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2-Azidothiazolo[5,4-*b*]pyridine and 2-azidothiazolo[4,5-*c*]pyridine were synthesized. Azido-tetrazolo isomerizations of these compounds were investigated and in both cases also the tetrazolo form could be obtained. In solution, equilibria at different temperatures were determined.

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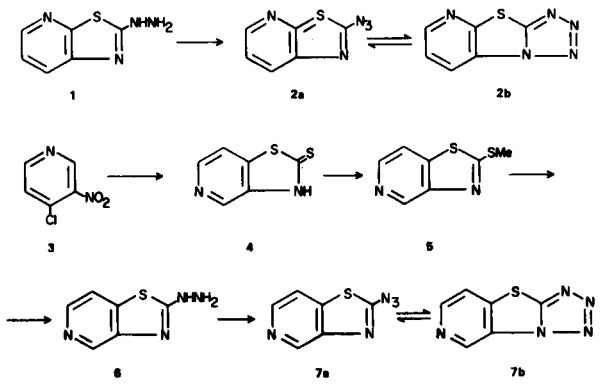
Recently, we have accumulated considerable experimental evidence concerning the problem of azido-tetrazolo isomerizations (2-22) and its implications. A review on this subject has also appeared (23). So far, all our studies were devoted to systems where the azido group was attached to a six-membered heterocycle and hence the isomerization to the tetrazolo form generated the corresponding tetrazoloazines. It was therefore of interest to investigate some systems in which fusion of the tetrazolo ring to a five-membered heterocycle may be possible.

From the published data it appears that in general the tendency of tetrazoloazole formation is less pronounced as compared to tetrazoloazines. Although for most 2-azidobenzothiazoles, with few exceptions (24, 25), the tetrazolo form is favoured in the solid state (24-29), these compounds exist in solution in general as azides (25,27,29). Infrared and ultraviolet spectroscopy have been used almost exclusively for the determination of particular forms. Recently, nmr spectroscopy was used and azido-tetrazolo equilibrium of 2-azidobenzothiazole could be determined ($K_T \cong 1$ in deuteriochloroform at 35°) (30). Furthermore, on hand of infrared examination 2-azidothiazole exists predominantly as azide (31) and also for 3-azidobenzisothiazole (26) and other azidobenzazoles (28) the azide form was claimed to be the preferred one.

Azido-tetrazolo isomerizations and equilibria in the azole series have been recently investigated in detail by Elguero (32-34). It could be established that for the neutral molecules the equilibrium is displaced towards the azide, whereas compounds where anion formation is possible (for example on the ring nitrogen unsubstituted pyrazoles, imidazoles) are transformed into the tetrazolo form (32,33,35). Similarly, 1-acetyl-2-azidoimidazole is in equilibrium with the tetrazolo form (36). A theoretical approach to the azido-tetrazolo isomerization showed that tetrazole formation should be preferred in polar solvents since these polarize and stabilize to a greater extent the transition state with respect to the azido form (37).



For our present investigation we have prepared the isomeric azidothiazolopyridines **2a** and **7a**. 2-Azidothiazolo[5,4-*b*]pyridine (**2a**) was prepared in the usual manner from the known 2-hydrazinothiazolo[5,4-*b*]pyridine (38). For the synthesis of 2-azidothiazolo[4,5-*c*]-pyridine (**7a**) the following series of transformations was necessary. 4-Chloro-3-nitropyridine was transformed with a mixture of sodium hydrosulfide, sodium sulfide and carbon disulfide into 2(3*H*)thioxothiazolo[4,5-*c*]pyridine (4). This compound was transformed into its *S*-methyl derivative (**5**) which upon hydrazinolysis afforded the corresponding hydrazino derivative (**6**). Nitrosation of compound **6** afforded the desired azido compound (**7a**).

