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Linear and Cyclic *N*-Acyl-α-arylglycines III [1]. Synthesis and Chemiluminescence Studies of Naphthol and Phenanthrol Amidoalkylation Products

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Summary. The synthesis of new linear and cyclic *N*-acetyl-α-arylglycine derivatives (**2–10**) and of the desoxybenzoin amidoalkylation product **13** is described. In addition, an investigation of the chemiluminescence observable upon base-induced oxidation with oxygen is reported.

Keywords. α-Amidoalkylation; *N*-Acetyl-α-arylglycines; Acetylaminonaphthofuranones; Acetylaminophenanthro[9,10-*b*]furanone; Chemiluminescence.

Lineare und Cyclische *N*-Acetyl-α-arylglycine, 3. Mitt. [1]. Synthese und Chemilumineszenz-Untersuchungen von Naphthol- und Phenanthrol-Amidoalkylierungsprodukten

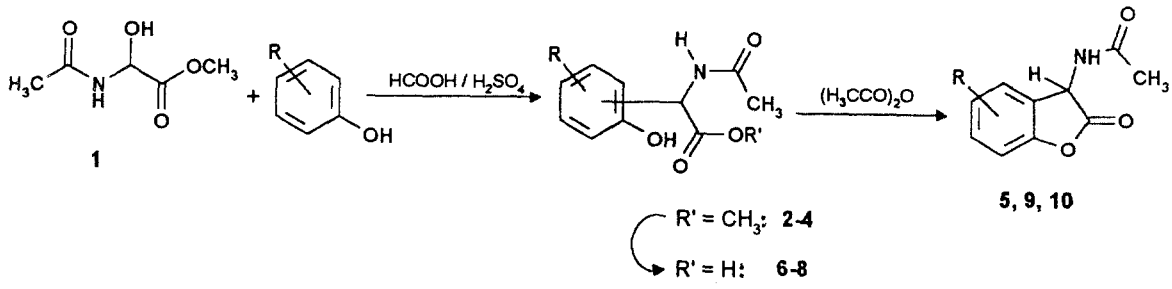
Zusammenfassung. Es wird über die Darstellung von linearen und cyclischen *N*-Acetyl-α-arylglycinderivaten (**2–10**) sowie jene des Desoxybenzoin-Amidoalkylierungsprodukts **13** berichtet. Weiters wird die Chemilumineszenz, welche bei basisch induzierter Oxidation mit Sauerstoff zu beobachten ist, untersucht.

Introduction

Recently, we have reported on the synthesis of a variety of substituted *N*-acetyl-α-phenylglycines and related 3-acetylaminobenzo[*b*]furan-2(3*H*)ones as well as on preliminary results of chemiluminescence investigations [1, 2]. In these new classes of compounds, the emission of visible light can be observed upon base-induced oxidation in the presence of (air)oxygen. We have found that the intensity and the colour of the emitted light varies depending on the substitution pattern of the phenyl ring. In order to get further insight into structural features critical for chemiluminescence in this series, compounds with an expanded aromatic system became an object of interest.

Results and Discussion

The target compounds were prepared by acid induced electrophilic α-amidoalkylation of naphthol and phenanthrol derivatives using methyl *N*-acetyl-α-



Scheme 1. Synthesis of *N*-acetyl-α-arylglycines **2–4** and **6–8** and of the corresponding 3-acetylaminobenzo[*b*]furan-2(3*H*)ones **5**, **9**, and **10**

hydroxyglycinate (**1**) [3]. The lactones became accessible by treatment of the carboxylic acids **6** and **8** with acetic anhydride. Treatment of **1** with 9-hydroxyphenanthrene, however, led to the lactone **5**; this direct cyclization has also been described for similar types of compounds [4].

Lofthouse et al. [5] had assigned structure **A** for the amidoalkylation product of 2-naphthol (substitution in β-position) [6]. According to our spectroscopic investigation (^{1}H NMR and H,H-COSY), this assignment is not correct. Structure **B** has to be formulated for the product resulting from the reaction of 2-naphthol with methyl *N*-acetyl-α-hydroxyglycinate (substitution in α-position of the naphthol). This follows from the ^{1}H NMR spectrum of **9** in *DMSO-d*$_6$ which shows doublets for the protons in positions 4, 5, 6, and 9 of the aromatic core with coupling constants of 8.2–8.8 Hz. Moreover, structure **B** is also in full accordance with observations that the α-position of naphthol is more reactive in electrophilic substitutions [7].

