Monatshefte für Chemie 130, 1481–1486 (1999)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Synthesis and Study of Isomeric Benzo[1,4]oxazines and Benzothiazolines by NMR Spectroscopy and X-Ray Crystallography

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Summary. Reaction of 2-aminophenol and 2-aminothiophenol with 1-phenyl-1,2-propanedione yields a mixture of both possible isomeric benzo[1,4]oxazines and benzothiazolines which were characterized by NMR spectroscopy. In addition, the structures for 3-methyl-2-phenyl-2*H*-benzo[1,4]-oxazin-2-ol and 1-(2-phenyl-2,3-dihydro-benzothiazol-2-yl)-ethanone were established by X-ray diffraction analysis.

Keywords. NMR; X-Ray; Benzo[1,4]oxazine; Benzothiazoline.

Synthese und Studium der isomeren Benzo[1,4]oxazine und Benzothiazine mit Hilfe von NMR-Spektroskopie und Röntgenstrukturanalyse

Zusammenfassung. Reaktion von 2-Aminophenol und 2-Aminothiophenol mit 1-Phenyl-1,2-propandion gibt eine Mischung der beiden möglichen isomeren Benzo[1,4]oxazine und Benzothiazoline, die durch NMR-Spektroskopie charakterisiert wurden. Darüber hinaus wurden die Strukturen von 3-Methyl-2-phenyl-2*H*-benzo[1,4]oxazin-2-ol und 1-(2-Phenyl-2,3-dihydro-benzothiazol-2-yl)-ethanon durch Röntgenstrukturanalyse gesichert.

Introduction

It is well known that the condensation reaction of 2-aminothiophenol with glyoxal or 2,3-butanedione affords 2,2′-dibenzothiazolidines [1–2], whereas benzil yields 2-benzoyl-2-phenylbenzothiazolines [3]. Studies concerning various aspects of the synthesis and chemistry of this interesting class of compounds have been undertaken recently [4–11].

We now report a study concerning 3-methyl-2-phenyl-2*H*-benzo[1,4]-oxazin-2-ol (**1a**), 2-methyl-3-phenyl-2*H*-benzo[1,4]-oxazin-2-ol (**1b**), (2-methyl-2,3-dihydro-benzothiazol-2-yl)-phenyl-methanone (**2a**), and 1-(2-phenyl-2,3-dihydro-benzothiazol-2-yl)-ethanone (**2b**) obtained from 2-aminophenol and 2-aminothiophenol with 1-phenyl-1,2-propanedione. In contrast to results described in

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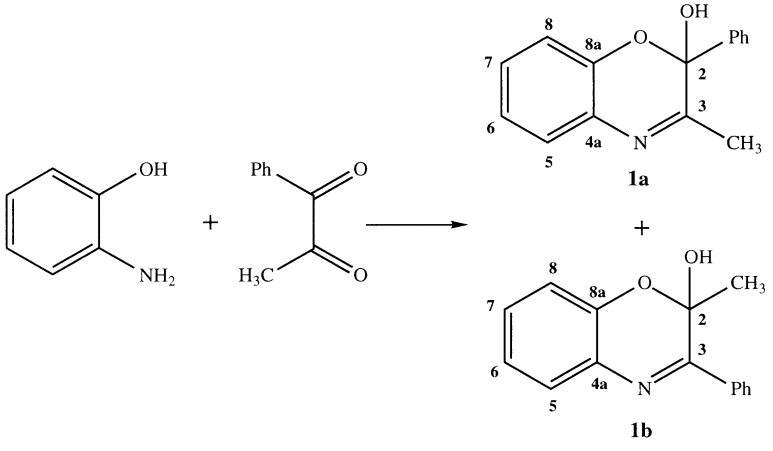
the literature [5] it is shown that the reaction provides a mixture of isomers, the major product being derived from an attack at the more reactive acetyl group.

