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Synthesis and Structure of *as*-Triazinoquinazolines, II[1]

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4-Amino-3-(methylthio)-6-R-1,2,4-triazin-5(4*H*)-ones **6** – **10** react with anthranilic acid to yield the 1-amino-3-R-2*H*-*as*-triazino[3,2-*b*]quinazoline-2,6(1*H*)-diones **17** – **21** rather than the expected *as*-triazino[3,4-*b*][1,3,4]benzotriazepines **12** – **16**. Compounds **17** – **21** were deaminated into compounds **22** – **26**. Heating of the *N*-benzylidene derivatives of **6** – **10** (**27** – **31**) with anthranilic acid also led to the formation of **22** – **26** with extrusion of benzonitrile.

Synthese und Struktur von *as*-Triazinochinazolinen, II[1]

Die 4-Amino-3-(methylthio)-6-R-1,2,4-triazin-5(4*H*)-one **6** – **10** ergaben bei der Umsetzung mit Anthranilsäure die 1-Amino-3-R-2*H*-*as*-triazino[3,2-*b*]chinazolin-2,6(1*H*)-dione **17** – **21** anstelle der erwarteten *as*-Triazino[3,4-*b*][1,3,4]benzotriazepine **12** – **16**. Die Verbindungen **17** – **21** ließen sich zu **22** – **26** desaminieren. Erhitzen der *N*-Benzylidenderivate von **6** – **10** (**27** – **31**) mit Anthranilsäure führte unter Freisetzung von Benzonitril ebenfalls zu **22** – **26**.

Several reported syntheses of triazepines and annelated triazepines have recently been reinvestigated, and in cases where a competitive five- or six-membered ring closure can be envisioned, these more favorable cyclizations usually result. Many reported triazepine syntheses, were thus shown to be, instead, other five- or six-membered heterocyclic rings[2 – 10]. The reaction of 3,4-diamino-1,2,4-triazin-5(4*H*)-ones with ethyl acetoacetate was found to give two isomeric *as*-triazinotriazepines together with triazolotriazepines by competitive cyclization[11]. The fact that 3-(alkylthio)-4-amino-1,2,4-triazines (e.g. **6** – **10**) undergo ready nucleophilic displacement with amines to give the corresponding 3,4-diamino-1,2,4-triazine derivatives[12 – 14], led us to investigate the reaction of compounds **6** – **10** with anthranilic acid as a possible avenue toward *as*-triazino[3,4-*b*][1,3,4]benzotriazepines **12** – **16**.

The reaction of compounds **6** – **10** with anthranilic acid gave a tricyclic system for which the 1-amino-2*H*-*as*-triazino[3,2-*b*]quinazoline-2,6(1*H*)-dione structures **17** – **21** are established rather than the expected condensed triazepines **12** – **16**.

Structure assignment of compounds **17** – **21** is based on the following facts:

1) The products **17** – **21** undergo ready deamination, when treated with nitrous acid to yield the corresponding 2*H*-*as*-triazino[3,2-*b*]quinazoline-2,6(1*H*)-diones **22** – **26**, identical with authentic samples[15] (this behaviour is similar to the action of nitrous acid on 3-amino-substituted 3,4-diamino-1,2,4-triazin-5(4*H*)-ones[12,13]).

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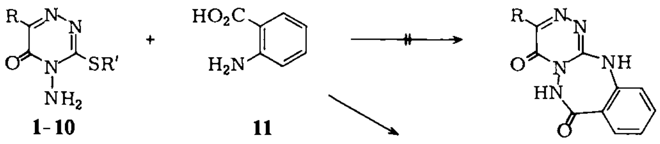
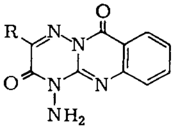


