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Neighbouring Group Participation in Formation of Condensed Azines. Formation of Pyrazolo(3,4—b)pyrazines, Isoxazolo (4,5—b)pyrazines and Isothiazolo(5,4—b)pyridine[1]

(Heterocycles, CCX)

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Pyrazine- and pyridinecarboxamidoximes with an amino, potentially tautomeric hydroxy or mercapto group in *ortho* position could be transformed in the appropriate condensed azines. In this manner, representatives of pyrazolo(3,4—b)pyrazine, isoxazolo(4,5—b)pyrazine and isothiazolo(5,4—b)-pyridine ring system were synthesized and some transformations investigated.

(Keywords: Cyclization with N—N, N—O *or* N—S *bond formation; Heterocyclic compounds)*

Nachbargruppenbeteiligung bei der Bildung von kondensierten Azinen. Über die Darstellung von Derivaten von Pyrazolo(3,4—b)pyrazin, Isoxazolo(4,5—b)-pyrazin und Isothiazolo(5,4—b)pyridin. (Heterocyclen, 210. Mitt.)

Mit einer Amino-, potentiell tautomerer Hydroxy- oder Mercaptogruppe wurden *ortho*-substituierte Pyrazin- oder Pyridincarboxamidoxime in die entsprechenden kondensierten Azine umgewandelt. Auf diese Weise wurden Derivate des Pyrazolo(3,4—b)pyrazin, des Isoxazolo(4,5—b)pyrazin und Isothiazolo(5,4—b)pyridin dargestellt und einige Umwandlungen studiert.

Introduction

Several syntheses of bicyclic and polycyclic heterocycles involving neighbouring group participation have been reported from our laboratory[2–7]. This prompted us to investigate the synthesis of some

* Dedicated to Prof. Dr. *E. Ziegler* on the occasion of his 70th birthday.

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heterocyclic systems where an 1,2-azole ring is fused to an azine ring. We wish now to report the synthesis of some pyrazolo(3,4—b)pyrazines, isoxazolo(4,5—b)pyrazines and of 3-aminoisothiazolo(5,4—b)-pyridine.

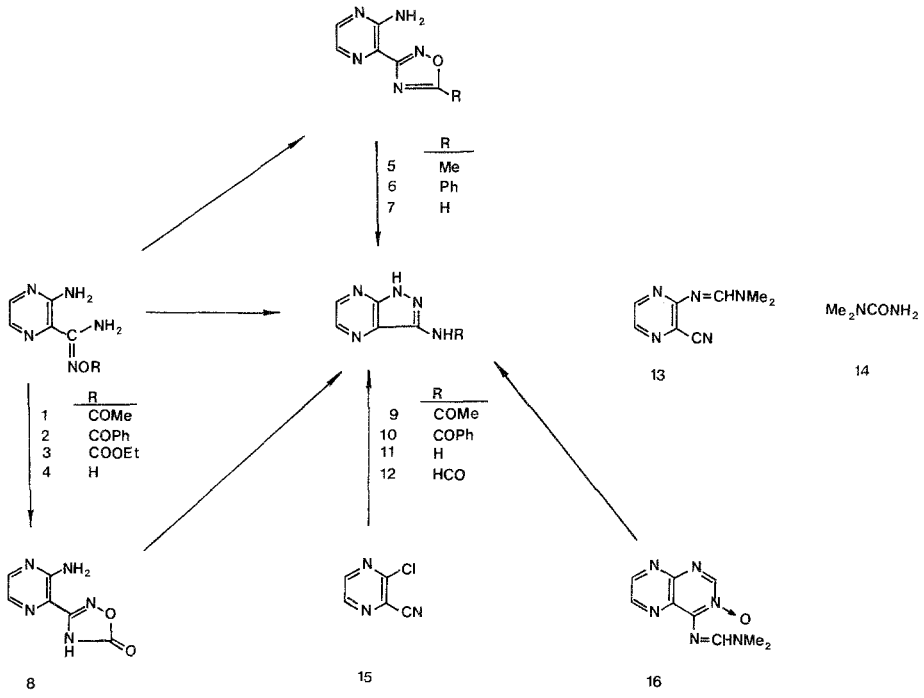
So far, only a few syntheses of pyrazolo(3,4—b)pyrazines have been reported. Only one synthetic approach from a pyrazine precursor is described without details[8], whereas all other syntheses use as starting material the corresponding 4,5-diaminopyrazoles and 1,2-dicarbonyl compounds[9–15]. There are only two papers dealing with the isoxazolo(4,5—b)pyrazine system and the synthesis has been achieved from appropriate isoxazoles[16, 17]. Also for the isothiazolo(5,4—b)pyridine system there are not many reports. In general, pyridine derivatives were used as starting material[18–23], and there are two publications describing the preparation of the 3-amino derivatives[19, 23].

Results

Syntheses and Transformations of Pyrazolo(3,4—b)pyrazines

As starting material for the preparation of pyrazolo(3,4—b)pyrazines 2-aminopyrazine-3-carboxamidoxime or its acylated derivatives (**1**-**4**) were used. The acetyl or benzoyl derivatives (**1** or **2**) underwent thermal transformation into the corresponding oxadiazolyl derivatives **5** and **6**. In a similar manner the oxadiazolinone derivative **8** was obtained from **3**. These oxadiazolyl derivatives can be transformed into the pyrazolo(3,4—b)pyrazine system in hot *N*,*N*-dimethylformamide (*DMF*) and in the presence of a base. In this manner, from **5** or **6** compounds **9** and **10** were obtained in good yield.

