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# Synthesis of Novel Bispyrimido[1,2-*b*:1′,2′-*e*][1,2,4,5]tetrazines

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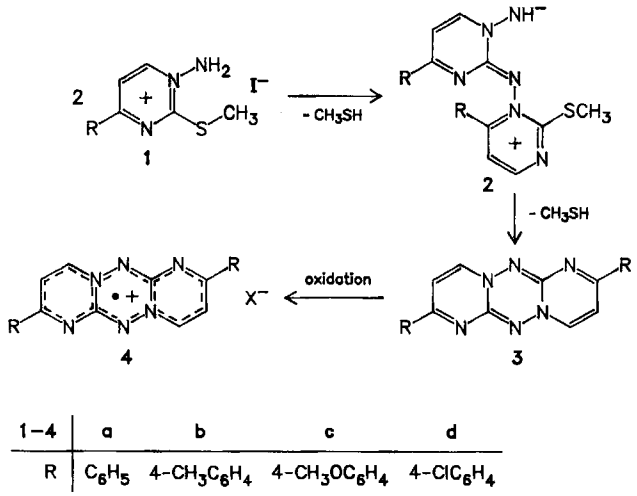
Novel bispyrimido[1,2-*b*:1′,2′-*e*][1,2,4,5]tetrazines **3** are obtained by self-condensation of 1-amino-2-(methylthio)pyrimidinium iodides **1**. Zwitterionic bispyrimidines act as intermediates and can be isolated after short heating. Compounds **3** are oxidized with bromine or perchloric acid in acetic acid to give the corresponding radical salts **4**. These very stable radicals are characterized by ESR spectra and by cyclic voltammetry.

A number of known 1,2,4,5-tetrazines which are fused with two heteroaromatic rings such as 1,2,4-triazole[1], benzazoles[2], pyridine[2], quinoline[2], isoquinoline[2], or triazines[3] have been synthesized by condensation of two molecules of *N*-amino-heterocycles having a leaving group, i.e. an alkylthio or chloro substituent at the carbon atom adjacent to the ring nitrogen atom.

Recently, we have found an efficient access to 1-amino-2-(methylthio)pyrimidinium salts **1**[4,5] by reaction of 3-thiocyanatopropeniminium salts with hydrazine and methylation of the resulting 1-amino-2(1*H*)-pyrimidinethiones. Occasionally, we have observed that these compounds undergo decomposition on longer heating during recrystallization. Since compounds **1** possess an isothiohydrazide moiety this decomposition may be due to a selfcondensation, possibly giving the hitherto unknown bispyrimido[1,2-*b*:1′,2′-*e*][1,2,4,5]-tetrazines*) in a similar manner as mentioned above. Systematic investigations have revealed[6] that the anticipated condensation takes place in two steps. Short heating of **1** in acetonitrile/triethylamine gives rise to the attack of the amino group of **1** at the position 2 of another molecule of the starting compound **1** while one molecule of methanethiol is eliminated (methods A and B). The intermediates **2** formed in this way are orange-red solids and are stable after isolation. Further heating in DMF or acetic anhydride causes intramolecular attack of the imido group at the methylthio-substituted carbon atom of the other pyrimidine nucleus. By elimination of another molecule of methanethiol bispyrimido[1,2-*b*:1′,2′-*e*]-[1,2,4,5]tetrazines **3** are formed (method C). Compounds **3** can more efficiently be prepared by a one-pot procedure by prolonged heating of 1-amino-2-(methylthio)pyrimidinium salts **1** in DMF/triethylamine (method D).




| 1–4 | a | b | c | d |
|---|---|---|---|---|
| R | $C_6H_5$ | 4-$CH_3C_6H_4$ | 4-$CH_3OC_6H_4$ | 4-$ClC_6H_4$ |

