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PREPARATIVE ISOLATION AND PROPERTIES OF DIASTEREOMERIC COPPER(II) CHELATES OF SCHIFF BASES OF DIPEPTIDES WITH (α-(*N*,*N*-DIMETHYLAMINO)ALKYL)FORMYLCYMANTRENES

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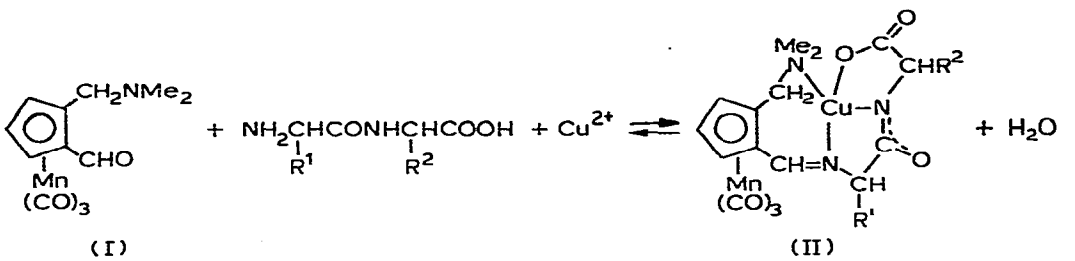
Summary

The effect of the planar and central chirality of 1,2-(α-(*N*,*N*-dimethylamino)-alkyl)formylcymantrene on the chromatographic properties of diastereomeric chelates of Cu^{2+} with Schiff bases from dipeptides and the aminoalkylformylcymantrenes, 1-(*N*, *N*-dimethylaminomethyl)-2-formylcymantrene (I) and 1,2-(α-(*N*, *N*-dimethylamino)ethyl)formylcymantrene (III), has been studied by liquid chromatography. The method described has been shown to allow the separation of diastereomeric chelates of the cymantrene derivative with differing metallocene chirality. The central chirality in III does not make any noticeable contribution to the chromatographic separation of chelates. Acid hydrolysis of chelates after the chromatographic separation gives enantiomers of I and III. The formation of chelates proceeds stereospecifically. 1,3-Isomers of aminoaldehydes of I and III do not form chelates with Cu^{2+} ion and dipeptides. The synthesis of chelates using L-Ala-L-Ala in the presence of oxygen is accompanied by epimerization of the N-terminal aminoacid moiety of the dipeptide.

The resulting diastereomeric chelates and optical isomers of aminoaldehydes of cymantrene I and III isolated from them are characterized by elemental analysis data, ORD, PMR, UV and IR spectra.

Introduction

A method of resolving (±)-1-(*N*,*N*-dimethylaminomethyl)-2-formylcymantrene (I) into enantiomers has been proposed and elaborated [1,2]. This method comprises the formation of diastereomeric chelates (II) of Cu^{2+} with Schiff bases of I with chiral dipeptides. Depending on the conditions of the reaction I with dipeptides and Cu^{2+}, either one of the diastereomers of II, containing (+) — I or (—) — I [1] is formed, or both the diastereomeric chelates II are present in the reaction mixture [2].



(I) (II)

Separation of the mixture of diastereomers II and analysis of their diastereomeric purity were carried out by the liquid chromatography (LC) method [2]. It was found that chelates II incorporating the (+) — I enantiomer of I have lower retention times compared with chelates II incorporating I with the opposite planar chirality (—) — I. Acid hydrolysis of individual diastereomers II results in optically pure (+) — I and (—) — I.

In this paper we report the application of LC to the analysis and isolation of Cu^{2+} diastereomeric chelates of Schiff bases formed by the interaction of a number of chiral dipeptides with 1,2-(α-(*N*,*N*-dimethylamino)ethyl)formylcymantrene (III). The aminoaldehyde of III, in contrast to that of I, has a centre of chirality in a side chain in addition to the planar chirality. This fact makes it possible to consider the effect of various elements of chirality on the stereoselectivity of formation of diasteromeric chelates, their chromatographic behavior and optical properties.

Results and discussion

Compound III was obtained by metallation of (α-(*N*,*N*-dimethylamino)ethyl) cymantrene, (*R*,*S*)-IV, with n-butyllithium followed by treatment of the reaction mixture with dimethylformamide. Analysis of the PMR-spectrum of the reaction product (Fig. 1), however revealed the latter to be a mixture of diastereomers IIIa and IIIb with the 1,3-isomer V in the ratio of 7.7 : 2.1 : 1 respectively. The observed ratio of IIIa and IIIb is caused by asymmetric induction of substitution in the metallation of the chiral amine (*R*,*S*)-IV. The absolute configuration of the chiral centre and plane * as presented in the formulae was established on the basis of X-ray data [3] of configurations (—) — $(R)_c$-III-$(S)_f$ and (+) — $(R)_c$-IV, as well as chemical and optical correlation methods (symbols c and f relate to the configuration of the chiral centre and plane respectively).

