# Tumor Inhibiting Properties of Stereoisomeric [1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-Complexes, Part I: Synthesis

**ARTICLE** *in* ARCHIV DER PHARMAZIE · JANUARY 1989

Impact Factor: 1.53 · DOI: 10.1002/ardp.19893220107 · Source: PubMed

# Tumor Inhibiting Properties of Stereoisomeric [1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-Complexes, Part I: Synthesis

Margaretha Jennerwein[+], Ronald Gust[+], Richard Müller[+], Helmut Schönenberger[+*], Jürgen Engel[++], Martin R. Berger[+++], Dietrich Schmähl[+++], Siegfried Seeber[++++], Reinhardt Osieka[+++++], Ghanem Atassi[++++++] and Danièle Maréchal-De Bock[++++++]

[+] Institut für Pharmazie, Lehrstuhl Pharmazeutische Chemie II, Sonderforschungsbereich 234, Universität Regensburg, Universitätsstraße 31, D-8400 Regensburg
[++] Forschung-Degussa Pharma Gruppe, Daimlerstraße 25, D-6000 Frankfurt 1
[+++] Institut für Toxikologie und Chemotherapie, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, D-6900 Heidelberg
[++++] Städt. Krankenhaus Leverkusen, Zentrum Innere Medizin, Medizinische Klinik III, Dhünnberg 60, D-5090 Leverkusen 1
[+++++] Innere Universitätsklinik und Poliklinik (Tumorforschung), Westdeutsches Tumorzentrum, Hufelandstraße 55, D-4300 Essen
[++++++] Institut Jules Bordet, Rue Heger-Bordet 1, 1000 Bruxelles

Received April 20, 1988

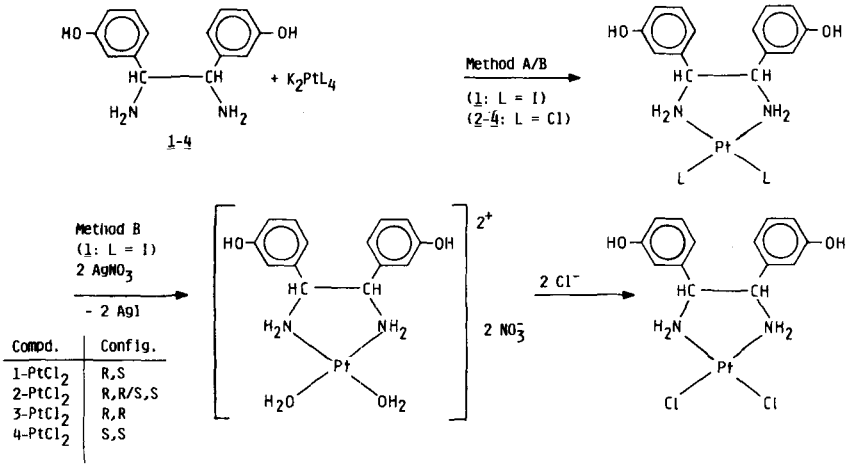
The synthesis of the stereoisomeric 1,2-bis(3-hydroxyphenyl)ethylenediamines (1-4) from meso-1,2-bis(2-hydroxyphenyl)ethylenediamine and 3-methoxybenzaldehyde by a diaza-*Cope*-rearrangement and subsequent ether cleavage with $BBr_3$ and their conversion into the [1,2-bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-complexes with $K_2PtCl_4$ (1-$PtCl_2$ - 4-$PtCl_2$) is described.

**Tumor-hemmende Eigenschaften der stereoisomeren [1,2-Bis(3-hydroxyphenyl)ethylendiamin]dichloroplatin(II)-Komplexe, Teil 1: Synthese**

Die Synthese der stereoisomeren 1,2-Bis(3-hydroxyphenyl)ethylendiamine (1-4) aus meso-1,2-Bis(2-hydroxyphenyl)-ethylendiamin und 3-Methoxybenzaldehyd durch Diaza-Cope-Umlagerung und anschließende Etherspaltung mit $BBr_3$ und ihre Reaktion mit $K_2PtCl_4$ zu den [1,2-Bis(3-hydroxyphenyl)ethylendiamin]dichloroplatin(II)-Komplexen (1-$PtCl_2$ - 4-$PtCl_2$) wird beschrieben.