The bispyrimido[1,2-*b*:1′,2′-*e*][1,2,4,5]tetrazines **3** are deeply red colored compounds, which are sparingly soluble in organic solvents. The structural assignment of **2** and **3** is in accordance with results of elemental analysis and with spectroscopic data. Intensive peaks $M^+ + 1$ and $M^+ + 2$, which are typical of uncondensed 1,2,4,5-tetrazines[7], are not observed in the mass spectra. Known fused 1,2,4,5-tetrazines are representatives of two-step redox systems and are described[2,8] as being very sensitive to oxidation giving cation radicals. This property usually permits to record proper NMR spectra. The novel bispyrimido[1,2-*b*:1′,2′-*e*][1,2,4,5]-tetrazines **3** are more stable.

Cyclic voltammetry has revealed oxidation potentials which are lower than those of the previously known condensed tetrazines[8]. The values increase with increasing electron-withdrawing properties of the substituent R. Due to the low solubility *N*,*N*-dimethylacetamide has to be used as solvent, permitting measurement of the oxidation potential of the second oxidation step (for voltammetric oxidation of the corresponding radical cation salt see below). Both oxidations are single electron-transfer steps and are reversible.

The potential of the second oxidation step can be determined, however, by cyclic voltammetry of the radical cation perchlorate **4b** (X = $ClO_4$) obtained by preparative oxidation of the corresponding tetrazine as described below. Preparative oxidation of bispyrimido[1,2-*b*:1′,2′-*e*][1,2,4,5]tetrazines **3** can easily be achieved by treatment with bromine in dichloromethane. The resulting cation radical tribromides **4** are

*) After we had finished our investigations, Schroth et al. found a related route to differently anellated bispyrimido[3,4-*b*:3′,4′-*e*]-[1,2,4,5]-tetrazines[12].

formed in high yields as black solids. UV-Vis absorption ranges from UV to near IR. The absorption at high wavelengths is probably caused by charge transfer from the complex anion to the heterocyclic cation radical. This argument is supported by the observation of violet cation radical salts **4** (X = $ClO_4$) if compounds **3** are oxidized with perchloric acid in acetic acid or by $FeCl_3$. The radical nature of the bispyrimido[1,2-*b*:1′,2′-*e*][1,2,4,5]tetrazinium salts **4** has been proved by ESR spectroscopy. The same spectrum (see Figure 1) is obtained if either separately prepared cation radical tribromides **4** (X = $Br_3$) are investigated or if a solution of bispyrimidotetrazines **3** in dichloromethane is treated with $FeCl_3$ or $Pb(CH_3CO_2)_4$ in 2N $H_2SO_4$.

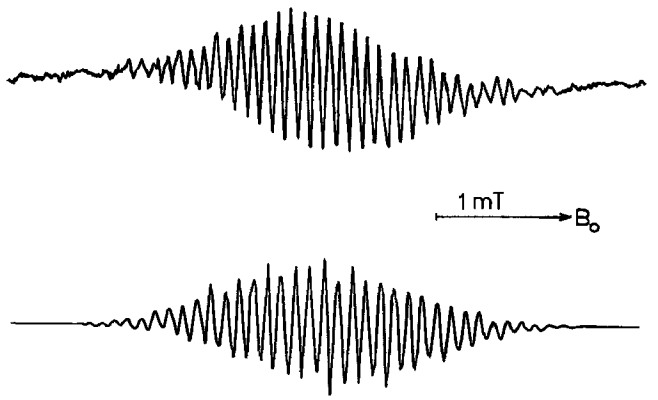



Figure 1. Experimental ESR spectrum (in DMF at 25°C, above) and simulated spectrum (below) of radical salt **4a** (X = $Br_3$)

The spin density in the radical cation is strongly determined by the structure of the delocalized system. The ratio of coupling constants which represent the spin densities in corresponding positions are related to the values observed with uncondensed tetrazine[9] or phenazine cation radicals[10]. The ESR spectrum is dominated by the coupling constant $a_1$, which belongs to the pyrazine-like $^{14}N$ atoms. The spectrum ($g$ = 2.004) is only poorly resolved, probably due to the existence of ion pairs. For this reason no full equivalence of the recorded spectrum with the corresponding simulation (Figure 1) is found. Voltammetric investigation of the radical cation perchlorate **4b** in acetonitrile gives 0.75 and 1.61 V for the first and second oxidation step with regard to the starting tetrazine **4**.