Hence, it could have been expected that the interaction of the resulting mixture of aminoaldehydes with dipeptides and $Cu(OCOCH_3)_2$ would give chelates of type II containing both $(R,S)_c$-III-$(R,S)_f$ and V. It was found, however, that the chelates isolated from the reaction mixture contain exclusively $(R,S)_c$-III-$(R,S)_f$ (Fig. 1). Consequently, aminoaldehyde V, the 1,3 substitution product, does not form stable chelates in solution; V, along with the unreacted IIIa and

* Nomenclature given in ref. 4 is used to describe chiral plane configuration.

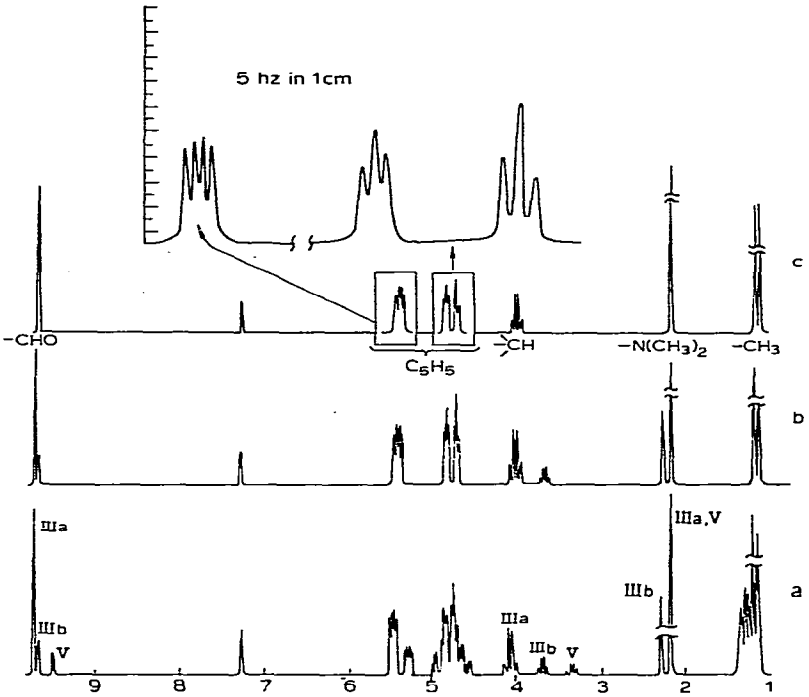
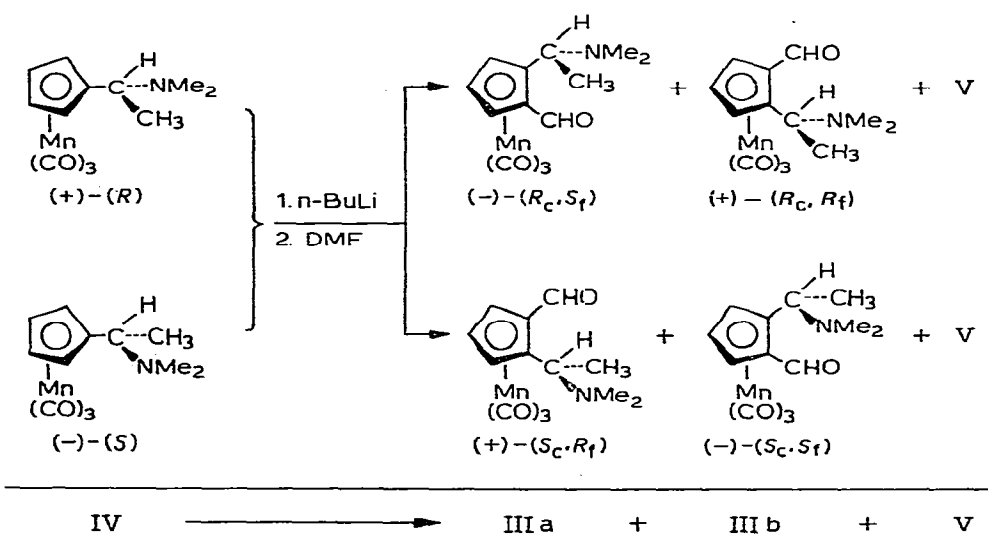
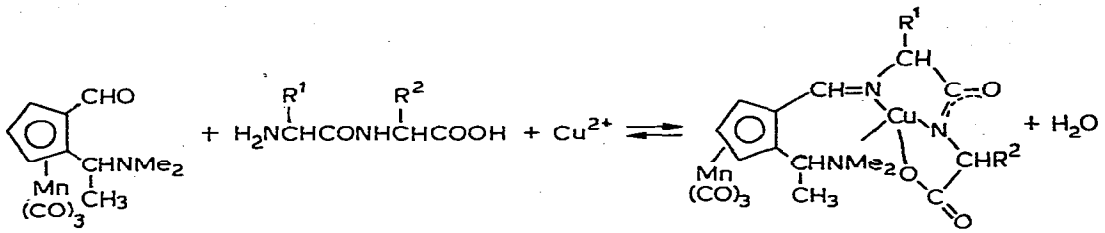


