Reaction of 1,3-Disubstituted Acetone Derivatives with Pseudohalides: A Simple Approach to Spiro[4.4]nonane-Type Bis-Oxazolidines and -Imidazolidines (Bicyclic Carbamates, Thiocarbamates, Ureas, and Thioureas)

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Dedicated to Professor Klaus Peseke on the occasion of his 60th birthday

Keywords: Heterocycles / Carbohydrates / Imidazolidines / Oxazolidines / Spiro[4.4]nonanes

Prochiral 1,3-dihydroxyacetone forms racemic oxazolidine- and oxazoline-type spiro[4.4]nonanes upon reactions with potassium (thio)cyanate and cyanamide. In contrast, 1,3-diaminoacetone yields only the corresponding spiro-bisimidazolidinethione under similar conditions together with monocyclic by-products, but the spiro-bisimidazolidinone is accessible by reaction of 1,3-dichloroacetone with urea. The resolution of the racemic spiro-bisoxazolidinethione **2a** was achieved by using brucine as the resolving agent.

Introduction

Aldoses are known to form glyco-oxazolidinones by a one-step reaction with potassium cyanate in buffered aqueous solution.[1] The analogous glyco-oxazolidinethiones are obtained when aldoses react with potassium thiocyanate in strongly acidic media.[2] Amino sugars, like 2-amino-2-deoxy-D-glucose, can also be transformed into the corresponding 1,2-imidazolidin-2′-one derivatives by treatment with potassium cyanate or aryliso(thio)cyanates.[3] Encouraged by these results we and others extended our investigations towards common ketohexoses like D-fructose and L-sorbose.[4] Complex product mixtures of glycosylamine-based cyclic carbamates with either annulated or spiro orientated oxazolidinone functions were found in the reaction with potassium cyanate. However, when potassium thiocyanate was used, compounds bearing a new structural motif became the main product: open-chain bis-thiocarbamates with spiro orientated oxazolidinethione rings. These spiro compounds were usually obtained as diastereomeric mixtures that could be separated by column chromatography. We now report on the behaviour of the simplest ketose, 1,3-dihydroxyacetone, and the closely related 1,3-diamino- and 1,3-dichloroacetone in the reaction with pseudohalides like cyanate, thiocyanate or cyanamide.

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Results and Discussion

Treatment of 1,3-dihydroxyacetone (**1**) with potassium thiocyanate gave the new racemic spiro-bisoxazolidine-2-thione **2a** in 80% yield. Isolation was facilitated by the fact that the compound was directly obtained as a nice crystalline material from the reaction mixture. The related transformations of **1** with potassium cyanate or cyanamide gave the racemic mixtures of the dissymmetric spiro[4.4]nonane derivatives **3a** and **4a**, respectively, although the yields were considerably lower. A higher yield of **3a** was obtained by treatment of **2a** with hydrogen peroxide, according to the method of Zemplén et al.[5]

For further characterization, and in order to examine the synthetic potential of these compounds, **2a**, **3a**, and **4a** were acetylated under standard conditions to yield **2b**, **3b**, and **4b**, respectively.[6]

It was interesting to note that a tautomerization of the heterocyclic ring system occurred during the acylation of **4a**. Whereas the NMR spectra of **4a** strongly indicate oxazoline-type rings with *endo*-cyclic double bonds, the tetraacetate **4b** contains oxazolidine rings with *exo*-cyclic double bonds. This is confirmed by NMR spectroscopy, which shows two different sets of signals for the acetyl groups in **4b**.

In order to further explore the synthetic properties we attempted to alkylate **2a**. The spiro-bisoxazolidine-2-thione **2a** was treated with *o*-chlorobenzyl chloride to give bis-alkylated **5**. Again we observed a tautomerization, but this time from the oxazolidine towards the oxazoline system. This is due to the fact that the sulfur is more nucleophilic than the ring nitrogen and is in accordance with the results of Pintér et al.,[7] who observed similar *S*-benzylated products when alkylating α-D-glucofurano[1,2-d]oxazolidine-2′-thione.