In order to elucidate structural features critical for chemiluminescence, an amidoalkylation product in which the phenolic substructure is formally replaced by an enol moiety (see Fig. 2) appeared to be of interest.

Initial attempts to prepare the amidoalkylation product **13** under conditions described above (reaction of **1** with desoxybenzoin in a mixture of formic acid and *conc.* sulfuric acid) failed; even after stirring for 7 days at room temperature only unchanged starting material was recovered. Thus, the desoxybenzoin trimethylsilyl ether **11** [8] was reacted with the α-chloro compound **12** [3] in dry dichloromethane in the presence of $SnCl_4$. By this procedure, the target compound

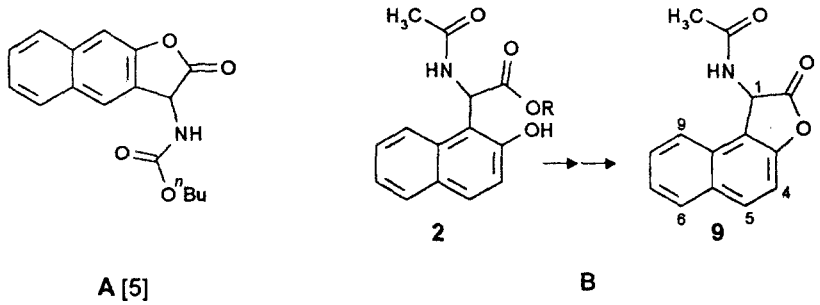


Fig. 1. Proposed structures for the amidoalkylation product of 2-naphthol

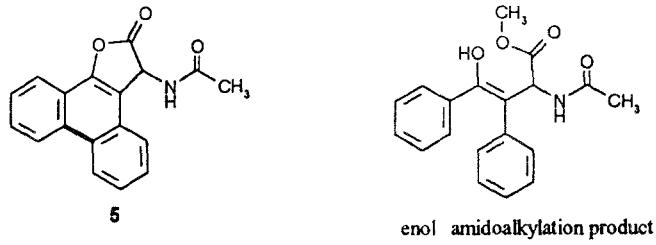


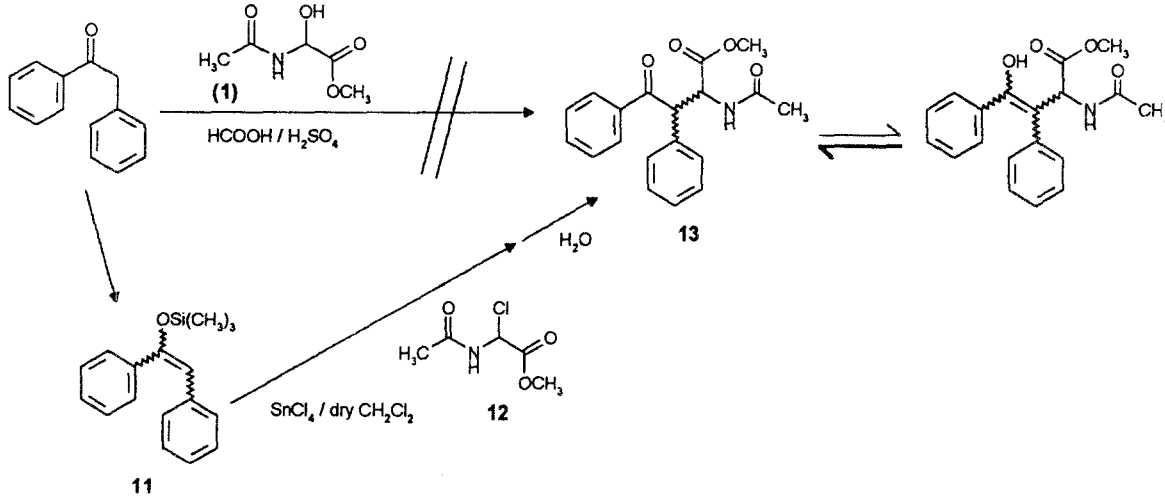
Fig. 2. Comparison of amidoalkylation products with phenolic and enolic substructures

13 could be obtained albeit in low yield (15%). Existence of **13** in the keto form in solution (*DMSO-d_6*) is evidenced by the observation of two coupling CH-protons and the absence of an enole-OH in the ^{1}H NMR spectrum.

