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# 2,4-DIAMINOTHIAZOLES: TAUTOMERIC STRUCTURES AND ACETYLATION–SUBSTITUTION STUDIES

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**Abstract**—NMR investigations on the hydrohalides of 2,4-diaminothiazole, **1**, and on its 5-methyl and 5-phenyl derivatives, **2** and **3** respectively, show that they exist as a single nonaromatic tautomer with C-5 tetrahedral. This is also true for the free base **1**, whereas **3** has C-5 trigonal. The di- and triacetyl derivatives of **1–3** are shown to be N,N'-di- and N,N,N'-triacetyl derivatives. Ethyl 2-cyano-3-ethoxyacrylate and 2-cyano-3-ethoxyacrylonitrile react with **1** at C-5.

It has been reported[1] that 2,4-diaminothiazoles are "almost devoid of aromatic character". Compounds **1–3** have been isolated as salts, but they are unstable as free bases; **1** and **3** can be prepared, while attempts to liberate the free base **2** from its hydrochloride result in formation of 2-amino-4-hydroxy-5-methylthiazole.[1] 2,4-Diaminothiazoles, as well as their salts, may thus exist in one of the nonaromatic tautomeric forms **b–e** (*cf* Chart 1).

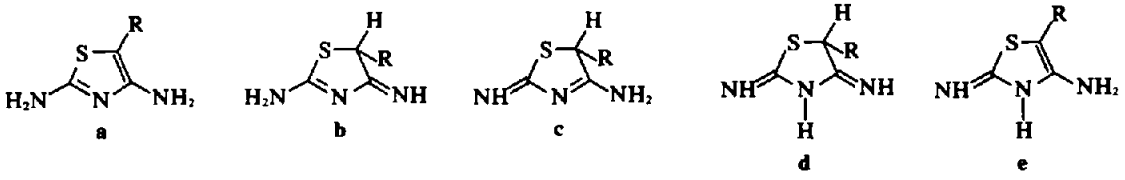
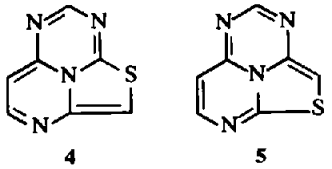


CHART 1. Tautomeric forms for **1–3**; **1**: R = H; **2**: R = $CH_3$; **3**: R = $C_6H_5$.

We needed information about the true structure of 2,4-diaminothiazoles[1,2] since we anticipated using them as starting materials for the synthesis of thiaazacyclazines[3] of types **4** and **5** (*cf* Chart 1 in Ref 4). The present communication describes spectroscopic studies on the tautomerism in the 2,4-diaminothiazoles **1–3**,[1] their behaviour towards acetic anhydride, and the reaction of **1** with ethyl 2-cyano-3-ethoxyacrylate, **6**,[5] and with 2-cyano-3-ethoxyacrylonitrile, **7**.



The NMR spectra (*cf* Table 5) of the hydrohalides of **1–3** display the following signals for the protons attached to C-5; $CH_2$-singlet at 4·58 ppm (**1**·HCl), CH-quartet at 5·13 ppm (**2**·HCl), and CH-singlet at 6·39 ppm (**3**·HBr). The NH and $NH_2$ signals are in no case sufficiently distinct to exclude a tautomer of type **d**, but the relatively intense UV absorption at *ca* 260 nm (*cf* Table 3) makes this nonconjugated structure unlikely for the predominant tautomer. On addition of $D_2O$ to dimethyl sulphoxide solutions of the hydrohalides of **1–3** a 50% exchange of the C-5 protons was observed (NMR) after *ca* 48 h for all three compounds. The free base **1** also has a tetrahedral C-5 atom shown by a $CH_2$-singlet at 4·10 ppm. The NMR spectrum of the free base **3** contains no CH-absorption, which indicates that this 5-phenyl derivative has the aromatic structure **3a**; however, the tautomeric form **3e** cannot be excluded on the basis of this NMR evidence.

