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Original article

Novel pyrrolinones as *N*-methyl-D-aspartate receptor antagonists

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Abstract

A series of oximes, deriving from 2-arylidene-pyrroline-3,4-diones (**7**, **8**, **22**, **23**) has been prepared. The presence of tautomers in their solutions has been established by spectroscopic means. The compounds reacted with diazomethane chiefly by *N*-methylation forming nitrones (**10**, **11**). The analogously prepared 2-arylidene-4-nitropyrrolin-3-ones (**12**, **13**, **24**, **25**), formally derived from nitrotetramic acids, yielded nitronic acid esters (**14**, **15**, **26**) upon reaction with diazomethane. The structures were elucidated by spectral evidence and—in the case of compounds **10** and **20b**—by X-ray diffraction analysis. The binding affinity of some of the new compounds toward the *N*-methyl-D-aspartate (NMDA) (glycine site) receptor has been measured thus providing the basis for further structure–activity relationship studies. Oxime **8b** showed the highest binding potency (K_i = 9.2 μM).

Keywords: Tetramic acids; Azafulvenes; Nitrones; Nitronic acid esters; Glycine antagonists

1. Introduction

The *N*-methyl-D-aspartate (NMDA) receptor is known to mediate neuronal signaling and to affect gene expression as well as the neuronal plasticity, outgrowth, and survival of cells [1–3]. On the other hand, excessive stimulation of NMDA receptors causes degeneration and death of neurons, which may play a role in the delayed neuronal loss following cerebral ischemia and in the etiology of neurodegenerative disorders [4] like epilepsy. It is also well known that glycine is an obligatory co-agonist for NMDA receptor activation. Therefore, the glycine site on NMDA receptors represents an interesting target in the development of potential neuroprotective drugs.

A number of compounds from different classes have been recognized as functional antagonists at the glycine site. Surveys on potential therapeutic uses of glycine site ligands and on aspects of a structure–activity relationship were published recently [5,6].

In recent papers the high affinity of pyrrolidine-2,3,4-trione 3-oximes **1**, dubbed PTOs [7], has been stated. Derivatives of **1** are the 3-nitrosopyrrol-2-ones **2** (Fig. 1) as well as their nitro analogs, which may have a potential for use in pain treatment [8]. The results of testing the affinity of these compounds at the NMDA (glycine site) receptor revealed that the stereochemistry of the side-chain substituents can play an important role. Generally the fixation of the aryl substituent *trans* to the ring nitrogen appears to be more favorable. All these findings prompted us to synthesize compounds of general formula **3** and their nitro analogs for further biological

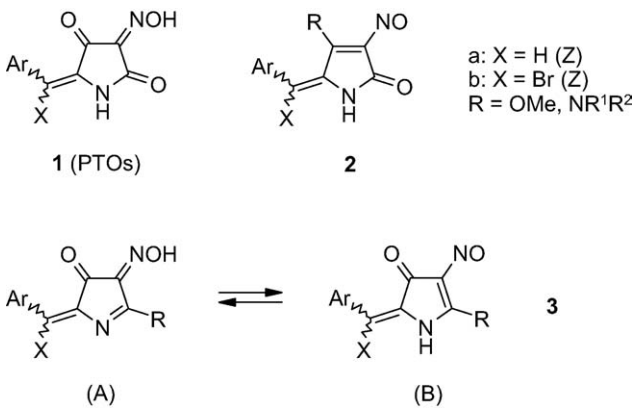

Fig. 1.

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testing. These compounds may be seen as formal derivatives of lactams **1** as well as regioisomers of compound **2**.

2. Chemistry

We started from pyrrolone **4**, which was prepared according to literature [9]. The already reported ^{1}H NMR spectrum of this compound in chloroform as solvent gave evidence of an equilibrium of two tautomers, depicted as A and B (R = OMe) in Fig. 2, with the cyclic imino ester (B) as chief component. In addition, traces of the enol form of this imino ester must be present in the solution because compound **4** reacts with diazomethane slowly yielding the enol ether **6** in low yield. Compound **6** has been obtained formerly by another route [9].

A noticeable detail in the ^{1}H NMR spectra of both compounds **4B** and **6** is the appearance of signals corresponding to two hydrogens at a field much lower (8.1 ppm) than the rest of the aromatic hydrogens. The deshielding effect on *ortho* protons is apparently due to the neighboring polar C=N bond. The split pattern of the phenyl signals proved to be a useful means to ascertain the imino ester partial structure in the derivatives of **4** described below.

By heating compound **4** with primary or secondary aliphatic amines the pyrrolones **5a–c** were obtained. The IR spectra of all compounds **5** showed the first bands in the double bond region below 1650 cm^{-1} in accordance with the ketene aminal structures, depicted as A (R = NR^{1}R^2) in Fig. 2. The ^{1}H NMR spectra indicated the existence of tautomers. Taking **5a** as an example, the solution in DMSO showed only signals of the corresponding ketene aminal A (R = NHMe), but, when dissolved in chloroform, alongside A the tautomeric cyclic amidine B (R = NHMe) was present in a ratio of 1:1. The latter compound was recognized by the characteristic split pattern of the phenyl signals as mentioned above.

Compound **4** reacted rapidly with nitrous acid forming oxime **7**. The structure results from the spectra. As to be expected for **7**, the ^{13}C NMR spectrum showed three signals above 150 ppm and in the IR spectrum a carbonyl band showed up at 1725 cm^{-1}. Compound **7** reacted smoothly with diazomethane to give a mixture of three new compounds. They were identified as the *O*-methylated *syn*- and *anti*-oximes **9**,

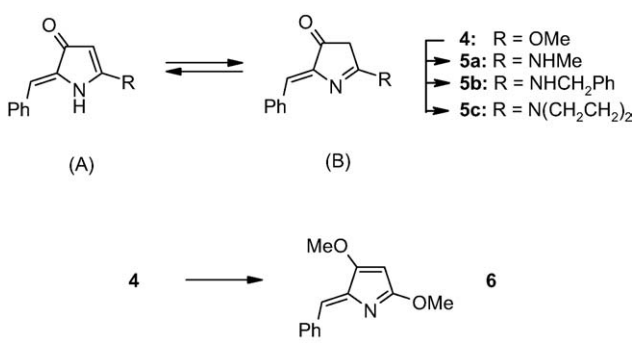

Fig. 2.

which were obtained only as an inseparable mixture, alongside the nitrone **10** as the main component. Accordingly, *N*-methylation of the oxime **7** by diazomethane had occurred rather than *O*-methylation. This mode of action of diazomethane has been observed with other *O*-hydroxyiminocarbonyl compounds [10].

The structure of the nitrone does not follow directly from its spectra. In fact, the ^{1}H NMR spectrum of compound **10** is almost congruent with that of one of the isomeric oxime ethers **9**. More conclusive information about the structure was obtained from the combination of ^{1}H and ^{13}C NMR spectroscopy used in the HMBC cross-coupling technique. From these experiments it was concluded that the C-4 atom was connected with another C atom across one heteroatom. The sequence C–X–C was possible only when *N*-methylation of oxime **7** had occurred to form nitrone **10**. This structure was finally confirmed by X-ray diffraction analysis (Fig. 4). It is to be noted that we have obtained only the *Z* isomer, shown in Fig. 3. The appearance of two more peaks of equal intensity at 4.22 and 4.24 ppm in the ^{1}H NMR spectrum of (*Z*)-**10** after standing 1 week at room temperature probably indicates slow equilibration with (*E*)-**10** to a very small extent.