In recent publications[1-3] we have shown that dichloro(1,2-diphenylethylenediamine)platinum(II)-complexes with fluorine and hydroxy substituents in 4-positions of both benzene rings possess marked antitumor activities. By variation of the position and number of the substituent (F or OH, resp.) or by combination of both substituents in one drug molecule a further increase of the tumor inhibiting properties was achieved[4].

In this connection the stereoisomeric [1,2-bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-complexes




| Compd. | Config. |
|---|---|
| 1-$PtCl_2$ | R,S |
| 2-$PtCl_2$ | R,R/S,S |
| 3-$PtCl_2$ | R,R |
| 4-$PtCl_2$ | S,S |

  0365-6233/89/0101-0025 $ 02.50/0

**Table 1.** [1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-Complexes - Analytical Data

| compd. | config. | yield % | formula | C% calcd. | C% found | H% calcd. | H% found | N% calcd. | N% found | Cl% calcd. | Cl% found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1-$PtCl_2$** | R,S | 53 | $C_{14}H_{16}Cl_2N_2O_2Pt$ | 32.95 | 33.0 | 3.16 | 3.20 | 5.5 | 5.4 | 13.9 | 14.4 |
| **2-$PtCl_2$** | R,R/S,S | 68 | | | 32.9 | | 3.12 | | 5.4 | | 14.1 |
| **3-$PtCl_2$** | R,R | 63 | | | 32.3 | | 2.84 | | 5.7 | | 13.7 |
| **4-$PtCl_2$** | S,S | 71 | | | 32.8 | | 3.27 | | 5.6 | | 14.1 |

**Table 2.** $^1$H-NMR-Data of [1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II) -Complexes and of their Ligandes ($\delta$ (ppm), TMS/*int*)

| compd. (config.) | arom. H | CH (benzylic) | NH | OH | $OCH_3$ |
|---|---|---|---|---|---|
| **1-$PtCl_2$** [a] (R,S) | 7.40 (s, 2 H)<br>6.98 (t, J=8 Hz, 2 H)<br>6.71 (m, 4 H) | 4.38 (br, 2 H) | 6.10 (br, 2 H)<br>5.49 (br, 2 H) | 9.7 (s, 2 H) | |
| **2-$PtCl_2$** [a] (R,R/S,S) | 7.39 (d, J=8 Hz, 2 H)<br>7.12 (s, 2 H)<br>7.07 (d, J=8 Hz, 2 H)<br>6.65 (m, 2 H) | 5.23 (br, 2 H) | 6.48 (br, 2 H)<br>5.83 (br, 2 H) | 9.5 (s, 2 H) | |
| **1** [c] (R,S) | 6.50-7.25 (m, 8 H) | 3.75 (s, 2 H) | | | |
| **2** [c] (R,R/S,S) | 6.20-7.07 (m, 8 H) | 4.00 (s, 2 H) | | | |
| **1a** [b] (R,S) | 6.30-7.38 (m, 8 H) | 4.02 (s, 2 H) | 1.42 (s, 4 H) | | 3.85 (s, 6 H) |
| **2a** [b] (R,R/S,S) | 6.75-7.34 (m, 8 H) | 4.09 (s, 2 H) | 1.51 (s, 4 H) | | 3.73 (s, 6 H) |

[a] 250 MHz, DMF-$D_7$. [b] 90 MHz, $CDCl_3$. [c] 90 MHz, $CD_3OD$/NaOD

proved to be of special interest. In part I we describe the synthesis and in part II the biological properties of this type of platinum complex.

