139. Permanganate Oxidation of Quinoxaline and Its Derivatives

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The oxidation reactions of a series of quinoxaline derivatives, using $KMnO_4$ in the presence or absence of NaOH, are described. Neutral oxidation of 2-chloro- and 2,3-dichloroquinoxalines **2–4** afforded the corresponding chloro- and dichloropyrazinedicarboxylic acids **13** and **14** in good yield. On the other hand, oxidation of quinoxalin-2(1*H*)-one and 1,4-dihydroquinoxaline-2,3-dione derivatives in alkaline medium gave different products, with the quinoxalin-2(1*H*)-one (**5**) forming 1,4-dihydroquinoxaline-2,3-dione (**9**), while various substituted quinoxalin-2,3-dione derivatives (see **9–11**) gave a new type of dimeric products. The structural assignments for the new compounds were based on spectroscopic data.

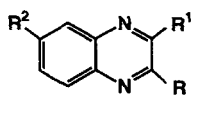
1. Introduction. – Condensed benzo-fused π-deficient N-heterocycles are regarded as versatile starting materials for the preparation of functionalized monocyclic ring-systems by oxidative degradation reactions. Quinoline and isoquinoline yield on vigorous oxidation with $KMnO_4$ pyridine-2,3- and pyridine-3,4-dicarboxylic acid, respectively [1]. Analogously, phthalazine reacts to pyridazine-4,5-dicarboxylic acid [2], and phenazine can either be oxidized to quinoxaline-2,3-dicarboxylic acid [3] or, on degradation of both benzene rings, to pyrazine-2,3,5,6-tetracarboxylic acid [4]. Oxidation of a fused benzene ring is facilitated in the presence of electron-donating groups, whereas electron-withdrawing functions retard this type of reactions. However, relatively few systematic investigations on oxidative degradations on N-heterocycles have been performed due to unpredictable reaction pathways.

Our main interest in this field was focussed on permanganate oxidations of quinoxaline derivatives to achieve various types of pyrazine compounds as synthons for the built-up of more complex condensed pyrazine ring systems.

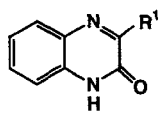
Quinoxaline (**1**) itself was oxidatively degraded to pyrazine-2,3-dicarboxylic acid (**12**) using permanganate in alkaline medium [2] [5–7]. *Mager* and *Berends* [8] reported on the $KMnO_4$ oxidation of 2,3-dichloroquinoxaline (**3**) which did, however, not lead to 5,6-dichloropyrazine-2,3-dicarboxylic acid (**14**) but to the corresponding 5,6-dioxotetrahydro derivative **16**, presumably formed through hydrolysis of the former compound during isolation. Similarly, *Elina* and *Musatova* [9] also could not isolate **14** and converted the primary oxidation product by treatment with MeOH/HCl into dimethyl 5,6-dichloropyrazine-2,3-dicarboxylate which on further treatment with NH_3/EtOH was claimed to give 5,6-diaminopyrazine-2,3-dicarboxamide in 88% yield. Furthermore, no defined product was obtained on oxidation of 1,2,3,4-tetrahydroquinoxaline-2,3-dione [8] **9**, stating the principal difficulties concerned with chemical oxidations, in general. A high stability of the quinoxaline ring was also observed on oxidation experiments with 2,3-dialkoxy- and 2,3-diaryloxy-quinoxalines [10]. Reactions in a sealed tube at elevated

temperatures with permanganate caused a more extensive breakdown of the heterocycle to unidentified products.

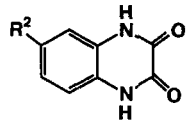
Results and Discussion. – The oxidation reactions of various quinoxaline derivatives **1–11** were carried out with 5 equiv. of $KMnO_4$ in H_2O or in presence of 1 mol-equiv. of NaOH at elevated temperatures. The chloroquinoxalines **2–4** were best oxidized at 90–100°, since higher temperatures caused hydrolysis as noticed by the conversion of **3** into 1,2,3,4-tetrahydroquinoxaline-2,3-dione (**9**) at 120°. Neutral oxidation of 2-chloro- (**2**), 2,3-dichloro-(**3**), and 2,3-dichloro-6-methylquinoxaline (**4**) worked well and gave 5-chloro-(**13**) and 5,6-dichloropyrazine-2,3-dicarboxylic acid (**14**) in good yields (see also **1**→**12**). Reaction of **14** with ammonia at 130–160° led to the displacement on only one Cl-atom forming 5-amino-6-chloropyrazine-2,3-dicarboxylic acid (**15**).



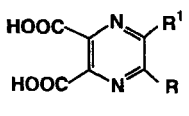
	R	R^1	R^2
1	H	H	H
2	Cl	H	H
3	Cl	Cl	H
4	Cl	Cl	CH_3



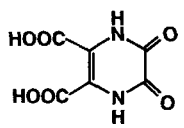
	R^1
5	H
6	COOEt
7	COOH
8	CH_3



	R^2
9	H
10	Cl
11	CH_3



	R	R
12	H	H
13	Cl	H
14	Cl	Cl
15	Cl	NH_2



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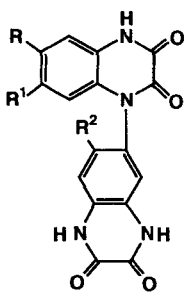
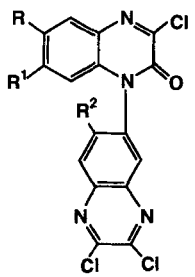
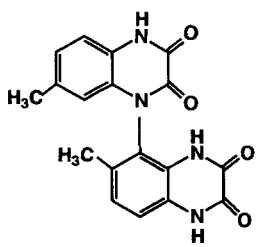


