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Transformations of N-Heteroarylformamidines and N-Heteroarylformamidine Oximes New Syntheses and Transformations of Oxazolo[5,4—*c*]pyridazines

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New approaches to the synthesis of oxazolo[5,4—*c*]pyridazine derivatives **7** and **15** starting from the substituted N-pyridazin-5-ylformamide oximes **5** and **13** are described. Under mild conditions the transformations of the amino or substituted amino group at position 2 of the oxazolo[5,4—*c*]pyridazine system were observed to give the compounds **16** and **17**, while under more drastic reaction conditions the nucleophilic attack at position 2 followed by the ring opening of the oxazole part of the molecule was taking place to give the compounds **18**, **20**, and **21**.

(Keywords: Cyclization with C—O *bond formation; Substituted N-pyridazin-5-ylformamidines and -formamide oximes; Ring opening of oxazolo[5,4—c]-pyridazines)*

Transformationen von N-Heteroarylformamidinen und N-Heteroarylformamidin-oximen. Neue Synthesen und Transformationen von Oxazolo[5,4—c]pyridazinen

Neue Synthesemöglichkeiten von Oxazolo[5,4—*c*]pyridazinen **7** und **15**, ausgehend von substitutierten N-Pyridazin-5-ylformamid-oximen **5** und **13** werden beschrieben. Unter milden Reaktionsbedingungen trat Transformation der Amino- oder substituierten Aminogruppe an der Position 2 des Oxazolo-[5,4—*c*]pyridazin-Systems unter Bildung der Verbindungen **16** und **17** ein, währenddessen unter drastischeren Reaktionsbedingungen ein nucleophiler Angriff am Kohlenstoff der Position 2, gefolgt von einer Ringöffnung des Oxazol-Teils des Moleküls zu Verbindungen **18**, **20** und **21** führte.

Introduction

The versatility of N-heteroarylformamidines and N-heteroarylformamide oximes has been demonstrated by the synthesis of many bicyclic and

polycyclic systems, such as triazolo[1,5—*a*]azines, imidazo[1,2—*x*]-azines, azolo- and azinopyrimidines, including purines and pteridines, isothiazolo[4,5—*d*]pyrazines, and a number of fused aminooxazoles, including 2-aminooxazolo[4,5—*c*]quinolines, oxazolo[4,5—*b*]pyridines and oxazolo[5,4—*d*]pyrimidines was prepared by cyclization of the corresponding *o*-hydroxy substituted N-heteroarylformamide oximes with N,N-dimethylformamide dimethyl acetal (*DMFDMA*) or N,N-dimethylchloroformiminium chloride (*DCFC*)[1,2].

Recently, two new approaches to the synthesis of oxazolo[4,5—*d*]-pyridazine system were reported[3].