With the exception of **1-$PtCl_2$** (R,S-configurated ligand) the stereoisomeric [1,2-bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-complexes were synthesized by reaction of the respective 1,2-bis(3-hydroxyphenyl)ethylenediamine with $K_2PtCl_4$ (Scheme I, Method A,L = Cl). Owing to the steric facts, the formation of the R,S-configurated complex proceeds very slowly and requires reaction times of several days. Therefore **1-$PtCl_2$** was synthesized via the easier accessible diaminediiodoplatinum(II)-complex (**1-$PtI_2$**). The exchange of iodine by chlorine was performed in a two step reaction: a) Transformation of **1-$PtI_2$** into **1-$Pt(OH_2)_2^{2+}$** with $AgNO_3$. b) Displacement of the Pt-bound $H_2O$-molecules by Cl- by addition of NaCl (Scheme I, Method A/B, L = I).

The analytical data are listed in tables 1 and 2.

**1-$PtCl_2$** to **4-$PtCl_2$** show IR-spectra typical for diaminedichloroplatinum(II)-complexes: 1. The N-H stretching vibration shifts considerably to lower wave numbers upon formation of the Pt-N bond (free ligand; ν N-H = 3400-3300 $cm^{-1}$; Pt-bond ligand; ν N-H = 3300-3100 $cm^{-1}$). - 2. Two absorption bands appear in the far IR region, one between 650 and 450 $cm^{-1}$ indicating a Pt-N stretching vibration and another between 345 and 320 $cm^{-1}$ indicating a Pt-Cl stretching vibration.

The $^1$H-NMR-spectra are also characteristic for (1,2-diphenylethylenediamine)dichloroplatinum(II)-complexes. By the formation of the platinum complexes all absorption

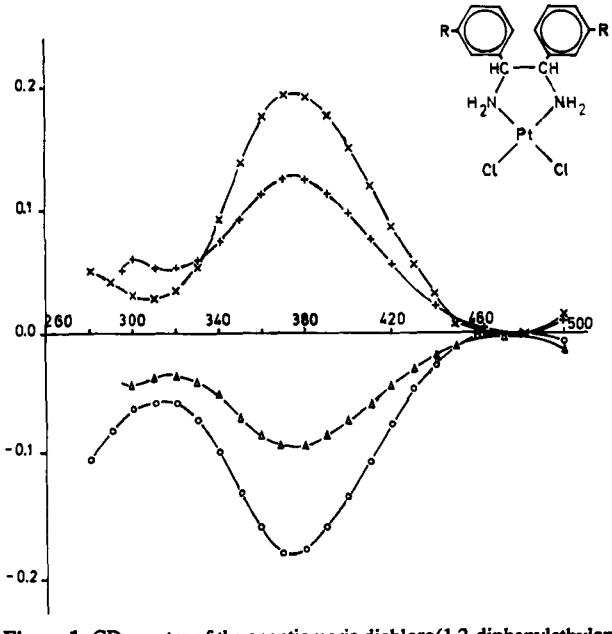
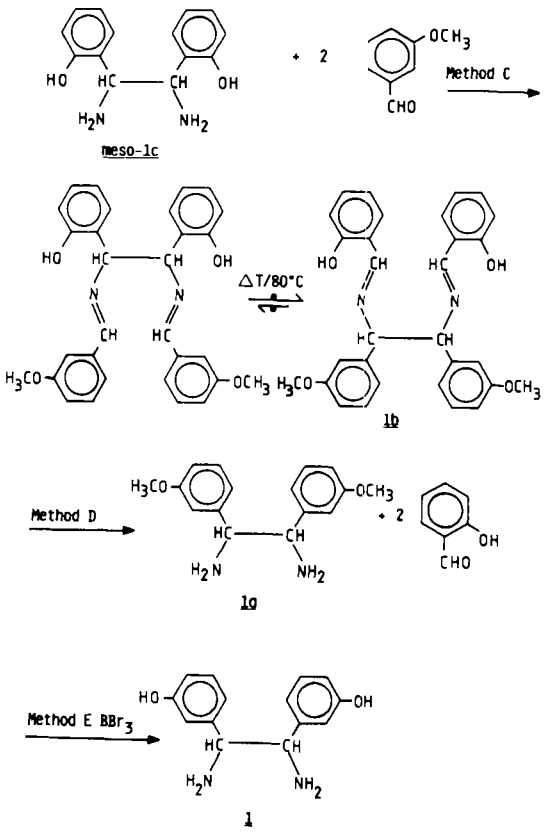