	R	R^1	R^2
17	H	H	H
18	Cl	H	Cl
19	CH_3	H	CH_3
20	H	CH_3	CH_3



	R	R^1	R^2
21	H	H	H
22	Cl	H	Cl
23	CH_3	H	CH_3
24	H	CH_3	CH_3



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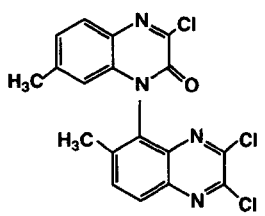

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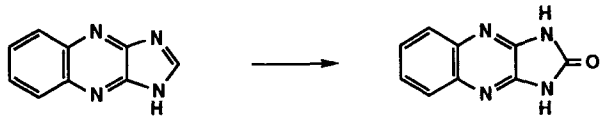
It was also found that analogous oxidation experiments with quinoxalin-2-(1*H*)-ones, which required NaOH for solubility reasons and somewhat higher temperatures (120–130°) gave entirely different results since no breakdown of the benzene ring took place. Thus, 3-methylquinoxalin-2-(1*H*)-one (**8**) was stable under these conditions, quinoxalin-2-(1*H*)-one (**5**) was oxidized to 1,2,3,4-tetrahydroquinoxaline-2,3-dione (**9**), and ethyl 1,2-dihydro-2-oxoquinoxaline-3-carboxylate (**6**) was only hydrolyzed to the corresponding carboxylic acid **7**.

A most interesting result was obtained on $KMnO_4$ oxidation of 1,2,3,4-tetrahydroquinoxaline-2,3-dione (**9**) and its 6-chloro-(**10**) and 6-methyl-(**11**) derivative in alkaline medium, leading to products of very similar polarity to the starting materials according to TLC analysis. The oxidation products were not soluble in $NaHCO_3$, indicating the absence of carboxyl groups (*e.g.* **16**) which was also confirmed by IR and ^{13}C-NMR studies. Furthermore, the UV spectra of these new compounds exhibited a very similar shape to those of the educts. Their structures were derived from the ^{1}H-NMR spectra. Thus, **9** and **10** yielded **17** and **18** in 62 and 20% yield, respectively, whereas **11** gave a complex mixture of **19**, **20**, and **25** which could not be separated. Compound **17** was also converted into its trichloro derivative **21** by treatment with thionyl chloride in presence of little DMF. This substance was better soluble in most organic solvents and could be recrystallized from hexane.

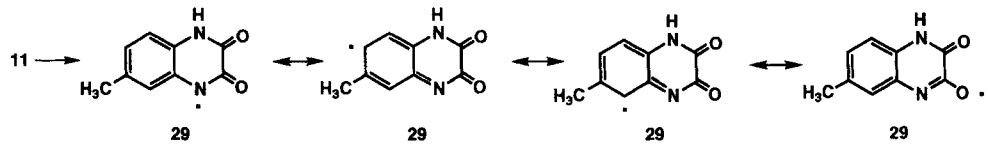
The ^{1}H-NMR spectrum of **17** exhibited 3 exchangeable *s*'s at 12.21, 12.19, and 12.15 ppm, counting for 3 NH groups and 7 aromatic protons indicating the presence of at least two benzene rings, as expected for a quinoxaline dimer. A FAB-MS confirmed this composition by revealing a molecular M^+ at mass of 322. The ^{1}H-NMR spectrum of **21** showed two sets of aromatic protons at 7.9 (*m*, 1 H), 7.4 (*m*, 2 H), and 6.7 (*m*, 1 H) and at 8.3 (*d*, 1 H), 8.1 (*s*, 1 H), and 7.7 ppm (*d*, 1 H), respectively, as established by decoupling experiments, indicating the connection of one quinoxaline ring *via* one N-atom to the aromatic benzene moiety of the second quinoxaline ring. The IR spectrum confirmed the presence of an amide function by a strong carbonyl absorption at 1690 cm^{-1}, and the MS revealed a molecular ion at *m/z* 376, 378, and 380 accounting for the correct isotope ratio of 3 Cl-atoms, a fragment $[M-28]^+$ (loss of CO), and successive cleavage of the Cl-atoms from the latter. Finally, the ^{13}C-NMR spectrum of **21** showed 16 C-atoms, the one at 151 ppm being assigned to C=O. The combination of all these data established umambiguously structures **17** and **21** as the only possible dimeric constitutions.

Thionyl chloride treatment of **18** gave **22** and the mixture **19**/**20**/**25** was converted into **23**/**24**/**26** which could be separated chromatographically into **23**/**24** and **26**. The lasting presence of a mixture, *i.e.* **23**/**24**, was indicated by the EI- and FAB-MS (M^+ at *m/z* 404) and the ^{13}C-NMR spectrum revealing 27 C-atoms which were, however, not due to a trimeric structure but to two closely releated compounds having one half of the molecule identical. The ^{1}H-NMR spectrum of **23**/**24** did not account for these small structural differences, and TLC analyses in various systems did not separate the mixture.

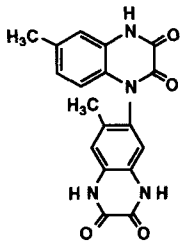
As an example of a higher condensed system, 1*H*-imidazo[4,5-*b*]quinoxaline (**27**) was also treated with $KMnO_4$ under similar conditions. The major isolable product turned out to be 1,3-dihydro-2*H*-imidazo[4,5-b]quinoxalin-2-one (**28**) the structure of which was established by comparison with authentic material prepared from 2,3-diaminoquinoxaline and urea [11].



