Metal Complexes of Functionalized Sulfur-Containing Ligands

Part XIX

Synthesis and Reactions of New Pyrroloisothiazoles

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Dedicated to Professor *Heinrich Nöth* on the occasion of his 75th birthday

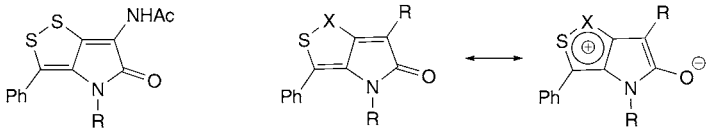
The title compounds were prepared starting from the dihydropyrrolones **4**–**6**. Nucleophilic displacement and ring closure yielded the 1*H*-pyrrolo[3,2-*c*]isothiazol-5(4*H*)-ones **8** and **10**. The fused systems formed salts with strong acids and electrophiles (**15**, **16**), as well as with bases. Oxidation led either to *S*(2)-oxides (**18a**, **20a**) or to the corresponding bicyclic sultams (**18b**, **20b**), depending on the reaction conditions. The sulfinamide **18a** was also obtained from the known 1,2-dithiolopyrrolone *S*-oxide **21** by a ring-opening/ring-closure reaction sequence. *O*-Methylation of **8** furnished the 'azafulvene' **17**. The oxidative addition of [Pt(η^2-C_2H_4)L_2] (**24a**: L = Ph_3P, **24b**: L = 1/2 dppf, **24c**: L = 1/2 (*R*,*R*)-diop) to **18a** and **20a** led to the *cis*-amido-sulfenato Pt complexes **25** and **26a**–**c**, respectively.

Introduction. – The natural antibiotics holomycin (**1**, R = H) and thiolutin (R = Me) have been known for a long time [1]. Thiolutin was found to suppress tumor-induced angiogenesis and may be of value in antitumor therapy [2].

Recently, we reported the synthesis and chemistry of differently substituted 1,2-dithiolopyrrolones of the general formula **2**, which are structurally related to the natural substances [3]. In spite of the disulfide partial structure, these heterocyclic compounds proved to be very stable due to marked resonance, so that the zwitterionic structure of **2** reflects their properties best, as corroborated by high dipole moments.

We describe here the synthesis and some reactions of 1*H*-pyrrolo[3,2-*c*]isothiazol-5(4*H*)-ones (**3**), which may also be regarded as 2-thia-1,4-diazapentalene derivatives. As aza-analogs of 1,2-dithiolo[4,3-*b*]pyrrol-5(4*H*)-ones **2**, these novel products represent stable cyclic sulfenamides thanks to mesomerism, as expressed by the resonance structure **3**.

Results and Discussion. – The synthesis started from the tetramic acid derivative (*Z*)-**4** [4]. With $MeNH_2$, nucleophilic displacement occurred selectively at the MeO group to furnish enamine **5** (*Michael*-type reaction). Upon reaction with a solution of Na_2S, the red sodium thiolate **7** was obtained. This salt could not be isolated in



1
Holomycin (R = H)
Thiolutin (R = Me)

2 X = S
3 X = NR

analytically pure form because of its tendency to be oxidized by air. After completing the oxidation in aqueous solution with I_2 or H_2O_2, the poorly soluble pyrroloisothiazole **8** was obtained in good yield. Similarly, the cyano analog **10** was prepared from (*E*/*Z*)-**6** [5] and H_2S in the presence of Et_3N, followed by oxidation with I_2.

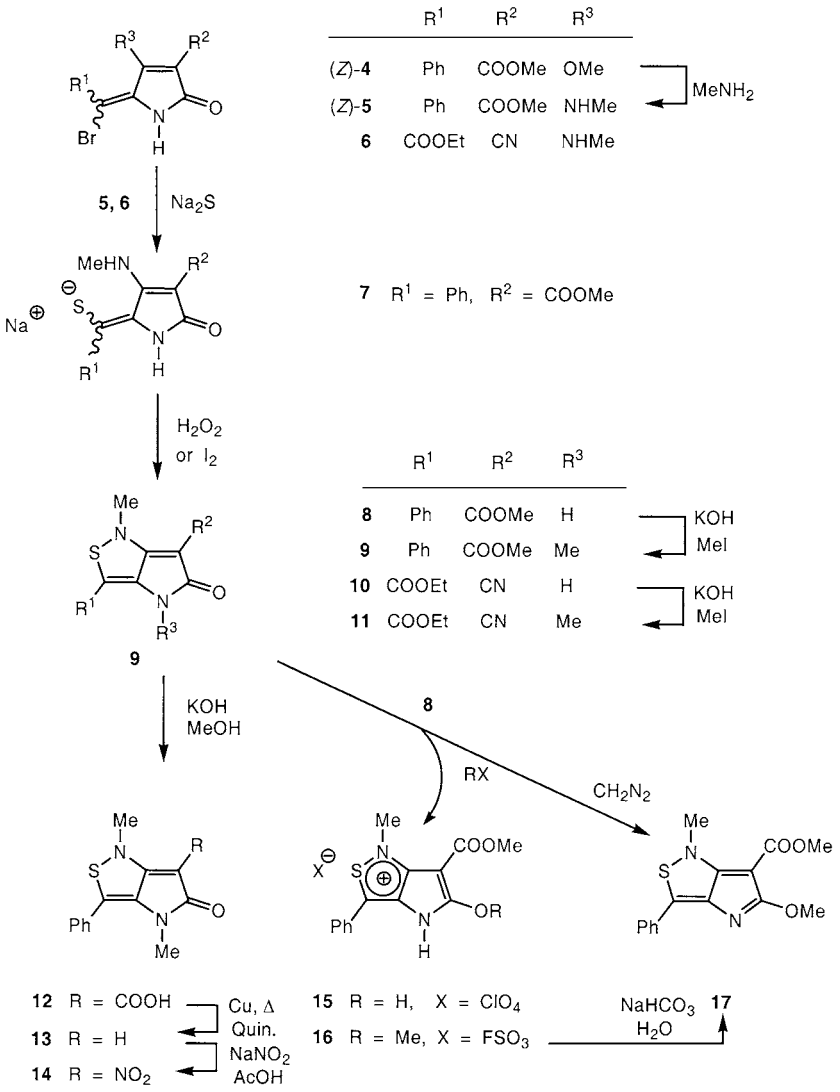
Due to considerable NH acidity, compounds **8** and **10** formed sparingly soluble K salts with 3N KOH in MeOH. The salts were stable for at least 24 h at room temperature in aqueous solutions and reacted with MeI to yield the corresponding *N*-methylated compounds **9** and **11**, respectively. The stabilities of **8** and **9** toward strong alkali, in contrast to other sulfenamides [6], opened the possibility to saponify the ester groups. While **8** was fully recovered after heating with methanolic KOH for 3 h, **9** was saponified under the same conditions to afford the carboxylic acid **12**. The latter was decarboxylated in the presence of Cu and quinoline at 150°. The resulting product **13** easily underwent electrophilic substitution in 6-position with $NaNO_2$ and AcOH to yield the nitro derivative **14**. Interestingly, and quite in contrast to **8** and **9**, compound **13** decomposed when dissolved in trifluoroacetic acid at room temperature, as well as in AcOH upon short heating, presumably due to cleavage of the sulfenamide bond and ensuing reactions [7]. However, the new heterocycles showed low basicity.