Results and Discussion

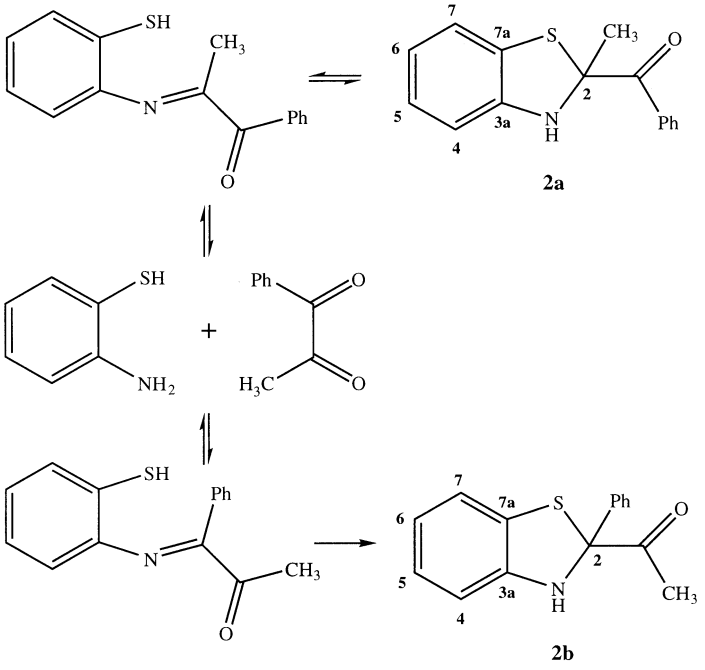
The reaction of 2-aminophenol with 1-phenyl-1,2-propanedione led to a mixture of the isomers **1a** and **1b** in a 3:2 ratio which was separated by crystallization (Scheme 1). The ^{13}C NMR spectra of **1a** and **1b** show that the chemical shifts for the two compounds are very similar; however, the signals for C-4a, C-2, and CH_3 in **1a** are at 141.0, 94.0 and 22.3 ppm, whereas those for **1b** are found at 136.2, 92.9, and 26.6 ppm. In the ^{1}H NMR spectra the signals for the methyl groups are at 1.87 and 1.66 ppm for **1a** and **1b**. Unequivocal ^{1}H and ^{13}C spectroscopic assignments for **1a** and **1b** was achieved by 2D correlated experiments. Although **1b** has been described in the literature [5], neither its ^{1}H nor its ^{13}C NMR spectra have been reported. The structure for **1a** was established by X-ray diffraction analysis (Fig. 1) which shows that the molecule is present in a *pseudo*-chair conformation where the phenyl group occupies a *pseudo*-equatorial and the hydroxyl group a *pseudo*-axial position as expected for this kind of compounds [10].

Reaction of 2-aminothiophenol with 1-phenyl-1,2-propanedione provides a mixture of (2-methyl-2,3-dihydro-benzothiazol-2-yl)-phenyl-methanone (**2a**) and 1-(2-phenyl-2,3-dihydro-benzothiazol-2-yl)-ethanone (**2b**) in a 6:1 ratio as shown by ^{1}H NMR (Scheme 2). Compound **2a** could not be separated neither by crystallization nor by columm chromatography; it was therefore characterized from the spectrum of the reaction mixture. On the other hand, compound **2b** was obtained in quantitative yield by isomerization of **2a** (Scheme 2).