Further structural evidence for the cation radical salts **4** is provided by elemental analysis and by well-resolved IR spectra. The latter fact rules out the existence of adducts[11] of cation radicals with non-oxidized tetrazines **3**. Attempts to convert tribromides **4** (X = $Br_3$) into perchlorates **4** (X = $ClO_4$) by treating acetonitrile suspensions of **4** with perchloric acid have been unsuccessfull, since the isolated salts consist of both perchlorate and tribromide anions (ratio about 6:1 according to elemental analysis). Unlike perchlorates the cation radical tribromides **4** (X = $Br_3$) exhibit peaks in the mass spectra, which are higher than the molecular ion. Since covalently bound bromine can be ruled out on the basis of the ESR experiments mentioned above, this phenomenon can be explained by a thermal reaction, where bromine atoms are incorporated in the heterocyclic cation under the conditions of mass spectrometry. The cation radical salts **4** are extremely persistent radicals. They can be stored for years without losing their radical character.

## Experimental

IR: IR-Specord 71 Carl-Zeiss-Jena. – $^1H$ NMR: BS 487/c (80 MHz) Tesla Brno, WP 200 (200 MHz) Bruker. – $^{13}C$ NMR: WP

Table 1. Bispyrimidine derivatives **2**, bispyrimidotetrazines **3**, and radical cation salts **4**

| | Yield [%]/ Method | m.p. [°C] | Molecular formula Elemental analysis Calcd. C H N Found |
|---|---|---|---|
| **2b** | 96/A | 260–265 (aceto-nitrile) | $C_{23}H_{22}N_6S$ (414.5) 66.64 5.35 20.28 66.68 5.61 19.85 |
| **2c** | 88/B | 367–373 (aceto-nitrile) | $C_{23}H_{22}N_6O_2S$ (446.5) 61.86 4.97 18.82 61.51 4.81 18.49 |
| **2d** | 94/A | 358–365 (aceto-nitrile) | $C_{21}H_{16}Cl_2N_6S$ (455.4) 55.39 3.54 18.46 55.69 3.66 18.51 |
| **3a** | 76/D | 330 (dec.) (DMF) | $C_{20}H_{14}N_6$ (338.4) 70.99 4.17 24.84 71.11 3.92 24.79 |
| **3b** | 78/D | 375–380 (DMF) | $C_{22}H_{18}N_6$ (366.4) 72.11 4.95 22.94 72.36 5.05 22.86 |
| **3c** | 75/C | 385– (DMF) | $C_{22}H_{18}N_6O_2$ (398.4) 66.32 4.55 21.10 66.51 4.48 21.04 |
| **3d** | 68/A | 260–265 (DMF) | $C_{20}H_{12}Cl_2N_6$ (407.3) 58.98 2.97 20.64 59.02 3.07 20.78 |
| **4a**[a] | 86/E | 220–270 (decomp.) (DMF) | $C_{20}H_{14}Br_3N_6$[c] |
| **4a**[b] | 87/F | 303–305 (acto-nitrile/ toluene) | $C_{20}H_{14}ClN_6O_4$[c] |
| **4b**[a] | 76/E | >320 (DMF) | $C_{22}H_{18}Br_3N_6$ (606.1) 43.59 2.99 13.87 43.05 2.90 13.45 |
| **4c**[a] | 81/E | >320 (DMF) | $C_{22}H_{18}Br_3N_6O_2$ |
| **4d**[a] | 78/E | 315–320 (DMF) | $C_{20}H_{12}Br_3Cl_2N_6$[c] |

[a] X = $Br_3$. – [b] X = $ClO_4$. – [c] No satisfactory elemental analysis available.

