Reaction of dihydropyrazine-1,4-dioxides with organolithium compounds. Synthesis of nitroxyl radicals — derivatives of tetrahydropyrazine oxide

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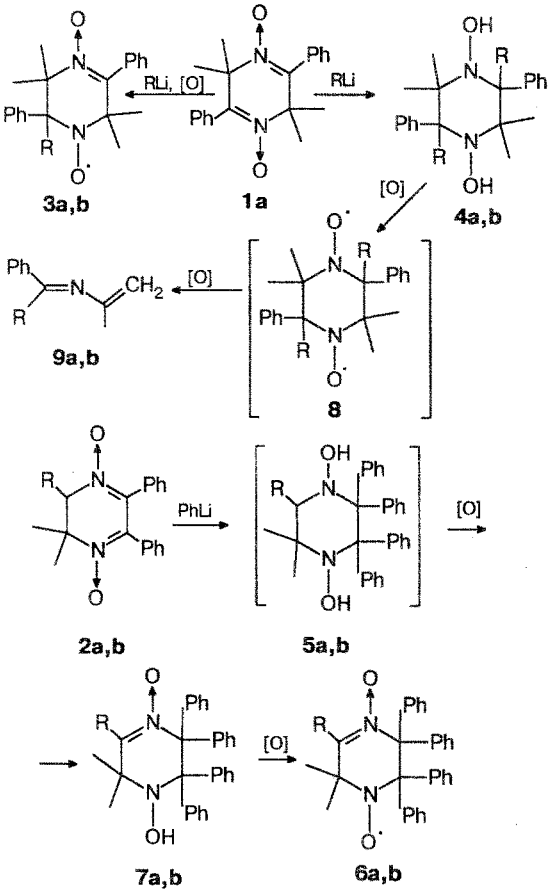
Reaction of dihydropyrazine-1,4-dioxides with organolithium compounds followed by oxidation with MnO_2 gives stable nitroxides of the pyrazine series. The reaction of a pyrazine containing methylnitrone groupings with ethylbenzoate in the presence of NaH or PhLi leads to mono- or diphenacyl derivatives, which have been shown to exist in solution as a mixture of tautomers. On treatment with hydroxylamine and subsequent oxidation the monophenacyl nitrone derivative yields a stable nitroxyl radical derived from spiroisoxazolopyrazine.

Key words: pyrazine; nitrone; nitroxyl radicals; tautomerism.

We showed earlier[1] that the endocyclic nitroxyl biradicals of imidazolidine can be obtained by the reaction of 3-imidazoline-3-oxide with organolithium compounds. However, although these biradicals were isolated in the individual state, their stability in solution is low. It was thought that the low stability of these compounds is due to the 1,3-position of nitroxyl groups in the heterocycle. Therefore it seems likely that the nitroxyl biradicals of the piperazine series with nitroxyl groups in the 1,4-positions would be more stable. Such compounds would represent a new class of endocyclic biradicals. In this work we have investigated the feasibility of synthesizing biradicals of this type using the reaction of 2,5- and 2,3-dihydropyrazine-1,4-dioxides (**1** and **2**, respectively) with organolithium compounds (Scheme 1).

On the reaction of dinitrone **1a** with methyllithium and subsequent oxidation the nitroxyl monoradical **3a** (see ref. 2) is formed. Its ESR spectrum is the triplet typical for monoradicals. The structure of **3a** is confirmed by its IR spectrum, where the band at 1560 cm^{-1}, corresponding to the C=N bond of a nitrone group is present whereas OH group absorption is absent. The addition of methyllithium to the second nitrone group does not occur even if a tenfold excess of the reagent is used and the time of the reaction is extended to three days. In the case of the reaction of pyrazine **1a** with excess phenyllithium the addition to both nitrone groups takes place easily. The product of this reaction is compound **4a**. The structure of **4a** is confirmed by the absence of absorption at $\lambda > 220$ nm in the UV spectrum and the absence of C=N bond absorption in the IR spectrum. The reaction of pyrazine **1a** with phenyllithium

Scheme 1



3a,b **1a** **4a,b** **9a,b** **8** **2a,b** **5a,b** **7a,b** **6a,b**

R = Me (**2b, 3a, 5b, 6b, 7b**); *n*-Bu (**4b, 9b**); Ph (**2a, 3b, 4a, 5a, 6a, 7a, 9a**).