Fig. 1. The PMR spectra of (a) the mixture III-a, III-b and V from reaction (±)-IV (Bruker-WH-180, $CDCl_3$); (b) the mixture III-a and III-b prepared from the chelate VI (180 MHz, $CDCl_3$); (c) the optically pure (—)-(R)$_C$-III-(S)$_f$ (Bruker-WH-360, $CDCl_3$).

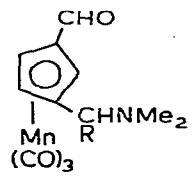


IIIb, may be isolated from the reaction mixture by extraction of its aqueous solution with an organic solvent (see Experimental).



(III)

(VI, IX; $R^1 = R^2 = Me$
VII; $R^1 = Me$, $R^2 = H$
VIII, XII; $R^1 = H$, $R^2 = Me$
X; $R^1 = R^2 = H$)



(V; $R = CH_3$
XI; $R = H$)

The result of the presence of two chiral elements in III should be the formation of twice the number of diastereomeric chelates compared with I, even in the absence of epimerization of amino acid moieties in the dipeptide. For this reason, we initially studied the poperties of the chelates formed from a mixture of isomers $(R)_c$-III-$(R,S)_f$ with the (R) configuration of the chiral centre in the substituent which had been isolated upon metallation of (+)-$(R)_c$-IV.

The conditions of preparation of chelates, type of chromatograms of reac-

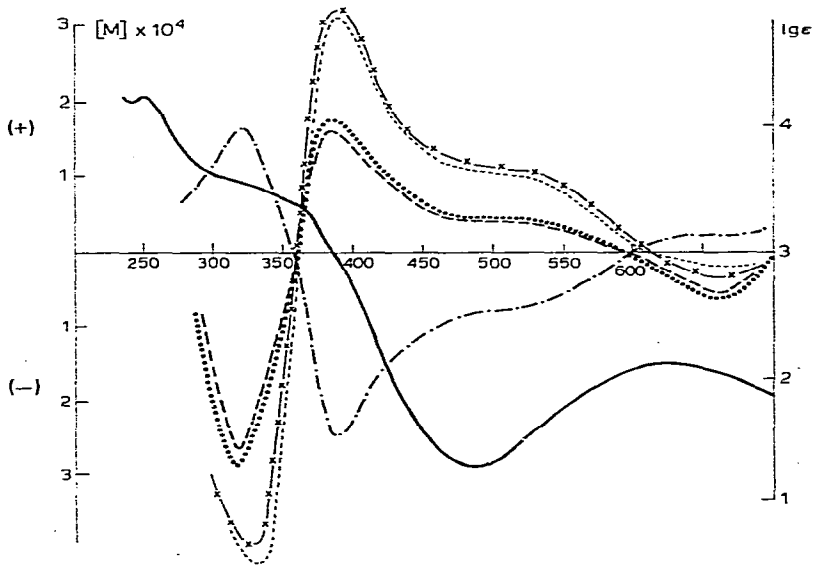


Fig. 2. Electronic spectrum (———) of chelate VI-B and ORD spectra of chelates VI-B (- X - X -), IX-A (· — · — ·), (VIII-B (· · · · · ·), VII-B (— — —), IX-B (- - - -) in 95% ethanol.

tion mixture and procedure of identification of their components are similar to those described in ref. 2. The composition and optical characteristics of the chelates formed upon the interaction of $(R)_c$-III-$(R,S)_f$ with optically pure dipeptides and $Cu(OCOCH_3)_2$ are shown in Table 1 and Fig. 2. These data, as well as the elemental analysis data, UV and IR spectra of the chelates (see the Experimental section) make it possible to assign to them the structure VI—VIII earlier suggested for chelates of Cu^{2+} with (±)-I-$(R,S)_f$ and dipeptides [1,2].