2-Azidothiazolo[5,4-*b*]pyridine (**2a**), when crystallized from water had m.p. 98-100° and the infrared spectrum of the solid did not reveal any absorption band characteristic for the presence of an azido group. The compound exists therefore in the solid state in the tetrazolo form (**2b**). When sublimed *in vacuo*, the tetrazolo compound was transformed into the azido isomer (**2a**), m.p. 72-75° and this, upon melting, is transformed again back into the tetrazolo form (**2b**). The azido compound revealed a characteristic azide absorption band at 2140 cm^{-1} in solid state or in chloroform solution. A nmr spectroscopic investigation of a solution of this compound in dimethylsulfoxide revealed an equilibrium between both forms, **2a** and **2b** ($\Delta H = 2.2 \pm 0.2$ kcal/mole for tetrazolo/azido form) (see also Table I). The equilibrium constant was determined by employing both forms, *i.e.*, the azido and tetrazolo form, as starting material.

A similar behaviour could be observed for the isomeric 2-azidothiazolo[4,5-*c*]pyridine (**7a**). The compound is converted at its m.p. at 75-85° into the tetrazolo isomer (**7b**) with m.p. 128-130°. Here again, in solution of dimethylsulfoxide an equilibrium of both isomers (**7a** and **7b**) could be established ($\Delta H = 1.5 \pm 0.2$ kcal/mole for tetrazolo/azido form) (see Table I).

The above results are consistent with the observations

Table I

Tetrazolo-azido Equilibria

a) Equilibrium **2b** ⇌ **2a** (in DMSO-d_6)

T (°K)	K_T
300	0.7
323	0.55
338	0.49
348	0.43

b) Equilibrium **7b** ⇌ **7a** (in DMSO-d_6)

T (°K)	K_T
296	0.26
316	0.23
336	0.19

of azido-tetrazolo isomerizations in the field of azidoazoles and azidobenzazoles. The solubility of the investigared compounds limits the number of solvents for investigation of equilibria and hence the dependency of these from the solvent polarity. However, the published results concerning the influence of solvent polarity upon azido-tetrazolo isomerization of 2-azidothiazoles revealed that with enhanced solvent polarity the tetrazolo forms are favoured (34).

Since in addition to the influence of the solvent, temperature and the neighbouring ring heteroatom, the isomerization is sensible also to substituent effects, it was of interest to establish the eventual influence of the fused pyridine ring. Unfortunately, a direct correlation of equilibrium constants of the investigated 2-azidothiazolopyridines with 2-azidothiazole or 2-azidobenzothiazole is not possible because the published data are either based on the interpretation of infrared spectra and allow only qualitative evaluation (31) or deuteriochloroform was used as solvent for the determination of the equilibrium constant by nmr spectroscopy (30). However, from the determined equilibrium constants for the isomeric 2-azidothiazolo[5,4-*b*]pyridine and 2-azidothiazolo[4,5-*c*]-pyridine it appears that the position of the pyridine ring nitrogen towards the fused thiazole ring has some influence on the azido-tetrazolo equilibrium. What regards the temperature effect the recorded measurements present evidence that with increased temperature the proportion of the azido form is increased.

A correlation of nmr spectra of the corresponding azido and tetrazolo forms revealed pronounced displacement of chemical shifts of pyridine protons towards lower field for the tetrazolo form. An explanation, based on the influence of steric effects, could be reasonable only for the proton H_5 of the tetrazolo form, but not for the more distant H_6 and H_7 protons. It must be therefore anticipated that the pyridine ring in **2b** or **7b** becomes more aromatic when compared to the azide forms. In the latter case, electron delocalization involves the whole bicyclic system, whereas in the tetrazole forms electrons are delocalized in two more or less separated aromatic parts, the pyridine ring and the tetrazole ring. An additional support for this comes also from the observation that the transformation of the tetrazolo into the azido form is an endothermic process as a result of resonance destabilization of the system.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. All nmr spectra were obtained on a JEOL JNM C60-HL spectrometer and mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L instrument.

2-Azidothiazolo[5,4-*b*]pyridine (**2a**).