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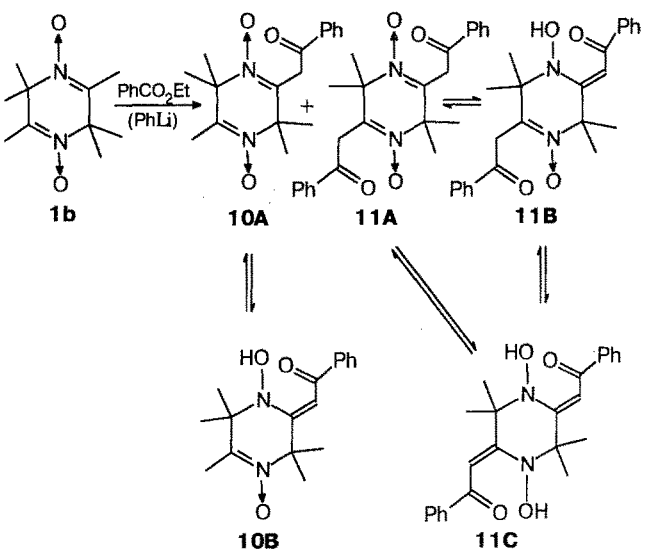
Scheme 2



taken in a moderate excess (1 : 1.5) followed by oxidation gives the monoradical **3b**. Similarly, the reaction of pyrazine **1a** with excess butyllithium gives a mixture of isomeric dihydroxypyrazines **4b**. Compounds **4b** could not be isolated as individual stereoisomers. However, the absence of absorption at $\lambda > 220$ nm in the UV spectrum of **4b** and the close similarity of the IR spectra of compounds **4a** and **4b** makes it possible to assign them the indicated structure.

The reaction of 2,3-dihydropyrazine-1,4-dioxides **2** with excess phenyllithium also affects both nitrone groups. On subsequent oxidation of the initially formed dihydroderivatives (**5**) nitroxyl monoradicals (**6**) were isolated. It is to be noted that in the case of pyrazine **2a**, the formation of radicals **6a** is accompanied by formation of compound **7a**. On oxidation compound **7a** easily gives radical **6a**. The IR spectra of compounds **6a** and **7a** are wery similar.

Type **8** biradicals could not be isolated after the oxidation of **4a** or **4b** with MnO_2. This may be due to the low stability of **8**. The products of this reaction are the diamagnetic α,β-unsaturated imines **9a,b**. A group of bands in the 1560–1660 cm^{-1} region of the IR spectrum of **9a** correspond to the vibrations of multiple C=C and C=N bonds. Absorption with $\lambda_{max} = 250$ nm ($\log\varepsilon = 4.21$) is observed in the UV spectrum.

In the ^1H NMR spectrum of compound **9a** singlets of methyl group protons at 1.76 ppm and protons at the C=C bond (4.0 and 4.15 ppm) together with a multiplet of protons of two methyl groups are present. On the basis of these data and the results of elemental analysis the structure of 1,1-diphenyl-3-methyl-2-azabutadiene-1,3 has been assigned for **9a**. The structure of **9a** was further confirmed by the ^{13}C NMR spectrum which displays signals of the carbon atoms of a terminal methylene group (96.79 ppm), an imino group (152.66 ppm), and an enamino group (165.60 ppm). The similarity of the spectral characteristics of **9a** and **9b** as well as the fact that the hydrolysis of **9a** proceeds easily to give valerophenone are compatible with this structure. However, an alternative structure with another arrangement of the multiple bonds cannot be ruled out.