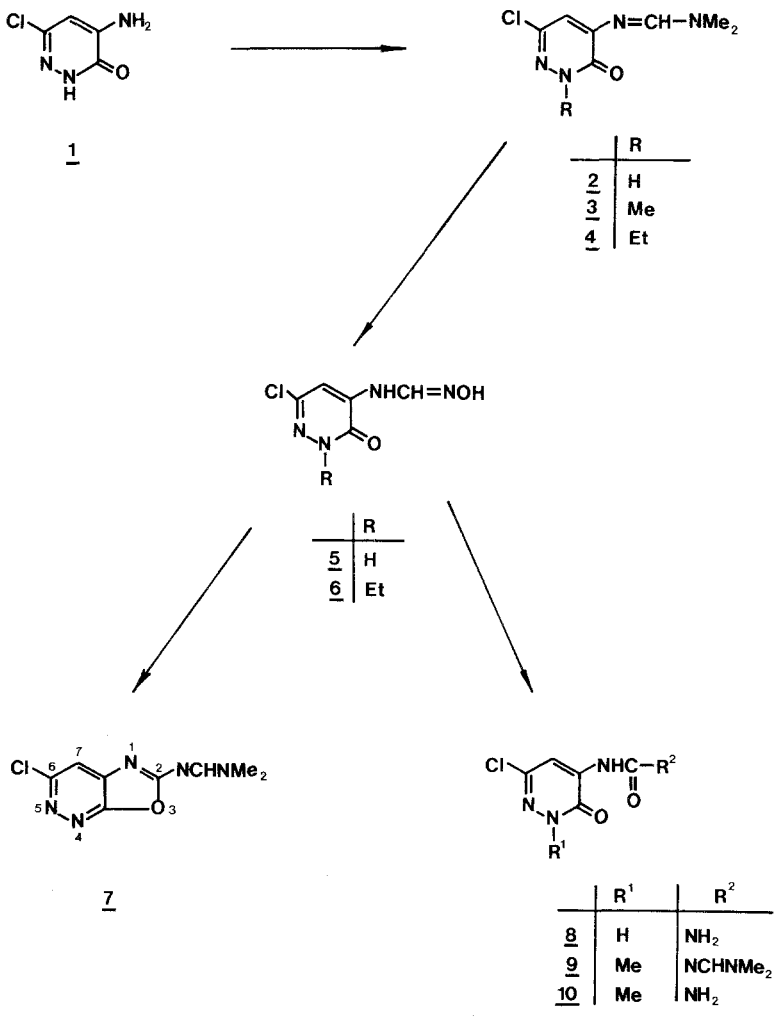
In this communication we report on a new synthesis of a little known oxazolo[5,4—*c*]pyridazine system as an extension of our previous studies about the transformations of N-heteroarylformamidines and -formamide oximes.

There are only two reports about the synthesis of this bicyclic system known in the literature. Namely, 2-phenyl derivative has been prepared either from 5-amino-3-chloropyridazin-6(1*H*)-one or 3,6-dichloro-4-aminopyridazine by cyclization with benzoyl chloride[4-6].

