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STUDY OF THE PRODUCTS OF IODOCYCLIZATION OF 4-ALLYL-5-PHENYL-1,2,4-TRIAZOLE-3-THIONE

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The interaction of 4-allyl-5-phenyl-1,2,4-triazole-3-thione with iodine proceeds with the formation of a mixture of 6-iodomethyl-3-phenyl-5,6-dihydrothiazolo[2,3-c]-1,2,4-triazole and 6-iodo-3-phenyl-6,7-dihydro-5H-1,2,4-triazolo[3,4-b]-1,3-thiazine. The structures of the cyclization products obtained were established on the basis of the ^{1}H NMR spectra of their dehydroiodinated derivatives. 6-Methyl-3-phenylthiazolo[2,3-c]-1,2,4-triazole, 3-phenyl-5H-1,2,4-triazolo[3,4-b]-1,3-thiazine, and 3-phenyl-7H-1,2,4-triazolo[3,4-b]-1,3-thiazine are formed on eliminating HI from the cyclization products.

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The interaction of 4-alkenyl derivatives of 1,2,4-triazole-3-thiones and analogous systems of the pyrimidine series with electrophilic reagents leads to the 5-*endo* products of cyclization containing a five-membered ring [1-6].

In the opinion of the authors of [1] the reaction of 4-allyl-5-phenyl-1,2,4-triazole-3-thione (**1**) with iodine in ethanol leads to the formation of the hydroiodide of 6-iodomethyl-3-phenyl-5,6-dihydrothiazolo-[2,3-*c*]-1,2,4-triazole (**2**) (Scheme 1).

We have investigated the interaction of thione **1** with iodine in CH_2Cl_2 at room temperature. In difference to the data of [1] it has been established that iodocyclization leads to a mixture of products, compound **2** and 6-iodo-3-phenyl-6,7-dihydro-5H-1,2,4-triazolo[3,4-*b*]-1,3-thiazine (**3**), which were isolated by treating the reaction mixture containing an excess of iodine with a solution of $Na_2S_2O_3$ and Na_2CO_3. Compounds **2** and **3** may also be isolated as the hydroiodides by treating the reaction mixture with sodium iodide in acetone. The thiazole compound **2** has melting point 156°C and thiazine **3** 194°C. The ratio of isomers **2** and **3** was 4:1.

The ^{1}H NMR spectra of cyclization products **2** and **3** have been studied (Table 1). Both products have, in addition to the signals of the aromatic ring protons, three further groups of signals. These are a multiplet at low field for the H-6 proton, multiplets for the protons of the CH_2I and $-NCH_2$ groups in thiazole **2**, and multiplets for the protons of the SCH_2 and $-NCH_2$ groups in thiazine **3**. The signals lying at lower field in both

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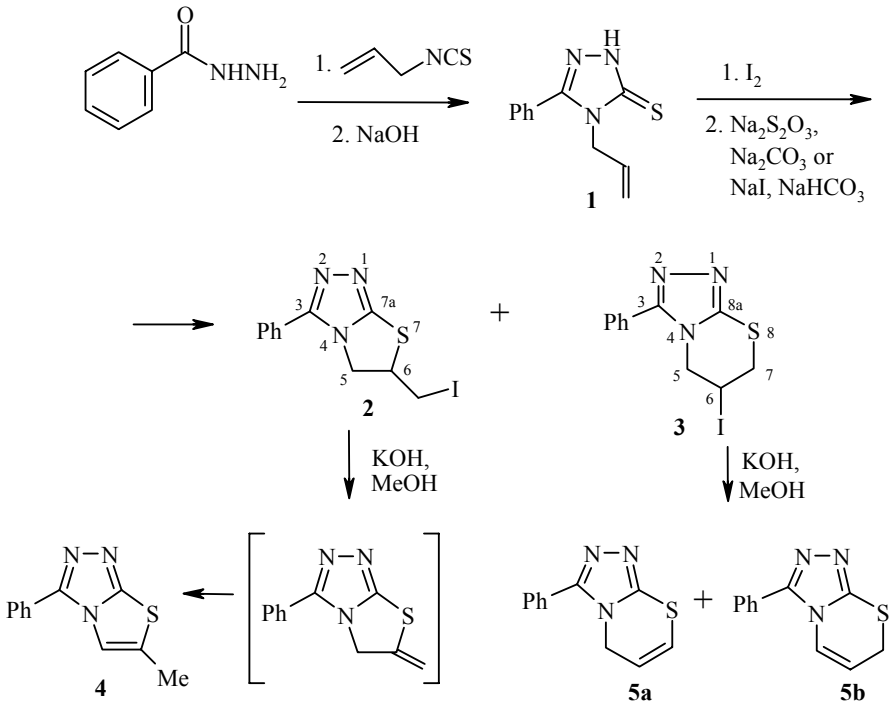
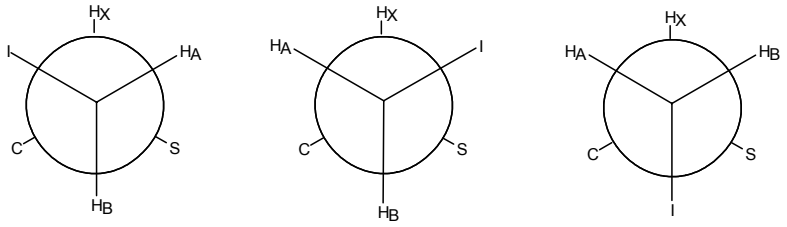
Scheme 1