Compound **7** underwent nucleophilic displacement reactions by heating with aliphatic or aromatic amines to give

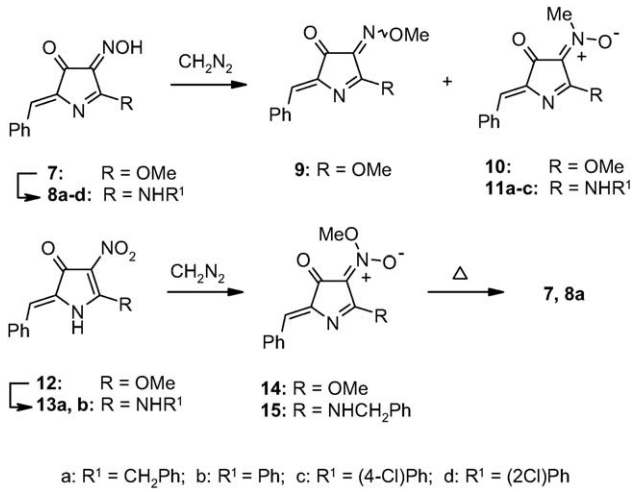

Fig. 3.

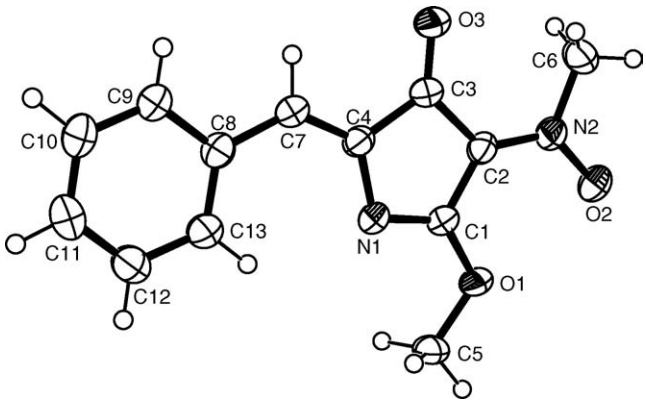

Fig. 4. Molecular structure of **10** with thermal ellipsoids at the 50% probability level.

oximes **8a–d**. Compound **8a** was also obtained by nitrosation of amidine **5b**. All the compounds **8** resemble the parent compound **7** with respect to their IR spectra. The carbonyl bands showed up between 1725 and 1730 cm^{-1}. However, in contrast to the parent compound, the ^1H NMR spectra revealed the existence of the tautomeric nitroso 1H-pyrrolinone in chloroform as solvent.

The reaction of oximes **8a–c** with diazomethane yielded only one compound each. The products were identified as nitrones **11a–c** by spectral evidence. The ^1H NMR spectra of all compounds **11** showed the characteristic split pattern of the phenyl signals and *N*-Me singlets at 4.3 ppm. The carbonyl bands in the IR spectra were found around 1700 $cm^{-1}$and in the mass spectra the typical $[M - 16]^+$ peaks appeared alongside the corresponding molecular ion peaks [11].

Compound **4** reacted quickly with nitric acid to give the nitro compound **12**, which was transferred into its derivatives **13a/b** by heating with benzylamine or aniline, respectively. In their IR spectra, all these compounds showed bands in the double bond region below 1690 cm^{-1}, and therefore, must be formulated as nitropyrrolinones **12/13**, respectively. This corresponds with the lack of split phenyl signals in the uniform ^1H NMR spectra of compounds **12/13** when dissolved in DMSO. Correspondingly it was to be expected that compounds **12/13** would prove to be inert against diazomethane. However, in ethereal solution the nitro compound **12** reacted smoothly with this reagent to give an inseparable mixture of two new compounds. They were identified as the geometrical isomers of the methyl nitronate **14**. Methyl esters of nitronic acids are known to disproportionate upon heating to give oximes and gaseous formaldehyde [11–14]. The thermolysis of the isomeric nitronates **14** was carried out at 150° and gave formaldehyde and oxime **7**. The methylation of nitro compound **13a** proceeded in the same way as described for **12** and gave the methyl nitronate **15** as a mixture of the geometrical isomers. As expected, thermolysis of **15** yielded oxime **8a**. A remarkable feature of both nitronates **14/15** is their stability with half-lives of certainly more than 1 year, contrasting in that aspect most of the known nitronates [15].

Since some of the newly prepared substances proved active in NMDA receptor binding tests, we were interested to produce analogs side-chain brominated compounds for comparison. For this purpose we needed compound **20a** as starting material. This compound was unknown and could not be obtained by bromination of imino ester **4**. It was described, however, that the benzoyloxy-pyrrolone **16** can be brominated to yield pyrrolone **17** [16]. Either of the enol esters **16** and **17** reacted with trimethyloxonium tetrafluoroborate and the methyl imidates **18** and **19a**, respectively, were isolated in moderate yield (Fig. 5). Not surprisingly, the analogs interaction of **17** with triethyloxonium tetrafluoroborate (*Meerwein's* reagent) gave the ethyl imidate **19b**. However, using the same reagent in dimethoxyethane as solvent we obtained the imidate **19a** instead, apparently because of an intermediate transalkylation reaction between reagent and solvent. This observation may be of interest because triethyloxonium tetrafluoroborate is the less expensive of the two reagents.

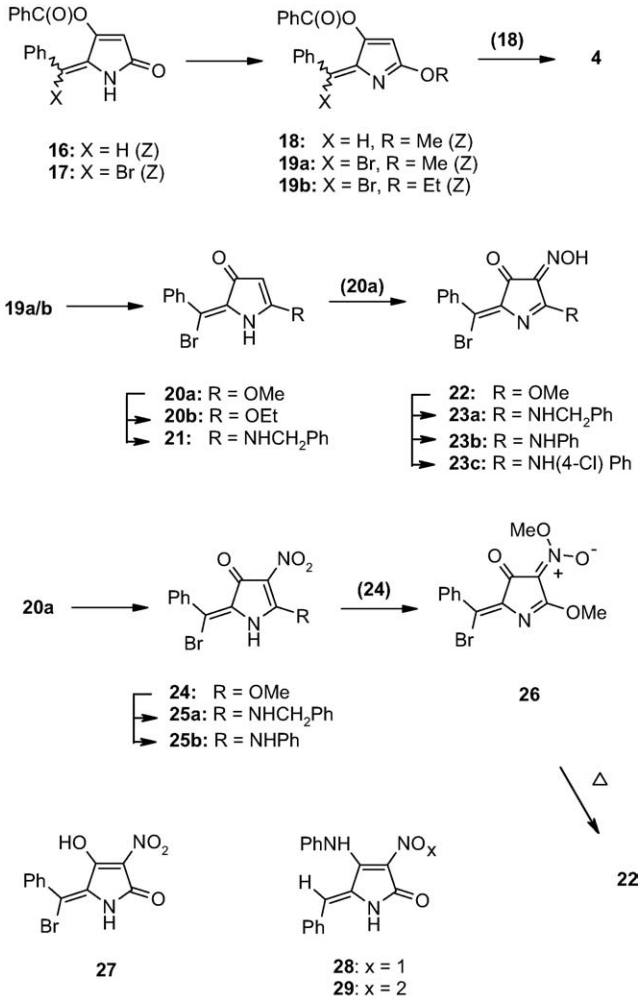

Fig. 5.

Saponification of the benzoate **18** with weak alkali led to imino ester **4**. In comparison with the synthesis of **4** given in literature, the new approach is more advantageous because no methylation with diazomethane was needed. The analogs saponification of benzoates **19a/b** furnished the brominated pyrrolones **20a/b**. The IR and NMR spectra of **20a** are quite similar to those of the non-brominated analog **4** with the exception, that no tautomerism was observed, neither in chloroform nor in DMSO solution. In addition to the spectra, the structure of compound **20b**, including the *Z*-configuration, was confirmed by X-ray diffraction analysis (Fig. 6). The substance crystallized as 1:1 adduct with benzene from the solvent. For clarity, benzene was omitted in the drawing.

