

## Synthesis and Structure of *as*-Triazinoquinazolines, I

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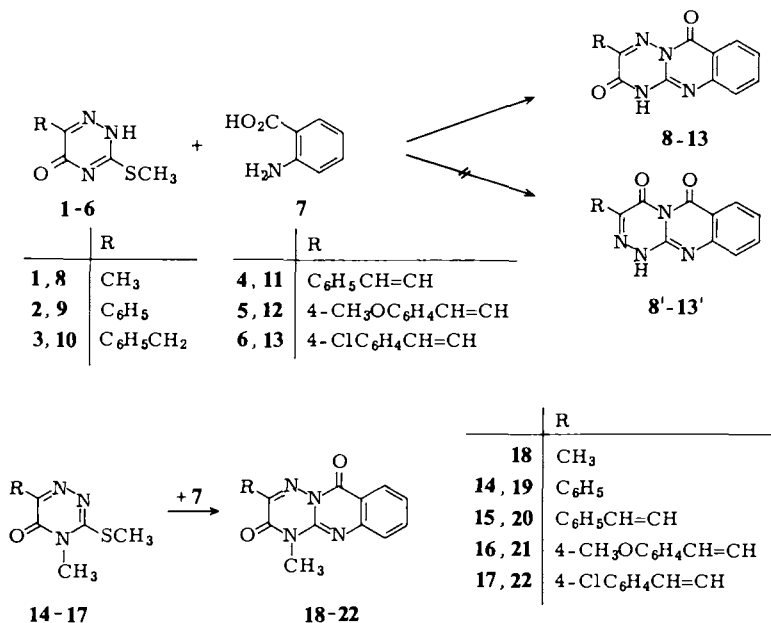
3-(Methylthio)-6-R-1,2,4-triazin-5(2*H*)-ones **1–6** have been converted into the 3-R-2*H*-*as*-triazino[3,2-*b*]quinazoline-2,6(1*H*)-diones **8–13** upon cyclocondensation with anthranilic acid. Reaction of 2-methyl-3-(methylthio)-6-phenyl-1,2,4-triazin-5(2*H*)-one (**23**) with anthranilic acid gave 1-methyl-3-phenyl-2*H*-*as*-triazino[3,4-*b*]quinazoline-4,6(1*H*)-dione (**29**) via the intermediate **26**. *N*-Methylantranilic acid and **2** or **5** afforded the 11-methyl-3-R-2*H*-*as*-triazino[3,2-*b*]quinazoline-2,6(1*H*)-diones **36** and **38**, respectively.

### Synthese und Struktur von *as*-Triazinochinazolinen, I

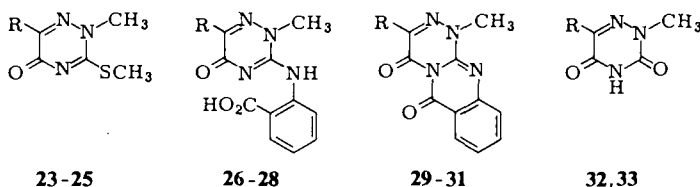
Die 3-(Methylthio)-6-R-1,2,4-triazin-5(2*H*)-one **1–6** wurden durch Cyclokondensation mit Anthranilsäure in die 3-R-2*H*-*as*-triazino[3,2-*b*]chinazolin-2,6(1*H*)-dione **8–13** übergeführt. Reaktion von 2-Methyl-3-(methylthio)-6-phenyl-1,2,4-triazin-5(2*H*)-on (**23**) mit Anthranilsäure ergab 1-Methyl-3-phenyl-2*H*-*as*-triazino[3,4-*b*]chinazolin-4,6(1*H*)-dion (**29**) über das Zwischenprodukt **26**. *N*-Methylantranilsäure setzte sich mit **2** und **5** zu den 11-Methyl-3-R-2*H*-*as*-triazino[3,2-*b*]chinazolin-2,6(1*H*)-dionen **36** und **38** um.

