Syntheses of *cis*-Dichlorodiammineplatinum Analogs Having Steroidal Hormones Bound to the Metal Atom via Malonato Bridges

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Abstract

In search for neutral, chemically stable, antitumor agents with target specificity, twenty-seven steroidal platinum(II) malonate conjugates have been prepared. Estrone, 17β-estradiol, testosterone, epitestosterone, pregnenolone, progesterone, 11α-hydroxyprogesterone, 21-desoxycortisone, prednisolone, litocholic, desoxycholic and etienic acid residues were attached either directly or through stable bridges to malonic esters. Hydrolysis of the modified diesters **1**–**14** with barium hydroxide followed by treatment of the barium salts **15**–**28**, so formed, with *cis*-diammine-, *cis*-[bis(cyclobutylamine)]-, (1,2-ethanediamine)-, or (1,2-cyclohexanediamine)diiodoplatinum in the presence of aqueous silver salts, afforded the desired steroidal *cis*-platinum complexes.

Introduction

The possibility of utilizing biological carriers for specific delivery of cytotoxic drugs in tumor cells raised the interest of several research groups in this area. Consequently, the approach of selective chemotherapy through the use of hormone-receptor transport mechanism has promoted, in the last two decades, the development of several agents containing steroidal hormones bound to a variety, though not always very efficient, antitumor units [1–4]. It seemed to us that optimal therapeutic efficacy with this class of compounds could be largely dependent upon the antitumor potency of the cytotoxic units being employed.

Previously we developed stable *cis*-platinum(II)–triphenylphosphine complexes as experimental models for the coupling with steroid molecules [5]. These complexes suffered, however, from some limitations which have already been pointed out [6]. Furthermore, it has now been recognized that optimization of antitumor activity of platinum complexes can be achieved by application of nitrogen rather than sulfur or phosphorus ligands, as the neutral ligands [7]. Among the second generation of antitumor platinum compounds those of the malonato type have emerged for their outstanding chemical and antitumor properties [7–9]. These compounds meet the requirements of chemical stability, high antitumor activity and aqueous solubility.

Following this trend, we report herein the syntheses of stable, neutral, malonato platinum(II) complexes covalently bound to a number of steroid hormones. The new molecules are designed in such a manner as to avoid the danger of hydrolysis of the bonds linking the steroid moiety and the platinum nucleus, and to enable the platinum complex to undergo the dissociative process, which is necessary for its antitumor activity.

Experimental

Infrared spectra were recorded with a Perkin-Elmer 457 spectrophotometer. NMR spectra were obtained using Varian T-60, Bruker WP-200 and Bruker WH-300 spectrometers. Reactions involving the use of active ester intermediates were performed under an argon atmosphere. Reagent-grade materials were used throughout the experiments. Solvents, unless analytical grade, were purified as described in the literature [10].

General Synthesis of Steroid-substituted N-Aminomalonates

In a typical example, 1.506 g (4 mmol) of lithocholic acid was reacted for 2 h at 0 °C with 460 mg (4 mmol) of *N*-hydroxysuccinimide (NHS) in the presence of 825 mg (4 mmol) of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 15 ml of freshly dried THF. The dicyclohexylurea was filtered off, and the filtrate was added at 0 °C to a stirred solution of diethyl aminomalonate [freshly prepared from 1.00 g (6.78 mmol) of diethylaminomalonate hydrochloride, 2 ml (6.9 mmol) of Et_3N and 10 ml of dry THF followed by thorough removal of the precipitated $Et_3N{\cdot}HCl$]. The solvent was removed under reduced pressure and the oily residue was dissolved

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TABLE 1. Selected IR bands for the steroid-substituted malonates and *N*-aminomalonates **1**–**14**[a]

Compound	νOH, NH	νC≡C	νC=O (sat.)	νC=O (unsat.), CONH(I)	νCONH(II)	νC=C (arom.)
1	3490, 3330		1740	1660	1535	
2	3420		1740	1660	1525	1495
3[b]	3415		1758, 1735	1685	1514	1497
4[b]	3415		1750	1685	1515	1495
5	3340	2215	1735	1660	1520	
6	3400, 3320	2220	1740	1650	1530	
7	3360		1740, 1720	1680	1505	
8[b]	3400		1750, 1700			
9[b]			1740, 1730, 1705	1670		
10	3480		1745, 1725, 1705	1660		
11[b]	3340		1745, 1723	1660		
12[c]			1735, 1725, 1707	1665		
13	3600		1725	1665, 1620		
14	3430		1757, 1740	1658		

[a]KBr pellets except if stated otherwise. [b]In CH_2Cl_2. [c]In $CHCl_3$.

in 400 ml of either Et_2O or CH_2Cl_2, washed with 0.2 N aqueous HCl and with H_2O. The resulting solution was dried on $MgSO_4$, filtered, and the solvent evaporated to give 1.430 (67%) of practically pure *N*-[3α-hydroxy-5β-cholan-24-amidato]propanedioic acid diethyl ester (**1**); colorless crystals; melting point (m.p.) 127 °C.

The infrared and ^1H NMR spectra of this ester as well as of compounds **2**–**14** are summarized in Tables 1 and 2.

To the above diester (1.430 g, 2.679 mmol) in 50 ml of MeOH was added dropwise at 25 °C during 3 h, 24 ml of 0.11 M clear aqueous $Ba(OH)_2$ (freshly prepared from $BaCl_2 \cdot 2H_2O$ and 1 N aqueous KOH). The pH of the solution was maintained below 12 during the addition. After a further 2 h at 25 °C, most of the MeOH was removed under reduced pressure and the white precipitate filtered and washed successively with water and acetone until the salt was free of contaminates (checked by TLC). Barium *N*-[3α-hydroxy-5β-cholan-24-amidato]propanedioate (**15**) was obtained as colorless crystals; yield 1.070 g (63%); m.p. 259–262 °C (dec.).

Selected IR bands for the various substituted barium malonates are given in Table 3; the elemental analyses are listed in Table 4.

N-[3α,12α-Dihydroxy-5β-cholan-24-amidato]propanedioic acid diethyl ester (**2**) was obtained as above in 75% yield from desoxycholic acid; m.p. 136 °C.

The barium salt **16** was obtained as the monohydrate. Yield 86%; colorless crystals; m.p. 262–265 °C (dec.).