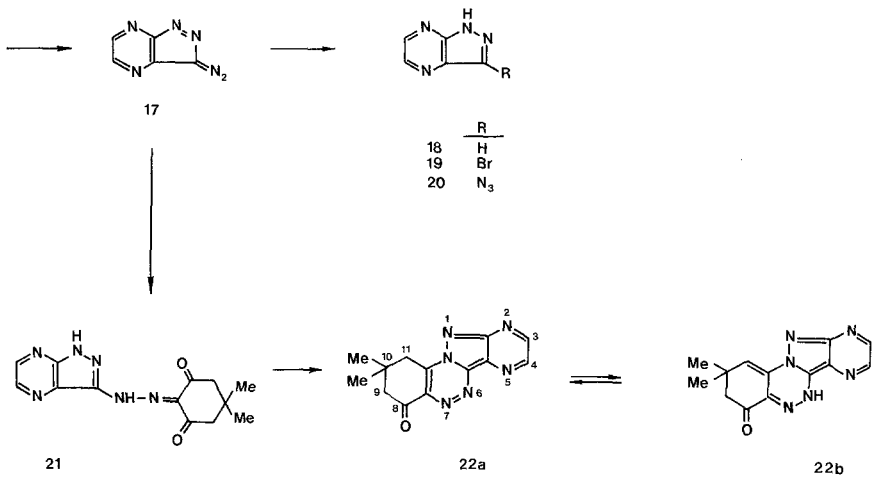
The pyrazolo(3,4—b)pyrazine system is also formed directly from 2-aminopyrazine-3-carboxamidoxime (**4**) after treatment with *DMF*-dimethylacetal, but the transformation proved to be quite complex. Besides the anticipated bicycle, in the form of the formylamino derivative (**12**), also the corresponding cyanopyrazine (**13**) and *N*,*N*-dimethylurea (**14**) were obtained in variable amount, depending upon the reaction conditions and on the amount of the reagent used. With a large excess of the reagent, both lastmentioned compounds were the sole products. 3-Aminopyrazolo(3,4—b)pyrazine can be synthesized in the most simple way from 2-chloro-3-cyanopyrazine and hydrazine hydrate in resonable yield. It can be prepared also from its acyl derivatives **9** and **12** or, in low yield, from the corresponding oxadiazolinone **8** after treatment with base. An interesting case represents the formation of the 3-formylamino derivative (**12**) from 4-*N*,*N*-dimethylaminomethyleneaminopteridine 3-oxide (**16**), either by heating or after 105 days at room temperature.



3-Aminopyrazolo(3,4—b)pyrazine is a usefuly synthon since it could be transformed into several other derivatives. It can be diazotized in the normal way and upon neutralization the neutral diazo heterocycle (**17**) was obtained. Upon irradiation of a methanolic solution of **17** the parent compound (**18**) was obtained or, after treatment with hydrobromic acid or hydroxylamine hydrochloride the corresponding 3-bromo (**19**) or the 3-azido (**20**) derivatives were formed in high yields.

An interesting case represents the formation of the tetracyclic system **22**, obtainable *via* the initially formed hydrazone **21**. The tetracyclic compound exists in solution as an equilibrium of two tautomers as established on hand of NMR spectra.

In a solution of dimethyl sulphoxide the tetracycle exhibits two sets of signals in a ratio of about 5 : 2. In the first set the following signals were observed and assigned to the following protons: there are two doublets at 9.08 and 9.17 ($J = 1.9$ Hz), corresponding to H_3 and H_4, two singlets at 2.88 and

