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Synthesis and Absolute Configurations of Hexahydro-Naphthoxazines as Rigid Congeners of Phenmetrazine

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As part of a project concerned with the synthesis of rigid congeners of adrenergic drugs, some naphthoxazines, *cis* and *trans* isomers of 2,3,4a,5,6,10b-hexahydro-4*H*-naphth[1,2-*b*][1,4]oxazine **(1)** and *cis* and *trans* isomers of its isoster 2,3,4a,5,6,10b-hexahydro-1*H*-naphth[2,1-*b*][1,4]oxazine **(2)** were prepared. The absolute configurations of these compounds were determined by means of chemical correlation and determination of the chiroptical properties.

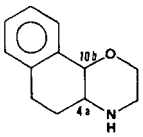
Synthese und absolute Konfiguration von Hexahydro-Naphthoxazinen, starren Phenmetrazin-Analogen

Als Teil eines Vorhabens im Zusammenhang mit der Synthese neuer starrer Analoga von Adrenergica wurden einige Napthoxazine synthetisiert: die *cis*- und *trans*-Isomere von 2,3,4a,5,6,10b-Hexahydro-4*H*-naphth[1,2-*b*][1,4]oxazin **(1)** und die *cis*- und *trans*-Isomere des isosteren 2,3,4a,5,6,10b-Hexahydro-1*H*-naphth[2,1-*b*][1,4]oxazins **(2)**. Die absolute Konfiguration dieser Verbindungen wurde durch chemische Korrelation und durch Messung der chiroptischen Eigenschaften bestimmt.

We have previously studied correlations between the absolute configuration and the chiroptical properties of some morpholinic derivatives[1] which can be taken as models in further structural studies on compounds of pharmaceutical interest. In this paper stereochemical studies on a set of amphetamine-like amines, bearing a nitrogen atom in a morpholinic ring such as in phenmetrazine, are undertaken.

The molecular models chosen for our investigations are quite rigid so that, when the absolute configuration of their chiral centers is known, the spatial shape of the drug to be tested in pharmacological screening, can be established with satisfactory precision.

We are in particular reporting the synthetic procedures and the determination of the absolute configuration of some naphthoxazines: *cis* and *trans* isomers of 2,3,4a,5,6,10b-hexahydro-4*H*-naphth[1,2-b][1,4]oxazine **(1)**, which can be considered as rigid analogues of phenmetrazine, and *cis* and *trans* isomers of its isoster 2,3,4a,5,6,10b-hexahydro-1*H*-naphth[2,1-b][1,4]oxazine **(2)**.



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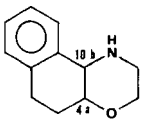

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Synthesis of 2,3,4a,5,6,10b-hexahydro-4*H*-naphth[1,2-b][1,4]oxazine (1)

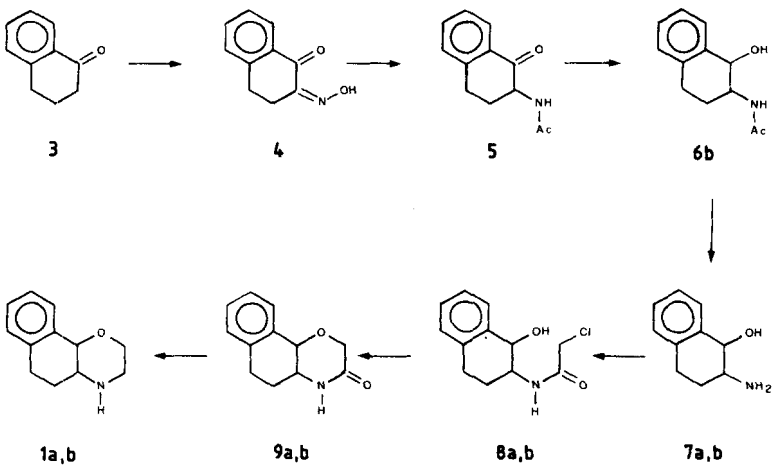
Both *trans* and *cis* isomers have been prepared by known methods[2], using α-tetralone as starting material. They cannot be prepared from 1,2-epoxy-1,2,3,4-tetrahydronaphthalene[3] and from *trans*-2-bromo-1,2,3,4-tetrahydro-1-naphthalenols[4], resp., (scheme 1).