From Table 1 and Fig. 2 it follows that chelates VI—VIII of chromatographic fractions with higher retention times (fractions B) have similar ORD curves. Similarity of ORD curves was also observed for fractions of chelates VI and VIII with lower retention times (fractions A), the signs of the optical rotation for chelates VI-B—VIII-B and VI-A, VIII-A within the range of similar wavelengths being opposite. Acid hydrolysis of VI-A and VIII-A results in separation of aminoaldehyde (+)-$(R)_c$-III-$(R)_f$ in both cases, whereas a similar treatment of VI-B—VIII-B gives (—)-$(R)_c$-III-$(S)_f$. The ORD curve (Fig. 3) for (—)-$(R)_c$-III-$(S)_f$ isolated from chelates VI-B—VIII-B coincides with the same curve for the optically pure (—)-$(R)_c$-III-$(S)_f$ obtained by repeated crystallization of the mixture $(R)_c$-III-$(R,S)_f$ with V (Fig. 1). Consequently, chelates VI-B—VIII-B are diastereomerically and enantiomerically pure compounds containing (—)-$(R)_c$-III-$(S)_f$, while the aminoaldehyde (+)-$(R)_c$-III-$(R)_f$ with the opposite planar configuration is incorporated in the chelates of fractions A. Thus, the method of preparing diastereomeric chelates described in this paper in combination with LC enables resolution of diastereomeric $(R)_c$-III-$(R,S)_f$ with the same configuration of the chiral centre into optical isomers with opposite configurations of the chiral plane.

In order to find out the effect of configuration of the chiral centre in III on the process of formation of diastereomeric chelates and their chromatographic

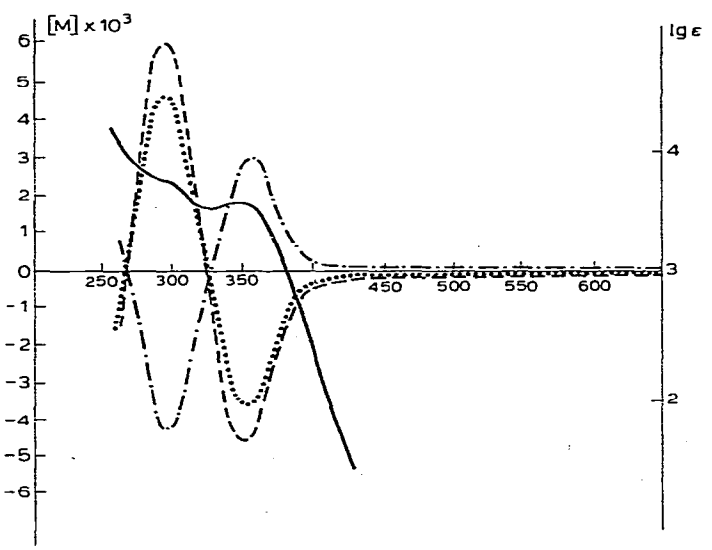


Fig. 3. Electronic spectrum (———) of racemic III in CCl_4 and ORD spectra of $(R)_c$-III-$(S)_f$ (— — —), $(R,S)_c$-III-$(S)_f$ (· · · · ·) and $(R,S)_c$-III-$(R)_f$ (· — · — ·) in CCl_4 (c 1.10^{-3} g/cm³).

TABLE 1

COMPOSITION AND PROPERTIES OF Cu^{2+} CHELATES OF SCHIFF BASES PRODUCED FROM 2-FORMYL-(α-(*N*, *N*-DIMETHYLAMINO)ETHYL)CYMANTRENE WITH DIPEPTIDES

Chelate	Starting		Chelate fraction	Yield of the fraction after 72 h (%)	Retention on time (min) [a]	$[\alpha]_{436}^{22}$ [b] (deg)	Chelate composition	
	dipeptide	aminoaldehyde					dipeptide	aminoaldehyde
VI	L-Ala-L-Ala	(R)c-III-$(R,S)_f$	A	8	97	(—) [c]	D-Ala-L-Ala	(R)c-III-$(R)_f$
			B	40	147	+3,858	L-Ala-L-Ala	$(R)_c$-III-$(S)_f$
VII	L-Ala-Gly	$(R)_c$-III-$(R,S)_f$	A	0	—	—		
			B	23	126	+1,575	L-Ala-Gly	$(R)_c$-III-$(S)_f$
VIII	Gly-L-Ala	$(R)_c$-III-$(R,S)_f$	A	2	106	(—)	Gly-L-Ala	$(R)_c$-III-$(R)_f$
			B	16	124	+1,682	Gly-L-Ala	$(R)_c$-III-$(S)_f$
IX	L-Ala-L-Ala	$(R,S)_c$-III-$(R,S)_f$	A	40	97	−2,840	D-Ala-L-Ala	$(R,S)_c$-III-$(R)_f$
			B	40	147	+3,240	L-Ala-L-Ala	$(R,S)_c$-III-$(S)_f$
X	Gly-Gly	$(R)_c$-III-$(R,S)_f$	A	27	160	+1250	Gly-Gly	$(R)_c$-III-$(R,S)_f$
		$(R,S)_c$-III-$(R,S)_f$	A	26	160	—	Gly-Gly	$(R,S)_c$-III-$(R,S)_f$
XII	Gly-D,L-Ala	$(R)_c$-III-$(S)_f$	A	14	106	+1,700	Gly-D-Ala	$(R)_c$-III-$(S)_f$
			B	15	124	+1,682	Gly-L-Ala	$(R)_c$-III-$(S)_f$