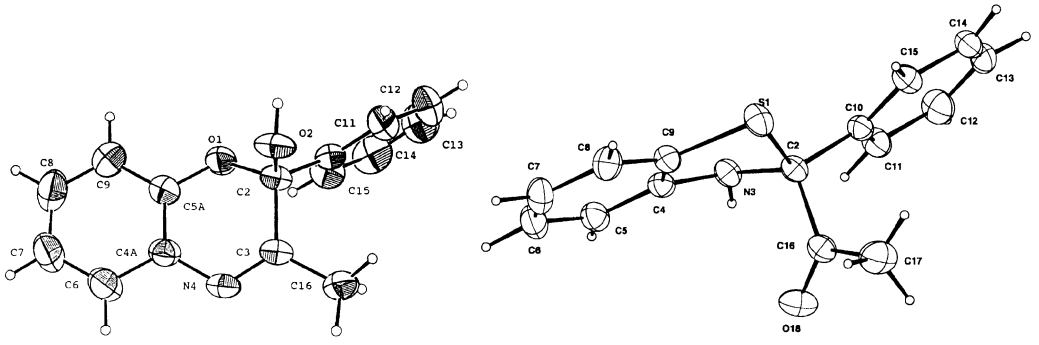
It is interesting to note that the signals for CO, C-2, and the methyl group in the ^{13}C NMR spectrum of **2a** are at 197.4, 78.4, and 30.5 ppm, whereas those for **2b** are shifted to 202.7, 86.3, and 24.4 ppm. Complete assignment was achieved by 2D correlated experiments and comparison with analogues described in a previous work [6]. In addition, the mass spectra show the ion $m/z = 212$ and $m/z = 150$ corresponding to loss of CH_3CO and PhCO groups in **2b** and **2a**. Examination of



Scheme 1



Scheme 2



1a **2b**

Fig. 1. X-Ray structures of **1a** and **2b**

2b by single crystal X-ray crystallographic analysis confirmed the proposed structure (Fig. 1).

We conclude that, in contrast to the high stereoselectivity observed in norephedrines and phenylglycinol, the reaction of 2-aminophenol and 2-aminothiophenol with 1-phenyl-1,2-propanedione is not stereoselective, since the two possible diastereomers are obtained. As expected, the major products for 2-aminophenol derivatives correspond to imine formation at the methyl ketone as observed in previous studies [9, 10]. In the case of 2-aminothiophenol, the

preferred products are of the benzothiazoline type structures. Nevertheless, (2-methyl-2,3-dihydro-benzothiazol-2-yl)-phenyl-methanone (**2a**) was found to be unstable, and after 24 hours it isomerizes to 1-(2-phenyl-2,3-dihydro-benzothiazol-2-yl)-ethanone (**2b**) which is thermodynamically more stable.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on Jeol-270 and Jeol Eclipse +400 spectrometers. Chemical shifts (ppm) are relative to internal *TMS*, coupling constants are quoted in Hz. The HETCOR standard pulse sequence, which incorporates quadrature detection in both domains, was used. Infrared spectra were recorded on a Perkin Elmer 16F-PC FT-IR spectrophotometer. Mass spectra were obtained with an HP 5989A mass spectrometer. Melting points were measured on a Gallenkamp MFB-595 apparatus and are uncorrected. Elemental analyses were found to be in good agreement with the calculated values. The X-ray crystallographic studies were done on an Enraf Nonius CAD4 diffractometer, $\lambda(\mathrm{Mo}K_\alpha) = 0.71$ Å, graphite monochromator, $T = 293$ K, $\omega/2\theta$ scan, range $2 < \theta < 25°$. Corrections were made for *Lorentz* and polarization effects. The structures were solved by direct methods using SHELXS-86 [12] and MOLEN. All nonhydrogen atoms were refined anisotropically using full-matrix least squares (MOLEN [13] for **1a** and CRYSTALS [14] for **2b**), and hydrogen atoms were found by difference *Fourier* maps and refined with an overall isotropic thermal parameter. Crystal data, collection, and refinement parameters are given in Table 1. Additional information has been deposited at the Cambridge Crystallographic Data Centre (CCDC 120973 for **1a**, CCDC 120974 for **2b**).

Preparation of compounds **1a** and **1b**

To a solution of 0.5 g 2-aminophenol (4.58 mmol) in 20 cm^3 of *THF*, 0.61 cm^3 1-phenyl-1,2-propanedione (4.58 mmol) were added. After stirring at −78 °C for 8 h the solvent was removed

Table 1. Crystallographic data for **1a** and **2b**.