Table 2. $^1$H-NMR data of bispyrimidine derivatives **2** and bispyrimido[1,2-*b*:1′,2′-*e*][1,2,4,5]tetrazines **3**

| Nr. | $^1$H-NMR ($CF_3COOH$) |
|---|---|
| **2b**[a] | 2.10 (s, 3H, $CCH_3$), 2.39 (s, 3H, $CCH_3$), 2.79 (s, 3H, $SCH_3$), 7.12 (d, J = 8 Hz, 2H, $C_6H_4$), 7.36 (d, J = 8 Hz, 2H, $C_6H_4$), 7.66 (d, J = 8 Hz, 2 H, $C_6H_4$), 7.72 (d, J = 7 Hz, 1H, CH), 7.99 (d, J =7 Hz, 1 H, CH), 8.22 (d, J = 8 Hz, 2H, $C_6H_4$), 8.55 (d, J = 7 Hz, 1H, CH), 8.60 (d, J = 7 Hz, 1H, CH) |
| **2c**[b] | 2.38 (s, 3H, $SCH_3$), 3.75 (s, 3H, $OCH_3$), 3.82 (s, 3H, $OCH_3$), 5.31 - 5.53 (m, 2H, $C_6H_4$), 6.50 (d, J = 7.4 Hz, 1H, CH), 6.80 - 7.06 (m, 5 H, $C_6H_4$, CH), 7.51 (d. J = 7.4 Hz, 1H), 7.79 (d, J = 9 Hz, 2 H, $C_6H_4$), 7.98 (d, J = 9 Hz, 2H, $C_6H_4$) |
| **3a** | 6.51 (d, J = 6.8 Hz, 2H, 2 CH), 7.45 (d, J = 6.8 Hz, 2H, 2 CH), 7.57 - 7.87 (m, 10 H, 2 $C_6H_5$) |
| **3b** | 6.05 (d, J = 7 Hz, 2H, 2 CH), 7.38 (d, 2H, J = 7 Hz, 2 CH), 7.40 (d, J = 8.3 Hz, 4 H, $C_6H_4$), 7.77 (d, J = 8.3, 4H, $C_6H_4$) |
| **3c** | 4.03 (s, 6H, 2 $OCH_3$), 6.46 (d, J = 7.3 Hz, 2H, 2 CH), 7.20 (d, J = 9.3 Hz, 4 H, 2 $C_6H_4$), 7.30 (d, J = 7.3 Hz, 2H, 2 CH), 7.91 (d, J = 9.3 Hz, 4 H, 2 $C_6H_4$) |
| **3d** | 5.52 (d, J = 6.8 Hz, 2 H, 2 CH), 7.45 (d, J = 6.6, 2 H, 2 CH), 7.62 (d, J = 9.3 Hz, 4 H, 2 $C_6H_4$), 7.81 (d, J = 9.3 Hz, 4 H, 2 $C_6H_4$) |

[a] $^1$H-NMR ([$D_6$]DMSO): δ = 2.40 (s, 3H, $SCH_3$), 2.47 (s, 3H, $CCH_3$), 2.50 (s, 3H, $CCH_3$), 5.51 - 5.80 (m, NH, CH), 6.78 (d, J = 7 Hz, 1H, CH), 7.25 (d, J = 7 Hz, 1H, CH), 7.40 (d, J = 8 Hz, 2 H, $C_6H_4$), 7,55 (d, J = 8 Hz, 2 H, $C_6H_4$). - [b] In [$D_6$]DMSO.