During our recent interest in the synthesis of condensed heterocyclic new ring systems of potential biological interest, we investigated the reaction of amino acids with nitrogen heterocyclic thioimidic esters. Thus we report here the reaction of 3-(methylthio)-1,2,4-triazines with anthranilic acid as a feasible avenue toward *as*-triazinoquinazoline derivatives. Heating an intimate mixture of 3-(methylthio)-6-R-1,2,4-triazin-5(2*H*)-ones **1–6** with anthranilic acid (**7**) gave a good yield of cyclocondensation products for which structures **8–13** and **8'–13'** of their tautomers may be assumed.

Based on chemical and spectroscopic evidences, these products were established to have the structure of triazino[3,2-*b*]quinazoline-2,6-diones (**8–13**) and not of the isomeric triazino[3,4-*b*]quinazoline-4,6-diones (**8'–13'**). Thus, methylation of the products **8** and **9** with methyl iodide in sodium methoxide gave the 1-methyl derivatives **18** and **19**. Structures **18** and **19** were established by the independent synthesis of compound **19** by condensation of 3-(methylthio)-4-methyl-6-phenyl derivative **14** with anthranilic acid. Similar condensation of the 6-(2-arylvinyl)triazines **15–17** gave the corresponding 1-methyltriazinoquinazolines **20–22**. Compound **18** was also obtained upon treatment of compound **8** with ethereal diazomethane.

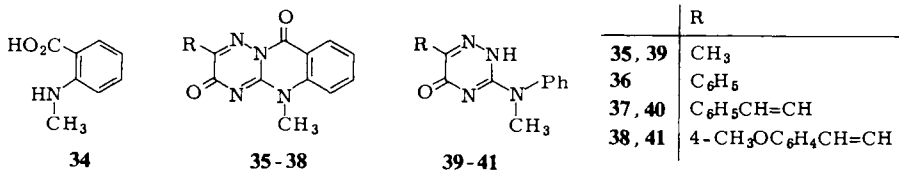


The isomeric 1-methyltriazino[3,4-*b*]quinazoline-4,6-dione **29** was obtained from 2-methyl-3-(methylthio)-6-phenyl-1,2,4-triazin-5(2*H*)-one (**23**). Thus heating compounds **23** with anthranilic acid at 180°C gave 3-(2-carboxyanilino)-2-methyl-6-phenyl-1,2,4-triazin-5(2*H*)-one (**26**), which was cyclized into compound **29** upon heating at its melting point for 10 minutes. Similar treatment of 6-(2-arylvinyl)-2-methyl-3-(methylthio)-1,2,4-triazin-5(2*H*)-ones **24**, **25** gave products which on the basis of analytical and spectral data were assigned the triazinedione structures **32**, **33** but none of the expected products **27**, **28** or the tricyclic derivatives **30**, **31**. The identity of compounds **32**, **33** was further confirmed by their independent synthesis from compounds **24**, **25** by the action of alcoholic HCl<sup>1-5</sup>. This finding is in line with our recent results indicating the hydrolysis of some 3-(methylthio)triazines when heated under reflux in acetic acid<sup>6</sup>.



	R
<b>23, 26, 29</b>	C <sub>6</sub> H <sub>5</sub>
<b>24, 27, 30, 32</b>	C <sub>6</sub> H <sub>5</sub> CH=CH
<b>25, 28, 31, 33</b>	4-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CH=CH

In an attempt to synthesize the 11-methyl-3-*R*-*as*-triazino[3,2-*b*]quinazolinediones **35**–**38**, we investigated the reaction of compounds **1**–**5** with *N*-methylantranilic acid (**34**). In this case only compounds **2** and **5** undergo cyclocondensation to give the expected products **36** and **38**, respectively. However, compounds **1** and **4** by similar treatment gave products which on the basis of spectral and analytical data were assigned the 3-(*N*-methylanilino)-6-*R*-1,2,4-triazin-5(2*H*)-ones **39** and **40**, respectively. Compounds **39**–**41** were independently synthesized by reacting compounds **1**, **4** and **5** with *N*-methylaniline.



We are thankful to *Khaled Abou-Hadeed* for running some of the NMR spectra presented in this work and Mr. *E. Pilz* for the determination of the mass spectra.