The amino compound **21** was formed by heating the pyrrolones **20a** or **20b** with benzylamine. Nitrosation of compound **20a** furnished oxime **22**. Nitration of **20a** gave the nitro derivative **24**. This compound reacted smoothly with diazomethane to give the methyl nitronate **26**. Thermolysis of **26** yielded the oxime **22**. Both, the oxime **22** and the nitro compound **24**, reacted easily with amines producing the amino substituted oximes **23a–c** or the amino substituted nitro compound **25a**, **b**, respectively. The spectral characteristics of compounds **21–26** are quite similar to those of the non-

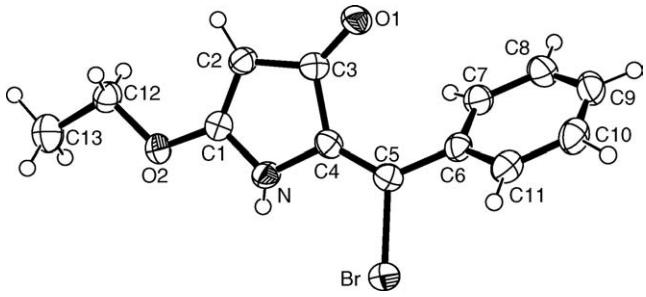

Fig. 6. Molecular structure of **20b** with thermal ellipsoids at the 50% probability level.

brominated analogs. However, because of the change in configuration with respect to the phenyl substituent, the brominated imino esters and cyclic amidines showed no splitting of the phenyl signals in the respective ^{1}H NMR spectra.

Since compound **24** is formally derived from the hitherto unknown tetramic acid **27**, we have prepared this substance by nitration of the side-chain brominated tetramic acid [16].

3. Pharmacological results and discussion

A selection of the new oximes and nitro compounds has been tested for affinity to the glycine modulatory site associated with the NMDA receptor. The determination of the affinities was carried out on pig cortical homogenates by measuring the inhibition of [^{3}H]MDL 105.519 binding [17] as described in Section 4. Because of the poor water solubility of the compounds 10 nM solutions in DMSO were used. The final fraction of DMSO in the binding assays did not exceed 1%. The K_i values of the new compounds with reference to glycine are given in Table 1.

No activity toward the receptor was observed with oximes **7** and **22**, formally iminoesters of the active lactams **1a** (K_i = 19.4 μM) and **1b** (K_i = 0.252 μM). This was to be expected in the light of the glycine antagonist pharmacophore model proposed by Mawer et al. [19] in which an unsubstituted lactam (NH) group, putatively involved in hydrogen bonding, was considered essential alongside an ionizable group whose relative location is not critical.

Table 1
Affinity toward glycine-binding site of the NMDA receptor channel

Compound	K_i ± S.E.M. (μM)
Glycine	0.200 ± 0.040
1a	19.4 ± 1.9
1b	0.252 ± 0.033
8a	56.9 ± 9.8
8b	9.22 ± 1.27
8c	15.9 ± 2.0
12	71.0 ± 8.2
13b	≥100
23b	36.3 ± 5.2
24	12.1 ± 4.5
25b	41.2 ± 0.9
27	60.7 ± 5.9
28	72 [8]
29	9 [8]

On the other hand, oximes of the amidine type exhibited distinct activity at the glycine site (**8b**: K_i = 9.2 μM, **23b**: K_i = 36 μM) despite the alleged essential NH group is lacking. This, however, does not directly devaluate the pharmacophore model because the oximes we are dealing with are prone to tautomerization to a high extent in polar solvents. Therefore, the actual structures of the biologically active tautomers are uncertain so that conclusions concerning structure–activity relations cannot be drawn at this stage of the investigation. It may be of interest to note that oxime **8b** was more potent at the glycine site than its structural isomer **28** (K_i = 72 μM) [8].

Distinctive receptor binding affinities were also observed for the nitro compounds of the ketene *N*,*O*-acetal type (**24**: K_i = 12.1 μM) as well as the aminal type (**25b**: K_i = 41 μM). In these cases the non-brominated analogs are somewhat less active (**12**: K_i = 71 μM or **13b**: $K_i \geq 100$ μM, respectively). It may be noted that compound **12** was less potent at the glycine site in comparison with its structural isomer **29** (K_i = 9 μM) [8] and that the nitrotetramic acid **27**, formally the parent compound of all brominated nitro compounds described here, exhibited only medium high activity (K_i = 60 μM). Due to their readiness to tautomerize, alike their oxime analogs, the testing results of the nitro compounds can presently be described only phenomenologically.

These initial findings encourage further investigation of derivatives of lactam **27** and similar pyrroles in order to gain insight into the structure–activity relationship, and to optimize the glycine site activity.

4. Experimental protocols

4.1. General methods

Melting points (m.p.) were determined by using a Büchi m.p. B-540 apparatus and are uncorrected. UV analysis was performed in methanolic solution if not stated otherwise on UV/VIS Spectrometer Lambda 20 (Perkin Elmer) or UV/VIS Spectrophotometer Jasco V-530. Infrared spectra were measured as potassium bromide plates by using a FT-IR-Spectrometer PARAGON 1000 (Perkin Elmer). ^{1}H NMR spectra (internal standard tetramethylsilane) were recorded on FT NMR Spectrometer Elipse 400 (JEOL) or FT NMR Spectrometer Elipse 500 (JEOL). The solvent was hexadeuteriodimethylsulfoxide if not indicated otherwise. Mass spectra were recorded with a Hewlett Packard 5989A mass spectrometer employing both EI (70 eV) and CI mode. MS-HR were obtained with a JMS-GCMATE II (JEOL), MS-ESI with a API 2000 (Sciex) mass spectrometer. Microanalyses were carried out with an CHN Analyzer Elementar Vario EL. CC: Flash column 250 ml (Baker) with silica gel 0.040–0.063 mm (Merck).

4.2. NMDA receptor assay

[^{3}H]MDL 105,519 binding to pig cortical brain membranes was performed as previously described [17]. Test com-

pounds insoluble in water were dissolved by addition of DMSO. The total amount of DMSO in the assay did not exceed 1% and inhibited binding only negligibly.

IC_{50} values for test compounds were calculated from experiments with at least six concentrations of test compounds using Prism 2.0 (GraphPad Software, San Diego, CA). The K_D value for [^3H]MDL 105,519 used in the Cheng–Prusoff equation [18] to calculate K_i values was determined in saturation experiments as 3.73 ± 0.43 nM. If not stated otherwise, data are expressed as mean ± S.E.M. of three experiments, each carried out in triplicate.

*4.3. (Z)-2-Benzylidene-5-methoxy-1,2-dihydropyrrol-3-one (**4**)*

A solution of sodium methanolate (0.80 g, 15 mmol) in methanol (10 ml) was added to a suspension of 1.5 g (5 mmol) of compound **18** in methanol (10 ml). The clear solution obtained within a few min was acidified with 1 N HCl (20 ml) and extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated in vacuo. The residue crystallized from diisopropyl ether/ethanol 1:1. Yellow crystals, yield 0.5 g (50%). M.p. 140 °C (lit. [9]: m.p. 139 °C). Analytical and spectral data identical with data of [9].

^{13}C NMR: δ 184.3 (C-3), 178.6 (C-5), 133.8 (C-2), 129.6–128.6 (C-ar.), 109.3 (CH=), 79.1 (C-4), 58.5 (MeO).