Compound **3** by reaction with n-butylnitrite and potassium n-butylate gave 2-hydroxyimino-1-tetralone **(4)** which, treated with acetic anhydride and zinc dust, gave 2-acetamido-1-tetralone **(5)**. The latter was reduced with sodium borohydride to give *trans*-2-acetamido-1-tetralol **(6b)**. After basic or acidic hydrolysis *trans*-2-amino-1-tetralol **(7b)** and the *cis* isomer **(7a)** were obtained.

Cis and *trans* configuration of these two isomers was established from chemical shift and coupling constant showed by the hydrogen atoms at C-1 and C-2.

The signals of the hydrogen at C-1 in the *cis* and in the *trans* isomer were found at $\delta = 4.45$ and 4.35 ppm, and their coupling constants with the hydrogen on C-2 were 4 and 9 Hz. These values are in full agreement with those reported[5] for similar structures and also with values found for the hydrogen atoms on C-4a and C-10b in compounds **9a, b** described in this paper.

Compounds **7a,b** after reaction with chloroacetyl chloride and successive cyclization[6] gave compounds **9a,b** which by reduction afforded naphthoxazine **1a,b**.



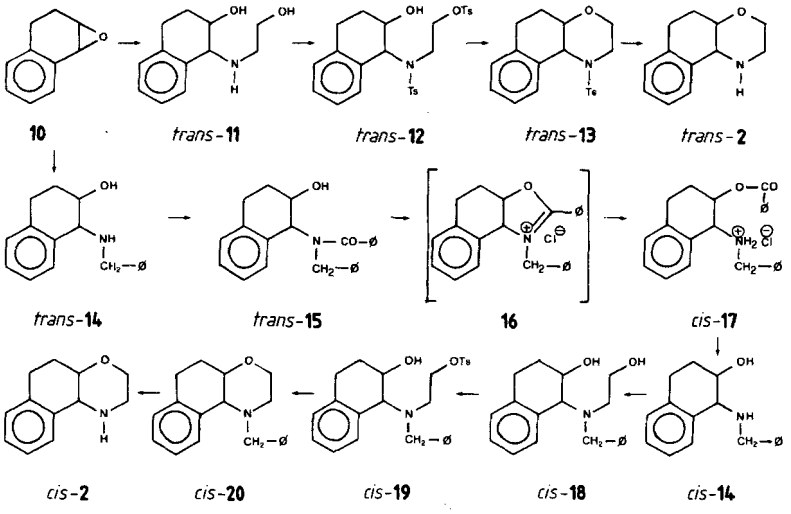
Scheme 1

Synthesis of 2,3,4a,5,6,10b-hexahydro-1*H*-naphth[2,1-b][1,4]oxazine (2)

Starting compound for the synthesis of both *cis* and *trans* isomers of **2** was 1,2-epoxy-1,2,3,4-tetrahydronaphthalene **(10)**, (scheme 2). The latter gave the diol-derivative *trans*-**11** and the amino-alcohol *trans*-**14**, by reaction with ethanolamine and benzylamine, resp. This behaviour is in agreement with reported data[3] because in

1,2-epoxy-1,2,3,4-tetrahydronaphthalenes the nucleophilic oxirane ring-opening occurs selectively at the benzylic C-1 position and does not depend on electronic effects of the aromatic ring substituents or steric hindrance around the epoxy group.

The cyclization of *trans*-**11** to naphthoxazine *trans*-**2** was achieved via the O,N-ditosyl-derivative *trans*-**12** in order to avoid *trans-cis*[7] isomerization. Compound **12** was first cyclized in alkaline medium to *trans*-**13** and then N-detosylated with sodium and n-amyl alcohol[8]. The synthetic pathway to the naphthoxazine *cis*-**2** was performed starting from amino-alcohol *trans*-**14** and utilizing the known method[9] for the *trans-cis* conversion of amino-alcohols. In this way, the N-benzoyl derivative *trans*-**15**, by reaction with $SOCl_2$, was converted, via oxazoline **16**, to O-benzoyl derivative *cis* **17**. After hydrolysis the latter was reacted with ethylene chlorohydrin[6] to give the diol *cis*-**18**. Cyclization of this compound was achieved via the O-tosyl derivative *cis* **19** in order to avoid *cis-trans*[7] isomerization. Finally naphthoxazine *cis* **2** was obtained by reduction[10] of the N-benzyl derivative *cis*-**20**.



