ASYMMETRIC BIOMIMETIC SYNTHESIS OF S-SUBSTITUTED L- and D-CYSTEINES VIA CHIRAL Ni(II) COMPLEXES OF DEHYDROALANINE

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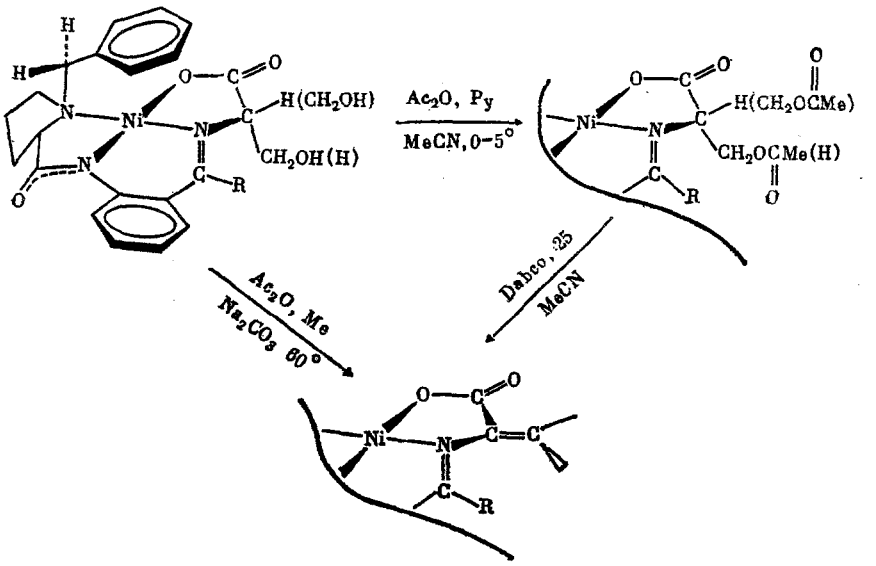
The synthesis of many natural α-amino acids occurs with the participation of pyridoxal enzymes via the intermediate formation of a Schiff base of dehydroalanine and pyridoxal [1, 2]. Typical of this is the synthesis of cysteine and its derivatives from serine [2].

S-substituted cysteines are used in the preparation of medical compounds [3] and for the selection of bacterial lines that are producers of different amino acids [4, 5]. S-substituted cysteines are also used in the synthesis of peptides that contain cysteine [6, 7]. Unfortunately, up to the present time there has been no convenient method for preparative asymmetric synthesis of cysteines.

We previously developed a method for the asymmetric synthesis of serine by condensation of CH_2O with glycine in a chiral Ni(II) complex with the Schiff base of (S)-o-(N-benzylprolyl)aminobenzophenone (BBP) or (S)-o-(N-benzylprolyl)aminoacetophenone (BPA) and glycine [8]. In the present work we describe the synthesis of a chiral Ni(II) complex with the Schiff base of dehydroalanine and BBP (or BPA) from the corresponding serine complexes as well as the synthesis of optically pure L-S-phenylcysteine and L-S-benzylcysteine by addition of thiols to the activated double bond of dehydroalanine in chiral Ni(II) complexes.

The serine fragment of the initial complexes [(s)-BPA-(R,S)-Ser]Ni(II) or [(S)-BBP-(R,S)-Ser]Ni(II) is readily acetylated by Ac_2O in the presence of pyridine or sodium carbonate in MeCN according to Scheme 1.

Scheme 1



R = Me, [(*S*)-BPA-(*S*)-Ser]Ni(II) (I); R = Me, [(*S*)-BPA-(*R*)-Ser]Ni(II) (II); R = Ph, [(*S*)-BBP-(*S*)-Ser]Ni(II) (III); R = Ph, [(*S*)-BBP-(*R*)-Ser]Ni(II) (IV); R = Me, [(*S*)-BPA-(*S*)-Ser(Ac)]Ni(II), (V); R = Me, [(*S*)-BPA-(*R*)-Ser(Ac)]Ni(II) (VI); R = Ph, [(*S*)-BBP-(*S*)-Ser(Ac)]Ni(II) (VII); R = Ph, [(*S*)-BBP-(*R*)-Ser(Ac)]Ni(II) (VIII); R = Me, [(*S*)-BPA-Δ-Ala]Ni(II) (IX); R = Ph, [(*S*)-BBP-Δ-Ala]Ni(II) (X).