N-[[[Estra-1,3,5(10)-trien-17-on-3-yl]oxy]acetamidato]propanedioic acid diethyl ester (**3**) was obtained in 79% yield from [[estra-1,3,5(10)-trien-

TABLE 2. Selected ^1H NMR data for the steroid-substituted malonates and *N*-aminomalonates **1**–**14**[a]

Compound	Recording frequency (MHz)	Chemical shift and assignment (δ, ppm)
1	60	0.70 [s, 3H, CH_3(18)], 0.90 [s, 3H, CH_3(19)], 1.26 (t, 6H, J = 7 Hz, OCH_2CH_3), 4.25 (q, 4H, J = 7 Hz, OCH_2CH_3)
2	60	0.70 [s, 3H, CH_3(18)], 0.90 [s, 3H, CH_3(19)], 1.28 (t, 6H, J = 7 Hz, OCH_2CH_3), 4.25 (q, 4H, J = 7 Hz, OCH_2CH_3)
3	60	0.89 [s, 3H, CH_3(18)], 1.29 (t, 6H, J = 7 Hz, OCH_2CH_3), 4.25 (q, 4H, J = 7 Hz, OCH_2CH_3), 4.46 (s, 2H, OCH_2CO), 5.17 (d, 1H, J = 8 Hz, NHCH), 6.90 (m, 3H, ArH), 7.49 (d, 1H, J = 8 Hz, NH).
4	60	0.76 [s, 3H, CH_3(18)], 1.27 (t, 6H, J = 7 Hz, OCH_2CH_3), 4.23 (q, 4H, J = 7 Hz, OCH_2CH_3), 4.46 (s, 2H, OCH_2CO), 5.16 (d, 1H, J = 8 Hz, NHCH), 6.90 (m, 3H ArH), 7.49 (d, 1H, J = 8 Hz, NH)
5	300	0.843 [s, 3H, CH_3(18)], 1.282 (t, 6H, J = 7 Hz, OCH_2CH_3), 4.287 (q, 4H, J = 7 Hz, OCH_2CH_3), 6.541 (d, 1H, J = 2 Hz, H4), 6.608 (dd, 1H, J_1 = 2 Hz, J_2 = 9 Hz, H2), 6.989 (d, 1H, J = 9 Hz, H1)
6	60	0.89 [s, 3H, CH_3(18)], 1.17 [s, 3H, CH_3(19)], 1.29 (t, 6H, J = 7 Hz, OCH_2CH_3), 4.23 (q, 4H, J = 7 Hz, OCH_2CH_3), 5.09 (d, 1H, J = 8 Hz, NHCH), 5.64 (s, 1H, H4), 6.45 (d, 1H, J = 8 Hz, NH)

(continued)

TABLE 2. *(continued)*

Compound	Recording frequency (MHz)	Chemical shift and assignment (δ, ppm)
7	300	0.700 [s, 3H, CH_3(18)], 1.023 [s, 3H, CH_3(19)], 1.302 (t, 6H, J = 7 Hz, OCH_3CH_3), 2.030 (s, 3H, $COCH_3$), 4.264 (q, 4H, J = 7 Hz, OCH_2CH_3), 5.201 (d, 1H, J = 7 Hz, $NHCH$), 5.377 (m, 1H, H6), 6.463 (d, 1H, J = 7 Hz, NH)
8	60	0.65 [s, 3H, CH_3(18)], 0.99 [s, 3H, CH_3(19)], 1.24 (t, 6H, J = 7 Hz, OCH_2CH_3), 2.97 [d, 2H, J = 7 Hz, CH_2(21)], 3.87 (t, 1H, J = 7 Hz, CH_2CH), 4.18 (q, 4H, J = 7 Hz, OCH_2CH_3), 5.29 (m, 1H, H6)
9	60	0.66 [s, 3H, CH_3(18)], 1.17 [s, 3H, CH_3(19)], 1.25 (t, 6H, J = 7 Hz, OCH_2CH_3), 3.00 [d, 2H, J = 7 Hz, CH_2(21)], 3.86 (t, 1H, J = 7 Hz, CH_2CH), 4.18 (q, 4H, J = 7 Hz, OCH_2CH_3), 5.68 (s, 1H, H4)
10	60	0.66 [s, 3H, CH_3(18)], 1.15 [s, 3H, CH_3(19)], 1.26 (t, 6H, J = 7 Hz, OCH_2CH_3), 4.17 (q, 4H, J = 7 Hz, OCH_2CH_3), 5.69 (s, 1H, H4)
11	60	0.66 [s, 3H, CH_3(18)], 1.24 (t, 6H, J = 7 Hz, OCH_2CH_3), 1.29 [s, 3H, CH_3(19)], 2.96 [d, 2H, J = 7 Hz, CH_2(21)], 3.88 (t, 1H, J = 7 Hz, CH_2CH), 4.18 (q, 4H, J = 7 Hz, OCH_2CH_3), 5.63 (s, 1H, H4)
12	200	0.661 [s, 3H, CH_3(18)], 1.274 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.285 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.405 [s, 3H, CH_3(19)], 2.194 (d, 1H, J = 12.4 Hz, H12), 2.905 (d, 1H, J = 12.4 Hz, H12'), 3.436 [dd, 1H, J_1 =
		(continued)

TABLE 2. *(continued)*

Compound	Recording frequency (MHz)	Chemical shift and assignment (δ, ppm)
		8.1 Hz, J_2 = 13.7 Hz, $CH_2CH(COOEt)_2$], 3.883 [dd, 1H, J_1 = 8.1 Hz, $CH(COOEt)_2$], 4.200 (q, 2H, J = 7.1 Hz, CH_2CH_3), 7.210 (q, 2H, J = 7.1 Hz, CH_2CH_3), 5.732 (s, 1H, H4)
13	200	0.957 [s, 3H, CH_3(18)], 1.275 (t, 3H, J = 7.1 Hz, CH_2CH_3), 1.288 (t, 3H, J = 7 Hz, CH_2CH_3), 1.454 [s, 3H, CH_3(19)], 2.932 [dd, 1H, J_1 = 7.6 Hz, J_2 = 18.3 Hz, $CH_2CH(COOEt_2$], 3.439 [dd, 1H, J_1 = 7.1 Hz, J_2 = 18.3 Hz, $CH_2CH(COOEt)_2$], 3.879 [dd, 1H, J_1 = 7.6 Hz, J_2 = 6.8 Hz, $CH(COOEt)_2$], 4.204 (q, 2H, J = 7.1 Hz, CH_2CH_3), 4.213 (t, 2H, J = 7.1 Hz, CH_2CH_3), 4.486 (m, 1H, H11), 6.018 (m, 1H, H4), 6.274 (dd, 1H, J_1 = 1.8 Hz, J_2 = 10 Hz, H2), 7.267 (d, 1H, J = 10 Hz, H1)
14	300	0.995 [s, 3H, CH_3(18), 1.312 (t, 6H, J = 7 Hz, CH_2CH_3), 4.286 (q, 4H, J = 7 Hz, CH_2CH_3), 4.471 (m, 1H, H11), 4.782 and 5.168 (ABq, 2H, J_{AB} = 17.6 Hz, OCH_2), 5.299 [d, 1H, J = 6.8 Hz, $CH(COOEt)_2$], 6.015 (m, 1H, H4), 6.253 (dd, 1H, J_1 = 1.8 Hz, J_2 = 10.1 Hz, H2), 6.910 (d, 2H, J = 8.8 Hz, H2', H6' arom.), 7.107 (d, 1H, J = 6.8 Hz, NH), 7.270 (d, 1H, J = 10.1 Hz, H1), 7.756 (d, 2H, J = 8.8 Hz, H3', H5' arom.)

[a]In $CDCl_3$.

17-on-3-yl]oxy]acetic acid [11]; colorless semi-solid, TLC on silica gel with 2.5% MeOH and 97.5% CH_2Cl_2 R_f = 0.69.