In contrast to compounds **1a** and **2**, pyrazine **1b**, which contains methyls instead of phenyls, does not give addition products with phenyl- or buthyllithium. This may be explained by the metallation of the methylnitrone group (*cf.* ref. 3). In fact, sequential treatment of pyrazine **1b** with phenyllithium and ethylbenzoate gives the products of mono- (**10**) and diacylation (**11**). Compound **10** can also be obtained by the reaction of **1b** with ethylbenzoate in the presence of NaH (see ref. 5), whereas the product of diacylation, **11**, cannot be obtained under these conditions (Scheme 2).

According to the ^1H NMR spectral data, compounds **10** and **11** exist in $CDCl_3$ solution as a mixture of enolyzed tautomers (*cf.* ref. 4). Thus, the spectrum of **10** contains the signals of $-CH_2-$ and $-CH=$ at 4.08 and 5.61 ppm for forms **A** and **B**, respectively, and the signal of a strongly hydrogen-bonded OH group (14.26 ppm) along with signals from the protons of phenyl and methyl groups. The fraction of non-enolyzed tautomeric form **A** is 15 %. The ^1H NMR spectrum of compound **11** contains signals of protons of the methylene groups of form **B** and non-enolyzed form **A** as well as signals of $-CH=$ groups at 5.65 and 5.66 ppm of forms **B** and **C**, respectively. The ratio of these forms cannot be easily determined; however, form **A** appears to be predominant in the mixture, whereas the fraction of form **C** is the smallest. Most probably, each tautomer is present, in its turn, in the ene-hydroxylamino keto and enol-nitrone forms (*cf.* ref. 4). The ratio of the latter two forms was not determined.

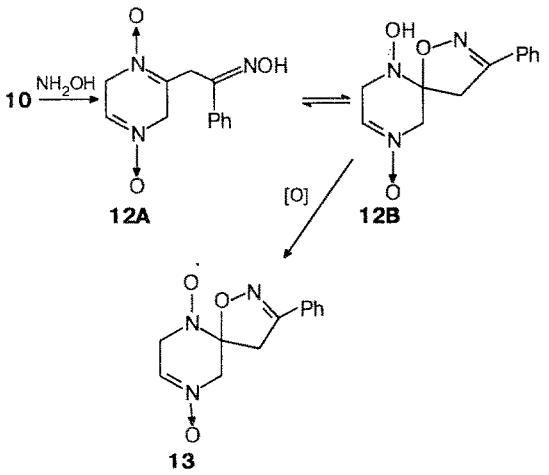
The reaction of pyrazine **10** with hydroxylamine gives compound **12** (Scheme 3). Judging by the ^{13}C NMR (DMSO-d_6) data[6], this compound exists in the tautomeric form **B**. Thus, in the region of sp^2-hybridized carbon atoms, signals corresponding to the C(3') and C(5) atoms (155.62 and 144.95 ppm, respectively) are observed in addition to the phenyl group signals. The carbon atom of the spiro unit is manifested by a signal at 105.23 ppm. The signals typical of form **A** are not present in the ^1H and ^{13}C NMR spectra.

Compound **12** is easily oxidized by MnO_2 to give the stable nitroxyl radical **13** (*cf.* ref. 6).

Experimental

The IR spectra were recorded using UR-20 and Specord M-80 instruments in KBr (0.25 %) in pellets or CCl_4 (5 % solutions). The UV spectra were taken on a Specord UV Vis instrument in ethanol. The ^1H and ^{13}C NMR spectra were recorded using Bruker WP-200 SY and Bruker AC-200 instruments in the pulse mode at 300 K in $CDCl_3$ and DMSO (5 %) solutions. The values of the chemical shifts were determined in

Scheme 3



relation to that of the solvent. Paramagnetic properties of the compounds were determined using a MINSK-12M ESR spectrometer. The mass spectrum of **3b** was recorded on a Finnigan MAT-8200 instrument. Compounds **1a,b** were prepared by a known procedure.[7] The characteristics and yields of the prepared compounds* are presented in Table 1.

