Synthesis and Antitumor Activity of Pt(II) Complexes of Benzyl-1,2-diaminoethane Ligands

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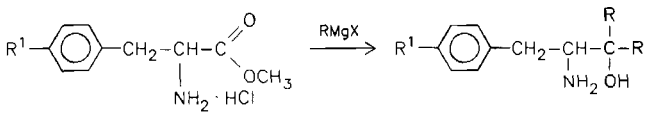
Twelve new diamine ligands are synthesized and characterized in which a benzyl group and another vicinal substituent or a benzyl group, a 4-Cl-benzyl group, and a 4-MeO-benzyl group, respectively, and two other geminal substituents are attached to the 1,2-diaminoethane skeleton. The diamine ligands are transformed into the dichloroplatinum(II) complexes. The chloride ligands of four complexes are replaced by the lactate anion. α-Cyclodextrin and polyvinylpyrrolidone are used to increase the water solubility of the Pt(II) complexes. The antitumor activity of the Pt(II) complexes is tested towards the P388 leukemia. The compounds with small alkyl substituents show antitumor activities which are much higher than the antitumor activity of *cis*-platinum. Compared to the insoluble dichloro complexes, the lactate complexes and the formulations with α-cyclodextrin and polyvinylpyrrolidone exhibit good water solubility, and no decrease of the antitumor activity is observed.

cis-Platinum, *cis*-$(NH_3)_2PtCl_2$, is the most widely used anticancer drug[1]. However, the clinical application causes a number of serious side effects[2,3]. World-wide research is directed towards the aim to improve the therapeutic activity by replacing the NH_3 ligands by other nitrogen ligands. It is known that two hydrogen atoms at the coordinating nitrogen atoms are essential for antitumor activity[4]. Thus, the alkyl groups of primary amines and the skeleton of 1,2-diaminoethane are open to variation.

We showed that benzyl-substituted dichloro(1,2-diaminoethane)platinum(II) and its derivatives substituted at the phenyl ring of the benzyl group have a high antitumor activity accompanied by a low toxicity compared to *cis*-platinum[5,6]. However, in view of a clinical use of these compounds their solubility in water has to be increased.

We tried to approach this goal with three strategies[7]. First, by substitution of the benzyl-1,2-diaminoethane ligands to make the platinum(II) complexes more bulky. Reducing intermolecular metal–metal and metal–ligand interactions should favor the solubility of the complexes. Second, by exchange of chloride for lactate. Substitution of the Cl anions in *cis*-platinum for the cyclobutanedicarboxylate anion led to carbo-platinum, a second-generation platinum drug, clinically introduced in 1986[8]. Third, by the use of cyclodextrins and polyvinylpyrrolidone as additives. Such additives are frequently applied to prepare pharmaceutical formulations of insoluble compounds[9,10].

Scheme 1



1-3 4-11

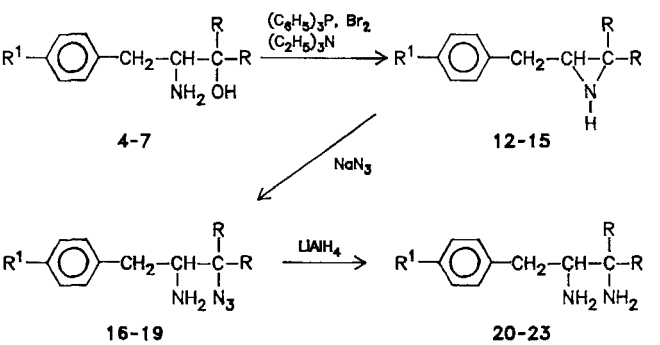
	1, 4	2, 5	2, 6	2, 7	2, 8
R	CH_3	CH_3	C_2H_5	n-C_5H_{11}	c-C_6H_{11}
R^1	Cl	H	H	H	H

	2, 9	2, 10	3, 11
R	C_6H_5	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$
R^1	H	H	CH_3O

Synthesis of Substituted Benzyl-1,2-diaminoethane Ligands and Complexes

The amino acid phenylalanine, its 4-Cl, and its 4-MeO derivative are converted into the methyl ester hydrochlo-

Scheme 2



4-7 12-15

16-19 20-23

	4, 12 16, 20	5, 13 17, 21	6, 14 18, 22	7, 15 19, 23
R	CH_3	CH_3	C_2H_5	n-C_5H_{11}
R^1	Cl	H	H	H

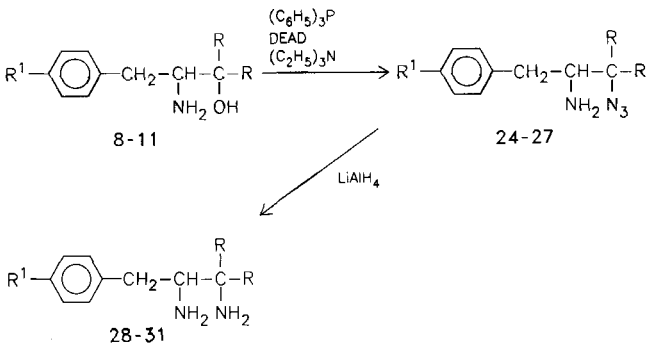
  0009–2940/90/0505–1029 $ 02.50/0

rides with thionyl chloride in methanol[5,11]. Their reactions with the Grignard reagents, shown in Scheme 1, give the amino alcohols **4**–**11**, containing two of the R substituents at the C-2 position of the future 1-benzyl-1,2-diaminoethane skeleton.

The transformation of the amino alcohols into the diamines depends on the substituents. The amino alcohols **4**–**7** are converted into the corresponding aziridines, using Ph_3PBr_2 and Et_3N as reagents[12]. The aziridine ring is opened with NaN_3 to give amino azides, the azido groups of which are reduced with $LiAlH_4$, yielding the 1,2-diaminoethanes **20**–**23**.

In the amino alcohols **8**–**11**, the hydroxy group is directly replaced by the azide group, using the system diethyl azodicarboxylate (DEAD), Ph_3P, and HN_3[13,14]. Reduction as above yields the 1,2-diaminoethanes **28**–**31**.

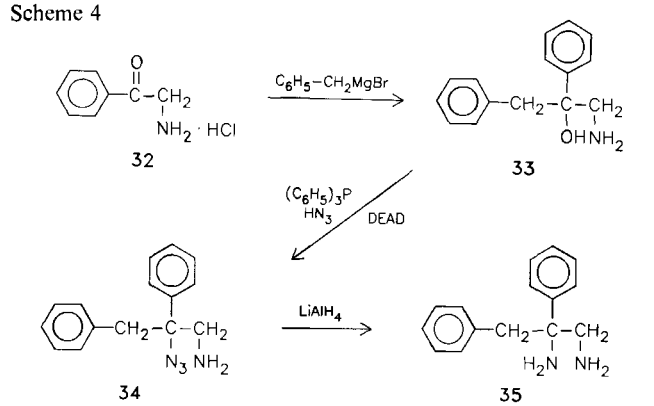
Scheme 3



	8, 24, 28	9, 25, 29	10, 26, 30	11, 27, 31
R	c-C_6H_{11}	C_6H_5	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$
R^1	H	H	H	CH_3O

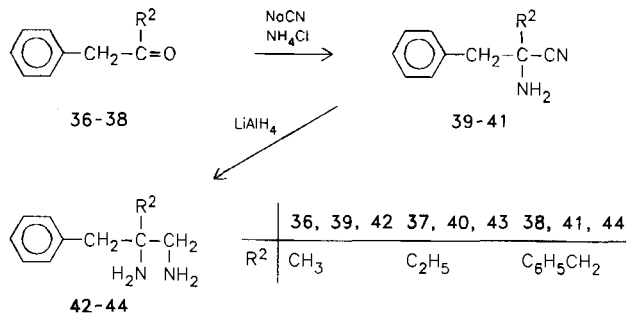
The synthesis of **35** (Scheme 4) starts from 2-aminoacetophenone to which two benzyl groups are added, using a benzyl Grignard reagent. The amino alcohol is transformed into the diamine **35** by a direct exchange of the hydroxy group for the azido group followed by subsequent reduction, as described above.

Scheme 4



The 1,2-diaminoethanes **42**–**44** with C-1 substituents other than phenyl are synthesized in a Strecker-type reaction, starting from the corresponding ketone (Scheme 5)[15,16]. The amino nitriles are reduced to the diamines **42**–**44** with $LiAlH_4$. This reduction yields by-products with the nitrile group converted into a methyl group. These by-products can be separated from the diamines by distillation.

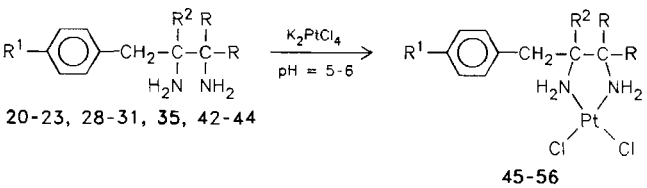
Scheme 5



	36, 39, 42	37, 40, 43	38, 41, 44
R^2	CH_3	C_2H_5	$C_6H_5CH_2$

The 1,2-diaminoethanes **20**–**23**, **28**–**31**, **35**, **42**–**44** were used as ligands to prepare the corresponding dichloroplatinum(II) complexes **45**–**56** by addition to a solution of K_2PtCl_4 (Scheme 6)[17,18]. The ligands **20**–**22**, **35**, and **42**–**44** are sufficiently soluble in water. Thus, water serves as the solvent for the synthesis of complexes **45**–**47** and **53**–**56**. For the preparation of the complexes **48**–**52**, a *t*BuOH/H_2O mixture has to be used as solvent due to the water insolubility of the ligands **23** and **28**–**31**. The pH is kept constant at 5 during the reaction by successive addition of 1 N NaOH. The complexes precipitate after some time as pale yellow solids.

