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Heterocyclic Derivatives of 2-Amino-4-nitrophenol

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Summary. A new pathway for the synthesis of cyclic derivatives of 2-amino-4-nitrophenol by application of dibromoalkanes is described. This general method was used for the preparation of several heterocycles (partially saturated 1,4-benzoxazines, 1,5-benzoxazepines, 1,6-benzoxazocines). Two rotamers are present in solution of the *N*-formyl derivatives, the relative amounts depending on the solvent used.

Keywords. 2-Amino-4-nitrophenol; Cyclization; Dibromoalkane; Rotamer.

Heterozyklische Derivate von 2-Amino-4-nitrophenol

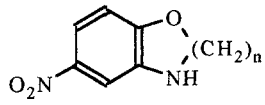
Zusammenfassung. Eine neue Methode zur Herstellung heterozyklischer Derivate von 2-Amino-4-nitrophenol wird vorgestellt. Dieses allgemeine Verfahren kann zur Synthese von verschiedenen Ringsystemen (partielle gesättigte 1,4-Benzoxazine, 1,5-Benzoxazepine, 1,6-Benzoxazocine) benutzt werden. In den Lösungen der *N*-Formyl-Derivate können zwei Rotamere identifiziert werden. Ihre relative Menge hängt vom Lösungsmittel ab.

Introduction

A new general synthesis was developed to produce compounds **1** (Scheme 1). These are important intermediates and may turn out as valuable products due to the well-known pharmacological and antimicrobial properties of unsubstituted 1,4-benzoxazine and its derivatives [1, 2].

2*H*-3,4-Dihydro-6-nitro-1,4-benzoxazine ($n = 2$) was prepared by the hydrolysis of the product of the reaction of 2-methoxy-5-nitroaniline with 2-chloroethyl chloroformate [3].

This benzoxazine derivative has also been obtained photochemically by irradiation of 1-amino-2-(4-nitrophenoxy)-ethane [4]. Ring types given in formula **1** (Scheme 1) with $n = 2$–4, unsubstituted or substituted with other groups (different from NO_2), can be synthesized by a *Beckmann* rearrangement [5, 6] or by reduction of the product obtained in the reaction of an *o*-amino-phenol with chloroalkanecarbonyl chloride [7, 8]. Since reducing agents are applied in the last two methods, these cannot be used for the preparation of any nitro-substituted compounds.



n > 1

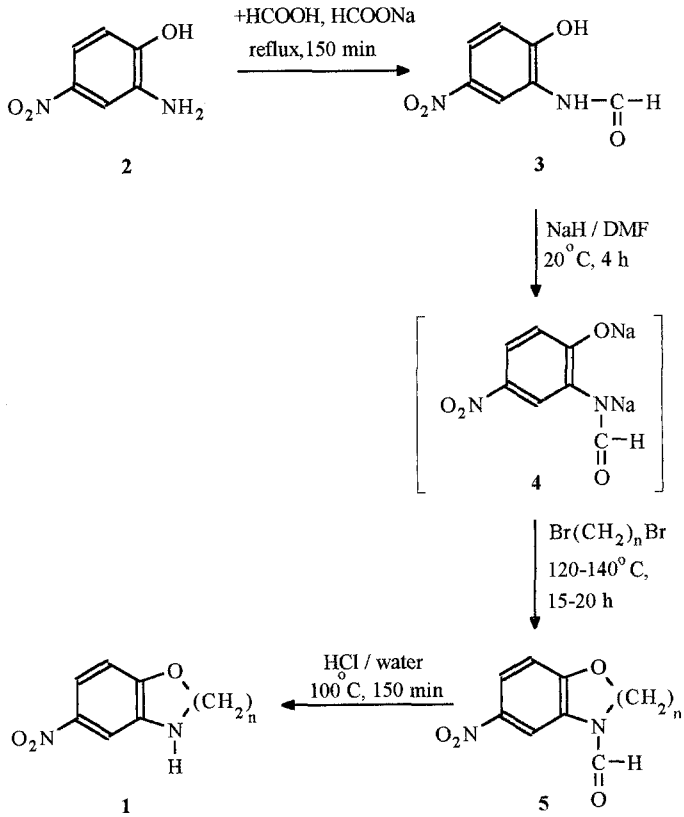
1

Scheme 1

Results and Discussion

Dihaloalkanes can be used in the production of open-chain and cyclic ($n = 2, 3$) derivatives of *o*-amino-phenol [2, 7–13]. These methods, however, have never been described for the preparation of compounds of type **1**. The partially saturated 1,6-benzoxazocine ($n = 4$) seems to be difficult to produce using dihaloalkanes, just like the nitro-substituted 1,4-benzoxazine ($n = 2$) and 1,5-benzoxazepine ($n = 3$).

