

# **On the Synthesis and Reactivity of** **4-(Oxiran-2-ylmethoxy)cinnoline:** **Targeting a Cinnoline Analogue of Propranolol**

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## **Abstract**

The title compound (**2**) was prepared by reaction of 4-chlorocinnoline with glycidol/sodium hydride in dry DMF, since treatment of cinnolin-4-ol with epichlorohydrin as well as oxidation of 4-allyloxycinnoline did not succeed. Reaction of **2** with primary and secondary amines leads to aminoalcohols characterized by a high tendency to rearrangement and/or elimination. The obtained products were subjected to detailed multinuclear ( $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$ ) NMR studies.

## **Keywords**

Cinnolines • Cinnolin-4(1*H*)-one • Epoxides • Nucleophilic Substitution • NMR Spectroscopy

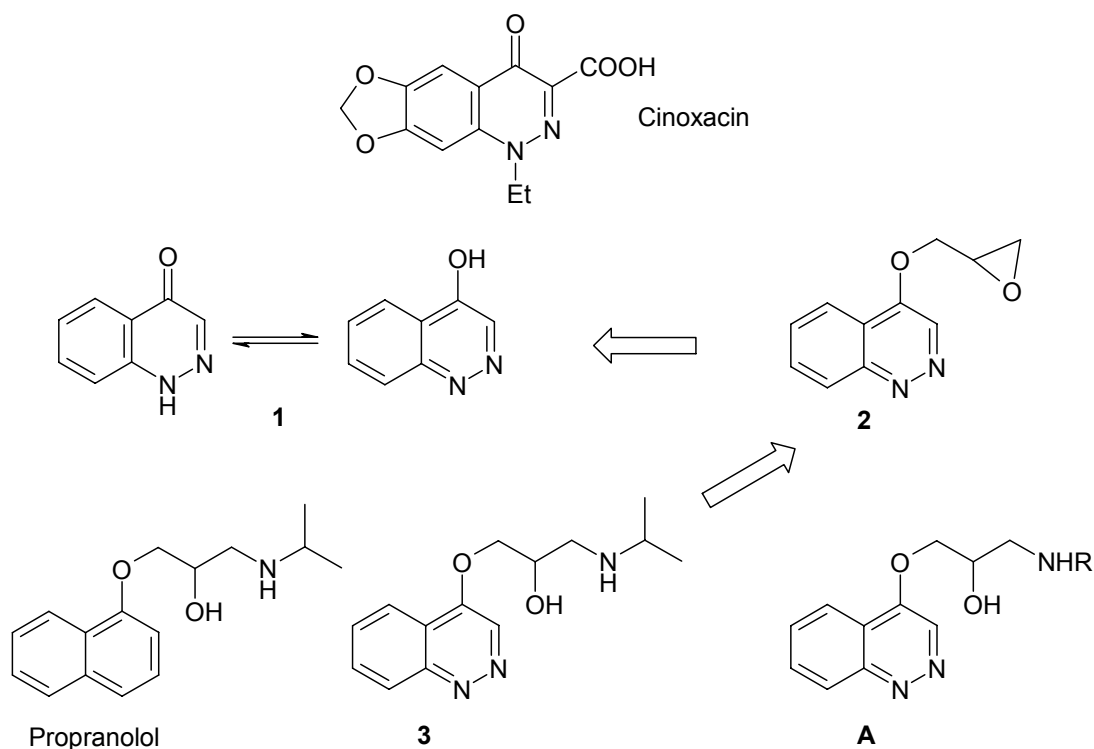
## **Introduction**

Although the pyridazine nucleus is the core of many biologically active compounds and drug molecules [1], benzo[*c*]pyridazine – i. e. cinnoline – is a rather rarely assayed system to which relatively little attention has been focused. Thus, the antibacterial agent Cinoxacin (Figure 1) is yet the only example on the market of a drug molecule containing a cinnoline moiety [2, 3]. In continuation of our studies on 4-substituted cinnolines capable of prototropic tautomerism [4], for instance cinnolin-4-ol (**1**), we were interested in aminoalcohols of type **A** which should be accessible from **1** *via* the epoxide **2** following established methods (Figure 1). Aminocompounds **A** seemed to be of high interest due to their structural

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similarity with well-known drug molecules. For example, the congener with R = *i*-Pr (**3**) is a diaza analogue of the beta-adrenergic receptor blocking agent Propranolol (Inderal<sup>®</sup>), which is used in the treatment of hypertension or cardiac arrhythmias [5] (Scheme 1). Moreover, closely related systems have been found to act as modulators of multi-drug resistance [6].



