Synthesis of Imidazo[4,5-*b*]quinoxaline 3-Oxides from Reactions of Furazano[3,4-*b*]quinoxaline 1-Oxides with Nitrones and Diazo Compounds

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The title compounds are prepared in good yields by simple procedures from readily available starting materials. They can be easily *O*-methylated by methyl iodide or deoxygenated by triphenylphosphine.

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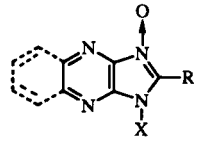
Various compounds containing the imidazo[4,5-*b*]pyrazine or imidazo[4,5-*b*]quinoxaline fused ring systems are known [1], but to the best of our knowledge, none of their 1-hydroxy-3-oxides **1** or solely 3-oxides **2** has been reported in the literature. The respective 1-hydroxyimidazole 3-oxides and their benzo derivatives are known [2], but their chemistry has not been well explored as yet. In contrast, derivatives of benzimidazole *N*-oxide have been much better investigated [2] and still attract interest [3] as natural purine analogues and potent biologically active compounds.



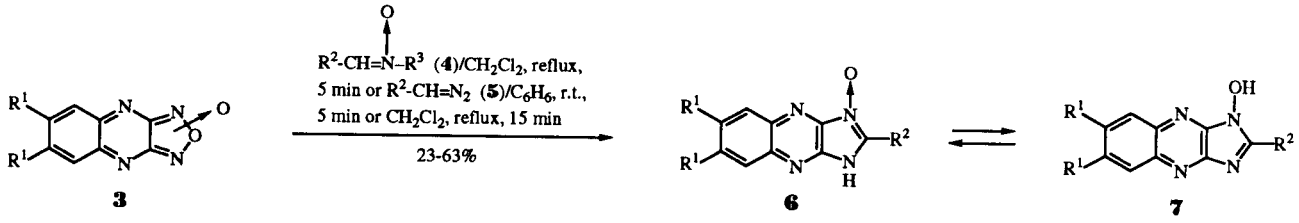
1, X = OH
2, X = H

A recent publication [4], reporting on the strong action of some imidazo[4,5-*b*]quinoxaline derivatives as competitive NK-1 antagonists, and the use of several benzimidazoles and azabenzimidazoles [5] as cardiotonic agents for heart failure therapy, prompted us to attempt the synthesis of the above hitherto unknown compounds **1** and **2**, both being of potential biological interest.

Since the direct oxidation of imidazoles has not yet been achieved [1], our approach towards compounds **1** and **2** (quinoxaline series) involved simultaneous construction of the imidazole ring and generation of the 1-hydroxy-3-oxide groups. For this purpose we utilized furazano[3,4-*b*]-quinoxaline 1-oxides **3** which were easily prepared in high yields from simple starting materials, according to the literature methods [6].

It was expected, that the reactions of furazano[3,4-*b*]-quinoxaline 1-oxides **3** with both nitrones and diazo compounds could afford 1-hydroxyimidazo[4,5-*b*]quinoxaline 3-oxides **1**, to be further reduced [2c] to **2**. Benzofurazan *N*-oxide gives in analogous reactions with nitrones [7] 1-hydroxybenzimidazole 3-oxides in high yields. Diphenyldiazomethane [8] also reacts with benzofurazan *N*-oxide, yielding various benzimidazole derivatives, depending upon the reaction conditions, while alkyl diazoacetates and diazomethane add to the benzene ring of nitrobenzo-

Scheme



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6

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3	R^1
a	H
b	Me

4	R^2	R^3
a	Ph	Ph
b	Ph	$PhCH_2$
c	4-C_6H_4Me	Me

5	R^2
a	4-C_6H_4Me
b	4-C_6H_4Cl
c	CO_2Et

6	R^1	R^2
a	H	Ph
b	Me	Ph
c	H	4-C_6H_4Me
d	Me	4-C_6H_4Me
e	H	4-C_6H_4Cl
f	Me	4-C_6H_4Cl
g	H	CO_2Et
h	Me	CO_2Et

furazan *N*-oxides [9].