*4.4. (Z)-2-Benzylidene-5-methylamino-1,2-dihydropyrrol-3-one (**5a**)*

A solution of compound **4** (0.10 g, 0.5 mmol) in methanol (15 ml) was refluxed with an ethanolic solution of methylamine (10 M, 1 ml, 10 mmol) for 15 min. The volatile components were removed in vacuo and the residue was washed several times with petroleum ether. Light yellow crystals (acetonitrile), yield 80 mg (80%). M.p. 209 °C. ^{1}H NMR: δ 8.83 (s, 1H), 7.57–7.25 (m, 5H), 6.97 (s, 1H), 6.16 (s, 1H), 4.49 (s, 1H), 2.85 (s, broad, 3H); IR: ν 3253, 1639, 1600, 1522 cm^{-1}; UV: λ_{max} (log ϵ) 223 nm (4.285), 321 (4.442); Anal. CHN $C_{13}H_{12}N_2O$ (200.24). MS: 201 $[M + 1]^+$.

^{1}H NMR ($CDCl_3$, tautomer B): δ 8.12 (d, 2H), 7.37–7.28 (m, 3H), 6.47 (s, 1H), 4.95 (br. s, 1H), 3.18 (d, 3H), 3.06 (s, 2H).

*4.5. (Z)-5-Benzylamino-2-benzylidene-1,2-dihydropyrrol-3-one (**5b**)*

A solution of compound **4** (0.21 g, 1 mmol) in methanol (10 ml) was refluxed with 0.22 g benzylamine (2 mmol) for 15 min. The product separated on cooling. Light yellow crystals (MeOH), yield 0.20 g (72%). M.p. 233 °C. ^{1}H NMR: δ 8.80 (s, 1H), 8.30 (s, 1H), 7.60–7.25 (m, 10H), 6.17 (s, 1H), 4.55 (br. s, 1H), 4.41 (br. s, 2H); IR: ν 3335, 1632, 1597, 1498 cm^{-1}; UV: λ_{max} (log ϵ) 222 nm (4.289), 322 (4.501); Anal. CHN $C_{18}H_{16}N_2O$ (276.3). MS: 277 $[M + 1]^+$.

*4.6. (Z)-2-Benzylidene-5-pyrrolidino-1,2-dihydropyrrol-3-one (**5c**)*

This compound was prepared from compound **4** (0.21 g, 1 mmol) and pyrrolidine (0.2 g, 3 mmol) analogously to the synthesis of compound **5a**. Light yellow crystals (acetonitrile), yield 0.20 g (83%). M.p. 213 °C. ^{1}H NMR: δ 8.56 (s, 1H), 7.58–7.26 (m, 5H), 6.25 (s, 1H), 4.50 (s, 1H), 3.63 (s, 2H), 3.38 (s, 2H), 1.94 (s, 4H); ^{13}C NMR: δ 181.3 (C-3), 166.2 (C-5), 135.3 (C-2), 129.6–127.6 (C-ar.), 106.6 (CH=), 82.2 (C-4), 49.6 (NCH_2), 25.1 (CH_2); IR: ν 3383, 1628, 1577; UV: λ_{max} (log ϵ) 227 nm (4.322), 330 (4.465); Anal. CHN $C_{15}H_{16}N_2O$ (240.30). MS: 241 $[M + 1]^+$.

*4.7. (Z)-2-Benzylidene-3,5-dimethoxy-2H-pyrrole (**6**)*

A solution of compound **4** (0.20 g, 1 mmol) in methanol (10 ml) was treated with an excess of an ethereal solution of diazomethane. After 6 h the volatile components were removed and the residue purified by column chromatography with petroleum ether as eluent. Yield 43 mg (20%). Analytical and spectral data identical with data of [9].

*4.8. (Z)-2-Benzylidene-5-methoxy-2H-pyrrole-3,4-dione 4-oxime (**7**)*

a: A solution of sodium nitrite (75 mg, 1.1 mmol) in 0.5 ml water was added dropwise to a stirred ice-cooled suspension of compound **4** (0.20 g, 1 mmol) in acetic acid (5 ml). After a short time of stirring the product began to crystallize. The precipitate was collected and washed several times with diethyl ether/petroleum ether 1:1. Orange crystals, yield 0.19 g (82%). M.p. 183 °C.

b: Compound **14** (26 mg, 0.1 mmol) was heated in diphenyl ether (10 ml) to 150 °C for 5 min. The product was precipitated with petroleum ether. Yield 10 mg (43%).

^{1}H NMR (geometrical isomers, ratio 3: 2): 8.12–8.18 (m, 2H), 7.32–7.51 (m, 3H), 6.74 (s, 0.6H), 6.68 (s, 0.4H), 4.12 (s, 1.2H), 4.09 (s, 1.8H); ^{1}H NMR ($CDCl_3$): 8.12–8.06 (m, 2H), 7.48–7.37 (m, 3H), 6.93 (s, 1H), 4.22 (s, 3H); ^{13}C NMR: 184.9 (C-3), 165.4/164.1 (C-5), 139.0 (C-2), 132.1–128.7 (C-4, C-ar.), 122.6 (CH=), 55.9 (OMe); IR: ν 3176, 1725, 1631, 1559 cm^{-1}; UV: λ_{max} (log ϵ) 304 nm (4.386), 316 (4.466), 331 (4.342); Anal. CHN $C_{12}H_{10}N_2O_3$ (230.23): MS-EI: 230 $[M^+]$.

*4.9. (Z)-5-Benzylamino-2-benzylidene-2H-pyrrole-3,4-dione 4-oxime (**8a**)*

a: To a suspension of compound **5b** (0.14 g, 0.5 mmol) in 2 ml acetic acid was added under stirring an aqueous solution of sodium nitrite (40 mg, 0.6 mmol). The product precipitated within a few min. Yield 80 mg (52%). M.p. 165 °C.

b: A solution of compound **7** (0.14 g, 0.5 mmol) and benzylamine (0.11 g, 1 mmol) in 15 ml methanol was refluxed for 30 min. The mixture was diluted with water, acidified with

1 N HCl (2 ml) and twice extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue crystallized from acetonitrile. Yield 50 mg (33%).

c: This compound was prepared from **15** (33 mg, 0.1 mmol) analogously to the synthesis of compound **7**, method b. Yield 15 mg (50%).

^{1}H NMR (geometrical isomers, ratio 3:1): δ 8.55 (br, 1H), 8.11–8.06 (m, 2H), 7.47–7.19 (m, 8H), 6.34 (s, 0.75H), 6.27 (s, 0.25H), 4.68 (d, 2H, J = 6 Hz); ^{1}H NMR ($CDCl_3$): 8.09 (s, 1H), 7.43–7.21 (m, 10H), 6.67 (s, 1H), 4.80 (br. s, 1H), 4.74 (d, 2H, J = 4.8 Hz); ^{13}C NMR: 181.0 (C-3), 160.1/155.9 (C-5), 138.9/136.3 (C-2), 130.5–126.8 (C-4, C-ar.), 110.9/110.5 (CH=), 44.6 (N-CH_2); IR: ν 3385, 1726, 1664, 1638, 1576 cm^{-1}; UV: λ_{max} (log ϵ) 258 nm (4.149), 327 (4.364), 340 (4.452), 356 (4.350); Anal. CHN $C_{18}H_{15}N_3O_2$ (305.24). MS: 306 [M + 1]$^+$.

*4.10. (Z)-2-Benzylidene-5-phenylamino-2H-pyrrole-3,4-dione 4-oxime (**8b**)*

A solution of compound **7** (0.23 g, 1 mmol) and 0.30 g (3 mmol) aniline in methanol (15 ml) was refluxed for 1 h. The product separated on cooling. Reddish-brown crystals (from MeOH), yield: 0.23 g (79%). M.p. 189 °C. ^{1}H NMR (geometrical isomers, ratio 2:1): 9.66 (s, 0.3H), 9.53 (s, 0.7H), 8.14–8.08 (m, 2H), 7.45–6.95 (m, 8H), 6.57 (s, 0.7H), 6.49 (s, 0.3H); IR: ν 3366, 1729, 1633, 1599, 1553 cm^{-1}; UV: λ_{max} (log ϵ) 249 nm (4.457), 354 (4.436), 369 (4.384); Anal. CHN $C_{17}H_{13}N_3O_2$ (291.31). MS: 292 [M + 1]$^+$.