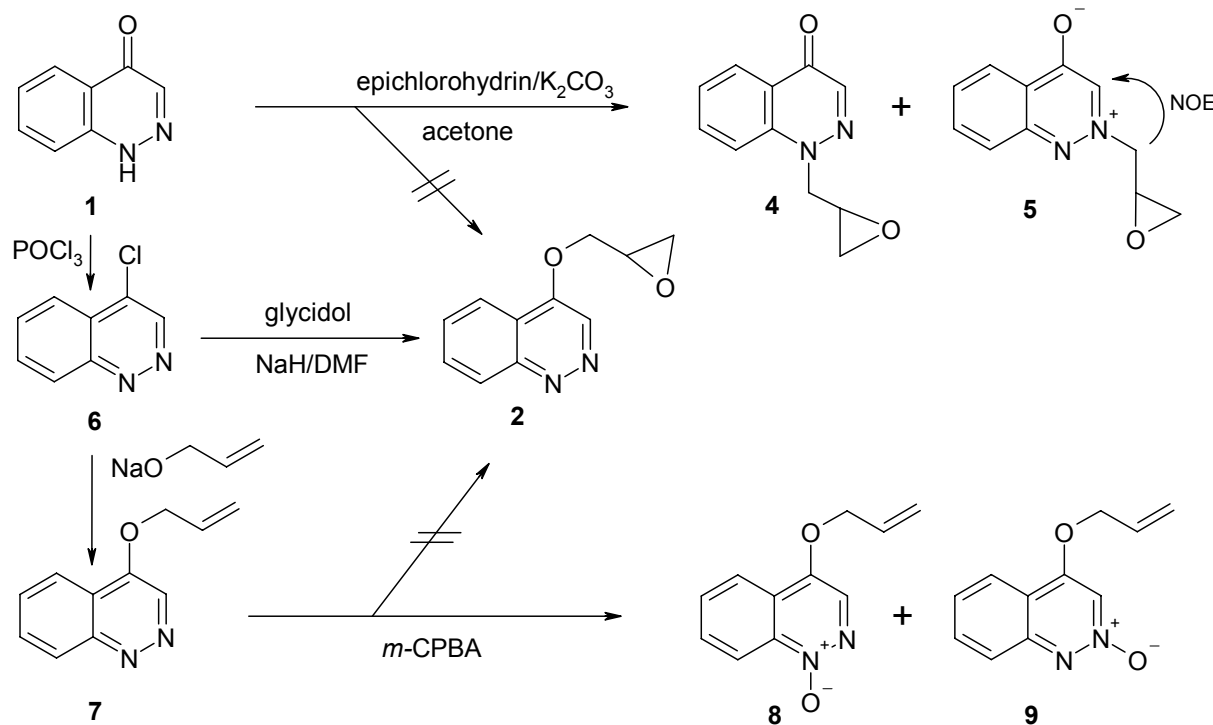
**Fig. 1.**

## Results and Discussion

### Chemistry

The hitherto unknown epoxide **2** is the crucial intermediate in the construction of compounds **A**. The latter should be accessible by ring-opening of the oxirane ring in **2** upon reaction with appropriate amines. Initially, for the attempted synthesis of **2**, cinnolin-4-ol (**1**) was reacted with epichlorohydrin in the presence of  $K_2CO_3$ . Expectedly, from the reaction mixture the desired *O*-alkyl product **2** could not be isolated, but the corresponding *N*-alkylation products **4** and **5** were obtained in low yields (Scheme 1). It should be mentioned that **1**, which is exclusively present in the cinnolin-4(1*H*)-one form in polar organic solvents [4], exhibited a similar reaction

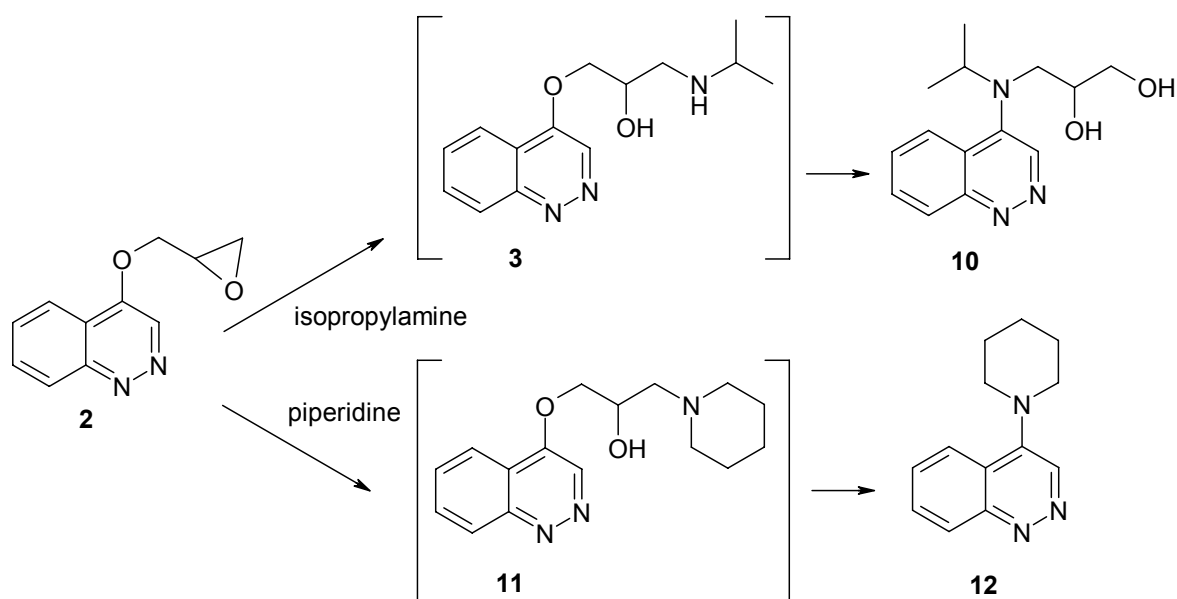
behavior in methylation reactions using different conditions such as iodomethane/ $K_2CO_3$ , dimethyl sulfate, 4-toluenesulfonic acid methyl ester, methanol (in a Mitsunobu-type reaction [7]) [4].