The barium salt **17** was formed in 97% yield; pale yellow crystals; m.p. > 258 °C (dec.).

N-[[[Estra-1,3,5(10)-trien-17β-ol-3-yl]oxy]acetamidato]propanedioic acid diethyl ester (**4**) was prepared from [[estra 1,3,5(10)-trien-17β-ol-3-yl]oxy]-acetic acid [11] in 81% yield; colorless semi-solid.

The barium salt **18** was obtained in 97% yield as colorless crystals; m.p. 270–274 °C (dec.).

N-[3-[Estra-1,3,5(10)-trien-3,17β-diol-17α-yl]propynamidato]propanedioic acid diethyl ester (**5**) was obtained when 2.02 g (5.93 mmol) of 3-[estra-1,3,5-(10)-trien-3,17β-diol-17α-yl]propynoic acid (prepared either by the method of Bucourt *et al.* [12] or by palladium-promoted carbonylation [13] of ethinyl-estradiol by the method described below for ethinyl-testosterone) was converted into the active ester with NHS, followed by treatment at room temperature with 13.33 mmol of freshly prepared diethyl aminomalonate in 50 ml of THF for 90 min. Yield 1.05 g (37%) of pale yellow crystals that proved difficult to purify. Purification of the dihydroxy ester was accomplished by acetylation with excess of acetyl chloride. The crude diacetate was chromatographed on silica gel using CH_2Cl_2 with 1% MeOH as eluent; pale yellow crystals; m.p. 79–80 °C; IR (KBr): 3320 (NH), 2220 (C≡C), 1755, 1735 (C=O), 1660, 1520 (CONH), 1490 (C=C arom.) cm^{-1}; 300 MHz ^1H NMR ($CDCl_3$) δ: 0.912 [s, 3H, CH_3-(18)], 0.917–1.260, 1.282–2.060, 2.070–2.250 and 2.260–3.850 (m, 15H), 1.279 (t, 6H, J = 7 Hz, OCH_2CH_3), 2.065 (s, 3H, $COCH_3$), 2.256 (s, 3H,

TABLE 3. Selected IR bands for steroid-substituted barium malonates 15–28[a]

Compound	νOH, NH, H_2O	νC≡C	νC=O (sat.)	νC=O (unsat.), CONH(I), COOBa	νCONH(II)	νC=C (arom.)
15	3380			1615	1505	
16	3400			1615	1505	
17	3380		1735	1610	1525	1490
18	3380			1640, 1610, 1580	1523	1500
19	3380	2215		1605	1515	1495
20	3420	2220	1700	1620	1515	
21	3420			1606	1505	
22	3400		1690	1575		
23	3420		1700	1660, 1575		
24	3420		1700	1655, 1575		
25	3400		1700	1655, 1575		
26	3410		1695	1650, 1575		
27	3400		1695	1650, 1580		
28	3395		1715	1647, 1600	1530	1490

[a]KBr pellets.

TABLE 4. Analytical data for the new steroid-substituted barium malonates

Compound	Formula	Found (%)			Calc. (%)		
		C	H	N	C	H	N
15	$C_{27}H_{41}BaNO_6 \cdot H_2O$	51.04	7.09	2.66	51.40	6.87	2.22
16	$C_{27}H_{41}BaNO_7 \cdot H_2O$	50.15	6.92	2.07	50.12	6.70	2.16
17	$C_{23}H_{25}BaNO_7$	49.06	4.27	2.48	48.89	4.46	2.48
18	$C_{23}H_{27}BaNO_7$	48.87	4.90	2.47	48.74	4.80	2.47
19	$C_{24}H_{25}BaNO_7 \cdot 3H_2O$	45.74	5.17	1.83	45.70	4.95	2.22
20	$C_{25}H_{29}BaNO_7 \cdot 2H_2O$	47.65	5.37	2.67	47.75	5.29	2.23
21	$C_{23}H_{31}BaNO_6 \cdot 2.5H_2O$	46.03	6.09	2.53	46.05	6.05	2.33
22	$C_{24}H_{32}BaO_6 \cdot H_2O$	50.43	5.90		50.41	5.99	
23	$C_{24}H_{30}BaO_2 \cdot 2H_2O$	49.12	5.77		49.04	5.83	
24	$C_{24}H_{30}BaO_7 \cdot 2H_2O$	47.53	5.60		47.74	5.68	
25	$C_{24}H_{30}BaO_7 \cdot 3H_2O$	46.39	5.77		46.35	5.84	
26	$C_{24}H_{28}BaO_8$	49.33	4.66		49.55	4.85	
27	$C_{24}H_{28}BaO_8 \cdot 2H_2O$	46.50	5.03		46.66	5.22	
28	$C_{31}H_{33}BaNO_{10} \cdot 2H_2O$	49.32	4.77	2.20	49.32	4.95	1.86

$COCH_3$), 4.268 (1, 4H, J = 7 Hz, OCH_2CH_3), 5.164 (d, 1H, J = 7 Hz, NHCH), 6.720–7.200 (m, 3H, ArH), 7.245 (d, 1H, J = 7 Hz, NH).

Hydrolysis with $Ba(OH)_2$ gave the acetyl-free barium salt **19** as trihydrate; m.p. > 200 °C (dec.).

N-[3-[17β-Hydroxyandrost-4-en-3-on-17α-yl]propynamidato]propanedioic acid diethyl ester (**6**). A stream of CO was bubbled through a stirred suspension of 6.000 g (19.2 mmol) of ethinyltestosterone, 5.163 g (38.4 mmol) of anhydrous cupric chloride, 3.150 g (38.4 mmol) of sodium acetate, 381 mg (2.15 mmol) of palladium dichloride and 400 ml of absolute MeOH. After 2.5 h the green solution darkened and a fresh solution of 2.58 g of cupric chloride, 1.57 g of sodium acetate and 190 mg of palladium dichloride in 30 ml of MeOH was added. After further 20 min the last traces of the solid steroid disappeared and the mixture was stirred for another 40 min. The black precipitate was filtered off, washed with MeOH, and the filtrate concentrated under reduced pressure. The residue was extracted with 220 ml of CH_2Cl_2 and the remaining solid refluxed with another portion of the same solvent. The extraction was repeated until the CH_2Cl_2 stayed colorless. The combined organic solutions were washed with H_2O, dried on $MgSO_4$ and evaporated under reduced pressure. The residue was triturated with Et_2O to give 6.66 g (93%) of methyl 3-(17β-hydroxyandrost-4-en-3-on-17α-yl)propynoate. The ester could be further purified by chromato-

graphy on silica gel (CH_2Cl_2 with 1% MeOH served as eluent); R_f = 0.33; m.p. 180–182 °C; IR (KBr): 3320 (OH), 2205 (C≡C); 1700, 1650 (C=O) cm^{-1}; 300 MHz ^1H NMR ($CDCl_3$) δ: 0.922 [s, 3H, CH_3-(18)], 0.930–1.19 and 1.21–3.72 (m, 20H), 1.201 [s, 3H, CH_3(19)], 3.771 (s, 3H, OCH_3), 5.754 (s, 1H, H4). *Anal.* Calc. for $C_{23}H_{30}O_4$: C, 74.56; N, 8.16. Found: C, 74.46; H, 8.18%. Hydrolysis was afforded by stirring of the ester with a 2.5% KOH solution in MeOH for 5 h at room temperature followed by acidification with aqueous 2 M $KHSO_4$, m.p. 258–261 °C (lit. [14] 257–261 °C).

