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Pyridazines. XI. Some Reactions of 1,2,5-Thiadiazolo-(3,4-*d*) pyridazines

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The synthesis of several substituted 1,2,5-thiadiazolo-(3,4-*d*)-pyridazines is described. In addition, two new tricyclic systems were obtained and some reactions with ring opening of the fused thiadiazolo ring are described.

Ten years ago the first compound belonging to the 1,2,5-thiadiazolo-(3,4-*d*)pyridazine ring system* was described.[1] 1,2,5-Thiadiazole-3,4-dicarboxylic acid *bis*-hydrazide was used as starting material for the preparation of this system. Another synthetic possibility starting with diaminopyridazines was mentioned in a review[2] but so far no such experiments were described. The lack of information about the reactivity of this ring system evokes our interest inasmuch as we report now about some transformations. It had been only noted[3] that hot alkali converted the bicyclic ring system into a 4,5-diaminopyridazine derivative.

Since the Kekulé resonance of the pyridazine ring of 1,2,5-thiadiazolo-(3,4-*d*)pyridazines is impaired these compounds are expected to be less stable than other fused azolopyridazines. MO calculations** of total π- and frontier electron densities for the parent symmetric heterocyclic compound are presented in Table I.

As starting material we have used 4-hydroxy-(1,2,5)-thiadiazolo-(3,4-*d*)-pyridazin-7(6H)one (I) which could be transformed into the 4,7-dichloro derivative (II, R = R_1 = Cl) in low yield. Attempted hydrogenolysis of the latter produced only 1,2,5-thiadiazolo(3,4-*d*)pyridazine-4-(5H)one (III). In a somewhat better fashion thiation could be performed to give IV (R = H). This, after being transformed into the monophenacylthio derivative (IV, R = CH_2COPh) readily afforded the tricyclic compound V upon cyclodehydration. Hydrazinolysis of the 4,7-*bis*-(methylthio) compound (II, R = R_1 = SMe) afforded only the monohydrazino derivative (II, R = $NHNH_2$, R_1 = SMe) which was transformed further into the tricyclic compound VI. In an attempt to synthesize the latter compound from the *bis*-(methylthio) derivative by treatment with sodium azide in *N,N*-dimethylformamide a compound was obtained

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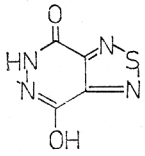
* In addition to the systematic name the system was named also as pyridazino(4,5-*d*)-2,1,5-thiadiazole.

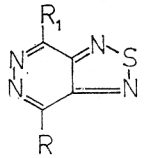
** Parameters for the Hückel MO calculations were taken from A. Streitwieser, *Molecular Orbital Theory for Organic Chemists*, J. Wiley, New York, 1961, p. 135. Data on this and other azolo- and azinoazines will appear in *Pyridazines* (Ed. R. N. Castle), J. Wiley.

TABLE I

Total and Frontier π-Electron Densities of 1,2,5-Thiadiazolo (3,4-d) pyridazines

Position	Total	Frontier
1	1.3549	0.2697
2	0.9859	0.000
3	1.3549	0.2697
3a	1.0301	0.0123
4	0.9426	0.1157
5	1.1794	0.1023
6	1.1794	0.1023
7	0.9426	0.1157
7a	1.0301	0.0123





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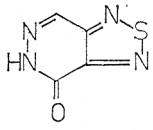

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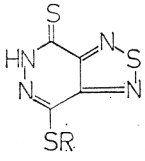

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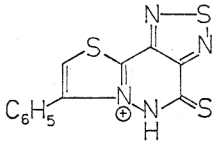

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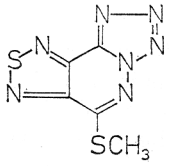

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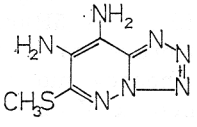

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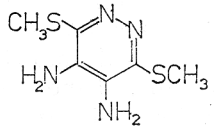

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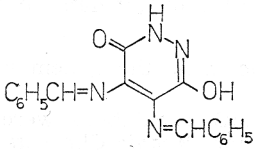