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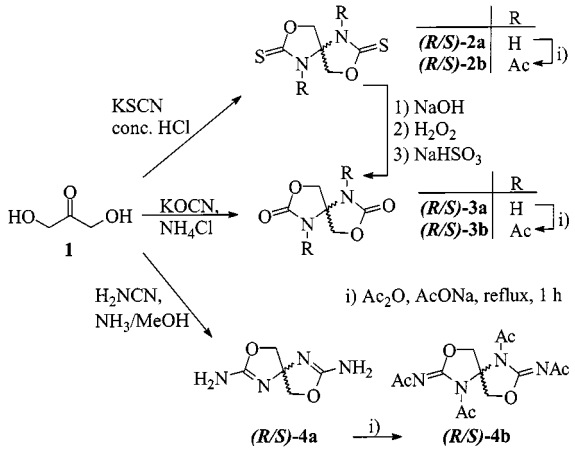
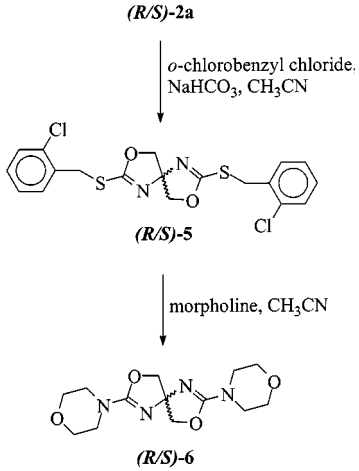


Scheme 1. Synthesis of *rac*-**2a**–**b**, *rac*-**3a**–**b**, and *rac*-**4a**–**b**

Since the *o*-chlorobenzyl thiolate group is known as a good leaving group in nucleophilic substitution reactions, compound **5** provides the opportunity to obtain access to a wide range of 2-substituted oxazoline derivatives. For example, we were able to substitute the thiolate by a morpholino group to obtain **6** as depicted in Scheme 2.

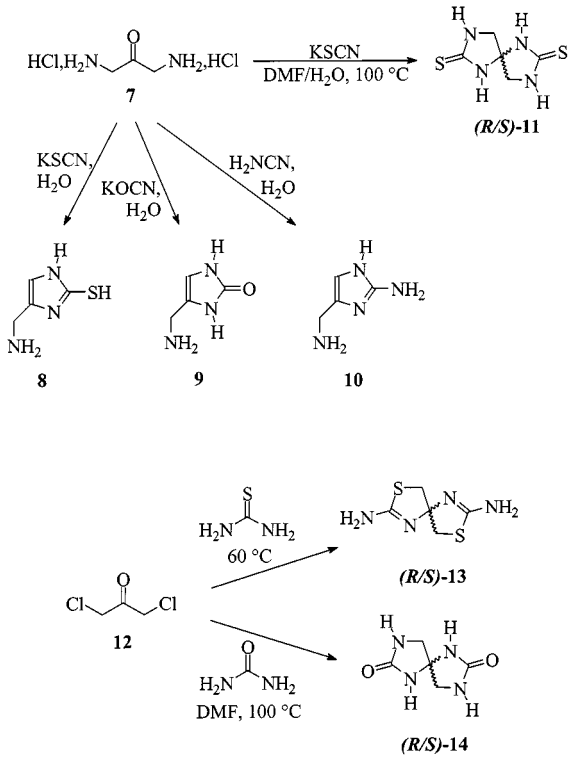


Scheme 2. S-Alkylation and subsequent nucleophilic substitution

Initial attempts to access spiro-bisimidazolidin-2-(thi)ones by treating 1,3-diaminoacetone[8] (**7**) with an excess of potassium (thio)cyanate in aqueous solution merely led to the monocyclic derivatives 4-aminomethyl-1*H*-imidazol-2-thiol (**8**) and 4-aminomethyl-1,3-dihydroimidazol-2-one (**9**) as described in the literature.[9][10] The analogous reaction with cyanamide yielded the diaminoimidazole derivative **10** in 36% yield.

After careful variation of the reaction conditions we were finally able to isolate the desired spiro-annulated bicyclic thiocarbamate. The 1,3,6,8-tetraazaspiro[4.4]nonane-2,7-dithione (**11**) was obtained upon stirring 1,3-diaminoacetone and potassium thiocyanate at 100°C for one hour in an *N*,*N*-dimethylformamide/water mixture.