The active ester formed from 5.24 (14.7 mmol) of the above acid and the required quantities of NHS and DCC, was treated for 2 h at 0 °C and 16 h at 20 °C with 19.11 mmol of diethyl aminomalonate as described for **1** except that the work up was in EtOAc. Yield of **6**, 96%; pale yellow crystals; TLC on silica gel with 97.5% CH_2Cl_2 and 2.5% MeOH: R_f = 0.37; m.p. 118–119 °C. 50 MHz ^{13}C NMR (DMF) δ: 13.04 (C18), 14.17 (OCH_2CH_3), 17.39 (C19), 21.26 (C11), 23.60 (C15), 32.21 (C16), 32.89 (C7), 33.42 (C6), 34.40 (C2), 36.68 (C1), 39.13 (C12), 39.28 (C10), 47.80 (C13), 50.79 (C14), 54.16(C9), 57.24 (NHCH), 62.65 (OCH_2CH_3), 79.36 (C17), 92.05, 92.85 (C20, C21), 123.97 (C4), 153.58 (C≡CCONH), 166.69 ($COOCH_2$), 171.51 (C5), 198.61 (C3).

The barium salt **20** was obtained as a colorless dihydrate in 41% yield; m.p. > 304 °C (dec.).

N-[[3β-Acetyloxyandrost-5-en-17α-yl]carboxamidato]propanedioic acid diethyl ester (7). The best results were obtained when 1.41 g (6.67 mmol) of diethyl aminomalonate hydrochloride was suspended in 20 ml of CH_2Cl_2 and treated under vigorous stirring with 0.32 g (8 mmol) of NaOH in 30 ml of ice cold water. To the water washed and dried organic phase was added successively at 0 °C, a solution of 1.14 g of DCC in 20 ml of THF and 2.00 g (6.28 mmol) of 3β-acetoxyethiocholenic acid. After 2 h at 0 °C and 16 h at 20 °C the reaction mixture was worked up to give 2.30 g (77%) of colorless 3β-acetate of **7**.

The barium salt **21** crystallized with 2.5 molecules of H_2O as colorless crystals. Yield 68%; m.p. > 265 °C (dec.).

General Synthesis of Steroid-substituted Malonates

In a typical example, a solution of diethyl sodiomalonate (from 9.8 ml (64.5 mmol) of diethyl malonate and 48.3 mmol NaH) in 20 ml of THF was added at 0 °C to a stirred solution of 7.13 g (16.12 mmol) of 21-iodopregnenolone [15] (prepared from pregnenolone by the general method of Ringold and Stork [16]) in 200 ml of the same solvent. After 90 min at room temperature the solvent was evaporated under reduced pressure and the resulting oil extracted with 300 ml of either Et_2O or CH_2Cl_2 and washed with 200 ml of 10% aqueous sodium bisulfite. The ether was evaporated and the oily ester was purified by column chromatography on silica gel using CH_2Cl_2 with 0–4% MeOH as eluent. Yield 4.60 g (60%) of semi-solid diethyl (3β-hydroxypregn-5-en-20-on-21-yl)propanedioate (**8**).

The substituted diethyl malonate was converted into the corresponding barium salts by the method described above for the hydrolysis of the substituted diethyl aminomalonates.

Compound **22** formed a colorless monohydrate. Yield 81%; m.p. > 304 °C (dec.).

(Pregn-4-ene-3,20-dion-21-yl)propanedioic acid diethyl ester (**9**) was obtained in 77% yield by reacting of 21-iodopregn-4-ene-3,20-dione [16, 17] and diethyl sodiomalonate in boiling THF for 2 h. A somewhat lower yield (55%) was obtained when the malonate was reacted with desoxycorticosterone tosylate [18] for 5 h at 25 °C. The ester was purified by column chromatography on silica gel using a mixture of 99% CH_2Cl_2 and 1% of MeOH as eluent; colorless semi-solid.

The barium salt **23** was obtained in 78% yield as a pale yellow dihydrate; m.p. > 310 °C (dec.).

(17α-Hydroxypregn-4-ene-3,20-dion-21-yl)propanedioic acid diethyl ester (**10**) was obtained in 63% yield from 17α-hydroxy-21-iodopregn-4-ene-3,20-dione (prepared according to Bowers and Ringold from 17α-hydroxyprogesterone [17]). After column chromatography on silica gel with a mixture of 99% CH_2Cl_2 and 1% MeOH, a pale yellow semi-solid was obtained.

The barium salt **24** was obtained in 64% yield as a colorless dihydrate; m.p. > 300 °C (dec.).

(11α-Hydroxypregn-4-ene-3,20-dion-21-yl)propanedioic acid diethyl ester (**11**) was formed in 47% yield from 11α-hydroxy-21-iodopregn-4-ene-3,20-dione (prepared by the method of Ringold and Stork [16] from 11α-hydroxyprogesterone). Purification was accomplished by column chromatography on silica gel using CH_2Cl_2 with 1 – 2% MeOH as eluent; colorless semi-solid.

The barium salt **25** was obtained in 69% yield as a pale yellow trihydrate; m.p. > 310 °C (dec.).

(17α-Hydroxypregn-4-ene-3,11,20-trion-21-yl)-propanedioic acid diethyl ester (**12**). A quantity of 4.38 g (10 mmol) of cortisone was converted in 96% yield into cortisone 21-methanesulfonate by treatment of the carbinol with 1.6 ml (21 mmol) of methanesulfonylchloride and 16 ml (0.2 mmol) of pyridine at −20 °C for 20 h; m.p. 190 °C [19]; IR (KBr): 1736; 1702, 1663 (C=O) cm^{-1}; 200 MHz ^1H NMR ($CDCl_3$) δ: 0.665 [s, 3H, CH_3(18)], 1.205–1.395, 1.430–2.000 and 2.250–2.883 (m, 16H), 1.406 (s, 3H, CH_3(19)], 2.173 and 2.909 (ABq, 2H, J_{AB} = 12.4 Hz, H12, H12'), 3.208 (s, 3H, SO_2CH_3), 4.898 and 5.345 (ABq, 2H, J_{AB} = 18.1 Hz, SO_2CH_2), 5.731 (s, 1H, H4).

A solution of 516 mg (1 mmol) of the methanesulfonate and 420 mg (3 mmol) of NaI in 15 ml of acetone was refluxed for 15 min, cooled and evaporated to dryness under reduced pressure. The residue was extracted into dry THF and filtered. To the clear filtrate was added dropwise at 5 °C a solution of 3.5 mmol of diethyl sodiomalonate in 15 ml of THF. The mixture was refluxed for 1 h, the solvent was removed under reduced pressure and the residue digested with CH_2Cl_2 and ice cold 1 N HCl. After the usual workup and chromatography on silica gel (using a gradient of CH_2Cl_2–THF as eluent), there was obtained 200 mg (40%) of **12** as colorless crystals; m.p. 142 °C.