Chemiluminescence of the title compounds can be observed by treatment with a base (preferably 1,8-diazabicyclo[5.4.0]undec-7-ene) in polar aprotic solvents in the presence of air or oxygen. As outlined in Table 1, only compounds with a phenolic hydroxy function *ortho* to the amidoalkyl substituent (**2, 4, 6, 8**) and the corresponding lactones (**5, 9, 10**) emit visible light upon base-induced oxidation. In this series, the lactones show the strongest and the carboxylic acids the weakest chemiluminescence. By contrast, the desoxybenzoin amidoalkylation product **13** does not emit visible light under these conditions.

Structure-chemiluminescence relationships

In the series of linear *N*-acyl-α-arylglycines, the following condition holds: substituents which increase the α-CH acidity are essential for visible chemiluminescence. This finding, which is in accordance with our results in the *N*-acetyl-α-phenylglycine series, can be explained by the recently proposed mechanism of the chemiluminescence reaction [1]. We suggest that the split off of the α-CH proton is



Scheme 2. Synthesis of the desoxybenzoin α-amidoalkylation product **13**

Table 1. Chemiluminescence of compounds **2–10** and **13**

	Structure	Colour and intensity of the emitted light[1]
2	derived from 2-naphthol	greenish *(weak)*
6		greenish *(very weak)*
9		greenish *(very weak)*
3	derived from 1-naphthol	no visible chemiluminescence
7		no visible chemiluminescence
4	derived from 4-chloro-1-naphthol	blue-green *(weak)*
8		blue-green *(very weak)*
10		greenish *(very weak)*
5	derived from 9-hydroxyphenanthren	orange *(weak)*
13	derived from desoxybenzoin	no visible chemiluminescence

[1] Based on observation (reaction in acetone with 1,8-diazabicyclo[5.4.0]undec-7-ene and air oxygen); due to too low solubility in acetonitrile/phosphate buffer, chemiluminescence measurements [1,2] could not be performed

the introductory step. In compounds **2, 4, 6,** and **8** as well as in the corresponding lactones **5, 9,** and **10**, the phenolic hydroxy function *ortho* to the amidoalkyl subunit causes the increased α-CH acidity. This interpretation complies with the *Hammett* values described for *ortho* and *para* substituents ($\sigma_{ortho\text{-}OH} = +1.22$ and $\sigma_{para\text{-}OH} = -0.37$) [9].

Expansion of the aromatic moiety (phenyl → naphthyl → phenanthryl) leads to a reduction of the intensity of the emitted light, an observation which may be explained by decreased α-CH acidity. The lack of visible chemiluminescence with the desoxybenzoin α-amidoalkylation product obviously stems from its too low α-CH acidity.

The **colour** of the emitted light depends on the structure. A bathochromic effect can be observed by expansion of the aromatic system. Most of the phenol derivatives emit bluish [1], the naphthol congeners (**2, 4, 6, 8–10**) greenish and the 9-phenanthrol derived lactone **5** orange coloured light.

Experimental

Melting points (uncorrected) were determined with a Linström apparatus. IR spectra (KBr pellets; ν in cm^{-1}) were recorded on a Pye Unicam SP 3-200S, ^1H NMR spectra (*DMSO-d_6*, *TMS* as internal standard, δ values in ppm) on Varian EM 360 (60 MHz) and varian Gemini 200 (200 MHz)

spectrometers. For analytical TLC, Polygram® SIL G/UV_{254} (Macherey-Nagel) plastic-backed plates (0.25 mm layer thickness) were used. Light petroleum refers to the fraction of b.p. 40 to 60°C. Elemental analyses were performed at the Institute of Organic Chemistry and Biochemistry, University of Hamburg. Their results were in acceptable agreements with the calculated values.

Methyl *N*-acetyl-α-hydroxyglycinate (**1**) was obtained by refluxing a solution of 1 equivalent of acetamide and 1.1 equivalents of methyl glyoxylate in ethyl acetate for 3 h. Methyl *N*-acetyl-α-chloroglycinate (**12**) was synthesized by treatment of methyl *N*-acetyl-α-hydroxyglycinate (**1**) with $SOCl_2$ in dry $CHCl_3$ at 0°C as described in the literature [3]. The trimethylsilyl ether of desoxybenzoin (**11**) was prepared by reaction of desoxybenzoin with trimethylsilyl chloride in the presence of $ZnCl_2$ and triethylamine as reported in the literature [8].

Observation of chemiluminescence

A few mg of the appropriate compound were dissolved in acetone and some drops of *DBU* were added. The colour and intensity of the emitted light were observed in a dark room.