Results and Discussion

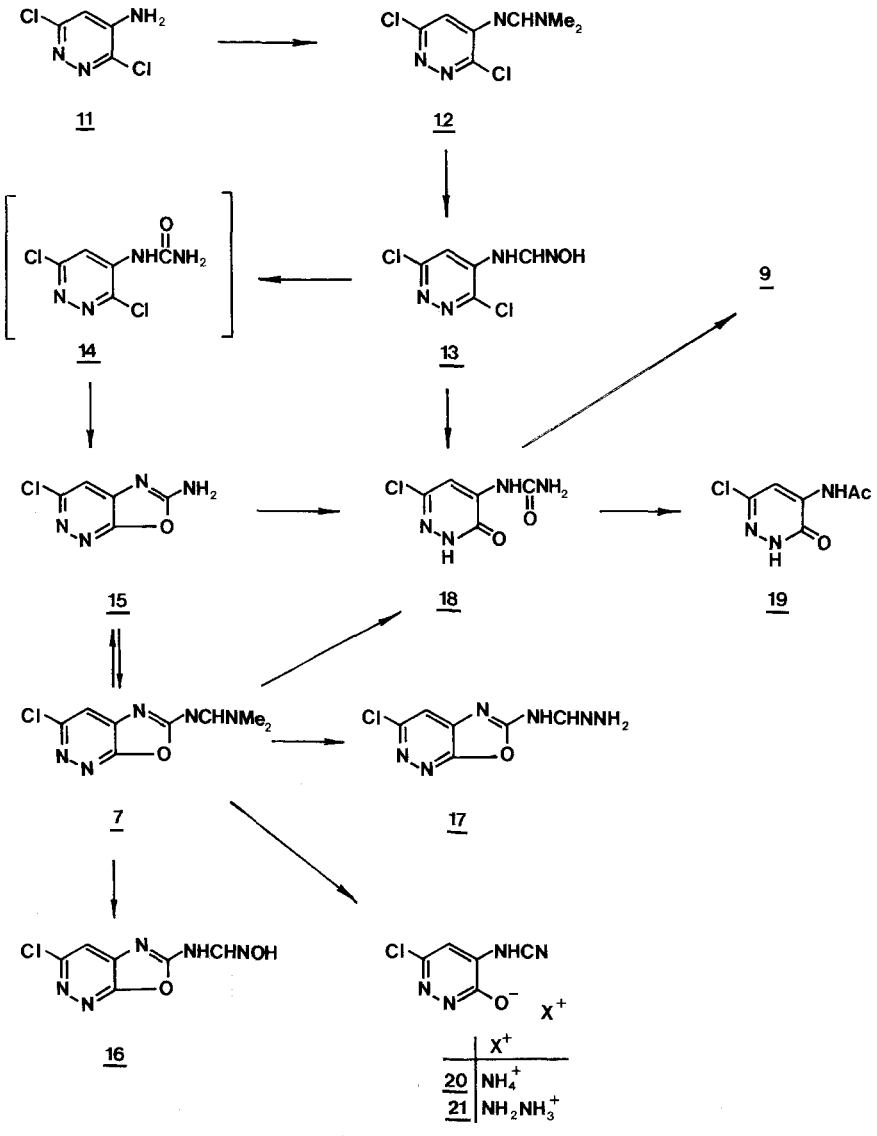
5-Amino-3-chloropyridazin-6(1*H*)-one (**1**) was chosen as the starting compound. **1** was transformed with N,N-dimethylformamide dimethyl acetal (*DMFDMA*) in 1 : 1 molar ratio into 3-chloro-5(N,N-dimethylaminomethyleneamino)-pyridazin-6(1*H*)-one (**2**), while with an excess of *DMFDMA* (in 1 : 3 molar ratio) 3-chloro-5-(N,N-dimethylaminomethyleneamino)-1-methylpyridazin-6(1*H*)-one (**3**) and with N,N-dimethylformamide diethyl acetal (*DMFDEA*) (in 1 : 3 molar ratio) the corresponding 1-ethyl derivative **4** isolated. The compounds **2** and **4** were easily converted with hydroxylamine hydrochloride in ethanol into 3-chloro-5-hydroxyiminomethyleneaminopyridazin-6(1*H*)-one (**5**) and 1-ethyl-5-hydroxyiminomethyleneaminopyridazin-6(1*H*)-one (**6**), respectively. Compound **5** was cyclodehydrated with *DMFDMA* in toluene at room temperature into 6-chloro-2-(N,N-dimethylamino-methyleneamino)-oxazolo[5,4—*c*]pyridazine (**7**) in 29% yield. On the other hand, in boiling toluene two compounds were formed. Besides the compound **7**, which was formed in 38% yield, 3-chloro-5-(N,N-dimethylaminomethyleneureido)-1-methylpyridazin-6(1*H*)-one (**9**) was isolated in 30% yield and further transformed with aqueous ammonia into 3-chloro-1-methyl-5-ureidopyridazin-6(1*H*)-one (**10**) in 76% yield. 1-Methyl- (**3**) and 1-ethyl- (**4**) derivatives are the products of N-alkylation with the excess of *DMFDMA* or *DMFDEA*, respectively. This is in agreement with many other examples reported earlier[3,7,8].

Scheme 1



2-Amino-6-chlorooxazolo[5,4—*d*]pyridazine could also be obtained from 4-amino-3,6-dichloropyridazine (**11**) according to the following reaction sequence. The compound **11** was transformed, when treated with *DMFDMA* in boiling toluene for two hours, into 3,6-dichloro-4-(N,N-dimethylaminomethyleneamino)-pyridazine **12** in 41% yield. This compound afforded with hydroxylamine hydrochloride in ethanol at room temperature the corresponding 3,6-dichloro-4-hydroxyimino-methyleneaminopyridazine **13** in 44% yield. On the other hand, by

Scheme 2



treatment of the compound **12** with hydroxylamine hydrochloride in methanol at room temperature for 20 hours 2-amino-6-chlorooxazolo[5,4—*c*]pyridazine (**15**) was obtained, most probably through 3,6-dichloro-4-ureidopyridazine (**14**), the intermediate which we were not able to isolate (Scheme 1, Scheme 2).