27 **28**



29 **29** **29** **29**



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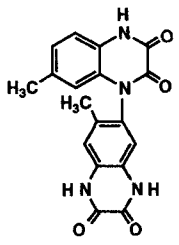

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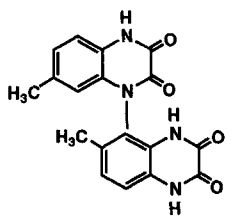

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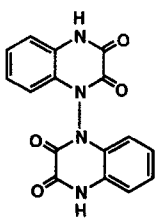

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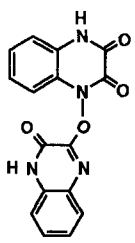

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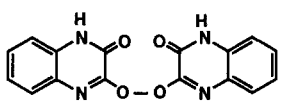

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The oxidative dimerization occurs most likely as a result of initial free-radical formation through H-abstraction by the MnO_4^- ion from one of the ring N-atoms. This neutral mesomeric radical, *e.g.* **29** (from **11**), is stabilized by resonance favoring position 6 and 8 in the benzene moiety for recombination with the N radical site leading to the three isomers **19**, **20**, and **25**. This explanation is in good agreement with the observed experimental facts pointing towards a thermodynamically more stable new C–N bond, whereas the formation of 1,1′,2,2′,3,3′,4,4′-octahydro-1,1′-biquinoxaline-2,3,2′,3′-tetrone (**30**; N–N bond), 1,4-dihydro-1-(1,2-dihydro-2-oxoquinoxalin-3-yloxy)quinoxalin-2,3-dione (**31**, N–O bond), and 3,3′-dioxybis(quinoxalin-2(1*H*)-one) (**32**, O–O bond), respectively, is less likely.

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Experimental Part

General. TLC: precoated cellulose thin-layer sheets *F1440 LS254* and silica gel thin-layer sheets *F1500 LS254* from *Schleicher & Schüll*. M.p.: *Büchi* apparatus, model Dr. *Tottoli*; no corrections. UV: *Lambda-5-Perkin-Elmer* spectrometer; λ_{max} in nm (log ε), sh = shoulder. IR: in cm^{-1}. ^1H- and ^{13}C-NMR: *Bruker-AC-250* and *Jeol-JNM-*

GX 400-MHz spectrometer: δ in ppm rel. to $SiMe_4$ and H_3PO_4. EI-MS: *Finnigan MAT 312*; in *m/z* (rel. %). FAB-MS: *Finnigan MAT 312-AMD-5000*.

Oxidation: General Procedure. The appropriate quinoxaline derivative (1 mol-equiv.) and $KMnO_4$ (5 mol-equiv.) in H_2O were heated in presence or absence of NaOH (1 equiv.) for 3 h with stirring. The $KMnO_4$ was added gradually within 2 h.

1. *1,2,3,4-Tetrahydroquinoxaline-2,3-diones* **9**–**11**. The diones **9**–**11** were prepared following the method of *Phillips* [12] from the appropriate benzene-1,2-diamines and oxalic acid dihydrate: A soln. of oxalic acid dihydrate (30.0 g, 238 mmol) in H_2O (100 ml) was heated to 100°, and conc. HCl soln. (45 ml) was added followed by benzene-1,2-diamine (22.0 g, 204 mmol) with continuous stirring. The temp. was maintained at *ca.* 100° for 20 min (→some crystalline precipitate). The mixture was cooled by addition of ice and the colorless precipitate filtered off, washed with H_2O, and dried at 90°: *1,2,3,4-tetrahydroquinoxaline-2,3-dione* (**9**; 30.7 g, 93%). M.p. > 340° ([13]: m.p. > 360°). UV (MeOH): 212 (4.51), 229 (3.91), 235 (sh, 3.86), 259 (3.61), 297 (sh, 3.92), 309 (4.02), 340 (sh, 3.57). IR (KBr): 3442*w* (NH), 3040, 2967, 2882; 1682 (C=O). ^{1}H-NMR (250 MHz, (D_6)DMSO): 11.99 (br. *s*, 2NH); 7.16 (*m*, H–C(5), H–C(8)); 7.10 (*m*, H–C(6), H–C(7)). MS: 162 (17, M^+), 134 (46, $[M - CO]^+$), 106 (100, $[M - 2CO]^+$).

Similarly, *6-chloro-1,2,3,4-tetrahydroquinoxaline-2,3-dione* (**10**) was obtained in 95% yield. M.p. > 320° (dec.). UV (MeOH): 215 (4.65), 232 (3.95), 239 (sh, 3.94), 261 (sh, 3.69), 312 (4.05), 323 (sh, 3.99), 340 (sh, 3.63). IR (KBr): 3141, 3046, 1494 (C=O), 1389. ^{1}H-NMR ((D_6)DMSO): 11.93 (br. *s*, 2NH); 7.08 (*s*, H–C(5), H–C(7), H–C(8)). MS: 196 (90, M^+), 168 (69, $[M - CO]^+$), 140 (18, $[M - 2CO]^+$), 113 (20, $[M - 2CO - HCN]^+$), 105 (100, $[M - 2CO - Cl]^+$).