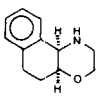
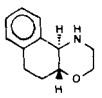
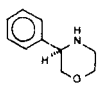
Scheme 2

Determination of the absolute configuration of *cis* and *trans* isomers 1 and 2

The isomeric aminoalcohols **7a,b**, obtained from compound **6b** through acidic and basic hydrolysis, resp., have been both separately resolved by fractional crystallization of their salts with D-(-)-dibenzoyltartaric acid. From resolution of the *cis* isomer **7a**, the (-)-enantiomer with the known absolute configuration[11], 1*R*, 2*S*, was isolated. Following the synthetic steps, from **7** to **1**, reported in scheme 1, in which the chiral carbon atoms were not involved, naphthoxazine **1a** with the absolute configuration, 4a*S*, 10b*R*, was obtained. In the same way from resolution of **7b** the (-)-enantiomer with a known absolute configuration[11], 1*S*, 2*S*, was isolated; the latter gave naphthoxazine **1b**, as reported in scheme 1, with an absolute configuration 4a*S*, 10b*S*.

As far as *cis* and *trans* isomers of naphthoxazine **2** are concerned, an easy direct chemical correlation was not possible since none of the intermediate products indicated in the synthetic pathway reported in scheme 2 has a known absolute configuration. Since *cis* and *trans* isomers of compound **2** can be regarded as cyclic derivatives of 3-phenylmorpholine, we compared the chiroptical properties of (-)-*cis*-**2** and (+)-*trans*-**2**, obtained by fractional crystallization of their salt with diaceton-2-keto-L(-)-gulonic-acid, with those of *R*-(-)-3-phenyl-morpholine **(21)** whose absolute configuration was previously chemically determined by us[1]. The dichroism curves obtained from the three mentioned compounds showed similar patterns with positive Cotton effect (Table 1). As a consequence it is possible to conclude that in (–)-*cis*-**2** and (+)-*trans*-**2** the chiral atom in position 10b has the same absolute configuration *R* as the C-3 of 3-(–)-phenyl morpholine **21** and it follows that C-4a has *S* and *R* configuration in *cis* and *trans* isomers, resp.

Table 1.

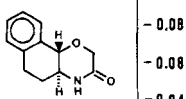
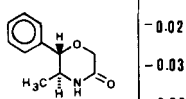
Compound	Δε (λ max)		
 4a*S*,10b*R* *cis*-(–)-**2**	+0,10 (272)	+0,08 (264)	+0,05 (258)
 4a*R*,10b*R* *trans*-(+)-**2**	+0,04 (273)	+0,05 (268)	
 3*R*-(–)-**21**	+0,11 (267)	+0,11 (261)	+0,07 (254)

The possibility of comparing the chiroptical properties of 3-monosubstituted morpholines with those of 2,3-disubstituted morpholines was recently reported by *Klyne* and co-workers[12] who suggested that for the latter compounds, the chiroptical properties depend only on the chirality of the phenyl substituted carbon atom and not on the chirality of the alkylic substituted one.

We have verified this behaviour also in structures much more rigid than those (**22** and **23**) reported by *Klyne*[12]. In fact the naphthoxazine, *trans*-(–)-**1**, and the corresponding lactame, *trans*-(–)-**9** whose absolute configuration has been determined through chemical correlation in this paper, show circular dichroism curves analogous to those obtained from compounds *trans*-(+)-**23** and *trans*-(+)-**22**, resp. (table 2).

Stereochemical studies on other rigid congeners of adrenergic drugs are now in progress.

Table 2.