However, the reaction with potassium cyanate and cyanamide still failed. For this reason we looked for other ways to synthesize analogous compounds with an imidazolidine skeleton. In 1947 Harley-Mason[11] described the synthesis of thiazoline compound **13** from 1,3-dichloroacetone and thiourea. Since no spectroscopic data were given for this compound we repeated this synthesis and were able to confirm the spiro-bisthiazoline structure by NMR spectroscopy. When we extended this reaction to the use of urea instead of thiourea under modified conditions we obtained the 1,3,6,8-tetraazaspiro[4.4]nonane-2,7-dione (**14**) in 39% yield rather than the initially expected **4a** (Scheme 3). This indicates again the strong tendency of the sulfur to avoid carbon–sulfur double bonds, in comparison to oxygen, thus leading to a much higher nucleophilicity of the sulfur.



Scheme 3. Synthesis of *rac*-**11**, *rac*-**13**, and *rac*-**14**

All of the described spiro-nonane derivatives are C_2-symmetric and are therefore chiral. Since there is no element of stereochemical control involved in the synthesis they are all obtained as racemates. Pope and Whitworth[12] described a classical route for the resolution of a racemic spiro-bishydantoin using (–)-brucine as the optically active base. Inspired by the similarity of this hydantoin and our systems we adapted this method for the resolution of *rac*-**2a**. (–)-Brucine was added to an ethanolic solution of *rac*-**2a**, leading to two adducts of each system containing a spiro compound and brucine. These could be separated by fractional crystallization. The adducts were cleaved by simple filtration on silica gel to afford the enantiomers with good optical purity.

From the laevorotatory enantiomer of **2a** single crystals, which seemed suitable for X-ray analysis, could be obtained by crystallization from ethanol. Unfortunately, slow decomposition was observed during measurement, probably due to loss of co-crystallized ethanol (1 molecule). The pre-

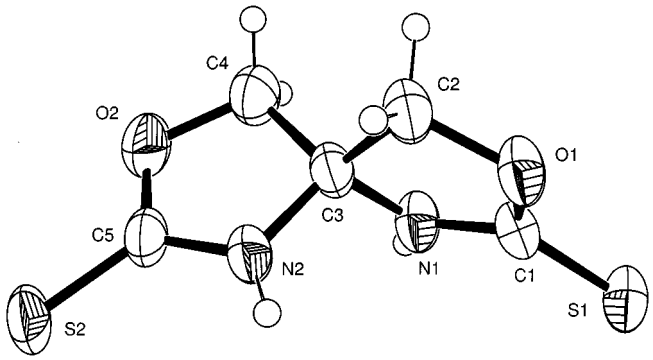


Figure 1. ORTEP plot of *rac*-**2a**

liminary results obtained, and the observed Flack parameter, indicate an (*S*)-configuration for the laevarotatory enantiomer (−)-**2a**, but this proposal is not absolutely certain.

Unfortunately we were not able to resolve *rac*-**3a** or *rac*-**4a** by this method nor by acylating with optically pure carboxylic acids. However, we were able to obtain enantiomerically pure (−)-**3a** from the reaction of resolved (−)-**2a** with alkaline hydrogen peroxide. Unfortunately, no suitable crystals of (−)-**3a** could be obtained.

In the course of the X-ray studies of enantiomerically pure **2a**, *rac*-**2a** was investigated. Suitable crystals were obtained from water and studied at 293 K. The structure was solved by direct methods with the SHELXS-97 program[13a] and refined with SHELXL-97.[13b] The refinement was performed on F^2 for all reflections. The validated threshold $F > 2\sigma(F)$ was used to calculate R_{obsd} only. All atoms, including hydrogens introduced at theoretical positions using the AFIX option, were refined. Table 1 gives the relevant crystallographic data of *rac*-**2a**. An ORTEP equivalent illustration of the compound, including the numbering scheme, was obtained with PLATON96[14] and is presented in Figure 1.