### Sch. 1.

Alternatively, it is known that 4-alkoxycinnolines are smoothly available from reaction of 4-chlorocinnoline (**6**) with appropriate sodium alkoxides [2]. As preliminary tests with the sodium salt of glycidol were not successful, **6** was reacted with 2-propen-1-ol/Na to afford the 4-allyloxycinnoline (**7**) in high yield (Scheme 1). Unfortunately, we did not succeed in the transformation of **7** into **2**: Treatment with various oxidizing agents (for instance *m*-chloroperbenzoic acid/ $CH_2Cl_2$ ) resulted in *N*-oxidation (formation of a mixture of *N*-oxides **8** and **9**), whereas the exocyclic double bond remained unaffected. Ultimately, the desired epoxide **2** was obtained in satisfactory yields (70%) from **6** and glycidol/NaH after optimization of the reaction conditions (simultaneous addition of **2** and glycidol to a suspension of NaH in dry DMF) (Scheme 1).

For the synthesis of the target structure **3**, epoxide **2** was refluxed with *iso*-propylamine. However, instead of **3** its structural isomer **10** was isolated (Scheme 2). The formation of **10** can be explained by rearrangement of the initially formed **3** *via* nucleophilic substitution of the amino nitrogen atom at cinnoline C-4. The lability of compounds **A** was also confirmed by the reaction of **2** with piperidine: Whereas in the raw product mainly the desired aminoalcohol **11** – accompanied by small amounts of 4-piperidin-1-ylcinnoline (**12**) – was detected by NMR analysis ( $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$ ), after preparative layer chromatography **12** remained as the sole product in 25% yield. Thus it can be suggested that in the course of the purification procedure **11** completely decomposed into **12** (Scheme 2). In conclusion, compounds of type **A** are, in principle, formed from the title compound **2** by reaction with appropriate amines but show a high tendency to convert into *N*-substituted cinnolines.



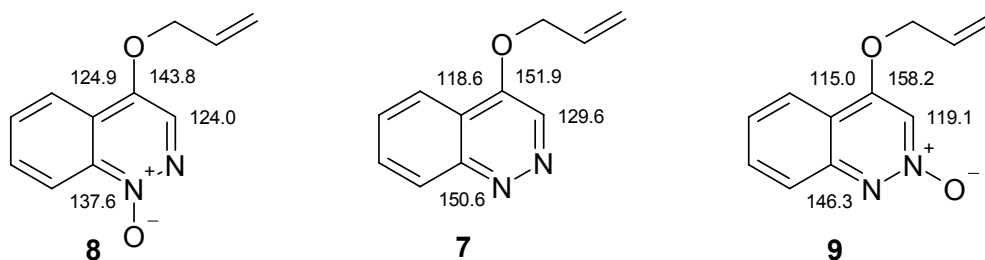
## Sch. 2.

### ***NMR Spectroscopic Investigations***

The NMR data of all investigated compounds are given in Tables 1–3. In DMSO- $d_6$  solution compound **1** is exclusively present in the NH-form – i. e. as cinnolin-4(1*H*)-one – what is clearly reflected by the appearance of two different

types of N-atoms in the  $^{15}\text{N}$ -NMR spectrum (N-1:  $\delta$  -206.8 ppm, N-2:  $\delta$  -42.4 ppm) as well as by the relatively large chemical shift of C-4 ( $\delta$  170.3 ppm), indicating the latter C-atom to be a carbonyl-type one [4]. In contrast, epoxide **2** – characterized by an aromatic cinnoline system – shows a remarkably smaller chemical shift for C-4 ( $\delta$  151.9 ppm) and two ‘pyridine-type’  $^{15}\text{N}$ -NMR resonances (N-1:  $\delta$  14.1 ppm, N-2:  $\delta$  35.2 ppm). Both the  $^{13}\text{C}$ - and the  $^{15}\text{N}$ -NMR chemical shifts of the cinnoline atoms in **2** resemble closely those found in 4-methoxycinnoline [4]. The ‘inner salt’ **5** can be easily distinguished from its N-1-substituted structural isomer **4** considering NOEs between the diastereotopic  $\text{NCH}_2$  protons of **5** and cinnoline H-3 as well as a correlation in the HMBC spectrum ( $\text{NCH}_2 \rightarrow \text{C-3}$  via  $^3J$ ). In the spectra of the 1-substituted cinnolin-4(1*H*)-one **4**, corresponding correlations are not detected owing to the larger distance between the involved nuclei. Moreover, it should be mentioned that the  $^1\text{H}$ -,  $^{13}\text{C}$ -, and  $^{15}\text{N}$ -NMR chemical shifts of the cinnoline ring atoms in **4** are very similar to those found for the related 1-methylcinnolin-4(1*H*)-one [4].