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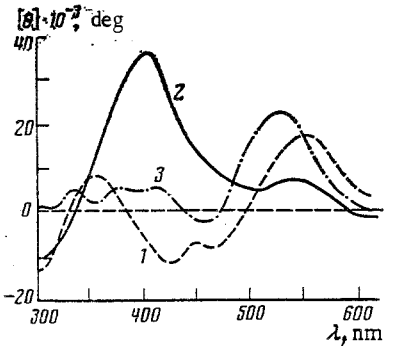


Fig. 1. Circular dichroism spectra of diastereomers (CH_3OH, 25°C): 1) (IX); 2) (II); 3) (I).

The acetylated complexes formed are, like the initial compounds, neutral diamagnetic compounds, readily soluble in $CHCl_3$. Their structure can be shown in comparison with the initial complex of (S)-serine, the structure of which was established by x-ray diffraction analysis [8]. The PMR spectral data of the acetylated complexes are fully consistent with the expected structure.

The optical rotatory dispersion curves of the O-acetyl derivatives of (S)- and (R)-serine complexes are shown in Fig. 2 together with complex (I) of similar structure for comparison. As can be seen from these results, O-acetylation does not change the configuration of the asymmetric centers in the complex.

Removal of the AcOH residue from these complexes is carried out in MeCN by the action of 1,4-diazabicyclooctane (Dabco) or Na_2CO_3 (see Scheme 1). The process is conveniently monitored using PMR by following the appearance of signals from the vinyl hydrogens of the dehydroalanine fragment at 4.96 and 5.95 ppm when (IX) is formed and 4.1 and 5.81 ppm when (X) is formed or from the disappearance of the proton signal from the acetoxy group at 2.08 and 2.2 ppm for (VI) and (VIII), respectively.

The complex was isolated from the reaction mixture by chromatography on silica gel and its structure was confirmed by elemental analysis and from its PMR spectra (see Experimental section). Moreover, in the electronic spectrum there is a shift of λ_{max} from 403 nm in the initial O-acetyl derivative to 428 nm in the elimination product, as would be expected when the conjugated system of the dehydroalanine Schiff base appears [9]. Finally, the circular dichroism spectra (Fig. 1) and optical rotatory dispersion curves (Fig. 2) of this compound differ from the spectra of the (S)-Ser and (R)-Ser complexes as should be the case when the asymmetric center of the amino acid fragment disappears.

The elimination of the acetoxy group is accompanied by side reactions of an undetermined nature. For (R)-Ser(Ac) complexes the relative significance of the side products is low (5%), while for the (S)-Ser(Ac) complexes it is high (30%).

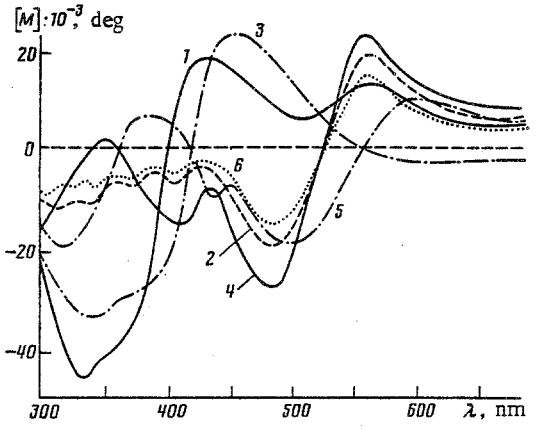


Fig. 2. Optical rotatory dispersion curves of diastereomers (CH_3OH, 25°C): 1) (VI); 2) (V); 3) (VIII); 4) (VII); 5) (IX); 6) (I).