General method for electrophilic α-amidoalkylation

1.471 g (10 mmol) of methyl *N*-acetyl-α-hydroxyglycinate (**1**) and 10 mmol of the appropriate phenol compound were dissolved in 10 ml of formic acid (98–100%); if necessary, the mixture was warmed up to 60°C for 1–2 min. After addition of 5 drops of *conc.* sulfuric acid, the solution was stirred for 3 days at room temperature. The formic acid was removed under reduced pressure, and the residue was dissolved in 50 ml of ethyl acetate, washed three times with 20 ml of water, dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The oily residue solidified under light petroleum. If the product precipitated, the crystals were filtered off, washed with water, light petroleum, and diethyl ether, and the filtrate was treated as described before.

Methyl N-acetyl-α-(2-hydroxy-1-naphthyl)glycinate (**2**; $C_{15}H_{15}NO_4$)

Yield: 2.56 g (94%); m.p.: 211°C (ethyl acetate); IR: 3370 (NH), 3080 (broad, OH), 1745 (COOMe), 1650 (CON); ^{1}H NMR: 1.90 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 6.34 (d, s after D_2O-exchange, 1H, α-CH), 7.11–7.98 (m, 6H, aromatic), 8.38 (d, 1H, D_2O-exchangeable, NH), 10.20 (s, 1H, D_2O-exchangeable, OH).

Methyl N-acetyl-α-(4-hydroxy-1-naphthyl)glycinate (**3**; $C_{15}H_{15}NO_4$)

Yield: 1.45 g (53%); m.p.: 201–202°C (*THF*/light petroleum); IR: 3310 (NH), 3000 (broad, OH), 1720 (COOMe), 1630 (CON); ^{1}H NMR: 1.87 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 6.01 (d, s after D_2O-exchange, 1H, α-CH), 6.76–8.31 (m, 6H, aromatic), 8.68 (d, 1H, D_2O-exchangeable, NH), 10.37 (s, 1H, D_2O-exchangeable, OH).

Methyl N-acetyl-α-(4-chloro-1-hydroxy-2-naphthyl)glycinate (**4**; $C_{15}H_{14}ClNO_4$)

Yield: 2.34 g (76%); m.p.: 225–230°C (ethyl acetate); IR: 3370 (NH), 3100 (broad, OH), 1720 (COOMe), 1645 (CON); ^{1}H NMR: 1.90 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 6.04 (d, s after D_2O-exchange, 1H, α-CH), 7.46–8.45 (m, 5H, aromatic), 8.76 (d, 1H, D_2O-exchangeable, NH), 9.0–10.5 (1H, D_2O-exchangeable, OH).

3-Acetylaminophenanthro[9,10-b]furan-2(3H)one (**5**; $C_{18}H_{13}NO_3$)

Yield: 2.50 g (86%); m.p.: 264–266 °C (ethanol); IR: 3290 (NH), 1825 (lactone-CO), 1655 (CON); ^{1}H NMR: 1.92 (s, 3H, $COCH_3$), 5.89 (d, 1H, D_2O-exchangeable, H-3), 7.50–9.08 (m, 8H, aromatic), 9.40 (d, 1H, D_2O-exchangeable, NH).

General method for hydrolysis

10 mmol of the appropriate methyl *N*-acetyl-α-arylglycinate (**2, 3,** or **4**) and 11.5 mmol of sodium carbonate were suspended in 15 ml of water and heated to reflux. After standing at room temperature for 15 min, the solution was heated once more, cooled, and treated carefully dropwise with 6 *N* HCl until a *pH* of 1 was achieved. The resulting crystals were filtered off and washed subsequently with water, light petroleum, and diethyl ether. If the free carbonic acid did not precipitate, the solution was extracted exhaustively with ethyl acetate. The organic layer was washed twice with water, dried over sodium sulfate, and evaporated *in vacuo*.

N-Acetyl-α-(2-hydroxy-1-naphthyl)glycine (**6**; $C_{14}H_{13}NO_4$)

Yield: 2.51 g (97%); m.p.: 217–218°C (*THF*); IR: 3410 (NH, OH), 2300–3150 (COOH), 1715 (COOH), 1635 (CON); ^{1}H NMR: 1.89 (s, 3H, $COCH_3$), 6.28 (d, s after D_2O-exchange, 1H, α-CH), 7.10–8.05 (m, 6H, aromatic), 8.25 (d, 1H, D_2O-exchangeable, NH), 8–10 (2H, D_2O-exchangeable, OH).