Compound	Δ ε	λ max nm	Compound	Δ ε	λ max nm
	-0.08	273		-0.08	273
	-0.08	268		-0.10	269
	-0.04	261		-0.08	262
4a*S*,10b*S* -(-)- **9b**			4a*S*,10b*S* -(-)- **1b**		
	-0.02	267		-0.02	265
	-0.03	261		-0.03	260
	-0.03	256		-0.02	249
2*S*, 3*S* -(+)- **22**			2*S*,3*S* -(+)- **23**		

Experimental

MP: Büchi capillary apparatus, uncorr. *Elementary analyses:* Hewlett-Packard Model 185 C.H.N.analyzer, laboratory for Microanalysis of Istituto di Chimica Farmaceutica of University of Bari, Italy. *^{1}H-NMR spectra* ($CDCl_3$): Varian HA200 spectrometer, chemical shifts δ (ppm), TMS as int. ref. *Optical rotations:* Perkin-Elmer 241 MC polarimeter. *Circular dichroism:* in methanol with Cary 61 dichograph.

The compounds **4, 5, 6b** and **7a,b** were prepared as previously described[2].

2,3,4a,5,6,10b-hexahydro-4H-naphth[1,2-b][1,4]oxazin-3-one **(9a,b)**

A suspension of the aminoalcohol **7a** (0.9 g)$[\alpha]_D^{20}$-21.4° c = 1.4 % in MeOH) and 0.53 g anhydrous sodium acetate in 10 ml dimethyl-formamide was cooled to 0–5°C and 0.70 g chloroacetyl chloride in 10 ml dimethyl-formamide was added dropwise maintaining the temperature at 5 °C. Stirring was continued for 1 h at 0°C and in addition 1 h at room temp. The reaction mixture was poured into 100 ml ice-water and extracted three times with chloroform. The combined chloroform extracts were dried (Na_2SO_4) and evaporated i. vac. to yield the chloroacetamide **8a** as a yellowish viscous oil. This substance was dissolved immediately in 10 ml 2-propanol, the solution was cooled to 5 °C, and 0.3 g 50 % aqueous sodium hydroxide was added dropwise. After stirring for 1 h at 5 °C, the mixture was neutralized with 6N-HCl. The solvents were evaporated as much as possible; the resulting residue was slurried in water and extracted with chloroform. The organic layer was evaporated i. vac. to yield the crude crystalline morpholinone **9a** (0.5 g). Recrystallization from acetone/petroleum ether afforded an analytically pure sample, m.p. 128–130 °C, $[\alpha]_D^{20}$ + 4.2° (c = 7.8 % in MeOH), $C_{12}H_{13}NO_2$(203.2) Calc. C 70.9 H 6.45 N 6.9 Found C 70.6 H 6.30 N 7.0. NMR: 7.5–7.0 (m,4H,Ar); 4.7(d,1H,Ar-C<u>H</u>-O,J=4Hz.); 4.2(m,1H,-C<u>H</u>-N-); 4.0(s,2H,-CH_2-O-); 2.9(m,2H,-C<u>H</u>$_2$-Ar); 2.6(br,1H,NH,D_2O-exchanged); 2.2–1.8 (complex,2H,-C<u>H</u>$_2$-CH-N-).

As described above, starting from **7b**, $[\alpha]_D^{20}$–75.0° (c = 0.8 % in MeOH), it was possible to obtain **9b**; recrystallization from acetone gave an analytically pure sample, m.p. 213–215 °C, $[\alpha]_D^{20}$–15.3° (c = 1 % in $CHCl_3$), $C_{12}H_{13}NO_2$(203.2) Calc. 70.9 H 6.45 N 6.9 Found C 70.7 H 6.52 N6.7.NMR: 7.5(m,2H,Ar); 7.2(m,2H,Ar); 4.55(s,2H,-C<u>H</u>$_2$-O-); 4.5(d,1H,Ar-CH-O-,J=9Hz); 3.6(m,1H,-C<u>H</u>-N-); 3.0(m,2H,-C<u>H</u>$_2$-Ar); 2.2–1.7 (complex, 3H,-C<u>H</u>$_2$-CH-N-, -N<u>H</u>,D_2O-exchanged).