TABLE 1. Chemical Yield and Ratio of Diastereomers Obtained by Addition of RSH to the Double Bond Fragment of Dehydroalanine Complexes

Experiment	Initial complex	RSH	Ratio of diastereomers, %		Total chemical yield, %
			S-*R*-*L*-Cys	S-*R*-*D*-Cys	
A	(IX)	PhSH	53,5	46,5	85
	(X)	PhSH	74	26	90
	(IX)	BzlSH	52	48	90
B	(X)	BzlSH	78	22	91
	(IX)	PhSH	78	22	91
	(IX)	BzlSH	66	34	92
C	(X)	PhSH	95	5	95
	(X)	BzlSH	97	3	96

The dehydroalanine complexes can be obtained in one stage from the corresponding Ser complexes by the action of Ac_2O in MeCN solution when Na_2CO_3 is used as a catalyst. The kinetics of elimination may conveniently be studied spectrophotometrically by following the increase in absorption at 435 nm. Measurements were made on the initial section of the kinetic curve, where it was possible to ignore the side reactions. The rate of reaction conforms to a mechanism of general base catalysis. The rate constant for elimination of AcOH from complex (VI) is 70 times higher than that from complex (V) when catalyzed by Dabco in MeCN.

It may be assumed that separation of the acetoxy group is accompanied by a greater reduction in intramolecular steric hindrance in the (R)-Ser(Ac) complex than in the (S)-Ser(Ac) complex, since in complexes of this type (R)-amino acids have a greater energy than (S)-amino acids [8, 10].

Chiral complexes (IX) and (X) add on thiophenol or benzylmercaptan in MeCN in the presence of Py or in the two-phase system MeCN:K_2CO_3:Bu_4NI (TBA), or in DMF in the presence of Na_2CO_3 according to Scheme 2 (see following page for scheme).

In this case a mixture of two diastereomers in approximately equal quantity is initially formed (PMR and TLC), which is a result of the low kinetic enantioselectivity of reaction (Table 1). During the reaction there is a gradual increase in the diastereomer that has the

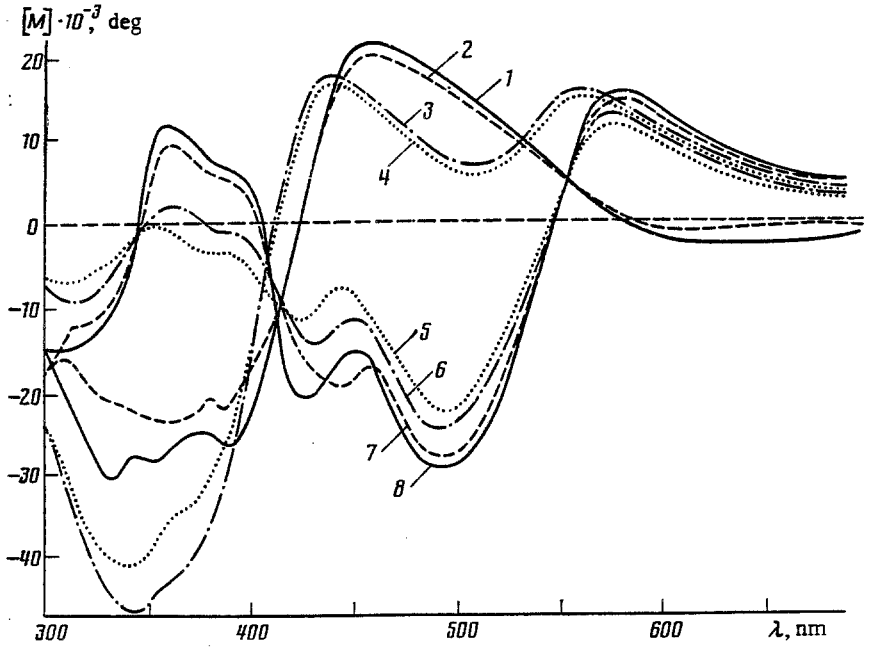
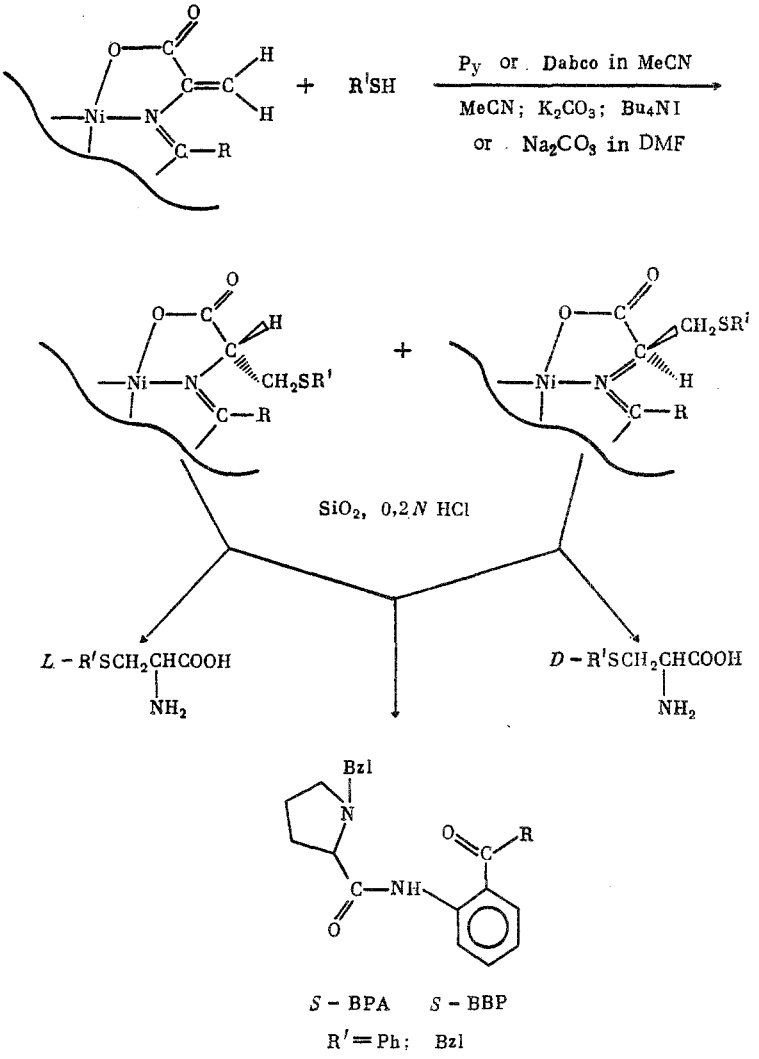