As above, *1,2,3,4-tetrahydro-6-methylquinoxaline-2,3-dione* (**11**) was obtained in 87% yield. M.p. > 300° (dec.). IR (KBr): 3180, 2980, 1690 (C=O). UV (MeOH): 212 (4.62), 231 (sh, 3.95), 238 (sh, 3.91), 304 (sh, 3.94), 314 (4.04), 327 (4.01), 346 (sh, 3.69). ^{1}H-NMR ((D_6)DMSO): 11.91, 11.88 (2*s*, 2NH); 7.03 (*d*, H–C(7)); 6.93 (*s*, H–C(5)); 6.89 (*d*, H–C(8)); 2.28 (*s*, Me). MS: 176 (100, M^+), 148 (72, $[M - CO]^+$), 120 (50, $[M - 2CO]^+$), 105 (48, $[M - 2CO - Me]^+$).

2. *2,3-Dichloroquinoxaline* [8] (**3**). A mixture of **9** (16.2 g, 0.1 mol), DMF (1.0 ml), and excess of $SOCl_2$ (60 ml) was heated to reflux for 1.5 h, with magnetic stirring. Excess $SOCl_2$ was distilled off and the last trace removed under vacuum. The resulting solid residue was washed 3 times with cold H_2O, dried in air, and recrystallized from petroleum ether (b.p. 100–140°): **3** (17.9 g, 90%). M.p. 150–152° ([8]: m.p. 151–153°). UV (MeOH): 204 (4.57), 242 (4.52), 245 (sh, 4.49), 314 (sh, 3.78), 321 (3.90), 335 (3.94). ^{1}H-NMR ($CDCl_3$): 8.06 (*m*, 2H); 7.94 (*m*, 2H). MS: 198 (16, M^+), 163 (33, $[M - Cl]^+$), 102 (63, $[M - 2Cl - CN]^+$).

Similarly, *2,3-dichloro-6-methylquinoxaline* (**4**) was prepared from **11** and $SOCl_2$ in 87% yield. M.p. 109–110° ([14]: m.p. 112°). ^{1}H-NMR ($CDCl_3$): 7.90 (*d*, H–C(7)); 7.79 (*s*, H–C(5)); 7.73 (*d*, H–C(8)); 2.54 (*s*, Me). MS: 212 (M^+).

3. *1,2-Dihydro-2-oxoquinoxaline-3-carboxylic Acid* (**7**) [15]. *Ethyl 1,2-dihydro-2-oxoquinoxaline-3-carboxylate* [15] (**6**; 5.0 g, 23 mmol) was added to a soln. of NaOH (0.9 g, 23 mmol) in H_2O (500 ml) and stirred with gradual heating to 100°. $KMnO_4$ (18.1 g, 115 mmol) in H_2O (200 ml) was added dropwise during 2 h with continuous stirring and the temp. increased to *ca.* 120°. After the addition, the mixture was stirred for another h, allowed to cool to *ca.* 60°, and the formed MnO_2 filtered off and washed twice with hot H_2O (100 ml). The combined filtrates were treated with charcoal, concentrated to 60 ml, cooled, and acidified with AcOH: **7** (3.8 g, 87%). Colorless crystals. M.p. 270–271° ([15]: m.p. 268°). IR (KBr): 3490 (OH), 1752, 1690 (C=O), 1180, 1115. ^{1}H-NMR ((D_6)DMSO): 13.46 (br. *s*, COOH); 11.95 (br. *s*, NH); 7.82 (*d*, H–C(5)); 7.61 (*m*, H–C(8)); 7.35 (*m*, H–C(6), H–C(7)). MS: 190 (46, M^+), 172 (7, $[M - H_2O]^+$), 146 (41, $[M - CO_2]^+$), 144 (100, $[M - H_2O - CO]^+$), 118 (41, $[M - CO_2 - CO]^+$), 90 (35).

4. *1,2,3,4-Tetrahydroquinoxaline-2,3-dione* [13] (**9**). To a boiling soln. of *quinoxalin-2-(1H)-one* [16] (**5**) (5.0 g, 34 mmol) in H_2O (300 ml) and NaOH (1.4 g, 35 mmol), $KMnO_4$ (27 g, 171 mmol) in H_2O (300 ml) was added dropwise within 2 h with stirring. After another h of reflux, the soln. was cooled to 60°, the MnO_2 filtered off and washed twice with hot H_2O (100 ml), and the united filtrate concentrated to 50 ml and then acidified by AcOH. The resulting solid was column chromatographed (neutral alumina, $CHCl_3$/MeOH 9:1, then AcOH): **5** (2.2 g) followed by **9** (2.9 g, 52%). **9**: Physical data identical to those of an authentic sample. M.p. > 340°. UV (MeOH): 212 (4.51), 229 (3.91), 235 (sh, 3.86), 259 (3.61), 297 (sh, 3.92), 309 (4.02), 3.40 (sh, 3.57). ^{1}H-NMR ((D_6)DMSO): 11.99 (br. *s*, 2, NH); 7.16 (*m*, H–C(5), H–C(8)); 7.10 (*m*, H–C(6), H–C(7)).