*4.11. (Z)-2-Benzylidene-5-(4-chloro-phenylamino)-2H-pyrrole-3,4-dione 4-oxime (**8c**)*

A solution of compound **7** (0.11 g, 0.5 mmol) and 0.25 g (2 mmol) 4-chloroaniline (0.13 g, 1 mmol) was refluxed for 5 h in methanol (15 ml). The volatile components were removed in vacuo and the residue was crystallized from ethanol. Reddish-brown powder, yield 70 mg (43%). M.p. 224 °C. ^{1}H NMR (geometrical isomers, ratio 1:1): δ 9.86 (s, 0.5H), 9.58 (s, 0.5H), 8.18–8.05 (m, 4H), 7.55–7.30 (m, 5H), 6.59 (s, 0.5H), 6.52 (s, 0.5H); IR: ν 3399, 1719, 1626, 1593, 1556 cm^{-1}; UV: λ_{max} (log ϵ) 259 nm (4.527), 354 (4.444), 370 (4.395); Anal. CHN $C_{17}H_{12}ClN_3O_2$ (325.75). MS: 326/328 [M + 1]$^+$.

*4.12. (Z)-2-Benzylidene-5-(2-chloro-phenylamino)-2H-pyrrole-3,4-dione 4-oxime (**8d**)*

This compound was prepared from **7** (0.11 g, 0.5 mmol) and 2-chloroaniline (0.13 g, 1 mmol) analogously to the synthesis of compound **8c**. Reddish-brown powder (from ethanol), yield 35 mg (21%). M.p. 187 °C. ^{1}H NMR: δ 10.13 (s, 1H), 8.88 (d, 1H, 8 Hz), 8.10 (d, 1H, 8 Hz), 7.65–7.19 (m, 7H), 6.63 (s, 1H); IR: ν 3342, 1717, 1631, 1594, 1555 cm^{-1}; λ_{max} (log ϵ) 252 nm (4.376), 334 (4.330), 352 (4.374), 368 (4.336). MS-HR Calc. for $C_{17}H_{12}ClN_3O_2$: 325.0618. Found 325.0612.

*4.13. (Z)-2-Benzylidene-5-methoxy-2H-pyrrole-3,4-dione 4-(O-methyl-oxime) (**9**)*

The mother liquor obtained in the preparation of **10** was concentrated to half of the volume. The product (geometrical isomers 1:1) separated on cooling. Yellow crystals, (20 mg, 17%). M.p. 143–145 °C. ^{1}H NMR (geometrical isomers, ratio 1:1, $CDCl_3$): 8.15–8.05 (m, 2H), 7.48–7.32 (m, 3H), 6.85 (s, 0.5H), 6.91 (s, 0.5H), 4.32 (s, 1.5H), 4.30 (s, 1.5H), 4.22 (s, 1.5H), 4.18 (s, 1.5H); IR: ν 2939, 1729, 1643, 1555 cm^{-1}; UV: λ_{max} (log ϵ) 316 nm (4.526), 331 (4.395); Anal. CHN $C_{13}H_{12}N_2O_3$ (244.25). MS: 245 [M+1]$^+$.

*4.14. (Z)-2-Benzylidene-5-methoxy-4-methylnitroryl-2,4-dihydropyrrol-3-one (**10**)*

A solution of compound **7** (0.11 g, (0.5 mmol) in methanol was treated with an excess of an ethereal solution of diazomethane. After the evolution of nitrogen had ceased the solution was evaporated to dryness and the residue crystallized from methanol (15 ml). (The mother liquor contains compound **9**). Red-brown crystals, yield 50 mg (41%). M.p. 139 °C. ^{1}H NMR ($CDCl_3$): δ 8.06 (dd, 2H), 7.45–7.35 (m, 3H), 6.90 (s, 1H), 4.33 (s, 3H, N-Me), 4.20 (s, 3H, O-Me); ^{13}C NMR ($CDCl_3$): δ 181.2 (C-3), 165.9 (C-5), 140.1 (C-2), 134.1 (C-ar.), 132.3 (C-4), 130.5–128.6 (C-ar.), 121.0 (CH=), 55.8 (OMe), 53.5 (NMe). HMBC-experiment: coupling of C(4) at 132.3 ppm and CH_3-N at 4.33 ppm; IR: ν 1703, 1635, 1552 cm^{-1}; UV: λ_{max} (log ϵ) 318 nm (4.593), 326 (4.532), 345 (1.884); Anal. CHN $C_{13}H_{12}N_2O_3$ (244.25). MS-EI: 244 [M$^+$]; 228 [M – 16]$^+$.

*4.15. (Z)-5-Benzylamino-2-benzylidene-4-methylnitroryl-2,4-dihydropyrrol-3-one (**11a**)*

A solution of compound **8a** (0.60 mg, 0.2 mmol) in methanol (5 ml) was treated with an excess of an ethereal solution of diazomethane. After the evolution of nitrogen had ceased the solution was evaporated to dryness. Red-brown crystals (diisopropyl ether/ethanol 1:1), yield 30 mg (47%). M.p. 165 °C (dec). ^{1}H NMR ($CDCl_3$): 8.12 (d, 2H, J = 7.5 Hz), 8.00 (br. s, 1H), 7.48–7.27 (m, 8H), 6.65 (s, 1H), 4.81 (d, 2H, J = 5.6 Hz), 4.28 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 182.4 (C-3), 157.9 (C-5), 143.2 (C-2), 135.3–127.7 (C-ar.), 115.2 (CH=), 51.3 (OMe), 45.4 (NCH_2); IR: ν 3341, 1707, 1638, 1574, 1563 cm^{-1}; UV: λ_{max} (log ϵ) 230 nm (4.191), 315 (4.497), 350 (4.420), 367 (4.353); Anal. CHN $C_{19}H_{17}N_3O_2$ (319.37). MS-EI: 319 [M$^+$]; 303 [M – 16]$^+$.

*4.16. (Z)-2-Benzylidene-4-methylnitroryl-5-phenylamino-2,4-dihydropyrrol-3-one (**11b**)*

This compound was prepared from **8b** (60 mg, 0.2 mmol) with an excess of an ethereal solution of diazomethane analo-

gously to the synthesis of compound **11a**. Red-brown crystals (MeOH), yield 25 mg (41%). M.p. 169 °C (dec). ^{1}H NMR ($CDCl_3$): δ 10.02 (s, 1H), 8.14 (d, 1H, 7.5 Hz), 7.90 (d, 1H, 7.5 Hz), 7.55–7.15 (m, 8 H), 6.79 (s, 1H), 4.34 (s, 3H); IR: ν 3254, 1701, 1634, 1602, 1572, 1551 cm^{-1}; UV: λ_{max} (log ϵ) 249 nm (4.234), 307 (4.283), 363 (4.278), 381 (4.257); Anal. CHN $C_{18}H_{15}N_3O_2$ (305.34). MS-EI: 305 [M$^+$], 289 [M – 16]$^+$.