compounds may be assigned to the $-NCH_2$ groups, and the signals at higher field correspond to the protons of the CH_2I group in compound **2** and the $-SCH_2$ group in compound **3**. The values of the chemical shifts and coupling constants were found by the known rules for higher order spectra [7].



2a **2b** **2c**

The coupling constants observed $^3J_{AX}$ = 4.4 and $^3J_{BX}$ = 10.8 Hz for the iodomethyl group protons in thiazole **2** indicate the large contribution of structures **2a** and **2b** to the conformational equilibrium. Quantum-chemical calculations of the heats of formation by the PM3 semiempirical method showed the higher stability of conformers **2a** and **2b** in comparison with conformer **2c** by 26.0 and 14.3 kJ/mol respectively.

The values found for the coupling constants in thiazine **3** indicate the more significant contribution of the structure with a pseudoaxial disposition of the iodine atom to the conformational equilibrium. According to the calculations by the PM3 method, the conformer with a pseudoaxial disposition of iodine atom is 126.0 kJ/mol more stable than the conformer with a pseudoequatorial disposition.

To confirm the structures of compounds **2** and **3** the ^{1}H NMR spectra of their dehydroiodinated derivatives, formed by treating isomers **2** and **3** with a methanolic solution of potassium hydroxide, were investigated.

TABLE 1. ^{1}H NMR Spectral Characteristics of 4-Allyl-5-phenyl-1,2,4-triazolo-3-thione and Its Cyclic Derivatives

Compound	Chemical shifts ($CDCl_3$), δ, ppm (J, Hz)
1	12.5 (1H, s, NH); 7.4-7.7 (5H, m, C_6H_5); 5.99 (1H, m, $CH_2C\underline{H}=CH_2$); 5.30 (1H, dt, $^3J_{cis}$ = 10.2, $CH_2CH=C\underline{H}H$); 5.08 (1H, dt, $^3J_{trans}$ = 17.2, $CH_2CH=CH\underline{H}$); 4.73 (2H, dt, ^3J = 5.0, ^4J = 1.7, $C\underline{H}_2CH=CH_2$)
2	7.4-7.6 (3H, m, C_6H_5); 7.7-7.8 (2H, m, C_6H_5); 4.74 (1H, m, –$SC\underline{H}CH_2N$–); 4.48* (1H, $^3J_{MX}$ = 6.4, $^2J_{MN}$ = –11.2, –$NCH\underline{H}_M$–); 4.42* (1H, $^3J_{NX}$ = 4.0, $^2J_{NM}$ = –11.2, –$NC\underline{H}_NH$–); 3.64* (1H, $^3J_{AX}$ = 4.4, $^2J_{AB}$ = –10.5, –$CH\underline{H}_AI$); 3.51* (1H, $^3J_{BX}$ = 10.8, $^2J_{AB}$ = –10.5, –$CH\underline{H}_BI$)
3	7.5–7.6 (5H, m, C_6H_5); 4.92 (1H, m, –$CH_2C\underline{H}ICH_2$–); 4.55* (1H, $^3J_{MX}$ = 3.7, $^2J_{MN}$ = –13.0, –$NCH\underline{H}_M$–); 4.45* (1H, $^3J_{NX}$ = 8.3, $^2J_{NM}$ = –13.0, –$NC\underline{H}_NH$–); 3.61* (1H, $^3J_{AX}$ = 2.2, $^2J_{AB}$ = –12.9, –$SCH\underline{H}_A$–); 3.59* (1H, $^3J_{BX}$ = 8.3, $^2J_{AB}$ = –12.9, –$SCH\underline{H}_B$–)
4	7.81-7.89 (2H, m, C_6H_5); 7.47–7.59 (3H, m, C_6H_5); 7.41 (1H, q, ^4J = 1.1, H-5); 2.46 (3H, d, ^4J = 1.1, CH_3)
5a*[2]	7.5-7.7 (5H, m, C_6H_5); 6.41 (1H, dt, ^3J = 10.0, ^4J = 1.7, –$SC\underline{H}$=); 5.96 (1H, dt, ^3J = 3.7, ^3J = 10.0, –$C\underline{H}$=); 4.79 (2H, dd, ^3J = 3.7, ^4J = 1.7, –$NC\underline{H}_2$–)
5b*[2]	7.5-7.7 (5H, m, C_6H_5); 6.89 (1H, dt, ^3J = 8.0, ^4J = 1.4, –$NC\underline{H}$=); 5.76 (1H, dt, ^3J = 8.0, ^3J = 5.4, –$C\underline{H}$=); 3.61 (2H, dd, ^3J = 5.4, ^4J = 1.4, –$SC\underline{H}_2$–)

* In the composition of the multiplet.
*[2] Mixture of isomers.