In our approach, the amino group of 2-amino-4-nitrophenol (**2**) is first activated by a formyl group (**3**). Then the product is reacted with NaH. The salt obtained in *DMF* (**4**) resulted in the *N*-formyl derivatives of **1** (**5**) upon reaction with dibromoalkanes (see Scheme 2 and Table 1; the ^{1}H NMR data of these compounds are summarized in Table 3). The *N*-formyl-3,4-dihydro-6-nitro-1,4-benzoxazine mentioned in Ref. [1] was synthesized from 2*H*-3,4-dihydro-6-nitro-1,4-benzoxazine with



Scheme 2

Table 1. Compounds of type **5**

n	Yield (%)	m.p. (°C)	EIMS (rel. int. %)
2	42	123–125[a]	208 (M^+, 100), 180 (9), 165 (5), 134 (20), 119 (5), 106 (15), 79 (12), 77 (10), 51 (14)
3	23	102–104	222 (M^+, 100), 205 (14), 193 (17), 165 (95), 119 (17), 92 (11), 79 (12), 65 (15), 51 (11)
4	10	73–74	236 (M^+, 100), 219 (10), 207 (26), 165 (79), 119 (11), 92 (7), 79 (12), 65 (13), 55 (44), 51 (12), 41 (14), 39 (14)

[a] Ref. [1]: m.p.: 126–128 °C (ethanol)

Table 2. Compounds of type **1**

n	Yield %	m.p. (°C)	^{1}H NMR data ($CDCl_3$/*TMS*) δ (ppm)	EIMS (rel. int. %)
2	78	111–114[a]	3.48 (2H, m, N–CH_2) 4.10 (1H, bs, NH) 4.33 (2H, m, O–CH_2) 6.82 (1H, d, 6-H) 7.46 (1H, d, 3-H) 7.56 (1H, dd, 5-H)	180 (M^+, 100), 165 (3), 134 (21), 119 (6), 106 (17), 77 (9), 51 (13)
3	60	70–73	2.06 (2H, m, CH_2–CH_2–CH_2) 3.37 (2H, t, N–CH_2) 3.98 (1H, bs, NH) 4.25 (2H, t, O–CH_2) 6.96 (1H, d, 6-H) 7.57 (1H, d, 3-H) 7.62 (1H, dd, 5-H)	194 (M^+, 79), 175 (13), 165 (100), 138 (18), 119 (14), 92 (14), 65 (19), 51 (8)
4	100	84–89	1.78 (2H, m, N–CH_2–CH_2) 1.87 (2H, m, O–CH_2–CH_2) 3.66 (2H, t, N–CH_2) 4.12 (1H, bs, NH) 4.23 (2H, t, O–CH_2) 6.94 (1H, d, 6-H) 7.41 (1H, d, 3-H) 7.42 (1H, dd, 5-H)	208 (M^+, 100), 191 (6), 179 (21), 165 (57), 119 (14), 79 (11), 65 (13), 55 (15)

[a] Ref. [3]: m.p.: 120 °C (benzol)

formic acid [3]. The spectral data are not given there. Hydrolysis of **5** by HCl results in the formation of compounds **1** (Table 2).

In spite of the formation of salt **4**, the application of dibromoalkanes leads to several by-products. In most cases, these compounds could not be analysed by GC. It is reasonable to suppose that these are open-chain derivatives of *o*-amino-phenol