*4.17. (Z)-2-Benzylidene-4-methylnitroryl-5-(4-chloro-phenylamino)-2,4-dihydropyrrol-3-one (**11c**)*

This compound was prepared from **8c** (65 mg, 0.2 mmol) with an excess of an ethereal solution of diazomethane analogously to the synthesis of compound **11a**. Red-brown crystals (MeOH), yield 30 mg (44%). M.p. 187 °C. ^{1}H NMR: δ 10.21 (s, 1H), 8.12 (d, 1H, 8.5 Hz), 8.05 (d, 1H, 8.5 Hz), 7.58–7.35 (m, 7H), 6.67 (s, 1H), 4.26 (s, 3H); IR: ν 3265, 1703, 1632, 1596, 1575, 1553 cm^{-1}; UV: λ_{max} (log ϵ) 250 nm (4.222), 306 (4.313), 363 (4.290), 382 (4.261). MS-HR Calc. for $C_{18}H_{14}ClN_2O_3$: 339.0775. Found: 339.0787. MS-EI: 339 [M$^+$]; 323 [M – 16]$^+$.

*4.18. (Z)-2-Benzylidene-5-methoxy-4-nitro-1,2-dihydropyrrol-3-one (**12**)*

To a stirred ice-cooled suspension of compound **4** (0.20 g, 1 mmol) in acetic acid (3 ml) were added 0.5 ml of concentrated nitric acid. The product precipitated in good purity. Colorless crystals (MeOH), yield 0.10 g (40%). M.p. 186 °C. ^{1}H NMR: δ 7.77–7.68 (m, 2H), 7.55–7.40 (m, 3H), 6.89 (s, 1H), 4.34 (s, 3H); ^{13}C NMR: δ 172.5 (C-3), 170.7 (C-5), 132.0 (C-2), 130.7–128.9 (ar.), 116.2 (CH=), 113.5 (C-4), 60.17 (OMe); IR: ν 2681, 1690, 1633, 1590, 1460 cm^{-1}; UV: λ_{max} (log ϵ) 310 nm (4.403); Anal. CHN $C_{12}H_{10}N_2O_4$ (246.22). MS: 247 [M + 1]$^+$.

*4.19. (Z)-5-Benzylamino-2-benzylidene-4-nitro-1,2-dihydropyrrol-3-one (**13a**)*

A solution of compound **12** (50 mg, 0.2 mmol) and benzylamine (1.1 g, 10 mmol) in MeOH (15 ml) was refluxed for 15 min. The volatile components were removed in vacuo. The residue crystallized from diisopropyl ether/ethanol 1:1. The orange powder (benzylammonium salt of **13a**, 55 mg) was collected and dissolved in acetic acid (3 ml). Slowly the product precipitated. Colorless powder (acetic acid), yield 35 mg (53%). M.p. 213 °C. ^{1}H NMR: δ 10.26 (s, 1H), 9.90 (br. s, 1H), 7.60–7.28 (m, 10H), 6.60 (s, 1H), 4.88 (d, 2H, J = 6 Hz); IR: ν 3323, 1683, 1626, 1525 cm^{-1}; UV: λ_{max} (log ϵ) 324 nm (4.512); Anal. CHN $C_{18}H_{15}N_3O_3$ (321.34). MS: 322 [M + 1]$^+$.

*4.20. (Z)-2-Benzylidene-4-nitro-5-phenylamino-1,2-dihydropyrrol-3-one (**13b**)*

A solution of compound **12** (50 mg, 0.2 mmol) and aniline (1.0 g, 10 mmol) in MeOH (15 ml) was refluxed for 15 min. The product precipitated on cooling. Colorless crystals (MeOH), yield 40 mg (66%). M.p. 264 °C. ^{1}H NMR: δ 10.83 (s, 1H), 10.45 (s, 1H), 7.65–7.30 (m, 10H), 6.67 (s, 1H); IR: ν 3194, 1694, 1619, 1585 cm^{-1}; UV: λ_{max} (log ϵ) 325 nm (4.533); Anal. CHN $C_{17}H_{13}N_3O_3$ (307.31). MS-ESI 308 [M + 1]$^+$.

*4.21. (Z)-2-Benzylidene-5-methoxy-4-methoxynitroryl-2,4-dihydropyrrol-3-one (**14**)*

A solution of compound **12** (50 mg, 0.2 mmol) in methanol (5 ml) was treated with an excess of an ethereal solution of diazomethane. After the evolution of nitrogen had ceased the solution was evaporated to dryness and the residue crystallized from diisopropyl ether/ethanol 1:1. Orange crystals, yield 25 mg (48%). M.p. 176–178 °C. ^{1}H NMR (geometrical isomers, ratio 3:1): δ 8.16–8.10 (m, 2H), 7.45–7.30 (m, 3H), 6.76/6.69 (2s, 1H), 4.15/4.13 (2s, 3H), 4.09/3.95 (2s, 3H); ^{13}C NMR: δ 181/177.9 (C-3), 165.0/164.9 (C-5), 140.3 (C-2), 134.1–128.5 (C-4, C-ar.), 118.2 (CH=), 55.8/55.6 (OMe), 54.8/54.6 (OMe); IR: ν 1712, 1641, 1582, 1551 cm^{-1}; UV: λ_{max} (log ϵ) 316 nm (4.525); Anal. CHN $C_{13}H_{12}N_2O_4$ (260.25). MS: 261 [M + 1]$^+$.

*4.22. (Z)-5-Benzylamino-2-benzylidene-4-methoxynitroryl-2,4-dihydropyrrol-3-one (**15**)*

0.1 g (0.03 mmol) of compound **13a** was treated with an excess of an etheral solution of diazomethane. After the evolution of nitrogen had ceased the solution was evaporated to dryness and the residue crystallized from diisopropyl ether/ethanol 1:1. Red-brown crystals, m.p. 134–136 °C, yield: 50 mg (50%). ^{1}H NMR ($CDCl_3$): 8.11 (m, 2H), 7.46–7.33 (m, 8H), 6.66 (s, 1H), 4.82 (d, 2H, J = 5.6 Hz), 4.04 (s, 3H); IR: ν 3383, 1711, 1636, 1584 cm^{-1}; UV: λ_{max} (log ϵ) 229 nm (4.205), 313 (4.388), 350 (4.407), 365 (4.3019. Anal. CHN $C_{19}H_{17}N_3O_3$ (335.37). MS: 336 [M + 1]$^+$.

*4.23. Benzoic acid (Z)-2-benzylidene-5-methoxy-2H-pyrrol-3-yl ester (**18**)*

A stirred suspension of **16** [16] (2.9 g, 10 mmol) and 2.2 g (15 mmol) trimethyloxonium tetrafluoroborate or 2.85 g (15 mmol) triethyloxonium tetrafluoroborate in 1,2-dimethoxyethane (30 ml) was heated to 65 °C for 30 min. Passing through a period of clear solution the product slowly precipitated. After completion of this process, the precipitate was collected, dissolved in dichloromethane and the solution washed with an aqueous solution of sodium carbonate (10%). The organic layer was dried (Na_2SO_4), the volatile components were removed in vacuo and the residue was crystallized from MeOH. Faintly yellow crystals, yield 2.0 g (66%). M.p 155 °C. ^{1}H NMR ($CDCl_3$): 8.25–8.15 (m, 4H), 7.68–7.34 (m, 6H), 6.86 (s, 1H), 6.47 (s, 1H), 4.14 (s, 3H); IR: ν 3464, 1747, 1644, 1589 cm^{-1}; UV: λ_{max} (log ϵ) 235 nm (4.363), 331 (4.424); Anal. CHN $C_{19}H_{15}NO_3$ (305.34). MS: 306 [M + 1]$^+$.