	1a	**2b**
Formula	$C_{15}H_{13}NO_2$	$C_{15}H_{13}NOS$
Fw ($g \cdot mol^{-1}$)	239.28	255.33
Crystal size (mm)	0.50×0.30×0.20	0.25×0.15×0.10
Crystal system	monoclinic	monoclinic
Space group	P 2_1/c	P 2_1/n
a (Å)	8.849(1)	11.865(2)
b (Å)	12.305(1)	7.3778(4)
c (Å)	11.474(1)	14.202(2)
β (deg)	96.55(7)	103.82(1)
V (Å^3)	1241.2(2)	1266.2(3)
Z	4	4
D_{calcd} (g/cm^3)	1.28	1.40
No. collecd. rflns.	2158	2783
No. of ind. rflns.	2158	2474
No. of obsd. rflns.	1299	1610
No. of parameters	216	204
R	0.037	0.035
R_w	0.048	0.032

under vacuum. The resulting precipitate was washed with ethanol to give 0.75 g (80%) of a mixture of **1a** and **1b** in a 3:2 ratio. Separation was carried out by recrystallization using a mixture of methanol/hexane.

3-Methyl-2-phenyl-2H-benzo[1,4]-oxazin-2-ol (**1a**; $C_{15}H_{13}NO_2$)

M.p.: 170–172°C; ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 8.01 (1H, s, OH), 7.54 (1H, dd, $J = 7.9$, 1.3 Hz, H-*o*), 7.49–7.40 (3H, m, H-*m*,*p*), 7.37 (1H, dd, $J = 7.9$, 1.3 Hz, H-5), 7.20 (1H, td, $J = 7.9$, 1.3 Hz, H-7), 7.03 (1H, td, $J = 7.9$, 1.3 Hz, H-6), 6.96 (1H, dd, $J = 7.9$, 1.3 Hz, H-8), 1.87 (3H, s, CH_3) ppm; ^{13}C NMR (67.80 MHz, δ, *DMSO*-d_6): 162.3 (C-3), 145.0 (C-8a), 141.0 (C-4a), 131.0 (C-*i*), 128.7 (C-*p*), 128.2 (C-7), 128.1 (C-*m*), 126.6 (C-5), 126.1 (C-*o*), 121.5 (C-6), 115.9 (C-8), 94.0 (C-2), 22.3 (C-CH_3) ppm; MS: *m/z* (%) = 239 (M^+, 7), 224 (1), 211 (3), 196 (100), 167 (4), 134 (30), 104 (13), 103 (2), 91 (2), 90 (1), 89(1), 78 (3), 77 (19), 65 (25), 64 (4); IR (KBr): $\tilde{\nu} = 3654$, 3442 (OH), 3350, 3000, 2788, 2000, 1700, 1652 (C=N), 1595, 1575, 1470, 1125, 1200, 1075, 1020 cm^{-1}.

2-Methyl-3-phenyl-2H-benzo[1,4]-oxazin-2-ol (**1b**; $C_{15}H_{13}NO_2$)

M.p.: 120–123°C (Ref. [5]: 120–122°C; ^{1}H NMR (270 MHz, δ, *DMSO*-d_6): 7.86 (1H, s, OH), 7.84 (1H, dd, $J = 6.59$, 1.3 Hz, H-*o*), 7.47–7.49 (3H, m, H-*m*, *p*), 7.44 (1H, dd, J = 7.9, 1.3 Hz, H-5), 7.24 (1H, td, $J = 7.9$, 1.3 Hz, H-7), 7.04 (1H, td, $J = 7.9$, 1.3 Hz, H-6), 6.99 (1H, dd, $J = 7.9$, 1.3 Hz, H-8), 1.66 (3H, s, CH_3) ppm; ^{13}C NMR (67.80 MHz, δ, *DMSO*-d_6): 161.6 (C-3), 145.1 (C-8a), 136.2 (C-4a), 132.0 (C-*i*), 129.9 (C-*p*), 128.8 (C-7), 128.2 (C-*o*), 128.0 (C-*m*), 127.3 (C-5), 121.6 (C-6), 116.1 (C-8), 92.9 (C-2), 26.6 (C-CH_3) ppm; MS: *m/z* (%) = 239 (M^+, 6), 222 (3), 196 (100), 167 (4), 104 (11), 103 (1), 93 (10), 92 (1), 77 (12), 65 (20), 64 (3); IR (KBr): $\tilde{\nu} = 3628$ (OH), 3158, 1670, 1616, 1576, 1456, 1254 cm^{-1}.