## Experimental Part

All melting points are uncorrected. – <sup>1</sup>H NMR spectra: JEOL JNM-MH-100. – Mass spectra: Finnigan MAT 312, 70 eV. – UV spectra (ethanol): Unicam SP 1750 spectrophotometer. – IR spectra (KBr): Unicam SP 1200 infrared instrument.

Compounds prepared by different procedures were confirmed by mixed melting points and by identity of IR spectra.

### 3*R*-2*H*-[1,2,4]triazino[3,2-*b*]quinazoline-2,6(1*H*)-diones **8**–**13**

**General Procedure:** An intimate mixture of the 3-(methylthio)-6-*R*-1,2,4-triazin-5(2*H*)-ones **1**–**6**, resp. (0.01 mol), and anthranilic acid (0.012 mol) was heated at 160–180 °C (oil bath) for 1½ h (in case of **6** the reaction was carried out at 235 °C for 10 min). After cooling the product was triturated with alcohol and then crystallized from DMF into compounds **8**–**13**, respectively.

Compound **8** (R = methyl): m. p. > 315 °C; yield 69%. – <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO): δ = 2.28 (s, CH<sub>3</sub>), 3.22 (s, NH), and 7.32–8.18 (m, ArH). – MS: *m/e* = 228 (M<sup>+</sup>). – UV: λ<sub>max</sub> (ε<sub>max</sub>) = 288 (1613), 332 nm (1695). – IR: 3170, 1710, 1655 cm<sup>-1</sup>.

C<sub>11</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub> (228.2) Calcd. C 57.89 H 3.53 N 24.55 Found C 57.90 H 3.60 N 24.50

Compound **9** (R = phenyl): m. p. > 315 °C; yield 92%. – <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO): δ = 3.28 (s, NH), 7.28–8.28 (m, ArH). – MS: *m/e* = 290 (M<sup>+</sup>). – UV: λ<sub>max</sub> (ε<sub>max</sub>) = 290 (2300), 350 nm (401). – IR: 3040, 1720, 1666 cm<sup>-1</sup>.

C<sub>16</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub> (290.2) Calcd. C 66.20 H 3.47 N 19.30 Found C 66.10 H 3.44 N 19.40

Compound **10** (R = benzyl): m. p. > 315 °C, yield 85%. – <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO): δ = 3.44 (s, NH), 4.08 (s, benzyl. CH<sub>2</sub>), 7.20–8.28 (m, ArH). – MS: *m/e* = 304 (M<sup>+</sup>). – UV: λ<sub>max</sub> (ε<sub>max</sub>) = 290 nm (4498). – IR: 3050, 1730, 1665 cm<sup>-1</sup>.

C<sub>17</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub> (304.3) Calcd. C 67.09 H 3.97 N 18.41 Found C 67.20 H 4.00 N 18.50

Compound **11** (R = styryl): m. p. > 315 °C; yield 75%. – UV: λ<sub>max</sub> (ε<sub>max</sub>) = 296 (6899), 332 (7277), 336 nm (6710).

C<sub>18</sub>H<sub>12</sub>N<sub>4</sub>O<sub>2</sub> (316.5) Calcd. C 68.30 H 3.82 N 17.76 Found C 68.40 H 3.60 N 17.80

Compound **12** (R = 4-methoxystyryl): m. p. > 315 °C; yield 73%. – UV:  $\lambda_{\max}$  ( $\epsilon_{\max}$ ) = 286 (4049), 291 (4517), 336 nm (4517).

$C_{19}H_{14}N_4O_3$  (346.5) Calcd. C 65.84 H 4.07 N 16.22 Found C 65.70 H 4.10 N 16.30

Compound **13** (R = 4-chlorostyryl): m. p. 315 °C; yield 81%. – UV:  $\lambda_{\max}$  ( $\epsilon_{\max}$ ) = 276 (7152), 311 (7713), 320 nm (6732).