*4.24. Benzoic acid (Z)-2-(bromo-phenyl-methylene)-5-methoxy-2H-pyrrol-3-yl ester (**19a**)*

This compound was prepared from **17** [16] (1.85 g, 5 mmol) and 1.42 g (7.5 mmol) triethyloxonium tetrafluoroborate analogously to the synthesis of compound **18**. Light yellow crystals (diisopropyl ether/ethanol 1:1), yield 1.30 g (68%). M.p. 119 °C. ^{1}H NMR ($CDCl_3$): δ 7.52–7.05 (m, 10H), 6.63 (s, 1H), 4.14 (s, 3H); IR: ν 1745, 1644, 1578 cm^{-1}; UV: λ_{max} (log ϵ) 240 nm (4.273), 290 (4.191), 304 (4.200); Anal. CHN $C_{19}H_{14}BrNO_3$ (384.23). MS: 384/386 $[M + 1]^+$.

*4.25. Benzoic acid (Z)-2-(bromo-phenyl-methylene)-5-ethoxy-2H-pyrrol-3-yl ester (**19b**)*

A solution of compound **17** [16] (0.74 g, 2 mmol) and 0.66 g (3.5 mmol) triethyloxonium tetrafluoroborate in $CHCl_3$ (30 ml) was refluxed for 3 h. The solution was washed with an aqueous solution of sodium carbonate (10%). The organic layer was dried (Na_2SO_4), the volatile components were removed in vacuo and the residue was purified by column chromatography with diethyl ether/petroleum ether (1:1) as eluent. Faintly yellow crystals, yield 0.10 g (13%). M.p. 82 °C. ^{1}H NMR ($CDCl_3$): 7.55–7.17 (m, 10H), 6.61 (s, 1H), 4.55 (q, 2H), 1.45 (t, 3H); IR: ν 2977, 1744, 1632, 1578; 1507 cm^{-1}; UV: λ_{max} (log ϵ) 241 nm (4.257), 289 (4.123), 305 (4.133); Anal. CHN $C_{20}H_{16}BrNO_3$ (398.30). MS: 398/400 $[M + 1]^+$.

*4.26. (Z)-2-(Bromo-phenl-methylene)-5-methoxy-1,2-dihydropyrrol-3-one (**20a**)*

This compound was prepared from **19a** (1.15 g, 3 mmol) and sodium methanolate (with 0.50 g, 9 mmol) in methanol (10 ml) analogously to the synthesis of compound **4**. Yellow crystals (diethyl ether/petroleum ether 1:1), yield 0.63 g, (75%). M.p. 119 °C. ^{1}H NMR: δ 9.65 (s, 1H), 7.45–7.30 (m, 5H), 4.77 (s, 1H), 3.93 (s, 3H); ^{1}H NMR ($CDCl_3$): δ 7.60–7.55 (m, 2H), 7.45–7.35 (m, 3H), 6.51 (br. s, 1H), 4.80 (d, 1H, J = 1.7 Hz); IR: ν 3139, 1674, 1550 cm^{-1}; UV: λ_{max} (log ϵ) 288 nm (4.200), 364 (3.549); Anal. CHN $C_{12}H_{10}BrNO_2$ (280.12). MS: 280/282 $[M + 1]^+$.

*4.27. (Z)-2-(Bromo-phenl-methylene)-5-ethoxy-1,2-dihydropyrrol-3-one (**20b**)*

This compound was prepared from **19b** (0.39 g, 1 mmol) and sodium methanolate (0.36 g, 3 mmol) in methanol (10 ml) analogously to the synthesis of compound **4**. Yellow crystals (benzene/diethyl ether 1:1). **20b** crystallized as 1:1 adduct with benzene; The analytical data were taken after heating the crystals to 120 °C for 20 min in vacuo. Yield 0.14 g (47%). M.p. 144 °C. ^{1}H NMR: 9.62 (s, 1H), 7.45–7.27 (m, 5H), 4.77 (s, 1H), 4.22 (q, 2H), 1.35 (t, 3H). IR: ν 3085, 1678, 1548 cm^{-1}; λ_{max} (log ϵ) 288 nm (4.260), 364 (3.532); Anal. CHN $C_{13}H_{12}BrNO_2$ (294.15). MS: 294/296 $[M + 1]^+$.

*4.28. (Z)-5-Benzylamino-2-(bromo-phenyl-methylene)-1,2-dihydropyrrol-3-one (**21**)*

This compound was prepared from **20a** (0.14 g, 0.5 mmol) and benzylamine (0.22 g, 2 mmol) analogously to the synthesis of compound **5b**. Yellow crystals (MeOH), yield 0.12 g, (70%). M.p. 193 °C. ^{1}H NMR: δ 8.43 (s, 1H), 7.55 (s, 1H), 7.45–7.25 (m, 10H), 4.53 (s, 1H), 4.38 (br. s, 2H); IR: ν 3256, 1630, 1581, 1507 cm^{-1}; UV: λ_{max} (log ϵ) 307 nm (4.373); Anal. CHN $C_{18}H_{15}BrN_2O$ (355.24). MS: 355/357 $[M + 1]^+$.

*4.29. (Z)-2-(Bromo-phenyl-methylene)-5-methoxy-2H-pyrrole-3,4-dione 4-oxime (**22**)*

a. This compound was prepared from **20a** (0.14 g, 0.5 mmol) and sodium nitrite (40 mg, 0.6 mmol) analogsly to the synthesis of compound **7**. Light yellow crystals (acetic acid), yield 0.85 mg (55%). M.p. 163 °C.
b. This compound was prepared from **26** (34 mg, 0.1 mmol) analogously to the synthesis of compound **7** method b, yield 15 mg (50%).

^{1}H NMR ($CDCl_3$): 7.48–7.37 (m, 5H), 4.21 (s, 3H); ^{1}H NMR (geometrical isomers, ratio 1:2): 7.55–7.45 (m, 5H), 4.07 (s, 0.66H), 4.04 (s, 0.33H); IR: ν 3448, 1729, 1625, 1565 cm^{-1}; UV: λ_{max} (log ϵ) 264 nm (4.238), 291 (4.189); Anal. CHN $C_{12}H_9BrN_2O_3$ (309.12). MS: 309/311 $[M + 1]^+$.

*4.30. (Z)-5-Benzylamino-2-(bromo-phenyl-methylene)-2H-pyrrole-3,4-dione 4-oxime (**23a**)*

A solution of compound **22** (62 mg, 0.2 mmol) and benzylamine (0.11 g, 1 mmol) in 15 ml methanol was refluxed for 30 min. The volatile components were removed in vacuo. After washing twice with petrol ether the residue crystallized upon addition of dichloromethane. Orange crystals, yield 35 mg (46%). M.p. 130 °C (dec). ^{1}H NMR: δ 8.50 (s, 1H), 7.52–7.25 (m, 10H), 5.74 (s, 1H), 4.64 (d, 2H, J = 5.6 Hz); IR: ν 34.18, 1731, 1669, 1616, 1560 cm^{-1}; UV: λ_{max} (log ϵ) 258 nm (4.176), 321 (4.283). MS-HR Calc. for $C_{18}H_{14}BrN_3O_2$ 383.0269. Found: 383.0227.

*4.31. (Z)-2-(Bromo-phenyl-methylene)-5-phenylamino-2H-pyrrole-3,4-dione 4-oxime (**23b**)*

A solution of compound **22** (62 mg, 0.2 mmol) and 0.1 g (1 mmol) aniline in methanol (15 ml) was refluxed for 15 min. The product crystallized on cooling. Red-brown crystals, yield: 35 mg (47%). M.p. 127 °C (dec). ^{1}H NMR: δ 9.64 (s, 1H), 9.50 (s, 1H), 8.15/8.06 (2d, 2H, J = 7.7 Hz), 7.51–7.31 (m, 7H), 7.18–7.12 (m, 1H); IR: ν 3398, 1727, 1622, 1561 cm^{-1}; UV: λ_{max} (log ϵ) 338 nm (4.352). MS-HR Calc. for $C_{17}H_{12}BrN_3O_2$ 352.9987. Found: 352.9955.