The discrimination between N-oxides **8** and **9** was accomplished on the basis of substituent effects. It is known that upon N-oxidation of pyridine or pyridazine the resonances of the carbons located in the ortho- or para position to the =N–O moiety receive a distinct upfield shift (what can be rationalized considering suitable resonance forms) [8]. Thus, in the  $^{13}\text{C}$ -NMR spectrum of **8** the resonances of C-3 ( $\delta$  124.0 ppm), C-4 ( $\delta$  143.8 ppm) and C-8a ( $\delta$  137.6 ppm) show smaller chemical shifts than the corresponding atoms in the ‘parent compound’ **7** ( $\delta$  C-3: 129.6 ppm,  $\delta$  C-4: 151.9 ppm,  $\delta$  C-8a: 150.6 ppm), whereas in **9** the signals due to C-3 ( $\delta$  119.1 ppm) and C-4a ( $\delta$  115.0 ppm) are shifted upfield (**7**:  $\delta$  C-3 129.6 ppm,  $\delta$  C-4a 118.6 ppm) (Figure 2). Unambiguous assignment of the  $^{15}\text{N}$ -NMR resonances of N-1 and N-2 in compounds **7–9** (and in the other cinnolines investigated) can be achieved from the  $^{15}\text{N}, ^1\text{H}$  HMBC spectra: Whereas both N-1 and N-2 give a correlation with cinnoline H-3, the N-1 signal is additionally correlated to H-8 via the vicinal  $^3J(\text{N-1}, \text{H-8})$  coupling.



**Fig. 2.**

The structure of **10** unequivocally follows from the observed NOEs and the HMBC spectra (correlation of  $\text{Me}_2\text{CH}$  and cinnoline C-4). The relatively small  $^{13}\text{C}$  chemical shift of the latter ( $\delta$  C-4 144.6 ppm) rules out a 4-alkoxycinnoline structure, which usually should have  $\delta$  C-4 approximately at 152–153 ppm – as found, for instance, in compounds **7**, **11**, and 4-methoxycinnoline [4].

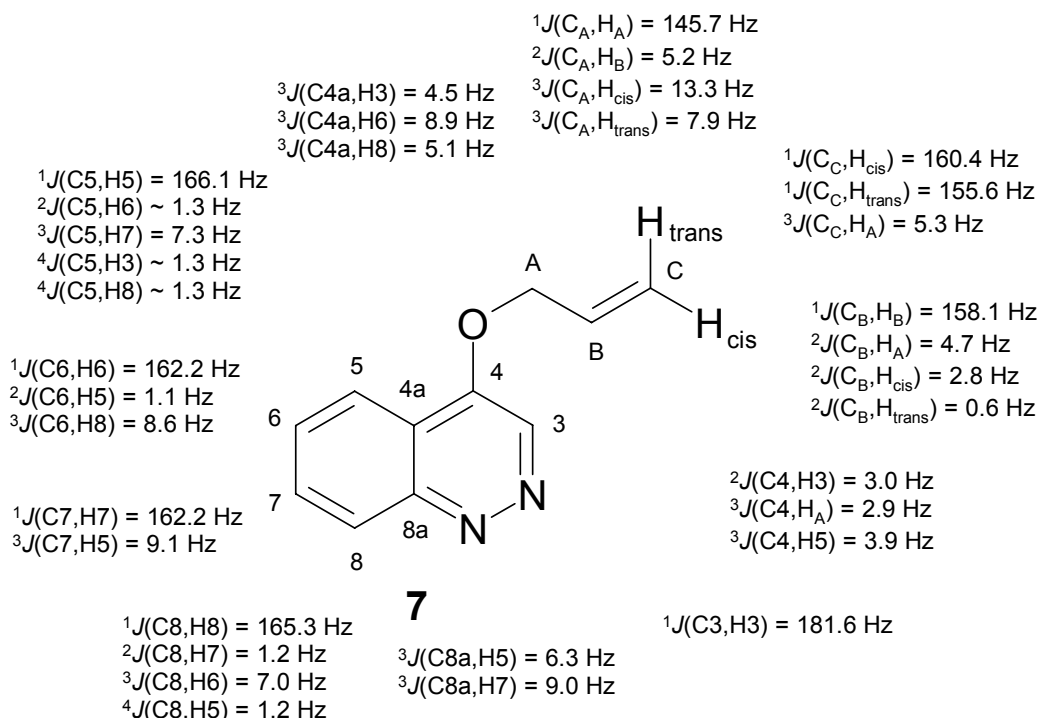
As far as possible, also the coupling network of the investigated cinnoline derivatives was determined. As a representative example, the  $^1\text{H}, ^1\text{H}$  and  $^{13}\text{C}, ^1\text{H}$  spin coupling constants extracted from the NMR spectra of **7** are presented in Figure 3.