From compound **8** and $HClO_4$ in AcOH, the crystalline perchlorate **15** was obtained, which hydrolyzed immediately upon contact with H_2O. Analogously, reaction of **8** with methyl fluorosulfonate gave the pyrroloisothiazolium salt **16**, the hydrolysis of which ($NaHCO_3$) led to the imino ester **17**, which may be regarded as an 'azafulvene' [8], and which was also obtained by reacting **8** with diazomethane in nearly quantitative yield. The preferential *O*-methylation of lactams is usually interpreted as a hint of the weakened double-bond character of the C=O group due to resonance [9].

The pyrroloisothiazolones **8**–**10** were oxidized stepwise with H_2O_2 in AcOH at ambient temperature to afford first the corresponding sulfinamides **18a**–**20a**, and then the sulfonamides **18b**–**20b**, depending on reaction time. Compound **18a** has been prepared earlier by '*S*/*N*-exchange' with $MeNH_2$ in the presence of I_2 from **21** [3]. The sulfinamides **18a**–**20a** underwent thermal disproportionation at temperatures just below their melting points. Their mass spectra showed both the $M^{+\cdot}$ and $[M-O]^+$ signals. The most prominent peak in the MS fragmentation of **8**/**9** and **18a**/**19a** was that of the thiobenzoyl ion (*m*/*z* 121). MS fragmentation of **18b** followed another pathway, the $[M-SO_2]^+$ fragment being the predominant peak.

Similar to the parent compound, **18a**/**18b** formed sparingly soluble salts with KOH in MeOH, but reacted with MeI to the corresponding *N*-methylated derivatives **19a**/**19b**. In aqueous solution, the K salt of **18a** decomposed within 1 h at room temperature. However, the potassium salt of **18b** was found to be stable in aqueous solution at room

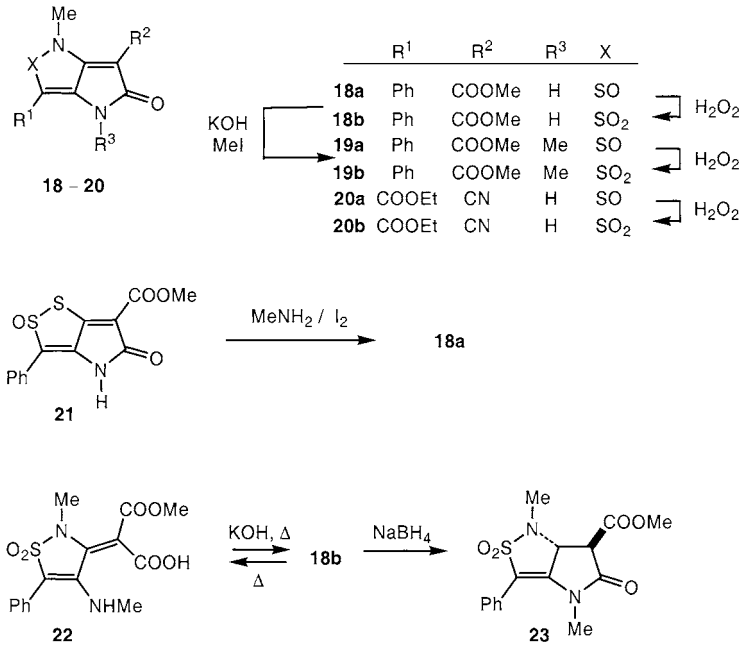
Scheme 1



temperature for 3 d. Upon heating with strong alkali, **18b** was reversibly transformed to the sultam **22** by cleavage of the lactam ring. Differing in basicity and nucleophilicity from the parent compounds (X = S), the *S*-oxides **18a**/**18b** did not react with $HClO_4$ or methyl fluorosulfonate. Both compounds were converted to the *N*-methylated derivatives **19a**/**19b** exclusively upon treatment with CH_2N_2.

The different degrees of resonance stabilization in the pyrroloisothiazolones mentioned above are mirrored in the ^{1}H-NMR chemical shifts of the *N*-Me H-atoms of the isothiazole ring. Whereas ^{1}H-NMR signals in *N*-methylated open-chain or cyclic

Scheme 2



sulfenamides are usually found below 3.0 ppm [10], the corresponding resonances in the spectra of **8**, **9**, and **14** appeared between 4.06 and 4.21 ppm. This downfield shift may be attributed to a strongly deshielding effect caused by a positive partial charge on the N-atom, as depicted in the zwitterionic resonance structure **3**. As expected, the *N*-Me ^{1}H-NMR signal of the perchlorate **15** was found in the same range (4.05 ppm). However, there was an exception: in the ^{1}H-NMR spectrum of **13**, the *N*-Me signal appeared at 3.48 ppm. This strong upfield shift relative to the corresponding signals of **8** and **9** can be rationalized by the loss of the acceptor substituent in 6-position, which reduces the resonance energy and, consequently, the chemical stability of **13**. The lesser degree of resonance stabilization of **18a**/**19a** in comparison to **8/9** – as apparent also from the chemical behavior – was also reflected by the *N*-Me signals in the NMR spectra (a shift to higher field of more than 0.4 ppm). The assignments of the *N*- *vs. O*-Me ^{1}H-NMR signals were achieved by CH-COSY measurements.