IX

which based on its spectral and analytical data must be VII. Its formation is understandable if we take into consideration the relatively facile ring opening of the bicyclic system in basic media.[3] Although 1,2,5-thiadiazoles are quite resistant towards the influence of bases[4], it appears that the relatively strong nucleophilicity of the azide is sufficient to bring about the ring opening. Another factor which contributes to this conversion is the initial formation of the fused tetrazolo ring. The formed tricyclic compound is, because of lesser stabilization than within the bicyclic analog more susceptible to ring opening of the thiadiazolo part. In agreement with this is the observation that the *bis*-(methylthio) derivative is unaffected by conc. ammonia, and ring opening to 4,5-diamino-3,6-*bis*-(methylthio)pyridazine (VIII) takes place only after heating under pressure. In a similar manner 80% hydrazine hydrate afforded a diamino-hydroxy-pyridazinone, identified as its *bis*-benzylidene derivative IX.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage and are corrected. All mass spectra were recorded on a CEC 21-110C instrument using direct sample insertion into the ion source which was operating at 170° and ionization voltage of 70 V.

*4,7-Dichloro-1,2,5-thiadiazolo(3,4-*d*)pyridazine* (II, R = R_1 = Cl)

Compound I (1.0 g.), phosphorus oxychloride (10 ml.) and pyridine (2. ml.) were heated under reflux for 3 hrs until a clear solution was obtained. Excess phosphorus oxychloride was removed *in vacuo* and the residue was added in small portions on crushed ice in such a manner that the temperature of the solution did not rise over 0°. The mixture was immediately extracted with chloroform, the combined extracts dried over anhydrous sodium sulfate and the solvent thereafter removed *in vacuo*. The crude product (yield 21%) with m. p. 115—130° was used without purification for further syntheses.

*1,2,5-Thiadiazolo(3,4-*d*)pyridazin-4(5H)one hydrochloride* (III)

A solution of the above dichloro compound (II, R = R_1 = Cl; 0.5 g.) in methanol (100 ml.) was hydrogenated in the presence of palladium on charcoal (0.25 g. of 10%) until about 120 ml. of hydrogen were absorbed. The filtrate was evaporated *in vacuo* and the residue was recrystallized from water (yield 55%); m. p. 245°.

Anal. $C_4H_3ClN_4OS$ (190.62) calc'd.: C 27.62; H 1.72; N 32.18%
found: C 27.82; H 1.92; N 32.02%

*4-Mercapto-1,2,5-thiadiazolo(3,4-*d*)pyridazine-7(6H)thione* (IV, R = H)

To a solution of compound I (1.0 g.) in anhydrous pyridine (50 ml.) at 100° under stirring phosphorus pentasulfide (5.0 g.) was added portionwise and the mixture was then heated for 2 hrs. at 115—120°. The solvent was distilled off and the residue was heated under reflux after water (40 ml.) has been added. Upon cooling and acidification the product precipitated. It was purified by dissolving it in a warm solution of sodium bicarbonate, filtering and adding conc. hydrochloric acid (yield 40%); m. p. 255—260°.

Anal. $C_4H_2N_4S_3$ (202.28) calc'd.: C 23.77; H 1.00; N 27.73%
found: C 24.14; H 1.41; N 27.64%

*4-Phenacylthio-1,2,5-thiadiazolo(3,4-*d*)pyridazine-7(6H)thione* (IV, R=CH_2COPh)

was obtained from compound IV (R=H) in the usual way in 76% yield. M. p. 232—235° (from *N,N*-dimethylformamide).

Anal. $C_{12}H_8N_4OS_3$ (320.41) calc'd.: C 45.01; H 2.52; N 17.50; S 29.99%
found: C 45.61; H 2.68; N 17.57; S 29.35%

4,7-Bis-(methylthio)-1,2,5-thiadiazolo(3,4-d)pyridazine (II, R = R_1 = SMe)

was also prepared in the usual way by methylation with methyl iodide in 77% yield. M. p. 221—223° (from *N,N*-dimethylformamide).

Anal. $C_6H_6N_4S_3$ (230.34) calc'd.: C 31.31; H 2.63; N 24.35; S 41.71%
found: C 31.73; H 2.80; N 23.94; S 41.80%

7-Phenyl-4(5H)thioxo-1,2,5-thiadiazolo(3,4-d)thiazolo(2,3-f)pyridazin-6-ium perchlorate (V)

The phenacylthio compound (IV, R = CH_2COPh; 0.3 g.) was left to stand overnight in conc. sulfuric acid (5.0 ml.) in a stoppered flask at room temperature. The ice cold solution was then treated with iced water (10 ml.) and perchloric acid (3 ml. of 70%). The separated product was recrystallized from methanol (yield almost quantitative), m. p. 180°.