Acetylation of **1–3** in the presence of a base under mild conditions yields diacetyl derivatives.[1] Their NMR spectral data are summarized in Table 1. The spectra of the diacetates show two broad amide signals and the NMR spectra of the diacetyl derivatives do not contain, contrary to what we observed for the starting compounds, any high-field signals from C-5 (methine or methylene) protons. These observations require an aromatic structure for the diacetates **8–10**. There is no indication (NMR) that a second tautomer, *cf* structure V in Ref 1, is present in dimethyl sulphoxide solution.

Table 1. NMR spectral data for **8–13** (Solvent: DMSO-$d_6$ for **8–12** and $CDCl_3$ for **13**)

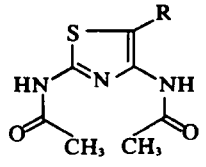
| Protons | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|
| Acetyl | 2·07(3H)<br>2·17(3H) | 2·00(3H)<br>2·12(3H) | 1·97(3H)<br>2·18(3H) | 2·15(3H)<br>2·21(6H) | 2·12(3H)<br>2·22(6H) | 2·10(3H)<br>2·27(6H) |
| Amide | 10·38(1H)<br>11·80(1H) | 9·70(1H)<br>11·95(1H) | 9·70(1H)<br>12·12(1H) | 12·10(1H) | 12·06(1H) | 10·05(1H) |
| C-5 substituent | 7·03(1H) | 2·12(3H) | 7·43(5H) | 7·18(1H) | 2·21(3H) | 7·38(5H) |

Table 2. NMR spectral data for **14–19**. (Solvent DMSO-$d_6$)

| Protons | 14 | 15 | 16 | 17 | 18 | 19 |
|---|---|---|---|---|---|---|
| $NH_2$; NH | 8·02(2H)<br>8·70(2H) | 8·14(2H)<br>8·86(2H) | 7·95(2H)<br>12·30(1H) | 8·10(2H)<br>12·15(1H) | 10·66(1H)<br>12·70(1H) | 10·83(1H)<br>12·95(1H) |
| Olefinic | 8·12(1H) | 7·84(1H) | 8·36(1H) | 8·16(1H) | 8·38(1H) | 8·58(1H) |
| Acetyl | | | 2·18(3H) | 2·19(3H) | 2·15(3H)<br>2·21(3H) | 2·25(3H)<br>2·27(3H) |
| Ethyl ester | 1·23(3H)<br>4·13(2H) | | 1·25(3H)<br>4·17(2H) | | 1·28(3H)<br>4·25(2H) | |

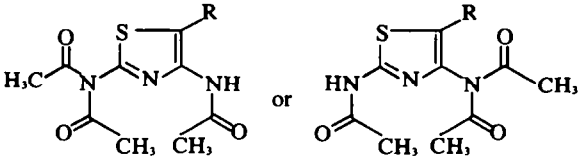
Under more forcing acetylating conditions the hydrobromide of **3** was reported to form a triacetyl derivative.[1] We found this to be true also for the hydrochlorides of **1** and **2**. Hydrolysis of the triacetyl derivatives under very mild conditions (*cf* Ref 1) converted them to diacetyl compounds, proved to be identical with the derivatives obtained by acetylation of the hydrohalides of **1–3** under mild conditions. The NMR spectral data (*cf* Table 1) for the triacetyl derivatives support the aromatic structures **11** and **13** (no high field H-5 absorption and one broad amide signal). N,N-Diacetyl compounds hydrolyse with extreme ease,[6] and their IR spectra (solid phase or solution) contain a characteristic doublet of high intensity at 1700–1790 $cm^{-1}$.[7] Since the triacetyl derivatives **11–13** all show pronounced sensitivity towards hydrolysis and display two strong IR bands at *ca* 1700 and 1750 $cm^{-1}$, we assume them to be N,N,N′-triacetyl derivatives. This was proved by acetylation of **10**, which with $(CD_3CO)_2O$ gave a triacetyl derivative, containing one $CD_3$ group (NMR, MS). Hydrolysis of this compound gave a diacetyl derivative which contained 50 ± 5% deuterium in one of the two Me groups (NMR). Further support for the N,N,N′-triacetyl structure was rendered by the observation that the NMR spectra of the triacetyl derivatives **11–13** display two N-acetyl signals in the ratio 1 : 2. The two acetyl proton signals in the NMR spectrum of **13** do not separate into three different bands when Eu(fod)$_3$[8] is added. This indicates that two of the acetyl groups are equivalent and thus attached to one and same amino group. The spectral data, however, do not establish at which amino group diacetylation occurs.