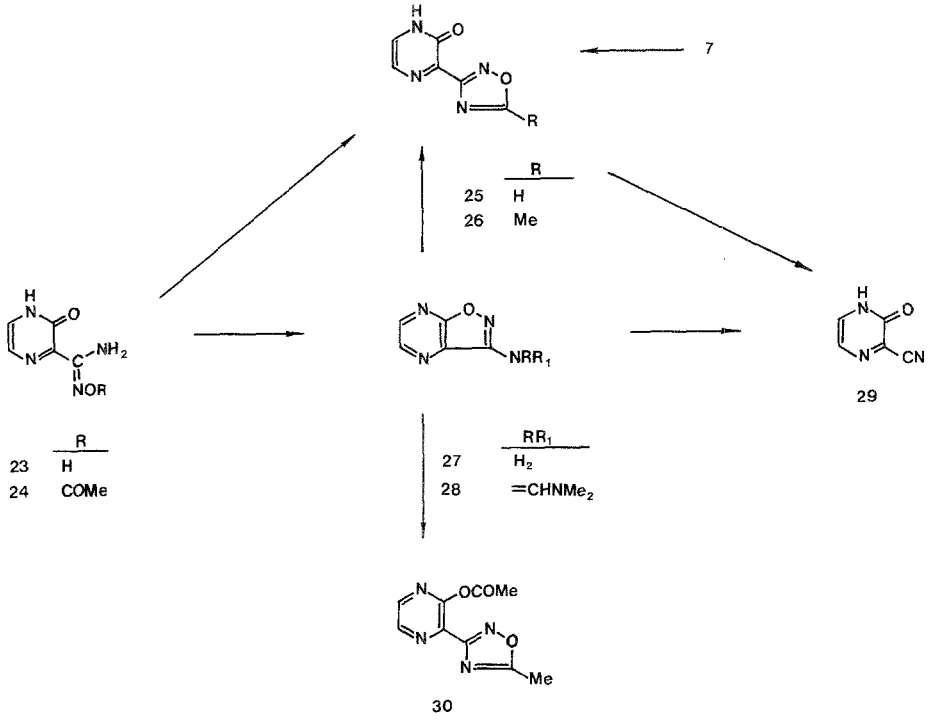


3.62, corresponding to 9-CH_2-group and 11-CH_2-group and a singlet corresponding to six protons of two methyl groups at position 10. These NMR characteristics correspond to the tautomer **22 a**. For the other tautomer **22 b** the following set of signals was observed: two doublets at 8.47 and 8.65 (J = 1.9 Hz), corresponding to H_3 and H_4, and three singlets at 5.94, 2.67 and 1.21, corresponding to H_{11}, 9-CH_2, and two methyl groups at position 10. A similar tautomeric equilibrium could be detected in trifluoroacetic acid, and here the ratio of both forms was about 16 : 1.

Syntheses of Isoxazolo(4,5—b)pyrazines

On the basis of the above experiences it was anticipated that also a hydroxy group as such or in the form of the potential tautomeric lactam group could participate in ring formation. In fact, the approach proved to be a successful variant for the synthesis of isoxazolo-(4,5—b)pyrazines. Several attempts directed towards the synthesis of this system led however to the corresponding oxadiazolyl derivative **25**. The carboxamidoxime **23** reacted either with triethyl orthoformate or diethoxymethyl acetate to give the oxadiazolyl derivative **25** in reasonable yield. This on the other hand is also obtainable from the corresponding amino derivative **7** upon diazotization. The sensitivity of the isoxazolo(4,5—b)pyrazine system towards acid was shown if the 3-amino derivative (**27**) was transformed after short treatment with hot formic acid into the oxadiazolyl compound (**25**), which is in turn degraded further upon prolonged action of acid into 3-cyano-2(1*H*)py-

razinone (**29**). The oxadiazolyl derivative and the isoxazolopyrazine **28** are both degraded also by alkalies. In a similar manner, the bicyclic compound **27** is transformed with acetic anhydride in to **30**, obtainable also from **26**.

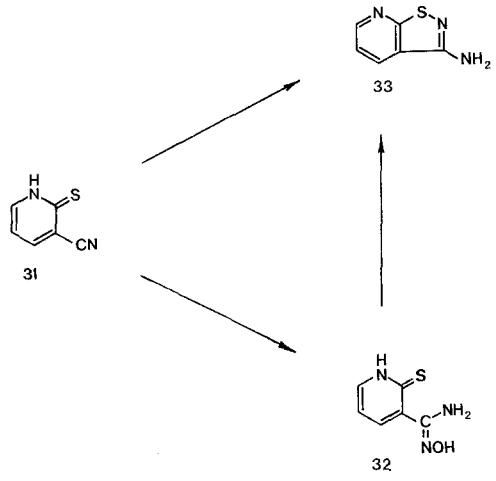


The bicyclic system was then synthesized in the form of the *N*,*N*-dimethylaminomethyleneamino derivative (**28**) either from the amidoxime **23** and *DMF*-dimethylacetal, or from its acetyl derivative **24** and the same reagent. A short treatment of this derivative (**28**) with hot alkali afforded then the 3-amino derivative (**27**).

Synthesis of 3-Aminothiazolo(5,4—b)pyridine

As a model compound—with which we intended to show the feasibility of another neighbouring group participation—we used 3-cyanopyridine-2(1*H*) thione. Here, the potential mercapto group should be involved in formation of a fused isothiazolo ring. The starting

compound (**31**) was first transformed into the corresponding carboxamidoxime (**32**) which is further cyclized in the presence of hot polyphosphoric acid or just thermally in boiling decaline into 3-aminoisothiazolo(5,4—b)pyridine (**33**).

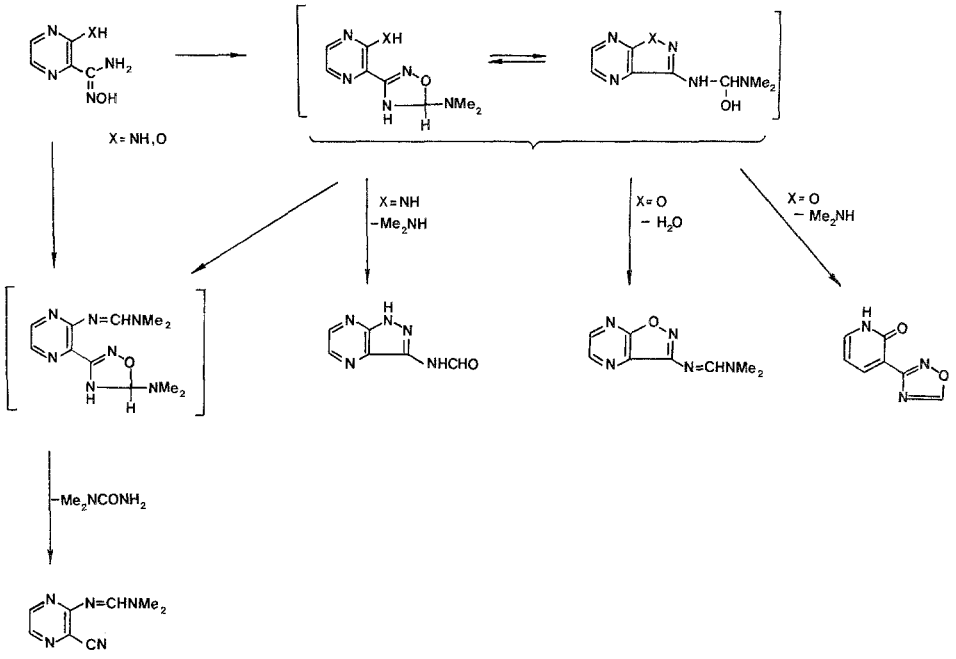


Compound **33** could be prepared in reasonable yield also directly from 3-cyanopyridine-2(1*H*)thione and free hydroxylamine upon heating.