In summary, we have shown the outstanding utility of multinuclear NMR spectroscopy for the structural and spectral assignment of the investigated cinnoline derivatives. Moreover, valuable data for this class of rarely investigated compounds has been provided.

## Experimental

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained either on a Shimadzu QP1000 or on a Finnigan MAT 8230 (HRMS) instrument (both EI, 70 eV). The NMR spectra were recorded on a Varian UnityPlus spectrometer (299.95 MHz for  $^1\text{H}$ , 75.43 MHz for  $^{13}\text{C}$ ) at 28°C or on a Bruker Avance 500 instrument with a ‘directly’ detecting broadband observe probe (500.13 MHz for  $^1\text{H}$ , 125.77 MHz for  $^{13}\text{C}$ , 50.69 MHz for  $^{15}\text{N}$ ) at 293K. The center of the solvent signal was used as an internal standard which was related to TMS with  $\delta$  7.26 ppm ( $^1\text{H}$ ,  $\text{CDCl}_3$ ),  $\delta$  2.49 ppm ( $^1\text{H}$ ,  $\text{DMSO}-d_6$ ),  $\delta$  77.0 ppm ( $^{13}\text{C}$ ,  $\text{CDCl}_3$ ) and  $\delta$  39.5 ppm ( $^{13}\text{C}$ ,  $\text{DMSO}-d_6$ ). Digital resolution were

0.27 Hz/data point for  $^1\text{H}$ -NMR spectra, 0.5 Hz/data point for the  $^{13}\text{C}$ -NMR spectra ( $^1\text{H}$  broad-band decoupled) and 0.33 Hz/data point for the  $^1\text{H}$ -coupled  $^{13}\text{C}$ -NMR spectra. Unambiguous assignment of all  $^1\text{H}$  and  $^{13}\text{C}$  resonances was achieved by combined application of standard NMR techniques [9] such as NOE-difference spectroscopy, attached proton test (APT), fully  $^1\text{H}$ -coupled  $^{13}\text{C}$ -NMR spectra (gated decoupling), TOCSY, HMQC and long-range INEPT spectra with selective excitation [10], the latter also as two-dimensional  $\delta, J$  spectra in order to unambiguously assign  $^{13}\text{C}, ^1\text{H}$  spin coupling constants [11]. The  $^{15}\text{N}$ -NMR spectra (mainly gradient selected, sensitivity enhanced HMBC [12]) were referenced against external nitromethane. Elemental analyses were performed by Microanalytical Laboratory, University of Vienna. Preparative layer chromatography was carried out on Merck PLC plates, silica gel 60F<sub>254</sub>, 20×20 cm, layer thickness 2 mm. Systematic names were generated with ACD/Name [13] according to the IUPAC recommendations and were also checked manually to ensure correct use of nomenclature within this publication [14]. Yields of products were not optimized.



**Fig. 3.**

**rac-4-[(2R)-Oxiran-2-ylmethoxy]cinnoline (2)**

To a suspension of NaH (60% in mineral oil, 400 mg, 10 mmol) in dry DMF (10 ml) was added dropwise a solution of 4-chlorocinnoline (**6**) (1.65g, 10 mmol) and epoxypropanol (glycidol) (741 mg, 10 mmol) in dry DMF (15 ml) and the mixture was stirred for 4 h at room temperature. Then the mixture was concentrated under reduced pressure, the dark residue was taken up in a mixture of EtOAc (20 ml) and water (20 ml) and transferred into a separatory funnel. The phases were separated, the aqueous phase was extracted with EtOAc (4 x 25 ml), the combined organic phases were dried (NaSO<sub>4</sub>) and the solvent was removed under reduced pressure to afford 1.42 g (70%) of slightly greenish crystals, which were pure according to <sup>1</sup>H-NMR. For analytical purposes a specimen was recrystallized from light petroleum leading to colourless crystals of mp 112–114 °C. MS (m/z, %): 202 (M<sup>+</sup>, 3), 73 (100). HRMS: Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: 202.0742. Found: 202.0746 ± 0.0010. Anal. Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub> (202.07): C, 65.34; H, 4.98; N, 13.85. Found: C, 65.02; H, 5.21; N, 13.63.

**rac-1-[(2R)-Oxiran-2-ylmethyl]cinnolin-4(1H)-one (4) and  
rac-2-[(2R)-Oxiran-2-ylmethyl]cinnolin-2-ium-4-olate (5)**

A mixture of cinnolin-4(1H)-one (**1**) (438 mg, 3 mmol), K<sub>2</sub>CO<sub>3</sub> (9.12 g, 66 mmol) und epichlorohydrin (278 mg, 3 mmol) in acetone (180 ml) was stirred at room temperature for 10 h. Then the solvent was removed under reduced pressure, the residue was subjected to preparative layer chromatography (silica gel, eluent: CH<sub>2</sub>Cl<sub>2</sub> – EtOAc, 4+1, desorption by treatment with hot EtOAc – MeOH, 4+1) to afford 50 mg (8%) of **4** as beige crystals (faster eluted component, R<sub>f</sub> ~ 0.4) of mp 125–127 °C, and 50 mg (8%) of **5** as ocher crystals (more retarded component, R<sub>f</sub> ~ 0.2) of mp 140–142 °C. Compound **4**: MS (m/z, %): 202 (M<sup>+</sup>, 12), 194 (16), 159 (64), 146 (13), 132 (100), 105 (11), 77 (46). HRMS: Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: 202.0742. Found: 202.0744 ± 0.0010. Compound **5**: MS (m/z, %): 202 (M<sup>+</sup>, 8), 189 (18), 160 (31), 146 (64), 132 (72), 119 (100), 104 (25), 92 (31), 90 (25), 77 (36). HRMS: Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: 202.0742. Found: 202.0747 ± 0.0010.