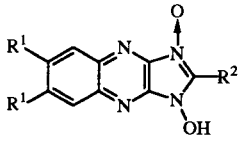
When a methylene chloride solution of furazano[3,4-*b*]-quinoxaline 1-oxides **3a,b** and nitrones **4a-c** in an 1:1 molar ratio was briefly refluxed, imidazo[4,5-*b*]quinoxaline 3-oxides **6a-d** were precipitated as yellow-orange microcrystals. Nitrones **4a** and **4b** gave identical products in their reactions with **3a** or **3b**.

Diazo compounds **5a,b** prepared from the corresponding tosylhydrazones [10] in benzene solution, were more reactive towards furazano[3,4-*b*]quinoxaline 1-oxides **3a,b**. Owing to their decomposition, diazo compounds **5a,b** were used in a threefold excess without refluxing and resulted imidazo[4,5-*b*]quinoxaline 3-oxides **6c-f**, which crystallized after evaporation of the solvent and addition of an 1:1 mixture of hexane/methylene chloride. Furazano-[3,4-*b*]quinoxaline 1-oxides **3a,b** reacted also with a threefold excess of ethyl diazoacetate **5c** at refluxing methylene chloride, and the resulting **6g,h** crystallized upon addition of an equal volume of hexane. The reaction products of diazo compound **5a** with **3a,b** were identical to those of the reactions of **3a,b** with nitrone **4c**.

Compounds **6a-f** are sparingly soluble in common organic solvents, in order that they were purified by thorough washing with methylene chloride after precipitation from the reaction mixture, or by passing through a column of silica gel with ethyl acetate as the eluant. An additional amount of **6** (*ca.* 5%) can be isolated in all reactions from the mother liquor by column chromatography, except for the products **6g,h**, which decompose on the column.

The structure of these products, which are tautomeric with 1-hydroxyimidazo[4,5-*b*]quinoxalines **7**, was elucidated from their spectral data and elemental analyses. Their ir spectra in nujol show a conjugated broad OH/NH stretching band [3] at *ca.* 2600-2700 cm^{-1}, while the characteristic furoxan strong absorption band [6] at *ca.* 1600 cm^{-1} is lacking, indicating thus that the reaction occurred at the furoxan ring. All compounds **6a-h** gave the parent ion in their mass spectra at 70 eV, as well as the characteristic M-16 peaks, which reveal the presence of an exocyclic oxygen. Both ^1H and ^{13}C nmr spectra, obtained in dimethyl sulfoxide-d_6, are also consistent with the given structures. Due to their sparing solubility in the usual nmr solvents, ^{13}C nmr spectra have not been obtained for all of them. The C-2 chemical shift of the imidazole ring appeared at δ 147-158.

The hypothesis that the reaction products are not compounds **6**, but the expected 1-hydroxy-3-oxides **8**, which in that case simply do not give the parent ion in their mass spectra, can be easily excluded from their nmr spectra, further to their microanalyses. Compounds **8** should have a symmetric pattern in their ^1H and ^{13}C nmr spectra, because of the expected rapid equilibrium between their two tautomeric forms [2], whereas the obtained spectra show the presence of an unsymmetrically substituted quinoxaline ring. Both ^1H and ^{13}C nmr spectra of compounds **6g,h** in deuteriochloroform solution are nearly identical to those in dimethyl sulfoxide-d_6, and still remain unsymmetric even in case that drops of trifluoroacetic acid are added to the nmr tube. Mass spectra at 25 eV or negative ion mass spectra of products isolated did not show any peak corresponding to the 1-hydroxy-3-oxides **8** parent ions.



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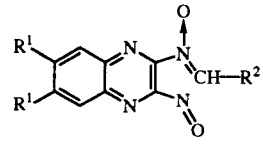

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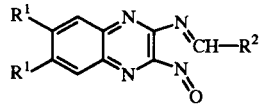

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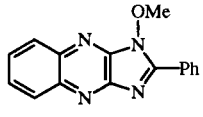
A reaction mechanism analogous to that suggested for the reactions of benzofurazan *N*-oxide with nitrones [7], could be considered for the reactions studied here. This mechanism involves an initial nucleophilic attack [11] by the carbon of the dipole on the nitrogen of the furoxan ring or of the open dinitroso form, with subsequent elimination of the neutral molecules R^3–N=O or N_2 and formation of the nitrosonitrone intermediate **9**. Cyclisation of the non-isolable **9** to the 1-hydroxy-3-oxide **8**, followed by deoxygenation, or firstly deoxygenation of **9** to **10** and then cyclisation, yields the final products **6**. Analogous oxygen expulsions have been observed [12] in relative nitrosonitrone intermediates, derived from reactions of nitrosoarenes with nitrile oxides, before or after their cyclisation to heterocyclic products.