2,3,4a,5,6,10b,hexahydro-4H-naphth[1,2-b][1,4]oxazine **(1a,b)**

A cooled solution of 0.7 g $NaBH_4$ in 20 ml anhydrous THF was treated at 0° under external cooling, dropwise with a solution of 3.0 ml $BF_3 \cdot Et_2O$ in 20 ml anhydrous THF and then with a solution of 0.7 g **9a** in 30 ml anhydr. THF. The reaction mixture was stirred at room temp. for 10 min, refluxed for 2 h, cooled, treated with 10 ml H_2O and 20 ml 10 % HCl. After evaporation of THF, the aqueous solution was washed with CH_2Cl_2, alkalized with KOH and extracted with CH_2Cl_2. The combined chloroform extracts were dried (Na_2SO_4) and evaporated i. vac. to yield **1a**, b.p. 110°C (0.04 mm Hg), $[\alpha]_D^{20}$ + 2.5° (c = 8 % in MeOH), $C_{12}H_{15}NO$ (189.3) Calc. C 76.2 H 7.99 N 7.4 Found C 76.3 H 7.83 N 7.3.

As described above, starting from compound **9b**, it was possible to obtain **1b**, b.p. 110°C (0.04 mm Hg), $[\alpha]_D^{20}$ – 77.9° (c = 5.9 % in MeOH), $C_{12}H_{15}NO$ (189.3) Calc. 76.2 H 7.99 N 7.4 Found C 75.9 H 7.73 N 7.2.

*Trans-N-(β-hydroxyethyl)-α-amino-β-tetralol (trans-***11***)*

A solution of 0.4 mol ethanolamine in 50 ml MeOH was treated with 0.1 mol epoxide **10**. The reaction mixture was stirred at 60°C for 14 h and then evaporated i. vac. to yield *trans*-**11**. Recrystallization from methylene chloride/hexane afforded an analytically pure sample, m.p. 60–62°C, $C_{12}H_{17}NO_2$ (207.3) Calc. C 69.5 H 8.27 N 6.8 Found C 69.9 H 8.10 N 6.6.

*Trans-N-tosyl-2,3,4a,5,6,10b-hexahydro-1H-naphth[2,1-b][1,4]oxazine (trans-***13***)*

The diol *trans*-**11** was reacted with TsCl in Py, the crude N,O-ditosylate derivative obtained (*trans*-**12**) was cyclized, according to a known method[7], to yield *trans*-**13**. Recrystallization from C_6H_6/hexane afforded an analytically pure sample, m.p. 168–170°, $C_{19}H_{21}NO_3$(343.4) Calc. C 66.5 H 6.16 N 4.1 Found C 66.3 H 6.10 N 4.0. NMR: 7.6 (d,2H,Ar); 7.2(m,6H,Ar); 4.6(d,1H,Ar-C<u>H</u>-N-,J=9 Hz); 3.5–4.0 (complex, 5H, -C<u>H</u>-O-C<u>H</u>$_2$-C<u>H</u>$_2$-N-); 2.9 (m, 2H, Ar-C<u>H</u>$_2$); 2.4 (s, 3H, -C<u>H</u>$_3$); 2.1 (m, 1H, -C<u>H</u>$_2$-CH-O-); 1.7 (m, 1H, -C<u>H</u>$_2$-CH-O-).

*Trans-(+)-2,3,4a,5,6,10b-hexahydro-1H-naphth[2,1-b][1,4]oxazine (trans-***2***)*

The compound *trans*-**13** was detosylated[8] to yield an oil, *trans*-**2**, b.p. 110°C (0.05 mm Hg), and the respective salt with HCl was analyzed. $C_{12}H_{15}NO \cdot HCl$ (225.8) Calc. C 63.9 H 7.15 N 6.2 Found C 63.9 H 7.17 N 6.1. The racemic compound obtained was resolved by fractional crystallization of the salt with diaceton-2-keto-L-(–)-gulonic-acid from ethanol/diethyl ether. The isolated enantiomer of the free amine was *trans*-(+)-**2**, $[\alpha]_D^{20}$ + 58.6° (neat, d 1.15). CD data are reported in table 1.

