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Synthesis of new pyridoquinoxalines, thienopyridoquinoxalines and pyrimidothienopyridoquinoxalines

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Synthesis of 3-chloro-2-cyanoquinoxaline (**1**) and its reactions with sodium azide, guanidine hydrochloride, semicarbazide and thioheterocycles have been investigated (**2**–**7**). Also, the reaction of the chloro compound **1** with cyanoacetamide or cyanothioacetamide gave the pyrido[2,3-*b*]quinoxaline derivatives **8**, **9**. Compound **9** was used as a key intermediate to produce the more polyheterocyclic systems **10**–**18**.

1. Introduction

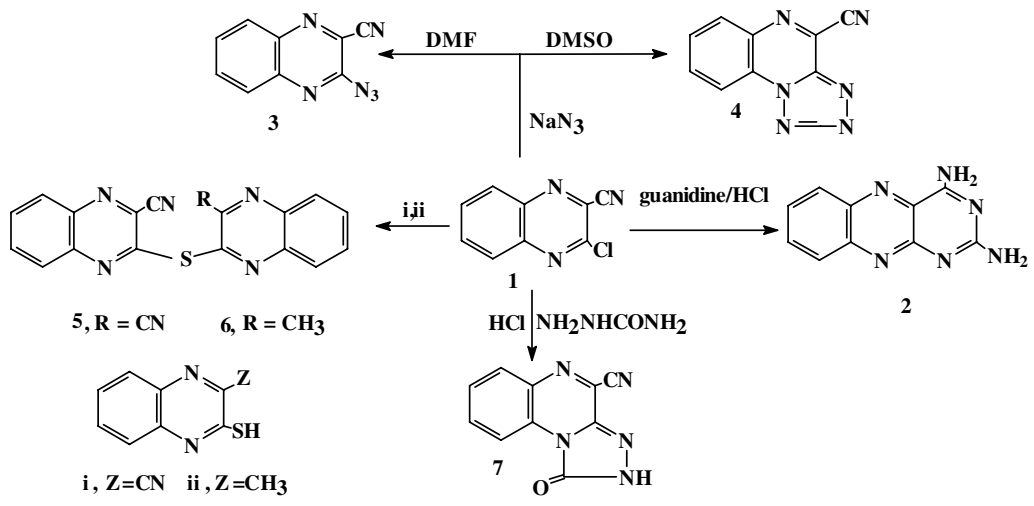
We have previously reported the synthesis and reactions of some new quinoxaline derivatives. Compounds with a quinoxaline nucleus significant have biological activities [1–4]. For example, pyridazinoquinoxaline and ditriazoloquinoxaline derivatives show excellent bactericidal and fungicidal activity [5, 6]. Also, 3,6,7-substituted-2-quinoxalinone and 6,7-difluoro-3-alkyl(aryl)-substituted-2-quinoxalinone have been used for their anti-microbial, anticancer, and anti HIV activities, and as interleukin receptor antagonists and can be used in the treatment of a chemokine-mediated disease, inflamatory bowel disease, Crohn's disease, Alzheimer's disease and allergic disease [7–9]. The present investigation which continues our work on the quinoxaline moiety [10–15] is concerned with the use of 3-chloro-2-cyanoquinoxaline [16] for the synthesis of many fused quinoxaline heterocycles of a new type and it therefore appears likely that these compounds will exhibit interesting biological properties.