Scheme 6



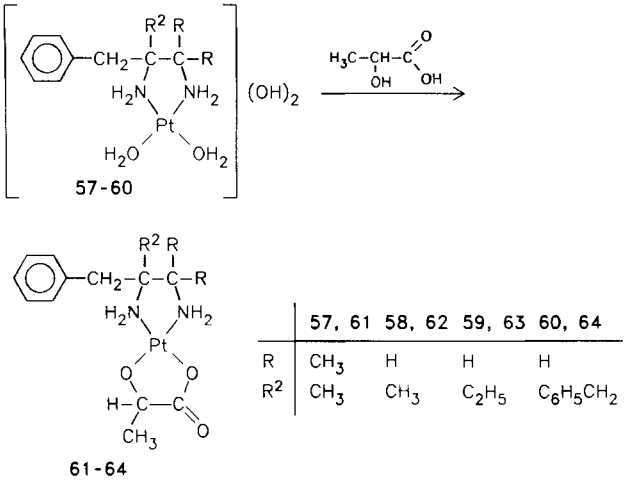
	20, 45	21, 46	22, 47	23, 48	28, 49	29, 50	30, 51
R	CH_3	CH_3	C_2H_5	n-C_5H_{11}	c-C_6H_{11}	C_6H_5	4-$CH_3OC_6H_4$
R^1	Cl	H	H	H	H	H	H
R^2	H	H	H	H	H	H	H

	31, 52	35, 53	42, 54	43, 55	44, 56
R	4-$CH_3OC_6H_4$	H	H	H	H
R^1	CH_3O	H	H	H	H
R^2	H	C_6H_5	CH_3	C_2H_5	$C_6H_5CH_2$

Hydroxycarboxylic acids such as glycolic acid can be converted into platinum complexes of good water solubility[19–21]. In order to exchange the chloride ligands for lactate, the diamino(diaqua)platinum(II) dinitrate complexes have to be prepared. This is achieved by treatment of a suspension of the corresponding dichloro complex with an equivalent amount of an $AgNO_3$ solution. The solution of

the "nitrate complex" is filtered off from the precipitated AgCl. To avoid nitrate impurities in the lactate complex, the aqueous solution of the diamino(diaqua)platinum(II) dinitrate is passed through a strongly basic anion exchange resin[22], in which the nitrate groups are replaced by hydroxy groups. The resulting aqueous solution, containing the corresponding complexes **57**–**60**, is treated with an equimolar amount of freshly distilled L-lactic acid. To isolate the complexes **61**–**64**, the solvent is evaporated, the resulting yellow oil is dissolved in ethanol and precipitated with ether to give the nearly colorless complexes **61**–**64** (Scheme 7).

Scheme 7



Use of Solubilizing Agents

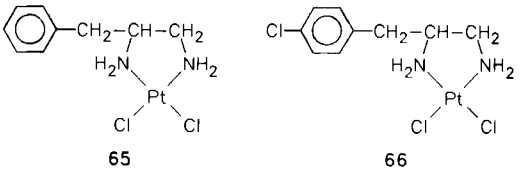
Cyclodextrins consist of a hydrophobic center and a hydrophilic surface. Trapping parts of a platinum complex in the apolar cavity should favor its solubility[9]. To prepare the solutions, the platinum complex is suspended in a 1:1 mixture of polyethylene glycol (PEG) 400 and 1.8% aqueous NaCl solution, the solvent used in the P388 leukemia in vivo tests. To this suspension, an aqueous solution of α-cyclodextrin (CD) is added. After stirring and heating to 60°C, clear solutions are obtained. In Table 1 are listed the amounts of platinum complexes **46**, **65**, and **66** (Scheme 8), soluble in 10 ml of PEG 400/1.8% aqueous NaCl solution with and without use of α-cyclodextrin as the solubilizing agent.

The water-soluble polymer polyvinylpyrrolidone (PVP) can be used as a solubilizing agent for platinum complexes by preparing coprecipitates. The platinum complex and

Table 1. Amounts of platinum complexes soluble in 10 ml of PEG 400/1.8% aqueous NaCl solution; 2 mol of α-cyclodextrin (CD) are used per mol of platinum complex

	without CD	with CD 2:1
46	6 mg	18 mg
L-**65**	–	9 mg
D-**65**	–	9 mg
66	3 mg	18 mg

Scheme 8



PVP are separately dissolved in ethanol. After combining the solutions, the solvent is evaporated. The product is a platinum complex/PVP coprecipitate with the complex in a PVP matrix[23]. The ratio of platinum complex and PVP is chosen such that there is one complex molecule per 50 monomeric units of the polymer (the average molecular weight of PVP is 10000). In Table 2 are listed the amounts of platinum complexes **46** and **54**–**56**, soluble in 10 ml of PEG 400/1.8% aqueous NaCl solution compared with the coprecipitates.

Table 2. Amounts of platinum complexes soluble in 10 ml of PEG 400/1.8% aqueous NaCl solution; 1 mol of complex is used per 50 mol of the monomeric unit of PVP

	without PVP	as coprecipitate
46	10 mg	18 mg
54	8.5 mg	18 mg
55	4.5 mg	18 mg
56	–	5 mg

Table 1 and 2 show that the solubility of the dichloro complexes **46**, **54**–**56**, **65**, and **66** is appreciably improved by the solubilizing agents α-cyclodextrin and polyvinylpyrrolidone.

Antitumor Tests

The dichloro complexes and the lactate complexes as well as the preparations with the solubilizing agents have been tested in vivo, using the lymphatic P388 leukemia of the CD_2F_1 mouse[24].

In order to determine the antitumor activity, 1.0×10^6 P388 leukemia cells, suspended in 0.1 ml of phosphate-buffered saline, were implanted intraperitoneally (i.p.) into female CD_2F_1 mice with a body weight of ca. 18 g. The animals were randomized in groups of six. The therapy started 24 hours after the transplantation (= day 1) with i.p. application of a solution of 1.0×10^{-5}, 2.0×10^{-5}, and 4.0×10^{-5} mol/kg body weight of complex, dissolved or suspended in the solvent PEG 400/1.8% aqueous NaCl solution. The therapy was repeated at day 5 and day 9. Animal deaths were recorded daily. Each experiment included one group with six animals as untreated control and also one group with six animals, treated with *cis*-platinum at 1.5 mg/kg as positive control. For the evaluation of the *T/C* value, the median survival time of the treated animals was compared with that of the untreated control animals which was about 10 days.

$$T/C(\%) = \frac{\text{median survival time of the treated animals}}{\text{median survival time of control animals}} \times 100$$

The T/C value of the *cis*-platinum group is about 180. In addition to the survival time, the changes of the animal weights from day 1 to day 5 (d5 – d1) are of interest. A decrease in body weight of the mice is an indication of the toxicity of the compound.

A comparison of the T/C values of Table 3 shows that compounds with linear alkyl groups attached to the C-2 atom of the 1-benzyl-1,2-diaminoethane skeleton exhibit high antitumor activities, decreasing with the chain length. **46** shows with 240% (4×10^{-5} mol/kg) the best T/C value in this series. Compounds **45** and **46** achieve higher antitumor activities than *cis*-platinum. In contrast, compounds having ring substituents at the C-2-position posses very low antitumor activity. It is conspicuous that **46** is the complex with the highest solubility, whereas the complexes which are so poorly soluble that, even at the lowest concentration, they have to be applied as a suspension, exhibit low antitumor activity.

Table 3. Antitumor activity of the dichloroplatinum(II) complexes **45**–**52**; sus = suspension, sol = solution

Compound	Concentration [10^{-5} mol/kg]	Solubility	Weight difference d5–d1 [g]	T/C value
45[a]	1	sol	±0	155
	2	sus	+0.4	173
	4	sus	−0.4	187
46[b]	1	sol	−0.1	165
	2	sol	−1.7	200
	4	sus	−4.4	240
47[a]	1	sus	+1.0	141
	2	sus	+0.4	150
	4	sus	±0	164
48[a]	1	sus	+0.1	100
	2	sus	+0.1	100
	4	sus	−0.6	100
49[c]	1	sus	+1.0	109
	2	sus	−0.1	109
	4	sus	+0.5	114
50[b]	1	sus	+0.1	110
	2	sus	+0.1	110
	4	sus	+0.5	110
51[c]	1	sus	+0.7	99
	2	sus	−0.9	101
	4	sus	+1.1	112
52[c]	1	sus	+0.4	109
	2	sus	−0.4	105
	4	sus	+0.6	110

T/C value of the positive control group (*cis*-Pt; 1.5 mg/kg): [a] 170; [b] 175; [c] 190.

The activities in the C-1-substituted series **53**–**56** are analogous to those in the C-2-substituted series, discussed before. The methyl and ethyl compounds **54** and **55** are well soluble and show a high antitumor activity. The benzyl- and phenyl-substituted compounds **53** and **56**, which have to be applied as suspensions, are weakly effective (Table 4).

Table 4. Antitumor activity of the dichloroplatinum(II) complexes **53**–**56** and the lactate complexes **61**–**64**; sus = suspension, sol = solution

Complex	Concentration [10^{-5} mol/kg]	Solubility	Weight difference d5–d1 [g]	T/C value
53[a]	1	sol	+0.7	140
	2	sol	+0.2	162
	4	sus	−0.2	168
54[b]	1	sol	+0.1	200
	2	sol	−0.6	236
	4	sus	−3.4	300
55[c]	1	sol	+0.4	180
	2	sus	−1.7	230
	4	sus	−3.0	270
56[c]	1	sus	+0.5	120
	2	sus	+0.8	130
	4	sus	+0.7	133
61[b]	1	sol	±0	136
	2	sol	±0	182
	4	sol	±0	182
62[d]	1	sol	+0.4	185
	2	sol	+0.9	200
	4	sol	−1.9	285
63[d]	1	sol	+0.3	160
	2	sol	+0.2	185
	4	sol	−1.1	240
64[e]	1	sol	+0.7	130
	2	sol	+0.3	137
	4	sol	+0.1	150

T/C value of the positive control group (*cis*-Pt; 1.5 mg/kg): [a] 190; [b] 200; [c] 210; [d] 160; [e] 190.

The exchange of chloride as leaving group for lactate yields complexes with good water solubility. The two lactate complexes **62** and **63** have the same high antitumor activity as their dichloro analogs **54** and **55**. The decrease in animal weight observed for the lactate complexes **62** and **63** is reduced compared to that of the dichloro complexes **54** and **55**, indicating reduced toxicity (Table 4). The antitumor activity of the lactate **61** is remarkably reduced compared to that of the dichloro complex, but toxicity could not be observed.