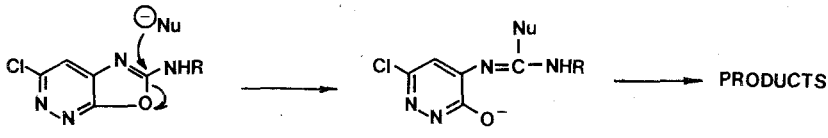
The oxazolo[5,4—*c*]pyridazine system is relatively stable under mild reaction conditions. Thus, the N,N-dimethylaminomethylene group in **7** could be converted either with sodium ethoxide or aqueous ammonia into the 2-amino derivative **15**, with hydroxylamine hydrochloride into 6-chloro-4-hydroxyiminomethyleneaminooxazolo[5,4—*c*]pyridazine (**16**) and with hydrazine hydrate into the corresponding 2-hydrazinomethyleneamino-6-chlorooxazolo[5,4—*c*]pyridazine (**17**). An attempt to convert **7** with aqueous sodium hydrogen sulphide into the corresponding thioformyl derivative, as observed with some other N-heteroarylformamidines[9], also resulted in the hydrolysis of the formamidine group and 2-amino derivative **15** was obtained.

Under more drastic reaction conditions addition of nucleophiles at position 2 is taking place followed by the ring opening of the oxazole system (Scheme 3). Accordingly, compounds **7** hydrolyzed with 10% hydrochloric acid into 3-chloro-5-ureidopyridazin-6(1*H*)-one (**18**). The same compound was also obtained either from 2-aminooxazolo[5,4—*c*]-pyridazine (**15**) when heated with hydroxylamine hydrochloride in ethanol, or from 3,6-dichloro-4-(N,N-dimethylaminomethyleneamino)-pyridazine (**12**) with hydroxylamine hydrochloride in boiling ethanol, as a consequence of *Beckmann* rearrangement followed by hydrolysis of the chlorine at position 3 of the intermediary formamide oxime derivative **13**. The transformations of compound **18** with acetic anhydride into the known 3-chloro-5-acetylaminopyridazin-6(1*H*)-one (**19**) and with *DMFDMA* into compound **9** further support the structure of **18**.

Attempts to substitute the chlorine at position 6 of oxazolo[5,4—*c*]-pyridazines also resulted in the clavage of the oxazole ring. In this respect, the treatment of **7** with aqueous ammonia or hydrazine hydrate afforded the corresponding 3-chloro-5-cyanoaminopyridazin-6(1*H*)-one in the form of its ammonium salt **20** or hydrazinium salt **21**, respectively. The salt **21** was obtained also by the reaction of hydrazine hydrate with **15**. By attempted crystallization from water the salt **20** cyclized into compound **15**. This ring opening is in agreement with some other examples reported in the literature[3,10].

In conclusion, the reactivity of the oxazolo[5,4—*c*]pyridazine system is very similar to that of the oxazolo[4,5—*d*]pyridazine system as reported recently[3].

Scheme 3



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Experimental[11]

Melting points were determined on a *Kofler* hot plate m.p. apparatus. ^{1}H NMR spectra were recorded on a JEOL C-60 HL spectrometer (*TMS* as internal standard, δ-values in ppm) and mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6 L spectrometer. Elemental analysis (C, H, N) were obtained with a Perkin-Elmer Analyser 240 C.