200 (50 MHz) Bruker. — MS (70 eV): HP 5995 A Hewlett Packard. — UV: UV/VIS spectrometer Specord, Carl-Zeiss-Jena. — Cyclic voltammetry: Rotating Pt-plate electrode, 0.1 N $NEt_4ClO_4$ in *N,N*-dimethylacetamide, $E_{1/2}$ (ω = 78.5 $s^{-1}$), $E_p$ ($dE/dt$ = 0.25 $Vs^{-1}$), $C_{Dep}$ = 5 × $10^{-4}$ mol $l^{-1}$. — ESR spectra: spectrometer $E_4$ (Varian). The following parameters were used for simulation of the ESR spectrum: 2 × $a_1$ ($^{14}$N) = 0.42 mT; 2 × $a_2$ ($^{14}$N) = 0.22 mT; 2 × $a_3$ ($^{14}$N) = 1.9 mT; 2 × $a_4$ ($^1$H) = 0.115 mT; 2 × $a_4$ ($^1$H) = 0.095 mT. The resulting stick diagram was adapted to the experimental spectrum by convolution with a Lorentz function with 0.025 mT line width. — Yields, physical and spectral data, elemental analyses, and peak potentials are listed in Tables 1–4.

*Condensation Products* **2**

*Method A:* A mixture of 0.01 mol of 1-amino-2-(methylthio)pyrimidinium iodide (**1**), 50 ml of acetonitrile, and 1.5 g (0.015 mol) of triethylamine was refluxed for 15 min. The red-colored product already precipitates in the heat. After cooling to room temp. it was filtered by suction and recrystallized.

*Method B:* A solution of 0.01 mol of **1** and 1.5 g (0.015 mol) of triethylamine in 20 ml of DMF was allowed to stand at room temp. for 20 min. The product was filtered by suction and recrystallized.

*Bispyrimido[1,2-b:1′,2′-e][1,2,4,5]tetrazines* **3**

*Method C:* A mixture of 0.01 mol of condensation product **2** and 30 ml of DMF was refluxed for 20 min and worked up according to method B.

*Method D:* A mixture of 0.01 mol of 1-amino-2-(methylthio)pyrimidinium iodide (**1**), 30 ml of DMF, and 1.5 g (0.015 mol) of triethylamine was refluxed for 30 min. Usually, the red product **3** crystallized already upon heating. After cooling to room temp. it was filtered by suction, washed with some acetonitrile and recrystallized from DMF.

Table 3. Spectroscopic data of bispyrimidine derivatives **2**, bispyrimido]1,2-*b*:1′,2′-*e*][1,2,4,5]tetrazines **3**, and radical cation salts **4**

| Nr. | MS (70 eV): m/z (%) |
|---|---|
| **2b**[a] | 414 (11) [$M^+$], 366 (49), 169 (33), 155 (16), 143 (20), 115 (57), 91 (43), 47 (100) |
| **2c** | 446 (0.2) [$M^+$], 231 (17), 186 (13), 47 (100) |
| **2d** | 454 (0.7) [$M^+$], 236 (13), 190 (10), 155 (11), 136 (12), 47(100) |
| **3a**[b] | 338 (100) [$M^+$], 206 (11), 169 (10), 155 (48), 129 (49), 115 (13), 103 (55), 77 (69) |
| **3b** | 366 (100) [$M^+$], 183 (8), 169 (31), 143 (24), 115 (39), 91 (37) |
| **3c** | 398 (100) [$M^+$], 201 (12), 185 (34), 159 (27), 133 (30), 103 (18), 92 (19) |
| **3d** | 408 (65), 406 (100) [$M^+$], 204 (12), 189 (40), 163 (35), 155 (15), 137 (41), 111 (33), 102 (33), 101 (31) |
| **4a**[c] | 498 (13), 496 (24), 494 (12) [$M^+$-Br], 418 (14), 338 (17), 155 (21), 129 (29), 103 (42), 102 (58), 77 (100) |
| **4a**[d] | 338 (100) [$M^+$-$ClO_4$], 156 (18), 155 (38), 129 (36), 128 (16), 103 (39), 77 (50), 51 (18), 36 (16) |
| **4b**[e] | 444 (1) [$M^+$-2 Br - 1], 367 (27), 366 (100), 169 (24), 143 (18), 115 (35), 91 (44) |
| **4d** | 588 (13) [$M^+$-Br], 564 (37), 486 (51), 408 (43), 406 (64), 189 (54), 163 (62), 137 (58), 136 (74), 111 (69), 75 (100) |