Discussion

There are several features, common to some of the observed reactions of formation or transformations of pyrazolo(3,4—b)pyrazines and isoxazolo(4,5—b)pyrazines. Although we have no evidence for the proposed intermediates, they are most probably involved in the transformation of the corresponding carboxamidoximes either into fused pyrazolo or isoxazolo systems or into the oxadiazolyl derivatives (Scheme 1). A plausible mechanism may be also given for the transformation of the carboxamidoxime into 2-(*N*,*N*-dimethylaminomethyleneamino)-3-cyanopyrazine with simultaneous formation of *N*,*N*-dimethylurea. All the described transformations represent a new approach towards the synthesis of these bicyclic heterocyclic systems.

Scheme 1



Acknowledgment

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Experimental

General: Melting points were determined on a *Kofler* hot plate m.p. apparatus. ^{1}H NMR spectra were recorded on a JEOL JNM C-60 HL spectrometer and mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L spectrometer (*TMS* as internal standard, δ-values in ppm). If not stated otherwise, *DMSO-d_6* was used as solvent. Elemental analyses (C, H, N) were in excellent agreement with the formulas given for **3**, **5**, **6**, **9**–**12**, **17**–**22**, **24**, **25**, **27**, **28**, **30**, **32**, and **33**.

2-Amino-3(5-methyl-1,2,4-oxadiazolyl-3)pyrazine (**5**)

A mixture of 0.23 g of *O*-acetyl 2-aminopyrazine-3-carboxamidoxime[2] (**1**) and 5 ml of glacial acetic acid was heated under reflux for 1.5 h. The reaction mixture was evaporated to dryness and the residue was crystallized from ethanol to give 0.15 g (72%) of **5**, m.p. 217–219 °C. MS (*m/e*): 177 (M^+). NMR: 7.64 and 7.84 (d, H_5 and H_6), 6.70 (broad s, NH_2), 2.57 (s, *Me*), $J_{5,6} = 2.2$ Hz. $C_7H_7N_5O$.

2-Amino-3-(5-phenyl-1,2,4-oxadiazolyl-3)pyrazine (**6**)

a) 0.1 g of **2**[2] and 0.9 g of polyphosphoric acid were mixed and the mixture was kept at 70 °C for 1 h. Upon cooling, the mixture was diluted with 3 ml of water and neutralized with solid $NaHCO_3$. The product was crystallized from a mixture of *Et*OH and *N*,*N*-dimethylformamide (*DMF*) (80 mg, 86%) and had m.p. 220-223 °C. MS (*m*/e): 239 (M^+). NMR (75 °C): 7.47 and 7.64 (H_5 and H_6), 7.72 (m, $H_{2'}$ and $H_{6'}$), 7.05-7.25 (m, $H_{3'}$, $H_{4'}$ and $H_{5'}$), $J_{5,6} = 2.2$ Hz. $C_{12}H_9N_5O$.

b) A mixture of 0.1 g of **2**[2] and 2 ml of 5% aqueous NaOH was heated under reflux for 35 min, the reaction mixture was cooled and acidified with *Ac*OH to $pH = 5$. The formed precipitate, 72 mg, consisted of **6** and on hand of TLC of a minute amount of **4**.

O-Ethoxycarbonyl 2-aminopyrazine-3-carboxamidoxime (**3**)

A solution of 0.14 g of **4** in 4 ml of $CHCl_3$ was treated with 0.15 g of triethylamine and 0.14 g of ethyl chloroformate and left at room temperature for 1 h. The reaction mixture was evaporated in vacuo to dryness, the residue was suspended in 3-4 ml of water and the product (0.15 g, 92%) was crystallized from *Et*OH, m.p. 157-158 °C. MS (*m*/e): 225 (M^+). NMR: 7.29 and 7.55 (d, H_5 and H_6), 6.35 (broad s, NH_2), 6.92 (broad s, NH_2), 3.94 (q, $OC\mathbf{H}_2Me$), 1.21 (t, $OCH_2\mathit{Me}$), $J_{5,6} = 2.2$, $J_{Et} = 6.6$ Hz. $C_8H_{11}N_5O_3$.

2-Amino-3-(1,2,4-oxadiazolin-5-on-3-yl)pyrazine (**8**)

A solution of 0.2 g of **3** in 4 ml of glacial acetic acid was heated under reflux for 5 h and thereafter evaporated to dryness. The residue was crystallized from *DMF* with a very small addition of *Et*OH to give 90 mg (57%) of **8**, m.p. 311-314 °C (dec.). MS (*m*/e): 179 (M^+). NMR (70 °C): 7.42 and 7.67 (d, H_5 and H_6), 6.48 (broad s, NH_2), $J_{5,6} = 2.3$ Hz.