The structure of compounds **6** was further chemically confirmed. Compound **6a** was easily methylated under basic conditions by methyl iodide to the *O*-methylated product **11** in 48% yield, while compound **6h** was quantitatively deoxygenated by triphenylphosphine to imidazo-[4,5-*b*]quinoxaline **12**. Both reactions confirm unequivocally the exocyclic position of the oxygen atom.



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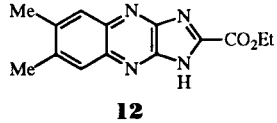

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In conclusion, we have developed a method for preparing in good yields new heterocyclic compounds, bearing the imidazole 3-oxide system fused with the quinoxaline ring and substituted at the 2-position; these are expected to be of multiple interest, including their potential biological applications.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The ^{1}H nmr spectra were obtained either at 300 MHz on a Varian VXR-300 spectrometer or at 80 MHz on a Bruker AW80 spectrometer, with tetramethylsilane as the internal standard. The ^{13}C nmr spectra were recorded at 75 MHz on the above Varian VXR-300 nmr spectrometer and are quoted relative to tetramethylsilane as internal reference. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer for nujol mulls and microanalyses were performed on a Perkin-Elmer 240B element analyser. Mass spectra were recorded at 70 eV either on a VG TS-250 or on a Hitachi-Perkin-Elmer MU-6L spectrometer.

General Procedure for the Reactions of Furazano[3,4-*b*]quinoxaline 1-Oxides **3a,b** with Nitrones **4a-c**.

A solution of furazano[3,4-*b*]quinoxaline 1-oxide **3a,b** [6] (1 mmole) and nitrone **4a-c** [14] (1 mmole) in anhydrous methylene chloride (10 ml) was refluxed for 5 minutes. The deep red colour of the solution disappeared and by cooling the reaction mixture at room temperature yellow-orange microcrystals were precipitated, which were collected with filtration and washed thoroughly with methylene chloride to give imidazo[4,5-*b*]quinoxaline 3-oxides **6a-d**.

2-Phenylimidazo[4,5-*b*]quinoxaline 3-Oxide **6a**.

This compound was prepared in 56% yield from reaction of **3a** with **4a**, mp 264-268° dec, and 44% yield from reaction of **3a** with **4b**, mp 267-270° dec; ir: ν NH/OH 2600 (br) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 7.72 (m, 3H), 7.84 (m, 2H), 8.22 (m, 2H), 8.48 (m, 2H); ^{13}C nmr (DMSO-d$_6$): δ 127.4, 127.6, 127.9, 128.5, 129.0 (two peaks), 129.5, 132.4, 139.4, 139.6, 141.1, 145.3, 158.2 (C-2); ms: m/z (%) 262 (M$^+$, 4), 246 (M$^+$-16, 15), 77 (100).

Anal. Calcd. for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.37. Found: C, 68.75; H, 3.80; N, 21.27.

6,7-Dimethyl-2-phenylimidazo[4,5-*b*]quinoxaline 3-Oxide **6b**.

This compound was prepared in 63% yield from reaction of **3b** with **4a**, mp 222-226° dec, and 52% yield from reaction of **3b** with **4b**, mp 230-234° dec; ir: ν NH/OH 2600 (br) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.48 (s, 6H), 7.69 (m, 3H), 7.92 (m, 2H) 8.45 (m, 2H); ^{13}C nmr (DMSO-d$_6$): δ 19.7, 19.9, 126.7, 127.6, 127.8, 129.0, 129.4, 132.1, 137.7, 138.3, 138.7, 139.1, 140.0, 144.7, 156.9 (C-2); ms: m/z (%) 290 (M$^+$, 17%), 274 (M$^+$-16, 100).

Anal. Calcd. for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.07; H, 4.66; N, 19.48.

2-(4-Tolyl)imidazo[4,5-*b*]quinoxaline 3-Oxide **6c**.