**Figure 1:** CD-spectra of the enantiomeric dichloro(1,2-diphenylethylenediamine)platinum(II) and of the enantiomeric [1,2-bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-complexes: x:R = H (R,R), (+); +:R = OH (R,R), (+); O:R = H (S,S), (-); Δ:R = OH (S,S); (-).




bands of the 1,2-diphenylethylenediamines, particularly those of the amine and benzylic protons are shifted to lower field. Since the complexation blocks rotation around the C-N axis, both N-bound protons become diastereotopic owing to the neighbourhood of the asymmetric C-atoms. This leads to the appearance of separate signals for the axially and for the equatorially orientated N-H atoms. Due to a coupling between $NH_2$, CH (benzylic) and $^{195}Pt$ the N-H and C-H signals are broadened.

The absolute configuration of **3**-$PtCl_2$ and **4**-$PtCl_2$ was determined by comparison of their CD spectra with those of (+) and (-) dichloro(1,2-diphenylethylenediamine)-platinum(II), whose absolute configuration is known ((+) ≙ R,R; (-) ≙S,S)[5]. Also in the case of the enantiomeric [1,2-bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)-complexes the (+) rotating compound **3**-$PtCl_2$ is R,R- and the (-) rotating compound **4**-$PtCl_2$ S,S-configurated (see Figure 1).

The diastereomeric 1,2-bis(3-hydroxyphenyl)ethylenediamines **1** and **2** were synthesized by the [3.3]sigmatropic diaza-*Cope* rearrangement reaction according to the method of *Vögtle* and *Goldschmitt*[6] (Scheme II and III). At a temp. below 120 °C N,N'-disalicylidene-meso-1,2-bis(3-methoxyphenyl)ethylenediamine (**1b**) is formed quantitatively from 3-methoxybenzaldehyde and meso-1,2-bis(2-hydroxyphenyl)ethylenediamine (**1c**) in a stereospecific reaction (Scheme II, Method C). Meso-1,2-bis(2-hydroxyphenyl)ethylenediamine (meso-**1c**), originally described by *Japp* and *Hooker*[7], was synthesized from benzil, salicylic aldehyde and ammonia using an improved method published by *Vögtle* and *Goldschmitt*[6].

By hydrolysis of **1b** with 3 N $H_2SO_4$ the meso-1,2-bis(3-methoxyphenyl)ethylenediamine (**1a**) is generated (Scheme II, Method D). The demethylation of the methoxy compound **1a** to **1** was readily effected with $BBr_3$ (Scheme II, Method E).

The d,l-configurated 1,2-bis(3-hydroxyphenyl)ethylenediamine (**2a**) was achieved by the meso d,l-stereoisomerisation of N,N'-bis(3-methoxybenzylidene)-meso-1,2-bis(3-methoxyphenyl)ethylenediamine which takes place during the diaza-*Cope* rearrangement at high temp. (> 120 °C; Scheme III, Method F).

The meso, d,l-mixture was first submitted to hydrolysis and the diastereomeric ligands were then separated by crystallisation of the bases in ether (Scheme III, Method G). The two enantiomers **3a** and **4a** were obtained by separation of (±)-1,2-bis(3-methoxyphenyl)ethylenediamine with tartaric acid. The free hydroxy derivatives (d,l-**1** to **3**) were synthesized by method E.