Table 1. Crystallographic data for *rac*-**2a**[a][13]

Molecular formula	$C_5H_6N_2O_2S_2$
Formula weight	190.24
Crystal dimensions [mm]	0.6 × 0.5 × 0.3
Melting point [°C]	206
Crystal system	monoclinic
Space group	$P2_1/c$
Cell dimensions:	
a [pm]	689.9(1)
b [pm]	1196.5(1)
c [pm]	931.9(1)
β [deg]	92.05(1)
V [pm^3]	768.8(2)·10^6
Z	4
F(000)	392
Calculated density, D_x [g·cm^{-3}]	1.6438 (3)
μ [cm^{-1}]	5.904
λ (Cu-K_α) [pm]	154.178
2θ range [deg]	6.02−76.32
Reflections measured	3444
Symmetry independent reflections	1609
Reflections with $F > 2\sigma(F)$	1470
Number of refined parameters	107
Ratio of valued reflections to parameters	13.7
Final residue factors *R*	
$R_{1(obsd)}$	0.062
$wR_{2(all)}$	0.173
$wR_{2(obsd)}$	0.168
Goodness of fit *S*	
S_{all}	1.11
S_{obsd}	1.11
Diffractometer	Enraf−Nonius CAD4

[a] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-133888. Copies of the data can be obtained free of charge from the following address: The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Conclusion

We have demonstrated that readily available 1,3-disubstituted acetone derivatives can be easily transformed into spiro-bisoxazolidine and spiro-bisimidazolidine derivatives by reaction with inexpensive pseudohalides. The resulting C_2-symmetric heterocyclic compounds are obtained as racemates. In the case of **2a** this racemic mixture could be resolved using brucine as a resolving agent. The chemical nature of the resulting spiro[4.4]nonane system can be tailored by altering the pseudohalide used in the synthesis. Therefore, the sulfur-containing derivatives seem to be especially promising candidates for further modification, as we have shown by alkylation and substitution reactions.

Experimental Section

General Remarks: All solvents were purified by standard procedures. Dihydroxyacetone was purchased from Aldrich. Products were purified, if necessary, by column chromatography on silica gel 60 F_{254} (0.063−0.200 mm or 0.040−0.063 mm). − Thin-layer chromatography was performed on aluminium TLC-layers (silica gel 60 F_{254}) from Merck. Detection was achieved by treatment with 10% sulfuric acid and heating with a heat-gun. − NMR-spectra were recorded on a Bruker AM 300 (^{1}H NMR = 300.1; ^{13}C NMR = 75.8 MHz) or on a Bruker AMX R 500 (^{1}H NMR = 500.1; ^{13}C NMR = 125.8 MHz) spectrometer. Chemical shifts are reported on the δ scale [ppm] relative to residual nondeuterated solvent signals in [D_6]DMSO, $CDCl_3$, or D_2O as internal standards. − Mass spectra were taken on a Finnigan MAT 212 with datasystem SS 300 and a Finnigan MAT 95 (high resolution mass spectrometry, HR MS) using chemical ionisation with isobutane as the reactant gas. − Melting points were determined with a hot-stage microscope SM-Lux from Leitz and are not corrected. − Specific optical rotations were measured on a Perkin−Elmer Polarimeter (241 MC or 343) in a 1 dm cell.

Acetylations − General Procedure: The compounds were refluxed in acetic anhydride together with sodium acetate for one hour. After cooling to room temperature the solution was poured into ice/water and extracted with dichloromethane. The organic layer was treated with charcoal and evaporated to dryness. Purification of the residue by column chromatography yielded the acylated product.

1,6-Dioxo-3,8-diazaspiro[4.4]nonane-2,7-dithione (2a): 6.3 g (70 mmol) of dihydroxyacetone and 17 g (0.17 mol) of potassium thiocyanate were dissolved in 34 mL of water and the solution was cooled to 0 °C. While stirring, 17 mL of concentrated hydrochloric

acid was added. After 1 h the precipitated crystals were filtered off and washed with cold water. Yield 10.0 g (52 mmol, 80%). TLC (ethyl acetate/ethanol/H_2O, 7:2:1): R_f = 0.9; M.p. 206°C. − ^{1}H NMR (300.1 MHz, [D$_6$]DMSO): δ = 4.59 (d, ^{2}J = −10.8 Hz, 2 H; CH_2), 4.71 (d, ^{2}J = −10.8 Hz, 2 H; CH_2), 10.95 (s, 2 H, NH). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 76.70, 80.52, 187.54. − MS (CI, isobutane); *m/z* (%): 191 (100) [MH^+]. − $C_5H_6N_2O_2S_2$ (190.2): calcd. C 31.58, H 3.15, N 14.73; found C 31.24, H 3.06, N 14.36.