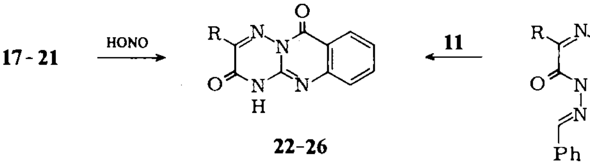
1-10 **11** **12-16**



17-21

	R	R'
1	CH_3	H
2	C_6H_5	H
3	$C_6H_5CH{=}CH$	H
4	$4\text{-}CH_3OC_6H_4CH{=}CH$	H
5	$4\text{-}ClC_6H_4CH{=}CH$	H
6	CH_3	CH_3
7	C_6H_5	CH_3
8	$C_6H_5CH{=}CH$	CH_3
9	$4\text{-}CH_3OC_6H_4CH{=}CH$	CH_3
10	$4\text{-}ClC_6H_4CH{=}CH$	CH_3

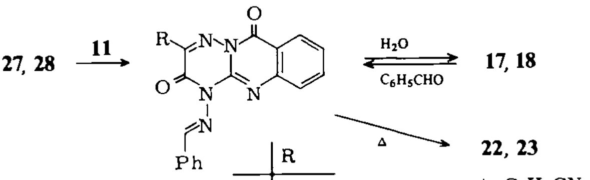
	R
12, 17	CH_3
13, 18	C_6H_5
14, 19	$C_6H_5CH{=}CH$
15, 20	$4\text{-}CH_3OC_6H_4CH{=}CH$
16, 21	$4\text{-}ClC_6H_4CH{=}CH$



22-26 **27-33**

	R
22	CH_3
23	C_6H_5
24	$C_6H_5CH{=}CH$
25	$4\text{-}CH_3OC_6H_4CH{=}CH$
26	$4\text{-}ClC_6H_4CH{=}CH$

	R	R'
27	CH_3	CH_3
28	C_6H_5	CH_3
29	$C_6H_5CH{=}CH$	CH_3
30	$4\text{-}CH_3OC_6H_4CH{=}CH$	CH_3
31	$4\text{-}ClC_6H_4CH{=}CH$	CH_3
32	CH_3	H
33	C_6H_5	H



17, 18

22, 23 + C_6H_5CN

	R
34	CH_3
35	C_6H_5

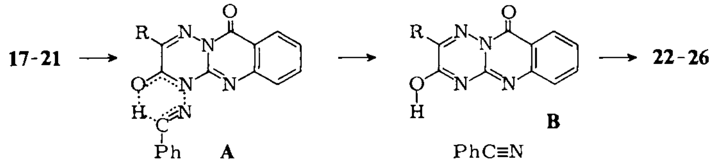
2) Independent synthesis of compounds **17**, **18** is accomplished by first converting compounds **1**, **2** into the corresponding aldimines **32**, **33** by condensing with benzaldehyde. Compounds **32**, **33** were then methylated with methyl iodide in sodium methoxide into the corresponding 3-methylthio derivatives **27**, **28**. Condensation of the latters with anthranilic acid at 160 – 170 °C yielded the corresponding 1-(benzylideneamino)-2*H*-*as*-

triazino[3,2-*b*]quinazoline-2,6(1*H*)-diones **34** and **35**, respectively. Compounds **34**, **35** were then hydrolyzed into the corresponding free 1-amino derivatives **17**, **18** by the action of alcoholic hydrochloric acid. The 6-(2-arylvinyl) derivatives **29** – **31** were directly obtained by condensing compounds **8** – **10** with benzaldehyde. Heating compounds **29** – **31** with anthranilic acid at 160°C yielded **24** – **26** together with benzonitrile.

3) Condensation of compounds **17**, **18** with benzaldehyde in acetic acid yielded compounds **34** and **35** respectively.

The formation of benzonitrile with the direct conversion of compounds **29** – **31** into **24** – **26** suggests the intervention of thermally allowed concerted reaction (this is similar to the retroene reactions[16)], and the thermal fragmentation of *N*-benzoylhydrazones[17,18)], and to the synthesis of arylnitriles from *N*-(arylideneamino)-2-pyridones[19)]).