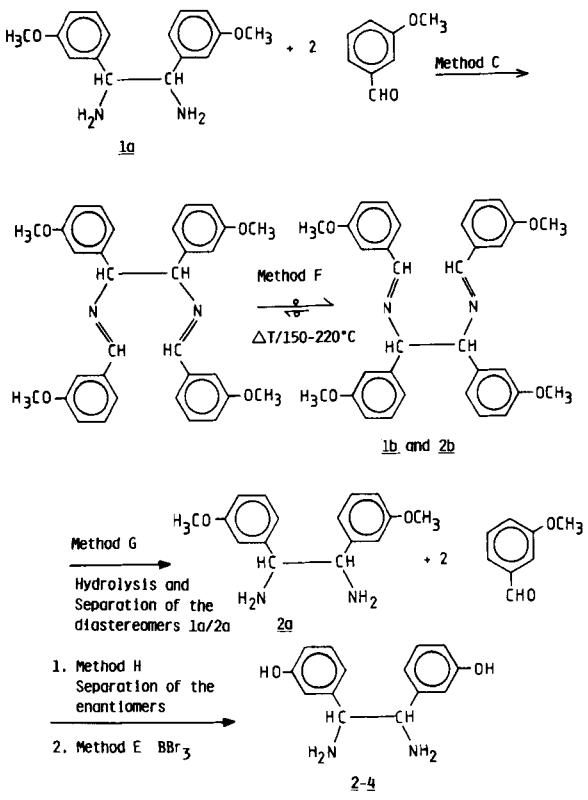
The biological properties of **1**-$PtCl_2$ to **4**-$PtCl_2$ are described in the subsequent publication.

This work was supported by the Deutsche Forschungsgemeinschaft (SFB 234), the Bundesministerium für Forschung und Technologie (grant 03 8715/6), the "Walter Schulz-Stiftung" and the "Matthias Lackas-Stiftung für Krebsforschung". Thanks are also due to the Fonds der Chemischen Industrie for financial support. The technical assistance of *F.Birk, S.Dehen, B.Hoffmann, P.Pistor* and *P.Richthammer* is gratefully acknowledged.

**Table 3.** 1,2-Bis(3-methoxyphenyl)ethylenediamines and 1,2-Bis(3-hydroxyphenyl)ethylenediamines - Analytical Data

| compd. | config. | yield % | mp. °C | formula | C% calcd. | C% found | H% calcd. | H% found | N% calcd. | N% found |
|---|---|---|---|---|---|---|---|---|---|---|
| **1-a** | R,S | 75 | 115-117 | $C_{16}H_{20}N_2O_2$ | 70.6 | 71.0 | 7.40 | 7.32 | 10.3 | 10.3 |
| **2-a** [a] | R,R/S,S | 38 | oil [a] | $C_{16}H_{20}N_2O_2 \cdot 2$ HCl | 55.6 | 55.5 | 6.42 | 6.44 | 8.1 | 8.1 |
| **3-a** [b,c] | R,R | 46 | oil | $C_{16}H_{20}N_2O_2$ | | | | | | |
| **4-a** [b,d] | S,S | 63 | oil | $C_{16}H_{20}N_2O_2$ | | | | | | |
| **1** | R,S | 55 | 225-226 | $C_{14}H_{16}N_2O_2 \cdot 0.75\ H_2O$ | 65.2 | 65.3 | 6.92 | 6.51 | 10.9 | 10.6 |
| **2** | R,R/S,S | 43 | 214-216 | $C_{14}H_{16}N_2O_2 \cdot 2$ HBr $\cdot H_2O$ | 39.7 | 40.1 | 4.75 | 4.50 | 6.6 | 6.6 |
| **3** [e] | R,R | 78 | 214-215 | $C_{14}H_{16}N_2O_2 \cdot 2$ HCl | 53.0 | 52.8 | 5.72 | 5.89 | 8.8 | 8.7 |
| **4** [f] | S,S | 63 | 214-215 | $C_{14}H_{16}N_2O_2 \cdot 2$ HBr | 41.4 | 41.5 | 4.47 | 4.39 | 6.9 | 6.9 |

[a] Dihydrochloride: mp = 248-250 °C. [b] Not analyzed for C, H, N. [c] $[\alpha]_{546}^{25}$ = + 130.9° (c = 1, methanol). [d] $[\alpha]_{546}^{25}$ = - 132.0° (c = 1, methanol). [e] $[\alpha]_{546}^{20}$ = - 22.6° (dihydrobromide, c = 1, methanol). [f] $[\alpha]_{546}^{20}$ = + 22.4° (dihydrobromide, c = 1, methanol).




