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Note

Pyridazines. LXII. Tetrazolo-Azido Equilibria of Tetrazolo[1,5-*b*]pyridazines

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Tetrazolo[1,5-*b*]pyridazines exist in solution exclusively in the tetrazolo form. In solutions of strong acids an equilibrium of both forms, azido and tetrazolo, is established. The equilibrium constants in concentrated sulfuric acid or in trifluoromethanesulfonic acid were determined.

Azido-tetrazolo isomerization of tetrazoloazines has been subject of many investigations.[1] The general conclusions that can be drawn from studies in the tetrazolo[1,5-*b*]pyridazine series are as follows. Tetrazolo[1,5-*b*]pyridazines exist in solid state or in solution exclusively in the tetrazolo form. However, it was reported that an examination of the IR spectrum of 6-pyrrolidinotetrazolo[1,5-*b*]pyridazine in the presence of trifluoroacetic acid revealed the presence of some azido form.[2]

Destabilization of the tetrazolo form is further observed in the case of 6-azidotetrazolo[1,5-*b*]pyridazines or other 6-azidoazolopyridazines[3-8] and 7--azidoazinopyridazines.[9,10] Similarly, *N*-oxidation of tetrazolo[1,5-*b*]pyridazine generates the azido form to give 3-azidopyridazine 1-oxide.[4,9] Moreover, for some methyl substituted 6-azidotetrazolo[1,5-*b*]pyridazines and azidopyridotetrazolo[1,5-*b*]pyridazines equilibria of the isomeric forms were established.[3,11]

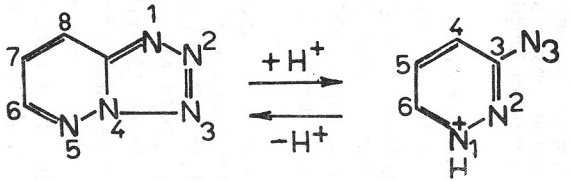
On the ground of these results one can anticipate that other reactions which would involve N_5 of the tetrazolo[1,5-*b*]pyridazine ring should follow the same pattern and give the corresponding azidopyridazines. We have therefore studied the behaviour of several tetrazolo[1,5-*b*]pyridazines in concentrated sulfuric and/or trifluoromethanesulfonic acid in order to determine the equilibrium between the tetrazolo and azido form. Indeed, it was possible on the ground of NMR measurements to determine the rate constants and equilibrium constants for several compounds. The results are presented in Table I.

For example, the characteristic pattern of signals for tetrazolo[1,5-*b*]pyridazine in $CDCl_3$ is H_6 ($\tau = 1.05$) $<$ H_8 ($\tau = 1.25$) $<$ H_7 ($\tau = 2.18$). In trifluoromethanesulfonic acid this order is changed to $H_6 < H_5 < H_4$ (H_6 corresponds to H_6 of tetrazolo[1,5-*b*]pyridazine, H_5 to H_7 and H_4 to H_8) which is consistent with 3-azidopyridazine in its protonated form. Similar behaviour was observed also with other compounds under investigation.

The determined enthalpy changes, ΔH, for these isomerizations in acid solution are somewhat lower as observed for 7-(or 8)-methyl-6-azidotetrazolo--[1,5-*b*]pyridazine[3] in dimethylsulfoxide. With increased temperature the pro-

TABLE I

Azido-tetrazolo isomerization of tetrazolo [1,5-b]pyridazines



Compound	K_T[a]						
	Acid	304 K	323 K	343 K	363 K	ΔH/kcal mol^{-1}	E_a/kcal mol^{-1}
Tetrazolo[1,5-*b*]pyridazine	B	0.86	1.3	1.77	2.1	— 3.4	19.
7-Methyltetrazolo[1,5-*b*]-pyridazine	B	0.75	1.2	1.6	2.2	— 4.4	18.7
6-Chloro-7-methyltetrazolo-[1,5-*b*]pyridazine	A	0.056	0.08	0.13	0.17	— 4.4	19.4
8-Methyltetrazolo[1,5-*b*]-pyridazine	B	3.9[b]	5.4	6.5	8.7	—2.7	13.4
6-Chloro-3-methyltetrazolo-[1,5-*b*]pyridazine	A	0.0175[c]	—	0.099	0.17 0.23[d]	— 4.9	21.7
7,8-Dimethyltetrazolo[1,5-*b*]-pyridazine	A	1.36	1.6	1.9	2.25	— 2.2	19.0
6-Chloro-7,8-dimethyltetrazolo--[1,5-*b*]pyridazine	B	0.13	0.21	0.34	0.49	— 5.1	17.5