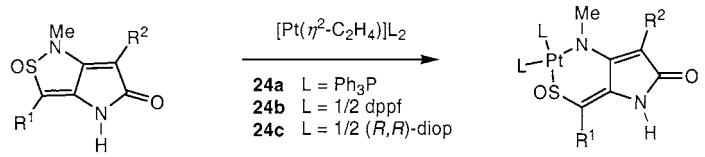
The longest-wavelength UV-absorptions of **8** and **9** in MeOH, MeCN, and dioxane showed 'negative solvatochromy'. Such behavior is in agreement with a marked dipolar character [11]. In contrast, solvatochromy was observed neither in the UV spectra of the nitriles **10** and **11**, nor in those of **18** and **19**.

The sulfenamides **8** and **9** were reduced by $NaBH_4$. The red color of the solutions obtained indicated the formation of sodium thiolate **7** or its *N*-methylated analog, respectively. Oxidative recyclization to **8** and **9** was promoted by air (O_2) or I_2. Likewise, **8** and **9** were obtained by executing the same reduction/oxidation sequence with **18a**/**19a**. Analogously, **20a** was reduced to **10**. Boronhydride reduction of the more-

stable bicyclic sulfonamide **18b** afforded only the *trans*-dihydrogenated sultam derivative **23**. As expected, hydrogenation took place at the activated C(6)=C(6a) double bond. The *N*-Me signal was shifted markedly upfield relative to that of the starting compound **18b**. NOE Experiments confirmed the neighbourhood of the *N*-Me group and H–C(6a). The latter coupled with H–C(6) ($J = 9$ Hz), and the signal for H–C(6) disappeared upon H/D-exchange. In the IR spectrum, hydrogenation caused a shift of the two C=O absorption bands of **18b** at 1720 and 1710 cm^{-1} to shorter wavelengths (1760 and 1735 cm^{-1}).

Previous work in our laboratory with $[(Ph_3P)_2Pt(\eta^2-C_2H_4)]$ (**24a**) showed that it is possible to activate N–S(O) bonds in *N*-(alkyl- and arylsulfinyl)phthalimides to yield sulfinato platinum(II) complexes [12]. This paper extends the study of Pt complexes formed between **24a** (L = Ph_3P), **24b** (L = 1/2 dppf), or **24c** (L = 1/2 (*R*,*R*)-diop[1]), and **18a** or **20a**, respectively. Slowly heating **18a** or **20a** with **24a–c** in toluene at 100° (**18a**) or 65° (**20a**), respectively, afforded the complexes **25** and **26a–c** *via* insertion of Pt^0 into the N–S(O) bond. When chiral **24c** was treated with 2 equiv. of **20a**, two products in a 1:1 ratio were observed by ^{31}P-NMR spectroscopy. Their structures were assigned on the basis of spectral similarities as the diastereoisomers (R^*_{SO},*R*,*R*)-**26c**; no diastereoselectivity was observed in this *thermodynamically* controlled reaction.

Scheme 3



18a R^1 = Ph, R^2 = COOMe
20a R^1 = COOMe, R^2 = CN

25 L = 1/2 dppf, R^1 = Ph, R^2 = COOMe
26a L = Ph_3P, R^1 = COOEt, R^2 = CN
26b L = 1/2 dppf, R^1 = COOEt, R^2 = CN
26c L = 1/2 (*R*,*R*)-diop, R^1 = COOEt, R^2 = CN

The ^{31}P-NMR spectra of **25** and **26a**,**b** display the typical *AB* pattern for *cis*-amido-sulfenato platinum(II) complexes [12] with two *doublets* and ^{195}Pt satellites (^1J(Pt,P) = 2217–2490 Hz for P *trans* to S(O), and ^1J(Pt,P) = 3588–3646 Hz for P *trans* to N). This is in accordance with our previous observation that the sulfenato group in *cis*-[(dppe)Pt[S(O)C_4H_9](Nphth)][1]) exhibits a stronger '*trans*-influence' than the amido group [12]. The ^{31}P-NMR spectrum of (R^*_{SO},*R*,*R*)-**26c** displays two well-defined *AB*-spin patterns and the expected ^{195}Pt/^{31}P couplings. In the ^{1}H-NMR spectra of **26a–c**, the signals of the *N*-Me H-atoms are shifted upfield by 0.7 ppm compared with those of **20a**. In **26a–c**, the ^4J(P,H) coupling constants are 3.4–3.9 Hz. Moreover, the ^{13}C-NMR resonances of the C-atoms directly bonded to the S-atom, and of the sp^2 C-atoms bonded to the N-atoms are shifted upfield by 2.4–2.9 and 4.0–3.3 ppm, respectively, compared with those of **20a**. In contrast, a significant downfield shift of *ca.* 14 ppm is observed for the Me C-atom bonded to the amido N-atom.

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[1]) Abbreviations: dppf = 1,1′-bis(diphenylphosphino)ferrocene, diop = 4,5-bis[(diphenylphosphino)methyl]-2,2-dimethyl-1,3-dioxolane, dppe = 1,2-bis(diphenylphosphino)ethane, Nphth = *N*-phthalimide.

The IR spectra of **25** and **26a–c** exhibit weak ν(SO) bands at 980–1000 cm^{-1}, in agreement with those of other sulfenato complexes [12][13]. These IR bands are shifted by *ca.* 65–85 cm^{-1} to lower wavenumbers relative to those of the corresponding sulfinamides **18a** and **20a**, respectively. Analogously, shifts of the C=O (**25**) and the C≡N (**26a–c**) IR absorptions to lower wavenumbers are observed.

In conclusion, we have demonstrated that it is possible to activate a N–S(O) bond in the pyrroloisothiazolone *S*-oxides **18a** and **20a** by oxidative addition of the Pt^0 complexes **24a–c**. The products isolated and characterized were the *cis*-amido-sulfenato platinum(II) complexes **25** and **26a–c**. Compared with the analogous reactions of the isoelectronic 1,2-dithiolo[4,3-*b*]pyrrolone *S*-oxide (**21**) [14] with Pt^0 complexes, higher reaction temperatures were necessary.