3,8-Diacetyl-1,6-dioxo-3,8-diazaspiro[4.4]nonane-2,7-dithione (2b): The general acetylation procedure was applied to **2a** (1 g, 5.2 mmol) and gave **2b** (0.52 g, 1.9 mmol, 37%). TLC (toluene/ethyl acetate, 1:1): R_f = 0.79; M.p. 192°C. − ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.70 (s, 6 H; CH_3), 4.66 (d, ^{2}J = −11.4 Hz, 2 H; CH_2), 4.91 (d, ^{2}J = −11.4 Hz, 2 H; CH_2). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.58, 74.49, 84.94, 171.65, 186.38. − MS (CI, isobutane); *m/z* (%): 275 (100) [MH^+]. − $C_9H_{10}N_2O_4S_2$ (274.3): calcd. C 39.40, H 3.60, N 10.22; found C 39.07, H 2.97, N 10.04.

1,6-Dioxo-3,8-diazaspiro[4.4]nonane-2,7-dione (3a). − Method A: 2.0 g (11 mmol) of **2a** was suspended in 50 mL of water and diluted with 20 mL of NaOH (1 N). 9 mL of hydrogen peroxide (30%) was added dropwise to the clear solution at 5°C. Sulfur was filtered off after 1 h and the remaining peroxide was destroyed with sodium hydrogen sulfite solution (37%). At pH 7−8 the concentrated solution was filtered through silica gel (ethyl acetate/ethanol/H_2O, 7:2:1) and evaporated to dryness. Yield 82 mg (4.9 mmol, 44%). **Method B:** 2 g (11 mmol) of dihydroxyacetone, 2 g (25 mmol) of potassium cyanate, and 1.35 g (25 mmol) of ammonium chloride were dissolved in 6 mL water and the solution heated to 60°C. After 6 h the mixture was concentrated together with 4 g of silica gel. Column chromatography (ethyl acetate/ethanol/H_2O, 7:2:1) yielded 90 mg (5 mmol, 22%) of the desired product. TLC (ethyl acetate/ethanol/H_2O, 7:2:1): R_f = 0.75; M.p. 158°C (decomposition). − ^{1}H NMR (300.1 MHz, [D$_6$]DMSO): δ = 4.27 (d, ^{2}J = −10.0 Hz, 2 H; CH_2), 4.38 (d, ^{2}J = −10.0 Hz, 2 H; CH_2), 8.74 (s, 2 H; NH). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 73.12, 73.64, 156.48. − MS (CI, isobutane); *m/z* (%): 159 (100) [MH^+]. − $C_5H_6N_2O_4$ (158.1): calcd. C 37.98, H 3.80, N 17.72; found C 38.23, H 3.98, N 17.61.

3,8-Diacetyl-1,6-dioxo-3,8-diazaspiro[4.4]nonane-2,7-dione (3b): 0.2 g (1.3 mmol) of **3a** was acetylated using the general procedure. Crystals of **3b** (0.24 g, 1 mmol, 79%) separated from ethanol. TLC (toluene/ethyl acetate, 1:1): R_f = 0.67; M.p. 160°C. − ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.38 (s, 6 H; CH_3), 4.40 (d, ^{2}J = −10.3 Hz, 2 H; CH_2), 4.65 (d, ^{2}J = −10.3 Hz, 2 H; CH_2). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.35, 69.89, 76.44, 152.59, 170.46. − MS (CI, isobutane); *m/z* (%): 243 (100) [MH^+]. − $C_9H_{10}N_2O_6$ (242.2): calcd. C 44.63, H 4.13, N 11.57; found C 44.67, H 4.19, N 11.31.