Condensation of **1** with ethyl 2-cyano-3-ethoxyacrylate, **6**,[5] and with 2-cyano-3-ethoxyacrylonitrile, **7**, both key-compounds in the synthesis of tri- and tetraazacycl[3.3.3]azines,[9,10,11] yielded **14** and **15** respectively. Their NMR spectra each display only a single one-proton signal at low field (*cf* Table 2); therefore substitution in the 5-position had occurred in both cases. Acetylation of **14** and **15** with acetic anhydride (pyridine, 70°) gave the monoacetyl derivatives **16** and **17** respectively. Under more forcing conditions (acetic anhydride–sulphuric acid, 25°) the corresponding diacetyl compounds **18** and **19** resulted. Their structures follow from the spectral data summarized in Table 2 and in Experimental.



**8–10**

**8**: R = H, **9**: R = $CH_3$, **10**: R = $C_6H_5$



**11–13**

**11**: R = H, **12**: R = $CH_3$, **13**: R = $C_6H_5$

2,4-Diaminothiazole, **1**, apparently reacts with **6** and **7** at the 5 position and **1** is therefore unsuitable for our synthetic purposes, which require instead that one of the amino groups reacts. A 5-substituted 2,4-diaminothiazole would consequently be a more useful starting material. The obvious choice would be the 5-Me homologue, but since its free base cannot be isolated, we turned to 5-phenyl-2,4-diaminothiazole. This approach, which led to successful results, has been described in an earlier communication.[4]

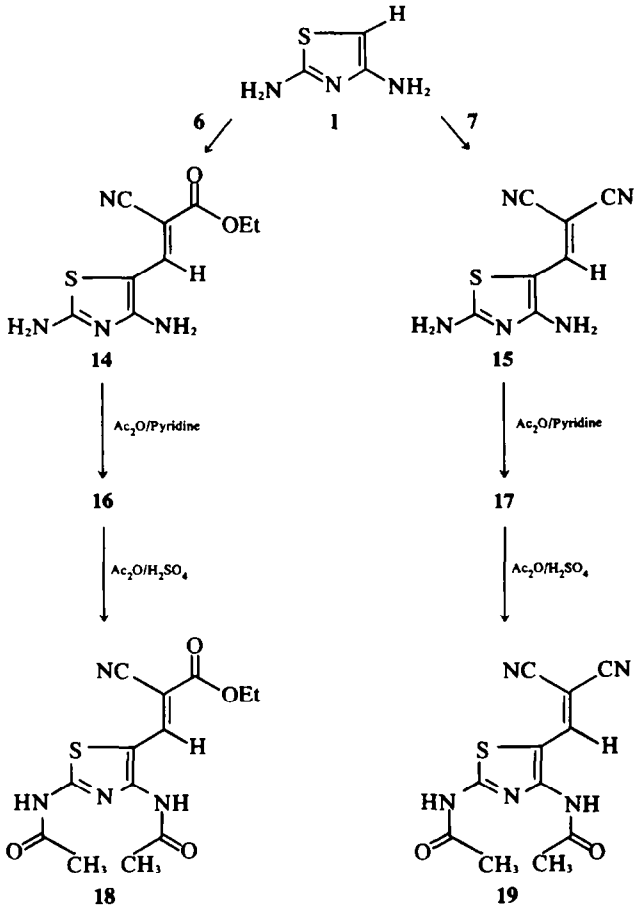



CHART 2

## EXPERIMENTAL

*General.* IR spectra were determined in KBr with a Perkin-Elmer 337 spectrophotometer. NMR spectra were recorded with a Varian Model A-60 or a Jeol Model MH-60 spectrometer, using TMS as internal reference. Chemical shifts are given in δ-values. UV and visible spectra were measured in EtOH with a Cary Model 15 spectrophotometer. The mass spectra habe been obtained from the Department of Medical Biochemistry, University of Göteborg, and were recorded with a GEC-AEI 902 instrument. The elemental analyses were carried out at the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna. TLC was performed on Silica Gel $GF_{254}$ (Merck) plates with EtOAc as the developing solvent, and the spots were visualized with short-wave UV light and with iodine vapour. Ethyl 2-cyano-3-ethoxyacrylate was obtained from Fluka AG and recrystallized from EtOH and $(CD_3CO)_2O$ was purchased from Ciba-Geigy AG.