Similarly compounds **34**, **35** were, now, found to undergo pyrolysis into the corresponding triazinoquinazoline derivatives **22**, **23** and benzonitrile upon heating at 180 – 190°C. Furthermore the 1-amino-*as*-triazinoquinazolines **17** – **21** were readily deaminated when heated under reflux with benzaldehyde to give the corresponding *as*-triazinoquinazolines **22** – **26**. Clearly in the last reaction compounds **17** – **21** first condense with benzaldehyde into the corresponding 1-benzylideneamino derivatives **A** which then thermally fragment into **B**, and the latters then tautomerize into compounds **22** – **26**.



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Experimental Part

All melting points are uncorrected. – ^{1}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.

4-Amino-3,4-dihydro-3-thioxo-1,2,4-triazin-5(2H)-ones (**1** – **5**)

a) Compounds **1**, **2** were prepared according the procedure described by *Dornow* et al.[20)].

b) To a hot solution of thiocarbonohydrazide (0.01 mol) in 15 ml of boiling water was added slowly with stirring an equimolecular amount of the appropriate arylidenepyruvic acid. The reaction mixture was refluxed for 5 min and then left to cool. The precipitate was collected, washed with water and recrystallized from DMF (cf. Table).

4-Amino-3-(methylthio)-1,2,4-triazin-5(4H)-ones (**6** – **10**)

a) Compounds **6**, **7** were prepared according the procedure described by *Dornow* et al.[20)].

Table. Yields and Analytical Characterization of Compounds **3** – **5**, **8** – **10**, **27** – **31**, and **33**

Compd.	M. p. [°C]	Yield [%]	Formula (Mol. wt.)		Analysis C	H	Cl	N	S
3	270	90	$C_{11}H_{10}N_4OS$	Calcd.	53.64	4.09		22.75	13.01
			(246.3)	Found	53.70	3.80		22.60	12.80
4	250	90	$C_{12}H_{12}N_4O_2S$	Calcd.	52.16	4.38		20.27	11.60
			(276.3)	Found	52.20	4.50		20.50	11.60
5	272	84	$C_{11}H_9ClN_4OS$	Calcd.	47.06	3.23	12.63	19.95	11.42
			(280.7)	Found	47.00	3.50	12.40	20.10	11.10
8	218	53	$C_{12}H_{12}N_4OS$	Calcd.	55.37	4.65		21.53	12.31
			(260.3)	Found	55.60	4.50		21.60	12.40
9	200	84	$C_{13}H_{14}N_4O_2S$	Calcd.	53.77	4.60		19.30	11.04
			(290.3)	Found	53.60	4.80		19.50	11.10
10	220	75	$C_{12}H_{11}ClN_4OS$	Calcd.	48.89	3.76	12.03	19.00	10.87
			(294.7)	Found	49.00	3.50	11.90	18.70	10.70
27	129	92	$C_{12}H_{12}N_4OS$	Calcd.	55.37	4.65		21.53	12.31
			(260.3)	Found	55.30	4.40		21.30	12.40
28	176	95	$C_{17}H_{14}N_4OS$	Calcd.	63.35	4.37		17.38	9.94
			(322.3)	Found	63.40	4.70		17.20	10.00
29	162	98	$C_{19}H_{16}N_4OS$	Calcd.	65.49	4.63		16.08	9.20
			(348.4)	Found	65.90	4.80		15.80	8.80
30	219	98	$C_{20}H_{18}N_4O_2S$	Calcd.	63.47	4.79		14.80	8.47
			(378.4)	Found	63.10	4.80		14.70	8.80
31	232	93	$C_{19}H_{15}ClN_4OS$	Calcd.	59.60	3.95	9.26	14.63	8.37
			(382.9)	Found	59.30	4.10	9.00	14.50	8.00
33	246	93	$C_{16}H_{12}N_4OS$	Calcd.	62.33	3.89		18.17	10.40
			(308.2)	Found	62.30	4.10		18.10	10.50

b) Each of compounds **3** – **5** (0.01 mol) was dissolved in cold sodium methoxide solution (prepared from 0.23 g of sodium in 20 ml of anhydrous methanol), then methyl iodide (0.01 mol) was added. The reaction mixture was stirred for 30 min and left overnight at room temperature. The precipitate was collected and recrystallized from butanol into crystals of compounds **8** – **10** (cf. Table).