The barium salt **26** was obtained in quantitative yield; m.p. > 305 °C (dec.).

(11β,17α-Dihydroxypregna-1,4-diene-3,20-dion-21-yl)propanedioic acid diethyl ester (**13**). Prednisolone 21-methanesulfonate was obtained in quantitative yield from prednisolone as a colorless powder; m.p. 193–194 °C [20]; IR (KBr): 3280 (OH), 1725, 1650 (C=O), 1620 (C=C), 1345, 1160 (SO_2) cm^{-1}; 300 MHz ^1H NMR (DMSO-d_6) δ: 0.815 [s, 3H, CH_3(18)], 0.832–1.390 and 1.410–2.593 (m, 15H), 1.397 [s, 3H, CH_3(19)], 3.228 (s, 3H, SO_2CH_3), 4.294 (m, 1H, H11), 4.833 and 5.284 (ABq, 2H, J_{AB} = 17.6 Hz, CH_2SO_2), 5.904 (s, 1H, H4), 6.150 (d, 1H, J = 10.3 Hz, H2), 7.319 (d, 1H, J = 10.3 Hz, H1).

A quantity of 1 mmol of the methanesulfonate was transformed to 11β,17α-dihydroxy-21-iodopregna-1,4-diene-3,20-dione by the method described above, and reacted with diethyl sodiomalonate to give, after trituration with hexane, 76% of **13** as colorless crystals; m.p. 202.5–203 °C. *Anal.* Calc. for $C_{28}H_{38}O_8$: C, 66.91; H, 7.62. Found: C, 66.98; H, 7.54%.

The barium salt **27** was obtained in 70% yield as a colorless dihydrate; m.p. > 290 °C (dec.).

N-[4-Hydroxybenzamidato]propanedioic Acid Diethyl Ester

To a solution of 20 mmol of diethyl aminomalonate (freshly prepared from the hydrochloride) in 50 ml of dry THF was added at 5 °C a solution of 2.06 g (10 mmol) of DCC and 1.38 g (10 mmol) of 4-hydroxybenzoic acid in 25 ml of the same solvent. After stirring for 48 h at room temperature, the *N,N*-dicyclohexylurea was filtered off, and the filtrate concentrated under reduced pressure. The residue was extracted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and NaCl solutions, dried, concentrated and chromatographed on silica gel using CH_2Cl_2–THF gradient as eluent. After crystallization from aqueous EtOH there was obtained 2.27 g (77%) of colorless needles; m.p. 99 °C. IR ($CHCl_3$): 3430 (NH), 3250 (OH), 1750, 1730 (C=O), 1650 (CONH) cm^{-1}. 300 MHz ^1H NMR ($CDCl_3$) δ: 1.311 (t, 6H, J = 7.0 Hz, CH_2CH_3), 4.304 (q, 4H, J = 7.0 Hz, CH_2CH_3), 5.327 (d, 1H, J = 6.6 Hz, NHCH), 6.868 (dd, 2H, J_1 = 1.9 Hz, J_2 = 6.6 Hz, H3, H5), 7.164 (d, 1H, J = 6.6 Hz, NH), 7.680 (dd, 2H, J_1 = 1.9 H, J_2 = 6.6 Hz, H2, H6), 8.037 (br s, 1H, OH). *Anal.* Calc. for $C_{14}H_{17}NO_6$: C, 56.95; H, 5.80; N, 4.74. Found: C, 57.24; H, 5.82; N, 5.02%.

N-[4-[[11β,17α-Dihydroxypregna-1,4-diene-3,20-dione-21-yl]oxy]benzamidato]propanedioic Acid Diethyl Ester (14)

To a stirred suspension of 1.58 g (5.36 mmol) of diethyl *N*-[4-hydroxybenzamidato]propanedioate and 3.5 g (18 mmol) of anhydrous K_2CO_3 in 70 ml of dry acetone, was added dropwise a solution of 11β,17α-dihydroxy-21-iodopregna-1,4-diene-3,20-dione [freshly prepared as described above, from 2.35 g (5.30 mmol) of predniosolone 21-methanesulfonate and 0.85 mg (5.67 mmol) of NaI] in 50 ml of acetone. After reflux for 16 h the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel 60, ASTM (using CH_2Cl_2 and 10–20% of wet-THF as eluent) to give 2.14 g (62%) of the substituted malonic ester as a colorless hemihydrate; m.p. 110–111 °C. *Anal.* Calc. for $C_{35}H_{43}NO_{10}\cdot 0.5H_2O$: C, 65.00; H, 6.86; N, 2.16. Found: C, 64.94; H, 6.97; N, 2.49%.

The barium salt **28** was obtained in 49% yield as a colorless dihydrate; m.p. > 280 °C.

General Procedures for Preparation of Steroidal Platinum Complexes

A suspension of 0.26 mmol of the appropriate platinum complex of type I_2PtZZ', 88 mg (0.52 mmol) of $AgNO_3$ and 12 ml of triply distilled H_2O was stirred in the dark at 20 °C for 22 h and for 30 min at 50 °C. The warm solution was filtered through a sintered glass funnel, the AgI precipitate was washed with 5 ml of warm water and the combined aqueous solutions of $[ZZ'Pt(H_2O)_2]^{2+}[NO_3]_2^{2-}$ [21] were pipetted to a suspension of 0.30 mmol of the steroid-substituted barium malonate in 5 ml of H_2O. The mixture was stirred at 50 °C for 12–24 h, cooled and filtered. The precipitate was washed with distilled water and extracted (repeatedly) either with hot (60 °C) 96% aqueous EtOH or with a mixture of 95% EtOH and 5% MeOH. After evaporation of the extraction solvents under reduced pressure, washing of the residue with H_2O, acetone and anhydrous ether (as long as TLC indicates any contaminant) pure platinum complexes were obtained. This method was employed for the preparation of the following compounds: *cis*-[*N*-[3α-hydroxy-5β-cholan-24-amidato]propanedioato(2–)-*O,O'*]diammineplatinum (**29a**) (from **15** and *cis*-diamminediiodoplatinum (**43a**) [22] in 58% yield); *cis*-[*N*-[[[estra-1,3,5(10)-trien-17-on-3-yl]oxy]acetamidato]propanedioato-(2–)-*O,O'*]diammineplatinum (**31a**) (from **17** and