Table 3. ^{1}H NMR data of **5** in $CDCl_3$ and *DMSO*-d_6

n	$CDCl_3$/*TMS* δ (ppm)		*DMSO*-d_6/*TMS* δ (ppm)	
2	**A**:**B** = 3.5:1		**A**:**B** = 1:1	
	A	**B**	**A**	**B**
	4.01 (2H, t, N–CH_2)	3.82 (2H, t, N–CH_2)	3.92 (2H, t, N–CH_2)	3.86 (2H, t, N–CH_2)
	4.36 (2H, t, O–CH_2)	4.44 (2H, t, O–CH_2)	4.34 (2H, t, O–CH_2)	4.46 (2H, t, O–CH_2)
	7.06 (1H, d, 6-H)	7.01 (1H, d, 6-H)	7.18 (overlapped)	(Σ2H, d, 6-H)
	8.01 (1H, dd, 5-H)	7.96 (1H, dd, 5-H)	7.96 (overlapped)	(Σ2H, dd, 5-H)
	8.18 (1H, d, 3-H)	9.36 (1H, d, 3-H)	8.48 (1H, d, 3-H)	9.26 (1H, d, 3-H)
	8.92 (1H, s, C(O)H)	8.32 (1H, s, C(O)H)	9.06 (1H, s, C(O)H)	8.4 (1H, s, C(O)H)
3	**A**:**B** = 6:1		**A**:**B** = 4:1	
	A	**B**	**A**	**B**
	2.2 (overlapped)	(Σ4H, m, CH_2–CH_2–CH_2)	2.02 (2H, m, CH–CH_2–CH_2)	2.10 (2H, m, CH_2–CH_2–CH_2)
	3.96 (2H, t, N–CH_2)	3.84 (2H, t, N–CH_2)	3.82 (overlapped)	(Σ4H, t, N–CH_2)
	4.31 (overlapped)	(Σ4H, t, O–CH_2)	4.30 (2H, t, O–CH_2)	4.26 (2H, t, O–CH_2)
	7.16 (1H, d, 6-H)	7.14 (1H, d, 6-H)	(partly overlapped)	
	(partly overlapped)		7.23 (1H, d, 6-H)	7.25 (1H, d, 6-H)
	8.01 (1H, d, 3-H)	8.4 (1H, d, 3-H)	8.10 (1H, dd, 5-H)	8.06 (1H, dd, 5-H)
	8.11 (1H, dd, 5-H)	8.08 (1H, dd, 5-H)	8.23 (1H, d, 3-H)	8.25 (1H, d, 3-H)
	(partly overlapped)		(partly overlapped)	
	8.47 (1H, s, C(O)H)	8.32 (1H, s, C(O)H)	8.46(1H, s, C(O)H)	8.37 (1H, s, C(O)H)
4	**A**:**B** = 5:1		**A**:**B** = 1:3	
	A	**B**	**A**	**B**
	1.85–2.05 (overlapped)	(Σ8H, m, CH_2–$(CH_2)_2$–CH_2)	1.64–1.84 (overlapped)	(Σ8H, m, CH_2–$(CH_2)_2$–CH_2)
	3.84 (2H, t, N–CH_2)	3.76 (2H, t, N–CH_2)	3.73 (2H, t, N–CH_2)	3.67 (2H, t, N–CH_2)
	4.34–4.44 (overlapped)	(Σ4H, m, O–CH_2)	4.32 (2H, t, O–CH_2) (partly overlapped)	4.34 (2H, t, O–CH_2)
	7.19 (overlapped)	(Σ2H, d, 6-H)	7.33 (overlapped)	(Σ2H, d, 6-H)
	8.00 (overlapped)	(Σ2H, d, 3-H)	8.09 (partly overlapped)	8.19 (Σ2H, d, 3-H)
	8.16 (1H, dd, 5-H) (partly overlapped)	8.12 (1H, dd, 5-H)	8.20 (overlapped)	8.14 (Σ2H, dd, 5-H)
	8.37 (1H, s, C(O)H)	8.41(1H, s, C(O)H)	8.37(1H, s, C(O)H)	8.32 (1H, s, C(O)H)

[2, 9]. Because of these by-products, compounds **5** had to be isolated by column chromatography. The ^{1}H NMR spectra indicate the presence of two isomers (**A** *exo* and **B** *endo*). Two approximate A_2X_2 spin systems were observed at 300 MHz in the ^{1}H NMR spectrum for the methylene protons of the oxazine ring. The relative amount of the two isomers is strongly solvent-dependent (Fig. 1). The integral ratios of the two systems were 3.5:1 in $CDCl_3$ and about 1:1 in *DMSO*-d_6.

The influence of the solvent on the population of the different isomers suggests conformational isomerism that is, most probably, due to the hindered rotation around the C(O)–N bond with partial double-bond character. Similar behaviour of