3-Acetylamino-1H-pyrazolo(3,4—b)pyrazine (**9**)

A mixture of 0.3 g of **5**, 0.26 g of *Et*ONa (or 0.3 g of NaOH) and 7 ml of dry *DMF* was heated under reflux for 1 h and evaporated in vacuo to dryness. The residue was suspended in 5 ml of water and after acidification with *Ac*OH to $pH = 5$-6, the product was filtered and crystallized from *Me*OH and *DMF*, m.p. 300-303 °C (dec). When NaO*Et* was used the yield was 0.18 g (60%) and with NaOH the yield was 0.204 g (68%). MS (*m*/e): 177 (M^+). NMR: 8.57 (s, H_5 and H_6), 2.10 (s, *Me*), 13.65 (broad s, NH), 10.19 (broad s, NH). $C_7H_7N_5O_2$.

3-Benzoylamino-1H-pyrazolo(3,4—b)pyrazine (**10**)

a) 0.115 g of **6**, 0.1 g NaOH and 4 ml of dry *DMF* were heated under reflux for 1 h, the solvent was evaporated in vacuo and the residue was dissolved in 4 ml of water. Upon acidification with conc. hydrochloric acid to $pH = 4$, the product was filtered and crystallized from *Et*OH to give 0.109 g (95%) of **10**, m.p. 231-234 °C. MS (*m*/e): 239 (M^+). NMR: 8.56 (s, H_5 and H_6), 10.4 (broad s, two NH), 7.90-8.10 (m, $H_{2'}$ and $H_{6'}$), 7.55 (m, $H_{3'}$, $H_{4'}$ and $H_{5'}$). $C_{12}H_9N_5O$.

b) A mixture of 85 mg of **11**, 92 mg of benzoyl chloride and 3 ml of pyridine was heated under reflux for 2 h. Upon evaporation in vacuo an oily residue was obtained and this was treated with 4 ml of *Me*OH and some charcoal. After boiling for 5 min, the mixture was filtered, the solvent was evaporated in vacuo and the oily residue was treated with 2 ml water. Upon acidification with dilute

hydrochloric acid (1 : 1) to $pH = 4$-5, the solid was filtered and crystallized from ethanol to give 15 mg (10%) of **10**. It was identical in all respects with the product obtained as described under a).

Reaction between 2-aminopyrazine-3-carboxamidoxime (**4**) *and N,N-dimethylformamide dimethyl acetal*

a) A mixture of 0.309 g of **4**, 0.322 g *N,N*-dimethylformamide dimethyl acetal (*DMFDMA*) and 10 ml of toluene was heated under reflux for 3 h. Upon cooling the precipitate was filtered and washed with 5 ml of *Me*OH to give 120 mg (36%) of **12**, identical with an authentic specimen. The filtrate was evaporated in vacuo and the residual oil was mixed with 5 ml water. The precipitated product was filtered and there were obtained 45 mg (15%) of the starting material. The filtrate was again evaporated in vacuo and the oily residue was treated with 2 ml of water and the mixture was left to stand at 0 °C. The separated product was identified (42 mg, 14%) as **13**, identical with an authentic specimen[2]. The filtrate was again evaporated in vacuo and the oily residue was sublimed at 170 °C/1.3 kPa. The sublimate was dissolved in a small amount of $CHCl_3$ and by addition of petroleum ether 15 mg (8%) of *N,N*-dimethylurea (**14**) was obtained, identical with an authentic specimen synthesized according to the published procedure[24].

b) In a similar experiment, starting from 0.2 g of **4**, 0.4 g of *DMFDMA* and 8 ml of toluene, after 6 h under reflux, there were obtained: 74 mg (35%) of **12**, 63 mg (28%) of **13** and 12 mg (10%) of **14**.

c) When starting with 0.15 g of **4**, 0.7 g of *DMFDMA* and 5 ml of toluene and heating the reaction mixture under reflux for 3 h, there were obtained: 80 mg (50%) of **13** and 7 mg (8%) of **14**.

d) A mixture of 0.3 g of **4** and 0.6 g of *DMFDMA* was heated at 75 °C for 5 min and then excess of the reagent was evaporated in vacuo. The oily residue was treated with 1 ml of $CHCl_3$ and petroleum ether until cloudiness appeared. Upon cooling to −10 °C, the separated product was filtered and sublimed at 170 °C/1.3 kPa to give 20 mg (12%) of **14**. The filtrate was evaporated in vacuo and the oily residue was treated with 2 ml of water. Upon cooling to 0 °C the precipitate was collected to give 226 mg (66%) of **13**.