2. Investigations, results and discussion

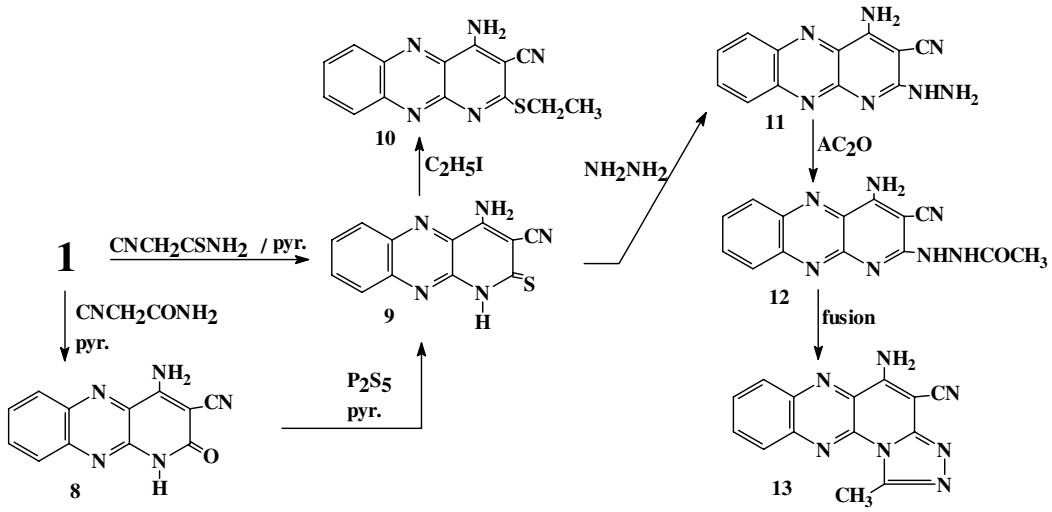
3-Chloro-2-cyanoquinoxaline (**1**) [16] with a vicinal chlorocyano group was envisaged as a potential starting material for the synthesis of fused heterocycle systems. Thus, treatment of **1** with guanidine hydrochloride in sodium ethoxide yielded pyrimido[4,5-*b*]quinoxaline **2**. Azidoquinoxaline **3** was prepared by the reaction of chloroquinoxaline **1** with sodium azide in DMF. Like similar heterocyclic azides having the azido group attached to the cyclic carbon atom adjacent to an annular nitrogen, it may exist as a true azide or as tetrazolo[1,5-*a*]quinoxaline **4** (through reaction with sodium azide in DMSO). Treatment of **1** with 3-mercapto-2-cyano-quinoxaline and 3-mercapto-2-methylquinoxaline yielded the bis(quinoxalin-2-yl)sulifed derivatives **5**, **6.** 5-Cyano-s-triazolo[4,3-*a*]quinoxaline **7** was obtained by treatment of **1** with semicarbazide hydrochloride (Scheme 1).

Reaction of **1** with cyanoacetamide in pyridine gave 4-amino-3-cyano-pyrido[2,3-*b*]quinoxalin-2(1*H*)-one (**8**) which was thionated by P_2S_5 in pyridine to yield 4-amino-3-cyano-pyrido[2,3-*b*]quinoxaline-2(1*H*)-thione (**9**). The latter thio compound was also produced directly by reaction of **1** with cyanothioacetamide in pyridine. Compound **9** was used as a key intermediate to produce other heterocycle rings thus, reaction of **9** with ethyliodide gave the 3-ethylthio-pyridoquinoxaline derivative **10,** while hydrazinolysis with hydrazine hydrate yielded 4-amino-3-cyano-2-hydrazino-pyrido[2,3-*b*]quinoxaline (**11**). Acylation of **11** by boiling with acetic anhydride yielded 4-amino-3-cyano-2-acetylhydrazino-pyrido[2,3-*b*]quinoxaline (**12**), and ring closure of **12** gave 6-amino-5-cyano-2-methyl-1,2,4-triazolo[4′,3′ : 1,6]-pyrido[2,3-*b*]quinoxaline (**13**, Scheme 2).