$C_{18}H_{11}ClN_4O_2$  (350.7) Calcd. C 61.63 H 3.16 Cl 10.10 N 15.97  
Found C 61.70 H 3.20 Cl 10.00 N 15.80

### 1,3-Dimethyl-2H-[1,2,4]triazino[3,2-b]quinazoline-2,6(1H)-dione (**18**)

a) Compound **8** (1.14 g) was dissolved in sodium methoxide solution (prepared from 0.115 g of sodium and 15 ml of anhydrous methanol), then methyl iodide (0.92 g) was added. The reaction mixture was refluxed for 1 h and left overnight at room temperature. The solid precipitated was collected and crystallized from DMF into compound **18**, m. p. 272 °C, yield 66%. –  $^1H$  NMR ( $[D_6]DMSO$ ):  $\delta$  = 2.24 (s, 3-CH<sub>3</sub>), 3.50 (s, NCH<sub>3</sub>), 7.30–8.10 (m, ArH). – MS:  $m/e$  = 242 ( $M^+$ ). – UV:  $\lambda_{\max}$  ( $\epsilon_{\max}$ ) = 294 (26400), 332 nm (21400). – IR: 1695, 1590  $cm^{-1}$ .

$C_{12}H_{10}N_4O_2$  (242.2) Calcd. C 59.49 H 4.16 N 23.13 Found C 59.40 H 4.10 N 23.00

b) Compound **8** (1.14 g) was treated with an ethereal solution of diazomethane (prepared from 3.0 g of *N*-methyl-*N*-nitrosourea and 50 ml of ether). The reaction mixture was kept in the refrigerator for 3 d, and the precipitate was collected and crystallized from DMF to give 70% of **18**.

### 1-Methyl-3-phenyl-2H-[1,2,4]triazino[3,2-b]quinazoline-2,6(1H)-dione (**19**)

a) Compound **9** (1.45 g) was dissolved in sodium methoxide solution (prepared from 0.115 g of sodium and 15 ml of anhydrous methanol), then methyl iodide (0.78 g) was added. The mixture was refluxed for 1 h, left overnight at room temperature and the solid precipitated was collected and crystallized from DMF, m. p. 199 °C, yield 67%. –  $^1H$  NMR ( $[D_6]DMSO$ ):  $\delta$  = 3.56 (s, NCH<sub>3</sub>), 7.40–8.40 (m, ArH). – MS:  $m/e$  = 304 ( $M^+$ ). – UV:  $\lambda_{\max}$  ( $\epsilon_{\max}$ ) = 295 (8555), 352 nm (1444). – IR: 1705, 1750  $cm^{-1}$ .

$C_{17}H_{12}N_4O_2$  (304.3) Calcd. C 67.09 H 3.97 N 18.41 Found C 67.00 H 4.10 N 18.30

b) An intimate mixture of **14** (1.16 g) and anthranilic acid (0.82 g) was fused at 150 °C (oil bath) for 3 h. After cooling and trituration with alcohol the product was crystallized from DMF, yield 77%.

3-(2-Arylviny)-1-methyl-2H-[1,2,4]triazino[3,2-b]quinazoline-2,6(1H)-diones **20–22**: Compounds **20–22** were prepared from **15–17** following procedure b) for the preparation of **19**.

Compound **20** (aryl = phenyl): m. p. 215 °C, yield 69%. –  $^1H$  NMR ( $[D_6]DMSO$ ):  $\delta$  = 3.71 (s, NCH<sub>3</sub>), 7.2–8.35 (m, Ar and CH=CH). – MS:  $m/e$  = 330 ( $M^+$ ).

$C_{19}H_{14}N_4O_2$  (330.3) Calcd. C 69.08 H 4.27 N 16.96 Found C 69.00 H 4.30 N 16.80

Compound **21** (aryl = 4-methoxyphenyl): m. p. 228 °C, yield 73%. –  $^1H$  NMR ( $[D_6]DMSO$ ):  $\delta$  = 3.6 (s, NCH<sub>3</sub>), 3.9 (s, OCH<sub>3</sub>), 7.05–8.4 (m, ArH and CH=CH). – MS:  $m/e$  = 360 ( $M^+$ ).