Compounds **1**, **1**·HCl, **2**·HCl, **3**, **3**·HBr, **8**, **10**, and **13** were prepared as described by Davies *et al.*[1] Their spectral data and those of **9**, **11**, and **12** are summarized in Tables 3–5.

2,4-*Diacetamido*-5-*methylthiazole*, **9**. The method of Davies *et al.*[1] led to a mixture of di- and triacetyl compounds and **9** was therefore prepared according to the following modified procedure, which gave only the diacetyl derivative. 2,4-Diamino-5-methylthiazole hydrochloride (1·0 g) was heated to 115° in pyridine (0·37 ml) and the soln was then cooled to room temp $Ac_2O$ (3·7 ml) was added and the mixture was allowed to stand for 6 days at room temp. The light-yellow ppt was filtered off, washed with water, and crystallized from EtOH, yield: 320 mg (24%) of white, crystalline **9**, m.p. 224–226°, MS: $M^+ = 213$.

*Triacetyl*-2,4-*diaminothiazole*, **11**. A mixture of 2,4-diaminothiazole hydrochloride (1·25 g), 10 ml freshly dis-

tilled $Ac_2O$, and 1 ml pyridine was refluxed for 14 h. The mixture was cooled to room temp and poured into 50 ml ice water; the new mixture was extracted with 3 × 25 ml of $CH_2Cl_2$. The combined organic layers were washed with 4 × 50 ml of 10% $NaHCO_3$ aq and 50 ml of sat NaCl aq and finally dried ($MgSO_4$). The solvent was then evaporated. The residue was chromatographed on 50 g of silica gel (Merck), using $CH_2Cl_2$ as the eluant, yield: 300 mg (15%) of **11**. Crystallization from benzene gave **11** as white cubes, m.p. 152–153°. (Found: C, 44·58; H, 4·53; N, 17·17; S, 13·14. $C_9H_{11}N_3O_3S$ requires: C, 44·80; H, 4·60; N, 17·42; S, 13·29%) MS: $M^+$ = 241 IR: 1700, 1760 $cm^{-1}$.

*Triacetyl-2,4-diamino-5-methylthiazole,* **12**. 2,4-Diamino-5-methylthiazole. HCl (1·25 g) was triacetylated as described for **1**. The crude, oily product was diluted with 5 ml anhyd EtOH and 5 ml ether, and the soln was then cooled in ice. A white ppt was filtered off and washed with ether, yield: 450 mg (24%) of **12**. Crystallization from benzene gave **12** as white cubes, m.p. 150°. (Found: C, 47·06; H, 5·09; N, 16·50; S, 12·95. $C_{10}H_{13}N_3O_3S$ requires: C, 47·05; H, 5·13; N, 16·46; S, 12·56%). MS: $M^+$ = 255. IR: 1690, 1740 $cm^{-1}$.

*NMR shift studies on* **13**. On addition of 50 mg of Eu(fod)$_3$-$d_{27}$ to a soln of **13** (25 mg) in 0·4 ml dry $CDCl_3$, the NMR spectrum signals for the acetyl protons at 2·27 and 2·10 ppm (*cf* Table 1) were displaced to 3·30 (6 H) and 3·47 ppm respectively.

*Hydrolysis of* **11**, **12**, *and* **13**. The triacetyl derivatives **11**, **12**, and **13** were hydrolysed in the following way: 40 mg was dissolved in 5 ml 25% EtOH aq and the soln refluxed for 12 h.[1] The solvent was evaporated under reduced pressure and the remaining diacetyl derivative was isolated by prep TLC. IR spectra, m.ps, and $R_f$ values proved these diacetyl derivatives to be identical with **8**, **9**, and **10** respectively.