[a] Chromatography on a column of 80 × 0.7 cm SiO_2. Eluent, ethanol at 20°C.

[b] Specific rotation of chelates VI—IX and XI was determined in abs. ethanol. The chelate solution concentration was 0.05%.

[c] Sigh of rotation at λ = 436 nm.

behavior, we further studied the properties of the chelates formed from $(R,S)_c$-III-$(R,S)_f$ containing a full set of diastereomers of this compound and L-Ala-L-Ala, L-Ala-Gly and Gly-L-Ala in the presence of $Cu(OCOCH_3)_2$. It was found that the chromatographic pattern (retention times and the number of fractions of chelates) and optical properties of chelates were similar to the data shown in Table 1 for the chelates VI—VIII prepared from $(R)_c$-III-$(R,S)_f$. As an example, we shall now consider in detail the properties of the chelates formed from $(R,S)_c$-III-$(R,S)_f$, L-Ala-L-Ala and Cu^{2+} (see Table 1 and Figs. 2, 3). Two fractions of chelates IX are observed in the chromatogram, their retention times coinciding with those for VI-A and VI-B. The ORD curves for IX-B and VI-B, as well as for (—)-$(R,S)_c$-III-$(S)_f$ and (—)-$(R)_c$-III-$(S)_f$ isolated from these compounds, respectively, are alike both in their shape and size. The same is observed for the pairs IX-A, VI-A and (+)-$(R,S)_c$-III-$(R)_f$, (+)-$(R)_c$-III-$(R)_f$.

These data allow a conclusion that the LC conditions employed in this study ensure separation of the chelates produced from enantiomerically pure dipeptides and III with differing configurations of the chiral plane. However, the central chirality in aminoaldehyde III does not make a noticeable contribution to chromatographic behavior of diastereomeric chelates incorporating aminoaldehyde III with identical planar chirality.

We obtained an unexpected result when studying the chromatographic behavior of diastereomeric chelates X formed in the interaction of III with the achiral dipeptide GlyGly. It was found that both in the case of racemic $(R,S)_c$-III-$(R,S)_f$ and of $(R)_c$-III-$(R,S)_f$ only one peak from the fraction containing diastereomeric chelates was observed in the chromatogram (see Table 1). In other words, the presence of a chiral centre in the dipeptide is necessary for a chromatographic separation of diastereomeric chelates incorporating aminoformylcymantrenes with different configurations of the chiral plane.

Analysis of the structure of the dipeptide in the chelates VI-A, VI-B and IX-IX-A, IX-B revealed what the chelates of fractions A contained exclusively D-Ala-L-Ala, whereas VI-B and IX-B contained only L-Ala-L-Ala. Hence, just as in the formation of chelates of (±)-I with L-Ala-L-Ala and Cu^{2+} [2], a mild epimerization of one of the amino acid moieties (probably the N-terminal one) in the starting L-Ala-L-Ala occured when carrying out the reaction in air in the absence of a strong base.

The above-described chromatographic behavior of diastereomeric chelates of aminoaldehydes III, optical properties of chelates of fractions A and B and the aminoaldehydes isolated from these chelates are in full agreement with the data obtained in the study of chelates of (±)-I with the same dipeptides and Cu^{2+} [2]. It should be noted that not only the shape, but the numerical values of the ORD curves for (+)-I and (+)-$(R)_c$-III-$(R)_f$ (or (+)-$(R,S)_c$-III-$(R)_f$), as well as (—)-I and (—)-$(R)_c$-III-$(S)_f$ (or (—)-$(R,S)_c$-III-$(S)_f$) are similar. Similar ORD curves were also observed for the chelates of copper with the same dipeptides corresponding to these pairs of aminoaldehydes. The comparison of the data obtained earlier [2] with the results of the present study allows a conclusion that chromatographic and optical properties of diastereomeric chelates of the type studied including a chiral dipeptides, as well as optical properties of individual optical isomers I and III are defined mainly by the chiral plane configuration of these cymantrene derivatives.