Experimental Part

General. M.p.: *Büchi* melting-point apparatus; uncorrected. IR Spectra: *Perkin-Elmer PARAGON 1000*; KBr pellets; in cm^{-1}. UV/VIS Spectra: *Kontron Uvikon-810 Anakomp-220* or *Perkin-Elmer Lambda-20*; λ_{max} in nm (log ε), in MeOH soln., unless stated otherwise. ^{1}H-NMR Spectra: *JEOL GSX-400*; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz, solvent A = (D_6)DMSO, B = CD_2Cl_2, unless indicated otherwise. ^{13}C-NMR Spectra: *JEOL EX-400*; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz, solvents A or B, unless indicated otherwise. ^{31}P-NMR Spectra: *JEOL GSX-270*; δ in ppm rel. to 85% aq. H_3PO_4 as external standard, *J* in Hz, solvent B, unless indicated otherwise. MS: *Hewlett-Packard 5989A*, 70 eV. Flash chromatography (FC): 250 ml column (*Baker*), silica gel (0.040–0.063 mm; *Merck*). Elemental analysis: *Heraeus CHNO-Rapid Analyser* or carried out by *I. Beetz*, *Mikroanalytisches Laboratorium*; Kronach, Germany.

*Methyl (Z)-5-[(Bromo)(phenyl)methylene]-2,5-dihydro-4-(methylamino)-2-oxo-1*H*-pyrrole-3-carboxylate* (**5**). A soln. of 1.01 g (3 mmol) of (*Z*)-**4** [4] in MeOH (25 ml) was heated with 0.5 ml of an aq. soln. (40%) of $MeNH_2$ at 50° for 5 min. The volatile components were removed under reduced pressure, and the residue was recrystallized from MeOH. Yield: 670 mg (66%). Yellow crystals. M.p. 170°. UV: 325 (4.312), 227 (3.981). IR: 3360, 3240, 3020, 2955, 1740, 1715, 1670, 1595. ^{1}H-NMR ($CDCl_3$): 7.43 (*s*, 5 H); 3.85 (*s*, 3 H); 2.28 (*d*, *J* = 5.1, 3 H). MS: 338/336 ($M^{+\bullet}$). Anal. calc. for $C_{14}H_{13}BrN_2O_3$ (337.17): C 49.87, H 3.89, N 8.31; found: C 49.93, H 3.99, N 8.37.

Sodium (1,5-dihydro-4-(methoxycarbonyl)-3-(methylamino)-5-oxopyrrol-2-ylidene)phenylmethanethiolate (**7**). A soln. of 1.35 g (4 mmol) of **5** and 1.2 g (5 mmol) of $Na_2S \cdot 5\ H_2O$ in MeOH (20 ml) was stirred at r.t. for 12 h. The red soln. obtained was evaporated *in vacuo* to dryness. The soln. of the residue in AcOEt (25 ml) was filtered through a column with silica gel and evaporated. The salt was obtained in almost pure form. Yield: 930 mg (75%). Orange crystals. UV: 332 (3.916), 294 (3.876), 226 (4.191). IR: 3420, 2980, 2940, 1685, 1575. ^{1}H-NMR (A): 12.15 (*d*, *J* = 5.1, 1 H); 7.38 (*s*, 1 H); 7.30 (*s*, 5 H); 3.65 (*s*, 3 H); 2.98 (*d*, *J* = 5.1, 3 H).

*Methyl 4,5-Dihydro-1-methyl-5-oxo-3-phenyl-1*H*-pyrrolo[3,2-c]isothiazole-6-carboxylate* (**8**). An aq. soln. (5 ml) of H_2O_2 (3%) was added dropwise to a stirred soln. of 0.93 g (3 mmol) of **7** in H_2O (20 ml). After 10 min, the precipitate was collected and recrystallized from MeOH. Yield: 575 mg (65%). Yellow crystals. M.p. 282–284° (MeOH). UV: 365 (4.226), 330 (3.825), 258 (sh), 243 (3.907). IR: 3120, 3000, 2940, 1660, 1570. ^{1}H-NMR (A): 10.36 (*s*, 1 H); 7.58–7.43 (*m*, 5 H); 4.08 (*s*, MeN); 3.69 (*s*, MeO). ^{13}C-NMR (A): 172.1 (C(5)); 163.8 (COOMe); 158.4 (C(6a)); 134.4 (C(3a)); 129.7–127.3 (Ph), 124.5 (C(3)); 120.4 (C(6)); 50.2 (MeO); 38.6 (MeN). MS: 288 ($M^{+\bullet}$), 121. Anal. calc. for $C_{14}H_{12}N_2O_3S$ (288.32): C 58.32, H 4.20, N 9.72, S 11.12; found: C 58.39, H 4.24, N 9.80, S 11.04.

*Methyl 4,5-Dihydro-1,4-dimethyl-5-oxo-3-phenyl-1*H*-pyrrolo[3,2-c]isothiazole-6-carboxylate* (**9**). A soln. of 0.29 g (1 mmol) of **8** in anh. DMF (5 ml) was stirred with 33 mg (1.1 mmol) of NaH (80%) for 1 h at r.t. After addition of MeI (2 ml), stirring was continued for another hour. The soln. was diluted with CH_2Cl_2 (20 ml) and then extracted twice with H_2O. The combined org. layers were dried (Na_2SO_4) and evaporated to dryness. The residue was recrystallized from MeOH. Yield: 130 mg (43%). Yellowish crystals. M.p. 195–196°. UV: 355 (4.368), 248 (3.970). IR: 3050, 2920, 1660, 1640, 1585. ^{1}H-NMR (A): 7.47 (*s*, 5 H); 4.18 (*s*, 3 H); 3.75 (*s*, 3 H); 3.01 (*s*, 3 H). MS: 302 ($M^{+\bullet}$), 121. Anal. calc. for $C_{15}H_{14}N_2O_3S$ (302.35): C 59.59, H 4.67, N 9.27, S 10.61; found: C 59.68, H 4.64, N 9.34, S 10.41.