2,7-Diamino-1,6-dioxo-3,8-diazaspiro[4.4]nonane-2,7-diene (4a): 2.0 g (22 mmol) of dihydroxyacetone and 2 g (44 mmol) of cyanamide were dissolved in 10 mL of water. 1 mL of methanolic ammonia was added. After 6 h at 60°C the mixture was cooled to 5°C and kept at this temperature for 8 h. The resulting solid was filtered off. Recrystallization from methanol gave 0.9 g of **4a** (6 mmol, 27%). M.p. 178°C. − ^{1}H NMR (300.1 MHz, [D$_6$]DMSO): δ = 3.96 (d, ^{2}J = −8.5 Hz, 2 H; CH_2), 4.00 (d, ^{2}J = −8.5 Hz, 2 H; CH_2), 5.96 (s, 4 H; NH_2). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 76.97, 95.60, 160.53. − MS (CI, isobutane); *m/z* (%): 157 (100) [MH^+]. − $C_5H_8N_4O_2$ (156.1): calcd. C 38.46, H 5.13, N 35.90; found C 38.35, H 4.94, N 36.26.

2,7-Diacetimido-3,8-diacetyl-1,6-dioxo-3,8-diazaspiro[4.4]nonane (4b): Using the general procedure 0.5 g (3.2 mmol) of **4a** was acetylated. Yield 0.87 g (2.7 mmol, 85%). M.p. 135°C. − ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 2.28 (s, 6 H; CH_3), 2.55 (s, 6 H; CH_3), 4.38 (d, ^{2}J = −10.2 Hz, 2 H; CH_2), 4.75 (d, ^{2}J = −10.2 Hz, 2 H; CH_2). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 25.57, 26.43, 72.58, 78.62, 146.26, 170.54, 181.36. − MS (CI, isobutane); *m/z* (%): 325 (100) [MH^+]. − $C_{13}H_{16}N_4O_6$ (324.3): calcd. C 47.85, H 5.52, N 17.17; found C 48.02, H 5.72, N 17.07.

2,7-Di(2-chlorobenzylthio)-1,6-dioxo-3,8-diazaspiro[4.4]nonane-2,7-diene (5): 1 g (5.2 mmol) of **2a**, 1.7 g (10.5 mmol) of 2-chlorobenzyl chloride, and 1.8 g (21 mmol) of potassium bicarbonate were refluxed in 22 mL of acetonitrile and 3 mL of water for 5 h. After 12 h at room temperature the residue was filtered off and washed with water. Recrystallization from chloroform yielded 0.7 g (1.5 mmol, 30%) of **5**. M.p. 124°C. − ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 4.20 (d, ^{2}J = −9.3 Hz, 2 H; CH_2), 4.37 (d, ^{2}J = −13.2 Hz, 2 H; CH_2-aryl), 4.46 (d, ^{2}J = −13.2 Hz, 2 H; CH_2-aryl), 4.52 (d, ^{2}J = −9.3 Hz, 2 H; CH_2), 7.20−7.60 (m, 8 H; aryl). − ^{13}C NMR (75.6 MHz, $CDCl_3$): δ = 34.14, 78.54, 97.91, 126.82, 129.18, 129.64, 131.37, 134.28, 168.86. − MS (CI, isobutane); *m/z* (%): 440 (100) [MH^+]. − $C_{19}H_{16}Cl_2N_2O_2S_2$ (439.3): calcd. C 51.94, H 3.63, N 6.37; found C 51.65, H 3.75, N 6.01.

2,7-Dimorpholino-1,6-dioxo-3,8-diazaspiro[4.4]nonane-2,7-diene (6): Morpholine (3 mL, 3.4 mmol) was added to a solution of 0.5 g (1.14 mmol) of **5** in 10 mL of acetonitrile. After refluxing for 24 h the solution was allowed to cool to room temperature and the crystals that precipitated were filtered off. 80 mg (28 mmol, 24%) of **6** was obtained. M.p. 128−130°C. − ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 3.37 (m, 4 H; NCH_2-morpho), 3.64 (m, 4 H; OCH_2-morpho), 4.12 (d, ^{2}J = −8.9 Hz, 2 H; CH_2), 4.35 (d, ^{2}J = −8.9 Hz, 2 H; CH_2). − ^{13}C NMR (75.6 MHz, $CDCl_3$): δ = 45.28, 66.03, 78.93, 95.10, 161.46. − HR MS (CI, isobutane); $C_{13}H_{21}N_4O_4$ [MH^+]: calcd. 297.1563; found 297.1507.