A = H_2SO_4, B = trifluoromethanesulfonic acid
[a] protonated azidopyridazine/tetrazolo[1,5-b]pyridazine
[b] at 298.5 K
[c] at 301 K
[d] at 383 K

tonated azidopyridazines become the predominant isomer, except for all substituted 6-chlorotetrazolo[1,5-*b*]pyridazines where the tetrazole form still prevails. These experiments show that in a solution of very strong acid tetrazolo[1,5-*b*]pyridazines are also capable of azido-tetrazolo isomerization.

In the case of 6-azidotetrazolo[1,5-*b*]pyridazine and its methyl analogs, 6-acetonylthio-, 6-methoxy-, 6-amino- or 6-hidrazinotetrazolo[1,5-*b*]pyridazine no ring opening of the fused tetrazole ring could be observed when these compounds were dissolved in strong acid at room temperature. At elevated temperatures, however, chemical reactions, other than protonation occured.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. NMR measurements made on a JEOL JNM-C-60HL spectrometer (TMS as internal standard).

The synthesis of the following compounds was reported previously: tetrazolo [1,5-*b*]pyridazine,[12] (NMR spectrum: DMSO-d_6: $\tau = 1.05$ (dd, H_6), 2.18 (dd, H_7) 1.25 (dd, H_8) $J_{6,7} = 4.5$, $J_{7,8} = 9.5$, $J_{6,8} = 1.5$ Hz), 6-chloro-8-methyltetrazolo[1,5-*b*]-pyridazine[13] (NMR spectrum: $CDCl_3$: $\tau = 2.75$ (q, H_7). 7.20 (d, 8-CH_3), $J_{7,8\text{-Me}} = 1.5$ Hz), 8--methyltetrazolo[1,5-*b*]pyridazine[14] and 6-chloro-7-methyltetrazolo[1,5-*b*]pyridazine[13] (NMR spectrum: $CDCl_3$: $\tau = 1.80$ (q, H_8), 7.35 (d, 7-CH_3), $J_{8,7\text{-Me}} = 1.5$ Hz.

6-Chloro-7,8-dimethyltetrazolo[1,5-b]pyridazine

To an ice cooled suspension of 6-chloro-4,5-dimethyl-3-hydrazinopyridazine[15] (0.86 g) (prepared from the 3,6-dichloro analog[16]) in water (10 ml) and hydrochloric acid (2 ml, conc.) a solution of sodium nitrite in water (0.4 g in 2 ml) was added. After 30 min the product was filtered off and crystallized from ethanol (0.72 g, 76%), m. p. 77—78 °C. NMR spectrum: DMSO-d_6: $\tau = 7.25$ (d, 8-CH_3), 7.50 (d, 7-CH_3), $J_{7\text{-Me},\,8\text{-Me}} = 1.0$ Hz.

Anal. $C_6H_6ClN_5$ (183.60) calc'd.: C 39.26; H 3.29; N 38.15%
found: C 39.09; H 3.44; N 38.33%

7,8-Dimethyltetrazolo[1,5-b]pyridazine

was prepared in a similar manner from 4,5-dimethyl-3-hydrazinopyridazine hydrochloride in 90% yield, m. p. 130—131 °C. NMR spectrum: $CDCl_3$: $\tau = 1.70$ (s, H_6), 7.29 (d, 8-CH_3), 7.51 (d, 7-CH_3), $J_{7\text{-Me},\,8\text{-Me}} = 0.9$ Hz.