When α-cyclodextrin is used, the dichloro complexes **65** and **66** show increased antitumor activity at low concentrations compared to the application as suspensions without α-cyclodextrin (Table 5). At higher concentrations the toxicity increases strongly. For the α-cyclodextrin preparation the dose-activity curve is obviously shifted to lower complex concentrations.

Contrary to **65** and **66**, the antitumor activity of **46** could not be increased by the use of α-cyclodextrin. So, the antitumor potency of **46** is not limited by solubility. The application of the PVP coprecipitate of **46** gives rise to an increased toxicity at highest concentration. The antitumor activities of **54** and **55** as PVP coprecipitates are negligible, whereas no toxicity is observed even at higher concentrations.

Table 5. Antitumor activity of the dichloroplatinum(II) complexes **46**, **54**–**56**, **65**, and **66** with solubilizing agents; sus = suspension, sol = solution

Compound	Concentration [10^{-5} mol/kg]	Solubility	Weight difference d5–d1 [g]	*T/C* value
46[CD][a]	1	sol	−0.2	150
	2	sol	−1.7	177
	4	sol	−3.2	222
D-65[CD][a]	1	sol	−0.2	178
	2	sol	−4.6	72
	4	sus	−3.7	44
L-65[CD][a]	1	sol	−1.9	205
	2	sol	−3.6	44
	4	sol	−5.6	61
DL-66[CD][a]	1	sol	−0.1	161
	2	sol	−0.6	178
	4	sol	−3.3	139
46[PVP][b]	1	sol	±0	180
	2	sol	−1.4	210
	4	sus	−4.0	130
54[PVP][c]	1	sol	+0.9	190
	2	sol	+0.9	210
	4	sol	±0	250
55[PVP][c]	1	sol	+1.0	170
	2	sol	+0.3	190
	4	sol	+0.7	205
56[PVP][c]	1	sus	+1.2	130
	2	sus	+1.2	140
	4	sus	+0.7	145

T/C value of the positive control group (*cis*-Pt; 1.5 mg/kg): [a] 200; [b] 210; [c] 160.

We thank the *Deutsche Forschungsgemeinschaft*, the *Fonds der Chemischen Industrie*, and the *Degussa AG*, Frankfurt, for the support of this work.

Experimental

IR: Beckman Spektralphotometer 4240. – ^{1}H NMR: Varian EM 360-L (60 MHz) and Bruker WM 250 (250 MHz); deuterated solvents, TMS as internal standard, coupling constants *J* in Hz. – Starting materials: Methyl DL-2-amino-3-(4-chlorophenyl)propanoate hydrochloride (**1**), methyl DL-2-amino-3-phenylpropanoate hydrochloride (**2**), methyl DL-2-amino-3-(4-methoxyphenyl)propanoate hydrochloride (**3**)[5,11]; 2-amino-1-phenyl-1-ethanone hydrochloride (**32**), 1-phenyl-2-propanone (**36**), 1-phenyl-2-butanone (**37**), and 1,3-diphenyl-2-propanone (**38**) are commercial products.

Synthesis of the Amino Alcohols **4**–**11**. – *General Procedure:* A solution of 100 mmol of the alkyl or aryl halide in 50 ml of anhydrous ether is prepared. About one third of this solution is added to 2.4 g (100 mmol) of magnesium turnings. After the reaction has started, the remaining halide solution is added dropwise with stirring. After complete addition, the mixture is heated at reflux for 30 min. On cooling, 17.0 mmol of the ester hydrochloride of the corresponding amino acid is added in portions, and the reaction mixture is heated at reflux for 15 h. – For hydrolysis, a saturated solution of 9.1 g (17.0 mmol) NH_4Cl in water is added dropwise with vigorous stirring. The insoluble product is filtered off, and the organic layer is separated and dried with Na_2SO_4. After evaporation of the solvent, a colorless oil is obtained. The aqueous layer is made alkaline by adding aqueous NH_3, extracted with ether, and worked up as above. The oily residues are combined and distilled.

DL-3-Amino-4-(4-chlorophenyl)-2-methyl-2-butanol (**4**): Ester hydrochloride: 4.3 g (17.0 mmol) of **1**; halide: 14.2 g (100 mmol) of CH_3I. – Colorless oil, b.p. 140°C/10^{-4} Torr, yield 1.5 g (41%). – IR (film): $\tilde{\nu}$ = 3420 cm^{-1} (OH), 3280 (NH), 2980 (aliphat. CH), 1650 (NH). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.11–7.30 (AA'BB', 4H, aromat. H), 2.98 (dd, 1H, ^3J = 2.7, ^3J = 13.5, CHN), 2.78 (AB, 1H, ^2J = 11.1, benzyl. H), 2.25 (AB, 1H, benzyl. H), 1.20 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.20–1.42 (m, 3H, NH_2, OH).

$C_{11}H_{16}ClNO$ (213.71) Calcd. C 61.18 H 7.55 N 6.51
Found C 61.04 H 7.42 N 6.51

DL-3-Amino-2-methyl-4-phenyl-2-butanol (**5**): Ester hydrochloride: 3.6 g (17.0 mmol) of **2**; halide: 14.2 g (100 mmol) of CH_3I. – Colorless oil, b.p. 120°C/10^{-4} Torr, yield 2.1 g (70%). – IR (film): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 3280 (NH), 3020 (aromat. CH), 2980 (aliphat. CH), 1600 (NH). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.18–7.36 (m, 5H, aromat. H), 3.03 (dd, 1H, ^3J = 2.5, ^3J = 13.5, CHN), 2.81 (AB, 1H, ^2J = 11.3, benzyl. H), 2.27 (AB, 1H, benzyl. H), 1.30 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.04–1.54 (m, 3H, NH_2, OH).

$C_{11}H_{17}NO$ (179.26) Calcd. C 73.68 H 9.56 N 7.81
Found C 73.11 H 9.42 N 7.72

DL-2-Amino-3-ethyl-1-phenyl-3-pentanol (**6**): Ester hydrochloride: 3.6 g (17.0 mmol) of **2**; halide: 10.9 g (100 mmol) of 1-bromoethane. – Colorless oil, b.p. 150°C/10^{-4} Torr, yield 1.7 g (48%). – IR (film): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 3280 (NH), 2980 (aliphat. CH), 1610 (NH). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.17–7.35 (m, 5H, aromat. H), 2.99 (dd, 1H, ^3J = 2.6, ^3J = 13.8, CHN), 2.96 (AB, 1H, ^2J = 11.7, benzyl. H), 2.31 (AB, 1H, benzyl. H), 1.48–1.64 (m, 4H, CH_2), 0.92–1.00 (m, 3H, NH_2, OH), 0.95 (t, 3H, ^3J = 7.5, CH_3), 0.62 (t, 3H, CH_3).

$C_{13}H_{21}NO$ (207.32) Calcd. C 75.31 H 10.21 N 6.76
Found C 74.74 H 10.07 N 7.01

DL-6-(1-Amino-2-phenylethyl)-6-undecanol (**7**): Ester hydrochloride: 3.6 g (17.0 mmol) of **2**; halide: 10.7 g (100 mmol) of 1-chloropentane. – Colorless oil, b.p. 160°C/10^{-4} Torr, yield 2.5 g (50%). – IR (film): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 3270 (NH), 2920 (aliphat. CH), 1610 (NH). – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 7.16–7.35 (m, 5H, aromat. H), 2.98 (dd, 1H, ^3J = 2.7, ^3J = 14.0, CHN), 2.94 (AB, 1H, ^2J = 12.0, benzyl. H), 2.30 (AB, 1H, benzyl. H), 1.33–1.60 (m, 16H, CH_2), 1.30–1.64 (m, 3H, NH_2, OH), 0.91 (2 t, 6H, ^3J = 6.9, CH_3).

$C_{19}H_{33}NO$ (291.48) Calcd. C 78.29 H 11.41 N 6.51
Found C 77.89 H 10.95 N 4.69

DL-2-Amino-1,1-dicyclohexyl-3-phenyl-1-propanol (**8**): Ester hydrochloride: 3.6 g (17.0 mmol) of **2**; halide: 11.9 g (100 mmol) of 1-chlorocyclohexane. – Yellow oil, b.p. 200°C/10^{-4} Torr, yield 1.0 g (18%). – IR (film): $\tilde{\nu}$ = 3300 cm^{-1} (OH), 3210 (NH), 2920 (aliphat. CH), 1670 (NH). – ^{1}H NMR ($CDCl_3$, 60 MHz): δ = 7.32–7.63 (m, 5H, aromat. H), 3.00 (m, 2H, CHN, benzyl. H), 0.92–2.10 (m, 26H, benzyl. H, NH_2, OH, C_6H_{11}).

DL-2-Amino-1,1,3-triphenyl-1-propanol (**9**): Ester hydrochloride: 3.6 g (17.0 mmol) of **2**; halide: 15.7 g (100 mmol) of 1-bromobenzene. – After evaporation of the solvent, a colorless solid is obtained, which is recrystallized from ethanol. – Colorless needles, m.p. 142°C, yield 3.5 g (67%). – IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 3280, 3200 (NH), 3020 (aromat. CH), 2940 (aliphat. CH), 1630 (NH). – ^{1}H NMR ($CDCl_3$, 60 MHz): δ = 7.02–7.78 (m, 5H, aro-

mat. H), 4.11 (m, 1H, CHN), 3.60 (m, 2H, benzyl. H), 2.54 (m, 3H, NH_2, OH).