*Ethyl 6-Cyano-4,5-dihydro-1-methyl-5-oxo-1*H*-pyrrolo[3,2-*c*]isothiazole-3-carboxylate* (**10**). H_2S was passed slowly through a soln. of 0.60 g (2 mmol) of (*E*/*Z*)-**6** [5] and 0.30 g (3 mmol) of Et_3N in anh. MeCN (50 ml) at r.t. for 5 min. The volatile components were removed *in vacuo*. A MeOH soln. of the red residue (5 ml) was titrated with a 0.1N soln. of I_2 (20 ml). The precipitate was collected after 4 h and recrystallized from AcOEt. Yield: 206 mg (41%). Yellow powder. M.p. 210° (dec.). Yellow fluorescence at 365 nm. UV: 328 (4.226), 310 (4.104), 231 (3.940), 207 (4.322). IR: 3112, 2984, 2722, 2207, 1688, 1673, 1608. ^{1}H-NMR (A): 11.21 (*s*, 1 H); 4.32 (*q*, *J* = 7.1, 2 H); 3.81 (*s*, 3 H); 1.30 (*t*, *J* = 7.1, 3 H). MS: 251 ($M^{+\bullet}$). Anal. calc. for $C_{10}H_9N_3O_3S$ (251.26): C 47.80, H 3.61, N 16.72, S 12.76; found: C 47.61, H 3.70, N 16.57, S 12.70.

*Ethyl 6-Cyano-4,5-dihydro-1,4-dimethyl-5-oxo-1*H*-pyrrolo[3,2-*c*]isothiazole-3-carboxylate* (**11**). This product was prepared analogously to **9** from 0.25 g (1 mmol) of **10**. 240 mg (91%). Yellow crystals. M.p. 200–202° (MeOH/diisopropyl ether 1:1). Yellow fluorescence at 365 nm. UV: 379 (4.307), 335 (3.980), 235 (4.128), 207 (4.227). IR: 2977, 2209, 1703, 1636 1608. ^{1}H-NMR (A): 4.31 (*q*, *J* = 7.1, 2 H); 3.87 (*s*, 3 H); 3.54 (*s*, 3 H); 1.31 (*t*, *J* = 7.1, 3 H). MS: 265 ($M^{+\bullet}$). Anal. calc. for $C_{11}H_{11}N_3O_3S$ (265.29): C 49.80, H 4.18, N 15.84, S 12.09; found: C 49.85, H 4.13, N 15.65, S 11.87.

*4,5-Dihydro-1,4-dimethyl-5-oxo-3-phenyl-1*H*-pyrrolo[3,2-*c*]isothiazole-6-carboxylic Acid* (**12**). A soln. of 0.30 g (1 mmol) of **9** in MeOH (6 ml) was refluxed with aq. 3N KOH (5 ml) for 3 h. After cooling (0°), the potassium salt of **12** precipitated. The aq. soln. was acidified with dilute HCl, and the precipitate was crystallized from H_2O. Yield: 190 mg (66%). Faintly yellow crystals. M.p. 260–263°. UV: 348 (4.197), 326 (sh), 244 (4.305). IR: 3060, 3020, 2920, 1705, 1630, 1590. ^{1}H-NMR (A): 7.57 (*s*, 5 H); 3.50 (*s*, 3 H); 3.00 (*s*, 3 H). MS: 288 ($M^{+\bullet}$), 121. Anal. calc. for $C_{14}H_{12}N_2O_3S$ (288.32): C 58.32, H 4.20, N 9.72, S 11.12; found: C 60.02, H 5.37 N 8.65, S 10.08.

*1,4-Dimethyl-3-phenyl-1*H*-pyrrolo[3,2-*c*]isothiazol-5(4*H*)-one* (**13**). A soln. of 0.58 g (2 mmol) of **12** in quinoline (3 ml) was heated with a small amount of powdered Cu until the evolution of CO_2 ceased. The cooled mixture was brought on a silica-gel column and eluted first with petroleum ether and then with Et_2O. The latter fraction was evaporated, and the residue was crystallized from Et_2O. Yield: 78 mg (16%). Dark yellow crystals. M.p. 262–264°. UV: 352 (sh), 318 (4.391), 266 (sh), 248 (4.176). IR: 3050, 2920, 1660, 1590. ^{1}H-NMR (A): 7.50 (*s*, 5 H); 4.90 (*s*, 1 H); 3.48 (*s*, 3 H); 3.13 (*s*, 3 H). MS: 244 ($M^{+\bullet}$); 121. Anal. calc. for $C_{13}H_{12}N_2OS$ (244.31): C 63.91, H 4.95, N 11.47, S 13.12; found: C 63.85, H 4.99, N 11.49, S 13.15.

*1,4-Dimethyl-6-nitro-3-phenyl-1*H*-pyrrolo[3,2-*c*]isothiazol-5(4*H*)-one* (**14**). A mixture of 0.29 g (1 mmol) of **12** and 0.35 g (5 mmol) of $NaNO_2$ in AcOH (15 ml) was stirred at r.t. for 15 min. Shortly after a clear soln. was obtained, a brownish intermediate product began to precipitate. After 15 min, the precipitate was collected and suspended in AcOH (10 ml). To this mixture, 3N HNO_3 (2 ml) was added while stirring. After 10 min, the yellow soln. obtained was diluted with H_2O (100 ml) and extracted twice with AcOEt. The combined org. layers were dried (Na_2SO_4), the solvent was evaporated, and the residue was crystallized from diisopropyl ether/EtOH 1:1. Yield: 153 mg (53%). Yellowish powder. M.p. 250° (dec.). UV: 383 (4.336), 285 (4.199). IR: 3052, 2940, 1678, 1570, 1390. ^{1}H-NMR (A): 7.55–7.58 (*m*, 5 H); 4.21 (*s*, 3 H); 2.95 (*s*, 3 H). MS: 289 ($M^{+\bullet}$), 121. Anal. calc. for $C_{13}H_{11}N_3O_3S$ (289.31): C 53.97, H 3.83,N 14.52, S 11.08; found: C 53.68, H 3.76, N 14.30, S 10.82.

*5-Hydroxy-6-(methoxycarbonyl)-1-methyl-3-phenyl-4*H*-pyrrolo[3,2-*c*]isothiazolium Perchlorate* (**15**). Upon addition of 0.16 g (1.1 mmol) of $HClO_4$ (70%) to a soln. of 0.29 g (1 mmol) of **8** in AcOH (5 ml), the product precipitated spontaneously. Yield: 280 mg (72%). Nearly colorless crystals. M.p. 224–226° (AcOH). UV ($HClO_4$): 320 (4.155), 248 (3.911), 214 (4.067). IR: 3000, 1725, 1625, 1570. ^{1}H-NMR (A): 8.45 (*s*, l H); 7.51 (*m*, 5 H); 4.05 (*s*, 3 H); 3.65 (*s*, 3 H).