* Compounds **2a,b** were kindly provided by D. G. Mazhukin.

2,5-Diphenyl-2,3,3,6,6-pentamethyl-1,2,3,6-tetrahydropyrazine-4-oxide-1-oxyl (3a). Pyrazine **1a** (0.64 g, 2 mmol) was added portionwise to a stirred solution of methyllithium prepared from methyl iodide (0.62 mL, 10 mmol) and lithium (0.14 g, 20 mmol) in 30 mL of abs. ether. The reaction was carried out under an argon atmosphere. The agitation was continued for 10 h at 20 °C, then 10 mL of water was added. The precipitate was collected by filtration, washed with water and ether, and dried. The organic layer of the filtrate was separated, and the aqueous layer was extracted with $CHCl_3$. The combined extract was dried with $MgSO_4$. Then $MgSO_4$ was filtered off, and the precipitate collected was added to the filtrate and agitated for 2 h at 20 °C with MnO_2 (2 g). The excess oxidant was filtered off and the clear solution was evaporated to give compound **3a** which was purified chromatographically on a column with silica gel using $CHCl_3$ as the eluent.

3,3,5,5-Tetramethyl-2,2,5-triphenyl-1,2,3,6-tetrahydropyrazine-4-oxide-1-oxyl (3b) was prepared under similar conditions by the reaction of 1.5 mmol of phenyllithium with 1 mmol pyrazine **1a**.

1,4-Dihydroxy-3,3,6,6-tetramethyl-2,2,5,5-tetraphenylpiperazine (4a). Pyrazine **1a** (0.64 g, 2 mmol) was added portionwise to a stirred solution of phenyllithium prepared from bromobenzene (1.1 mL, 10 mmol) and lithium (0.14 g, 20 mmol). The reaction was carried out under an argon atmosphere. The agitation was continued for 3 h at 20 °C, then 10 mL of water was added. The precipitate of dihydroxy-

Table 1. Characteristics of the prepared compounds

Compound	Yield (%)	M.p.[a] /°C	IR spectrum (KBr), ν/cm^{-1}	UV spectrum, λ_{max}/nm (log ε)	Molecular formula	Found / Calculated (%) C	H	N
3a	95	145–146	1565 (C=N)	250 (3.91)	$C_{21}H_{25}N_2O_2$	75.0 74.7	7.7 7.4	8.1 8.4
3b	40	198–200	1570 (C=N)	252 (3.90)	$C_{26}H_{27}N_2O_2$[b]	77.9 78.3	6.7 6.8	6.8 7.0
4a	100	314–315[c]	3520 (OH)	—	$C_{32}H_{34}N_2O_2$	80.5 80.3	7.3 7.1	6.0 5.9
6a	35	108–110	1575, 1600, 1620 (C=N, C=C)	299 (4.22)	$C_{36}H_{31}N_2O_2$	82.8 82.5	5.6 5.9	5.6 5.4
6b	10	210–212	1570, 1595, 1620 (C=N, C=C)	250 (4.14)	$C_{31}H_{29}N_2O_2$	81.0 80.6	6.3 6.3	6.1 6.1
7a	40	244–245	1570, 1600, 1620 (C=N, C=C)	254 (3.98)	$C_{36}H_{32}N_2O_2$	82.7 82.4	6.2 6.1	5.4 5.4
9a	70	74–76	1605, 1630 (C=N, C=C)	248 (4.22)	$C_{16}H_{15}N$	86.7 86.9	6.8 6.8	6.0 6.3
9b	50	Oil	1545, 1570, 1595, 1620 (C=C, C=N)	243 (4.08)	$C_{14}H_{19}N$	83.3 83.6	9.4 9.5	6.6 7.0
10	45	163–165	1555, 1580, 1595, 1620 (C=C, C=N); 1680 (C=O)	237 (4.46), 353 (3.70)	$C_{17}H_{22}N_2O_3$	67.9 67.6	7.2 7.3	9.2 9.3
11	5	160–164	1595, 1605 (C=C, C=N); 1690 (C=O)	223 (4.16), 244 (4.26), 356 (3.63)	$C_{24}H_{26}N_2O_4$	71.2 70.9	6.4 6.4	6.8 6.9
12	90	223–226	1600 (C=N)	250 (4.04)	$C_{17}H_{23}N_3O_3$	64.3 64.3	7.3 7.3	13.0 13.3
13	90	174–177	1570 (C=N)	246 (4.31)	$C_{17}H_{22}N_3O_3$	64.2 64.6	7.0 6.9	12.9 13.3