3-Chloro-5-(N,N-dimethylaminomethyleneamino)-pyridazin-6(1H)-one (**2**)

A mixture of 200 mg 5-amino-3-chloropyridazin-6(1*H*)-one (**1**)[4], 0.2 ml of N,N-dimethylformamide dimethyl acetal (*DMFDMA*) and 10 ml of anhydrous toluene was heated under reflux for 5 h. The solvent was evaporated in vacuo and the residue recrystallized from ethanol to give 200 mg (73%) of the product, m.p. 200–204 °C. MS (*m/e*): 200 (M^+). NMR (*DMSO-d*$_6$): 2.97 (s), 3.06 (s) (N*Me*$_2$), 6.60 (s, H$_4$), 8.60 (s, CH=N), 12.6 (br. s, NH).

$C_7H_9N_4ClO$ (200.63). Calcd. C 41.90 H 4.52 N 27.93.
Found. C 41.56 H 4.44 N 27.53.

3-Chloro-5-(N,N-dimethylaminomethyleneamino)-1-methylpyridazin-6(1H)-one (**3**)

A solution of 145 mg **1**[4] and 0.5 ml of *DMFDMA* in 10 ml of anhydrous toluene was heated under reflux for 4 h. Evaporation of the solvent in vacuo gave 40 mg (19%) of the product, m.p. 70–72 °C (from cyclohexane). MS (*m/e*): 214 (M^+). NMR (*DMSO-d*$_6$): 2.93 (s), 3.03 (s) (N*Me*$_2$), 3.53 (s, N*Me*), 6.53 (s, H$_4$), 8.47 (s, CH=N).

$C_8H_{11}N_4ClO$ (214.66). Calcd. C 44.76 H 5.17 N 26.10.
Found. C 45.31 H 5.25 N 26.13.

3-Chloro-5-(N,N-dimethylaminomethyleneamino)-1-ethylpyridazin-6(1H)-one (**4**)

A mixture of 145 mg **1**[4] 0.5 ml of N,N-dimethylformamide diethyl acetal (*DMFDEA*) and 10 ml of anhydrous toluene was heated under reflux for 4 h. The solvent was evaporated in vacuo, the dry residue dissolved in chloroform and separated by thin layer chromatography [PSC-Fertigplatten Kieselgel 60 F 254, Merck, with a mixture of chloroform and ethanol (9 : 1) as a solvent]. Elution with chloroform gave, after evaporation of chloroform, 30 mg (10%) of the product, m.p. 184–185 °C (from ethanol). MS (*m/e*): 228 (M^+). NMR (*DMSO-d*$_6$): 1.30 (t, *Me*CH$_2$), 4.0 (q, *Me*CH$_2$), 6.80 (s, N*Me*$_2$), 7.85 (s, H$_4$), 8.42 (s, CH=N).

$C_9H_{13}N_4ClO$ (228.68). Calcd. C 47.27 H 5.73 N 24.50.
Found. C 47.36 H 3.96 N 24.85.

3-Chloro-5-hydroxyaminomethyleneaminopyridazin-6(1H)-one (**5**)

A solution of 360 mg **2** and 200 mg of hydroxylamine hydrochloride in 15 ml of methanol was heated under reflux for 1 h. Methanol was evaporated in vacuo, the residue recrystallized from water to give 300 mg (65%) of the product, m. p. 203–205 °C. MS (*m/e*): 188 (M^+). NMR (*DMSO-d_6*): 7.17 (s, H_4), 7.77 (d, CH), 8.27 (d, NH), 9.20 (br. s, NH), 13.1 (br. s, OH).

$C_5H_5N_4ClO_2 \cdot \frac{1}{2} H_2O$ (197.58). Calcd. C 30.39 H 3.06 N 28.36.
Found. C 30.43 H 3.05 N 28.53.