[a] UV ($CH_2Cl_2$): $\lambda_{max}$ (lg ε) = 264 nm (4.39), 299 (4.62), 352 sh (4.02), 460 (3.26). - IR (KBr): ν = 3240 $cm^{-1}$ (NH), 1650 (C=N), 1630 (C=N). - [b] UV ($CH_2Cl_2$): $\lambda_{max}$ (lg ε) = 305 nm (4.66), 472 sh (3.78), 500 (3.90), 535 sh (3.79).-IR (KBr): ν = 1635 $cm^{-1}$ (C=N), 1600. - [c] X = $Br_3$. - [d] X = $ClO_4$. - UV ($CH_3CN$): $\lambda_{max}$ = 372 nm, 435 sh, 484 sh, 528 sh, 605. - IR (KBr): ν = 1630 $cm^{-1}$ (C=N). - [e] UV ($CH_3CN$) $\lambda_{max}$ (lg ε) = 238 nm (4.04), 264 (3.97), 338 (4.40), 411 sh (3.48), 475 (3.54), 503 (3.60), 530 sh (3.51), 565 sh (3.07), 687 sh (3.02), 765sh (2.77). - IR (KBr): ν = 1600 $cm^{-1}$

Table 4. Half-wave and peak potentials [V] (SCE) of bispyrimido[1,2-*b*:1′,2′-*e*][1,2,4,5]tetrazines **3** in *N,N*-dimethylacetamide (Pt electrode)

| | $E_{1/2}$ | $E_p^a$ | $E_p^c$ |
|---|---|---|---|
| **3a** | 0.50 | 0.53 | 0.47 |
| **3b** | 0.48 | 0.52 | 0.45 |
| **3c** | 0.44 | 0.49 | 0.41 |
| **3d** | 0.54 | 0.56 | 0.50 |

*Bispyrimido[1,2-b:1',2'-e][1,2,4,5]tetrazines Cation Radical Salts* **4**

*Method E:* 1.6 g (0.01 mol) of bromine was added to a suspension of 0.005 mol of bispyrimidotetrazine **3** in 50 ml of dichloromethane. If the black product did not precipitate immediately the mixture was briefly heated to boiling temp. After standing at room temp. for 1 h the tribromide **4** ($X = Br_3$) was filtered by suction and washed with some dichloromethane.

*Method F:* 0.3 g (0.003 mol) of 70% perchloric acid was added to a mixture of 1 g (0.003 mol) of bispyrimidotetrazine **3a**, 15 ml of glacial acetic acid, and 5 ml of water. A violet color developed immediately, and all the tetrazine was dissolved. The solution was briefly heated to boiling temp. The acetic acid was removed by evaporation in a rotatory evaporator. The semisolid residue was treated with about 10 ml of acetonitrile. After dilution with toluene the product precipitated. It was filtered by suction and recrystallized.

CAS Registry Numbers

**1a**: 126838-05-9 / **1b**: 126838-07-1 / **1c**: 126838-08-2 / **1d**: 126838-06-0 / **2b**: 126838-09-3 / **2c**: 135990-13-5 / **2d**: 135990-14-6 / **3a**: 126838-01-5 / **3b**: 126838-03-7 / **3c**: 126838-04-8 / **3d**: 126838-02-6 / **4a** ($X = Br_3$): 135990-16-8 / **4a** ($X = ClO_4$): 135990-23-7 / **4b** ($X = Br_3$): 135990-18-0 / **4c** ($X = Br_3$): 135990-20-4 / **4d** ($X = Br_3$): 135990-22-6

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