[a]Compound **3a** was purified by recrystallization from hexane, **3a, 6b** — from an AcOEt—hexane mixture, **4a** — from pyridine, **6a** — from EtOH, **7a** — from a PhH—EtOH mixture, **9a** — from pentane, **12** — from aqueous EtOH. Compounds **10, 11, 13** were purified chromatographically. [b]By mass spectrometry. Found: mol. mass 399.2144. Calculated: mol. mass 399.2072. [c] In a sealed capillary.

piperazine **4a** was collected by filtration, washed with water and ether, and dried. Compound **4a** forms a crystallosolvate with pyridine, which is decomposed at 90—100 °C.

A mixture of isomeric dihydroxypiperazines **4b** was obtained under similar conditions. Their chromatographic separation was unsuccessful due to rapid oxidative decomposition.

Compounds **6a,b** and **7a** were synthesized by reacting pyrazines **2a** or **2b** with a tenfold excess of phenyllithium and oxidizing the resulting intermediates under the above conditions. The mixture of **6a** and **7a** was partitioned chromatographically on a silica gel column (elution with a 1 : 1 benzene—hexane system).

1,1-Diphenyl-3-methyl-2-azabutadiene (9a). A suspension of dihydroxypiperazine **4a** (0.2 g) in a mixture of ether (20 mL) and pyridine (1 mL) was agitated with 2 g of MnO_2 for 1 h at 20 °C. The excess oxidant was filtered out and the solution was evaporated. Compound **9a** was purified chromatographically on a silica gel column with $CHCl_3$—hexane (1:1) as the eluent. ^1H NMR ($CHCl_3$), δ: 1.76 (s, 3 H, CH_3); 4.00 (s, 1 H, $=CH_2$); 7.2—7.7 (m, 10 H, $(C_6H_5)_2$). ^{13}C NMR ($CDCl_3$), δ: 21.78 (CH_3); 96.79 ($=CH_2$); 127.7—139.1 (m, C_6H_5); 152.66 (C=N); 165.60 (=C—N).

Compound **9b** was obtained by the oxidation of the dihydroxy derivative of **4b** in hexane under the above conditions. Partial hydrolysis of **9b** took place either in the course of chromatography on silica gel or on the short exposure of its solutions to the moisture present in commercial solvents. The structure of the resulting valerophenone was determined by ^1H and ^{13}C NMR spectra.