Preparation of compounds **2a** *and* **2b**

To a solution of 1.07 cm^3 2-aminothiophenol (10 mmol) in 10 cm^3 *THF*, 1.3 cm^3 1-phenyl-1,2-propanedione (10 mmol) were added at 0°C. After being stirring for 3 h, the solvent was removed under vacuum affording 2.42 g (95%) of a mixture of **2a** and **2b** in a 6:1 ratio as determined by ^{1}H NMR.

(2-Methyl-2,3-dihydro-benzothiazol-2-yl)-phenyl-methanone (**2a**; $C_{15}H_{12}NSO$)

^{1}H NMR (400 MHz, δ, $CDCl_3$): 8.07 (1H, d, $J = 7.3$, Hz, H-*o*), 7.58 (1H, t, $J = 7.3$ Hz, H-*m*), 7.48 (1H, t, $J = 7.3$ Hz, H-*p*), 7.05 (1H, d, $J = 7.8$, Hz, H-4), 7.01 (1H, t, $J = 7.3$ Hz, H-5), 6.83 (1H, d, $J = 7.3$ Hz, H-6), 6.80 (1H, d, $J = 7.3$ Hz, H-7), 2.05 (3H, s, CH_3) ppm; ^{13}C NMR (100.5 MHz, δ, $CDCl_3$): 197.4 (C=O), 145.5 (C-3a), 136.9 (C-*i*), 131.9 (C-*p*), 131.6 (C-7a),129.9 (C-*o*), 128.5 (C-*m*), 126.0 (C-5), 121.5 (C-7), 121.3 (C-6), 112.1 (C-4), 78.4 (C-2), 30.5 (C-CH_3) ppm; MS: *m/z* (%) = 255 (M^+, 1), 150 (100), 109 (30).

1-(2-Phenyl-2,3-dihydro-benzothiazol-2-yl)-ethanone (**2b**; $C_{15}H_{12}NSO$)

M.p.: 153–155°C; ^{1}H NMR (270 MHz, δ, $CDCl_3$): 7.59 (1H, dt, $J = 7.6$, 1 Hz, H-*o*), 7.44–7.32 (3H, m, H-*m*,*p*), 7.08 (1H, dd, $J = 8$, 1 Hz, H-4), 6.97 (1H, td, $J = 8$, 1 Hz, H-5), 6.80 (1H, td, $J = 8$, 1, Hz, H-6), 6.79 (1H, dd, $J = 8$, 1 Hz, H-7), 2.21 (3H, s, CH_3) ppm; ^{13}C NMR (67.8 MHz, δ, $CDCl_3$): 202.7 (C=O), 145.9 (C-3a), 138.8 (C-*i*), 128.9 (C-*m*, *p*), 127.0 (C-*o*), 126.1 (C-5), 125.0 (C-7a), 121.7 (C-7), 121.4 (C-6), 112.0 (C-4), 86.3 (C-2), 24.4, (C-CH_3) ppm; MS: *m/z* (%) = 255 (M^+, 1), 212 (100), 109 (21), 135 (7), 77 (7); IR (KBr) $\tilde{\nu} = 3338$, 1460, 1580, 1702, 1446, 1178, 724, 640 cm^{-1}.

Acknowledgements

We are grateful to CONACYT for financial support and to Prof. Dr. *H. Nöth* for elemental analyses.

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Received April 7, 1999. Accepted (revised) May 20, 1999