43a in 54% yield); [*N*-[[[estra-1,3,5(10)-trien-17-on-3-yl]oxy]acetamidato]propanedioato(2−)-*O,O'*]-(1,2-ethanediamine-*N,N'*)platinum (**31c**) (from **17** and (1,2-ethanediamine-*N,N'*)diiodoplatinum (**43c**) [23] in 62% yield); [*N*-[[[estra-1,3,5(10)-trien-17-on-3-yl]oxy]acetamidato]propanedioato(2−)-*O,O'*]-(1,2-cyclohexanediamine-*N,N'*)platinum (**31d**) (from **17** and **43d** in 48% yield); *cis*-[*N*-[[[estra-1,3,5(10)-trien-17β-ol-3-yl]oxy]acetamidato]propanediato(2−)-*O,O'*]-diammineplatinum (**32a**) (from **18** and **43a** in 57% yield); [*N*-[[[estra-1,3,5(10)-trien-17β-ol-3-yl]oxy]acetamidato]propanedioato(2−)-*O,O'*](1,2-ethanediamine-*N,N'*)platinum (**32c**) (from **18** and 43c in 60% yield); [*N*-[[[estra-1,3,5(10)-trien-17β-ol-3-yl]oxy]acetamidato]propanedioato-(2−)-*O,O'*]-(1,2-cyclohexanediamine-*N,N'*)platinum (**32d**) (from **18** and (1,2-cyclohexanediamine-*N,N'*)diiodoplatinum (**43d**) [6] in 64% yield); *cis*-[*N*-[3-[estra-1,3,5-(10)-trien-3,17β-diol-17α-yl]propynamidato]propanedioato(2−)-*O,O'*]diammineplatinum (**33a**) (from **19** and **43a** in 25% yield); *cis*-[*N*-[3-[17β-hydroxyandrost-4-en-3-on-17α-yl]propynamidato]propanedioato(2−)-*O,O'*]diammineplatinum (**34a**) (from **20** and **43a** in 37% yield); *cis*-[*N*-[3-[17β-hydroxyandrost-4-en-3-on-17α-yl]propynamidato]propanedioato(2−)-*O,O'*]bis(cyclobutanamine-*N*)platinum (**34b**) (from **20** and *cis*-bis(cyclobutanamine-*N*)diiodoplatinum (**43b**) [24] in 20% yield); [*N*-[3-[17β-hydroxyandrost-4-en-3-on-17α-yl]propynamidato]propanedioato-(2−)-*O,O'*](1,2-ethanediamine-*N,N'*)platinum (**34c**) (from **20** and **43c** in 32% yield); [*N*-[3-[17β-hydroxyandrost-4-en-3-on-17α-yl]propynamidato]-propanedioato(2−)-*O,O'*](1,2-cyclohexanediamine-*N,N'*)platinum (**34d**) (form **20** and **43d** in 52% yield); *cis*-[*N*-[[androst-5-en-3β-ol-17α-yl]carboxamidato]propanedioato(2−)-*O,O'*]diammineplatinum (**35a**) (from **21** and **43a** in 58% yield); *cis*-[[3β-hydroxypregn-5-en-20-on-21-yl]propanedioato(2−)-*O,O'*]diammineplatinum (**36a**) (form **22** and **43a** in 32% yield); [[3β-hydroxypregn-5-en-20-on-21-yl]-propanedioato(2−)-*O,O'*](1,2-cyclohexanediamine-*N,N'*)platinum (**36d**) (from **22** and **43d** in 22% yield); *cis*-[[pregn-4-ene-3,20-dion-21-yl)propanedioato(2−)-*O,O'*]diammineplatinum (**37a**) (from **23** and **43a** in 63% yield); [[pregn-4-ene-3,20-dion-21-yl]propanedioato(2−)-*O,O'*](1,2-ethanediamine-*N,N'*)platinum (**37c**) (from **23** and **43c** in 64% yield); [[pregn-4-ene-3,20-dion-21-yl]propanedioato-(2−)-*O,O'*](1,2-cyclohexanediamine-*N,N'*)platinum (**37d**) (from **23** and **43d** in 18% yield); *cis*-[[17α-hydroxypregn-4-ene-3,20-dion-21-yl]propanedioato-(2−)-*O,O'*]diammineplatinum (**38a**) (from 24 and **43a** in 56% yield); [17α-hydroxypregn-4-ene-3,20-dion-21-yl]propanedioato(2−)-*O,O'*](1,2-ethanediamine-*N,N'*)platinum (**38c**) (from **24** and **43c** in 69% yield); *cis*-[[11α-hydroxypregn-4-ene-3,20-dion-21-yl]propanedioato(2−)-*O,O'*]-diammineplatinum (**39a**) (from **25** and **43a** in 23% yield); [[11α-hydroxypregn-4-ene-3,20-dion-21-yl]propanedioato(2−)-*O,O'*](1,2-cyclohexanediamine-*N,N'*)platinum (**39d**) (from **25** and **43d** in 24% yield); *cis*-[[17α-hydroxypregn-4-ene-3,11,20-trion-21-yl]propanedioato(2−)-*O,O'*]diammineplatinum (**40a**) (from **26** and **43a** in 49% yield); *cis*-[[11β,17α-dihydroxypregna-1,4-diene-3,20-dion-21-yl]propanedioato(2−)-*O,O'*]diammineplatinum (**41a**) (from 27 and **43a** in 44% yield); and *cis*-[*N*-[4-[[11β,17α-dihydroxypregna-1,4-diene-3,20-dion-21-yl]oxy]benzamidato]propanedioato(2−)-*O,O'*]diammineplatinum (**42**) (from **28** and **43a** in 68% yield).

In an alternative procedure $AgNO_3$ was replaced by the equivalent amount of $AgSO_4$. Treatment of the substituted barium malonate with the appropriate aqueous solution of $ZZ'Pt(SO_4)(H_2O)$ [4] gave the steroid-bound platinum complex admixed with $BaSO_4$. Separation of the mixture was accomplished by Soxhlet extraction of the organometallic complex with 96% aqueous EtOH. This method was employed for the preparation of *cis*-[*N*-[[3α,12α-dihydroxy-5β-cholan-24-amidato]propanedioato(2−)-*O,O'*]diammineplatinum (**30a**) (from **16** and **43a** in 61% yield); [*N*-[[3α,12α-dihydroxy-5β-cholan-24-amidato]propanedioato(2−)-*O,O'*](1,2-ethanediamine-*N,N'*)platinum (**30c**) (from **16** and **43c** in 64% yield), and [*N*-[[[estra-1,3,5(10)-trien-17-on-3yl]oxy]acetamidato]propanedioato(2−)-*O,O'*](1,2-cyclohexanediamine-*N,N'*)platinum (**31d**) (from **17** and **43d** in 57% yield).

The melting points, analytical data and infrared spectra of the various steroidal platinum complexes are given in Tables 5 and 6.

Results and Discussion

Each of the twenty-seven platinum complexes **29**–**42** described hereby consists of an amine stabilized malonato- or aminomalonatoplatinum nucleus to which a steroid moiety is attached either directly or through a chemically stable bridging unit. Lithocholic acid, desoxycholic acid, etienic acid, estrone, 17β-estradiol, testosterone, epitestosterone, pregnenolone, progesterone, 11α-hydroxyprogesterone, 21-desoxycortinsone and prednisolone, were chosen to represent the steroidal parts in these molecules. (For further possible examples see ref. 25.)

The general synthesis of the complexes comprises the following three steps: (i) attachment of a malonic ester to the steroid; (ii) hydrolysis of the modified ester with aqueous barium hydroxide, and (iii) reaction of the barium salt of the steroid–malonate conjugate with a prehydrolyzed platinum(II) nitrate or sulfate complex (eqn. (1)).