A solution of the 2-hydrazino compound (**1**) (0.166 g.) in hydrochloric acid (3 ml. of 1:1) was cooled to -5° and under stirring a solution of sodium nitrite (0.138 g.) in water (1 ml.) was added dropwise. After some time water (5 ml.) was added and the reaction mixture was neutralized with sodium bicarbonate to *p*H 7 and the separated product was filtered (0.13 g., 74% yield), m.p. 72-75° (from the melt crystals of the tetrazolo form separated, m.p. 98-100°); mass spectrum: $M^+ = 177$; infrared spectrum: 2140 cm^{-1} (-N_3 group); nmr spectrum of the azide form: (deuteriochloroform): τ = 1.92 (dd, H_4), 2.6 (dd, H_5), 1.48 (dd, H_6), $J_{4,5}$ = 7.5, $J_{5,6}$ = 4.5, $J_{4,6}$ = 1.5 Hz; (DMSO-d_6): τ = 1.70 (dd, H_4), 2.42 (dd, H_5), 1.43 (dd, H_6), $J_{4,5}$ = 8.0, $J_{5,6}$ = 4.5, $J_{4,6}$ = 1.5 Hz. If crystallized from water, the tetrazolo form was obtained, m.p. 98-100°; nmr (DMSO-d_6): τ = 1.15 (m, H_5 and H_7), 2.15 (dd, H_6), $J_{5,6}$ = 6.5, $J_{6,7}$ = 4.5 Hz.

The tetrazolo compound when sublimed *in vacuo* was transformed back into the lower melting azido isomer.

Anal. Calcd. for $C_6H_3N_5S$: C, 40.69; H, 1.71. Found: C, 41.05; H, 1.98.

2(3*H*)Thioxothiazolo[4,5-*c*]pyridine (**4**).

A solution of sodium hydrosulfide was prepared in the following manner: into a solution of sodium hydroxide (3 g. in 16 ml. of water) hydrogen sulfide was bubbled until saturation. Into this hot solution 4-chloro-3-nitropyridine (**3**) (4 g.) was added and the reaction mixture was heated under reflux for 5 minutes. Into the boiling solution sodium sulfide nonahydrate (12 g.) was added portionwise and hydrogen sulfide was bubbled into the boiling reaction mixture for 2.5 hours. Thereafter, the reaction mixture was treated with aqueous sodium hydroxide (1.4 g. in 6 ml. water), saturated with hydrogen sulfide, and finally carbon disulfide (11 ml.) was added. The reaction mixture was heated at 110° for 5-6 hours, cooled and neutralized with acetic acid. The separated product was filtered, dissolved in aqueous ammonia, charcoaled and filtered. The filtrate was acidified with acetic acid, the product was filtered off and washed with some ethanol, m.p. over 275° dec. (2.8 g., 66% yield); mass spectrum: $M^+ = 168$; nmr (DMSO-d_6, 88°): τ = 1.56 (d, H_4), 1.75 (d, H_6), 2.41 (dd, H_7), $J_{6,7}$ = 5.1, $J_{4,7}$ = 0.75 Hz.

2-Methylthiothiazolo[4,5-*c*]pyridine (**5**).

The above thione **4** (0.336 g.) was dissolved in ethanolic sodium ethylate (prepared from 46 mg. of sodium and 10 ml. of absolute ethanol) and the solution was evaporated to dryness. The residue was dissolved in 1,2-dimethoxyethane (15 ml.) and

methyl iodide (0.352 g.) was added. The reaction mixture was heated under reflux for 10 minutes, the solvent was evaporated, water (5 ml.) was added and the separated product was filtered (yield 0.15 g., 41%). For analysis the product was sublimed at 90°/10 mm and had m.p. 83-85°; nmr (DMSO-d_6): τ = 0.87 (d, H_4), 1.53 (d, H_6), 1.91 (dd, H_7), 7.18 (s, Me), $J_{6,7}$ = 6.0, $J_{4,7}$ = 0.8 Hz.

Anal. Calcd. for $C_7H_6N_2S_2$: C, 46.13; H, 3.32; N, 15.37. Found: C, 45.91; H, 3.48; N, 15.25.