Anal. $C_6H_7N_5$ (149.16) calc'd.: C 48.31; H 4.73; N 46.96%
found: C 48.31; H 4.82; N 47.31%

7-Methyltetrazolo[1,5-b]pyridazine

To a solution of 6-chloro-7-methyltetrazolo[1,5-*b*]pyridazine[13] (1.06 g) in methanol (30 ml) palladized charcoal (0.3 g of 5%) and ammonia (1 ml of 25%) were added and the reaction mixture was stirred in an atmosphere of hydrogen. After consumption of the necessary amount of hydrogen, the mixture was extracted with chloroform. The extracts were mixed with fivefold amount of ice cold petroleum ether and the separated product was collected and crystallized from a mixture of chloroform and petroleum ether. Yield 0.7 g (83%), m. p. 132 °C. NMR spectrum: $CDCl_3$: $\tau = 1.50$ (d, H_6), 1.90 (dq, H_8), 7.37 (d, 7-CH_3), $J_{6,8} = 1.8$, $J_{8,7\text{-Me}} = 1.2$ Hz.

Anal. $C_5H_5N_5$ (135.13) calc'd.: C 44.44; H 3.73; N 51.83%
found: C 44.24; H 3.76; N 51.28%

Kinetic measurements

A sample of about 30 mg of the corresponding compound was dissolved in 0.5 ml of conc. sulfuric or trifluoromethanesulfonic acid and the solution was left at room temperature for several days to allow equilibration. The rate of equilibrium formation and the equilibrium constants were measured at 304, 323, 343, and 363 K

(in some cases also at 298.5, 301, and 383 K). The equilibrium constants as well as values of ΔH and E_a are presented in Table I and were calculated as described previously.[3] 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 ± 0.6 kcal/mol to ΔH and E_a values.

REFERENCES

1. M. Tišler, *Synthesis* (1973) 123.
2. N. B. Smirnova, I. J. Postovskii, N. N. Vereščagina, I. B. Lundina, and I. I. Mudrecova, *Khim. Geterotsikl. Soedin.* (1968) 167.
3. B. Stanovnik and M. Tišler, *Tetrahedron* **25** (1969) 3313.
4. T. Itai and S. Kamiya, *Chem. Pharm. Bull.* **11** (1963) 348; *Chem. Abstr.* **59** (1963) 8734.
5. T. Sasaki, K. Kanematsu, and M. Murata, *J. Org. Chem.* **36** (1971) 446.
6. W. D. Guither, D. G. Clark, and R. N. Castle, *J. Heterocycl. Chem.* **2** (1965) 67.
7. I. B. Lundina, J. N. Sheinker, and I. J. Postovskii, *Izv. Akad. Nauk SSSR Ser. Khim.* (1967) 66.
8. S. Polanc, B. Verček, B. Stanovnik, and M. Tišler, *Tetrahedron Lett.* (1973) 1677.
9. B. Stanovnik, M. Tišler, M. Ceglar, and V. Bah, *J. Org. Chem.* **35** (1970) 1138.
10. B. Stanovnik and M. Tišler, *Synthesis* (1970) 180.
11. B. Stanovnik, M. Tišler, and B. Stefanov, *J. Org. Chem.* **36** (1971) 3812.
12. N. Takahayashi, *J. Pharm. Soc. Jap.* **76** (1965) 765; *Chem. Abstr.* **51** (1957) 1192.
13. S. Linholter and R. Rosenoern, *Acta Chem. Scand.* **16** (1962) 2389.
14. V. Pirc, B. Stanovnik, M. Tišler, J. Marsel, and W. W. Paudler, *J. Heterocycl. Chem.* **7** (1970) 639.
15. M. Japelj, B. Stanovnik, and M. Tišler, *Monatsh. Chem.* **100** (1969) 671.
16. *US Pat.* 2.858.311; *Chem. Abstr.* **53** (1959) 6270.

IZVLEČEK

Piridazini. LXII. Tetrazolo-azido ravnotežja pri tetrazolo[1,5-b]piridazinih

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Tetrazolo[1,5-b]piridazini obstajajo v raztopini izključno v tetrazolski obliki. V raztopinah jakih kislin pa se vzpostavi ravnotežje med obema oblikama, azidno in tetrazolsko. Določili smo ravnotežne konstante v koncentrirani žvepleni kislini in v trifluormetansulfonski kislini.

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