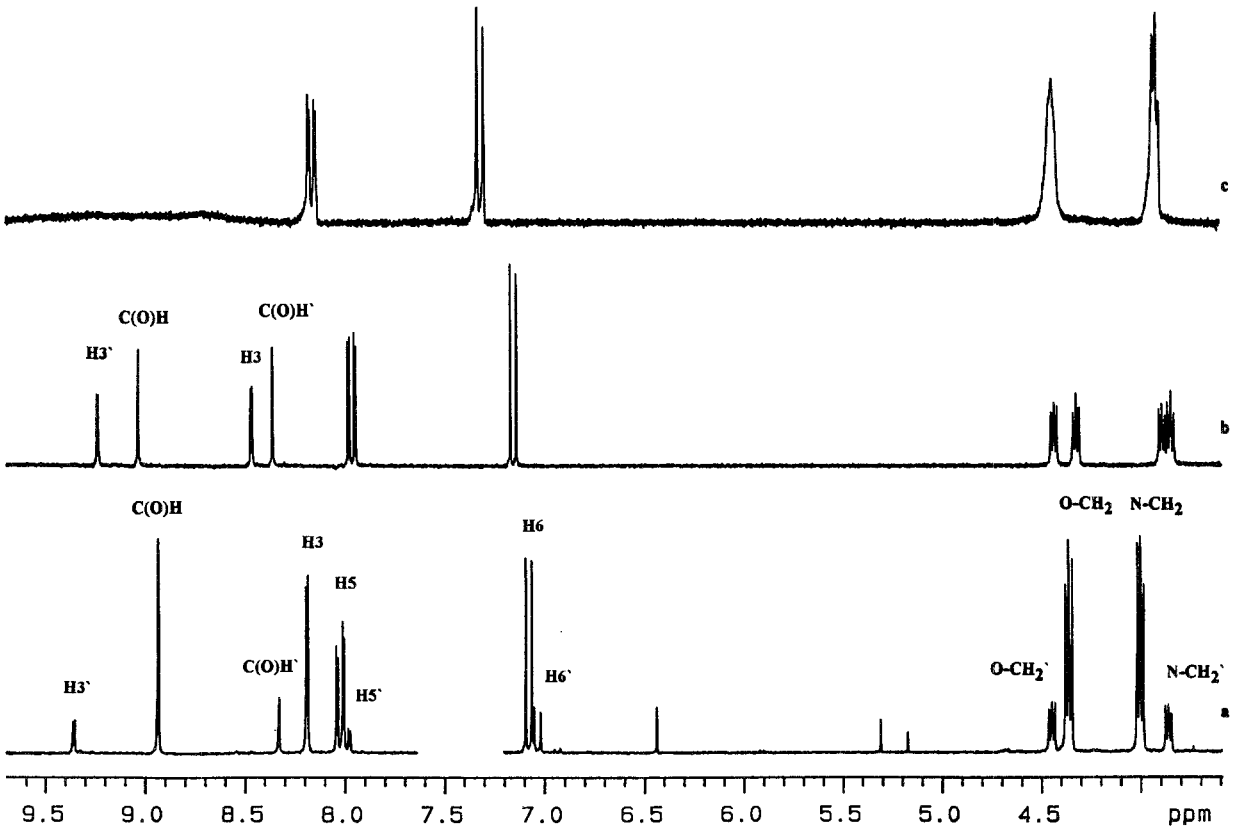
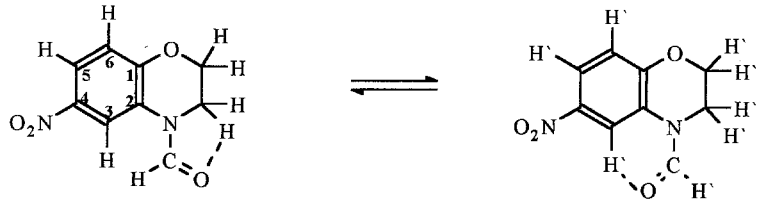


Fig. 1. Temperature and solvent dependence of the ^{1}H NMR spectrum of **5** ($n = 2$); (a) solvent: $CDCl_3$, temperature: 293 K; (b) solvent: *DMSO*-d_6, temperature: 293 K; (c) solvent: *DMSO*-d_6, temperature: 453 K

the amide bond has already been described [14, 15] in *N*-acyl- and *N*-formyl-1,2,3,4-tetrahydroquinoline derivatives. At elevated temperatures (453 K), the signals of the two rotamers collapse (Fig. 1c). As it was shown for the benzoxazine derivative by NOE difference experiments [16], the rotamers are stabilized further by hydrogen bonding between the formyl oxygen and either the methylene hydrogens or the aromatic protons at position 3 (see structures **A** and **B** in Scheme 3). It seems that **A** is the favoured rotamer in $CDCl_3$, whereas in *DMSO*-d_6 both isomers are approximately equally populated.