$C_{20}H_{16}N_4O_3$  (360.3) Calcd. C 66.65 H 4.47 N 15.54 Found C 66.70 H 4.40 N 15.60

Compound **22** (aryl = 4-chlorophenyl): m. p. 224 °C, yield 78%. –  $^1H$  NMR ( $[D_6]DMSO$ ):  $\delta$  = 3.55 (s, NCH<sub>3</sub>), 7.2–8.2 (m, ArH and CH=CH). – MS:  $m/e$  = 364 ( $M^+$ ), 366 ( $M^+ + 2$ ).

$C_{19}H_{13}ClN_4O_2$  (364.7) Calcd. C 62.55 H 3.59 N 15.36 Found C 62.40 H 3.60 N 15.30

1-Methyl-3-phenyl-4H-[1,2,4]triazino[3,4-b]quinazoline-4,6(1H)-dione (**29**): An intimate mixture of **23** (1.16 g) and anthranilic acid (0.82 g) was fused at 150 °C (oil bath) for 1½ h. The solid obtained was trituated with ethanol and recrystallized from DMF to give compound **26**, m. p.

247°C (dec.), yield 77%. –  $^1\text{H NMR}$  ( $[\text{D}_6]\text{DMSO}$ ):  $\delta = 3.86$  (s,  $\text{NCH}_3$ ), 7.20–8.88 (m, ArH), 11.16 (br,  $\text{CO}_2\text{H}$ ). – MS:  $m/e = 322$  ( $\text{M}^+$ ). – UV:  $\lambda_{\text{max}}$  ( $\epsilon_{\text{max}}$ ) = 292 nm (13636).

$\text{C}_{17}\text{H}_{14}\text{N}_4\text{O}_3$  (322.5) Calcd. C 63.34 H 4.36 N 17.38 Found C 63.40 H 4.30 N 17.40

Compound **26** upon fusion at 250°C (metal bath) for 10 min gave **29** which was crystallized from DMF, m. p. 229°C, yield 74%. –  $^1\text{H NMR}$  ( $[\text{D}_6]\text{DMSO}$ ):  $\delta = 3.92$  (s,  $\text{NCH}_3$ ), 7.40–9.20 (m, ArH). – MS:  $m/e = 304$  ( $\text{M}^+$ ). – UV:  $\lambda_{\text{max}}$  ( $\epsilon_{\text{max}}$ ) = 340 nm (3043). – IR: 1700, 1655  $\text{cm}^{-1}$ .

$\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_2$  (304.3) Calcd. C 67.09 H 3.97 N 18.41 Found C 67.10 H 4.00 N 18.30

*6-(2-Arylviny)-2-methyl-1,2,4-triazine-3,5(2H,4H)-diones (32, 33)*

a) An intimate mixture of **24** and **25**, resp. (0.001 mol), and anthranilic acid (0.001 mol) was heated at 150°C for  $1\frac{1}{2}$  h. After cooling and trituration with ethanol, the product was crystallized from DMF.

Compound **32** (aryl = phenyl): m. p. 216°C, yield 59%. –  $^1\text{H NMR}$  ( $[\text{D}_6]\text{DMSO}$ ):  $\delta = 3.60$  (s,  $\text{NCH}_3$ ), 7.05–7.90 (m, ArH and  $\text{CH}=\text{CH}$ ), 12.20–12.40 (NH). – MS:  $m/e = 229$  ( $\text{M}^+$ ).

$\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_2$  (229.3) Calcd. C 62.83 H 4.83 N 18.38 Found C 62.80 H 4.90 N 18.30

Compound **33** (aryl = 4-methoxyphenyl): m. p. 247°C, yield 40%. –  $^1\text{H NMR}$  ( $[\text{D}_6]\text{DMSO}$ ):  $\delta = 3.50$  (s,  $\text{NCH}_3$ ), 3.75 (s,  $\text{OCH}_3$ ), 6.80–7.70 (m, ArH and  $\text{CH}=\text{CH}$ ), 12.06 (NH). – MS:  $m/e = 259$  ( $\text{M}^+$ ).