5. *Pyrazine-2,3-dicarboxylic Acid* [2] [5] (**12**). A soln. of quinoxaline (**1**, 5.0 g, 38 mmol) was added to H_2O (400 ml) and heated to 95° with mechanical stirring. A hot soln. of $KMnO_4$ (35.0 g, 222 mmol) in H_2O (300 ml) was

added dropwise for 2 h and stirred for another h. The mixture was filtered hot to remove the MnO_2 washed well with hot H_2O (200 ml), and the combined filtrate concentrated to 80 ml, cooled in ice, and acidified with conc. HCl soln.: colorless crystals of **12**. Recrystallization from H_2O gave pure **12** (4.5 g, 71%). M.p. 192–194° ([5]: m.p. 190°). UV MeOH): 206 (3.77), 272 (3.60), 315 (sh, 2.72). IR (KBr): 3511 (OH), 1733 (C=O), 1331. ^{1}H-NMR ((D$_6$)DMSO): 8.84 (*s*, H–C(2), H–C(3)). ^{13}C-NMR ((D$_6$)DMSO): 166.0 (COOH); 145.5 (C(2), C(3)); 145.2 (C(5), C(6)). MS: 168 (0.2, M^+), 124 (17, $[M - CO_2]^+$), 106 (10, $[M - CO_2 - H_2O]^+$), 80 (100, $[M - CO_2 - H_2O - CN]^+$), 78 (16, $M - CO_2 - H_2O - CO]^+$).

6. *5-Chloropyrazine-2,3-dicarboxylic Acid* (**13**). A suspension of 2-chloroquinoxaline ([17] **2**; 5.0 g, 30.4 mmol) in H_2O (250 ml) was heated under reflux with vigorous stirring and then $KMnO_4$ (24.0 g, 152 mmol) in H_2O (250 ml) dropwise added within 2 h. The mixture was boiled for another h, cooled to *ca.* 60°, and filtered, the MnO_2 washed twice with hot H_2O (150 ml) and the combined filtrate concentrated to 80 ml, cooled to 0°, acidified with cold conc. HCl soln. to pH < 0, and scratched with a glass rod: colorless crystals (6.5 g). Recrystallization from 1N HCl gave **13**·HCl (5.1 g, 70%). M.p. 199–202° (dec.). UV (MeOH): 210 (3.95), 232 (sh, 3.88), 285 (3.80). IR (KBr): 3531 (OH), 1725 (C=O). ^{1}H-NMR ((D$_6$)DMSO): 10.18 (br. *s*, 2COOH); 8.88 (*s*, H–C(3)). ^{13}C-NMR ((D$_6$)DMSO): 164.5 (COOH); 164.1 (COOH); 147.7 (C(2)); 146.1 (C(3)); 144.6 (C(6)); 144.4 (C(5)). Anal. calc. for $C_6H_3ClN_2O_4$·HCl (239.0): C 30.15, H 1.69, N 11.72; found: C 29.60, H 1.30, N 11.29.

7. *5,6-Dichloropyrazine-2,3-dicarboxylic Acid* (**14**). A suspension of **3** (10.0 g, 50.2 mmol) in H_2O (500 ml) was heated with stirring to 95° and $KMnO_4$ (40.0 g, 253 mmol) in hot H_2O (600 ml) added dropwise within 2 h. The reaction was continued for another h and then worked up as described for **13**. Recrystallization from 1N HCl gave **14**·HCl (10.0 g, 73%). Colorless crystals. M.p. 290–292° (dec.). MS: 235 (0, M^+), 174 (100, $[M - H_2O - CO_2]^+$), 146 (45, $[M - H_2O - CO_2 - CO]^+$). Anal. calc. for $C_6H_2Cl_2N_2O_4$·HCl (273.5): C 26.35, H 1.11, N 10.24; found: C 25.66, H 0.44, N 9.87.

Treatment of **14**·HCl with aq. NaOH soln. and of the resulting clear soln. with AcOH gave a white precipitate which was recrystallized from H_2O: **14**·H_2O (5.2 g, 41%). M.p. 280–282° (dec.). UV (MeOH): 206 (3.91), 234 (3.93), 294 (3.88). IR (KBr): 3492 (OH), 1729 (C=O), 1601, 1300, 1246, 1115. ^{1}H-NMR ((D$_6$)DMSO): 10.16 (br., COOH). ^{13}C-NMR ((D$_6$)DMSO): 163.4 (COOH); 146.6 (C(5), C(6)); 143.4 (C(2), C(3)). Anal. calc. for $C_6H_2Cl_2N_2O_4$·H_2O (255.0): C 28.26, H 1.58, N 10.99; found: C 28.13, H 1.19, N 10.88.

Extraction of the MnO_2 cake with warm $CHCl_3$ gave 1.0 g of the starting compound **3**.

8. *5-Amino-6-chloropyrazine-2,3-dicarboxylic Acid* (**15**). To **14** (5.0 g, 19.6 mmol) in an autoclave, cooled in liq. N_2, liq. NH_3 (20 ml) was added and, after closing, heated at 130° for 24 h. After cooling in liq. N_2, the mixture was poured into a beaker and excess NH_3 allowed to evaporate. The resulting dark brown solid (10.0 g) was dissolved in hot H_2O, decolorized with charcoal, and then acidified with cold AcOH. The obtained colorless crystals were recrystallized from aq. AcOH: **15** (3.7 g, 88%). M.p. 300° (dec.). IR (KBr): 3438 (OH), 3291, 3171 (NH_2), 1690 (C=O), 1626, 1582, 1551, 1435. UV (MeOH): 203 (4.09), 277 (4.05), 325 (3.84). ^{1}H-NMR ((D$_6$)DMSO): 7.44 (br. *s*, 2OH); 7.18 (br. *s*, 2NH). ^{13}C-NMR ((D$_6$)DMSO): 165.9 (COOH); 164.3 (COOH); 151.9 (C(3)); 146.1 (C(6)); 132.3 (C(5)); 131.6 (C(2)). MS: 217 (3, M^+), 199 (5, $[M - H_2O]^+$), 173 (29, $[M - CO_2]^+$), 155 (61, $[M - H_2O - CO_2]^+$), 129 (100, $[M - H_2O - CO_2 - CN]^+$), 127 (19, $[M - H_2O - CO_2 - CO]^+$). Anal. calc. for $C_6H_4ClN_3O_4$ (217.6): C 33.12, H 1.85, N 19.31; found: C 32.82, H 1.50, N 19.70.