$C_{21}H_{21}NO$ (303.41) Calcd. C 83.13 H 6.98 N 4.62
Found C 82.67 H 7.00 N 4.38

DL-2-Amino-1,1-bis(4-methoxyphenyl)-3-phenyl-1-propanol (**10**): THF is used as solvent instead of ether. – Ester hydrochloride: 3.6 g (17.0 mmol) of **2**; halide: 18.7 g (100 mmol) of 4-bromoanisol. – After evaporation of the solvent, a yellow product is obtained. For purification, it is dissolved in 75 ml of ether, and the insoluble residue is filtered off. Finally, the solvent is evaporated. – Colorless oil, b.p. >200°C/10^{-4} Torr, yield 4.5 g (73%). – IR (film): $\tilde{\nu}$ = 3460 cm^{-1} (OH), 3400, 3340 (NH), 3040 (aromat. CH), 2980 (aliphat. CH), 1610 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.54–7.45 (AA'BB', 4H, aromat. H), 7.15–7.29 (m, 5H, aromat. H), 6.82–6.87 (AA'BB', 4H, aromat. H), 4.06 (AB, 1H, benzyl. H), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.66 (dd, 1H, CHN), 2.41 (AB, 1H, benzyl. H), 1.18–1.23 (m, 3H, NH_2, OH).

DL-2-Amino-1,1,3-tris(4-methoxyphenyl)-1-propanol (**11**): THF is used as solvent instead of ether. – Ester hydrochloride: 4.2 g (17.0 mmol) of **3**; halide: 18.7 g (100 mmol) of 4-bromoanisol. – After evaporation of the solvent, an orange oil is obtained which is dissolved in 80 ml of ether and stirred for 3 h. The insoluble orange solid is filtered off and the solvent evaporated. – Yellow oil, b.p. >200°C/10^{-4} Torr, yield 4.4 g (66%). – IR (film): $\tilde{\nu}$ = 3400 cm^{-1} (OH), 3300 (NH), 3020 (aromat. CH), 2980 (aliphat. CH), 1610 (NH).

Synthesis of the 1,2-Diamines **20–23**, **28–31**. – *The Aziridine Pathway:* 40 mmol of the amino alcohol, dissolved in 100 ml of acetonitrile, is added at 0°C to a solution of Ph_3PBr_2, prepared from 10.5 g (40 mmol) of Ph_3P in 100 ml of acetonitrile and 6.4 g (40 mmol) of Br_2 in 40 ml of acetonitrile. A solution of 8.1 g (80 mmol) of Et_3N in 10 ml of acetonitrile is added dropwise with stirring. After standing at room temp. for 15 h, the precipitated Et_3NHBr is filtered off. The filtrate is concentrated and the residue extracted with 250 ml of hexane in a liquid-liquid extraction apparatus for 24 h. The extract is filtered once more before the solvent is evaporated. The residue is distilled.

DL-3-(4-Chlorobenzyl)-2,2-dimethylaziridine (**12**): Amino alcohol: 8.5 g (40 mmol) of **4**. – Colorless oil, b.p. 160°C/10^{-4} Torr, yield 5.7 g (73%). – IR (film): 3240 cm^{-1} (NH), 2960 (aliphat. CH), 1600 (NH).

DL-3-Benzyl-2,2-dimethylaziridine (**13**): Amino alcohol: 7.2 g (40 mmol) of **5**. – Colorless oil, b.p. 90°C/10^{-4} Torr, yield: 2.6 g (40%). – IR (film): $\tilde{\nu}$ = 3240 cm^{-1} (NH), 2970 (aliphat. CH), 1610 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.18–7.35 (m, 5H, aromat. H), 2.66–2.85 (m, 2H, CHN, benzyl. H), 2.04 (AB, 1H, benzyl. H), 1.30 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 0.70 (m, 2H, NH_2).

DL-3-Benzyl-2,2-diethylaziridine (**14**): Amino alcohol: 8.3 g (40 mmol) of **6**. – Colorless oil, b.p. 80°C/10^{-4} Torr, yield 1.9 g (25%). – IR (film): $\tilde{\nu}$ = 3240 cm^{-1} (NH), 2960 (aliphat. CH), 1610 (NH).

DL-3-Benzyl-2,2-dipentylaziridine (**15**): Amino alcohol: 11.7 g (40 mmol) of **7**. – Yellow oil, b.p. 120°C/10^{-4} Torr, yield 2.7 g (25%). – IR (film): $\tilde{\nu}$ = 3240 cm^{-1} (NH), 2960 (aliphat. CH), 1610 (NH).

The Amino Azides: A solution of 2.6 g (40 mmol) of NaN_3 and 2.1 g (40 mmol) of NH_4Cl in 15 ml of water is added to a solution of 10 mmol of the corresponding aziridine in 40 ml of ethanol. The mixture is heated at reflux for 18 h. After cooling, the reaction mixture is diluted with water and extracted with CH_2Cl_2. The organic layer is dried with Na_2SO_4 before the solvent is evaporated.

DL-3-Azido-1-(4-chlorophenyl)-3-methyl-2-butanamine (**16**): Aziridine: 1.9 g (10 mmol) of **12**. – Dark, yellow oil, yield 2.1 g (90%). – IR (film): $\tilde{\nu}$ = 3320 cm^{-1} (NH), 2980 (aliphat. CH), 2100 (N_3), 1610 (NH).

DL-3-Azido-3-methyl-1-phenyl-2-butanamine (**17**): Aziridine: 1.6 g (10 mmol) of **13**. – Dark, yellow oil, yield 1.2 g (60%). – IR (film): $\tilde{\nu}$ = 3300 cm^{-1} (NH), 2920 (aliphat. CH), 2100 (N_3), 1610 (NH).

DL-3-Azido-1-phenyl-3-ethyl-2-pentanamine (**18**): Aziridine: 1.8 g (10 mmol) of **14**. – Yellow oil, yield 2.2 g (95%). – IR (film): $\tilde{\nu}$ = 3350 cm^{-1} (NH), 2960 cm^{-1} (aliphat. CH), 2100 (N_3), 1610 m (NH).

DL-3-Azido-1-phenyl-3-pentyl-2-octanamine (**19**): Aziridine: 2.7 g (10 mmol) of **15**. – Yellow oil, yield 2.2 g (70%). – IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (NH), 2980 (aliphat. CH), 2100 (N_3), 1610 (NH).

The Diethyl Azodicarboxylate Pathway: For the preparation of hydrazoic acid solutions see ref.[25]. The concentration of the toluene solution of hydrazoic azid is determined by titration with a standard alkali solution (0.1 N). 3.9 g (22 mmol) of diethyl azodicarboxylate, dissolved in 20 ml of toluene, is added dropwise to a solution of 5.8 g (22 mmol) of Ph_3P and 20 mmol of the corresponding amino alcohol in 100 ml of toluene. After addition of 22 mmol of HN_3 in toluene solution, a colorless precipitate is formed. The mixture is stirred at room temp. for 15 h. The precipitate is filtered off, and the solvent is evaporated. The residual brown oil is dissolved in a small amount of toluene and chromatographed on a silica gel column (50 cm × 5 cm) using ether/toluene (1:1) as eluent. The eluate is collected in two portions of 140 ml. After evaporation of the solvent, the IR spectra of the second fraction showed the azide peak of the amino azide.

DL-1-Azido-1,1-dicyclohexyl-3-phenyl-2-propanamine (**24**): Amino alcohol: 3.9 g (20 mmol) of **8**. – Brown-yellow oil, yield 1.9 g (30%). – IR (film): $\tilde{\nu}$ = 3300 cm^{-1} (NH), 2920 (aliphat. CH), 2100 (N_3), 1600 (NH).

DL-1-Azido-1,1,3-triphenyl-2-propanamine (**25**): Amino alcohol: 6.1 g (20 mmol) of **9**. – Yellow oil, yield 2.3 g (35%). – IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (NH), 3080 (aromat. CH), 2980 (aliphat. CH), 2100 (N_3), 1610 (NH).

DL-1-Azido-1,1-bis(4-methoxyphenyl)-3-phenyl-2-propanamine (**26**): Amino alcohol: 7.3 g (20 mmol) of **10**. – Yellow oil, yield 4.3 g (60%). – IR (film): $\tilde{\nu}$ = 3300 cm^{-1} (NH), 3040 (aromat. CH), 2980 (aliphat. CH), 2100 (N_3), 1620 (NH).

DL-1-Azido-1,1,3-tris(4-methoxyphenyl)-2-propanamine (**27**): Amino alcohol: 7.9 g (20 mmol) of **11**. – Dark, yellow oil, yield 4.2 g (50%). – IR (film): $\tilde{\nu}$ = 3280 cm^{-1} (NH), 3060 (aromat. CH), 2980 (aliphat. CH), 2100 (N_3), 1620 (NH).

Reduction of the Amino Azides: 9 mmol of the corresponding azide is dissolved in 30 ml of anhydrous ether and added at 0°C to a suspension of 20 mmol (0.8 g) of $LiAlH_4$ in 30 ml of anhydrous ether. After heating to reflux for 5 h, the mixture is hydrolyzed at 0°C with moist ether and a small amount of water. The solid is filtered off, and the filtrate is dried with Na_2SO_4. After evaporation of the solvent, the residue is distilled. The solid is extracted in a Soxhlet apparatus with 100 ml of CH_2Cl_2 for 15 h. After drying, the solvent is evaporated, and the residue is distilled.

DL-1-(4-Chlorophenyl)-3-methyl-2,3-butanediamine (**20**): Azide: 2.2 g (9 mmol) of **16**. – Colorless oil, b.p. 120°C/10^{-4} Torr, yield 1.0 g (54%). – IR (film): $\tilde{\nu}$ = 3360, 3280 cm^{-1} (NH), 3040 (aromat. CH), 2980, 2960 (aliphat. CH), 1600 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.11–7.31 (AA'BB', 4H, aromat. H), 2.97 (dd, 1H, ^3J = 2.5, ^3J = 13.4, CHN), 2.71 (AB, 1H, ^2J = 11.0, benzyl. H), 2.23

(AB, 1H, benzyl. H), 1.22–1.34 (m, 4H, NH_2), 1.18 (s, 3H, CH_3), 1.14 (s, 3H, CH_3).