**4-(Allyloxy)cinnoline (7)**

To sodium (181 mg, 7.5 mmol) was slowly added allyl alcohol (5.97 g, 103 mmol) and the mixture was stirred at room temperature for 1 h. Then a solution of 4-chlorocinnolin (**6**) (494 mg, 3 mmol) in 8 ml (6.82 g, 117 mmol) of allyl alcohol was added dropwise and the mixture was then heated at reflux for 1 h. Then the solvent was removed under reduced pressure, the residue was taken up in water (20 ml) and the solution neutralized with 2N HCl. The aqueous mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 ml), the combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed *in vacuo* to afford 520 mg (93%) of yellowish crystals. For analytical purposes a sample was purified by preparative layer chromatography (silica gel, eluent: CH<sub>2</sub>Cl<sub>2</sub> - MeOH, 9+1) to give crystals of mp 93–95 °C. MS (m/z, %): 186 (M<sup>+</sup>, 85), 157 (22), 130 (41), 129 (41), 115 (29), 105 (46), 104 (39), 90 (80), 75 (26), 64 (35), 63 (76), 41 (100). HRMS: Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O: 186.0793. Found: 186.0799 ± 0.0009.

**4-(Allyloxy)cinnolin-1-oxide (8) and 4-(Allyloxy)cinnolin-2-oxide (9)**

To a solution of **7** (186 mg, 1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 ml) was slowly added a mixture of *m*-chloroperbenzoic acid (335 mg, 1.94 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (3 ml) and stirring was continued at room temperature for 20 h. Then the mixture was washed with saturated aqueous NaHCO<sub>3</sub> (2 x 10 ml) and water (2 x 10 ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure. The residue was subjected to preparative layer chromatography (silica gel, eluent: EtOAc – CH<sub>2</sub>Cl<sub>2</sub>, 1+1, desorption with hot EtOAc – MeOH, 4+1) to afford 21 mg (10%) of **8** as colorless crystals of mp 146–150 °C (faster eluted component, R<sub>f</sub> ~ 0,7) and 40 mg (20%) of **9** as yellowish crystals of mp 95–97 °C (more retarded component, R<sub>f</sub> ~ 0,5). Compound **8**: MS (m/z, %): 202 (M<sup>+</sup>, 64), 144 (15), 130 (22), 115 (20), 105 (17), 90 (32), 76 (24), 58 (100), 41 (82). HRMS: Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: 202.0742. Found: 202.0739 ± 0.0010. Compound **9**: MS (m/z, %): 202 (M<sup>+</sup>, 37), 161 (21), 134 (31), 104 (73), 76 (47), 68 (21), 41 (100). HRMS: Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: 202.0742. Found: 202.0745 ± 0.0010.