6-(2-Arylvinyl)-4-(benzylideneamino)-3-(methylthio)-1,2,4-triazin-5(4H)-ones **29** – **31**: Each of compounds **8** – **10** (0.01 mol) was heated under reflux in ethanol (35 ml) with benzaldehyde (0.01 mol) for 1 h. The solid obtained was crystallized from DMF (cf. Table).

4-(Benzylideneamino)-3,4-dihydro-6-phenyl-3-thioxo-1,2,4-triazin-5(2H)-one (**33**): Compound **2** (2.0 g) and benzaldehyde (2 ml) were heated under reflux in acetic acid (50 ml) containing sodium acetate (anhydrous, 1.0 g) for 1 h. After cooling the precipitated crystals were collected and recrystallized from DMF (cf. Table).

4-(Benzylideneamino)-3-(methylthio)-6-R-1,2,4-triazin-5(4H)-ones (**27**, **28**): Each of compounds **32** and **33** (0.005 mol) was dissolved in sodium methoxide solution (prepared from 0.12 g of sodium in 15 ml of anhydrous methanol) and then methyl iodide (0.75 g) was added and left overnight at room temperature. The precipitated needles were collected and recrystallized from ethanol (cf. Table).

Compound **27** (R = methyl): MS: *m/e* = 260 (M^+). – ^1H NMR ([D_6]DMSO): δ = 2.54 (s, 6-CH_3), 2.64 (s, SCH_3), 7.4 – 8.04 (m, ArH) and 9.52 (s, benzal. CH).

Compound **28** (R = phenyl): MS: *m/e* = 322 (M^+). – ^1H NMR ([D_6]DMSO): δ = 2.62 (s, SCH_3), 7.40 – 8.44 (m, ArH) and 9.42 (s, benzal. CH).

1-Amino-3-methyl-2H-[1,2,4]triazino[3,2-b]quinazoline-2,6(1H)-dione (**17**): An intimate mixture of **6** (1.72 g) and anthranilic acid (1.64 g) was heated at 180 °C (oil bath) for 1 h. The solid formed upon cooling was triturated with alcohol and crystallized from DMF into yellow crystals of **17**, m. p. 278 – 280 °C, yield 70%. – MS: *m/e* = 243 (M^+). – UV: λ_{max} (ε_{max}) = 313 (2200), 350 nm (1738).

$C_{11}H_9N_5O_2$ (243.2) Calcd. C 54.31 H 3.72 N 28.79 Found C 54.50 H 3.70 N 29.00

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

a) An intimate mixture of 7 (1.17 g) and anthranilic acid (0.82 g) was heated at 180 °C (oil bath) for 1 h. After cooling the product was triturated with alcohol and crystallized from DMF into yellow crystals of **18**, m. p. 201 – 203 °C, yield 72%. – MS: *m/e* = 305 (M^+). – UV: λ_{max} (ε_{max}) = 310 (5615), 356 nm (1062). – IR: 3300, 3200, 1720, 1670 cm^{-1}.

$C_{16}H_{11}N_5O_2$ (305.2) Calcd. C 62.95 H 3.63 N 22.94 Found C 62.70 H 3.70 N 22.80

b) Compound **35** (0.5 g) in 30 ml of ethanol and 2 ml of conc. HCl was heated under reflux for 30 min. After cooling the precipitate was collected and recrystallized from DMF into yellow crystals of **18**, m. p. 201 – 203 °C, yield 65%.