## Experimental Part

General Procedures. Melting points, (uncorrected): Büchi 510 melting point apparatus or Petri melting point apparatus if higher than 220 °C. - IR data: Perking Elmer Model 580 A. - $^1$H-NMR spectra: Varian EM 390 A 80 MHz spectrometer. $^1$H-NMR spectra of the platinum complexes: Bruker PFR-NMR spectrometer WM 250 at 250 MHz. - Elemental analyses: microlaboratory of the University of Regensburg.

*Syntheses*

Methods A-H are representative for the syntheses of the compounds reported in Tables I and III.

*Method A*

*[d,1-1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)* (**2-$PtCl_2$**)

An aqueous solution of d,1-1,2-bis(3-hydroxyphenyl)ethylenediamine dihydrochloride (**2** · 2 HCl, 634 mg = 2 mmol in 20 ml $H_2O$) was slowly added to an aqueous K2PtCl4 solution (830 mg = 2 mmol in 20 ml H2O). The mixture was stirred in the dark, while the forming HCl was repeatedly neutralized with 0.5 N NaOH (pH 5.5 – 6.5). After 6 to 10 h **2**-$PtCl_2$ was collected as a yellow powder by suction filtration using a no. 3 fritted glass filter and washed with 0.5 N HCl and $H_2O$. For purification the complex was dissolved in DMF and precipitated with $H_2O$. Yield 68 %.

*Method B*

*[meso-1,2-Bis(3-hydroxyphenyl)ethylenediamine]dichloroplatinum(II)* (**1-$PtCl_2$**)

1 mmol $K_2PtCl_4$ and 4 mmol KI were stirred in 10 mL $H_2O$ for about 20 min in the dark. Then the ligand **1** (244 mg = 1 mmol) was added and the mixture was stirred for about 7 h while the pH was repeatedly adjusted to 5.5 - 6.5 with 0.5 N NaOH. After isolation, the diiodoplatinum(II-complex was suspended in $H_2O$, 2 mmol $AgNO_3$ were added per mmol complex and the mixture was stirred overnight. The precipitated AgI was filtered off using a no. 4 fritted glass filter and the $Ag^+$-free solution stirred with an excess of NaCl overnight. **1**-$PtCl_2$ (yellow powder) was isolated and purified as described in Method A. Yield 53%.

*Method C*

*N,N'-Disalicylidene-meso-1,2-bis(3-methoxyphenyl)ethylenediamine* (**1b**)

meso-1,2-Bis(2-hydroxyphenyl)ethylenediamine (**1c**, 24.4 g = 100 mmol) and 3-methoxybenzaldehyde (27.2 g = 200 mmol) were refluxed in 200 mL MeCN for 3 h. The solution was concentrated and the yellow precipitate was collected in an Buchner funnel, washed with small amounts of ice-cold MeCN and and acetone and dried over $P_2O_5$. Yield 88%, yellow powder, mp. 205-206.5 °C.

*Method D*

*meso-1,2-Bis(3-methoxyphenyl)ethylenediamine* (**1a**)

**1b** (40.8 g = 85 mmol) was hydrolyzed with 500 mL 3 N $H_2SO_4$ and the forming salicylic aldehyde was removed by steam distillation. The hot solution was filtered and alkalized with 20% NaOH under ice cooling. The diamine was extracted with $CH_2Cl_2$, the org. layer was washed with $H_2O$, dried over $MgSO_4$, and evaporated. The rude product was recrystallized in acetonitril. Yield 75%, colorless crystals, mp. 115-117 °C.