**Tab. 1.**  $^1\text{H-NMR}$  Data of Investigated Compounds ( $\delta$ , ppm)

No.	Solvent	Cinnoline-H					Other H
		H-3	H-5	H-6	H-7	H-8	
1 <sup>a</sup>	DMSO- <i>d</i> <sub>6</sub>	7.74	8.02	7.42	7.79	7.58	13.52 (NH)
2	CDCl <sub>3</sub>	8.94	8.18	7.68	7.80	8.41	4.62 <sup>b</sup> and 4.20 <sup>c</sup> (OCH <sub>2</sub> ), 3.50 (oxirane CH), 2.98 <sup>d</sup> and 2.85 <sup>e</sup> (oxirane CH <sub>2</sub> )
4	CDCl <sub>3</sub>	7.57	7.97	7.29	7.70	7.64	4.57 (NCH <sub>2</sub> ), 4.53 (oxirane CH), 3.76 (oxirane CH <sub>2</sub> )
5	DMSO- <i>d</i> <sub>6</sub>	8.16	8.09	7.52	7.77	7.82	4.66 and 4.43 (NCH <sub>2</sub> ), 4.36 (oxirane CH), 3.76 and 3.72 (oxirane CH <sub>2</sub> )
6 <sup>a</sup>	CDCl <sub>3</sub>	9.32	8.16	7.84	7.90	8.53	—
7 <sup>f</sup>	CDCl <sub>3</sub>	8.95	8.18	7.68	7.80	8.42	4.86 (OCH <sub>2</sub> ), 6.11 (=CH-CH <sub>2</sub> ), 5.52 (CH=CH <sub>trans</sub> ), 5.41 (CH=CH <sub>cis</sub> )
8 <sup>g</sup>	DMSO- <i>d</i> <sub>6</sub>	8.16	8.15	7.91	7.91	8.45	4.89 (OCH <sub>2</sub> ), 6.14 (=CH-CH <sub>2</sub> ), 5.55 (CH=CH <sub>trans</sub> ), 5.37 (CH=CH <sub>cis</sub> )
9	DMSO- <i>d</i> <sub>6</sub>	8.29	8.01	7.61	7.83	7.76	4.90 (OCH <sub>2</sub> ), 6.13 (=CH-CH <sub>2</sub> ), 5.54 (CH=CH <sub>trans</sub> ), 5.39 (CH=CH <sub>cis</sub> )
10	CDCl <sub>3</sub>	8.94	7.80	7.48	7.61	8.20	3.97 <sup>h</sup> (isopropyl CH), 3.83 (CHOH), 3.73 <sup>i</sup> and 3.60 <sup>j</sup> (CH <sub>2</sub> OH), 3.45 <sup>k</sup> and 3.41 <sup>l</sup> (NCH <sub>2</sub> ), 1.22 <sup>m</sup> and 1.15 <sup>n</sup> (isopropyl CH <sub>3</sub> ), OH not found
11	DMSO- <i>d</i> <sub>6</sub>	9.21	8.24	7.81	7.91	8.35	4.41 and 4.32 (OCH <sub>2</sub> ), 4.15 (CHOH), 3.60 (OH), 2.57 and 2.50 (NCH <sub>2</sub> ), 2.50 (pip H-2,6), 1.49 (pip H-3,5), 1.35 (pip H-4)
12 <sup>o</sup>	CDCl <sub>3</sub>	8.87	7.93	7.62	7.74	8.40	3.35 (pip H-2,6), 1.86 (pip H-3,5), 1.73 (pip H-4)

<sup>a</sup> For coupling constants (and chemical shifts) see ref. [4]. <sup>b</sup>  $^2J = 11.0$  Hz,  $^3J = 2.6$  Hz.

<sup>c</sup>  $^2J = 11.0$  Hz,  $^3J = 6.2$  Hz. <sup>d</sup>  $^2J = 4.8$  Hz,  $^3J = 4.2$  Hz. <sup>e</sup>  $^2J = 4.8$  Hz,  $^3J = 2.6$  Hz.

<sup>f</sup> Cinnoline system:  $^3J(5,6) = 8.4$  Hz,  $^4J(5,7) = 1.3$  Hz,  $^3J(6,7) = 6.8$  Hz,  $^4J(6,8) = 1.1$  Hz,

$^3J(7,8) = 8.5$  Hz; allyl system:  $^3J(\text{OCH}_2,=\text{CH}) = 5.3$  Hz,  $^4J(\text{OCH}_2,=\text{CHH}) = 1.4$  Hz,

$^4J(\text{OCH}_2,=\text{CHH}) = 1.4$  Hz,  $^3J(=\text{CH},=\text{CH}_{\text{cis}}) = 10.6$  Hz,  $^3J(=\text{CH},=\text{CH}_{\text{trans}}) = 17.2$  Hz,

$^2J(=\text{CH}_{\text{cis}},\text{CH}_{\text{trans}}) = 1.2$  Hz. <sup>g</sup> Coupling constants in the allyl system identical with the

corresponding ones in 7. <sup>h</sup>  $^3J = 6.6$  Hz. <sup>i</sup>  $^2J = 11.7$  Hz,  $^3J = 3.2$  Hz. <sup>j</sup>  $^2J = 11.7$  Hz,  $^3J = 5.7$  Hz.

<sup>k</sup>  $^2J = 14.2$  Hz,  $^3J = 5.9$  Hz. <sup>l</sup>  $^2J = 14.2$  Hz,  $^3J = 7.3$  Hz. <sup>m</sup>  $^3J = 6.6$  Hz. <sup>n</sup>  $^3J = 6.6$  Hz. <sup>o</sup>

Cinnoline system:  $^3J(5,6) = 8.5$  Hz,  $^4J(5,7) = 1.3$  Hz,  $^5J(5,8) = 0.6$  Hz,  $^3J(6,7) = 6.8$  Hz,

$^4J(6,8) = 1.3$  Hz,  $^3J(7,8) = 8.5$  Hz.