$\text{C}_{13}\text{H}_{13}\text{N}_3\text{O}_3$  (259.4) Calcd. C 60.18 H 5.04 N 16.26 Found C 60.10 H 5.10 N 16.30

b) A solution of **24** and **25**, resp. (0.001 mol), in ethanol (15 ml) and conc. HCl (3 ml) was heated under reflux for 1 h. After cooling the precipitate was collected and recrystallized from DMF as colourless crystals of **32** and **33**, resp.

*11-Methyl-3-R-2H-[1,2,4]triazino[3,2-b]quinazoline-2,6(11H)-diones (36, 38)*: An intimate mixture of **2** and **5**, resp. (0.01 mol), and *N*-methylantranilic acid (0.012 mol) was heated at 180°C (oil bath) for  $2\frac{1}{2}$  h. After cooling and trituration with ethanol, the remaining solid was crystallized from DMF.

Compound **36** (R = phenyl): m. p. 228°C, yield 76%. –  $^1\text{H NMR}$  ( $[\text{D}_6]\text{DMSO}$ ):  $\delta = 3.35$  (s,  $\text{NCH}_3$ ), 7.28–8.16 (m, ArH). – UV:  $\lambda_{\text{max}}$  ( $\epsilon_{\text{max}}$ ) = 296 nm (7183). – IR: 1710  $\text{cm}^{-1}$ .

$\text{C}_{17}\text{H}_{12}\text{N}_4\text{O}_2$  (304.3) Calcd. C 67.09 H 3.97 N 18.41 Found C 67.20 H 4.10 N 18.50

Compound **38** (R = 4-methoxystyryl): m. p. 254°C, yield 80%. –  $^1\text{H NMR}$  ( $[\text{D}_6]\text{DMSO}$ ):  $\delta = 3.35$  (s,  $\text{NCH}_3$ ), 7.00–7.95 (m, ArH and  $\text{CH}=\text{CH}$ ). – UV:  $\lambda_{\text{max}}$  ( $\epsilon_{\text{max}}$ ) = 330 (242), 346 nm (156).

$\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_3$  (360.3) Calcd. C 66.65 H 4.47 N 15.54 Found C 66.80 H 4.40 N 15.70

*3-(N-Methylanilino)-6-R-1,2,4-triazin-5(2H)-ones 39–41*

a) An intimate mixture of **1** and **4**, resp. (0.01 mol), and *N*-methylantranilic acid (0.012 mol) was heated at 180°C (oil bath) for  $1\frac{1}{2}$  h. The product obtained was trituated with ethanol and crystallized from DMF.

Compound **39** (R = methyl): m. p. 240°C, yield 74%. –  $^1\text{H NMR}$  ( $[\text{D}_6]\text{DMSO}$ ):  $\delta = 2.0$  (s, 6- $\text{CH}_3$ ), 3.28 (s,  $\text{NCH}_3$ ), 7.24–7.60 (m, ArH). – MS:  $m/e = 216$  ( $\text{M}^+$ ). – UV:  $\lambda_{\text{max}}$  ( $\epsilon_{\text{max}}$ ) = 296 nm (306). – IR: 3400, 3170, 1760  $\text{cm}^{-1}$ .

$\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}$  (216.2) Calcd. C 61.03 H 5.58 N 25.98 Found C 61.10 H 5.50 N 26.10

Compound **40** (R = styryl): m. p. 239°C, yield 78%. – <sup>1</sup>H NMR ([D<sub>6</sub>]DMSO): δ = 3.40 (s, NCH<sub>3</sub>), 7.10–8.00 (m, ArH and CH=CH), 12.37 (NH).

C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O (304.3) Calcd. C 71.03 H 5.29 N 18.47 Found C 71.20 H 5.10 N 18.30

b) A mixture of **1**, **4**, and **5**, resp. (0.001 mol), and *N*-methylaniline (0.0012 mol) was heated at 185°C (oil bath) for 1 h. After cooling and trituration with ethanol, the remaining solid was crystallized from DMF to give compound **39** (90%), **40** (79%), and **41** (85%), resp.

Compound **41** (R = 4-methoxystyryl): m. p. 206°C.

C<sub>19</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub> (334.5) Calcd. C 68.20 H 5.42 N 16.80 Found C 68.00 H 5.30 N 17.00

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