*Trans-N-benzyl-α-amino-β-tetralol (trans-***14***)*

A solution of 0.4 mol benzylamine in 50 ml MeOH was treated with 0.1 mol epoxide **10**. The reaction mixture was stirred at 60°C for 14 h and then evaporated i. vac. to yield *trans*-**14**, b.p. 140°C (0.04 mm Hg). $C_{17}H_{19}NO$ (253.3) Calc. C 80.6 H 7.56 N 5.5 Found C 80.9 H 7.63 N 5.5. NMR: 7.2 (m, 9H, Ar); 4.0–3.7 (complex, 4H, Ar-C<u>H</u>$_2$-N-, -N-C<u>H</u>-C<u>H</u>-O-); 2.9 (m, 2H, Ar-C<u>H</u>$_2$-); 2.7 (br, 2H, N<u>H</u>, O<u>H</u>, D_2O exchanged); 2.2 (m, 1H, -C<u>H</u>$_2$-CH$_2$-); 1.8 (m, 1H, -C<u>H</u>$_2$-CH$_2$-).

*Trans-N,N-(benzyl-benzoyl)-α-amino-β-tetralol (trans-***15***)*

To a stirred suspension of 0.1 mol *trans*-**14** in 100 ml H_2O first a solution of 0.15 mol benzoyl chloride in 20 ml C_6H_6 and then a solution of 5 g NaOH 5 % was added. Stirring was continued for 3 h at room temp. The reaction mixture was extracted with benzene and the organic phase was washed first with 2N-HCl and then with 5 % NaOH. The combined chloroform extracts were dried (Na_2SO_4) and

evaporated i. vac. to yield *trans*-**15**. Recrystallization from MeOH afforded an analytically pure sample, m.p. 168–170°, $C_{24}H_{23}NO_2$ (357.5) Calc. C 80.6 H 6.49 N 3.9 Found C 80.5 H 6.60 N 3.8.

*Cis-N-benzyl-O-benzoyl-α-amino-β-tetralol (cis-***17***)*

The compound *trans*-**15** was converted in the corresponding *cis*-isomer[9] through a non isolated intermediate, oxazoline **16**. In this way it was possible to obtain *cis*-**17** hydrochloride. Recrystallization from absol. alcohol afforded an analytically pure sample, m.p. 202–204 °C. $C_{24}H_{24}NO_2Cl$ (393.9) Calc. C 73.2 H 6.14 N 3.6 Found C 73.4 H 6.23 N 3.6.

*Cis-N-benzyl-α-amino-β-tetralol (cis-***14***)*

A solution of 25 g *cis*-**17** hydrochloride in 500 ml EtOH with 20 % of KOH was refluxed for 6 h. The reaction mixture after cooling was filtered. The residue, *cis*-**14**, washed with EtOH, was crystallized with EtOH, m.p. 117–119°. $C_{17}H_{19}NO$ (253.3) Calc. C 80.6 H 7.56 N 5.5 Found C 80.5 H 7.57 H 5.5. NMR: 7.2 (m, 9H, Ar); 4.2–3.7 (complex, 4H, Ar-C<u>H</u>$_2$-N-, N-C<u>H</u>-C<u>H</u>-O-); 3.1–2.6 (complex, 4H, Ar-C<u>H</u>$_2$-, N<u>H</u>, O<u>H</u>, D_2O exchanged); 1.9 (m, 2H-C<u>H</u>$_2$-CH$_2$-).

*Cis-N,N-(benzyl-β-hydroxyethyl)-α-amino-β-tetralol(cis-***18***)*

A suspension of 10.4 g *cis*-**14** and 78 g $NaHCO_3$ in 100 ml ethylene chlorohydrine was refluxed for 20 h. After evaporation i.vac. the residue crystallized from C_6H_6/hexane, m.p. 92–94 °C. $C_{19}H_{23}NO_2$(297.4) Calc. C 76.7 H 7.80 N 4.7 Found C 76.7 H 7.90 N 4.5.