(−)-1,6-Dioxo-3,8-diazaspiro[4.4]nonane-2,7-dithione [(−)-2a]: 0.5 g (2.6 mmol) of **2a** was dissolved in 250 mL of absolute ethanol. 2.0 g (5 mmol) of dried (−)-brucine (*very toxic!*) was added with vigorous stirring. Within 1 min crystallization occurred, after 15 min the mixture was filtered and the solid residue dried in vacuo. Column chromatography (ethyl acetate/ethanol/H_2O, 7:2:1) and concentration to dryness gave 135 mg of (−)-**2a** (0.7 mmol, 27%). TLC (ethyl acetate/ethanol/H_2O, 7:2:1): R_f = 0.9 (brucine remained on the column, R_f = 0); M.p. 195°C; $[\alpha]_D^{20}$ = −31 (*c* = 0.9, THF). − For ^{1}H-NMR and ^{13}C-NMR data see **2a**. − MS (CI, isobutane); *m/z* (%): 191 (100) [MH^+].

(+)-1,6-Dioxo-3,8-diazaspiro[4.4]nonane-2,7-dithione [(+)-2a]: After an additional 2 h at 5°C the filtrate from the above workup was filtered again and concentrated to its half volume at 30°C. Storage at 5°C for 8 h yielded another crop of the brucine/**2a** complex, which was filtered off and dried in vacuo. Column chromatography (ethyl acetate/ethanol/H_2O, 7:2:1) of the complex and recrystallization from ethanol gave 110 mg (0.6 mmol, 23%) of (+)-**2a**. TLC (ethyl acetate/ethanol/H_2O, 7:2:1): R_f = 0.9; M.p. 203°C (ethanol); $[\alpha]_D^{20}$ = +27 (*c* = 1.0, THF); *op* = 84%. − For ^{1}H-NMR and ^{13}C-NMR data see **2a**. − MS (CI, isobutane); *m/z* (%): 191 (100) [MH^+].

(−)-1,6-Dioxo-3,8-diazaspiro[4.4]nonane-2,7-dione [(−)-3a]: To a suspension of 0.25 g (1.3 mmol) of (−)-**2a** in 5 mL of H_2O and 2 mL of NaOH (1 N) was added 2 mL of hydrogen peroxide (30%) at 0°C. Precipitated sulfur was filtered off after 1 h, peroxides were destroyed with sodium hydrogen sulfite solution and the solution was concentrated to dryness. Column chromatography (ethyl acet-

ate/ethanol/H_2O, 7:2:1) of the residue yielded 63 mg (0.3 mmol, 25%) of (−)-**3a**. TLC (ethyl acetate/ethanol/H_2O, 7:2:1): R_f = 0.75; M.p. 152°C (decomposition); $[\alpha]_D^{20}$ = −38 (*c* = 0.7, DMSO). − For ^{1}H-NMR and ^{13}C-NMR data see **3a**. − MS (CI, isobutane); *m/z* (%): 159 (100) [MH^+].

4-Aminomethyl-1*H*-imidazol-2-ylamine Dihydrochloride (10): A solution of 1.0 g (5.6 mmol) of **7** and 0.25 g (6 mmol) of cyanamide in 5 mL of water was heated at 100°C for 1 h. The solution was evaporated to dryness and the residue extracted with diethyl ether. The insoluble residue was dissolved in water and treated with charcoal. Recrystallization from water afforded 0.30 g (1.6 mmol, 36%) of **10**. M.p. 182°C. − ^{1}H NMR (500.1 MHz, D_2O): δ = 4.12 (s, 2 H; CH_2), 6.92 (s, 1 H; NCH). − ^{13}C NMR (125.8 MHz, D_2O): δ = 33.44, 114.41, 118.86, 147.76. − MS (CI, isobutane); *m/z* (%): 113 (100) [MH^+ − 2 HCl]. − $C_4H_{10}Cl_2N_4$ (185.1): calcd. C 25.95, H 5.45, N 30.28; found C 25.63, H 5.82, N 29.93.