Fig. 3. Optical rotatory dispersion curves of diastereomers (CH_3OH, 25°C): 1) (XVIII); 2) (XVI); 3) (XII); 4) (XIV); 5) (XI); 6) (XIII); 7) (XVII); 8) (XV).

Scheme 2



higher R_f value on silica gel ($CHCl_3$:acetone) as a result of the formation of thermodynamic equilibrium between diastereomers. This process occurs much more rapidly in DMF on treatment with Na_2CO_3 so that it is possible to obtain diastereomeric complexes in the ratio 96:4 after 1.5-2 h at 20°C. The diastereomers can easily be separated by preparative chromatography on SiO_2.

Comparison of the optical rotatory dispersion curves of the pure isomers (Fig. 3) and the analogous Ser complexes (Fig. 2) shows that the isomer with the greatest mobility on SiO_2 has an L configuration of the cysteine fragment and the less mobile isomer has a D configuration.

After decomposition of the pure diastereomeric complexes with HCl, S-phenyl-L-cysteine $[\alpha]_D^{25}$ +47.6° (hydrochloride in D_2O, C 0.84) was isolated with a yield >80%; S-phenyl-D-cysteine $[\alpha]_D^{25}$ −47.8° (hydrochloride in D_2O, C 0.92 (cf. [12]); S-benzyl-L-cysteine $[\alpha]_D^{25}$ −18.6° (5N HCl, C 0.1) (cf. [11]), and S-benzyl-D-cysteine $[\alpha]_D^{25}$ +19.2° (5N HCl, C 0.14) (cf. [11]). The initial reagents BPA and BBP were isolated after decomposition of the diastereomeric complexes with a yield >97% without loss of optical purity.

EXPERIMENTAL

For the study we used amino acids from Reanal (Budapest), 1,4-diazabicyclooctane (Dabco) from Merck, thiophenol from Fluka, $PhCH_2SH$ from Reakhim, and Bu_4NI, Na_2CO_3, and K_2CO_3 from Reakhim. Acetic anhydride, thiophenol, and Py were distilled before use. MeCN and DMF were purified according to [12] and [13], respectively. PMR spectra were recorded on Tesla NMR-

BS-467A (60 MHz) and Bruker WP (200 MHz) instruments, optical rotatory dispersion curves were recorded on a Jasco ORD/UV-5 instrument, and circular dichroism spectra were recorded on a Jasco J-20 instrument; $[\alpha]_D$ values were determined on a Perkin–Elmer-241 polarimeter.