However, the presence of a chiral substituent in III provides a marked effect on the stereoselectivity of the formation of diastereomeric chelates. Thus, in the preparation of chelates IX from L-Ala-L-Ala and $(R,S)_c$-III-$(R,S)_f$, only one peak (fraction B) corresponding to chelate IX of the composition (—)-$(R,S)_c$-III-$(S)_f$/L-Ala-L-Ala/Cu^{2+} is observed in the chromatogram of the reaction mixture after 24 hours reaction time. Only after 72 hours reaction are two peaks (fractions A and B) observed in the chromatogram. The chelates of fraction A contain (+)-$(R,S)_c$-III-$(R)_f$ and D-Ala-LAla, the latter formed in the reaction mixture due to epimerization of the starting L-Ala-L-Ala.

Analysis of the structure of the dipeptide of fraction B chelates both 24 and 72 hours after the beginning of the reaction shows complete absence of D-Ala-L-Ala. A similar phenomenon in observed in the case of a partly cleaved aminoaldehyde $(R)_c$-III-$(R,S)_f$. Hence, a dipeptide with the N-terminal L-alanine forms chelates only with (—)-$(R,S)_c$-III-$(S)_f$, whereas in the case of the N-terminal D-alanine chelates with (+)-$(R,S)_c$-III-$(R)_f$ are exclusively formed. In contrast, the chelate of fraction A, in the case of the reaction of (±)-I with L-Ala-L-Ala and copper acetate, is already present in the initial stages of the reaction and consists exclusively of L,L-dipeptide and (+)-I. As the D,L-epimer accumulates in the solution, fraction A contains two chelates of the composition (+)-I/D-Ala-LAla/Cu^{2+} and (+)-I/L-Ala-LAla/Cu^{2+} with their ratio after 24 hours reaction being 1 : 2.5 [2]. In other words, the presence of a chiral centre in III (in contrast to I) increases the degree of stereoselectivity of the interaction of the N-terminal moiety of a dipeptide with aminoaldehydes having R_f- and S_f-configuration of the planar chirality.

The above-mentioned selectivity of the formation of chelates from aminoaldehyde III in the presence of 1,3-isomer of V impelled us to investigate the ability of 3-formyl-1-(*N*,*N*-dimethylaminomethyl)cymantrene (XI) (the 1,3-isomer of I) to form Cu^{2+} chelates with dipeptides. To this end, a mixture of aminoaldehydes was used containing 30% (±)-I and 70% XI [5]. The interaction of this mixture with L-Ala-L-Ala and copper acetate in abs. ethanol resulted in chelates having chromatographic and optical characteristics coinciding with those for chelates II (for $R^1 = R^2 = CH_3$) [1,2]. Aminoaldehydes isolated from these chelates were (+)- and (—)-I, whereas extraction of an aqueous solution of the reaction mixture with CCl_4 resulted in aminoaldehyde with a PMR spectrum corresponding to isomer XI contaminated with I (see the experimental section). Hence, the method involving the formation of Cu^{2+} chelates of Schiff bases of dipeptides with aminoformyl derivatives of cymantrene enabled identification and resolution of 1,2- and 1,3-isomers of these compounds from their mixtures.

Therefore, the procedure as employed in this study may be useful in resolving cymantrene aminoaldehydes into optical and geometrical isomers with the use of optically pure dipeptides. On the other hand, it is logical to assume that individual optical isomers I and III may be used, in turn, as the reagents for resolution of racemic mixtures of dipeptides. Indeed, we have shown that in the interaction of (—)-$(R)_c$-III-$(S)_f$ with Gly-D,L-Ala and $Cu(OCOCH_3)_2$ two diastereomeric chelates XII are formed with the yield of 14 and 15% (Table 1). Chromatographic separation of these chelates, followed by acid hydrolysis resulted in isolation of Gly-D-Ala and Gly-L-Ala respectively.

Experimental

The synthesis of (±)-I and XI was carried out following the published procedure [1,5]. A mixture of aminoaldehydes IIIa, IIIb and V was obtained from acetylcymantrene oxime [6] according to the scheme: oxime → (α-aminoethyl)-cymantrene (XIII) → IV → IIIa, IIIb and V.