*5-Methoxy-6-(methoxycarbonyl)-1-methyl-3-phenyl-4*H*-[3,2-*c*]isothiazolium Fluorosulfonate* (**16**). A soln. of 0.29 g (1 mmol) of **8** in anh. 1,2-dimethoxyethane (10 ml) and 0.5 ml (4 mmol) of methyl fluorosulfonate was refluxed for 15 min. The soln. was concentrated to half of the initial volume. The salt precipitated while cooling and was used immediately for the synthesis of **17**.

*Methyl 5-Methoxy-1-methyl-3-phenyl-1*H*-pyrrolo[3,2-*c*]isothiazole-6-carboxylate* (**17**). *a*) Compound **16** was stirred with a sat. aq. soln. of $NaHCO_3$ (50 ml) and then extracted with CH_2Cl_2 (3×). The combined org. layers were dried (Na_2SO_4), and the solvent was removed. Yield: 227 mg (76%).

b) An ethereal soln. of CH_2N_2 (excess) was added to a stirred suspension of 0.29 g (1 mmol) of **8** in Et_2O (10 ml). A clear soln. was obtained after stirring for 2 h. After removal of the volatile components, the product was isolated in nearly quant. yield. Faintly yellow crystals. M.p. 151° (MeOH). UV: 341 (4.210), 258 (4.329). IR: 2940, 1680, 1595. ^{1}H-NMR (A): 8.13–7.90 (*m*, 2 H); 7.65–7.47 (*m*, 3 H); 4.18 (*s*, 3 H); 4.07 (*s*, 3 H); 3.70 (*s*, 3 H). MS: 302 ($M^{+\bullet}$); 121. Anal. calc. for $C_{15}H_{14}N_2O_3S$ (302.35): C 59.59, H 4.67, N 9.27, S 10.61; found: C 59.73, H 4.58, N 9.14, S 10.60.

*Methyl 4,5-Dihydro-1-methyl-2,5-dioxo-3-phenyl-1*H*-2λ^4-pyrrolo[3,2-*c*]isothiazole-6-carboxylate* (**18a**). A soln. of 0.29 g (1 mmol) of **8** in AcOH (10 ml) and 3 ml of an aq. soln. of H_2O_2 (30%) were mixed and kept at r.t.

for 12 h. The product precipitated. Yield: 101 mg (33%). Yellowish crystals. M.p. 241–244° dec. (MeOH). UV: 370 (sh), 334 (4.245), 232 (4.107). IR: 3170, 3050, 2950, 1720, 1700, 1665, 1610, 1075. ^{1}H-NMR (A): 10.92 (*s*, l H); 7.66–7.42 (*m*, Ph); 3.75 (*s*, MeO), 3.67 (*s*, MeN). ^{13}C-NMR (A): 171.5 (C(5)); 162.0 (COOMe); 158.3 (C(6a)); 135.7 (C(3a)); 129.5–127.9 (Ph, C(3)); 122.0 (C(6)); 51.2 (MeO); 32.8 (MeN). MS: 304 ($M^{+\bullet}$), 121. Anal. calc. for C_{14} $H_{12}N_2O_4S$ (304.32): C 55.25, H 3.97, N 9.21, S 10.54; found: C 55.41, H 3.93, N 9.18, S 10.64.

*Methyl 4,5-Dihydro-1-methyl-2,2,5-trioxo-3-phenyl-1*H-*2λ⁶-pyrrolo[3,2-*c*]isothiazole-6-carboxylate* (**18b**). A soln. of 0.29 g (1 mmol) of **8** in AcOH (30 ml) and 3 ml of an aq. soln. of H_2O_2 (30%) were mixed and kept at r.t. for 7 d. The product precipitated upon dilution with H_2O (250 ml). Yield: 61 mg (19%). Faintly yellow crystals. M.p. 252–254° (MeOH). UV: 370 (sh), 324 (4.214), 233 (4.105). IR: 3240, 3080, 2960, 1720, 1710, 1680, 1625, 1320, 1160. ^{1}H-NMR (A): 11.36 (*s*, l H); 7.75–7.50 (*m*, Ph); 3.79 (*s*, MeO); 3.56 (*s*, MeN). ^{13}C-NMR (A): 169.1 (C(5)); 161.4 (*C*OOMe); 149.6 (C(6a)); 133.8 (C(3a)); 130.1–127.3 (Ph, C(3)); 124.8 (C(6)); 51.7 (MeO); 29.6 (MeN). MS: 320 ($M^{+\bullet}$). Anal. calc. for $C_{14}H_{12}N_2O_5S$ (320.32): C 52.49, H 3.78, N 8.75, S 10.01; found: C 52.46, H 3.74, N 8.80, S 9.97.

*Methyl 4,5-Dihydro-1,4-dimethyl-2,5-dioxo-3-phenyl-1*H-*2λ⁴-pyrrolo[3,2-*c*]isothiazole-6-carboxylate* (**19a**). The product was prepared analogously to **9** from 0.30 g (1 mmol) of **18a**. Yield: 162 mg (51%). Yellowish crystals. M.p. 190° (MeOH). UV: 320 (4.213), 249 (3.879). IR: 2950, 2920, 1720, 1700, 1670, 1605, 1070. ^{1}H-NMR (A): 7.53 (*s*, Ph); 3.76 (*s*, MeO); 3.66 (*s*, Me–N(1)); 2.92 (*s*, Me–N(4)). MS: 318 ($M^{+\bullet}$). 121. Anal. calc. for $C_{15}H_{14}N_2O_4S$ (318.35): C 56.59, H 4.43, N 8.80, S 10.07; found: C 56.67, H 4.52, N 8.85, S 10.12.

*Methyl 4,5-Dihydro-1,4-dimethyl-2,2,5-trioxo-3-phenyl-1*H-*2λ⁶-pyrrolo[3,2-*c*]isothiazole-6-carboxylate* (**19b**). The product was prepared analogously to **9** from 0.32 g (1 mmol) of compound **18b**. Yield: 117 mg (35%). Yellowish crystals. M.p. 210–212° (MeOH). UV: 308 (4.297), 249 (3.911). IR: 2960, 2920, 1740, 1705, 1690, 1635, 1310, 1150. ^{1}H-NMR (A): 7.60 (*s*, 5 H); 3.77 (*s*, MeO); 3.55 (*s*, Me–N(1)); 2.83 (*s*, Me–N(4)). MS: 334 ($M^{+\bullet}$). Anal. calc. for $C_{15}H_{14}N_2O_5S$ (334.35): C 53.88, H 4.22, N 8.38, S 9.59; found: C 53.94, H 4.25, N 8.46, S 9.41.