1-Amino-3-(2-arylvinyl)-2H-[1,2,4]triazino[3,2-b]quinazoline-2,6(1H)-diones (**19** – **21**): These were prepared from compounds **8** – **10**, respectively, and anthranilic acid as described for compounds 17 and **18**.

Compound **19** (aryl = phenyl): m. p. 225 – 227 °C, yield 79%.

$C_{18}H_{13}N_5O_2$ (331.6) Calcd. C 65.19 H 3.95 N 21.20 Found C 65.00 H 4.20 N 21.50

Compound **20** (aryl = 4-methoxyphenyl): m. p. 268 – 270 °C, yield 82%.

$C_{19}H_{15}N_5O_3$ (361.6) Calcd. C 63.10 H 4.18 N 19.44 Found C 63.00 H 4.20 N 19.30

Compound **21** (aryl = 4-chlorophenyl): m. p. 296 – 298 °C, yield 75%.

$C_{18}H_{12}ClN_5O_2$ (365.8) Calcd. C 59.10 H 3.30 Cl 9.69 N 19.63
Found C 59.20 H 3.70 Cl 9.50 N 19.90

1-(Benzylideneamino)-3-methyl-2H-[1,2,4]triazino[3,2-b]quinazoline-2,6(1H)-diones (**34**)

a) Compound **27** (0.52 g) and anthranilic acid (0.3 g) was heated at 160 – 170 °C (oil bath) for $1\frac{1}{2}$ h, then triturated with alcohol and crystallized from DMF into yellow crystals of **34**, m. p. 270 – 273 °C, yield 30%. – MS: *m/e* = 331 (M^+). – UV: λ_{max} (ε_{max}) = 350 nm (2274).

$C_{18}H_{13}N_5O_2$ (331.3) Calcd. C 63.94 H 4.10 N 21.90 Found C 63.80 H 4.00 N 21.80

b) Compound **17** (1.2 g) in acetic acid (30 ml) together with benzaldehyde (1.0 g) and anhydrous sodium acetate (1.0 g) was heated under reflux for 2 h. The solid precipitated after cooling was collected and recrystallized from DMF into compound **34**, yield 80%.

1-(Benzylideneamino)-3-phenyl-2H-[1,2,4]triazino[3.2-b]quinazoline-2,6(1H)-dione (**35**)

a) From compound **28** and anthranilic acid as described for **34**, crystallized from DMF, m. p. 251 – 253 °C, yield 95%. – MS: *m/e* = 393 (M^+). – UV: λ_{max} (ε_{max}) = 306 (6084), 360 nm (2071). – ^1H NMR ([D_6]DMSO): δ = 7.40 – 8.44 (m, 14H, ArH), 8.96 (s, benzal. CH).

$C_{23}H_{15}N_5O_2$ (393.4) Calcd. C 70.21 H 3.84 N 17.80 Found C 70.40 H 4.00 N 17.70

b) From compound **18** and benzaldehyde as described for the synthesis of **34**. The yield of **35** in this case is 98%.

3-Methyl-2H-[1,2,4]triazino[3,2-b]quinazoline-2,6(1H)-dione (**22**): Compound **17** (0.5 g) in 10 ml of 6 N HCl was treated dropwise while cooling and stirring with sodium nitrite solution (0.5 g in 5 ml of water). The immediately formed precipitate was left at room temperature for 15 min, collected and crystallized from DMF to give 88% of compound **22**, m. p. > 315 °C[15].

3-Phenyl-2H-[1,2,4]triazino[3,2-b]quinazoline-2,6(1H)-dione (**23**)

a) Compound **18** was deaminated by the action of nitrous acid as in the previous procedure to give compound **23**, yield 90%, m. p. > 315 °C[15].

b) Compound **35** (0.5 g) was heated at 250 °C (metal bath) for 30 min, during which benzonitrile was noticeably evolved. The solid remained was crystallized from DMF into compound **23**, yield 70%.

c) An intimate mixture of **28** (0.5 g) and anthranilic acid (0.3 g) was heated at 200 °C (oil bath) for $1\frac{1}{2}$ h, during which benzonitrile was noticeably evolved. The remaining solid was crystallized from DMF into compound **23**, yield 45%.

