Pharmacology on Rat Ileum of Certain 2-Substituted 3-(Dimethylamino)-5,6-dimethoxyindenes Related to 5,6-(Methylenedioxy)indene Calcium Antagonists[1]

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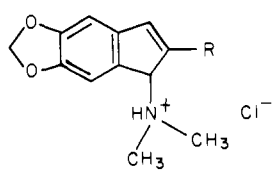
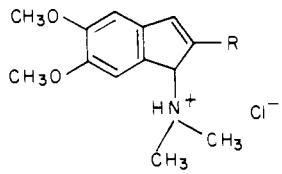
Whereas the 2-propyl- and 2-butyl-5,6-(methylenedioxy)indene calcium antagonists reversed the spasmogenic action of several agonists including $PGF_{2\alpha}$ and acetylcholine at 5×10^{-5} to 10^{-4} M on the rat ileum, the corresponding 5,6-dimethoxy analogues exhibited spasmogenic activity at higher concentration (10^{-4}–10^{-3} M) and exhibited neither spasmogenic nor spasmolytic activity at lower (10^{-6}–10^{-5} M) concentration. The results are compared to the methyl and 2-ethyl analogues. At 10^{-4} M only the butyl analogue was capable of moderate antagonism of acetylcholine and at 10^{-3} M all four analogues were capable of moderately antagonizing the actions of acetylcholine.

The synthesis[2] and pharmacological properties, on nonvascular smooth muscle,[3] coronary smooth muscle,[4] cardiac muscle,[4] and adrenomedullary hormone secretion,[5] of a new series of intracellular calcium antagonists, the 2-substituted 3-(dimethylamino)-5,6-(methylenedioxy)-indene hydrochlorides **1**–**4**, were recently reported from



1, R = Me
2, R = Et
3, R = *n*-Pr
4, R = *n*-Bu

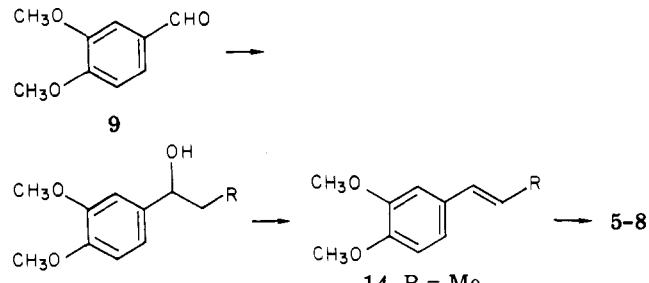


5, R = Me
6, R = Et
7, R = *n*-Pr
8, R = *n*-Bu

our laboratories. Compounds **1** and **2** had weaker spasmolytic activity than compounds **3** and **4** and were not extensively studied.[3] Compounds **3** and **4** (5×10^{-5} to 10^{-4} M) reversibly blocked the calcium-dependent spasmogenic action of prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), oxytocin, barium, acetylcholine, and ergonovine on the isolated rat uterus as well as the spasmogenic action of acetylcholine and histamine on the isolated rat and guinea pig ileum.[3] Furthermore, compounds **3** and **4** (5×10^{-6} to 10^{-4} M) reversed the potassium-induced calcium-dependent contraction of the isolated bovine coronary vessel, produced coronary dilation and negative inotropic actions (at 3×10^{-5} to 10^{-4} M) in the isolated rabbit heart,[4,6] and blocked (at 10^{-8}–10^{-4} M) the calcium-dependent[7] carbachol-induced catecholamine secretion from the isolated bovine adrenal medulla without inhibiting calcium influx into the adrenomedullary cells.[5] However, the calcium-independent[8] catecholamine secretion evoked by acetaldehyde could not be blocked by compounds **3** or **4**.[5] In none of the above experiments did compounds **1**–**4** exhibit agonist activity. Compound **3** was tested in vivo and found to reverse ouabain-induced cardiac arrhythmias in the dog at doses of 13 and 26 mg/kg of body weight.[4] It was concluded on the basis of these findings[3-6] that compounds **3** and **4** were antagonizing the action of calcium at an intracellular site.

In the present investigation, compounds **5**–**8** were tested on the isolated rat ileum to determine if structural modification involving conversion of the 5,6-methylenedioxy bridge to the 5,6-dimethoxy derivatives would alter pharmacological activity.