3-Amino-1H-pyrazolo(3,4—b)pyrazine (**11**)

a) A mixture of 0.165 g of **9** and 2.5 ml of 10% aqueous NaOH was heated under reflux for 1 h. After addition of charcoal and 1 ml of water, the reaction mixture was heated to boil for 5 min, filtered hot and acidified with dilute hydrochloric acid (1 : 1) to $pH = 5$. The separated product (25 mg, 20%) was collected and the filtrate was evaporated to dryness. The residue was extracted two times with 4 ml of absolute *Et*OH to give after evaporation of the solvent additional 45 mg (36%) of the amino compound (**11**) which was crystallized from ethanol, m.p. 244-246 °C. MS (*m/e*): 135 (M^+). NMR: 7.92 and 8.00 (d, H_5 and H_6), 5.39 (broad s, NH_2), 11.7 (broad s, NH), $J_{5,6} = 2.1$ Hz. $C_5H_5N_5$.

b) 0.12 g of **12** and 3 ml of hydrochloric acid (1 : 1) were stirred at room temperature for 2 h. The reaction mixture was neutralized with solid $NaHCO_3$ and the product (60 mg, 60%, of **11**) was filtered.

c) A mixture of 0.45 g of **15**, 0.45 g of 98% hydrazine hydrate and 6 ml of *Et*OH was heated under reflux for 1.5 h. The reaction mixture was evaporated in vacuo to dryness and the residue was crystallized from *Et*OH to give 0.23 g (53%) of **11**, identical with the product, obtained as described under a).

d) A mixture of 0.3 g of **8**, 0.3 g of NaO*Et* (or 0.23 g of NaO*Me*) and 10 ml of dry of *DMF* was heated under reflux for 3 h and then evaporated in vacuo to dryness. The residue was treated with 8 ml of water, charcoaled, filtered hot and the filtrate was acidified with hydrochloric acid (1 : 1) to $pH = 5$-6. The separated product (0.15 g, 50%), was the starting material. The filtrate was evaporated in vacuo to dryness and the residue was extracted two times with 3 ml of absolute ethanol to give upon evaporation of the solvent 15 mg (7%) (when using NaO*Et*) or 25 mg (11%) (when using NaO*Me*) of the amino compound **11**, identical with the product, obtained as described under a).

3-Formylamino-1H-pyrazolo(3,4—b)pyrazine (**12**)

a) 13 mg of 3-amino compound **11** were dissolved in 1 ml of formic acid and the mixture was heated under reflux for 1 h and thereafter evaporated to dryness. The residue was treated with 0.5 ml of *Me*OH and upon filtration there were obtained 10 mg (64%) of **12**, m.p. 247-250 °C. The compound was crystallized from water. MS (*m*/e): 163 (M^+). NMR (CF_3COOH): 8.56 and 8.98 (d, H_5 and H_6), 8.27 (s, CHO), $J_{5,6} = 2.6$ Hz. $C_6H_5N_5O$.

b) A solution of 0.18 g of **16**[25] in 5 ml of $CHCl_3$ was heated under reflux for 28 h (or left at room temperature for 105 days). The separated product was filtered and crystallized from water to give 79 mg (59%) (or 94 mg, 70%, from the experiment at room temperature) of the formylamino derivative, identical in all respects with the product obtained as described under a).

3-Diazopyrazolo(3,4—b)pyrazine (**17**)

To a solution of 0.15 g of **11** in 3 ml of water and 1.5 ml of conc. hydrochloric acid, cooled to 0 °C, was added dropwise during 1 min a solution of 0.105 g of $NaNO_2$ in 1 ml of water. The reaction mixture was left to stand at room temperature for 20 min and thereafter neutralized with solid $NaHCO_3$. The separated product was filtered and the filtrate was extracted three times with 4 ml of $CHCl_3$ to give some more of the product. The combined products were crystallized from a mixture of $CHCl_3$ and petroleum ether to give 0.70 g (43%) of the diazo compound, m.p. about 180 °C (dec). MS (*m*/e): 146 (M^+). NMR ($CDCl_3$): 8.31 and 8.41 (d, H_5 and H_6), $J_{5,6} = 2.1$ Hz. $C_5H_2N_6$.

1H-Pyrazolo(3,4—b)pyrazine (**18**)

A solution of 80 mg of the diazo compound **17** in 15 ml of *Me*OH was irradiated 9 h in a *Rayonet* photoreactor ($\lambda = 254$ nm). The solvent was evaporated to dryness and the residue was sublimed at 150 °C/1.3 kPa to give 35 mg (53%) of **18**, m.p. 183-186 °C (Ref.[10], gives m.p. 198-200 °C, Ref.[14] gives m.p. 196-198 °C). MS (*m*/e): 120 (M^+). $C_5H_4N_4$.

3-Bromo-1H-pyrazolo(3,4—b)pyrazine (**19**)

A mixture of 0.101 g of **17** and 2 ml of 48% hydrobromic acid was heated under reflux for 30 min. The resulting solution was cooled, neutralized with solid $NaHCO_3$ and the separated product was collected and crystalized from *Et*OH to give 0.115 g (84%) of the bromo compound **19**, m.p. 278-281 °C. MS (*m*/e): 198 and 200 (M^+). NMR: 8.63 (s, H_5 and H_6), 14.0 (broad s, NH). $C_5H_3BrN_4$.

3-Azido-1H-pyrazolo(3,4—b)pyrazine (**20**)

0.1 g of the amino compound **11** was diazotized as described for **17**. However, the solution was not neutralized, but treated with 90 mg of hydroxylamine hydrochloride. The reaction mixture was left to stand at 0 °C for 0.5 h and then 1.5 h at room temperature. Upon neutralization with solid $NaHCO_3$ the precipitate was filtered and crystallized from *Et*OH to give 0.108 g (95%) of the azido compound **20**, m.p. 163–165 °C (dec). MS (*m/e*): 161 (M^+). NMR: 8.46 and 8.53 (d, H_5 and H_6), 13.50 (broad s, NH), $J_{5,6}$ = 2.1 Hz. $C_5H_3N_7$.