1-Ethyl-5-hydroxyiminomethyleneaminopyridazin-6(1H)-one (**6**)

A solution of 220 mg **4** and 70 mg of hydroxylamine hydrochloride in 15 ml of methanol was heated under reflux for 4 h. The precipitate was collected (after cooling) by filtration to give 70 mg (34%) of the product, m. p. 190 °C (dec.) (from ethanol). MS (*m/e*): 216 (M^+). NMR (*DMSO-d_6*): 1.26 (t, *Me*), 4.07 (q, CH_2), 7.22 (s, H_4), 7.73 (d, CHNH), 8.35 (d, CHNH), 11.9 (s, OH), $J_{CHNH} = 10.0$ Hz, $J_{CH_2Me} = 7.0$ Hz.

$C_7H_9N_4ClO_2$ (216.63). Calcd. C 38.81 H 4.19 N 25.86.
Found C 38.80 H 4.13 N 26.04.

6-Chloro-2-(N,N-dimethylaminomethyleneamino)-oxazolo[5,4—c]pyridazine (**7**) *and 3-Chloro-5-(N,N-dimethylaminomethyleneureido)-1-methylpyridazin-6(1H)-one* (**9**)

a) A mixture of 1.6 g **5**, 2.4 ml of *DMFDMA* and 15 ml of anhydrous toluene was heated under reflux for 3 h. The precipitate was (after cooling) collected and recrystallized from ethanol to give 0.5 g (38%) of compound **7**, m. p. 180–183 °C. MS (*m/e*): 225 (M^+). NMR ($CDCl_3$): 3.23 (s), 5.32 (s) (NMe_2), 7.30 (s, H_7), 8.67 (br. s, CH=N).

$C_8H_8N_5ClO$ (225.64). Calcd. C 42.58 H 3.57 N 31.04.
Found. C 42.64 H 3.48 N 31.05.

The filtrate obtained above was evaporated in vacuo, the dry residue was dissolved in chloroform and separated by preparative layer chromatography [PSC Fertigplatten Kieselgel 60 F 254, Merck, with a mixture of chloroform and ethanol (9:1)]. The elution of the band with $R_f = 0.9$ with chloroform gave after evaporation of the solvent in vacuo 400 mg (30%) of compound **9**, m. p. 210 °C (dec.) (from ethanol). MS (*m/e*): 257 (M^+). NMR ($CDCl_3$): 3.07 (s), 3.14 (s) (NMe_2), 3.78 (s, *NMe*), 7.98 (s, H_4), 8.29 (br. s, NH), 8.45 (s, CH=N).

$C_9H_{12}N_5ClO_2$ (257.68). Calcd. C 41.29 H 4.67 N 26.81.
Found. C 41.25 H 4.68 N 26.53.

b) A mixture of 1.6 g **15**, 1.1 ml of *DMFDMA*, and 20 ml of anhydrous toluene was stirred at room temperature for 24 h. The precipitate was collected by filtration and recrystallized from ethanol to give 0.5 g (29%) of **7**. The IR spectrum of it was identical with that of the compound obtained under a).

c) A solution of 200 mg **8** and 0.5 ml of *DMFDMA* in 10 ml of anhydrous toluene was heated under reflux for 3 h. The precipitate was (after cooling), collected by filtration and recrystallized from ethanol to give 135 mg (54%) of **9**. The IR spectrum of it was identical with that of the compound described under a).

3-Chloro-1-methyl-5-ureidopyridazin-6(1H)-one (**10**)

A mixture of 100 mg **9** and 10 ml of 28% aqueous ammonia was heated under reflux for 1 h. The precipitate was (after cooling) collected to give 60 mg (76%) of the product, m. p. 295 °C (from ethanol). MS (*m/e*): 202 (M^+). NMR (*DMSO-d*$_6$): 3.67 (N*Me*$_2$), 6.83 (br. s, NH_2), 7.78 (s, H_4), 9.13 (br. s, NH).

$C_6H_7N_4ClO_2$ (202.60). Calcd. C 35.56 H 3.48 N 27.65.
Found. C 35.79 H 3.50 N 27.65.