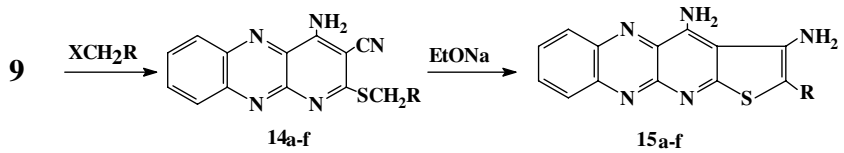
Scheme 1



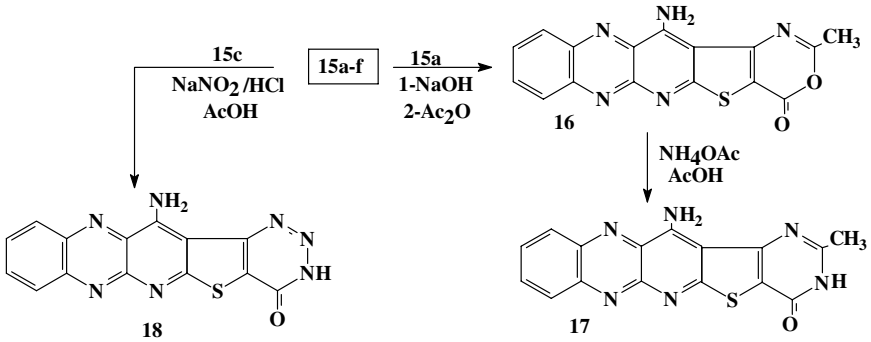
Scheme 2



Scheme 3



Scheme 4



Also, alkylation of **9** with α-halo compounds (e.g. ethyl chloroacetate, chloroacetic acid, chloroacetamide, phenacyl bromide, chloroacetanilide or *p*-chloro-chloroacetanilide) in alcoholic solution of anh. sodium acetate yielded the substituted thio intermediates **14a**–**f**, respectively, which upon treatment with sodium ethoxide produce the thienopyridoquinoxaline derivatives **15a**–**f** (Scheme 3).

Some of the latter derivatives were chosen and subjected to additional reaction to build up pentacyclic heterocycles e.g. the alkaline hydrolysis of **15a** with sodium hydroxide gave the sodium salt. This on refluxing in acetic anhydride yielded the oxazino compound **16** which in turn was reacted with ammonium acetate in acetic acid to give the pyrimidinone derivative **17.** Also, compound **15c** was reacted with concentrated hydrochloric acid and sodium nitrite in the presence of acetic acid at −5 °C to give the triazinothienopyridoquinoxaline derivative **18** (Scheme 4).

3. Experimental

Melting points were determined on a Gallenkamp apparatus and were uncorrected. IR spectra were recorded on a Pye-Unicam SP^3-100 spectrophotometer using the KBr wafer technique. ^1H NMR spectra were measured on a Varian 390–90 MHz NMR spectrometer in a suitable deuterated solvent, using TMS as internal standard. Elemental analyses were performed on a Perkin-Elmer 240 C microanalyzer. Elemental analysis

Table 1: Melting points, yields and analytical data of compounds 2–18

Compd.	M.P °C (Yield %)	Formula Mol.Wt
2	310 (80)	$C_{10}H_8N_6$, 212
3	180 (68)	$C_9H_4N_6$, 196
4	220–221 (75)	$C_9H_4N_6$ 196
5	240 (83)	$C_{18}H_8N_6S$, 340
6	190 (80)	$C_{18}H_{11}N_5S$, 329
7	290 (70)	$C_{10}H_5N_5O$, 211
8	225 (77)	$C_{12}H_7N_5O$, 237
9	>360 (70)	$C_{12}H_7N_5S$, 253
10	115 (90)	$C_{14}H_{11}N_5S$, 281
11	320 (81)	$C_{12}H_9N_7$, 251
12	260 (82)	$C_{14}H_{11}N_7O$, 293
13	360 (75)	$C_{14}H_9N_7$, 275
14a	120 (90)	$C_{16}H_{13}N_5O_2S$, 339
14b	150 (78)	$C_{14}H_9N_5O_2S$, 311
14c	240 (83)	$C_{14}H_{10}N_6OS$, 310
14d	160 (70)	$C_{20}H_{13}N_5OS$, 371
14e	190 (80)	$C_{20}H_{14}N_6OS$, 386
14f*	155 (85)	$C_{20}H_{13}N_6OSCl$, 420.5
15a	255 (77)	$C_{16}H_{13}N_5O_2S$, 339
15b	240 (68)	$C_{14}H_9N_5O_2S$, 311
15c	330 (72)	$C_{14}H_{10}N_6OS$, 310
15d	235 (72)	$C_{20}H_{13}N_5OS$, 371
15e	255 (65)	$C_{20}H_{14}N_6OS$, 386
15f**	260 (70)	$C_{20}H_{13}N_6OSCl$, 420.5
16	225 (75)	$C_{16}H_9N_5O_2$ S, 335
17	295 (65)	$C_{16}H_{10}N_6OS$, 334
18	>360 (68)	$C_{14}H_7N_7OS$, 321

*, ** Cl (calc. 8.44, found 8.41, 8.38% on respectively)

gave acceptable results unless otherwise stated. Melting points, yields and spectroscopic data are listed in Tables 1 and 2.

3.1. 3-Chloro-2-cyanoquinoxaline (**1**)

Compound **1** was prepared according to the literature [16], m.p. 160 °C.