Chiral reagents S-o-(N-benzylprolyl)aminobenzophenone (BBP) and (S)-o-(N-benzylprolyl)-aminoacetophenone (BPA) were synthesized according to [8]. The initial Ni(II) complexes of Schiff bases of (R)- and (S)-Ser with BBP and BPA were obtained according to [8] by condensation of the respective Gly complexes with CH_2O.

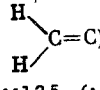
Ni(II) Complexes of Schiff Bases of BBP and BPA with (R)-Ser(Ac) and (S)-Ser(Ac). To a mixture of 1 g ($2.15 \cdot 10^{-3}$ mole) of (II) or 1.14g ($2.15 \cdot 10^{-3}$ mole) of (IV) and 2 ml of Py in 20 ml of anhydrous MeCN at ~20°C under argon with agitation was added dropwise 2.02 ml ($2.14 \cdot 10^{-2}$ mole) of Ac_2O, and the mixture was heated to 50°C and maintained at this temperature for 2 h. The acetylation was monitored by means of TLC on silica gel in the system $CHCl_3$:acetone (5:1) until the initial complex had disappeared. When the reaction was complete 15 ml of alcohol was added to the mixture, which was evaporated to dryness at 45-50°C under vacuum. The residue was dissolved in the minimum quantity of a C_6H_6:alcohol (2:1) mixture and purified by column chromatography on Sephadex LH-20 using a C_6H_6:alcohol (2:1) mixture as eluent. Yields of acetylated complexes were 80-96%; the complexes were unstable and eliminated AcOH, so it was not possible to obtain satisfactory elemental analysis data.

Preparation of (IX) and (X). 1) The two complexes were obtained from (VI) and (VIII), respectively. Complex (VI) (1 g, $1.96 \cdot 10^{-3}$ mole) or complex (VIII) (1.12 g, $1.96 \cdot 10^{-3}$ mole) was dissolved in 5 ml of anhydrous MeCN and 0.38 g ($1.96 \cdot 10^{-3}$ mole) of Dabco was added with agitation under an argon atmosphere, the process being monitored by TLC on SiO_2 in the system chloroform–acetone (5:1) (dehydroalanine complexes had higher R_f values than the initial compounds) and also by means of PMR.

The reaction mixture was dissolved in $CHCl_3$ and washed successively with 0.2 N HCl, 1 M Na_2CO_3, and H_2O. The chloroform extract was evaporated under vacuum and the residue dissolved in the minimum quantity of an alcohol:C_6H_6 (1:3) mixture and further purified on Sephadex LH-20 in the system alcohol:C_6H_6 (1:3). Yield 0.83 g (95%) of (IX) or 0.96 g (96%) of (X).

[(S)-BPA-Δ-Ala]Ni(II). PMR spectrum (in $CDCl_3$, δ, ppm): 6.8-8.85 m (9H, Ar), 3.50 m (1H, α-H-Pro), 3.30 m (2H, β-H-Pro), 1.95-2.40 m (4H, γ- and δ-H-Pro), 3.30 d and 4.24 d (AB, J = 12.5 Hz, 2H, CH_2-Bz-Pro), 4.96 s and 5.94 s (2H, ), 2.59 s (3H, CH_3). UV spectrum (λ_{max}, nm ($\log \varepsilon$)]: 230 (4.35), 270 (4.1), 340 (3.6), 428 (3.35), 540 (2.44). $[M]^{25}$ (MeOH): 578 (+7600), 546 (−5000), 436 (−6300), 365 (−1700).

Found, %: C 61.78; H 5.52; N 9.6. $C_{23}H_{23}O_3N_3Ni$. Calculated, %: C 61.64; H 5.14; N 9.38.

[(S)-BBP-Δ-Ala]Ni(II). PMR spectra (in $CDCl_3$, δ, ppm): 6.6-8.15 m (14H, Ar), 3.52 m (1H, α-H-Pro), 1.9-3.45 m (6H, β-, γ-, and δ-H-Pro), 3.38 d and 4.3 d (AB, J = 12 Hz, 2H, CH_2-Bz-Pro), 4.1 s and 5.8 s (2H, ). UV spectrum [λ_{max}, nm ($\log \varepsilon$)]: 235 (4.48), 278 (4.29), 440 (3.55), 546 (2.85). $[M]^{25}$ (MeOH): 578 (+15,000), 546 (−15,400), 436 (+7600), 365 (−13,000).