*Ethyl 6-Cyano-4,5-dihydro-1-methyl-2,5-dioxo-1*H-*2λ⁴-pyrrolo[3,2-*c*]isothiazole-3-carboxylate* (**20a**). The product was prepared analogously to **18a** from 0.25 g (1 mmol) of compound **10**. Yield: 200 mg (76%). Yellow powder. M.p. 235° (AcOEt). UV: 380 (sh), 306 (4.625), 209 (4.353). IR: 3190, 3002, 2225, 1740, 1687, 1636, 1070. ^{1}H-NMR (A): 11.85 (*s*, 1 H); 4.30 (*q*, *J* = 7.1, 2 H); 3.49 (*s*, 3 H); 1.28 (*t*, *J* = 7.1, 3 H). MS: 267 ($M^{+\bullet}$). Anal. calc. for $C_{10}H_9N_3O_4S$ (267.26): C 44.94, H 3.39, N 15.72, S 12.00; found: C 45.14, H 3.46, N 15.66, S 11.78.

*Ethyl 6-Cyano-4,5-dihydro-1-methyl-2,2,5-trioxo-1*H-*2λ⁶-pyrrolo[3,2-*c*]isothiazole-3-carboxylate* (**20b**). A soln. of 0.25 g (1 mmol) of **10** in AcOH (10 ml) and 3 ml of an aq. soln. of H_2O_2 (30%) were mixed and heated to 80° for 4 h. After cooling, the soln. was diluted with H_2O (150 ml) and extracted with CH_2Cl_2 (3×). The combined org. layers were washed with $NaHSO_3$ soln. and H_2O, dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by FC (AcOEt/cyclohexane 2:1). 72 mg (26%). Yellow powder. R_f (0.51). M.p. 200–202° (AcOEt/cyclohexane). UV: 370 (3.272), 303 (4.380), 206 (4.195). IR: 3253, 2225, 1765, 1715 1687, 1655, 1310, 1160. ^{1}H-NMR (A): 4.33 (*q*, *J* = 7.1, 2 H); 3.40 (*s*, 3 H); 1.29 (*t*, *J* = 7.1, 3 H). MS: 283 ($M^{+\bullet}$). Anal. calc. for $C_{10}H_9N_3O_5S$ (283.26): C 42.40, H 3.20, N 14.83, S 11.32; found: C 42.46, H 3.29, N 14.69, S 11.12.

*Monomethyl (*Z*)-2-(2,3-Dihydro-2-methyl-4-(methylamino)-1,1-dioxo-5-phenyl-1λ⁶-isothiazol-3-ylidene)-malonate* (**22**). A suspension of 0.67 g (2 mmol) of **19b** in MeOH (10 ml) was heated with 1.0 ml (3 mmol) of 3N KOH at reflux for 10 min. The potassium salt of **22** precipitated during cooling. The aq. soln. was acidified with HCl and extracted with CH_2Cl_2 (2×). The combined org. layers were dried with Na_2SO_4, and the solvent was evaporated. Yield: 834 mg (80%). Colorless crystals. M.p. 131° (CH_2Cl_2). UV: 304 (4.200), 242 (4.087). IR: 3320, 3230, 2950, 2920, 1755, 1740, 1695, 1625, 1260, 1170. ^{1}H-NMR (A): 8.63 (*s*, 1 H); 8.15 (*d*, *J* = 6, 1 H); 7.53 (*s*, 5 H); 3.83 (*s*, 3 H); 2.85 (*d*, *J* = 6, 3 H); 2.51 (*s*, 3 H). MS: 352 ($M^{+\bullet}$). Anal. calc. for $C_{15}H_{16}N_2O_6S$ (352.36): C 51.13, H 4.58, N 7.95, S 9.10; found: C 51.31, H 4.67, N 7.99, S 9.01.

*Methyl (6*R**,6a*R**)-4,5,6,6a-Tetrahydro-1-methyl-2,2,5-trioxo-3-phenyl-1*H-*2λ⁶-pyrrolo[3,2-*c*]isothiazole-6-carboxylate* (**23**). To a stirred soln. of 0.32 g (1 mmol) of **18a** in MeOH (10 ml) were added 0.38 g (10 mmol) of $NaBH_4$. After 10 min, the solvent was removed *in vacuo*. An aq. soln. of the residue was acidified with HCl and extracted with CH_2Cl_2 (3×). The combined org. layers were washed with H_2O, dried (Na_2SO_4), and the solvent was evaporated. Yield: 177 mg (55%). Colorless crystals. M.p. 181° (diisopropyl ether/EtOH). UV: 272 (4.253). IR: 3200, 3070, 2930, 1760, 1735, 1680, 1595, 1295, 1135. ^{1}H-NMR (A): 11.80 (*s*, 1 H); 7.50 (*m*, Ph); 4.61 (*d*, *J* = 9, H–C(6a)); 4.14 (*d*, *J* = 9, H–C(6), H/D-exchange with D_2O); 3.82 (*s*, MeO); 2.70 (*s*, MeN). MS: 322 ($M^{+\bullet}$). Anal. calc. for $C_{14}H_{14}N_2O_5S$ (322.34): C 52.17, H 4.38, N 8.69, S 9.95; found: C 52.12, H 4.43, N 8.76, S 9.85.