$C_{11}H_{17}ClN_2$ (212.72) Calcd. C 62.11 H 7.58 N 13.17
Found C 62.21 H 7.91 N 12.04

DL-3-Methyl-1-phenyl-2,3-butanediamine (**21**): Azide: 1.8 g (9 mmol) of **17**. – Colorless oil, b.p. 90°C/10^{-4} Torr, yield 0.8 g (50%). – IR (film): $\tilde{\nu}$ = 3390, 3300 cm^{-1} (NH), 3020 (aromat. CH), 2980 (aliphat. CH), 1600 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.18–7.35 (m, 5H, aromat. H), 3.02 (dd, 1H, ^3J = 2.5, ^3J = 13.9, CHN), 2.75 (AB, 1H, ^2J = 10.6, benzyl. H), 2.24 (AB, 1H, benzyl. H), 1.18 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.43–1.15 (m, 4H, NH_2).

$C_{11}H_{18}N_2$ (178.27) Calcd. C 74.10 H 10.28 N 15.71
Found C 73.69 H 10.20 N 14.79

DL-3-Ethyl-1-phenyl-2,3-pentanediamine (**22**): Azide: 2.1 g (9 mmol) of **18**. – Colorless oil, b.p. 90°C/10^{-4} Torr, yield 1.7 g (90%). – IR (film): $\tilde{\nu}$ = 3380, 3320 cm^{-1} (NH), 3040 (aromat. CH), 2980, 2960 (aliphat. CH), 1610 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.28 (m, 5H, aromat. H), 2.97 (dd, 1H, ^3J = 2.3, ^3J = 13.1, CHN), 2.88 (AB, 1H, ^2J = 10.9, benzyl. H), 2.30 (AB, 1H, benzyl. H), 1.52 (m, 4H, CH_2), 1.11 (m, 4H, NH_2), 0.96 (2 t, 6H, CH_3).

$C_{13}H_{22}N_2$ (206.33) Calcd. C 75.67 H 10.75 N 13.58
Found C 75.26 H 10.43 N 13.01

DL-1-Phenyl-3-pentyl-2,3-octanediamine (**23**): Azide: 2.9 g (9 mmol) of **19**. – Colorless oil, yield 2.4 g (90%). – IR (film): $\tilde{\nu}$ = 3400, 3320 cm^{-1} (NH), 3040 (aromat. CH), 2980, 2960 (aliphat. CH), 1610 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.19–7.36 (m, 5H, aromat. H), 2.97 (dd, 1H, ^3J = 2.4, ^3J = 13.1, CHN), 2.86 (AB, 1H, ^2J = 10.9, benzyl. H), 1.32–1.47 (m, 16H, CH_2), 1.13 (m, 4H, NH_2), 0.91 (t, 3H, ^3J = 6.9, CH_3), 0.89 (t, 3H, CH_3).

$C_{19}H_{34}N_2$ (290.50) Calcd. C 78.56 H 11.80 N 9.65
Found C 79.20 H 11.23 N 7.22

DL-1,1-Dicyclohexyl-3-phenyl-1,2-propanediamine Dihydrochloride (**28** · 2 HCl): Azide: 2.8 g (9 mmol) of **24**. – Yellow oil. – IR (film): $\tilde{\nu}$ = 3340 cm^{-1} (NH), 3040 (aromat. CH), 2940, 2860 (aliphat. CH), 1660 (NH). – Synthesis of the dihydrochloride: 1.5 g of the diamine is dissolved in 10 ml of ether, and the solution is cooled to –70°C. By passing HCl gas into the solution, a pale-yellow precipitate is obtained, which is filtered off, washed with ether, and dried. – Pale-yellow, hygroscopic solid, yield 1.6 g (50%). – ^1H NMR (CD_3OD, 250 MHz): δ = 7.18–7.50 (m, 5H, aromat. H), 4.00 (AB, 1H, benzyl. H), 3.12 (dd, 1H, CHN), 2.80 (AB, 1H, benzyl. H), 1.05–2.20 (m, 26H, C_6H_{11}, NH_2).

DL-1,1,3-Triphenyl-1,2-propanediamine (**29**): Azide: 3.0 g (9 mmol) of **25**. – Brown oil, b.p. 130°C/10^{-4} Torr, yield 1.9 g (67%). – IR (film): $\tilde{\nu}$ = 3380, 3300 cm^{-1} (NH), 3060, 3040 (aromat. CH), 2920, 2860 (aliphat. CH), 1610 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.57–7.67 (m, 5H, aromat. H), 7.13–7.48 (m, 10H, aromat. H), 4.13 (AB, 1H, ^2J = 10.5, benzyl. H), 2.85 (dd, 1H, ^3J = 3.3, ^3J = 14.8, CHN), 2.31 (AB, 1H, benzyl. H), 1.87 (m, 4H, NH_2).

$C_{21}H_{22}N_2$ (302.42) Calcd. C 83.41 H 7.33 N 9.26
Found C 83.73 H 7.28 N 9.43

DL-1,1-Bis(4-methoxyphenyl)-3-phenyl-1,2-propanediamine (**30**): Azide: 3.2 g (9 mmol) of **26**. – Pale-yellow oil, b.p. 200°C/10^{-4} Torr, yield 1.0 g (30%). – IR (film): $\tilde{\nu}$ = 3400, 3340 cm^{-1} (NH), 3040, 3020 (aromat. CH), 2960, 2920 (aliphat. CH), 1620 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.46–7.50 (AA'BB', 4H, aromat. H), 7.19–7.32 (m, 5H, aromat. H), 6.79–6.88 (AA'BB', 4H, aromat. H), 4.00 (AB, 1H, ^2J = 10.5, benzyl. H), 3.76, 3.73 (s, 6H, OCH_3), 2.85 (dd, 1H, ^3J = 1.9, ^3J = 13.5, CHN), 2.25 (AB, 1H, benzyl. H), 1.73–2.00 (m, 4H, NH_2).

$C_{23}H_{26}N_2O_2$ (362.48) Calcd. C 76.21 H 7.23 N 7.73
Found C 75.92 H 7.22 N 6.98

DL-1,1,3-Tris(4-methoxyphenyl)-1,2-propanediamine (**31**): Azide: 3.8 g (9 mmol) of **27**. – The product is purified by chromatography on a silica gel column (50 × 5 cm). With toluene/ether (1:1) as eluent, a first zone is separated. Finally, the diamine is washed from the column using methanol as eluent. – Yellow oil, yield 0.7 g (20%). – IR (film): $\tilde{\nu}$ = 3360 cm^{-1} (NH), 3040, 3020 (aromat. CH), 2960, 2920 (aliphat. CH), 1620, 1580 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.44–7.49 (AA'BB', 4H, aromat. H), 6.82–7.14 (AA'BB', 4H, aromat. H), 6.80–6.89 (AA'BB', 4H, aromat. H), 3.97 (AB, 1H, ^2J = 10.6, benzyl. H), 3.78, 3.75 (2 s, 6H, OCH_3), 3.75 (s, 3H, OCH_3), 2.80 (dd, 1H, ^3J < 3, ^3J = 13.7, CHN), 2.21 (AB, 1H, benzyl. H), 1.91–2.57 (m, 4H, NH_2).

Synthesis of DL-2,3-Diphenyl-1,2-propanediamine (**35**). – *DL-1-Amino-2,3-diphenyl-2-propanol* (**33**): See synthesis of the amino alcohols **4**–**11**. – Ketone hydrochloride: 8.6 g (0.05 mol) of **32**; halide: 38.0 g (0.30 mol) of benzyl chloride. – Orange, waxy product, yield 5.9 g (52%). – IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (OH), 3250 (NH), 3020 (aromat. CH), 2940 (aliphat. CH), 1610 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.20–7.38 (m, 10H, aromat. H), 3.18 (AB, 1H, CHN), 3.10 (AB, 1H, benzyl. H), 2.98 (AB, 1H, benzyl. H), 2.86 (AB, 1H, CHN), 1.91 (m, 2H, NH_2).

DL-2-Azido-2,3-diphenyl-1-propanamine (**34**): See synthesis of the azides **24**–**27**. – Amino alcohol: 4.5 g (20 mmol) of **33**. – Dark-yellow oil, yield 4.2 g (83%). – IR (film): $\tilde{\nu}$ = 3300 cm^{-1} (NH), 3040 (aromat. CH), 2980 (aliphat. CH), 2100 (N_3), 1610 (NH).

DL-2,3-Diphenyl-1,2-propanediamine (**35**): See synthesis of the diamines **20**–**23**, **28**–**31**. – Azide: 2.3 g (9 mmol) of **34**. – Colorless oil, b.p. 180°C/10^{-4} Torr, yield 1.7 g (83%). – IR (film): $\tilde{\nu}$ = 3390, 3000 cm^{-1} (NH), 3040 (aromat. CH), 2920, 2860 (aliphat. CH), 1610, 1590 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.01–7.31 (m, 5H, aromat. H), 6.81–6.87 (m, 5H, aromat. H), 3.11 (AB, 1H, ^2J = 12.9, CHN), 3.03 (AB, 1H, ^2J = 13.1, benzyl. H), 2.89 (AB, 1H, benzyl. H), 2.76 (AB, 1H, CHN), 1.47 (m, 4H, NH_2).

$C_{15}H_{18}N_2$ (226.32) Calcd. C 79.60 H 8.02 N 12.38
Found C 79.15 H 7.94 N 12.16

Synthesis of the 1,2-Diamines **42**–**44**. – *The Amino Nitriles:* 29.4 g (0.55 mol) of NH_4Cl is dissolved in 100 ml of water and mixed with 100 ml of conc. NH_3 solution. To this solution, first 27.0 g (0.55 mol) of NaCN in 50 ml of water and then 0.50 mol of the corresponding ketone in 100 ml of methanol are added dropwise. The mixture is stirred for 15 h at 50°C. To isolate the product, the reaction mixture is adjusted to pH = 6 with 1 N HCl and extracted with ether. The aqueous layer is made alkaline with conc. NH_3 solution, and the amino nitrile is extracted with ether. After evaporation of the solvent, the product is reduced to the 1,2-diamine without further purification.

DL-2-Amino-2-benzyl-1-propanenitrile (**39**): Ketone: 67.1 g (0.50 mol) of **36**. – Yellow oil, yield 48.1 g (60%). – IR (film): $\tilde{\nu}$ = 3400, 3320 cm^{-1} (aromat. CH), 3000, 2960 (aliphat. CH), 2040 (CN), 1610 (NH). – ^1H NMR ($CDCl_3$, 60 MHz): δ = 7.45 (m, 5H, aromat. H), 2.95 (m, 5H, aromat. H), 1.80 (s, 4H, NH_2), 1.60 (s, 3H, CH_3).