It turned out that only 6-methyl-3-phenylthiazolo[2,3-*c*]-1,2,4-triazole (**4**) is formed under these conditions from product **2**. In the ^{1}H NMR spectrum of compound **4**, apart from two groups of signals for the benzene ring protons, two further signals were present with relative intensity 3:1 corresponding to the protons of the methyl group at 2.45 ppm and the H-5 proton of the thiazole ring at 7.42 ppm. This is in agreement with literature data on the chemical shifts of protons of thiazole ring and a methyl group in related systems [8-10].

Thiazine **3** gives a mixture of elimination products, 3-phenyl-5H-1,2,4-triazolo[3,4-*b*]-1,3-thiazine (**5a**) and 3-phenyl-7H-1,2,4-triazolo[3,4-*b*]-1,3-thiazine (**5b**). In the ^{1}H NMR spectrum of this mixture, apart from the multiplet common to compounds **5a** and **5b** corresponding to the aromatic ring protons, a further six signals are observed dividing into two groups according to integral intensity. In each group there are two one-proton doublets of triplets at low field, corresponding to the proton at the double bond, and a two-proton doublet of doublets at high field belonging to the two methylene protons. The signal from the H-7 protons in compound **5b** is close in chemical shift to the analogous signal in 3-phenyl-5-(2-propynylthio)-4H-1,2,4-triazole [11] (3.61 and 3.83 ppm respectively), but the signal from the H-5 protons in compound **5a** is observed at lower field, as for the signal of the analogous methylene protons in thione **1** (4.79 and 4.71 ppm respectively). This is in agreement with the disposition of the signal from the H-5 proton in compound **5b** at lower field compared with the signal from the H-7 proton in compound **5a** (6.89 and 6.19 ppm respectively). The coupling constant between the proton at the double bond and the methylene group protons is ^4J = 1.7 in compound **5a** and ^4J = 1.4 Hz in compound **5b**, which is characteristic of spin-spin interactions in allylic systems [7].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker spectrometer (200 MHz) in $CDCl_3$. TLC was carried out on Sorbfil PTSKh-V-UF plates, visualization was in UV light or with iodine vapor.

4-Allyl-5-phenyl-1,2,4-triazole-3(4H)-thione (1). Mixture of KSCN (3.92 g, 40.0 mmol) and allyl bromide (3.90 ml, 45.0 mmol) in dry acetone (20 ml) was boiled in a round-bottomed flask for 2 h. Acetone was distilled off on a rotary evaporator, xylene (30 ml) was added to the residue, KBr was filtered off, and the resulting solution boiled for a further hour. Solution of benzoic acid hydrazide (5.44 g, 40.0 mmol) in hot xylene (20 ml) was added to the obtained solution of allyl isothiocyanate. The precipitated solid was filtered off, washed with pentane, and dried. 1-Allyl-4-benzoylthiosemicarbazide (8.93 g, 95%) was obtained, which was dissolved in 2.5% NaOH solution (80 ml) and heated on a water bath for 3 h. The obtained solution was acidified with glacial acetic acid (7.0 ml) to pH 6. An oil separated, which crystallized. After two recrystallizations of the product from a benzene–hexane mixture (50 ml) thione **1** (6.60 g, 70% on benzoic acid hydrazide) was obtained having mp 120°C (mp 118°C [1]), R_f 0.47 (ethyl acetate–hexane, 1:3).

6-Iodomethyl-3-phenyl-5,6-dihydrothiazolo[2,3-*c*]-1,2,4-triazole (2) and 6-Iodo-3-phenyl-6,7-dihydro-5H-1,2,4-triazolo[3,4-*b*]-1,3-thiazine (3). 4-Allyl-5-phenyl-1,2,4-triazole-3-thione (2.17 g, 10.0 mmol) was dissolved in CH_2Cl_2 (100 ml) and sublimed iodine (6.34 g, 25.0 mmol) was added. The mixture was left to stand at room temperature in the dark for several days, then CH_2Cl_2 was evaporated under reduced pressure. Further treatment may be carried out by two procedures.

