8),7.32 d (2H, $^3J$ 7.8)/7.25 d (2H, $^3J$ 7.8), 7.30 d (2H, $^3J$ 7.8) | 7.62 d (2H, 3,5-H, $^3J$ 7.8), 7.97 d (2H, 2,6-H, $^3J$ 7.8)/7.62 d (2H, 3,5-H, $^3J$ 7.8), 7.91 d (2H, 2,6-H, $^3J$ 7.8) | 10.81/ 10.44 |
| **IIIo/ IVo** | 4-Me | 2,5-$Cl_2$ | 2.42/ 2.35 | 5.80/ 4.90 | 7.18 d.d (1H, 4-H, $^3J$ 7.8, $^4J$ 2.0), 7.46 d (1H, 3-H, $^3J$ 7.8), 7.99 s (1H, 6-H)/7.13 d.d (1H, 4-H, $^3J$ 7.8, $^4J$ 2.0), 7.46 d (1H, 3-H, $^3J$ 7.8), 7.99 s (1H, 6-H) | 7.32 d (2H, 3,5-H, $^3J$ 7.8), 7.98 d (2H, 2,6-H, $^3J$ 7.8)/7.28 d (2H, 3,5-H, $^3J$ 7.8), 7.94 d (2H, 2,6-H, $^3J$ 7.8) | 10.35 |
| **IIIp** | 4-Me | 4-NHAc | 2.02, 2.42 | 5.61 | 7.47 d (2H, $^3J$ 7.8), 7.52 d (2H, $^3J$ 7.8) | 7.32 d (2H, 3,5-H, $^3J$ 7.8), 7.98 d (2H, 2,6-H, $^3J$ 7.8) | 10.44, 9.75 s |

**Table 2.** (Contd.)

| Comp. no. | $R^1$ | $R^2$ | $^1$H NMR chemical shifts, δ, ppm, *J*, Hz; solvent DMSO-$d_6$ | | | | |
|---|---|---|---|---|---|---|---|
| | | | $CH_3$ (s) | $CH_2$ (s) | Aryl fragment in chloroacetamide | Aryl fragment in tetrazole | NH (br.s) |
| **IIIq** | 2-Cl | 2-Me | 2.30 | 5.76 | 7.08 t (1H, 4-$H_{NHAr}$, $^3J$ 7.8), 7.15 t (1H, 5-$H_{NHAr}$, $^3J$ 7.8), 7.19 d (1H, 3-$H_{NHAr}$, $^3J$ 7.8), 7.45–7.55 m (3H, 6-$H_{NHAr}$ + 4,5-$H_{Ar}$), 7.60 d (1H, 3-$H_{Ar}$, $^3J$ 7.8), 7.97 d.d (1H, 6-$H_{Ar}$, $^3J$ 7.8, $^4J$ 2.0) | | 9.85 |
| **IIIr** | 2-Cl | 4-Me | 2.37 | 5.70 | 7.09 d (2H, 3,5-H, $^3J$ 7.8), 7.46 d (2H, 2,6-H, $^3J$ 7.8) | 7.50–7.56 m (2H, 4,5-H), 7.60 d (1H, 3-H, $^3J$ 7.8), 7.97 d.d (1H, 6-H, $^3J$ 7.8, $^4J$ 2.0) | 10.48 |
| **IIIs** | 2-Cl | 3-As | 3.08 | 5.75 | 7.48–7.62 m (3H, 4,5-$H_{NHAr}$ + 4-$H_{Ar}$), 7.85 d (1H, 6-$H_{NHAr}$, $^3J$ 7.8), 8.17 s (1H, 2-$H_{NHAr}$), 7.66 d (1H, 3-$H_{Ar}$, $^3J$ 7.8), 7.44 t (1H, 5-$H_{Ar}$, $^3J$ 7.8), 7.96 d.d (1H, 6-$H_{Ar}$, $^3J$ 7.8, $^4J$ 2.0) | | 10.82 |
| **IIIt** | 4-Cl | 2-Me | 2.30 | 5.74 | 7.08 t (1H, 4-H, $^3J$ 7.8), 7.15 t (1H, 5-H, $^3J$ 7.8), 7.20 d (1H, 3-H, $^3J$ 7.8), 7.47 d (1H, 6-H, $^3J$ 7.8) | 7.56 d (2H, 3,5-H, $^3J$ 7.8), 8.11 d (2H, 2,6-H, $^3J$ 7.8) | 9.89 s |
| **IIIu** | 4-Cl | 3-Me | 2.32 | 5.67 | 6.88 d (1H, 4-H, $^3J$ 7.8), 7.17 t (1H, 5-H, $^3J$ 7.8), 7.36 d (1H, 6-H, $^3J$ 7.8), 7.42 s (1H, 2-H) | 7.56 d (2H, 3,5-H, $^3J$ 7.8), 8.11 d (2H, 2,6-H, $^3J$ 7.8) | 10.50 |
| **IIIv** | 4-Cl | 4-Me | 2.30 | 5.67 | 7.09 d (2H, 3,5-H, $^3J$ 7.8), 7.47 d (2H, 2,6-H, $^3J$ 7.8) | 7.55 d (2H, 3,5-H, $^3J$ 7.8), 8.10 d (2H, 2,6-H, $^3J$ 7.8) | 10.50 |
| **IIIw** | 4-Cl | 2,6-$Me_2$ | 2.23 | 5.72 | 7.02–7.10 m (3H) | 7.56 d (2H, 3,5-H, $^3J$ 7.8), 8.06 d (2H, 2,6-H, $^3J$ 7.8) | 9.87 |
| **IIIx/ IVx** | 4-Cl | 2-Cl | | 5.81/ 5.00 | 7.18 t (1H, 4-H, $^3J$ 7.8), 7.30 t (1H, 5-H, $^3J$ 7.8), 7.46 d (1H, 3-H, $^3J$ 7.8), 7.84 d (1H, 6-H, $^3J$ 7.8) / 7.14 t (1H, 4-H, $^3J$ 7.8), 7.26 t (1H, 5-H, $^3J$ 7.8), 7.41 d (1H, 3-H, $^3J$ 7.8), 7.80 d (1H, 6-H, $^3J$ 7.8) | 7.57 d (2H, 3,5-H, $^3J$ 7.8), 8.11 d (2H, 2,6-H, $^3J$ 7.8) / 7.52 d (2H, 3,5-H, $^3J$ 7.8), 8.06 d (2H, 2,6-H, $^3J$ 7.8) | 10.15 |