With the other heterocycles (1,5-benzoxazepine and 1,6-benzoxazocine), the *exo* form is the more populated one in most cases. The *endo* form of the benzoxazocine derivative, however, is favoured in *DMSO*-d_6 (Table 3).

We also attempted to synthesize compound **1** ($n = 5$, 1,7-benzoxazonine), but the corresponding intermediate **5** could not be isolated by our method. We found, however, a peak at $m/e = 250$ by GC-MS analysis of the crude product which corresponds to the molecular ion of the desired compound. Data in Table 1 indicate that the yield of the cyclic products decreases with the size of the heterocycle.



A **B**

(exo) ***(endo)***

Scheme 3

Experimental

Melting points were determined on a Boëtus hot-stage apparatus. IR spectra were obtained on a Specord 75 IR spectrometer. NMR spectra were recorded on a Varian UNITY-300 NMR spectrometer. $CDCl_3$ and *DMSO*-d_6 were used as solvents with *TMS* as internal standard. Mass spectra were recorded on a Hewlett Packard GC-MSD under conditions as follows: GC: 5890 II, carrier gas: He, column: HP-1 (12 m × 0.2 mm × 0.33 μm); MSD: 5971A, EI mode, ionization electron energy 70 eV, ion source temperature: 280 °C. All starting materials were purchased form Fluka AG and used without further purification.

2-(N-formyl)amino-4-nitrophenol (**3**)

Sodium formate (7.0 g, 100 mmol) and 2-amino-4-nitrophenol (15 g, 100 mmol) were suspended in formic acid (75 ml). The mixture was stirred under reflux for 150 minutes. The precipitate was filtered at room temperature and washed with water until neutral. After drying on air, 15.1 g (94%) light brown crystals were collected. M.p.: 257–261 °C (decomposition); Ref. [17]: m.p.: 245 °C (decomposition); IR (KBr): ν(NH) = 3325, ν(Amid) = 1660, $\nu_{as}(NO_2)$ = 1540, $\nu_s(NO_2)$ = 1340, ν(CO) = 1290 cm^{-1}; ^1H NMR (*DMSO*-d_6): δ = 7.03 (1H, d, 6-H), 7.9 (1H, dd, 5-H); 8.38 (1H, s, C(O)H), 9.1 (1H, d, 3-H), 10.0 (1H, s, NH) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 160.86 (CO), 153.17(C-1), 126.47 (C-2), 115.49 (C-3), 139.38 (C-4), 120.71 (C-5), 114.61 (C-6) ppm; ^{13}C NMR (*DMSO*-d_6), Ref. [17]: δ = 161.0 (CO), 153.2 (C-1), 126.5 (C-2), 115.6 (C-3), 139.5 (C-4), 120.7 (C-5), 114.6 (C-6) ppm.

General procedure for the synthesis of **5**

3 (3.6 g, 20 mmol) was dissolved in *DMF* (45 ml); then, 80% NaH (1.8 g, 60 mmol) was added slowly in little portions to the solution which was stirred for four h forming an orange suspension. It was allowed to stand overnight and then stirred and heated to 120 °C. The suspension transformed into a thick dark brown solution to which dibromoalkane (30 mmol) was added dropwise at 120–140 °C. This step was repeated with the same quantity of dibromoalkane after 7 h of heating. After 9 h, the reaction mixture was cooled to room temperature, and 80% NaH (0.9 g, 30 mmol) was added, followed by further heating for 6 to 11 h. The reaction was monitored by TLC on silica gel with 3% methanol in chloroform as the mobile phase. When the reaction was complete, the mixture was filtered at room temperature. The precipitate was washed with ethyl acetate (2 × 50 ml) and the washings were combined with the filtrate. The combined phases were washed with saturated sodium carbonate solution (1 × 200 ml, 3 × 100 ml), dried over anhydrous magnesium sulfate, filtered, and evaporated to yield the crude product which was chromatographed on Kieselgel 60 (20 g, 0.2–0.5 mm, elution with 20 and 30% chloroform in hexane). Crystallization yielded 10–42% yellow product. Yields, physical, and spectral data are summarized in Tables 1 and 3.

General procedure for the synthesis of **1**

5 (2 mmol) was suspended in 1 *N* hydrochloric acid (40 ml) and stirred and refluxed for 150 min. After cooling to room temperature, 1 *N* sodium hydroxide solution (70 ml) was added to the mixture. The precipitate formed was extracted with ethyl acetate (1 × 100, 3 × 30 ml). The latter was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was crystallized from diethyl ether/petroleum ether to yield 60–100% reddish product (Table 2).

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