*Method E*

*meso-1,2-Bis(3-hydroxyphenyl)ethylenediamine* (**1**)

A solution of **1a** (4.08 g = 15 mmol) in 150 mL dry $CH_2Cl_2$ was cooled to -60 °C. $BBr_3$ (15.0 g = 60 mmol) was added in a $N_2$ atmosphere. The reaction mixture was stirred for 30 min at -60 °C and overnight at room temp. Then 50 mL MeOH were added slowly under cooling and the solvents were removed under reduced pressure. The residue was dissolved in 50 mL $H_2O$, filtered and the product was precipitated with NaOH at pH 9-11 under cooling. The precipitate was sucked off, washed with great amounts of $H_2O$, and dried over $P_2O_5$. Yield 55 %, colorless powder, mp. 225 °C.

*Method F and G*

*d,1-1,2-Bis(3-methoxyphenyl)ethylenediamine* (**2a**)

Stereoisomerisation was performed by heating **1b** (50.8 g = 100 mmol) to 210-220 °C for about 10 min. Thereafter, 300 mL 3N $H_2SO_4$ were added to the mixture of **1c** and **2c**. The mixture was heated, and the forming 3-methoxybenzaldehyde was removed by steam distillation. The hot solution was filtered and made alkaline with 20 % NaOH under icecooling. The precipitated diastereomeric bases **1a** and **2a** were extracted with $CH_2Cl_2$, the org. layer was separated, washed with $H_2O$ and dried over $MgSO_4$. After removal of the solvent the residue was treated with ether. **2a** which is soluble in ether, was readily separated from the unsoluble, **1a**. After evaporation of the solvent **2a** remained as oil.

*Method H*

*(+)and(-)-1,2-Bis(3-methoxyphenyl)ethylenediamine* (**3a** and **4a**)

**2a** (10.0 g = 36.8 mmol), dissolved in 40 ml 75 % EtOH, was given to the solution of L-(+)-tartaric acid (5.25 g = 36.8 mmol in 35 ml 75 % EtOH) and boiled under reflux for 10 min. The solution was allowed to cool slowly and **4a**-tartrate crystallized at room temp. It was recrystallized from 75 % EtOH several times, then treated with 5 % NaOH and $CHCl_3$.

The org. layer was separated and dried and, after removal of the solvent, **4a** remained as colorless oil (Yield 62 %; $[\alpha] = -132.0°$, c = 1, MeOH). From the above filtrate **3a** was isolated and purified in the same manner by crystallization of the D-(-)-tartrate (Yield 46 %; $[\alpha] = +131°$, c = 1, MeOH).

*CD Spectra*

The spectra were obtained with a JASCO J-40 A spectropolarimeter (time constant 16 s; scan speed 5 nm/min) and recorded in $Me_2SO$ at room temp. in 5-cm quartz cells. The concentrations were $2 \times 10^{-3}$ M 3-$PtCl_2$ (R,R), 4-$PtCl_2$ (S,S) and (S,S)-dichloro(1,2-diphenylethylenediamine)platinum(II) and $4 \times 10^{-3}$M (R,R)-dichloro(1,2-diphenylethylenediamine)platinum(II).

## References


1 B. Wappes, M. Jennerwein, E. von Angerer, H. Schönenberger, J. Engel, M. Berger, and K.-H. Wrobel, J. Med. Chem. *27*, 1280 (1984).
2 R. Müller, R. Gust, M. Jennerwein, H. Reile, R. Laske, W. Krischke, G. Bernhardt, Th. Spruß, J. Engel, and H. Schönenberger, Eur. J. Med. Chem., in press.
3 J. Karl and H. Schönenberger, Arch. Pharm. (Weinheim) *321*, 405 (1988).
4 R. Gust, Ph. D. Thesis, University of Regensburg 1987
5 R. Meric and J. Vigueron, Tetrahedron Lett. *24*, 2059 (1974).
6 F. Vögtle and E. Goldschmitt, Chem. Ber. *109*, 1 (1976).
7 F. R. Japp and S. C. Hooker, Chem. Ber. *117*, 2402 (1984).


[Ph516]