Found, %: C 65.61; H 4.76; N 7.95. $C_{28}H_{25}O_3N_3Ni$. Calculated, %: C 65.92; H 4.90; N 8.24.

2) Complex (VI) (1 g, $1.96 \cdot 10^{-3}$ mole) or complex (VIII) (1.12 g, $1.96 \cdot 10^{-3}$ mole) was dissolved in 3 ml of anhydrous MeCN, 1.24 g ($1.17 \cdot 10^{-2}$ mole) of Na_2CO_3 was added, and the mixture was heated with agitation to 60°C for 30 min, with the reaction being monitored by TLC on silica gel in the system $CHCl_3$:acetone (5:1) or $CHCl_3$:ethyl acetate (3:1). The reaction mixture was filtered and the Na_2CO_3 washed with $CHCl_3$. The product was purified on a SiO_2 column (150 × 5 cm) in the system $CHCl_3$:ethyl acetate (3:1). Yield obtained was 0.84 g (96%) of (IX) or 0.97 g (97%) of (X).

Single-Stage Method for Preparing (X) from (VIII). A mixture (5.07 g, $9.6 \cdot 10^{-3}$ mole) of (IV) and (III) in the ratio 95:5, obtained according to [8], was dissolved in 10 ml of

MeCN, 4.9 g ($4.65 \cdot 10^{-2}$ mole) of Na_2CO_3 was added, and 7.5 g ($7.44 \cdot 10^{-2}$ mole) of Ac_2O was added with agitation at ~20°C. The course of the reaction was followed by TLC on silica gel in the system $CHCl_3$:acetone (5:1). The reaction mixture was heated to 60°C, the process being monitored by TLC on silica gel in the system $CHCl_3$:ethyl acetate (3:1). Yield obtained was 4.5 g (92%) of (X).

Preparation of Ni(II) Complexes of Schiff Bases of (S)-BPA and (S)-BPP with S-substituted Cysteines by Addition of PhSH and BzlSH to (IX) and (X). A. Complex (IX) (0.128 g, $2.86 \cdot 10^{-4}$ mole) or complex (X) (0.146 g, $2.86 \cdot 10^{-4}$ mole) was dissolved in 2 ml of anhydrous MeCN and 0.04 ml ($5.2 \cdot 10^{-4}$ mole) of Py and 0.05 ml ($4.9 \cdot 10^{-4}$ mole) of thiophenol were added in a current of argon. The addition was monitored by following the disappearance of the signals from the protons on C=C in the PMR spectra (5.94 and 4.96 ppm), spectrophotometrically (400-430 nm), and also by TLC on silica gel in the system $CHCl_3$:acetone (5:1). After addition of PhSH (5 min) the mixture was diluted with 20 ml of $CHCl_3$ and washed successively with 0.2 N HCl (3 × 10 ml), 1 M Na_2CO_3 (3 × 10 ml), and water. The chloroform extract was evaporated to dryness. Diastereomers [(S)-BPA-S-Ph-L-Cys]Ni(II) (XI) and [(S)-BPA-S-Ph-D-Cys]Ni(II) (XII) were separated by preparative TLC on silica gel. The eluents used were $CHCl_3$:acetone (2:1) or C_6H_6:THF (1:1). The S-substituted L-cysteine complexes have a higher R_f value than the S-substituted D-cysteine complexes. Yields of products and ratios of diastereomers are given in Table 1.

The addition of BzlSH to (IX) and that of PhSH and BzlSH to (X) were carried out in a similar manner as were the separation of diastereomers [(S)-BPA-S-Bzl-L-Cys]Ni(II) (XIII) and [(S)-BPA-S-Bzl-D-Cys]Ni(II) (XIV), and also [(S)-BBP-S-Bzl-L-Cys]Ni(II) (XV) and [(S)-BBP-S-Bzl-D-Cys]Ni(II) (XVI), [(S)-BBP-S-Ph-L-Cys]Ni(II) (XVII) and [(S)-BBP-S-Ph-D-Cys]Ni-(II) (XVIII). The total yields of products and ratios of diastereomers are shown in Table 1.