2,5-Dihydro-2,2,3,5,5-pentamethyl-6-phenacylpyrazine-1,4-dioxide (10) and 2,5-dihydro-3,6-diphenacyl-2,2,5,5-tetramethylpirazine-1,4-dioxide (11). *A.* Pyrazine **1b** (1 g, 5 mmol) was added to a stirred solution of phenyllithium prepared from bromobenzene (1.1 mL, 10 mmol) and lithium (0.14 g, 20 mmol) in 20 mL of abs. ether. The reaction was carried out under an argon atmosphere. Agitation at the boiling temperature was continued for 3 h, then the reaction mixture was cooled and a solution of ethylbenzoate (1.5 mL, 10 mmol) in abs. ether (5 mL) was added dropwise with agitation. The stiring and boiling were continued for 1 h, then 20 mL of water was added. The ether layer was separated and discarded. The aqueous layer was washed with ether (3×20 mL), acidified to pH 5 with 10 % aqueous HCl, and extracted with $CHCl_3$ (3×20 mL). The extract was dried with $MgSO_4$, filtered and evaporated. The mixture of compounds **10** and **11** was partitioned chromatographically on a silica gel column with $CHCl_3$ as the eluent. Compound **10** was eluted first. ^1H NMR ($CDCl_3$), δ: 1.68 (s); 1.74 (s); 1.85 (s, 12 H, 2,5-$(CH_3)_2$); 2.20 (s, 3 H, 3-CH_3, form **B**); 2.22 (s, 3 H, 3-CH_3, form **A**); 4.08 (s, 2 H, $-CH_2$, form **A**); 5.61 (s, 1 H, −CH=, form **B**); 7.4 (m, 5 H, C_6H_5); 14.26 (s, 1 H, OH, form **B**). Further elution afforded compound **11**. ^1H NMR ($CDCl_3$), δ: 1.76 (s); 1.81 (s); 1.86 (s); 1.91 (s, 12 H, 2,5-Me_2); 4.12 (s); 4.13 (s, 2 H, $-CH_2-$, forms **A** and **B**); 5.66 (s, 1 H, −CH=, forms **B** and **C**); 7.4—8.0 (m, 10 H, 2 Ph); 14.21 (s); 14.30 (s, 1 H, forms **B** and **C**).

B. A mixture of pyrazine **1b** (0.5 g, 2.5 mmol), 0.6 g of an 80 % suspension of NaH in silicon oil (20 mmol), and ethylbenzoate (0.8 mL, 5.4 mmol) in abs. THF was stirred and boiled for 20 h, then cooled and poured into 20 mL of water. The aqueous solution was extracted with ether (3×20 mL), the extract was dried with $MgSO_4$, and the solution was evaporated. Compound **11** was purified chromatographically on a silica gel column, eluting first with ether, and then with chloroform—methanol (25:1).

1-Hydroxy-1,2,3,6-tetrahydro-3,3,5,6,6-pentamethyl-2-spiro-(4',5'-dihydro-3'-phenylisooxazolo)pyrazine-4-oxide (12). A solution of pyrazine **10** (0.4 g, 1.32 mmol), $NH_2OH \cdot HCl$ (0.46 g, 6.6 mmol), and MeONa (0.22 g, 4.0 mmol) in 20 mL methanol was kept at 20 °C for 3 days and then evaporated. The residue was diluted with 5 mL of water, and the precipitate of compound **12** was collected by filtration, washed with water and dried. ^1H NMR (DMSO-d_6), δ: 1.31 (s, 3 H); 1.36 (s, 3 H); 1.47 (s, 3 H); 1.56 (s, 3 H, 3,6-Me_2); 1.98 (s, 3 H, 5-Me); 3.65 (s, 2 H, $-CH_2-$); 7.45 (m, 3 H); 7.65 (m, 2 H, Ph); 8.56 (s, 1 H, N—OH). ^{13}C NMR (DMSO-d_6), δ: 15.37 (5-Me); 19.90, 21.07, 25.85, 27.00 (3,6-Me_2); 62.16 (C(6)); 72.67 (C(3)); 105.23 (C(2)); 126.30, 128.75, 129.28, 129.93 (Ph); 144.95 (C(5)); 155.62 (C(3')). The signal of the C(4') atom is masked by the signal of the solvent.

1,2,3,6-Tetrahydro-3,3,5,6,6-pentamethyl-2-spiro-(4',5'-dihydro-3'-phenylisooxazolo)pyrazine-4-oxide-1-oxyl (13). A suspension of compound **12** (0.2 g) with MnO_2 (2 g) in a $CHCl_3$—MeOH mixture (10 mL, 1:1) was agitated for 20 min at 20 °C. The excess oxidant was filtered off, and the solution was evaporated. Compound **13** was purified chromatographically on a silica gel column with the $CHCl_3$—MeOH system (30:1) as the eluent.

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