**Tab. 2.**  $^{13}\text{C}$ -NMR Chemical Shifts ( $\delta$ , ppm) of Investigated Compounds (solvents as in Table 1)

No.	Cinnoline-C								Other C
	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	
1 <sup>a</sup>	140.2	170.3	122.8	123.8	124.9	133.8	116.8	140.9	—
2	129.1	151.9	118.4	120.7	129.9	130.8	128.8	150.5	69.6 (OCH <sub>2</sub> ), oxirane ring: 49.5 (CH), 44.3 (CH <sub>2</sub> )
4	140.0	170.6	124.1	125.4	125.2	134.1	115.4	141.4	58.0 (NCH <sub>2</sub> ), oxirane ring: 69.7 (CH), 46.4 (CH <sub>2</sub> )
5	134.1	169.7	125.6	122.9	127.3	132.5	126.1	148.9	67.3 (N <sup>+</sup> CH <sub>2</sub> ), oxirane ring: 69.2 (CH), 46.9 (CH <sub>2</sub> )
6 <sup>a</sup>	144.3	134.7	124.7	122.9	132.9	131.4	130.0	150.9	—
7	129.6	151.9	118.6	120.8	129.7	130.6	128.8	150.6	69.5 (OCH <sub>2</sub> ), 131.2 (=CH), 119.2 (=CH <sub>2</sub> )
8	124.0	143.8	124.9	121.9	132.1	131.8	120.7	137.6	69.7 (OCH <sub>2</sub> ), 132.3 (=CH), 118.6 (=CH <sub>2</sub> )
9	119.1	158.2	115.0	120.9	127.7	132.9	124.1	146.3	70.4 (OCH <sub>2</sub> ), 131.7 (=CH), 119.0 (=CH <sub>2</sub> )
10	136.6	144.6	122.0	122.9	128.6	130.0	129.2	150.5	68.8 (CHOH), 64.7 (CH <sub>2</sub> OH), 56.6 (CHMe <sub>2</sub> ), 44.6 (NCH <sub>2</sub> ), 19.9 (CH <sub>3</sub> ), 19.4 (CH <sub>3</sub> )
11	130.2	152.0	117.9	120.9	129.9	131.0	128.1	149.8	72.1 (OCH <sub>2</sub> ), 66.0 (CHOH), 61.0 (NCH <sub>2</sub> ), 54.5 (pip C- 2,6), 25.2 (pip C-3,5), 23.6 (pip C-4)
12	135.2	145.7	120.6	122.9	128.6	129.7	129.9	150.5	52.8 (pip C-2,6), 25.9 (pip C-3,5), 24.2 (pip C-4)

<sup>a</sup> For coupling constants (and chemical shifts) see ref. [4].

**Tab. 3.**  $^{15}\text{N}$ -NMR Chemical Shifts ( $\delta$ , ppm) of Investigated Compounds (solvents as in Table 1)

No.	N-1	N-2	No.	N-1	N-2	No.	N-1	N-2
1 <sup>a</sup>	-206.8	-42.4	6 <sup>a</sup>	34.3	34.7	10 <sup>c</sup>	-6.7	14.4
2	14.1	35.2	7	11.6	34.6	11 <sup>d</sup>	14.5	40.6
4	-210.1	-35.2	8	-75.3	-45.2	12 <sup>e</sup>	5.7	27.6
5	<sup>b</sup>	<sup>b</sup>	9	-63.8	-54.2			

<sup>a</sup> See ref. [4]. <sup>b</sup> Not determined. <sup>c</sup> -309.1 (C4-NR<sup>1</sup>R<sup>2</sup>). <sup>d</sup> -336.1 (pip-N). <sup>e</sup> -315.0 (pip-N).

**rac-(2R)-3-[Cinnolin-4-yl(1-methylethyl)amino]propane-1,2-diol (10)**

A mixture of **2** (303 mg, 1.5 mmol), isopropylamine (1.4 g, 23.7 mmol) and MeOH (4 ml) was stirred at room temperature for 24 h. Then the solvents were removed *in vacuo* and the dark red residue was subjected to preparative layer chromatography (silica gel, eluent: EtOAc – MeOH – NH<sub>3</sub>, 50+50+1, desorption with hot EtOAc – MeOH, 4+1) to afford 80 mg (20%) of a yellowish solid, mp > 300 °C. MS (m/z, %): 261 (M<sup>+</sup>, 6), 200 (43), 158 (49), 155 (36), 147 (35), 146 (30), 101 (20), 72 (100). HRMS: Calcd. for C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>: 261.1477. Found: 261.1480 ± 0.0013.

**rac-(2R)-1-(Cinnolin-4-yloxy)-3-piperidin-1-ylpropan-2-ol (11) and 4-Piperidin-1-ylcinnoline (12)**

A mixture of **2** (606 mg, 3 mmol), piperidine (766 mg, 9 mmol) and THF (30 ml) was heated to reflux for 24 h. After removing the solvents *in vacuo* a dark brown oil remained, which according to NMR analysis (<sup>1</sup>H, <sup>13</sup>C, <sup>15</sup>N, see Tables 1-3) mainly consisted of aminoalcohol **11**. However, after purification by preparative layer chromatography (silica gel, eluent: EtOAc – NH<sub>3</sub>, 100+5, desorption with hot EtOAc – MeOH, 4+1) 216 mg (34%) of compound **12** were obtained as brown-orange crystals of mp 125-130 °C (lit. [15] mp: 134-136 °C). Compound **11**: MS (m/z, %): 287 (M<sup>+</sup>, 0.2), 146 (4), 98 (100). HRMS: Calcd. for C<sub>16</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>: 287.1634. Found: 287.1629 ± 0.0015. Compound **12**: MS (m/z, %): 213 (M<sup>+</sup>, 100), 184 (20), 156 (24), 128 (18), 115 (13), 102 (38), 101 (30), 75 (24), 55 (43).

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