3.2. 2,4-Diamino-pyrimido[4,5-b]quinoxaline (**2**)

To a solution of sodium ethoxide [0.5 g (0.02 mol) of sodium and 50 ml abs. ethanol] guanidine hydrochloride (0.01 mol) was added and refluxed for 2 h. Compound **1** (0.01 mol) in abs. ethanol (20 ml) was added dropwise. After being well stirred the reaction mixture was refluxed for 6 h. The solid obtained upon dilution with water was filtered off and recrystallized from ethanol as yellow crystals.

3.3. 3-Azido-2-cyanoquinoxaline (**3**)

A mixture of **1** (0.01 mol) in DMF (20 ml) and sodium azide (0.01 mol) was stirred for 3 h, diluted with water and neutralized with HCl. The solid obtained upon dilution with water was filtered off and recrystallized from acetic acid as yellow crystals.

3.4. Tetrazolo[1,5-a]quinoxaline-4-carbonitrile (**4**)

A mixture of **1** (0.01 mol) in DMSO (20 ml) and sodium azide (0.01 mol) was stirred for 4 h, diluted with water and neutralized with HCl. The solid obtained upon dilution with water was filtered off and recrystallized from acetic acid as brown crystals.

3.5. Bis (3-cyanoquinoxaline-2-yl)sulfide (**5**)

A mixture of **1** (0.01 mol) in 20 ml of 25% aqueous NaOH and 2-cyanoquinoxaline-3(1*H*)-thione (0.01 mol) was heated for 2 h. The reaction mixture was cooled, diluted with water and neutralized with dilute acetic acid. The solid obtained was filtered off and recrystallized from ethanol as pale red crystals.

3.6. 3-Cyano-3′-methyl-bis(quinoxalin-2-yl)sulfide (**6**)

A mixture of **1** (0.01 mol) in 20 ml of 25% aqueous NaOH and 3-methylquinoxaline-2(1*H*)-thione (0.01 mol) was heated for 2 h. The reaction mixture was cooled, diluted with water and neutralized with dilute acetic acid. The solid obtained was filtered off and recrystallized from ethanol as red crystals.