DL-2-Amino-2-benzyl-1-butanenitrile (**40**): Ketone: 74.1 g (0.50 mol) of **37**. – Yellow oil, yield 61.0 g (70%). – IR (film): $\tilde{\nu}$ = 3320, 3280 cm^{-1} (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 2020 (CN), 1610 (NH). – ^1H NMR ($CDCl_3$, 60 MHz): δ = 7.40 (m, 5H, aromat. H), 2.95 (AB, 1H, benzyl. H), 2.72 (AB, 1H, benzyl. H), 1.80 (m, 4H, CH_2, NH_2), 1.15 (m, 3H, CH_3).

2-Amino-2-benzyl-3-phenyl-1-propanenitrile (**41**): Ketone: 105.1 g (0.50 mol) of **38**. – After addition of the NH_3 solution, the amino nitrile precipitates as a colorless solid. Nevertheless, the suspension is extracted with ether. – Colorless solid, m.p. 114°C, yield 41.4 g (35%). – IR (KBr): $\tilde{\nu}$ = 3400, 3320 cm^{-1} (NH), 3020 (aromat. CH), 2940 (aliphat. CH), 2100 (CN), 1570 (NH). – ^1H NMR ($CDCl_3$, 60 MHz): δ = 7.45 (m, 5H, aromat. H), 3.20 (AB, 2H, benzyl. H), 2.80 (AB, 2H, benzyl. H), 1.62 (s, 2H, NH_2).

Reduction of the Amino Nitriles: 15.2 g (0.4 mol) of $LiAlH_4$ is suspended in 100 ml of anhydrous THF. To this suspension, a solution of 0.1 mol of the corresponding nitrile in 150 ml of anhydrous THF is added dropwise while cooling the mixture to 0°C. The reaction mixture is heated at reflux for 15 h. On cooling to 0°C, 28.8 ml (1.6 mol) of water is added dropwise for hydrolysis with vigorous stirring. The solid is filtered off and extracted in a Soxhlet apparatus with 250 ml of THF for 15 h. The extract is combined with the filtrate of the reaction mixture, the solvent is evaporated, and the residue is distilled.

DL-2-Benzyl-1,2-propanediamine (**42**): Nitrile: 16.0 g (0.1 mol) of **39**. – At 70°C/10^{-4} Torr, the by-product may be distilled off before the product is obtained. – Colorless oil, b.p. 100°C/10^{-4} Torr, yield 6.9 g (42%). – IR (film): $\tilde{\nu}$ = 3300, 3290 cm^{-1} (NH), 3020 (aromat. CH), 2920, 2860 (aliphat. CH), 1610, 1590 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.16–7.33 (m, 5H, aromat. H), 2.66 (s, 2H, benzyl. H or CHN), 2.56 (s, 2H, CHN or benzyl. H), 1.25 (m, 4H, NH_2), 1.00 (s, 3H, CH_3).

$C_{10}H_{16}N_2$ (164.25) Calcd. C 73.13 H 9.81 N 17.06
Found C 72.93 H 9.81 N 17.13

DL-2-Benzyl-1,2-butanediamine (**43**): Nitrile: 17.4 g (0.1 mol) of **40**. – At 60°C/10^{-4} Torr, the by-product may be distilled off. – Colorless oil, b.p. 95°C/10^{-4} Torr, yield 5.0 g (28%). – IR (film): $\tilde{\nu}$ = 3300, 3390 cm^{-1} (NH), 3020 (aromat. CH), 2860, 2920 (aliphat. CH), 1590, 1610 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.17–7.33 (m, 5H, aromat. H), 2.66 (s, 2H, CHN), 2.58 (AB, 1H, ^2J = 13.0, benzyl. H), 2.48 (AB, 1H, benzyl. H), 1.37 (q, 2H, ^3J = 7.7, CH_2), 1.13 (m, 4H, NH_2), 0.94 (t, 3H, CH_3).

$C_{11}H_{18}N_2$ (178.28) Calcd. C 74.10 H 10.18 N 15.71
Found C 74.15 H 9.92 N 15.60

2-Benzyl-3-phenyl-1,2-propanediamine (**44**): Nitrile: 23.6 g (0.1 mol) of **41**. – At 100°C/10^{-4} Torr, the by-product may be distilled off. – Yellow oil, b.p. 150°C/10^{-4} Torr, yield 7.7 g (32%). – IR (film): $\tilde{\nu}$ = 3390, 3300 cm^{-1} (NH), 3040 (aromat. CH), 2920, 2860 (aliphat. CH), 1610, 1590 (NH). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 7.19–7.33 (m, 5H, aromat. H), 2.82 (AB, 2H, ^2J = 13.2, benzyl. H), 2.68 (AB, 2H, ^2J = 13.2, benzyl. H), 1.10 (m, 4H, NH_2).

$C_{16}H_{20}N_2$ (240.35) Calcd. C 79.96 H 8.39 N 11.66
Found C 79.55 H 8.61 N 11.26

Synthesis of the Dichloroplatinum(II) Complexes **45**–**56**. – A. *Synthesis in Water:* 5.0 mmol of the corresponding diamine is dissolved in 25 ml of water. The solution is adjusted to pH = 7 using 1 N HCl. 2.08 g (5.0 mmol) of K_2PtCl_4, dissolved in 25 ml of water, is added to this solution. The mixture is heated to 50°C and the pH kept constant by addition of 1 N NaOH. The reaction is finished, if the pH does not change anymore. The complexes precipitate as pale-yellow solids which are filtered off, washed successively with water and ethanol, and dried.

B. *Synthesis in Water/tert-Butyl Alcohol:* 0.5 mmol of the corresponding diamine is dissolved in 50 ml of *tert*-butyl alcohol. 208 mg (0.5 mmol) of K_2PtCl_4, dissolved in 5 ml of water, is added to that solution. The precipitate dissolves on addition of another 25 ml of water. The solution is neutralized with 1 N HCl.

Dichloro[DL-1-(4-chlorophenyl)-3-methyl-2,3-butanediamine]-platinum(II) (**45**): Diamine: 1.1 g (5.0 mmol) of **20**. – Method A. – Pale-yellow solid, m.p. 300°C (dec.), yield 1.8 g (76%). – IR (KBr): $\tilde{\nu}$ = 3240, 3110 cm^{-1} (NH), 3040 (aromat. CH), 2980 (aliphat. CH), 1580 (NH), 330, 320 (PtCl). – ^1H NMR ([D_7]DMF, 250 MHz): δ = 7.34–7.44 (AA'BB', 4H, aromat. H), 5.43 (m, 4H, NH_2), 3.13 (m, 1H, CHN), 2.73–3.00 (m, obscured by solvent peaks, benzyl. H), 1.49 (s, 3H, CH_3), 1.40 (s, 3H, CH_3).

$C_{11}H_{17}Cl_3N_2Pt$ (478.72) Calcd. C 27.60 H 3.58 N 5.85
Found C 27.58 H 3.50 N 5.76

Dichloro(DL-3-methyl-1-phenyl-2,3-butanediamine)platinum(II) (**46**): Diamine: 0.9 g (5.0 mmol) of **21**. – Method A. – 50 mg of the complex could be recrystallized in 100 ml of hot acetonitrile, cooling the solution first to room temp. and then to 10°C. – Pale-yellow needles, m.p. 300°C (dec.), yield 0.8 g (37%). – IR (KBr): $\tilde{\nu}$ = 3190, 3110 cm^{-1} (NH), 3020 (aromat. CH), 2980 (aliphat. CH), 1570 (NH), 300 (PtCl). – ^1H NMR (CD_3CN, 250 MHz): δ = 7.21–7.29 (m, 5H, aromat. H), 4.72, 4.44, 4.26, 4.07, 3.91 (5 m, 4H, NH_2), 3.21 (m, 1H, $^3J_{CH-CH}$ = 3.8, $^3J_{CH-CH}$ = 11.0, $^3J_{CH-NH}$ = 3.8, $^3J_{CH-NH}$ = 18.0, CHN), 2.88 (AB, 1H, ^2J = 14.3, benzyl. H), 2.61 (AB, 1H, benzyl. H), 1.40 (s, 3H, CH_3), 1.31 (s, 3H, CH_3).

$C_{11}H_{18}Cl_2N_2Pt$ (444.28) Calcd. C 29.74 H 4.08 N 6.31
Found C 29.82 H 4.18 N 6.23

Dichloro(DL-3-ethyl-1-phenyl-2,3-pentanediamine)platinum(II) (**47**): Diamine: 1.03 g (5.0 mmol) of **22**. – Method A. – Pale-yellow solid, m.p. 300°C (dec.), yield 1.6 g (68%). – IR (KBr): $\tilde{\nu}$ = 3190, 3120 cm^{-1} (NH), 3030 (aromat. CH), 2970 (aliphat. CH), 1590 (NH), 330, 320 (PtCl). – ^1H NMR ([D_7]DMF, 250 MHz): δ = 7.25–7.49 (m, 5H, aromat. H), 5.37, 5.40 (2 m, 1H, NH_2), 5.20, 5.25 (2 m, 1H, NH_2), 5.06, 5.11 (2 m, 1H, NH_2), 4.28, 4.32 (2 m, 1H, NH_2), 2.93–3.12 (m, 3H, benzyl. H, CHN), 1.95–2.23, 1.72–1.91 (2 m, 4H, CH_2), 0.97–1.08 (2 t, 6H, ^3J = 7.6, CH_3).