Methyl 3,3-[(Ferrocen-1,1′-diyl)bis(diphenylphosphino)]-1-methyl-4,8-dioxo-5-phenyl-4-thia-2,7-diaza-3-platinabicyclo[4.3.0]nona-1(9),5-diene-9-carboxylate (**25**). A mixture of **24b** (78 mg, 0.1 mmol; [15]) and **18a** (30 mg, 0.1 mmol) in 10 ml of toluene was heated slowly with stirring to 100°; the color of the resulting soln.

changed from orange to red. The soln. was stirred at this temp. for 0.5 h, and an orange solid began to separate. At this point, the heating was stopped and the mixture was cooled to r.t. After stirring for 1 h, the soln. was concentrated *in vacuo* to 5 ml. Addition of hexane (20 ml) caused precipitation of the crude material, which was collected by centrifugation, washed with Et_2O (2 × 20 ml), and dried *in vacuo*. Yield: 71 mg (67%). Orange-brown powder. M.p. 205–206°. IR: 3282*w*, 1695 (sh), 1670*s*, 1000*m*. ^{1}H-NMR (B): 9.98 (*s*, NH); 7.14–8.03 (*m*, 25 arom. H); 3.43–4.51 (*m*, 8 H, Cp); 4.36 (*s*, CO_2Me); 3.53 (*s*, NMe). ^{31}P-NMR: 9.73, 9.86 (^1J(Pt,P) = 2490, 3646, ^2J(P,P) = 30.5). Anal. calc. for $C_{48}H_{40}FeN_2O_4P_2PtS$ (1053.10): C 54.70, H 3.80, N 2.66, S 3.04; found: C 53.85, H 4.05, N 2.65, S 3.59.

Methyl 1-Methyl-4,8-dioxo-5-phenyl-3,3-bis(triphenylphosphino)-4-thia-2,7-diaza-3-platinabicyclo[4.3.0]-nona-1(9),5-diene-9-carboxylate (**26a**). Compound **20a** (27 mg, 0.1 mmol) was added to a soln. of **24a** (75 mg, 0.1 mmol; [16]) in toluene (10 ml). The mixture was heated with stirring to 60–70°, leading to a clear soln. The color changed from orange to red. The soln. was stirred at this temp. for 1 h and then cooled to r.t. An orange solid began to separate. The soln. was concentrated *in vacuo* to 5 ml, and addition of hexane (20 ml) afforded an orange-ochre precipitate, which was collected by centrifugation. The crude material was washed with Et_2O (2 × 10 ml) and dried *in vacuo*. Yield: 79 mg (80%). Orange-ochre powder. M.p. 210–211°. IR: 3405 (br.), 2199*m*, 1706*m*, 1661*s*, 980*w*. ^{1}H-NMR (B): 8.86 (*s*, NH); 7.13–7.58 (*m*, 30 arom. H); 4.01 (*m*, C*H*^{a}H^{b}Me); 3.67 (*m*, CH^a*H*^{b}Me); 2.83 (*d*, *J* = 3.4, NMe); 0.90 (*m*, CH_2*Me*). ^{13}C-NMR (B): 170.97; 167.10 (*J* = 7.4); 161.43; 155.08; 127.5–134.7; 117.19; 109.34 (*J* = 3.7); 70.53; 61.41; 44.64 (*J* = 3.7); 13.75. ^{31}P-NMR: 11.48, 15.99 (^1J(Pt,P) = 2217, 3588, ^2J(P,P) = 26.9). Anal. calc. for $C_{46}H_{39}N_3O_4P_2PtS$ (986.93): C 55.98, H 3.98, N 4.26, S 3.25; found: C 55.37, H 3.86, N 4.05, S 3.53.

Ethyl 9-Cyano-3,3-[(ferrocen-1,1′-diyl)bis(diphenylphosphino)]-1-methyl-4,8-dioxo-4-thia-2,7-diaza-3-platinabicyclo[4.3.0]nona-1(9),5-diene-5-carboxylate (**26b**). Preparation similar to that of **26a**, but with 78 mg (0.1 mmol) of **24b** and 27 mg (0.1 mmol) of **20a**. Yield: 75 mg (74%). Orange-ochre solid. M.p. 187–189°. IR: 3436 (br.), 2198*m*, 1704*s*, 1666*m*, 999*w*. ^{1}H-NMR (B): 8.85 (*s*, NH); 7.15–8.85 (*m*, 20 arom. H); 3.59–4.99 (*m*, 8 H, Cp); 4.13 (*m*, C*H*^{a}H^{b}Me); 3.78 (*m*, CH^a*H*^{b}Me); 2.94 (*d*, *J* = 3.9, NMe); 1.16 (*m*, CH_2Me). ^{31}P-NMR: 9.99, 16.93 (^1J(Pt,P) = 2285, 3662, ^2J(P,P) = 31.7). Anal. calc. for $C_{44}H_{37}FeN_3O_4P_2PtS$ (1016.76): C 51.98, H 3.67, N 4.13, S 3.15; found: C 51.08, H 3.85, N 3.87, S 3.49.

Ethyl 9-Cyano-3,3-[(2,2-dimethyl-1,3-dioxolan-4,5-diyl)bis(diphenylphosphino)]-1-methyl-4,8-dioxo-4-thia-2,7-diaza-3-platinabicyclo[4.3.0]nona-1(9),5-diene-5-carboxylate (**26c**). Preparation similar to that of **26a**, but with 72 mg (0.1 mmol) of **24c** [17] and 27 mg (0.1 mmol) of **20a**. 1:1 Mixture of two diastereoisomers (DS I/DS II). Yield: 44 mg (46%). M.p. 194–196°. IR: 3436, 3385 (br.), 2198*m*, 1703*s*, 1666*s*, 995*w*. ^{1}H-NMR (B): 9.00; 8.90 (*s*, NH); 7.28–8.08 (*m*, 20 arom. H); 3.81–4.24 (*m*, CH_2Me); 3.84–3.96 (*m*, CHO); 2.76; 2.74 (*s*, NMe); 1.00–1.19 (*m*, CH_2Me). ^{13}C-NMR (B): 171.49/171.40; 167.86/167.79; 162.06/161.88 (*J* = 4.3); 155.66/155.60; 117.60/117.48; 110.12/109.37; 109.93/109.42 (*J* = 3.6); 71.15/71.11; 62.07/61.87; 44.85/44.81 (*J* = 2.7); 26.91; 26.87/26.82; 26.36; 14.29/14.09. ^{31}P-NMR: 4.57, 0.78/1.17, −6.78 (^1J(Pt,P) = 2064, 3411, ^2J(P,P) = 27.2/^1J(Pt,P) = 2042, 3387, ^2J(P,P) = 29.3). Anal. calc. for $C_{41}H_{41}N_3O_6P_2PtS$ (962.92): C 51.25, H 4.30, N 4.37, S 3.34; found: C 50.74, H 4.53, N 4.07, S 3.54.

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