(R,S)-(α-Aminoethyl)cymantrene (XIII)

The synthesis of XIII was carried out following a modified published procedure [6] by reducing acetylcymantrene oxime with zinc in glacial CH_3COOH. The reaction mixture, cooled after a hot filtration, was neutralized with 2 *N* NaOH and extracted with hexanol. The alcoholic extract was shaken with 6 *N* NaOH, washed with water to pH 8 and dried over a Na_2SO_4-$MgSO_4$ mixture. The amine was isolated by distillation in a 6×10^{-2} mmHg vacuum; b.p. 80—82° C. $n_D^{20} = 1.5915$; yield 66.5%.

The (—)-(*R*)-enantiomer of amine XIII was produced by separation of racemic XIII by means of (+)-*d*-tartaric acid in 70% ethanol. Crystals of the initially precipitated tartrate were decomposed with 4 *N* NaOH after recrystallization (2 times) from methanol, and the amine was isolated in a conventional manner. The yield of (*R*) XIII was 49%; b.p. 81° C at 4×10^{-2} mmHg; $n_D^{20} = 1.5918$; $[\alpha]_{578}^{22} = -10.4°$ (*c* 2, ethanol). Analysis: Found: C, 48.43; 48.51; H, 4.08, 4.14; $C_{10}H_{10}NMnO_3$ calcd.: C, 48.64; H, 4.07%.

(R,S)-(α-(N,N-dimethylamino)ethyl)cymantrene, (R,S)-IV

To a flask containing 19.5 g (0.41 mol) of 90% HCOOH there was slowly added with stirring 19.1 g (0.07 mol) of XIII and then 17.1 ml of 37% aqueous CH_2O. The resulting mixture was refluxed on a bath at 95—100° C for 8 h. Then the reaction mixture is poured into 200 ml of water, acidified with 2 *N* HCl and extracted with benzene. The aqueous solution was treated with 4 *N* NaOH to pH 10—11, extracted with ether; ethereal extracts were washed with water until the washings were neutral, dried with the Na_2SO_4-$MgSO_4$ mixture and after the removal of solvent, distilled in vacuum at 3×10^{-2} mmHg. The yield of (*R,S*)-IV is 16.1 g (83%), b.p. 72—75° C; $n_D^{20} = 1.5720$; m.p. 28—30° C.

(R)-(α-(N,N-dimethylamino)ethyl)cymantrene, (R)-IV

(*R*)-IV was obtained in a similar manner from (*R*)-XIII. B.p. 86—87° C at 6×10^{-2} mmHg; m.p. 54—55° C, $[\alpha]_{578}^{24} = +17.2°$ (*c* 2, ethanol). Analysis: Found: C, 52.33; 52.19; H, 4.96, 4.90; Mn, 20.20, 20.19. $C_{12}H_{14}NMnO_3$ calcd.: C, 52.37; H, 5.12; Mn, 19.96%.

(α-(N,N-dimethylamino)ethyl)formylcymantrene (mixture of isomers IIIa, IIIb and V)

Aminoaldehydes IIIa, IIIb and V were obtained by metallation of (*R,S*)-IV with n-butyllithium, followed by treatment with dimethylformamide following a published procedure [5]. From 7.5 g (0.027 mol) of (*R,S*)-IV and 7.5 ml (0.01 mol) of DMF 5.8 g (70%) of a mixture of isomers were obtained; b.p. 109—112° C at 3×10^{-2} mmHg; $n_D^{20} = 1.5830$ (crystallizes upon long term storage). Analysis: Found: C, 52.21, 51.68; H, 4.64, 4.67; N, 5.00, 4.95; Mn, 17.96, 18.00; $C_{13}H_{14}NO_4Mn$; calc.: C, 51.49; H, 4.65; N, 4.62; Mn, 18.12%.

(R_c, S_f)-2(α-(N,N-dimethylamino)ethyl)formylcymantrene, (R_c)-III-(S)$_f$

In a similar manner, from 14 g (0.05 mol) of (*R*)-IV and 13.5 ml (0.18 mol) of DMF 8.2 g (56%) of a mixture of isomeric aminoaldehydes were obtained; from this mixture an optically pure (—)-(*R*)$_c$-III-(*S*)$_f$ (Fig. 1) was isolated by recrystallization from hexane (4 times); m.p. 55—56°C, $[\alpha]_{436}^{20} = -127.5$ (*c* 0.031, $CHCl_3$); $[\alpha]_{436}^{25} = -295°$ (*c* 1.0; CCl_4). Analysis: Found: C, 51.36; 51.61; H, 4.61, 4.89; N, 4.55, 4.46; $C_{13}H_{14}NO_4Mn$, calcd.: C, 51.49; H, 4.65; N, 4.62%.

Synthesis of diastereomeric chelates VI-X, XII

Synthesis of VI—X and XII and analysis of their composition were effected by the procedure described in ref. 2.