N-Acetyl-α-(4-hydroxy-1-naphthyl)glycine (**7**; $C_{14}H_{13}NO_4$)

Yield: 1.30 g (50%); m.p.: 210–211°C (*THF*/light petroleum); IR: 3380 (broad, NH, OH), 1715 (COOH), 1640 (CON); ^{1}H NMR: 1.86 (s, 3H, $COCH_3$), 5.95 (d, s after D_2O-exchange, 1H, α-CH), 6.73–8.25 (m, 6H, aromatic), 8.48 (d, 1H, D_2O-exchangeable, NH), 8–10 (2H, D_2O-exchangeable, OH).

N-Acetyl-α-(4-chloro-1-hydroxy-2-naphthyl)glycine (**8**; $C_{14}H_{12}ClNO_4$)

Yield: 2.41 g (82%); m.p.: 192–193°C (*THF*/light petroleum); IR: 3270 (br, NH, OH), 1740 (COOH), 1610 (CON); ^{1}H NMR: 1.95 (s, 3H, CH_3), 6.00 (d, s after D_2O-exchange, 1H, α-CH), 7.48–8.46 (m, 5H, aromatic), 8.72 (d, 1H, D_2O-exchangeable, NH), 9–13 (broad, 2H, D_2O-exchangeable, OH).

General method for cyclisation

10 mmol of the appropriate *N*-acetyl-α-(2-hydroxyaryl)-glycine (**6** or **8**) were suspended in 8 ml of acetic anhydride and refluxed for some minutes. The cooled solution was treated with 20 ml of diethyl ether, and the resulting crystals were filtered off and washed subsequently with water, light petroleum, and diethyl ether.

1-Acetylaminonaphtho[2,1-b]furan-2(1H)one (**9**; $C_{14}H_{11}NO_3$)

Yield: 2.07 g (86%); m.p.: 234–236°C (decomp.;*THF*); IR: 3320 (NH), 1835 (lactone-CO), 1650 (CON); ^{1}H NMR: 1.89 (s, 3H, $COCH_3$), 5.77 (d, J = 7.3 Hz, 1H, D_2O-exchangeable, H-1), 7.42–7.51 (m, 1H, H-7/-8), 7.47 (d, J = 8.8 Hz, 1H, H-4/-5), 7.55–7.63 (m, 1H, H-7/-8), 7.85 (d, J = 8.3 Hz, 1H, H-6/-9), 7.99 (d, J = 8.8 Hz, 2H, H-4/H-5, H-6/-9), 9.29 (d, J = 7.3 Hz, 1H, D_2O-exchangeable, NH).

3-Acetylamino-5-chloronaphtho[1,2-b]furan-2(3H)one (**10**; $C_{14}H_{10}ClNO_3$)

Yield: 1.60 g (58%); m.p.: 239–240°C (decomp.; ethyl acetate); IR: 3300 (NH), 1835 (lactone-CO), 1660 (CON); ^{1}H NMR: 1.92 (s, 3H, $COCH_3$), 5.54 (d, 1H, D_2O-exchangeable, H-3), 7.56–8.38 (m, 5H, aromatic), 9.18 (d, 1H, D_2O-exchangeable, NH).

Methyl 2-acetylamino-4-oxo-3,4-diphenylbutyrate (**13**; $C_{19}H_{19}NO_4$)

To a solution of 1.34 g (5 mmol) of the trimethylsilyl ether of desoxybenzoin (**11**, [8]) in 10 ml of dry dichloromethane, a solution of 0.83 g (5 mmol) methyl *N*-acetyl-α-chloro-glycinate (**12**) [3] in 10 ml of dry dichloromethane and a solution of 2.61 g (10 mmol) of $SnCl_4$ in 10 ml of dry dichloromethane were added successively. After stirring at room temperature for 3 days, the mixture was treated with ice (25 g). The layers were separated, the water phase was extracted 3 times with dichloromethane, the organic phase was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The oily residue was washed with light petroleum and crystallized from diethyl ether.

Yield: 0.25 g (15%); m.p.: 143–144°C (*THF*/light petroleum); IR: 3350 and 3340 (NH), 1725 (COOR), 1670, 1675 (shoulder, CON, keto-CO); ^{1}H NMR: 1.77 (s, broad, 3H, $COCH_3$), 3.09 (s, broad, 3H, $COOCH_3$), 4.71–5.36 (m, 2H, 2×CH), 7.25–8.06 (m, 10H, aromatic), 8.41 (d, 1H, D_2O-exchangeable, NH).

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