*4.32. (Z)-2-(Bromo-phenyl-methylene)-5-(4-chloro-phenyl-amino)-2H-pyrrole-3,4-dione 4-oxime (**23c**)*

This compound was prepared from **22** (62 mg, 0.2 mmol) and 40 mg (0.3 mmol) 4-chloroaniline analogously to the synthesis of compound **23b**. Red-brown crystals (MeOH), yield: 35 mg (43%). M.p. 146 °C. ^{1}H NMR: δ 9.85 (s, 1H), 9.52 (s, 1H), 8.25–8.05 (m, 2H), 7.55–7.30 (m, 7H); IR: ν 3402, 1727, 1615, 1557 cm^{-1}; UV: λ_{max} (log ϵ) 242 nm (4.413), 344 (4.401); Anal. CHN $C_{17}H_{11}BrClN_3O_2$ (404.65). MS: 405/407 $[M + 1]^+$.

*4.33. (Z)-2-(Bromo-phenyl-methylene)-5-methoxy-4-nitro-1,2-dihydropyrrol-3-one (**24**)*

This compound was prepared from **20a** (0.14 g, 0.5 mmol) and nitric acid analogously to the synthesis of compound **12**. Colorless crystals (MeOH), yield 0.11 g (68%). M.p. 199 °C. ^{1}H NMR: δ 7.49–7.35 (m, 5H), 4.36 (s, 3H); IR: ν 3115, 1692, 1597 cm^{-1}; UV: λ_{max} (log ϵ) 309 nm (4.329); Anal. CHN $C_{12}H_9BrN_2O_4$ (325.12). MS: 325/327 $[M^+ + 1]$.

*4.34. (Z)-5-Benzylamino-2-(bromo-phenyl-methylene)-4-nitro-1,2-dihydropyrrol-3-one (**25a**)*

A solution of compound **24** (65 mg, 0.2 mmol) and benzylamine (1.1 g, 10 mmol) in MeOH (15 ml) was refluxed for 1 h. The volatile components were evaporated. The residue was washed twice with petroleum ether and recrystallized from diisopropyl ether/ethanol 1:1. Faintly yellow crystals, yield 25 mg (31%). M.p. 203 °C. ^{1}H NMR: δ 9.90 (s, 1H), 7.51–7.25 (m, 11H), 4.96 (d, 2H, J = 4.9 Hz); IR: ν 3347, 1688, 1658, 1524 cm^{-1}; UV: λ_{max} (log ϵ) 284 nm (4.324), 316 (4.411). MS-HR Calc. for $C_{18}H_{14}BrN_3O_3$ 399.0219. Found: 399.0221.

*4.35. (Z)-2-(Bromo-phenyl-methylene)-5-phenylamino-4-nitro-1,2-dihydropyrrol-3-one (**25b**)*

This compound was prepared from **24** (65 mg, 0.2 mmol) and aniline (1.0 g, 10 mmol) in MeOH (15 ml) analogously to the synthesis of compound **25a**. Light yellow powder (diisopropyl ether/ethanol 1:1), yield 50 mg (64%). M.p. 202 °C. ^{1}H NMR: δ 10.87 (s, 1H), 9.64 (s, 1H), 7.65–7.32 (m, 10H); IR: ν 3271, 3063, 1691, 1628, 1590 cm^{-1}; UV: λ_{max} (log ϵ) 315 nm (4.498); Anal. CHN $C_{17}H_{12}BrN_3O_3$ (386.21). MS: 386/388 $[M + 1]^+$.

*4.36. (Z)-2-(Bromo-phenyl-methylene)-5-methoxy-4-methylnitroryl-2,4-dihydropyrrol-3-one (**26**)*

This compound was prepared from **24** (65 mg, 0.2 mmol) and excessive diazomethane analogously to the synthesis of compound **14**. Orange crystals (diisopropyl ether/ethanol 1:1), yield 40 mg (59%). M.p. 126–128 °C. ^{1}H NMR ($CDCl_3$, geometrical isomers, ratio 1:1): δ 7.48–7.35 (m, 5H), 4.21 (s, 3H), 3.96 (s, 1H), 3.93 (s, 2H); IR: ν 1720, 1627, 1586, 1547 cm^{-1}; UV: λ_{max} (log ϵ) 303 nm (4.431); Anal. CHN $C_{13}H_{11}BrN_2O_4$ (339.15). MS: 339/341 $[M + 1]^+$.

*4.37. (Z)-2-(Bromo-phenyl-methylene)-3-hydroxy-4-nitro-1H-pyrrol-5-one (**27**)*

This compound was prepared from 0.28 g (1 mmol) (*Z*)-2(Bromo-phenyl-methylene)-3-hydroxy-1H-pyrrol-5-one [16] and nitric acid analogously to the synthesis of compound **12**. Light yellow crystals (MeOH), yield 0.17 g (52%). M.p. 112–114 °C. ^{1}H NMR: δ 8.77 (s, 1H), 7.40–7.22 (m, 5H); IR: ν 3166, 3063, 1726, 1600 cm^{-1}; UV: λ_{max} (log ϵ) 254 nm (4.041), 316 (4.282); Anal. CHN $C_{11}H_7BrN_2O_4$ (311.09).

*4.38. X-ray diffraction analysis of **10** and **20b***

Diffraction data were collected with MoKα radiation (λ = 0.71073 Å, graphite monochromator) on a Nonius KappaCCD. Crystal data are given in Table 2. The structures were

Table 2
Summary of crystal data for compounds **10** and **20b**

	10	**20b**
Formula	$C_{13}H_{12}N_2O_3$	$C_{16}H_{15}BrNO_2$
M_r (g mol^{-1})	244.246	333.200
Crystal system	Triclinic	Monoclinic
Space group	*P*-1	$P2_1/c$
a (Å)	4.5344(2)	7.8138(2)
b (Å)	11.4755(5)	16.8341(3)
c (Å)	11.9738(7)	11.1207(2)
α (°)	73.3569(16)	90
β (°)	82.5614(17)	102.1691(10)
γ (°)	80.022(2)	90
V (Å^3)	585.81(5)	1429.93(5)
Z	2	4
ρ (g cm^{-3})	1.38470(12)	1.54777(5)
μ (mm^{-1})	0.100	2.875
Crystal size (mm)	0.20 × 0.12 × 0.04	0.26 × 0.05 × 0.03
Temperature (K)	200(2)	200(2)
θ-range (°)	3.55–24.98	3.16–27.50
Reflections for metrics	3231	9634
Absorption correction	no	Numerical
Transmission min/max	–	0.6054–0.9295
Reflections collected	6037	30033
Independent reflections	2050	3273
R_{int}	0.0458	0.0978
$\sigma(I)/I$	0.0587	0.0635
Observed reflections ($I \geq 2\sigma(I)$)	1492	2140
x, *y* (weighting scheme)	0.0637, 0	0.0453, 0.0471
Extinction	–	0.0116(11)
Parameters refined	211	242
Restraints	0	0
$R(F_{obs})$	0.0437	0.0419
$R_w(F^2)$	0.1154	0.0962
S	1.025	1.040
Shift/error$_{max}$	0.001	0.001
Largest diff. peak (e Å^{-3})	0.233	0.609
Largest diff. hole (e Å^{-3})	–0.193	–0.515

solved with SIR97 [20] and refined using full-matrix least squares on F2 with SHELXL-97 [21]. The drawings (Figs. 4 and 6 were generated with ORTEP [22]. Further details are available under the depository numbers CCDC 243280 (**10**) and CCDC 243281 (**20b**) from the Cambridge Crystallographic Data Center, 12, Union Road Cambridge CB2 1EZ, UK (Fax: +44-1233-336-033; email: deposit@ccdc.cam.ac.uk).

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