*Acetylation of* **10** *with* $(CD_3CO)_2O$. A soln of **10** (100 mg) in 0·3 ml $(CD_3CO)_2O$ was kept in a sealed tube at 130–140° for 2 h. The mixture was evaporated to dryness *in vacuo* at 40°. The residue was purified by prep TLC to give 65 mg of **13a**, containing one $CD_3$ group (NMR); MS: $M^+$ = 320; NMR: ($CDCl_3$): acetyl protons at 2·10 (3H) and at 2·27 (3H), instead of 6H as observed for **13**, phenyl protons at 7·38 (5H), and one amide proton at 10·05 ppm.

*Hydrolysis of* **13a**. The deuterated triacetyl compound **13a** was hydrolysed as described for **13** to give a diacetyl derivative which had the same $R_f$ value as **10**. NMR (DMSO-$d_6$): acetyl protons at 1·97 (1·5H) and at 2·18 (3H) and phenyl protons at 7·43 ppm (5H).

*Preparation of* **14**. A soln of ethyl 2-cyano-3-ethoxyacrylate (19·1 g; 0·113 mol) in 1000 ml anhyd EtOH was added dropwise to a stirred suspension of 2,4-diaminothiazole (13·0 g; 0·113 mol) in 200 ml anhyd EtOH kept at − 5–0°. An orange ppt formed immediately, and the mixture was allowed to attain room temp. After 16 h, the ppt was filtered off and washed first with EtOH and then with ether, yield: 15·3 g (57%) of orange **14**, m.p. > 300°, homogeneous on TLC. MS: $M^+$ found 238·051 ± 0·003. $C_9H_{10}N_4O_2$ $^{32}S$ requires: 238·052.$(M+2)^+$ found 240·048 ± 0·003. $C_9H_{10}N_4O_2$ $^{34}S$ requires: 240·048; UV: $\lambda_{max}$ at 236 ($\epsilon$ = 10500), 282 ($\epsilon$ = 6900), and 428 nm ($\epsilon$ = 46000).

*Preparation of* **15**. 2,4-Diaminothiazole (13·0 g; 0·113 mol) was treated with 2-cyano-3-ethoxyacrylonitrile (13·8 g; 0·113 mol) as described in the preparation of **14**, yield: 9·6 g (45%) of brown-yellow **15**, m.p. > 300°, homogeneous on TLC, MS: $M^+$ found 191·025 ± 0·003. $C_7H_5N_3$ $^{32}S$ requires: 191·027. $(M+2)^+$ found 193·020 ± 0·003. $C_7H_5N_3$ $^{34}S$ requires: 193·022; UV: $\lambda_{max}$ at 241 ($\epsilon$ = 8800), 280 ($\epsilon$ = 6700) and 425 nm ($\epsilon$ = 43500).

*Preparation of* **16**. A suspension of **14** (500 mg) in 1 ml freshly distilled $Ac_2O$ and 10 ml pyridine was stirred at

Table 3. UV spectral data for **1**, **3**, **1**·HCl, **2**·HCl, and **3**·HBr

| **1** (nm) ($\epsilon$) | **3** (nm) ($\epsilon$) | **1**·HCl (nm) ($\epsilon$) | **2**·HCl (nm) ($\epsilon$) | **3**·HCl (nm) ($\epsilon$) |
|---|---|---|---|---|
| 235 (15700) | 227 sh (6500) | 232 (16300) | 235 (19900) | 229 (17400) |
| | 327 (11800) | 260 (10200) | 262 (12400) | 262 (8950) |
| | | | | 327 (3500) |

Table 4. UV spectral data for **8**–**13**.

| **8** (nm) ($\epsilon$) | **9** (nm) ($\epsilon$) | **10** (nm) ($\epsilon$) | **11** (nm) ($\epsilon$) | **12** (nm) ($\epsilon$) | **13** (nm) ($\epsilon$) |
|---|---|---|---|---|---|
| 220 (20000) | 214 (12400) | 218 (14200) | 266 (8300) | 273 (9300) | 293 (15100) |
| 247 (7300) | 277 (8050) | 297 (14400) | | | |
| 282 (4600) | | | | | |