Table 2: Spectroscopic data of compounds 2–18

Compd.	IR(ν cm^{-1})/^{1}H NMR δ (ppm)
2	3120 (NH_2), 1620 (C=N); (DMSO-d_6): δ 4.2 (s, 2 H, NH_2), δ 6.2 (s, 2 H, NH_2), δ 7.3–7.8 (m, 4 H, Ar-H).
3	2210 (CN), 2120 (N3); (CF_3COOD): δ 7.3–8.0 (m, 4 H, Ar-H).
4	2200 (CN), 1620 (C=N); (CF_3COOD): δ 7.4–8.1 (m, 4 H, Ar-H).
5	2220 (bro. 2 CN), 1620 (C=N); ($CDCl_3$): δ 7.5–8.0 (m, 8 H, Ar-H).
6	2220 (CN), 1610 (C=N); ($CDCl_3$): δ 2.8 (s, 3 H, CH_3), δ 7.5–8.3 (m, 8 H, Ar-H).
7	3230 (NH), 2220 (CN), 1680 (C=O); (DMSO-d_6): δ 7.5–7.8 (m, 4 H, Ar-H), δ 10.5 (s, 2 H, NH).
8	3180–3420 (NH, NH_2), 2220 (CN), 1670 (C=O); (DMSO-d_6): δ 6.2 (s, 2 H, NH_2), δ 7.4–7.9 (m, 4 H, Ar-H), 9.1 (s, 1 H, NH).
9	3200–3380 (NH, NH_2), 2210 (CN), 1230 (C=S); (DMSO-d_6): δ 4.9 (s, 2 H, NH_2), δ 7.4–8.1 (m, 4 H, Ar-H), δ 9.5 (s, 1 H, NH).
10	3400 (NH_2), 2980 (CH, aliph.), 2220 (CN); (DMSO-d_6): δ 1.3–1.6 (t, 3 H, CH_3), δ 3.2–3.5 (q, 2 H, CH_2), δ 5.8 (s, 2 H, NH_2), δ 7.6–8.2 (m, 4 H, Ar-H).
11	3220, 3430 (NH, NH_2), 2200 (CN); (CF_3COOD): δ 7.5–8.2 (m, 4 H, Ar-H).
12	3220, 3500 (NH, NH_2), 2220 (CN), 1620 (C=N); (CF_3COOD): δ 2.4 (s, 3 H, CH_3), δ 7.6–8.1 (m, 4 H, Ar-H).
13	3320 (NH_2), 2220 (CN); ($CDCl_3$): δ 2.4 (s, 3 H, CH_3), δ 6.0 (s, 2 H, NH_2), δ 7.6–8.2 (m, 4 H, Ar-H).
14a	3400 (NH_2), 2980 (CH, aliph.), 2200 (CN), 1730 (C=O); ($CDCl_3$): δ 1.5–1.9 (t, 3 H, CH_3), δ 3.9–4.1 (q, 2 H, CH_2), δ 4.6 (s, 2 H, CH_2), δ 6.1 (s, 2 H, NH_2), δ 7.2–8.0 (m, 4 H, Ar-H).
14b	3580 (OH), 3420 (NH_2), 2220 (CN), 1690 (C=O); (DMSO-d_6): δ 4.2 (s, 2 H, CH_2), δ 5.9 (s, 2 H, NH_2), δ 7.5–7.9 (m, 4 H, Ar-H).
14c	3400 (NH_2), 2200 (CN), 1680 (C=O); (CF_3COOD): δ 4.3 (s, 2 H, CH_2), δ 7.4–8.00 (m, 4 H, Ar-H).
14d	3250, 3400 (NH_2), 2200 (CN), 1740 (C=O); (CF_3COOD): δ 4.1 (s, 2 H, CH_2), δ 7.4–8.2 (m, 9 H, Ar-H).
14e	3150, 3330 (NH, NH_2), 2200 (CN), 1700 (C=O); (DMSO-d_6): δ 4.2 (s, 2 H, CH_2), δ 6.1 (s, 2 H, NH_2), δ 7.5–8.4 (m, 9 H, Ar-H), 8.9 (s, 1 H, NH).
14f	3100, 3390 (NH, NH_2), 2200 (CN). 1660 (C=O); (CF_3COOD): δ 4.3 (s, 2 H, CH_2), δ 7.3–8.2 (m, 8 H, Ar-H).
15a	3300, 3400 (NH_2), 1660 (C=O); ($CDCl_3$): δ 1.2–1.5 (t, 3 H, CH_3), δ 3.9–4.1 (q, 2 H, CH_2), δ 6.4 (s, 2 H, NH_2), δ 7.4–8.0 (m, 4 H, Ar-H).
15b	3280, 3400 (NH_2), 1700 (C=O); (DMSO-d_6): δ 5.9 (s, 2 H, NH_2), δ 7.6–7.9 (m, 4 H, Ar-H).
15c	3180 (NH_2), 1660 (C=O); (CF_3COOD): δ 7.3–8.1 (m, 4 H, Ar-H)
15d	3320 (NH_2), 1680 (C=O); (DMSO-d_6): δ 6.3 (s, 2 H, NH_2), δ 7.5–8.4 (m, 9 H, Ar-H).
15e	3200–3420 (NH, NH_2), 1650 (C=O); (CF_3COOD): δ 7.5–8.4 (m, 9 H, Ar-H).
15f	3300, 3480 (NH, NH_2), 1640 (C=O); (CF_3COOD): δ 7.5–8.4 (m, 8 H, Ar-H).
16	3350 (NH_2), 1690 (C=O); ($CDCl_3$): δ 2.3 (s, 3 H, CH_3), δ 6.0 (s, 2 H, NH_2), δ 7.2–8.1 (m, 4 H, Ar-H).
17	3160–3400 (NH, NH_2), 1660 (C=O); (DMSO-d_6): δ 6.1 (s, 2 H, NH_2), δ 7.6–8.2 (m, 4 H, Ar-H), 9.8 (s, 1 H, NH).
18	3200, 3420 (NH, NH_2), 1650 (C=O); (CF_3COOD): δ 7.5–8.3 (m, 4 H, Ar-H).

3.7. 5-Cyano-1,2,4-triazolo[4,3-a]quinoxaline (**7**)

A mixture of **1** (0.01 mol) and semicarbazide hydrochloride (0.012 mol) in abs. ethanol (25 ml) was treated with a few drops of conc HCl and refluxed for 7 h. The solid obtained was filtered off and recrystallized from ethanol as yellow crystals.

3.8. 4-Amino-3-cyano-pyrido[2,3-b]quinoxalin-2(1H)-one (**8**)

A mixture of **1** (0.01 mol) and cyanoacetamide (0.01 mol) in pyridine (30 ml) was refluxed for 4 h, poured onto cold water and neutralized with dilute acetic acid. The solid obtained was filtered off and recrystallized from ethanol as brown crystals.