3,6-Dichloro-4-(N,N-dimethylaminomethyleneamino)-pyridazine (**12**)

A solution of 1.5 g **11**, 1.7 ml of *DMFDMA*, and 10 ml of anhydrous toluene was heated under reflux for 2 h. The volatile components were evaporated in vacuo and the residue recrystallized from ethanol to give 1.0 g (50%) of the product, m. p. 110–112 °C. MS (*m/e*): 218 (M^+). NMR (*DMSO-d*$_6$): 3.08 (s), 3.18 (s) (N*Me*$_2$), 7.45 (s, H_5), 8.29 (s, CH=N).

$C_7H_8N_4Cl_2$ (219.08). Calcd. C 38.37 H 3.67 N 25.58.
Found C 38.39 H 3.66 N 25.75.

3,6-Dichloro-4-hydroxyiminomethyleneaminopyridazine (**13**)

A mixture of 240 mg **12** and 80 mg of hydroxylamine hydrochloride in 5 ml of ethanol was heated under reflux until all the starting material was dissolved. By further heating a new precipitate was formed which was (after cooling) collected by filtration to give 100 mg (44%) of the product, m. p. 210 °C (dec.) (from a mixture of ethanol and petroleum ether). MS (*m/e*): 206 (M^+). NMR (*DMSO-d*$_6$): 7.75 (s, H_5), 7.87 (s, CHNH), ~ 7.7 (br. s, CHN**H**), 11.1 (s, OH).

$C_5H_4N_4Cl_2O$ (207.03). Calcd. C 29.01 H 1.95 N 27.07.
Found. C 29.24 H 1.90 N 26.83.

2-Amino-6-chlorooxazolo[5,4—c]pyridazine (**15**)

a) A mixture of 100 mg **7** and 50 mg of sodium ethoxide in 10 ml of ethanol was heated under reflux for 2 h. Ethanol was evaporated in vacuo and the residue dissolved in 5 ml of water and neutralized with 10% hydrochloric acid. The precipitate was collected to give 50 mg (66%) of the product, m. p. 260 °C (dec.) (from water). MS (*m/e*): 170 (M^+). NMR (*DMSO-d*$_6$): 7.45 (s, H_7), 8.73 (br. s, NH_2).

$C_5H_3N_4ClO$ (170.56). Calcd. C 35.21 H 1.77 N 32.85.
Found. C 34.93 H 1.78 N 32.45.

b) A solution of 110 mg **7** and 100 mg of sodium hydrogen sulphide in 10 ml of water and 5 ml of ethanol was heated under reflux for 3 h. After cooling the precipitate was collected to give 60 mg (70%) of the product. The IR spectrum of it was identical with that of the compound described under a).

c) A solution of 220 mg **12** and 80 mg of hydroxylamine hydrochloride in 10 ml of methanol was stirred at room temperature for 20 h. Ethanol was evaporated in vacuo to give after recrystallization from water 110 mg (65%) of the product. The IR spectrum of it was identical with that of the compound described under a).

6-Chloro-2-hydroxyiminomethyleneaminooxazolo[5,4—c]pyridazine (**16**)

A solution of 220 mg **7** and 100 mg of hydroxylamine hydrochloride in 10 ml of ethanol was heated under reflux for 18 h. The precipitate was (after cooling)

collected by filtration to give 180 mg (86%) of the product, m. p. 265–270 °C (dec.) (from ethanol). MS (*m*/e): 213 (M^+). NMR (*DMSO-d*$_6$, 160 °C): 7.33 (s, H_7), 9.2 (s, CH).

$C_6H_4N_5ClO_2$ (213.59). Calcd. C 33.74 H 1.88 N 32.79.
Found. C 33.83 H 1.84 N 33.06.

6-Chloro-2-hydrazinomethyleneaminooxazolo[5,4—c]pyridazine (**17**)

A solution of 225 mg **7** and 0.2 ml of 80% hydrazine hydrate in 10 ml of ethanol was heated under reflux for 2 h. Ethanol was evaporated in vacuo and the solid residue recrystallized from water to give 120 mg (57%) of the product, m. p. 300 °C. MS (*m*/e): 212 (M^+). NMR (*DMSO-d*$_6$): 7.61 (s, H_7), 8.28 (s, CH).