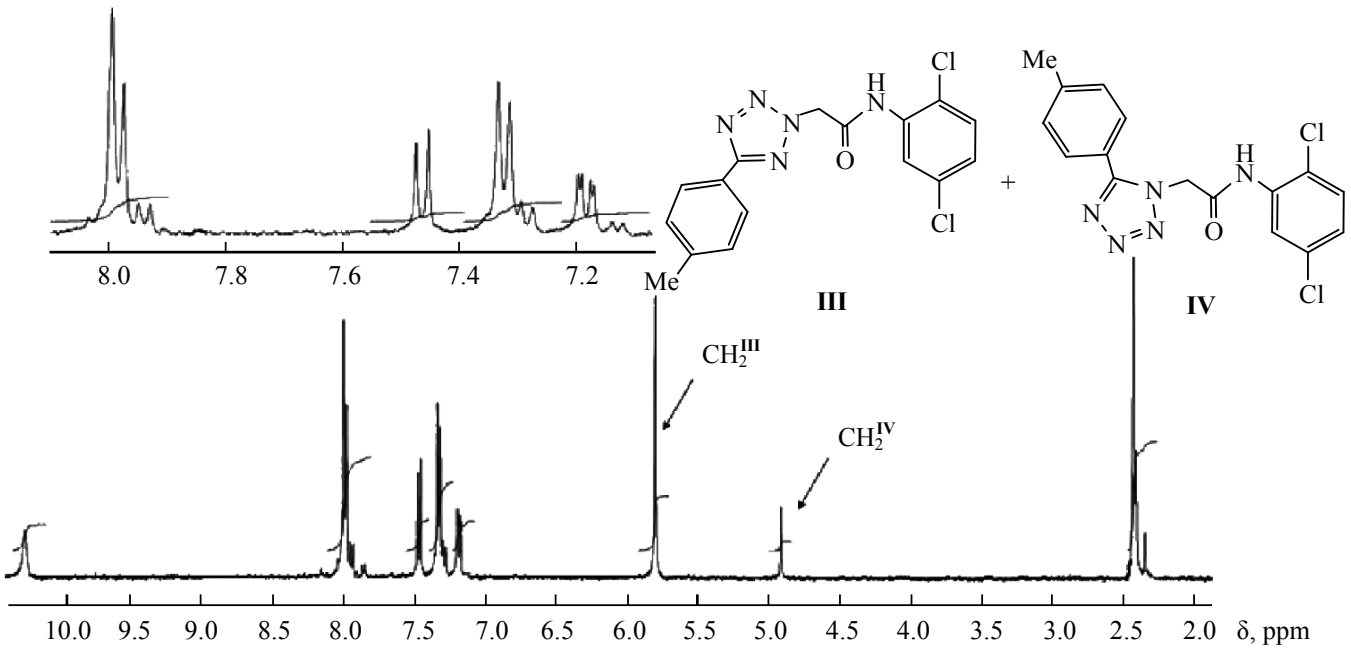



**Fig. 1.** $^1$H NMR spectrum of a mixture of regioisomers **IIIo** and **IVo**.

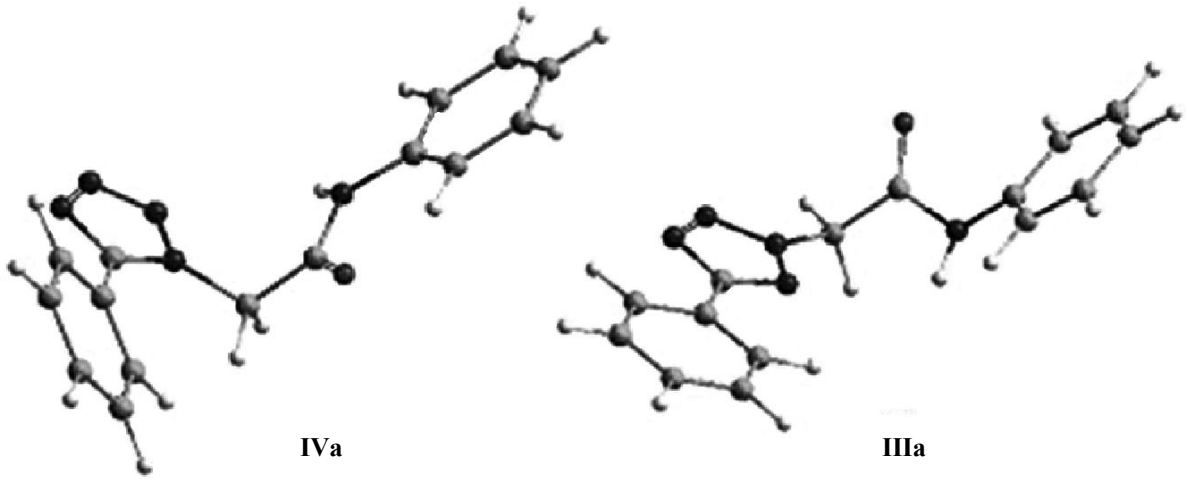



**Fig. 2.** The steric structure of the regioisomers **IIIa** and **IVa** optimized by semiempirical PM3 method with WinMopac 7.2 program package.

respective signals of 2,5-disubstituted tetrazoles I**IIe, IIIn, IIIo,** and **IIIx**. The maximum difference in the chemical shifts is observed for the protons of $CH_2$ groups of the regioisomers ($\Delta\delta$ = 0.23–0.90 ppm). Such a significant upfield shift of the signals of methylene protons of 1,5-disubstituted tetrazoles **IV** compared with the 2,5-regioisomers **III** can be attributed to the features of their structures. We carried out quantum-chemical optimization of geometry of the molecules of 1,5- and 2,5-regioisomers by semi-empirical PM3 method with WinMopac 7.2 program package. The data obtained indicate that in the 1,5-regioisomers the coplanar arrangement of the benzene and tetrazole rings is hardly probable, as the substituent in 1 position creates steric hindrances and promotes deviation of benzene ring from the plane of the molecule (Fig. 2). In this case the protons of methylene groups fall into the cone of anisotropy of the benzene ring, that is, into the area of shielding. For the 2,5-regioisomers such steric hindrances do not exist, and therefore owing to the conjugation of benzene and tetrazole rings they are in the same plane (Fig. 2). A similar approach was applied in [29, 30] to the analysis of the structure of regioisomeric *N*-phenyltriazoles. Signals of protons of the substituent $R^1C_6H_4$ in 1,5-regioisomers **IV** also is shifted upfield due to a decrease in the conjugation of the benzene ring with the acceptor tetrazole ring.

Thus, it is shown that in most cases the alkylation of 5-substituted tetrazoles with *N*-arylchloroacetamides proceeds regioselectively at the position 2 of the tetrazole ring and therefore such reaction can find a preparative application to the molecular design of tetrazole derivatives.

## EXPERIMENTAL

The $^1$H NMR spectra of synthesized compounds were recorded on a Varian Mercury 400 instrument at the operating frequency 400 MHz, solvent DMSO-$d_6$, internal reference TMS. The data of elemental analysis (C, H, N) of all synthesized compounds correspond to the calculated values with the accuracy: C ±0.34, H ±0.19, N ±0.20.

**General procedure for the alkylation of tetrazoles I**. To a solution of 0.56 g (0.01 mol) of KOH in 15 ml of ethanol was added at heating and stirring 0.01 mol of tetrazole **I**. To the resulting solution was added 0.01 mol of chloroacetamide **II**, and the mixture was heated under reflux for 5 h. Then the mixture was diluted with water, the formed precipitate was filtered off and recrystallized from ethanol. In the case of the formation of two regioisomers, the pure 2,5-disubstituted tetrazole **III** was isolated after triple recrystallization (see Tables 1, 2).

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