*Cis-N-benzyl-2,3,4a,5,6,10b-hexahydro-1H-naphth[2,1-b][1,4]oxazine (cis-***20***)*

The diol *cis*-**18** was reacted with TsCl in Py, the crude O-tosylderivative obtained (*cis*-**19**) was cyclized, according to a known method[7], to yield *cis*-**20**, b.p. 180 °C (0,5 mmHg). $C_{19}H_{21}NO$(279.4) Calc. C 81.7 H 7.58 N 5.0 Found C 81.5 H 7.49 N 5.1. NMR: 7.8(m,1H,Ar); 7.4–7.0(complex, 8H,Ar); 4.2 (m, 1H, -C<u>H</u>-O-); 3.9 (s, 2H, Ar-C<u>H</u>$_2$-N-); 3.5 (d, 1H, -C<u>H</u>-N-, J = 4Hz); 3.2–2.3 (complex, 4H, Ar-C<u>H</u>$_2$-C-, -O-C<u>H</u>$_2$-); 2.2 (m, 1H, -C<u>H</u>$_2$-N-); 1.8 (m, 1H, -C<u>H</u>$_2$-N-); 1.3 (m, 2H, -C<u>H</u>$_2$-CH-O-).

*Cis-(–)-2,3,4a,5,6,10b-hexahydro-1H-naphth[2,1-b][1,4]oxazine (cis-***2***)*

The N-benzyl-amine *cis*-**20** was hydrogenated in a stainless steel autoclave in acetic acid in the presence of 10 % Pd/C (about 25 mmol/0.5 g of catalyst) for 12 h at room temp. After filtration, 10 ml of conc. HCl was added and the solution was evaporated i. vac. The residue was treated with 20 % NaOH in H_2O and continuously extracted with ether. After distillation of the solvent, the liquid naphthoxazine *cis*-**2** was obtained, b.p. 180 °C (0.5 mm Hg), and the respective salt with HCl was analyzed. $C_{12}H_{15}NO \cdot HCl$ (225.8) Calc C 63.9 H 7.15 N 6.2 Found C 63.9 H 7.17 N 6.1. The racemic compound obtained was resolved by fractional crystallization of the salt with diacetone-2-keto-L-(–)-gulonic-acid from ethanol/ethylether. The isolated enantiomer of the free amine was *cis*-(–)-**2**, $[\alpha]_D^{20}$–38.0° (c = 4.2 % in MeOH). CD data are reported in table 1.

References

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Zur Synthese des Phaeantharins, 3. Mitt.[1]

Untersuchungen zur Diphenylether-Synthese nach Ullmann

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Zur Untersuchung der Synthese von Diphenylethern nach *Ullmann* wurden die sechs Brombenzolderivate **1–6** und die vier Phenole **7–10** eingesetzt. Dabei zeigte sich, daß die Ausbeute an Diphenylether mit steigender Elektronendichte am phenolischen Sauerstoffatom und mit sinkender Elektronendichte am C-Atom, das das Halogen trägt, zunimmt. Diese Ergebnisse deuten auf einen Reaktionsverlauf analog einer nucleophilen aromatischen Substitution. Die Pyridinmethode erweist sich der klassischen Methode als überlegen.

On the Synthesis of Phaeantharine, III: Investigation of the Ullmann Synthesis of Diaryl Ethers

The *Ullmann* synthesis of diaryl ethers was examined using the bromobenzene derivatives **1–6** and the phenols **7–10**. It was found that the yield of diphenyl ether increases with increasing electron density at the phenolic oxygen and with decreasing electron density at the carbon atom to which the halogen atom is attached. These results indicate a reaction course analogous to that of a nucleophilic aromatic substitution. The pyridine method turns out to be more successful than the classical method.

Vergebliche Bemühungen zur Herstellung des für die Phaeantharin-Synthese benötigten Spaltstückes **B** durch *Ullmann*-Reaktion, über die in der vorigen Mitt.[1] berichtet wurde, waren der Anlaß, die Synthese von Diphenylethern nach *Ullmann* aus Phenolen und aromatischen Halogenverbindungen etwas näher zu untersuchen. Hierzu wurden die sechs Brombenzolderivate **1–6** und die vier Phenole **7–10** eingesetzt. Die *Ullmann*-Syn-

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