B. Complex (IX) (0.093 g, $2.07 \cdot 10^{-4}$ mole) was dissolved in 2 ml of anhydrous MeCN, and 0.075 g ($2.13 \cdot 10^{-4}$ mole) of Bu_4NI, 0.087 g ($6.3 \cdot 10^{-4}$ mole) of anhydrous K_2CO_3, and 0.046 ml ($4.5 \cdot 10^{-4}$ mole) of thiophenol were added with agitation in a current of argon. After addition of PhSH (20 min) the mixture was treated as described above. The addition of BzlSH to (X) and the separation of the diastereomeric complexes obtained were carried out in a similar manner. The total yield and ratio of diastereomers are given in Table 1.

C. To a mixture of 2.01 g ($3.94 \cdot 10^{-3}$ mole) of (X) and 1.3 g ($1.22 \cdot 10^{-2}$ mole) of Na_2CO_3 in 3 ml of DMF was added 0.51 g ($4.12 \cdot 10^{-3}$ mole) of BzlSH in a current of argon and with agitation. The mixture was agitated for 1 h, the addition being monitored by TLC on silica gel in the system $CHCl_3$:ethyl acetate (3:1) according to the disappearance of (X). The mixture was neutralized with 0.1 N HCl, supplemented with 10 ml of water, extracted with $CHCl_3$, and the extract was evaporated. The residue was chromatographed on silica gel in the system $CHCl_3$:acetone (5:1), leading to separation of diastereomeric complexes (XV) and (XVI).

The addition of thiophenol to (X) and the separation of diastereomeric complexes (XVII) and (XVIII) were carried out in a similar manner. The yields of complexes and ratios of diastereomers are given in Table 1. The complexes were further purified on Sephadex LH-20 in the system alcohol:C_6H_6 (1:2) and characterized by spectroscopy. All complexes gave satisfactory elemental analysis data.

Isolation of S-phenyl-L(D)-cysteine or S-benzyl-L(D)-cysteine from the complexes and recovery of the initial BPA and BBP were carried out according to [8].

CONCLUSIONS

1. We have synthesized chiral Ni(II) complexes containing a Schiff base of dehydroalanine with (S)-o-(N-benzylprolyl)aminoacetophenone and (S)-o-(N-benzylprolyl)aminobenzophenone.

2. Addition of thiophenol and benzylmercaptan to the double bond of dehydroalanine in these complexes with subsequent separation of the diastereomeric complexes of S-phenylcysteine and S-benzylcysteine formed gives optically pure L-S-phenylcysteine and L-S-benzylcysteine.

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SYNTHESIS AND CRYSTAL STRUCTURE OF CYCLOTRIS(m-PHENYLENESULFIDE)

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Macrocyclic phenylenesulfides of general formula $\boxed{-(C_6H_4S)_{2-7}}$ [1-3] have recently been detected among the low-molecular-weight side products from the polycondensation of dihalobenzenes with Na_2S, which is used in the synthesis of polyphenylenesulfides; the former macrocyclic compounds are of independent interest as potential metal complexating and extracting agents. The sizes and yields of the macrocycles are determined by the position of substitution in the aromatic fragment. Thus, in the polycondensation of o-dichlorobenzene with Na_2S the reaction product (37% of theoretical) is the dimeric rin, a thianthrene, whereas in the polycondensation of p-dichlorobenzene with Na_2S the macrocyclic fraction (3% of the polymer weight) consists primarily of a mixture of cyclotetra- to cyclohexa(p-phenylenesulfides) [2]. These macrocycles are also readily formed upon thermal decomposition of poly-p-phenylenesulfide under vacuum [4].

In order to study the mechanism of formation and structure of these cyclic polyphenylenesulfides, we have isolated cyclotris(m-phenylenesulfide) (I) and have carried out an x-ray structural investigation on it.

EXPERIMENTAL

Polycondensation of m-dibromobenzene with Na_2S, at a monomer concentration of 0.1 mole/liter, was carried out at 200°C for 16 h, in analogy with a previously reported method [5]. After being cooled the reaction mixture was transferred to water and acidified with HCl to pH 4.5; the resulting precipitate was washed with water to a neutral reaction. The low-molecular weight fraction was separated from the polymer fraction by extraction with CH_2Cl_2 in a Soxhlet extractor for 16 h. After evaporation of the CH_2Cl_2 mother liquor the cyclotris(m-phenylenesulfide) product was isolated by extraction with refluxing ethanol. After

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