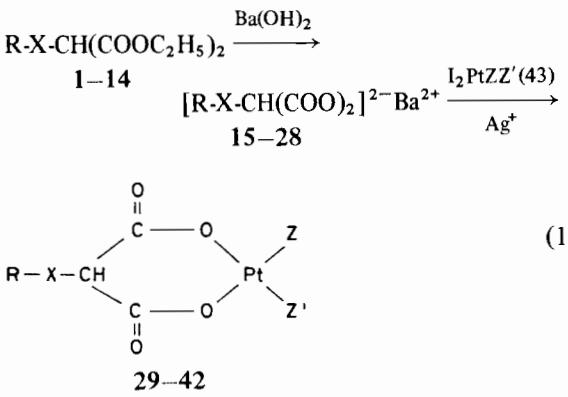
The steroid–malonate esters were prepared either from diethyl malonate or from amino-functionalized malonate. In the former case, the malonic ester was

alkylated in the usual manner with the halide, tosylate or mesylate derivative of the appropriate steroid. In the latter case, the aminomalonate was coupled to a carboxyl-functionalized steroid through a peptide bond [5].

The steroid–malonate intermediates **1–13** were characterized by their IR and NMR spectra (see Tables 1 and 2). The prednisolone derivative **14** in which a spacer unit was built-in, was obtained by a combination of the above two approaches, i.e. first 4-hydroxybenzoic acid was coupled with diethyl aminomalonate through the formation of a peptide bond, and subsequently it was reacted with the preiodinated steroid in the presence of anhydrous potassium carbonate.

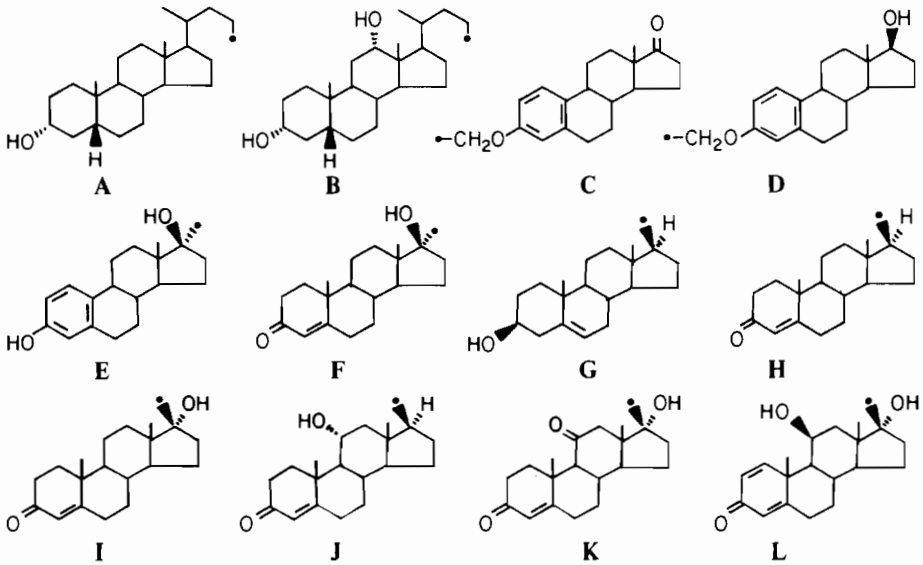
Treatment of the substituted malonic esters with aqueous barium hydroxide gave smoothly the barium salts of the steroid-substituted malonates. The appearance of strong C=O stretching bands at 1600–1620 cm^{-1} for the aminomalonates, and at 1570–1580 cm^{-1} for the malonato groups in the IR spectra (Table 3), was indicative for the formation of the $Ba(OCO)_2$ moiety [6]. In contrast to the corresponding sodium or potassium salts that gave poor results, the substituted barium malonates led to good to excellent yields of heavy precipitates that could easily be purified to the analytical state just by washing with water and acetone (see Table 4).

Reaction of the barium salts with aqueous solutions of *cis*-platinum(II) nitrates or sulfates having amino ligands Z and Z′ as shown in eqn. (1) yielded the desired steroidal platinum conjugates. The use



(1)

of barium as the counter ion for the formation of steroid-substituted malonato salts, has already proved useful in our previous syntheses [6] as they stabilize the malonate intermediates and provide the required pH during the course of the reactions. Analytical data and IR measurements of the steroid–malonato–platinum(II) complexes (compounds **29–42**) are listed in Tables 5 and 6, respectively. The coordination of the dicarboxylic acid to the platinum nucleus was confirmed by the disappearance of the strong bands between 1570 and 1620 cm^{-1} of $Ba(OCO)_2$, and by the appearance of new C=O peaks between 1630 and



1, 15, 29, RX = A-CONH
2, 16, 30, RX = B-CONH
3, 17, 31, RX = C-CONH
4, 18, 32, RX = D-CONH
5, 19, 33, RX = E-C≡CCONH
6, 20, 34, RX = F-C≡CCONH
7, 21, 35, RX = G-CONH
8, 22, 36, RX = G-$COCH_2$
9, 23, 37, RX = H-$COCH_2$
10, 24, 38, RX = I-$COCH_2$
11, 25, 39, RX = J-$COCH_2$
12, 26, 40, RX = K-$COCH_2$
13, 27, 41, RX = L-$COCH_2$
14, 28, 42, RX = L-$COCH_2OC_6H_4$-4-CONH

a, Z = Z′ = NH_3 b, Z = Z′ = $C_4H_7NH_2$ c, ZZ′ = $H_2NCH_2CH_2NH_2$ d, ZZ′ = 1,2-$C_6H_{10}(NH_2)_2$

TABLE 5. Melting points and analytical data for the new steroidal platinum complexes