Analogues **5**–**8** were synthesized from 3,4-dimethoxybenzaldehyde (**9**) via the respective alcohols (**10**–**13**) and olefins (**14**–**17**) through the use of the Vilsmeier–Haack cyclization reaction developed previously[2] for the preparation of 5,6-(methylenedioxy)indenes **1**–**4**. Except for **5**, which was prepared from **14** in 45% yield, cyclizations generally afforded aminoindenes in 60–65% isolated yield.



9

10, R = Me
11, R = Et
12, R = *n*-Pr
13, R = *n*-Bu

14, R = Me
15, R = Et
16, R = *n*-Pr
17, R = *n*-Bu

Results and Discussion

The biological activity of compounds **5**–**8** is summarized in Tables I and II. It is clear that at concentrations of 10^{-6} and 10^{-5} M none of these compounds exhibited either spasmogenic or spasmolytic activity against $PGF_{2\alpha}$ or AcCh. At higher concentrations of 10^{-4} and 10^{-3} M, compounds **5**–**8** exhibited spasmogenic activity when incubated in contact with the ileum (bracketed data in Tables I and II). At 10^{-4} M, only the butyl derivative **8** was capable of a moderate antagonism of the spasmogenic action of $PGF_{2\alpha}$ and AcCh. At the very high concentration of 10^{-3} M, all of the dimethoxyindenes were capable of moderately antagonizing the spasmogenic action of AcCh, and all but the methyl derivative (**5**) were capable of moderately antagonizing the spasmogenic action of $PGF_{2\alpha}$.

These results indicate that structural modification of the methylenedioxy compounds (**1**–**4**) to the dimethoxy derivatives (**5**–**8**) results not only in a significant reduction of the antispasmodic activity of the series but also in the appearance of spasmogenic action at the higher concentrations. We have previously observed[6] that the 2-*n*-propyl-3-(dimethylamino)-5,6-(methylenedioxy)indene (**3**) produced a weak positive inotropic action (36% increase in force of contraction) on the isolated perfused rabbit heart at the concentration of 10^{-6} M, which is lower than the concentration necessary for calcium antagonism in any system we tested. However, the potent calcium antagonistic properties of this compound as well as its 2-*n*-butyl analogue (**4**) exhibited at concentrations of 10^{-5} M or greater clearly obliterated any weak agonist activity they possess. On the other hand, with respect to the 2-substituted 5,6-dimethoxy compounds (**5**–**8**), the substantial agonist activity appears to significantly modify the antagonist properties of this series. We do not have an explanation for the rather marked differences in agonist

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Table I. Effect of 2-Substituted 3-(Dimethylamino)-5,6-dimethoxyindenes on Contractility of Rat Ileum and on Spasmogenic Action of $PGF_{2\alpha}$

conen of compd 5-8, M	contractions to 3×10^{-7} M $PGF_{2\alpha}$ as % of control response to $PGF_{2\alpha}$[a-c]			
	methyl (5)	ethyl (6)	propyl (7)	butyl (8)
10^{-6}	111.2 ± 4.3	98.7 ± 4.5	103.5 ± 6.6	101.3 ± 5.7
10^{-5}	107.6 ± 2.1	108.3 ± 4.2	99.3 ± 8.0	91.1 ± 4.0
10^{-4}	113.2 ± 13.2	109.7 ± 3.1	99.7 ± 6.4	60.5 ± 4.8
	[59.8 ± 12.0]	[74.7 ± 11.4]	[80.7 ± 6.2]	[37.1 ± 2.7]
10^{-3}	124.1 ± 18.5	62.0 ± 2.6	49.1 ± 6.0	65.2 ± 5.7
	[118.9 ± 14.5]	[77.3 ± 1.6]	[61.7 ± 1.3]	[58.1 ± 5.1]

[a] Values represent mean ± SEM of four experiments. [b] Bracketed values represent agonist activity of compounds 5-8 (observed during the 3-min incubation with the tissue prior to addition of the test dose of $PGF_{2\alpha}$) and are expressed as a percent of the control $PGF_{2\alpha}$ response. [c] The control response to $PGF_{2\alpha}$ represented 76 ± 4% of the maximal response attainable with this spasmogen.