VI-B. Found: C, 44.69; H, 4.78; N, 7.18; Cu, 11.47; Mn, 9.86; $C_{19}H_{22}O_6N_3MnCu \cdot H_2O \cdot \frac{1}{2} C_2H_5OH$, calcd.: C, 43.85; H, 4.97; N, 7.67; Cu, 11.60; Mn, 10.03%.

XI-A. Found: C, 45.69; H, 4.83; N, 7.32; Cu, 11.21; Mn, 10.01. $C_{19}H_{22}O_6N_3MnCu \cdot \frac{1}{2} C_2H_5OH$, calcd.: C, 45.34; H, 4.76; N, 7.93; Cu, 11.99; Mn, 10.36%.

XI-B. Found: C, 43.94; H, 4.73; N, 7.18; $C_{19}H_{22}O_6MnCu \cdot H_2O \cdot \frac{1}{2} C_2H_5OH$, calcd.: C, 43.85; H, 4.97; N, 7.67%.

IR-spectra for VI-X and XIII were determined in KBr using a UR-20 instrument. Frequences: 2025, 1940 (CO); 1650 (C=N); 2790—3100 cm^{-1} (CH of cyclopentadiene ring); no band for C=O of formyl group of compound III (1690 cm^{-1}) was observed.

Electronic spectra for VI-X and XII were determined in 96% C_2H_5OH on a Specord UV-VIS instrument; λ_{max}: 260, 340, 620 nm; λ_{min}: 250, 490 nm.

The diastereomeric purity of chelates was examined under analytical conditions on a 80 × 0.7 cm column packed with SiO_2 ("G" Berlin, GDR) with abs. ethanol at 20°C. The eluent flow rate was 20 ml/h. The chromatogram is obtained by means of a recording photometer with λ 440, 570, 640 nm.

ORD curves were taken on a Jasco ORD/UV-5 instrument.

Quantitative analysis of dipeptides was made on a AAA-881 aminoacid analyzer (Czechoslavakia), column of 40 × 0.8 cm with Ampex A-5 resin. Eluent-Na-citrate buffer, pH 4.25.

Isolation of individual 1,2- and 1,3-isomers of N,N-dimethylaminoalkylformylcynatrene. Isolation was carried out following a standard procedure:

To a solution of 1.65×10^{-3} mole of the dipeptide in 10 ml of abs. ethanol at 25°C, 300 mg of molecular sieves ("WolfenZbosorb" 3 Å), 0.360 g (1.65×10^{-3} mol) of copper acetate and 1.65×10^{-3} mole of a mixture of isomers IIIa, IIIb and V or I and XI were added. The reaction mixture was stirred for 24 hours at room temperature, filtered and evaporated to 3 ml, added to 20 ml of water and extracted with CCl_4. The CCl_4 layer was separated, dried with Na_2SO_4 and its PMR spectrum was determined.

For compound V (yield 86%), PMR (90 MHz) in CCl_4, δ (ppm) relative to external TMS: 1.46 d (J = 6.5 Hz $CHCH_3$); 2.42 s ($N(CH_3)_2$); 3.73 br.q. ($CHCH_3$); 4.84 m (H-5) and 5.55 m (H-2,4)(C_5H_3); 9.84 s (CHO).

For compound XI (yield 85%), PMR (60 MHz) in CCl_4, δ (ppm): 2.32 s ($N(CH_3)_2$); 3.09 br. s (CH_2); 4.80 m (H-5) and 5.33 m (H-2,4)(C_5H_3); 9.52 s (CHO).

The aqueous layer containing chelates of I or IIIa, IIIb was treated with 5 ml of 3 *N* HCl, and then neutralized with an excess of Na_2CO_3; aminoaldehydes were extracted with CCl_4. The yield of I or a mixture of IIIa, IIIb was 90% of theoretical UV, IR and PMR spectra for I were identical to those previously reported [1]. Properties of IIIa and IIIb are illustrated in Figs. 1 and 3. IR spectra of IIIa, IIIb in KBr have frequencies: 2030, 1960—1930 (CO); 1690 (CHO); 2790—3100 cm^{-1} (C—H cyclopentadiene ring).

For $(R)_c$-III-$(S)_f$: $[\alpha]^{25}_{436} = -295°$, $[\alpha]^{20}_{546} = -146°$ (*c* 1, CCl_4).

For $(R,S)_c$-III-$(S)_f$: $[\alpha]^{25}_{546} = -110°$ (*c* 0.11, CCl_4).

For $(R,S)_c$-III-$(R)_f$: $[\alpha]^{25}_{546} = +92°$ (*c* 0.09, CCl_4).

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