9. *1,2,3,4-Tetrahydro-1-(1,2,3,4-tetrahydro-2,3-dioxoquinoxalin-6-yl)quinoxaline-2,3-dione* (**17**). A suspension of **9** (5.0 g, 31 mmol) in H_2O (300 ml) containing NaOH (1.2 g, 32.5 mmol) was heated under reflux with vigorous stirring, and then a hot soln. of $KMnO_4$ (24.9 g, 157 mmol) in H_2O (300 ml) was added dropwise within 2 h. The mixture was boiled with continuous vigorous stirring for another h, cooled to *ca.* 60°, the MnO_2 filtered off and washed well with hot H_2O (200 ml), and the combined filtrate reduced to *ca.* 100 ml and acidified with cold AcOH: **17** (3.1 g, 62%). Yellowish powder. M.p. > 350°. UV (MeOH): 212 (4.73), 237 (sh, 4.25), 259 (sh, 4.12), 309 (4.23), 319 (sh, 4.17), 337 (sh, 3.84). IR (KBr): 3284 (NH), 3183, 3063, 1721, 1679 (C=O), 1393. ^{1}H-NMR ((D$_6$)DMSO): 12.21, 12.19, 12.15 (3*s*, 3NH); 7.35 (*d*, 1H); 7.24 (*d*, 1H); 7.10 (*m*, 3H); 6.96 (*dd*, 1H); 6.38 (*d*, 1H). Anal. calc. for $C_{16}H_{10}N_4O_4$ (322.3): C 59.63, H 3.13, N 17.38; found: C 59.40, H 3.22, N 17.10.

10. *6-Chloro-1-(7-chloro-1,2,3,4-tetrahydro-2,3-dioxoquinoxalin-6-yl)-1,2,3,4-tetrahydroquinoxaline-2,3-dione* (**18**). To a boiling soln. of **10** (10.0 g, 51 mmol) in H_2O (600 ml) and NaOH (2.0 g, 50 mmoles) was added a hot soln. of $KMnO_4$ (40.2 g, 254 mmol) in H_2O (500 ml) within 2 h with stirring, as described for **17**. After workup, the resulting yellowish product (9.8 g) was examined by TLC: mixture of **10** (major) and **18** (minor) with almost identical polarity. UV (MeOH): 215, 239 (sh), 300 (sh), 313, 325, 340 (sh). IR (KBr): 3282 (NH), 2905, 1713, 1674 (C=O), 1497, 1377.

Column chromatography could not successfully separate **10**/**18**. Hence they were converted to their chloro derivatives **3** and **22**, which are easily separable by column chromatography (see below).

11. *1,2,3,4-Tetrahydro-6-methyl-1-(1,2,3,4-tetrahydro-7-methyl-2,3-dioxoquinoxalin-6-yl)quinoxaline-2,3-dione* (**19**), *1,2,3,4-Tetrahydro-7-methyl-1-(1,2,3,4-tetrahydro-7-methyl-2,3-dioxoquinoxalin-6-yl)quinoxaline-2,3-dione* (**20**), *1,2,3,4-Tetrahydro-7-methyl-1-(1,2,3,4-tetrahydro-6-methyl-2,3-dioxoquinoxalin-5-yl)quinoxaline-2,3-dione* (**25**). A suspension of **11** (10.0 g, 57 mmol) in H_2O (650 ml) containing NaOH (2.3 g, 57.5 mmol) was stirred vigorously and heated to 130°. A soln. of $KMnO_4$ (44.9 g, 284 mmol) in H_2O (500 ml) at 90° was added in portions within 2 h. After another h of reflux, the mixture was cooled to 70°, the MnO_2 filtered off and washed twice with hot H_2O (200 ml), and the combined filtrate treated with charcoal, concentrated to 100 ml, cooled in ice-water, and then treated with cold AcOH. **19/20/25** (6.5 g, 65%). Yellowish crystal powder. M.p. 210–213° (dec.). UV (MeOH): 211 (4.75), 239 (sh, 4.20), 314 (4.11), 325 (sh, 4.18), 343 (sh, 3.87). IR (KBr): 3472 (NH), 1694 (br., C=O). Anal. calc. for $C_{18}H_{14}N_4O_4$ (350.3): C 61.71, H 4.03, N 15.99; found: C 61.32, H 4.12, N 15.69.

12. *3-Chloro-1-(2,3-dichloroquinoxalin-6-yl)quinoxalin-2(1H)-one* (**21**). A mixture of **17** (3.0 g, 9.3 mmol), DMF (0.2 ml), and $SOCl_2$ (6.0 ml) was heated to reflux with magnetic stirring for 1.5 h (→clear brown soln.). Excess $SOCl_2$ was distilled off under vacuum and the solid residue washed thrice with ice-water (150 ml), filtered, dried in air, and recrystallized from petroleum ether (b.p. 100–140°): **21** (3.1 g, 89%). Colorless crystals. M.p. 203–204°. UV (MeOH): 206 (4.80), 243 (4.60), 292 (sh, 4.01), 328 (4.13), 336 (4.17). IR (KBr): 1690, 1670 (C=O), 1605. ^{1}H-NMR ($CDCl_3$): 8.30 (*d*, 1H); 8.06 (*d*, 1H); 7.90 (*m*, 1H); 7.72 (*dd*, 1H); 7.40 (*m*, 2H); 6.68 (*m*, 1H). MS: 376 (23, M^+), 348 (34, $[M - CO]^+$), 313 (33, $[M - CO - Cl]^+$), 278, 242, 217. Anal. calc. for $C_{16}H_7Cl_3N_4O$ (377.6): C 50.89, H 1.87, N 14.84; found: C 50.90, H 1.94, N 14.68.