$C_{13}H_{22}Cl_2N_2Pt$ (472.33) Calcd. C 33.06 H 4.70 N 5.93
Found C 33.22 H 4.67 N 5.93

Dichloro(DL-1-phenyl-3-pentyl-2,3-octanediamine)platinum(II) (**48**): Diamine: 145 mg (0.5 mmol) of **23**. – Method B. – Pale-yellow solid, m.p. 300°C (dec.), yield 54 mg (37%). – IR (KBr): $\tilde{\nu}$ = 3240, 3110 cm^{-1} (NH), 3040 (aromat. CH), 2960, 2940 (aliphat. CH), 1580 (NH), 330, 320 (PtCl). – ^1H NMR ([D_7]DMF, 250 MHz): δ = 7.17–7.34 (m, 5H, aromat. H), 5.54, 5.58 (2 m, 1H, NH_2), 4.97, 3.69 (2 m, 2H, NH_2), 3.48, 3.52 (2 m, 1H, NH_2), 2.93–2.99 (m, 2H, ^2J = 11.1, ^3J = 14.8, benzyl. H, CHN), 2.45 (AB, 1H, benzyl. H), 1.25–1.69 (m, 16H, CH_2), 0.95 (t, 3H, CH_3), 0.88 (t, 3H, CH_3).

$C_{19}H_{34}Cl_2N_2Pt$ (556.50) Calcd. C 41.01 H 6.16 N 5.04
Found C 41.43 H 5.93 N 4.66

Dichloro(DL-1,1-dicyclohexyl-3-phenyl-1,2-propanediamine)platinum(II) (**49**): Diamine: 194 mg (0.5 mmol) of **28** · 2 HCl. – Method B. – 50 mg of the precipitated complex is dissolved in 10 ml of hot acetonitrile. After cooling to room temp., the product may be precipitated by addition of 100 ml of ether. – Pale-yellow solid, m.p. 300°C (dec.), yield 93 mg (32%). – IR (KBr): $\tilde{\nu}$ = 3200 cm^{-1} (NH), 3040 (aromat. CH), 2940, 2860 (aliphat. CH), 1610 (NH), 320 (PtCl).

$C_{21}H_{34}Cl_2N_2Pt$ (580.52) Calcd. C 43.45 H 5.90 N 4.83
Found C 43.15 H 4.60 N 5.13

Dichloro(DL-1,1,3-triphenyl-1,2-propanediamine)platinum(II) (**50**): 1.5 g (5.0 mmol) of **29** is dissolved in 12 ml of 1 N HCl. This solution is neutralized with 1 N NaOH giving an emulsion. 2.1 g (5.0 mmol) of K_2PtCl_4, dissolved in 25 ml of water, is added. After 5 h, the precipitated complex is filtered off, washed with ether and

water, and dried. – Pale-yellow solid, m.p. 300°C (dec.), yield 0.2 g (56%). – IR (KBr): $\tilde{\nu}$ = 3220, 3160 cm^{-1} (NH), 3110 (aromat. CH), 2960 (aliphat. CH), 1580 s (NH), 330, 320 (PtCl). – ^1H NMR ([D_7]DMF, 250 MHz): δ = 7.95–8.13 (m, 5H, aromat. H), 7.33–7.56 (m, 10H, aromat. H), 6.62 (m, 2H, NH_2), 4.94, 5.00 (2 m, 1H, NH_2), 4.32, 4.38 (2 m, 1H, NH_2), 3.92 (m, 1H, ^3J < 3, ^3J = 14.8, CHN), 3.26 (AB, 1H, ^2J = 11.1, benzyl. H), 3.11 (AB, 1H, benzyl. H).

$C_{21}H_{22}Cl_2N_2Pt$ (568.42) Calcd. C 44.36 H 3.90 N 4.93
Found C 44.13 H 4.11 N 4.83

Dichloro[DL-1,1-(4-methoxyphenyl)-3-phenyl-1,2-propanediamine]platinum(II) (**51**): Diamine: 181 mg (0.5 mmol) of **30**. – Method B. – Pale-yellow solid, m.p. 300°C (dec.), yield 176 mg (56%). – IR (KBr): $\tilde{\nu}$ = 3260, 3160 cm^{-1} (NH), 3090 (aromat. CH), 2960, 2940 (aliphat. CH), 1610, 1580 (NH), 330 (PtCl). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 6.87–8.31 (AA'BB', 4H, aromat. H), 7.23–7.32 (m, 5H, aromat. H), 6.89–7.17 (AA'BB', 4H, aromat. H), 6.11, 6.19 (2 m, 1H, NH_2), 4.83, 4.79 (2 m, 2H, NH_2), 3.97, 3.87 (2 m, 1H, NH_2), 3.89, 3.80 (2 s, 6H, OCH_3), 3.26 (AB, 1H, benzyl. H), 2.46 (m, 1H, CHN), 2.22 (AB, 1H, benzyl. H).

$C_{23}H_{26}Cl_2N_2O_2Pt$ (628.48) Calcd. C 43.95 H 4.17 N 4.46
Found C 44.49 H 4.54 N 4.19

Dichloro[DL-1,1,3-tris(4-methoxyphenyl)-1,2-propanediamine]platinum(II) (**52**): 196 mg (0.5 mmol) of **31**. – Method B. – For purification, the complex is precipitated as described for the complex **49**. – Pale-yellow solid, m.p. 300°C (dec.), yield 105 mg (32%). – IR (KBr): $\tilde{\nu}$ = 3240, 3180 cm^{-1} (NH), 3100 (aromat. CH), 2960, 2940 (aliphat. CH), 1610, 1580 (NH), 330 (PtCl). – ^1H NMR ($CDCl_3$, 250 MHz): δ = 6.86–8.32 (AA'BB', 4H, aromat. H), 7.01–7.29 (AA'BB', 4H, aromat. H), 6.80–7.07 (AA'BB', 4H, aromat. H), 6.14, 6.22 (2 m, 1H, NH_2), 4.82, 4.79 (2 m, 2H, NH_2), 3.95, 4.02 (2 m, 1H, NH_2), 3.89, 3.80, 3.20 (3 s, 9H, OCH_3), 3.20 (AB, 1H, benzyl. H), 2.46 (m, 1H, CHN), 2.12 (AB, 1H, benzyl. H).

Dichloro(DL-2,3-diphenyl-1,2-propanediamine)platinum(II) (**53**): Diamine: 113 mg (0.5 mmol) of **35**. – Method B. – Pale-yellow solid, m.p. 300°C (dec.), yield 152 mg (62%). – IR (KBr): $\tilde{\nu}$ = 3280, 3200 cm^{-1} (NH), 3060 (aromat. CH), 2960, 2920 (aliphat. CH), 1610, 1580 (NH), 330 (PtCl). – ^1H NMR ([D_7]DMF, 250 MHz): δ = 7.59–7.64, 7.38–7.48, 7.08–7.34, 6.92–6.96 (4 m, 10H, aromat. H), 5.52–5.57 (m, 4H, NH_2), 3.65 (AB, 1H, ^2J = 13.4, benzyl. H), 3.53 (AB, 1H, benzyl. H), 3.13–3.30 (m, 2H, CH_2).

$C_{15}H_{18}Cl_2N_2Pt$ (492.32) Calcd. C 36.59 H 4.23 N 6.53
Found C 36.53 H 3.71 N 5.36

(DL-2-Benzyl-1,2-propanediamine)dichloroplatinum(II) (**54**): Diamine: 0.8 g (5.0 mmol) of **42**. – Method A. – Pale-yellow solid, m.p. 300°C (dec.), yield 1.6 g (73%). – IR (KBr): $\tilde{\nu}$ = 3300, 3200 cm^{-1} (NH), 3140 (aromat. CH), 2960, 2940 (aliphat. CH), 1610, 1580 (NH), 320 (PtCl). – ^1H NMR ([D_7]DMF, 250 MHz): δ = 7.26–7.42 (m, 5H, aromat. H), 5.37–6.07 (m, 2H, NH_2), 5.37, 5.41 (2 m, 1H, NH_2), 5.02, 5.06 (2 m, 1H, NH_2), 3.21 (s, 2H, benzyl. H), 2.86–2.95, 2.53–2.58 (2 m, 2H, obscured by solvent peaks, CH_2N), 1.39 (s, 3H, CH_3).

$C_{10}H_{16}Cl_2N_2Pt$ (430.25) Calcd. C 27.92 H 3.75 N 6.51
Found C 28.11 H 3.66 N 6.42

(DL-2-Benzyl-1,2-butanediamine)dichloroplatinum(II) (**55**): Diamine: 0.9 g (5.0 mmol) of **43**. – Method A. – Pale-yellow solid, m.p. 300°C (dec.), yield 1.2 g (54%). – IR (KBr): $\tilde{\nu}$ = 3200, 3180 cm^{-1} (NH), 3140 (aromat. CH), 2960, 2940 (aliphat. CH), 1610, 1580 (NH), 320 (PtCl). – ^1H NMR ([D_7]DMF, 250 MHz): δ = 7.46–7.56, 7.33–7.37 (2 m, 5H, aromat. H), 5.54 (m, 2H, NH_2), 5.08, 5.11 (2 m, 1H, NH_2), 4.72, 4.77 (2 m, 1H, NH_2), 3.33 (AB, 1H, ^2J = 13.8, benzyl. H), 3.10 (AB, 1H, benzyl. H), 2.72–2.76 (obscured by solvent peaks, 2H, CH_2N), 1.67–1.86 (m, 2H, CH_2), 1.06, 1.12 (t, 3H, ^3J = 7.6, CH_3).

$C_{11}H_{18}Cl_2N_2Pt$ (444.27) Calcd. C 29.74 H 4.08 N 6.31
Found C 29.91 H 4.13 N 6.28

(2-Benzyl-3-phenyl-1,2-propanediamine)dichloroplatinum(II) (**56**): Diamine: 1.2 g (5.0 mmol) of **44**. – Method A. – Pale-yellow solid, m.p. 300°C (dec.), yield 1.6 g (63%). – IR (KBr): $\tilde{\nu}$ = 3260, 3220 cm^{-1} (NH), 3120 (aromat. CH), 2960 (aliphat. CH), 1610, 1580 (NH), 330 (PtCl). – ^1H NMR ([D_7]DMF, 250 MHz): δ = 7.44–7.59, 7.31–7.43 (2 m, 10H, aromat. H), 5.60 (m, 2H, NH_2), 4.63 (m, 2H, NH_2), 3.37 (AB, 2H, ^2J = 13.7, benzyl. H), 3.10 (AB, 2H, ^2J = 13.7, benzyl. H), 2.67 (m, 2H, CH_2N).