1,3,6,8-Tetraazaspiro[4.4]nonane-2,7-dithione (11): 1.0 g (5.6 mmol) of 1,3-diaminoacetone (**7**) and 1.63 g (16.8 mmol) of potassium thiocyanate were dissolved in 5 mL of *N*,*N*-dimethylformamide and 2 mL of water. The solution was heated for 1 h at 100°C. After cooling, the residue was filtered and the solid washed with water. 0.42 g (2.2 mmol, 39%) of white crystals were isolated. M.p. 215°C (decomposition). − ^{1}H NMR (300.1 MHz, [D_6]DMSO): δ = 3.54 (d, ^{2}J = −11.4 Hz, 2 H; CH_2), 3.69 (d, ^{2}J = −11.4 Hz, 2 H; CH_2), 8.30 (s, 2 H; NH), 9.07 (s, 2 H; NH). − ^{13}C NMR (75.6 MHz, [D_6]DMSO): δ = 55.68, 80.41, 180.49. − MS (CI, isobutane); *m/z* (%): 189 (100) [MH^+]. − $C_5H_8N_4S_2$ (188.2): calcd. C 31.90, H 4.28, N 29.76; found C 31.67, H 4.11, N 29.43.

2,7-Diamino-1,6-dithio-3,8-diazaspiro[4.4]nonane-2,7-diene (13):[11] 4.0 g (31.5 mmol) of 1,3-dichloroacetone and 5.1 g (67.3 mmol) of thiourea were heated slowly to 60°C. A violent exothermal reaction started and the temperature increased up to 220°C. The resulting yellow-brown residue was cooled and extracted with boiling ethanol. The residue was dissolved in 25 mL of water and boiled with charcoal. The hot filtrate was treated with ammonia. The precipitated product was filtered off. Recrystallization from water gave 4.4 g of **13** [23.4 mmol, 74% (78%)[11]]. M.p. 191°C (192−194°C).[11] − ^{1}H NMR (300.1 MHz, [D_6]DMSO): δ = 3.18 (d, ^{2}J = −10.7 Hz, 2 H; CH_2), 3.69 (d, ^{2}J = −10.7 Hz, 2 H; CH_2), 6.53 (s, 4H; NH_2). − ^{13}C NMR (75.6 MHz, [D_6]DMSO): δ = 44.29, 110.31, 158.94. − MS (CI, isobutane); *m/z* (%): 189 (100) [MH^+]. − $C_5H_8N_4S_2$ (188.2): calcd. C 31.90, H 4.28, N 29.76; found C 31.50, H 4.19, N 29.44.

1,3,6,8-Tetraazaspiro[4.4]nonane-2,7-dione (14): A solution of 1.0 g (7.9 mmol) of 1,3-dichloroacetone (**12**) and 1.42 g (23.6 mmol) of urea in 10 mL of *N*,*N*-dimethylformamide and 3 mL of water was heated to 100°C. After 1 h the mixture was cooled to 20°C and the precipitate was filtered off. The crude product was washed with cold methanol and dried in vacuo to give 0.48 g (3.1 mmol, 39%) of **14**. M.p. 204°C (decomposition). − ^{1}H NMR (300.1 MHz, D_2O): δ = 4.92 (d, ^{2}J = −11.0 Hz, 2 H; CH_2), 4.98 (d, ^{2}J = −11.0 Hz, 2 H; CH_2). − ^{13}C NMR (75.6 MHz, D_2O): δ = 77.60, 80.14, 162.26. − MS (CI, isobutane); *m/z* (%): 157 (100) [MH^+]. − $C_5H_8N_4O_2$ (156.1): calcd. C 38.46, H 5.16, N 35.88; found C 38.16, H 5.01, N 35.51.

Acknowledgments

We would like to thank Mrs. M. Rundshagen, Mrs. Dipl.-Ing. M. Ehmen, Mr. D. Neemeyer, and Mr. Dipl.-Ing. K.-H. Plate for performing the analytical work. Financial support from the Fonds der Chemischen Industrie, the Gesellschaft Deutscher Chemiker and the EG-Hochschulbüro, Hannover (Germany) is gratefully acknowledged.

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Received June 14, 1999
[O99345]