Table 5. NMR spectral data for **1**, **3**, **1**·HCl, **2**·HCl, and **3**·HBr (Solvent DMSO-$d_6$)

| | **1** | **3** | **1**·HCl | **4**·HCl | **3**·HCl |
|---|---|---|---|---|---|
| Amino/ Imino | 7·73(3H) | 5·12(2H) 6·80–7·35(2H) | 13·60(4H) | 9·33–10·15(4H) | 9·42–10·75(4H) |
| 5-Methyl/ 5-Phenyl | | 6·80–7·35(5H) | | 1·75 d (3H) | 7·42(5H) |
| 5-Methine/ 5-Methylene | 4·10(2H) | | 4·58(2H) | 5·13 q (1H) | 6·39(1H) |

room temp for 24 h. The mixture was then poured into 50 ml ice water. The ppt was filtered off and washed first with water and then with acetone, yield: 450 mg of an orange solid, containing *ca* 5% of starting material (TLC). Chromatography on 50 g of silica gel ($\phi < 0{\cdot}08$ mm) using EtOAc as the eluant gave 390 mg (68%) of **16**, m.p. > 300°, homogeneous on TLC. (Found: C, 46·90; H, 4·48; N, 18·89; S, 10·50. $C_{11}H_{12}N_4O_3S$ requires: C, 47·13; H, 4·32; N, 19·99; S, 11·44%); MS: $M^+ = 280$; UV: $\lambda_{max}$ at 246 ($\epsilon = 10100$), 295 ($\epsilon = 7000$), and 441 nm ($\epsilon = 27600$).

*Preparation of* **17**. A suspension of **15** (5 g) in 10 ml freshly distilled $Ac_2O$ and 100 ml pyridine was stirred at 75° for 15 h. The mixture was cooled to room temp and then poured into *ca* 500 ml ice water. The ppt was filtered off and washed first with water and then with acetone, yield: 4·1 g (61%) of **17** as a green-yellow solid, m.p. > 300°, homogeneous on TLC. (Found: C, 46·28; H, 3·13; N, 29·55; S, 13·43. $C_9H_7N_5OS$ requires: C, 46·34; H, 3·03; N, 30·03; S, 13·75%); MS: $M^+ = 233$; UV: $\lambda_{max}$ at 249 ($\epsilon = 10900$), 296 ($\epsilon = 7600$), and 443 nm ($\epsilon = 28200$)

*Preparation of* **18**. To a stirred suspension of **16** (1·7 g) in 65 ml $Ac_2O$, 1·0 g conc. $H_2SO_4$ was added at room temp. After 16 h, the mixture was poured into 250 ml water. The ppt was filtered off and washed first with water and then with acetone, yield: 1·07 g (55%) of **18** as a yellow solid, m.p. > 300°, homogeneous on TLC. (Found: C, 48·31; H, 4·34; N, 17·11; S, 9·93. $C_{13}H_{14}N_4O_4S$ requires: C, 48·44; H, 4·38; N, 17·38; S, 9·95%); MS: $M^+ = 322$; UV: $\lambda_{max}$ at 251 ($\epsilon = 12400$), 272 ($\epsilon = 7100$), and 390 nm ($\epsilon = 18100$).

*Preparation of* **19**. To a stirred suspension of **17** (350 mg) in 14 ml $Ac_2O$, 400 mg conc $H_2SO_4$ was added at room temp. After 2 h, the mixture was poured into 100 ml sat NaCl aq. The new mixture was extracted with 3 × 100 ml of EtOAc. The organic layer was washed with 3 × 100 ml of NaCl aq and then dried ($MgSO_4$). After evaporation of the solvent, 310 mg (75%) of **19** as a yellow solid remained; m.p. > 300°, homogeneous on TLC. (Found: C, 47·58; H, 3·41; N, 25·58; S, 11·89. $C_{11}H_9N_5O_2S$ requires: C, 47·99; H, 3·30; N, 25·44; S, 11·65%); MS: $M^+ = 275$; UV: $\lambda_{max}$ at 248 ($\epsilon = 14100$), 274 ($\epsilon = 8240$), and 407 nm ($\epsilon = 14700$).

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