This compound was prepared in 23% yield, mp 272-275° dec; ir: ν NH/OH 2650 (br) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.45 (s, 3H), 7.49 (d, 2H, J = 8 Hz), 7.80 (m, 2H), 8.18 (m, 2H), 8.39 (d, 2H, J = 8 Hz); ^{13}C nmr (DMSO-d$_6$): δ 21.2, 124.6, 127.4, 127.8, 128.2, 128.9, 129.4, 129.5, 139.3, 139.8, 141.0, 142.7, 145.3, 158.2 (C-2); ms: m/z (%) 276 (M$^+$, 44), 260 (M$^+$-16, 100).

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.53; H, 4.51; N, 20.52.

6,7-Dimethyl-2-(4-tolyl)imidazo[4,5-*b*]quinoxaline 3-Oxide **6d**.

This compound was prepared in 31% yield, mp 257-260 dec; ir: ν NH/OH 2650 (br) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.45 (s, 3H), 2.49 (s, 3H), 2.50 (s, 3H), 7.47 (d, 2H, J = 8 Hz), 7.92 (s, 2H), 8.34 (d, 2H, J = 8 Hz); ^{13}C nmr (DMSO-d$_6$): δ = 19.6, 19.8, 21.1, 124.7, 126.7, 127.7, 129.2, 129.5, 137.5, 138.1, 138.5, 139.1, 139.9, 142.3, 144.7, 157.0 (C-2); ms: m/z (%) 304 (M$^+$, 33), 288 (M$^+$-16, 52), 119 (100).

Anal. Calcd. for $C_{18}H_{16}N_4O$: C, 71.03; H, 5.30; N, 18.41. Found: C, 71.04; H, 5.48; N, 18.47.

General Procedure for the Reactions of Furazano[3,4-*b*]quinoxaline 1-Oxides **3a,b** with Diazo Compounds **5a,b**.

A solution of diazo compound **5a,b** (3 mmoles) in benzene (50 ml) was prepared from the corresponding tosylhydrazones according to the literature procedure [10]. Then, furazano[3,4-*b*]-quinoxaline 1-oxide **3a,b** [6] was added at room temperature, followed by spontaneous reaction and evolution of gas nitrogen. After 5 minutes the solvent was evaporated off and the reaction mixture was treated with a mixture of methylene chloride (5 ml) and hexane (5 ml). The precipitated solid was collected with filtration and chromatographed on silica gel using ethyl acetate as the eluant to give the respective imidazo[4,5-*b*]quinoxaline 3-oxides **6c-f**.

2-(4-Tolyl)imidazo[4,5-*b*]quinoxaline 3-Oxide **6c**.

This compound was prepared in 47% yield, mp 270-273° dec.

6,7-Dimethyl-2-(4-tolyl)imidazo[4,5-*b*]quinoxaline 3-Oxide **6d**.

This compound was prepared in 32% yield, mp 257-261° dec.

2-(4-Chlorophenyl)imidazo[4,5-*b*]quinoxaline 3-Oxide **6e**.

This compound was prepared in 42% yield, mp 288-291° dec; ir: ν NH/OH 2600 (br) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 7.74 (d, 2H, J = 8.5 Hz), 7.80 (m, 2H), 8.17 (m, 2H), 8.48 (d, 2H, J = 8.5 Hz); ms: m/z (%) 296/298 (M$^+$/M$^+$+2, 40/13), 280/282 (100/35).

Anal. Calcd. for $C_{15}H_9ClN_4O$: C, 60.72; H, 3.06; N, 18.88. Found: C, 60.84; H, 3.33; N, 18.92.

2-(4-Chlorophenyl)-6,7-dimethylimidazo[4,5-*b*]quinoxaline 3-Oxide **6f**.

This compound was prepared in 51% yield, mp 298-300° dec; ir: ν NH/OH 2650 (br) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.48 (s, 3H), 2.50 (s, 3H), 7.68 (d, 2H, J = 8.5 Hz), 7.85 (s, 1H), 7.89 (s, 1H), 8.44 (d, 2H, J = 8.5 Hz); ms: m/z (%) 324/326 (M$^+$/M$^+$+2, 35/12), 308/310 (100/34).

Anal. Calcd. for $C_{17}H_{13}ClN_4O$: C, 62.87; H, 4.03; N, 17.25. Found: C, 62.60; H, 4.08; N, 17.10.

General Procedure for the Reactions of Furazano[3,4-*b*]quinoxaline 1-Oxides **3a,b** with Ethyl Diazoacetate **5c**.