Compound	Formula	Melting point (dec.) (> °C)	Found (%)			Calc. (%)		
			C	H	N	C	H	N
29a	$C_{27}H_{47}N_3O_6Pt$	184	46.08	6.64	5.94	46.02	6.72	5.96
30a	$C_{27}H_{47}N_3O_7Pt$	200	44.85	6.83	5.73	44.99	6.57	5.83
30c	$C_{29}H_{49}N_3O_7Pt \cdot H_2O$	210	45.62	6.83	5.52	45.54	6.72	5.49
31a	$C_{23}H_{31}N_3O_7Pt \cdot H_2O$	214	41.16	5.22	6.15	40.95	4.93	6.23
31c	$C_{25}H_{33}N_3O_7Pt$	218	44.18	4.94	5.85	43.99	4.87	6.15
31d	$C_{29}H_{39}N_3O_7Pt \cdot 2H_2O$	232	44.96	5.81	5.48	45.07	5.61	5.44
32a	$C_{23}H_{33}N_3O_7Pt \cdot H_2O$	208	41.04	5.30	6.05	40.83	5.21	6.21
32c	$C_{25}H_{35}N_3O_7Pt$	190	43.89	5.36	6.20	43.86	5.15	6.14
32d	$C_{29}H_{41}N_3O_7Pt$	226	47.27	5.90	5.71	47.15	5.59	5.69
33a	$C_{24}H_{31}N_3O_7Pt$	300	43.22	4.90	6.05	43.11	4.67	6.28
34a	$C_{25}H_{35}N_3O_7Pt \cdot 2H_2O$	228	41.35	5.57	5.64	41.66	5.45	5.83
34b	$C_{33}H_{47}N_3O_7Pt \cdot 2H_2O$	222	47.75	6.08	5.17	47.82	6.20	5.07
34c	$C_{27}H_{37}N_3O_7Pt \cdot H_2O$	232	44.60	5.41	5.84	44.50	5.39	5.77
34d	$C_{31}H_{43}N_3O_7Pt \cdot 2H_2O$	280	46.33	6.00	4.99	46.50	5.91	5.25
35a	$C_{23}H_{37}N_3O_6Pt$	213	42.46	5.74	6.16	42.72	5.77	6.50
36a	$C_{24}H_{38}N_2O_6Pt \cdot 2H_2O$	230	42.08	6.07	3.83	42.29	6.21	4.11
36d	$C_{30}H_{46}N_2O_6Pt \cdot H_2O$	224	48.45	6.59	3.39	48.44	6.50	3.76
37a	$C_{24}H_{36}N_2O_6Pt \cdot H_2O$	212	43.83	5.85	3.96	43.57	5.79	4.23
37c	$C_{26}H_{38}N_2O_6Pt$	215	46.44	5.71		46.63	5.72	
37d	$C_{30}H_{44}N_2O_6Pt \cdot 3H_2O$	275	46.11	6.35	3.41	46.32	6.47	3.60
38a	$C_{24}H_{36}N_2O_7Pt \cdot H_2O$	208	42.32	5.50	4.03	42.54	5.65	4.13
38c	$C_{26}H_{38}N_2O_7Pt$	219	45.80	5.43	4.36	45.54	5.59	4.09
39a	$C_{24}H_{36}N_2O_7Pt$	210	43.49	5.39	4.02	43.70	5.51	4.25
39d	$C_{30}H_{44}N_2O_7Pt \cdot H_2O$	265	47.50	5.92	3.69	47.55	6.12	3.70
40a	$C_{24}H_{34}N_2O_8Pt \cdot H_2O$	228	41.83	5.33	4.10	41.68	5.25	4.05
41a	$C_{24}H_{34}N_2O_8Pt \cdot H_2O$	218	41.85	5.52	4.41	41.68	5.25	4.05
42a	$C_{31}H_{39}N_3O_{10}Pt$	260	46.25	5.07	5.38	46.04	4.86	5.20

1690 cm^{-1} characteristic for the COOPt group [6, 26, 27].

Compounds **29–42** were found to be thermally stable (cf., their very high decomposition points listed in Table 5), and resistant to oxidation even upon prolonged exposure to air.

The antitumor activity of platinum–malonato compounds is believed to be associated with metabolic activation of the dicarboxylato moiety [7, 28]. Therefore, it can be assumed that the structural design of this new class of steroid–platinum conjugates permits the required dissociative mechanism to take place within the cell.

A variety of neutral amine ligands have been introduced in the platinum unit for optimization of the antitumor activity of the drug. In this study we applied monodentate ammine and cyclobutylamine as well as chelating 1,2-ethanediamine and 1,2-cyclohexanediamine groups. Most of the cytotoxic-steroid derivatives described in the literature [3, 29, 30] were prepared by esterification of the hydroxyl functions of the steroid carriers with suitable alkylating molecules containing carboxylic groups. Examples of such compounds are estramustine and prednimustine. However, as the ester groups of these compounds tend to hydrolyze under phyisological conditions, they are of little practical use. In our case, the malonate ligand is covalently bound to the steroid molecule either through a C–C or through a C–N bond, thus avoiding the danger of hydrolysis before the complex reaches the target cell. Their only drawback is their low solubility caused by the lipophilic steroid moieties. In fact their solubility is intermediate between our previously reported steroid–catecholato–platinum conjugates [5] and the water soluble aminomalonate complexes [6]. Nevertheless, several of the present steroid–platinum conjugates could be applied successfully as suspensions similarly to other steroid containing drugs. The suspensions are prepared by initially dissolving the compounds in ethanol followed by diluting with water. In this manner concentrations of about 4 μM of the compounds (somewhat less than 4 μM for complexes **40–42**) could be obtained. One should, of course, bear in mind that many steroids containing drugs, may be effective in nanograms or even smaller quantities.

It is well known that one of the main problems in the use of carrier molecules for the delivery of cytotoxic units is the retention of the receptor af-

TABLE 6. Selected IR bands for the steroidal platinum complexes (cm^{-1})[a]

Compound	νOH, NH, H_2O	νPtNH	νC≡C	νC=O (sat.)	νC=O (unsat.), CONH(I), COOPt		νCONH(II)	νC=C (arom.)	νC–O
29a	3440	3380			1630		1530		1390
30a	3425	3325			1635		1540		1375
30c	3440	3225			1635		1538		1370
31a	3435	3230		1740	1690	1643	1520	1495	1405
31c	3400	3210		1730	1690	1640		1495	1402
31d	3380	3180		1720	1645	1610		1490	1390
32a	3400	3250			1680	1648		1500	1400
32c	3390	3210			1680	1642		1497	1405
32d	3370	3180			1645	1600		1495	1385
33a	3400	3260	2215		1620(br)			1497	1425
34a	3410	3250	2215		1640(br)				1395
34b	3400	3205	2210		1635(br)				1390
34c	3420	3220	2205		1645(br)				1400
34d	3400	3210	2215		1635(br)				1380
35a	3400	3260			1670	1640			1400
36a	3410	3260		1700	1640				1385
36d	3420	3200		1695	1650(br)				1385
37a	3440	3260		1695	1655	1620			1380
37c		3210		1700	1665	1630			1395
37d	3420	3210		1700	1650	1620			1380
38a	3420	3280		1690	1640	1625			1385
38c	3440	3210		1700	1650	1630			1400
39a	3410	3280		1690	1650	1620			1390
39d	3430	3220		1690	1650	1615			1390
40a	3440	3270		1700	1630(br)				1390
41a	3420	3280		1690	1650	1610			1390
42a	3400	3280		1720	1650	1610	1535	1495	1395

[a]KBr pellets.

finity of the drug [3]. Therefore, also in our case the achievement of a highly selective antitumor platinum drug may depend mainly on the appropriate choice of the steroid molecule and on its mode of attachment. In this respect we would like to draw attention to compound **42** in which the steroid is connected to the platinum nucleus through an organic spacer. The 4-hydroxybenzamide moiety which is inserted between the platinum unit and the biological carrier might appear necessary in some endocrine–tumor systems in order to reduce the interference of the cytotoxic moiety in a hormone–receptor interaction.

In summary, the synthetic approach outlined in this work provides the lines and the methodology for the preparation of a great number of steroid molecules or of other biological carriers (not necessarily of steroids) bound chemically to potent antitumor platinum–malonate complexes.

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