2-Hydrazinothiazolo[4,5-*c*]pyridine (**6**).

The methylthio compound (**5**) (0.17 g.) was treated with few drops of ethanol and hydrazine hydrate (3 ml. of 80%) and the reaction mixture was heated at 60° for 45 minutes. Upon cooling the product was filtered, dried and crystallized from ethanol, m.p. 272-274° (yield 0.1 g., 64%); nmr (DMSO-d_6, 115°): τ = 1.4 (d, H_4), 1.9 (d, H_6), 2.31 (dd, H_7), 5.0 (broad, NH), $J_{6,7}$ = 5.0, $J_{4,7}$ = 0.8 Hz.

Anal. Calcd. for $C_6H_6N_4S$: C, 43.36; H, 3.64; N, 33.71. Found: C, 43.15; H, 3.81; N, 33.55.

2-Azidothiazolo[4,5-*c*]pyridine (**7a**).

The above hydrazino compound (0.166 g.) was dissolved in hydrochloric acid (3 ml. of 1:1), the solution was cooled to -5° and under stirring an aqueous solution of sodium nitrite (0.138 g. in 1 ml. water) was added. After 5 minutes some water was added and the reaction mixture was neutralized with sodium bicarbonate to *p*H 7. The separated product was filtered and sublimed at 100°/100 mm, m.p. 75-85° (from the melt new crystals of the tetrazolo isomer separated and had m.p. 128-130°); nmr spectrum of the azido form (**7a**): (deuteriochloroform): τ = 0.85 (s, H_4), 1.51 (d, H_6), 2.32 (d, H_7), $J_{6,7}$ = 5.7 Hz; (DMSO-d_6): τ = 1.67 (d, H_4), 2.25 (d, H_6), 2.65 (dd, H_7), $J_{6,7}$ = 5.0, $J_{4,7}$ = 0.8 Hz; nmr spectrum of the tetrazolo form (**7b**): (DMSO-d_6): τ = 1.15 (s, H_5), 1.9 (d, H_7), 2.35 (d, H_8), $J_{7,8}$ = 6.0 Hz.

Anal. Calcd. for $C_6H_3N_5S$: C, 40.69; H, 1.71; N, 39.54. Found: C, 40.87; H, 1.92; N, 39.65.

Kinetic Measurements.

A sample of about 18 mg. of the corresponding compound was dissolved in 0.5 ml. of DMSO-d_6 and the solution was left at the corresponding temperature to allow equilibration. The rate of equilibrium formation and the equilibrium constants were measured at different temperatures (see Table I). The equilibrium constants as well as values of Δ H were calculated as described previously (5). Temperature measurements are accurate to ± 0.5 K at the sample and the measurements of $\Delta \nu$ are accurate to ± 0.5 Hz. We assign a maximum error of ± 0.2 kcal/mol to ΔH values.

REFERENCES AND NOTES

(1) Heterocycles, Pt. CLXII.

(2) B. Stanovnik and M. Tišler, *Chimia*, **22**, 141 (1968).

(3) A. Kovačič, B. Stanovnik, and M. Tišler, *J. Heterocyclic Chem.*, **5**, 351 (1968).

(4) B. Stanovnik, M. Tišler, M. Ceglar, and V. Bah, *J. Org. Chem.*, **35**, 1138 (1970).

(5) B. Stanovnik and M. Tišler, *Tetrahedron*, **25**, 3313 (1969).

(6) V. Pirc, B. Stanovnik, M. Tišler, J. Marsel, and W. W. Paudler, *J. Heterocyclic Chem.*, **7**, 639 (1970).

(7) A. Pollak, S. Polanc, B. Stanovnik, and M. Tišler, *Monatsh. Chem.*, **103**, 1591 (1972).

(8) V. Pirc, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta*, **45**, 547 (1973).

(9) S. Polanc, B. Stanovnik, and M. Tišler, *J. Heterocyclic Chem.*, **10**, 565 (1973).