A solution of furazano[3,4-*b*]quinoxaline 1-oxide **3a,b** [6] (1 mmole) and ethyl diazoacetate **5c** (342 mg, 3 mmoles) in anhydrous methylene chloride (10 ml) was refluxed for 15 minutes. Hexane (10 ml) was then added and the mixture was allowed to stand at room temperature for 24 hours. The light yellow crystals formed, were collected by filtration and dried in the air to give products **6g,h** of analytical purity.

2-Ethoxycarbonylimidazo[4,5-*b*]quinoxaline 3-Oxide **6g**.

This compound was prepared in 33% yield, mp 195-198° dec; ir: ν CO 1735, ν NH/OH 2700 (br) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.39 (t, 3H, J = 7.5 Hz), 4.51 (q, 2H, J = 7.5 Hz), 7.85 (m, 2H), 8.20 (m, 2H); ^{13}C nmr (DMSO-d$_6$): δ 14.0, 62.8, 128.2, 128.4, 129.4, 129.8,

138.3, 140.7, 141.7, 143.6, 148.2 (C-2), 157.6 (C=O); ms: m/z (%) 258 (M^+, 12), 242 (M^+-16, 35), 170 (100).

Anal. Calcd. for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70. Found: C, 55.87; H, 3.83; N, 21.69.

2-Ethoxycarbonyl-6,7-dimethylimidazo[4,5-*b*]quinoxaline 3-Oxide **6h**.

This compound was prepared in 37% yield, mp 193-195° dec; ir: ν CO 1735, ν NH/OH 2700 (br) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.44 (t, 3H, J = 7 Hz), 2.47 (s, 3H), 2.48 (s, 3H), 4.55 (q, 2H, J = 7 Hz), 7.91 (s, 1H), 7.92 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 14.0, 19.7, 19.9, 62.7, 126.7, 127.9, 137.6, 138.8, 139.7, 140.5, 140.8, 142.8, 146.7 (C-2), 157.6 (C=O); ms: m/z (%) 286 (M^+, 14), 270 (M^+-16, 33), 198 (100).

Anal. Calcd. for $C_{14}H_{14}N_4O_3$: C, 58.73; H, 4.93; N, 19.57. Found: C, 58.85; H, 4.96; N, 19.36.

1-Methoxy-2-phenylimidazo[4,5-*b*]quinoxaline **11**.

To a suspension of **6a** (262 mg, 1 mmole) and potassium hydroxide (112 mg, 2 mmole) in dimethylformamide (10 ml), an excess of methyl iodide (1 ml) was added and the mixture was allowed to stand with stirring at room temperature for 24 hours. Then, water (300 ml) was added and the resulting mixture was extracted twice with methylene chloride (2 x 50 ml). The organic layer was dried over magnesium sulfate, the solvent was evaporated off and the product was chromatographed on silica gel using ethyl acetate/hexane (1:3) as the eluant to give compound **11** (126 mg, 48%), mp 178-180° (from methylene chloride/hexane); ^1H nmr (deuteriochloroform): δ 4.25 (s, 3H), 7.6 (m, 3H), 7.75 (m, 2H), 8.2 (m, 2H), 8.45 (m, 2H); ms: m/z (%) 276 (M^+, 76), 246 (100).

Anal. Calcd. for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.73; H, 4.60; N, 20.37.

2-Ethoxycarbonyl-6,7-dimethylimidazo[4,5-*b*]quinoxaline **12**.

A solution of **6h** (71.5 mg, 0.25 mmole) and triphenylphosphine (655 mg, 2.5 mmoles) in chloroform (10 ml) was refluxed for 24 hours. The resulting compound **12** was crystallized upon cooling the reaction mixture at room temperature and collected with filtration (35 mg). An additional amount of **12** (25 mg) was obtained by chromatographing the mother liquor on silica gel using ethyl acetate as the eluant, total yield 89%, mp 250-252° (from chloroform); ir: ν CO 1720, ν NH 3100 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (t, 3H, J = 7 Hz), 2.45 (s, 6H), 4.6 (q, 2H, J = 7 Hz), 8.05 (s, 2H); ms: m/z (%) 270 (M^+, 36), 198 (100).

Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.31; H, 4.99; N, 20.92.

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