Anal. $C_{12}H_7ClN_4O_4S_3$ (402.86) calc'd.: C 35.75; H 1.74; N 13.91; S 23.84%
found: C 35.90; H 2.08; N 13.73; S 23.56%

4-Hydrazino-7-methylthio-1,2,5-thiadiazolo(3,4-d)pyridazine (II, R = $NHNH_2$, R_1 = SMe)

The *bis*-(methylthio) compound (II, R=R_1=SMe; 1.0 g.), ethanol (20 ml.) and hydrazine hydrate (16 ml. of 80%) were heated under reflux for 30 min. until the solution become dark coloured. Upon cooling the product separated (yield 73%) and had m. p. 245—250°. All attempts to purify the product by crystallization were not successful. Therefore the benzylidene derivative (II, R = NHN=CHPh, R_1 = SMe) was prepared in the usual way in 60% yield. M. p. 194°. Mass spectrum: M^+ = 302.

Anal. $C_{12}H_{10}N_6S_2$ (302.39) calc'd.: C 47.68; H 3.34; N 27.81%
found: C 47.44; H 3.30; N 28.12%

6-Methylthio-1,2,5-thiadiazolo(3,4-d)tetrazolo(1,5-b)pyridazine (VI)

Compound II (R = $NHNH_2$, R_1 = SMe; 0.6 g.) was dissolved in a minimum quantity of 2 *N* hydrochloric acid and the cold (0°) solution was treated dropwise under stirring with a solution of sodium nitrite (0.3 g. in 2 ml. of water). The separated product was filtered off and crystallized from *N,N*-dimethylformamide (yield almost quantitative); m. p. 232°. Mass spectrum: M^+ = 225.

Anal. $C_5H_3N_7S_2$ (225.26) calc'd.: C 26.67; H 1.33; N 43.56; S 28.45%
found: C 26.98; H 1.83; N 43.38; S 28.70%

7,8-Diamino-6-methylthiotetrazolo(1,5-b)pyridazine (VII)

A solution of the *bis*-(methylthio) compound (II, R = R_1 = SMe; 0.5 g.) in *N,N*-dimethylformamide (20 ml.) was treated with sodium azide (280 mg.) and the mixture was stirred at 115° for 2 hrs. Upon cooling the separated product was filtered off and crystallized from *N,N*-dimethylformamide (yield 28%); M. p. 244°. Mass spectrum: M^+ = 197.

Anal. $C_5H_7N_7S$ (197.21) calc'd.: C 30.46; H 3.55; N 49.75; S 16.24%
found: C 29.98; H 3.22; N 50.12; S 15.99%

4,5-Diamino-3,6-bis-(methylthio)pyridazine (VIII)

A mixture of the bicyclic compound II (R = R_1 = SMe; 1.0 g.) and conc. aqueous ammonia (50 ml.) was heated under pressure at 120° for 2 hrs. The autoclave was vented and the product which separated from the residual solution was collected and recrystallized by dissolving it in *N,N*-dimethylformamide, filtering and adding water for precipitation (yield 51%); m. p. 187°. Mass spectrum M^+ = 202.

Anal. $C_6H_{10}N_4S_2$ (202.31) calc'd.: C 35.64; H 4.95; N 27.72; S 31.68%
found: C 35.75; H 4.99; N 27.92; S 31.95%

4,5-Bis-(benzylideneimino)-3-hydroxypyridazin-6(1H)one (IX)

A mixture of the bis-(methylthio) compound II (R = R_1 = SMe; 1.0 g.), *N,N*-dimethylformamide (40 ml.) and hydrazine hydrate (5 ml. of 80%) was heated under reflux for 2 hrs. Upon cooling some water was added to precipitate the product (0.2 g.). The latter (0.1 g.), ethanol (3 ml.), acetic acid (0.3 ml.) and benzaldehyde (50 mg.) were heated under reflux for 10 min. Upon cooling the separated product was filtered off (yield 41%); m. p. 130°.

Anal. $C_{18}H_{14}N_4O_2$ (318.35) calc'd.: C 67.91; H 4.43; N 17.60%
found: C 67.72; H 4.66; N 17.42%

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IZVLEČEK

Piridazini. XI. Nekatere reakcije 1,2,5-tiadiazolo(3,4-*d*)-piridazinov

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Opisana je sinteza nekaterih substituiranih 1,2,5-tiadiazolo(3,4-*d*)-piridazinov. Poleg tega sta bila pripravljena dva nova triciklična sistema, opisane so pa še nekatere reakcije odprtja kondenziranega tiadiazolovega obroča.

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