3.9. 4-Amino-3-cyano-pyrido[2,3-b]quinoxaline-2(1H)-thione (**9**)

A mixture of **1** (0.01 mol) and cyanothioacetamide (0.01 mol) in pyridine (35 ml) was refluxed for 4 h, poured onto cold water and neutralized with dilute acetic acid. The solid obtained was filtered off and recrystallized from acetic acid as bright deep red crystals.

3.10. 4-Amino-3-cyano-2-ethylthio-pyrido[2,3-b]quinoxaline (**10**)

A mixture of **9** (0.01 mol), ethyl iodide (0.01 mol) and anhydrous sodium acetate (5 g) in ethanol (40 ml) was refluxed for 2 h, poured onto cold water. The solid obtained was filtered off and recrystallized from ethanol as pale yellow crystals.

3.11. 4-Amino-3-cyano-2-hydrazino-pyrido[2,3-b]quinoxaline (**11**)

A mixture of **9** (0.01 mol) and hydrazine hydrate (6 ml) was refluxed in ethanol (35 ml) for 4 h or until evolution of H_2S ceased) then cooled, and the yellow precipitate was filtered off and recrystallized from ethanol.

3.12. 4-Amino-3-cyano-2-acetylhydrazino-pyrido[2,3-b]quinoxaline (**12**)

A solution of **11** (0.01 mol) in acetic anhydride (25 ml) was refluxed for 3 h, then cooled and poured onto ice/water. The precipitate thus formed was collected and recrystallized from ethanol as pale yellow crystals.

3.13. 6-Amino-5-cyano-2-methyl-1,2,4-triazolo[4′,3′ : 1,6]pyrido[2,3-b] quinoxaline (**13**)

Acetylhydrazino **12** (0.5 g) was heated to melting and refluxed for 15 min, then cooled. The solid thus formed was recrystallized from acetic acid as pale brown crystals.

3.14. 4-Amino-3-cyano-2-substitutedthio-pyrido[2,3-b]quinoxaline (**14a**–**f**)

A mixture of **9** (0.1 mol) and α-halo carbonyl compound (0.1 mol) in ethanol (30 ml) in the presence of anh. sodium acetate (5 g) was refluxed for 2 h, and poured onto cold water. The solid obtained was filtered off and recrystallized from ethanol. The physical constants and spectral data of compounds **14a**–**f** are summarized in Table 1.

3.15. 3,4-Diamino-2(substituted)thieno[2′,3′ : 5,6]pyrido[2,3-b]quinoxaline (**15**)

A sample of compounds **14a**–**f** (0.5 g) in (25 ml) ethanolic ethoxide solution was refluxed for 1 h. The solid product separated from the hot mixture was filtered off and recrystallized from the proper solvent. The physical constants and spectral data of compounds **15a**–**f** are summarized in Tables 1, 2.

3.16. 13-Amino-2-methyl-oxazino[4″,5″ : 4′,5′]thieno[2′,3′ : 2,3]pyrido-[2,3-b]quinoxalin-4-one (**16**)

A sample of **15a** (1 g) was refluxed in 30 ml alcoholic NaOH 10% for 2 h. The red sodium salt was separated and was then was filtered off, and washed several times with ethanol. The latter sod. salt was refluxed in acetic anhydride (25 ml) for 2 h. The solid product which was produced on heating was filtered off and recrystallized from ethanol as yellow crystals.

3.17. 13-Amino-2-methyl-pyrimido[4″,5″ : 4′,5′]thieno[2′,3′ : 2,3]pyrido-[2,3-b]quinoxalin-4(3H)-one (**17**)

A mixture of the oxazino compound **16** (0.5 g) and ammonium acetate (4 g) in acetic acid (20 ml) was refluxed for 2 h, and the solid product separated from the hot mixture was filtered off, washed with water and recrystallized from acetic acid as yellow crystals.

3.18. 13-Amino-1,2,3-triazino[4″,5″: 4′,5′]thieno[2′,3′ : 2,3]pyrido[2,3-b]-quinoxalin-4-(3H)-one (**18**)

The title compound was prepared by treatment of compound **15c** (0.01 mol) with hydrochloric acid while adding dropwise sodium nitrite solution (20 ml) at −5 °C in presence of acetic acid (10 ml) and stirring for 2 h. The solid separated was filtered off and recrystallized from acetic acid as yellow crystals.

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