13. *3,6-Dichloro-1-(2,3,7-trichloroquinoxalin-6-yl)quinoxalin-2(1H)-one* (**22**). For 1.5 h, **10/18** (obtained from the $KMnO_4$ oxidation of **10**; 9.0 g), DMF (0.5 ml), and $SOCl_2$ (25 ml) were refluxed. Excess $SOCl_2$ was evaporated and the resulting solid treated as described for **21**. TLC: 2 major spots corresponding to 2,3,6-trichloroquinoxaline [18] and **22**. Column chromatography (silica gel, petroleum ether (b.p. 100°)/EtOH 200:1) gave first 2,3,6-trichloroquinoxaline (7.2 g, 61%). M.p. 142–144° ([18]: m.p. 143–144°). ^{1}H-NMR ($CDCl_3$): 8.01 (*s*, H–C(5)); 7.96 (*d*, H–C(8)); 7.75 (*d*, H–C(7)). MS: 232 (100, M^+), 197 (49, $[M - Cl]^+$), 136 (19).

Further elution gave **22** (1.7 g, 15%). Colorless crystals. M.p. 159–169° (dec.). UV (MeOH): 211 (4.93), 245 (4.77), 330 (sh, 4.27), 343 (4.33). IR (KBr): 1724, 1678 (C=O), 1605. ^{1}H-NMR ($CDCl_3$): 8.37 (*s*, 1H); 8.10 (*s*, 1H); 7.92 (*s*, 1H); 7.38 (*d*, 1H); 6.47 (*d*, 1H). MS: 448, 446, 444 (10, 15, and 9, resp., $[M + 4]^+$, $[M + 2]^+$, and M^+, resp.); 411 (100, $[M - Cl]^+$). Anal. calc. for $C_{16}H_5Cl_5N_4O$ (446.5): C 43.04, H 1.13, N 12.55; found: C 42.91, H 1.26, N 12.26.

14. *3-Chloro-1-(2,3-dichloro-7-methylquinoxalin-6-yl)-6-methylquinoxalin-2(1H)-one* (**23**), *3-Chloro-1-(2,3-dichloro-7-methylquinoxalin-6-yl)-7-methylquinoxalin-2(1H)-one* (**24**), *and 3-Chloro-1-(2,3-dichloro-6-methylquinoxalin-5-yl)-7-methylquinoxalin-2(1H)-one* (**26**). For 1.5 h, **19/20/25** (6.4 g, 18 mmol; obtained by $KMnO_4$ oxidation of **11**), DMF (0.2 ml), and $SOCl_2$ (20 ml) were refluxed. Removal of excess $SOCl_2$ gave crude **23/24/26** (7.3 g, 63%). Column chromatography (silica gel, petroleum ether/EtOH 200:1) gave **23/24** (2.6 g, 23%) and **26** (0.5 g, 4.3%).

23/24: Colorless solid. M.p. 216–217° (dec.). UV (MeOH): 208 (4.82), 233 (sh, 4.53), 246 (4.60), 297 (sh, 3.97), 331 (4.13), 341 (4.19). IR (KBr): 2928, 1686 (C=O), 1616. ^{1}H-NMR ($CDCl_3$): 8.14 (*s*, 1H); 8.12 (*s*, 1H); 7.93 (*s*, 2H); 7.79 (*d*, 1H); 7.71 (*s*, 1H); 7.21 (2*d*, 2H); 6.41 (*d*, 1H); 6.27 (*s*, 1H); 2.46 (*s*, 3H); 2.30 (*s*, 3H); 2.26 (*s*, 3H); 2.25 (*s*, 3H). MS: 408, 406, 404 (15,44, and 41, resp., $M + 4]^+$, $[M + 2]^+$, and M^+, resp.), 389 (36, $[M - Me]^+$), 369 (28, $[M - Cl]^+$), 341 (38, $[M - Cl - CO]^+$). Anal. calc. for $C_{18}H_{11}Cl_3N_4O$ (405.7): C 53.29, H 2.73, N 13.81; found: C 52.90, H 2.82, N 13.35.

26: Colorless powder. M.p. 287–288°. UV (MeOH): 210 (4.87), 245 (4.54), 324 (4.23), 338 (4.14). IR (KBr): 3067, 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 8.16 (*d*, 1H); 7.88 (*d*, 1H); 7.72 (*s*, 1H); 7.15 (*s*, 1H); 6.24 (*d*, 1H); 2.44 (*s*, 3H); 2.30 (*s*, 3H). Anal. calc. for $C_{18}H_5Cl_3N_4O$ (405.7): C 53.29, H 2.73, N 13.81; found: C 52.99, H 2.79, N 13.68.