(10) A. Gorup, M. Kovačič, B. Kranjc-Škraba, B. Mihelčič, S. Simonič, B. Stanovnik, and M. Tišler, *Tetrahedron*, **30**, 2251 (1974).

(11) B. Mihelčič, S. Simonič, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta*, **46**, 275 (1974).

(12) M. Jurgec, M. Kovačič, B. Stanovnik, M. Tišler, and M. Volk, *J. Heterocyclic Chem.*, **12**, 253 (1975).

(13) S. Polanc, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, **41**, 3152 (1976).

(14) B. Stanovnik, M. Tišler, and B. Stefanov, *ibid.*, **36**, 3812 (1971).

(15) J. Kobe, B. Stanovnik, and M. Tišler, *Monatsh. Chem.*, **101**, 724 (1970).

(16) A. Krbavčič, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta*, **40**, 181 (1968).

(17) J. Kobe, A. Krbavčič, B. Stanovnik, and M. Tisler, *ibid.*, **41**, 245 (1969).

(18) B. Stanovnik, M. Tišler and P. Skufca, *J. Org. Chem.*, **33**, 2910 (1968).

(19) B. Stanovnik and M. Tišler, *J. Heterocyclic Chem.*, **8**, 785 (1971).

(20) B. Stanovnik and M. Tišler, *Synthesis*, 180 (1970).

(21) B. Stanovnik, *J. Heterocyclic Chem.*, **8**, 1055 (1971).

(22) B. Stanovnik, *Tetrahedron Letters*, 3211 (1971).

(23) M. Tišler, *Synthesis*, 123 (1973).

(24) L. F. Avramenko, V. J. Pochinok, and J. S. Rozum, *Zh. Khim.*, **33**, 980 (1963).

(25) V. J. Pochinok and L. F. Avramenko, *Ukr. Khim. Zh.*, **28**, 511 (1962).

(26) J. H. Boyer and E. J. Miller, *J. Am. Chem. Soc.*, **81**, 4671 (1959).

(27) J. N. Sheinker, I. J. Postovskii, N. P. Bednyagina, L. B. Benyavina, and L. F. Lipatova, *Dokl. Akad. Nauk SSSR*, **141**, 1388 (1961).

(28) G. A. Reynolds, J. A. Van Allan, and J. F. Tinker, *J. Org. Chem.*, **24**, 1205 (1959).

(29) I. J. Postovskii, N. P. Bednyagina, L. B. Senyavina, and J. N. Sheinker, *Izv. Akad. Nauk SSSR, Ser. Fiz.*, **26**, 1298 (1962).

(30) R. Faure, J. P. Galy, G. Giusti, E. J. Vincent, and J. Elguero, *Org. Magn. Reson.*, **6**, 485 (1974).

(31) L. F. Avramenko, T. A. Zaharova, V. J. Pochinok, and J. B. Rozum, *Khim. Geterotsikl. Soedin*, 423 (1968).

(32) E. Alcalde, J. De Mendoza, and J. Elguero, *J. Chem. Soc. Chem., Commun.*, 411 (1974).

(33) E. Alcalde, J. De Mendoza, and J. Elguero, *J. Heterocyclic Chem.*, **11**, 921 (1974).

(34) J. Elguero, R. Faure, J. P. Galy, and E. J. Vincent, *Bull. Soc. Chim. Belg.*, **84**, 1189 (1975).

(35) E. Alcalde and R. M. Claramunt, *Tetrahedron Letters*, 1523 (1975).

(36) R. Granados, M. Rull, and J. Vilarrasa, *J. Heterocyclic Chem.*, **13**, 281 (1976).

(37) L. A. Burke, J. Elguero, G. Leroy, and M. Sana, *J. Am. Chem. Soc.*, **98**, 1685 (1976).

(38) N. P. Bednyagina, N. N. Gulemina, G. N. Lipunova, L. V. Saloutina, *Khim. Geterotsikl. Soedin.*, 925 (1975).