10,10-Dimethyl-8,9,10,11-tetrahydropyrazino(2',3':4,5)-pyrazolo(3,2—c)benzo[e]-1,2,4-triazine (**22**)

a) A mixture of 0.115 g of **17**, 0.13 g of 5,5-dimethyl-cyclohexan-1,3-dione (dimedone) and 4 ml of *Et*OH was stirred at room temperature for 8 h, chilled to 0 °C and the formed hydrazone (**21**) was filtered. The compound was crystallized from *Et*OH to give 0.165 mg (73%) of the pure compound, m.p. 190–193 °C (conversion into the tetracyclic product **22**). MS (*m/e*): 286 (M^+). NMR: 8.61 (s, H_5 and H_6), 14.0 (broad s, NH), 2.63 (s, two CH_2), 1.07 (s, two *Me*). $C_{13}H_{14}N_6O_2$.

b) A solution of 95 mg of the above hydrazone (**21**) in 5 ml of *DMF* was heated under reflux for 25 min and the mixture was evaporated in vacuo to dryness. The residue was crystallized from *Et*OH to give 62 mg (70%) of the tetracycle **22**, m.p. 213–216 °C. MS (*m/e*): 268 (M^-). NMR (tautomer **22a**): 9.08 and 9.17 (d, H_3 and H_4), 3.62 (s, 11-CH_2), 2.88 (s, 9-CH_2), 1.24 (s, two *Me*), $J_{3,4}$ = 1.9 Hz. Tautomer **22b**: 8.47 and 8.65 (d, H_3 and H_4), 5.94 (s, H_{11}), 2.67 (s, 9-CH_2), 1.21 (s, two *Me*), $J_{3,4}$ = 1.9 Hz. $C_{13}H_{12}N_6O$.

2-Oxo-1,2-dihydropyrazin-3-carboxamide O-acetyloxime (**24**)

To 0.4 g of **23** 2.5 ml of acetic anhydride were added and the reaction mixture was left to stand at room temperature for 4 h. The solvent was evaporated in vacuo and the residue crystallized from *Et*OH to give 0.355 g (70%) of **24**, m.p. 132–135 °C (with cyclization into compound **26**). MS (*m/e*): 196 (M^-). NMR: 7.87 and 8.01 (d, H_5 and H_6), 2.17 (s, *Me*), 12.5 (broad s, NH), 7.2 (broad s, NH_2), $J_{5,6}$ = 3.2 Hz. $C_7H_8N_4O_3$.

3-(1,2,4-Oxadiazolyl-3)-2(1H)-pyrazinone (**25**)

a) A mixture of 0.15 g of **23** and 2 ml of triethyl orthoformate was heated under reflux for 8 h. Upon evaporation in vacuo the residue was suspended in 3 ml of *Me*OH and the unsoluble part filtered to give 88 mg (55%) of the product (**25**), which was crystallized from a mixture of *Et*OH and *DMF*, m.p. 194–196 °C. MS (*m/e*): 164 (M^+). NMR (CF_3COOH): 7.78 and 7.98 (d, H_5 and H_6), 9.12 (s, $H_{5'}$), $J_{5,6}$ = 3.9 Hz. $C_6H_4N_4O_2$.

b) A mixture of 0.154 g of **23**, 0.4 g of diethoxymethyl acetate and 5 ml of toluene was heated under reflux for 3 h. The solid residue which was obtained after evaporation of the solvent in vacuo was suspended in 3 ml of *Me*OH and filtered to give 0.12 g (73%) of **25**, m.p. 194–196 °C, identical with the compound, prepared as described under a).

c) To a solution of 22 mg of **7** in 1 ml of water few drops of conc. sulphuric acid were added. The solution was cooled to 5 °C and thereafter treated with an aqueous solution containing 22 mg of $NaNO_2$. After 1 h at room temperature the separated product was filtered to give 17 mg (77%) of **25**, identical with the product as described under a).

d) The oxadiazolyl-pyrazinone (**25**) was obtained in 50% yield if **27** was heated in the presence of formic acid for 5 min, together with a small amount of 3-cyano-2(1*H*)pyrazinone. If the amino compound **27** was heated in the presence of formic acid for 3 h, only 3-cyano-2(1*H*)pyrazinone (**29**) was obtained in 47% yield. The latter compound is also obtainable in 54% yield from **25** with formic acid or with 5% NaOH (41% yield).

3-(N,N-Dimethylaminomethyleneamino)-isoxazolo(4,5—b)pyrazine (**28**)

a) A mixture of 0.154 g of **23**, 0.36 g of *DMFDMA* and 5 ml of $CHCl_3$ was heated under reflux for 1.5 h. The clear solution was evaporated in vacuo to dryness, the residue was treated with 3 ml of water and the separated product was filtered to give 0.13 g (68%) of **28**, which was crystallized from *Me*OH, m.p. 130–132 °C. MS (*m/e*): 191 (M^+). NMR: 8.59 and 8.73 (d, H_5 and H_6), 8.76 (s, CH), 3.16 (s, *Me*), 3.07 (s, *Me*), $J_{5,6} = 2.5$ Hz. NMR ($CDCl_3$): 8.44 and 8.58 (d, H_5 and H_6), 8.75 (s, CH), 3.16 (s, NMe_2), $J_{5,6} = 2.5$ Hz. $C_8H_9N_5O$.