15. *1H-Imidazo[4,5-b]quinoxaline* [11] (**27**). In an autoclave, **3** (10.0 g, 50 mmol) was heated with conc. NH_3 soln. to 95° for 15 h, as described for **15**. The resulting yellow solid was washed 3 times with hot H_2O (300 ml), dried at 90°, dissolved in hot DMF, treated with a large amount of charcoal, and left to cool: 2,3-diaminoquinoxaline [13] (7.5 g, 94%). Fine colorless crystals. M.p. > 340° ([11]: m.p. 331°). UV (MeOH): 209 (sh, 4.40), 222 (4.49), 257 (sh, 3.95), 328 (sh, 4.07), 341 (4.14), 357 (3.97). ^{1}H-NMR ((D_6)DMSO): 7.33 (*m*, H–C(5), H–C(8)); 7.13 (*m*, H–C(6), H–C(7)); 6.67 (br. *s*, $2NH_2$).

A mixture of 2,3-diaminoquinoxaline (5.0 g, 31 mmol) and triethyl orthoformate (50 ml) was heated under reflux with stirring for 6 h, after which the excess triethyl orthoformate was distilled off. The resulting residue was dissolved in hot 10% NaOH soln. and filtered to remove insoluble materials. The clear filtrate was treated with charcoal, filtered, and then neutralized with AcOH and cooled to give colorless crystals of **27** which were recrystallized from aq. AcOH: pure **27** (4.2 g, 80%). M.p. 284–286° ([11]: m.p. 286°). UV (MeOH): 211 (4.34), 240

(4.30), 244 (sh, 4.23), 329 (4.01). ^{1}H-NMR ((D$_6$)DMSO): 13.50 (br. *s*, NH); 9.13 (*s*, H–C(2)); 8.13 (*m*, H–C(5), H–C(8)); 7.77 (*m*, H–C(6), H–C(7)). MS: 170 (100, M^+), 143 (51, $[M - HCN]^+$), 116 (27, $[M - 2HCN]^+$).

16. *2,3-Dihydro-1*H*-imidazo[4,5-*b*]quinoxalin-2-one* [11] (**28**). With stirring, **27** [11] (1.0 g, 5.9 mmol) was added to a soln. of NaOH in H_2O (80 ml) and heated to 90°. A hot soln. of $KMnO_4$ (5.3 g, 33 mmol) in H_2O (40 ml) was added in portions within 2 h and the mixture boiled for another h, cooled to *ca.* 70°, and filtered from MnO_2. The MnO_2 was washed twice with hot H_2O (50 ml) and the combined filtrate treated with charcoal, evaporated to 100 ml, acidified with AcOH, and then allowed to cool: **28** (0.63 g, 58%). Colorless crystals. M.p. > 330°. UV (MeOH): 208 (4.54), 248 (4.26), 251 (sh, 4.26), 321 (sh, 4.09), 326 (4.19), 334 (4.13), 341 (4.16). IR (KBr): 3098 (NH), 1740 (C=O), 1628, 1495. ^{1}H-NMR ((D$_6$)DMSO): 11.90 (*s*, 2NH); 7.79 (*m*, 2H); 7.52 (*m*, 2H). MS: 186 (100, M^+), 158 (50, $[M - CO]^+$), 116 (23), 105 (20). Anal. calc. for $C_9H_6N_4O$ (186.2): C 58.06, H 3.25, N 30.09; found: C 57.90, H 3.50, N 29.84.

REFERENCES

[1] R. Goutarel, M.M. Janot, V. Prelog, W.I. Taylor, *Helv. Chim. Acta* **1950,** *33*, 150; R.G. Jones, E.C. Kornfeld, *J. Am. Chem. Soc.* **1951,** *73*, 107.
[2] S. Gabriel, A. Sonn, *Ber. Dtsch. Chem. Ges.* **1907,** *40*, 4850.
[3] I. Yoshioka, H. Otomasu, *Chem. Pharm. Bull.* **1957,** *5*, 277.
[4] *Mead, Johnson & Co.*, Brit. Pat. 565777 (*CA*: **1946,** *40*, 5458).
[5] R.G. Jones, K.C. McLaughlin, *Org. Synth.* **1950,** *30*, 86.
[6] J.W. Sausville, P.E. Spoerri, *J. Am. Chem. Soc.* **1941,** *63*, 3165.
[7] T. Kimura, S. Yamada, K. Yoshizue, T. Nagoya, *J. Pharm. Soc. Jpn.* **1957,** *77*, 891.
[8] H.I.X. Mager, W. Berends, *Recl. Trav. Chim. Pays-Bas* **1958,** *77*, 842.
[9] A.S. Elina, I.S. Musativa, *Khim. Geterotsikl. Soedin.* **1973,** *11*, 1548.
[10] H.I.X. Mager, W. Berends, *Recl. Trav. Chim. Pays-Bas* **1959,** *78*, 5.
[11] E. Schipper, A.R. Day, *J. Am. Chem. Soc.* **1951,** *73*, 5672.
[12] M.A. Phillips, *J. Chem. Soc.* **1928,** 2397.
[13] A.P. Komin, M. Carmack, *J. Heterocycl. Chem.* **1976,** *13*, 13.
[14] J.K. Landquist, *J. Chem. Soc.* **1953,** 2816.
[15] M.S. Habib, C.W. Rees, *J. Chem. Soc.* **1960,** 3371.
[16] G.W. Cheeseman, *J. Chem. Soc.* **1957,** 3236.
[17] A.H. Gowenlock, G.T. Newbold, F.S. Spring, *J. Chem. Soc.* **1945,** 622.
[18] K. Tanaka, H. Takahashi, K. Takimoto, M. Sugita, K. Mitsuhashi, *J. Heterocycl. Chem.* **1922,** *29*, 771.