$C_{16}H_{20}Cl_2N_2Pt$ (506.35) Calcd. C 37.95 H 3.98 N 5.53
Found C 38.32 H 4.27 N 5.47

Synthesis of the Lactate Complexes **61–64**. – *General Procedure:* 5.0 mmol of the corresponding dichloro complex is suspended in 25 ml of water, using alternatively vigorous stirring and ultrasound. A solution of 1.9 g (10 mmol) of $AgNO_3$ in 5 ml of water is added to the suspension, and the mixture is stirred, excluding light, at 30°C for one week. 25 g of a strongly basic anion exchange resin (Merck Ionenaustauscher III; exchanging capacity 4 mval/g) is filled into a chromatography column, with a ratio of diameter to length between 1:4 and 1:10. The resin is treated with eight times the volume of the column of 2 N NaOH. Then it is washed with water until the pH of the eluate is 9. The solution of the corresponding diamino(diaqua)platinum(II) complex **57–60** is passed through the column with 2 cm/min, dropping into a solution of 0.5 g (5.0 mmol) of freshly distilled L-(+)-lactic acid. After complete addition, the solution is stirred at 40°C for 4 h. To isolate the lactate complex, the water is evaporated completely. The residue is dissolved in 5 ml of ethanol, and 100 ml of ether is added to this solution, precipitating a colorless solid, which is filtered off. The solid should be dried immediately, because it decomposes, when remaining wet.

L-Lactato(DL-3-methyl-1-phenyl-2,3-butanediamine)platinum(II) (**61**): Dichloro complex: 2.2 g (5.0 mmol) of **46**. – Colorless solid, yield 1.5 g (67%). – IR (KBr): $\tilde{\nu}$ = 3200, 3080 cm^{-1} (NH), 3060 (aromat. CH), 2980 (aliphat. CH), 1680, 1610 (C=O), 380 (PtO). – ^1H NMR (D_2O, 250 MHz): δ = 7.25–7.34 (m, 5H, aromat. H), 4.35, 4.02, 3.57 (3 m, 1H, CH), 2.83–2.93 (m, 1H, CHN), 2.46–2.72 (m, 2H, benzyl. H), 1.09–1.46 (m, 9H, CH_3).

$C_{14}H_{22}N_2O_3Pt$ (461.44) Calcd. C 36.50 H 4.80 N 6.07
Found C 36.34 H 5.04 N 5.84

(DL-2-Benzyl-1,2-propanediamine)(L-lactato)platinum(II) (**62**): Dichloro complex: 2.2 g (5.0 mmol) of **54**. – Colorless solid, yield 0.7 g (32%). – IR (KBr): $\tilde{\nu}$ = 3200, 3100 cm^{-1} (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 1750, 1610 (C=O), 370 (PtO). – ^1H NMR (D_2O, 250 MHz): δ = 7.23–7.32 (m, 5H, aromat. H), 3.98–4.02 (m, 1H, CH), 2.83–3.55, 2.38–2.62 (2 m, 4H, benzyl. H, CH_2N), 1.14–1.35 (m, 6H, CH_3).

$C_{13}H_{20}N_2O_3Pt$ (447.42) Calcd. C 34.90 H 4.51 N 6.26
Found C 34.79 H 5.04 N 6.01

(DL-2-Benzyl-1,2-butanediamine)(L-lactato)platinum(II) (**63**): Dichloro complex: 2.2 g (5.0 mmol) of **55**. – Colorless solid, yield 1.2 g (54%). – IR (KBr): $\tilde{\nu}$ = 3200, 3080 cm^{-1} (NH), 3040 (aromat. CH), 2980, 2940 (aliphat. CH), 1730, 1610 (C=O), 760, 700 (PtO). – ^1H NMR (D_2O, 250 MHz): δ = 7.21 (m, 5H, aromat. H), 4.34, 4.10, 3.99, 3.56 (4 m, 1H, CH), 2.88–2.99, 2.41–2.55 (2 m, 4H, benzyl.

H, CH_2N), 1.46–1.76 (m, 2H, CH_2), 1.34, 1.22, 1.17, 1.10 (4 d, 3H, ^3J = 6.9, CH), 0.91–0.96 (m, 3H, CH_3).

$C_{14}H_{22}N_2O_3Pt$ (461.44) Calcd. C 36.44 H 4.81 N 6.07
Found C 35.73 H 4.99 N 5.55

(2-Benzyl-3-phenyl-1,2-propanediamine)(L-lactato)platinum(II) (**64**): Dichloro complex: 2.5 g (5.0 mmol) of **56**. – Colorless solid, yield 0.8 g (32%). – IR (KBr): $\tilde{\nu}$ = 3200, 3080 cm^{-1} (NH), 3040 (aromat. CH), 2980 (aliphat. CH), 1730, 1610 (C=O), 370 (PtO).

$C_{19}H_{24}N_2O_3Pt \cdot 2\,H_2O$ (559.55) Calcd. C 40.78 H 5.04 N 5.00
Found C 40.60 H 4.92 N 5.00

The Cyclodextrin Preparations. – *With* **46**: $1 \cdot 10^{-5}$ mol (4 mg) of **46** is dissolved in 50 ml of ethanol at 30°C. $2 \cdot 10^{-5}$ mol (19 mg) of α-cyclodextrin is dissolved in 10 ml of water. After mixing the two solutions, the solvent is evaporated. The residue is dried and, using ultrasound, dissolved in 10 ml of the solvent mixture PEG 400/1.8% NaCl solution (1:1).

With Dichloro(D- or L-3-phenyl-1,2-propanediamine)platinum(II) (**65**) *or Dichloro[DL-3-(4-chlorophenyl)-1,2-propanediamine)platinum(II)* (**66**): $1 \cdot 10^{-5}$ mol of **65** (4 mg) or **66** (5 mg) together with $2 \cdot 10^{-5}$ mol (9 mg) of α-cyclodextrin are suspended in 10 ml of the solvent mixture PEG 400/1.8% NaCl solution (1:1), using ultrasound. The suspension is heated with vigorous stirring to 60°C. After 1 h, a clear solution is obtained which is used in the P388 test.

Preparation of the PVP Coprecipitates: $1 \cdot 10^{-5}$ mol of the dichloroplatinum complexes **46** (4 mg), **54** (4 mg), **55** (4 mg), or **56** (5 mg) is dissolved in 50 ml of ethanol and heated to 30°C. 56 mg of PVP-10 (Sigma) is dissolved in 10 ml of ethanol and mixed with the solution of the platinum complex. After evaporation of the solvent, the yellow residue is dried. For the preparation of the solution for the P388 test, the coprecipitate is dissolved in 10 ml of the solvent mixture of PEG 400/1.8% NaCl solution (1:1).

[1] B. Rosenberg, L. VanCamp, J. E. Trosko, V. H. Mansour, *Nature* **222** (1969) 385.
[2] A. J. Lippman, C. Helson, I. H. Krakoff, *Cancer Chemother. Rep., Part 1*, **57** (1973) 191.
[3] J. A. Gottlieb, B. Drewinko, *Cancer Chemother. Rep., Part 1*, **59** (1975) 621.
[4] F. K. Leh, W. Wolf, *J. Pharm. Sci.* **65** (1976) 315.
[5] H. Brunner, M. Schmidt, G. Unger, H. Schönenberger, *Eur. J. Med. Chem. Chim. Ther.* **6** (1985) 509.
[6] H. Brunner, P. Hankofer, U. Holzinger, B. Treittinger, *Eur. J. Med. Chem. Chim. Ther.* in the press.
[7] P. Hankofer, *Dissertation*, University of Regensburg, 1989.
[8] A. Pasini, F. Zunino, *Angew. Chem.* **99** (1987) 632; *Angew. Chem. Int. Ed. Engl.* **26** (1987) 615.
[9] K.-H. Fromming, *Dtsch. Apoth. Ztg.* **127** (1987) 2040.
[10] R. Voigt, D. Terborg, *Pharmazie* **35** (1980) 311.
[11] R. A. Boissonas, S. Guttman, P. A. Jaquenoud, J. P. Waller, *Helv. Chim. Acta* **39** (1956) 1421.
[12] I. Okada, K. Ichimura, R. Sudo, *Bull. Chem. Soc. Jpn.* **43** (1970) 1185.
[13] O. Mitsunobu, M. Yamada, *Bull. Chem. Soc. Jpn.* **40** (1967) 2380.
[14] O. Mitsunobu, M. Eguchi, *Bull. Chem. Soc. Jpn.* **44** (1971) 342.
[15] *Organikum*, Organisch-Chemisches Grundpraktikum, 17th ed., p. 447, VEB Deutscher Verlag der Wissenschaften, Berlin 1986.
[16] R. M. Herbst, T. B. Johnson, *J. Am. Chem. Soc.* **54** (1932) 2463.
[17] G. L. Johnson, *Inorg. Synth.* **8** (1966) 242.
[18] L. M. Hall, R. J. Speer, H. J. Ridgway, S. J. Norton, *J. Inorg. Biochem.* **11** (1979) 2520.
[19] T. Totani, K. Aono, M. Komura, Y. Adachi, *Chem. Lett.* **1986**, 429.
[20] Shianogi and Co., Ltd. (K. Shima, T. Tsukada, H. Kagawa, Inv.) Eur. Pat. 86113122.5 (April 1, 1986) [*Chem. Abstr.* **107** (1987) P161684u].
[21] Shianogi and Co., Ltd. (T. Totani, K. Aono, M. Komura, Inv.) Eur. Pat. 84106210.2 (March 1, 1984) [*Chem. Abstr.* **102** (1985) P198004v].
[22] P. Schwartz, S. J. Meischen, G. D. Gale, L. P. Atkins, A. B. Smith, E. M. Walker, *Cancer Treat. Rep.* **61** (1977) 1519.
[23] H. Sekikawa, M. Nakono, T. Arita, *Chem. Pharm. Bull.* **26** (1978) 118.
[24] R. I. Geran, N. H. Greenberg, M. M. Macdonald, A. M. Schumacher, B. J. Abbot, *Cancer Chemother. Rep., Part 3*, **3** (1972) 1.
[25] H. Wolff, *Org. React.* **3** (1949) 327.

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