A. The residue was dissolved in acetone (20 ml) and poured with cooling into solution of $Na_2S_2O_3 \cdot 5H_2O$ (8.69 g, 35.0 mmol) and Na_2CO_3 (1.27 g, 12.0 mmol) in water (150 ml). The solid which precipitated was a mixture (3.29 g, 96%) of cyclization products. A sample (500 mg) of the mixture was separated chromatographically on a column of silica gel (eluent was ethyl acetate) and thiazole **2** (388 mg, 77.6%) and thiazine **3** (96 mg, 19.2%) were obtained. It is possible to obtain the individual products by fractional extraction of the more soluble isomer **2** from the mixture of isomers with chloroform. From the mixture (3.00 g) of isomers compound **2** (2.04 g, 68%) and product **3** (0.40 g, 13%) were obtained.

6-Iodomethyl-3-phenyl-5,6-dihydrothiazolo[2,3-*c*]-1,2,4-triazole (2). Mp 156°C (acetonitrile), R_f 0.28 (ethyl acetate). Found, %: I 36.6; S 9.40. $C_{11}H_{10}IN_3S$. Calculated, %: I 36.98; S 9.34.

6-Iodo-3-phenyl-6,7-dihydro-5H-1,2,4-triazolo[3,4-*b*]-1,3-thiazine (3). Mp 194°C (70% AcOH), R_f 0.21 (ethyl acetate). Found, %: I 36.50; S 9.30. $C_{11}H_{10}IN_3S$. Calculated, %: I 36.98; S 9.34.

B. The reaction mixture was dissolved in acetone and treated with $NaI \cdot 2H_2O$ (3.72 g, 20.0 mmol) in acetone (20 ml). The precipitated hydroiodide was filtered off, washed with acetone, and the solid obtained was dried in the dark. Mixture (4.19 g, 89%) of hydroiodides of compounds **2** and **3** was obtained, which was stirred for 1 h in solution of $NaHCO_3$ (0.84 g, 10 mmol) in water (50.0 ml). The obtained solid was filtered off, washed with water, and dried in the dark. Mixture (2.99 g, 98%) of compounds **2** and **3** was obtained. Separation of the isomers was carried out as in method A.

6-Methyl-3-phenylthiazolo[2,3-*c*]-1,2,4-triazole (4). Compound **2** (343 mg, 1.0 mmol) was dissolved in 5% solution (15 ml) of KOH in methanol, the solution was heated to boiling, then left for several hours at room temperature. MeOH was evaporated under reduced pressure, the residue was extracted with $CHCl_3$ (3×10 ml), the combined extracts dried over anhydrous Na_2SO_4, $CHCl_3$ was evaporated, and the residue recrystallized from benzene–hexane. Thiazole **4** (185 mg, 86%) was obtained; mp 196°C, R_f 0.26 (ethyl acetate). Found, %: S 14.80. $C_{11}H_9N_3S$. Calculated, %: S 14.89.

Mixture of 3-Phenyl-5H-1,2,4-triazolo[3,4-*b*]-1,3-thiazine (5a) and 3-Phenyl-7H-1,2,4-triazolo[3,4-*b*]-1,3-thiazine (5b). Elimination of HI from thiazine **3** (100 mg, 0.29 mmol) was carried out analogously to the preparation of compound **4**. After evaporation of the solvent the mixture (59 mg, 95%) of isomers **5a** and **5b** was obtained. Found, %: S 14.71. $C_{11}H_9N_3S$. Calculated, %: S 14.89.

REFERENCES

1. M. N. Tsitsika, S. M. Khripak, and I. V. Smolanka, *Ukr. Khim. Zh.*, **42**, 841 (1976).
2. S. Ernst, S. Jelonek, J. Silez, and K. Schulze, *Tetrahedron*, **52**, 791 (1996).
3. L. Strzemecka, *Polish J. Chem.*, **57**, 567 (1983).

4. M. Tamaru and Z. Yoshida, *J. Org. Chem.*, **50**, 764 (1985).
5. D. G. Kim and V. I. Shmygarev, *Khim. Geterotsikl. Soedin.*, 211 (1995).
6. P. Wippich, C. Hendreich, M. Gutshow, and S. Leistner, *Synthesis*, 741 (1996).
7. B. I. Ionin, B. A. Ershov, and A. I. Kol'tsov, *NMR Spectroscopy in Organic Chemistry* [in Russian], Khimiya, Leningrad (1983).
8. K. T. Potts and S. Husain, *J. Org. Chem.*, **36**, 10 (1971).
9. Y. Tamura, H. Hayashy, J. H. Kim, and M. Ikeda, *J. Heterocycl. Chem.*, **10**, 947 (1973).
10. Y. Tamura, H. Hayashy, E. Saeki, J. H. Kim, and M. Ikeda, *J. Heterocycl. Chem.*, **11**, 459 (1974).
11. V. P. Upadhyaya, T. G. S. Nath, and V. R. Srinivasan, *Synthesis*, 283 (1978).