b) A mixture of 50 mg of **27**, 87 mg of *DMFDMA* and 3 ml of $CHCl_3$ was heated under reflux for 30 min. Upon evaporation to dryness the residue was recrystallized from *Et*OH to give 10 mg (14%) of **28**, identical with the compound as prepared under a).

c) 0.3 g of **23** and 0.4 g of *DMFDMA* was heated at 75 °C for 5 min. Excess of the reagent was evaporated to obtain a semisolid residue which was suspended in 3–4 ml of $CHCl_3$ and the separated product filtered. The product (40 mg, 13%) was identified as **25**. The filtrate was again evaporated and the oily residue was treated with 1 ml of water. After standing several h at 0 °C, there were separated 78 mg (21%) of **28**.

d) 0.155 g of **24**, 0.158 g of *DMFDMA* and 4 ml of $CHCl_3$ were heated under reflux for 5 h. Upon cooling, the separated solid was filtered (36 mg, 28%) and identified as **25**. From the filtrate upon evaporation of the solvent an oily product was obtained which was treated with 1 ml of water and after standing at 0 °C for some h, the separated product (9 mg, 6%) was identified as **28**.

3-Aminoisoxazolo(4,5—b)pyrazine (**27**)

After a mixture of 0.4 g of **28** and 3 ml of aq. NAOH was boiled for 1 min and cooled to 0 °C, 0.11 (39%) of **27** was separated and from the filtrate upon acidifilation to *pH* 2-3, evaporation to dryness and extraction with absolute *Et*OH 12 mg (5%) of **29** were obtained. 3-Aminoisoxazolo(4,5—b)pyrazine (**27**) had m.p. 207–208 °C (dec). MS (*m/e*): 136 (M^+). NMR: 8.58 and 8.68 (d, H_5 and H_6), 6.80 (broad s, NH_2), $J_{5,6} = 2.5$ Hz. $C_5H_4N_4O$.

2-Acetoxy-3-(5-methyl-1,2,4-oxadiazolyl-3)pyrazine (**30**)

a) 83 mg of **27**, 1 ml of acetic anhydride and 1 ml of glacial acetic acid were heated under reflux for 1 h. The reaction mixture was evaporated to dryness, 2 ml of acetic anhydride were added and the mixture was heated again under reflux for 1 h. The solid residue, obtained after evaporation the mixture in vacuo, was heated in the presence of 7 ml of ethyl acetate and charcoal under reflux for 5 min, filtered hot and there were obtained 0.105 g (78%) of **30** which was crystallized from *Me*OH, m.p. 103–105 °C (dec). MS (*m/e*): 220 (M^+). NMR: 8.77 and 8.91 (d, H_5 and H_6), 2.71 (s, *Me*), 2.38 (s, CO*Me*), $J_{5,6} = 2.4$ Hz. $C_9H_8N_4O_3$.

b) A mixture of 0.1 g of **26** and 3 ml of acetic anhydride was heated under reflux for 3 h. The solid residue, which was obtained after evaporation of the mixture in vacuo, was boiled for 5 min in the presence of ethyl acetate and some charcoal, filtered hot and there were obtained 0.11 g (89%) of **30**, identical in all respects with the compound obtained as described under a).

2(1H)Thioxopyridine-3-carboxamidoxime (**32**)

A salt free solution of hydroxylamine, prepared from 30 ml of *Et*OH, 0.7 g of sodium and 2.1 g of hydroxylamine hydrochloride, and 1.0 g of 3-cyanopyridine-2(1*H*)thione (**31**) was left in a closed flask at room temperature for 8 days. The separated product was filtered (0.73 g, 58%) and crystallized from *Et*OH, m.p. 175–178 °C (dec. with cyclization into **33**). MS (*m/e*): 169 (M^+). NMR: 7.82 and 7.83 (dd, H_4 and H_6), 6.88 (deg. dd, H_5), 6.28 (broad s, NH_2), $J_{4,5} = J_{5,6} = 6.3$, $J_{4,6} = 1.6$ Hz. $C_6H_7N_3OS$.

3-Aminoisothiazolo(5,4—b)pyridine (**33**)

a) A mixture of 25 mg of **32** and 1 g of polyphosphoric acid was heated 2 h at 150 °C. Upon cooling, the reaction mixture was diluted with water, neutralized with solid $NaHCO_3$ and the separated product was filtered to give 15 mg (67%) of **33**, m.p. 244–247 °C. MS (*m/e*): 151 (M^+). NMR: 8.23 (dd, H_6), 8.03 (dd, H_4), 7.01 (dd, H_5), 6.60 (broad s, NH_2), $J_{4,5} = 7.8$, $J_{5,6} = 4.3$, $J_{4,6} = 1.5$ Hz. $C_6H_5N_3S$.

b) 20 mg of **32** were heated in 3 ml of decaline until complete dissolution and until no gas evolution was observed. Upon cooling the separated product was filtered and there were obtained 3 mg (16%) of **33**, identical with the product obtained as described under a).

c) A mixture of 1 g of 3-cyanopyridine-2(1*H*)thione (**31**), 1 g of hydroxylamine hydrochloride, 0.65 g NaOH and 20 ml of water was heated under reflux. After 1 h, additional 0.5 g of hydroxylamine hydrochloride were added to the reaction mixture and the total time of reflux amounted 1.5 h. The product, which separated upon cooling, was filtered and crystallized from water to give 0.517 g (41%) of **33**. On hand of TLC examination, some starting compound was still present in the filtrate.

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