$C_6H_5N_6ClO$ (212.61). Calcd. C 33.89 H 2.37 N 39.53.
Found. C 34.10 H 2.52 N 39.14.

3-Chloro-5-ureidopyridazin-6(1H)-one (**18**)

a) A mixture of 220 mg **7** and 5 ml of 10% hydrochloric acid was heated under reflux for 2 h. The precipitate was (after cooling) collected to give 135 mg (73%) of the product, m. p. 295 °C (from water). MS (*m*/e): 188 (M^+). NMR (*DMSO-d*$_6$): 6.73 (br. s, NH), 7.65 (s, H_5), 8.76 (br. s, NH), 12.95 (br. s, H_1).

$C_5H_5N_4ClO_2$ (188.58). Calcd. C 31.84 H 2.67 N 29.71.
Found. C 31.74 H 2.67 N 29.71.

b) A solution of 100 mg **12** and 50 mg of hydroxylamine hydrochloride in 5 ml of ethanol was heated under reflux for 2 h. After cooling the precipitate was collected to give 60 mg (70%) of the product. The IR spectrum of it was identical with that of the compound described under a).

c) A solution of 85 mg **15** and 40 mg of hydroxylamine hydrochloride in 10 ml of ethanol was heated under reflux for 2 h. The precipitate was (after cooling) collected and recrystallized from ethanol to give 40 mg (48%) of the product. The IR spectrum of it was identical with that of the compound described under a).

5-Acetylamino-3-chloropyridazin-6(1H)-one (**19**)

A solution of 300 mg **18** in 10 ml of acetic anhydride was heated under reflux for 3 h. The volatile components were evaporated in vacuo and the dry residue recrystallized from ethanol to give 230 mg (77%) of the product, m. p. 260–265 °C. (Lit.[4] m. p. 255–256 °C). MS (*m*/e): 187 (M^+). NMR (*DMSO-d*$_6$): 2.2 (s, CO*Me*), 7.92 (s, H_4), 9.19 (br. s, NH), 13.2 (br. s, H_1).

$C_6H_6N_3ClO_2$ (187.59). Calcd. C 38.41 H 3.21 N 22.40.
Found. C 38.51 H 3.22 N 22.57.

Ammonium salt of 3-Chloro-5-cyanoaminopyridazin-6(1H)-one (**20**)

A solution of 225 mg **7** in 10 ml of 28% aqueous ammonia was heated under reflux for 1 h. The precipitate was (after cooling) collected and washed with ethanol to give 120 mg (64%) of the product, m. p. 250 °C (dec.). NMR (*DMSO-d*$_6$): 6.07 (s, H_5), 8.05 (s, NH).

$C_5H_6N_5ClO$ (187.60). Calcd. C 32.01 H 3.22 N 37.33.
Found. C 30.16 H 2.36 N 30.00.

Hydrazinium salt of 3-Chloro-5-cyanoaminopyridazin-6(1H)-one (**21**)

a) A solution of 220 mg **21** and 0.15 ml of 80% hydrazine hydrate in 10 ml of ethanol was stirred at room temperature for 1 h. The precipitate was collected by filtration to give 90 mg (45%) of the product, m. p. 165 °C (dec.) (from ethanol). NMR (*DMSO-d_6*): 6.09 (s, H_5).

$C_5H_7N_6ClO$ (202.61). Calcd. C 29.65 H 3.49 N 41.50.
Found. C 29.85 H 3.49 N 41.09.

b) A solution of 440 mg **15** and 0.3 ml of 80% hydrazine hydrate in 15 ml of ethanol was heated under reflux for 2 h. After cooling the precipitate was collected to give 170 mg (52%) of the product. The IR spectrum of it was identical with that of the compound described under a).

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[11] The yields of purified products are given.