3-(2-Arylvinyl)-2H-[1,2,4]triazino[3,2-b]quinazoline-2,6(1H)-diones (**24** – **26**)

a) By deamination of **19** – **21** with nitrous acid as described for compound **22**.

b) From compounds **29** – **31** by their reaction with anthranilic acid as described for compound **23**.

Compound **24** (aryl = phenyl): m. p. > 315 °C[15]

Compound **25** (aryl = 4-methoxyphenyl): m. p. > 315 °C[15]

Compound **26** (aryl = 4-chlorophenyl): m. p. > 315 °C[15]

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[1] Part I: *S. A. L. Abdel-Hady, M. A. Badawy, Y. A. Ibrahim*, and *W. Pfleiderer*, Chem. Ber. **117**, 1077 (1984), preceding.

[2] *N. P. Peet, S. Sunder*, and *R. J. Barbuch*, J. Heterocycl. Chem. **19**, 747 (1982).

[3] *N. P. Peet* and *S. Sunder*, J. Org. Chem. **40**, 1909 (1975).

[4] *N. P. Peet* and *S. Sunder*, Indian J. Chem., Sect. B **16**, 207 (1978).

[5] *N. P. Peet, S. Sunder*, and *D. L. Trepanier*, Indian J. Chem., Sect. B **14**, 701 (1976).

[6] *S. Sunder* and *N. P. Peet*, J. Heterocycl. Chem. **18**, 1601 (1981).

[7] *A. Ebnöther, E. Jucker, E. Rissi, J. Rutschmann, E. Schreier, R. Steiner, R. Süess*, and *A. Vogel*, Helv. Chim. Acta **42**, 918 (1959).

[8] *M. Takahashi, S. Onizawa*, and *T. Satoh*, Bull. Chem. Soc. Jpn. **47**, 2724 (1974).

[9] *R. M. Claramont, J. M. Fabrega*, and *J. Elguero*, J. Heterocycl. Chem. **11**, 751 (1974).

[10] *C. W. Rees, D. L. R. Reeves*, and *R. C. Storr*, J. Chem. Soc., Perkin Trans. 1 **1976**, 2178.

[11] *J. P. Lavergne, Ph. Viallefont*, and *J. Daunis*, J. Heterocycl. Chem. **12**, 1095 (1975).

[12] *Y. A. Ibrahim, M. M. Eid*, and *S. A. Abdel-Hady*, J. Heterocycl. Chem. **17**, 1733 (1980).

[13] *A. Dornow, H. Menzel*, and *P. Marx*, Chem. Ber. **97**, 2173 (1964).

[14] *M. M. Eid, M. A. Ghazala*, and *Y. A. Ibrahim*, Egypt J. Chem., in press.

[15] See pervious paper[1].

[16] *H. M. R. Hoffmann*, Angew. Chem. **81**, 597 (1969), Angew. Chem., Int. Ed. Engl. **8**, 556 (1969).

[17] *A. F. M. Fahmy, M. S. Fayed*, and *Y. A. Ibrahim*, Chem. Ind. (London) **1978**, 36.

[18] *S. A. El-Bahaie, G. Abdel-Latif*, and *Y. A. Ibrahim*, X. Symposium on Organic Sulphur Chemistry, Bangor, U. K., Sept. 1982, CP 16.

[19] *I. B. Bopat, R. I. Blode, A. J. Bonlton, J. Epaztain, A. R. Katritzky, J. Lewis, P. Molina-Buendia, Pai-Lin Nie*, and *C. A. Ramsden*, Tetrahedron Lett. **1976**, 2691.

[20] *A. Dornow* and *H. Pietsch*, Chem. Ber. **100**, 2585 (1967).

[190/83]