Table II. Effect of 2-Substituted 3-(Dimethylamino)-5,6-dimethoxyindenes on Contractility of Rat Ileum and on Spasmogenic Action of AcCh

conen of compd 5-8, M	contractions to 10^{-6} M AcCh as % of control response to AcCh[a-c]			
	methyl (5)	ethyl (6)	propyl (7)	butyl (8)
10^{-6}	113.1 ± 10.9	104.6 ± 3.0	104.2 ± 1.0	104.2 ± 1.5
10^{-5}	112.8 ± 3.6	105.3 ± 3.3	110.5 ± 2.8	108.3 ± 4.9
10^{-4}	94.4 ± 3.0	91.5 ± 2.1	96.6 ± 4.9	78.6 ± 9.5
	[20.6 ± 2.6]	[28.9 ± 2.8]	[42.7 ± 2.4]	[25.3 ± 4.1]
10^{-3}	64.0 ± 3.0	513 ± 1.3	56.7 ± 5.2	64.3 ± 2.5
	[49.5 ± 2.9]	[45.3 ± 1.7]	[43.6 ± 1.5]	[46.7 ± 5.6]

[a] Values represent mean ± SEM of four experiments. [b] Bracketed values represent agonist activity of compounds 5-8 (observed during the 3-min incubation with the tissue prior to addition of the test dose of AcCh) and are expressed as a percent of the control AcCh response. [c] The control response to AcCh represented 80 ± 5% of the maximal response attainable with this spasmogen.

vs. antagonist activity between the methylenedioxy and dimethoxy analogues.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries on a Thomas-Hoover apparatus and are uncorrected. Spectra were recorded using a Beckman Model 4230 spectrophotometer and Varian A-60 or Bruker HX-90E spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Analyses were within ±0.4% of calculated values.

1-(3,4-Dimethoxyphenyl)-1-propanol (10). To a cold solution (−78 °C) containing 1.66 g (0.24 mol) of Li wire (1% Na dispersion) and 250 mL of Et_2O was added dropwise 16.24 g (0.14 mol) of bromoethane. The reaction was stirred under N_2 at −78 °C for 3 h. Following addition of 16.6 g (0.1 mol) of 3,4-dimethoxybenzaldehyde (9) in 100 mL of Et_2O, the reaction was stirred overnight while warming to room temperature. The mixture was cooled to 0 °C and saturated NH_4Cl solution (100 mL) was added. The aqueous layer was washed with Et_2O and the combined Et_2O solutions were washed with H_2O followed by saturated NH_4Cl solution, dried (Na_2SO_4), and concentrated under reduced pressure. The resultant, light yellow oil was distilled, affording 10.5 g (53.5%) of a clear oil: bp 70–72 °C (0.03 mm); IR (neat) 3530–3460 cm^{-1} (OH); NMR δ ($CDCl_3$) 0.90 (t, 3, CH_2CH_3, J = 7.0 Hz), 1.5–1.9 (m, 2, CH_2CH_3), 1.99 (s, 1, OH), 3.87 (s, 6, $2CH_3O$), 4.4–4.7 (m, 1, benzyl), 6.7–7.0 (m, 3, aromatic). Anal. ($C_{11}H_{16}O_3$) C, H.

1-(3,4-Dimethoxyphenyl)-1-butanol (11). Under conditions similar to the preparation of 10 and using 1.66 g (0.24 mol) of Li wire, 125 mL of Et_2O, 18.2 g (0.14 mol) of bromopropane, and 16.6 g (0.1 mol) of 9 in 100 mL of Et_2O was obtained 16.1 g (76.6%) of a clear oil, 11: bp 76–78 °C (0.05 mm); IR (neat) 3540–3490 cm^{-1} (OH); NMR δ ($CDCl_3$) 0.8–1.9 (m, 5, CH_2CH_3), 2.01 (s, 6, $2CH_3O$), 4.5–4.7 (m, 1, benzyl), 6.8–7.1 (m, 3, aromatic). Anal. ($C_{12}H_{18}O_3$) C, H.

1-(3,4-Dimethoxyphenyl)-1-pentanol (12). To a cold solution (−78 °C) containing 16.6 g (0.1 mol) of 9 in 200 mL of anhydrous Et_2O was added dropwise 50 mL (0.12 mol) of BuLi (2.3 M in hexane). The reaction was stirred under N_2 and allowed to continue overnight while warming to room temperature. The mixture was cooled to 0 °C and saturated NH_4Cl solution (100 mL) was added. The aqueous layer was washed twice with Et_2O and the combined Et_2O solutions were washed with H_2O followed by saturated NH_4Cl solution, dried (Na_2SO_4), and concentrated under reduced pressure. The resultant, light yellow oil was distilled, affording 16.6 g (74.1%) of a clear oil: bp 66–68 °C (0.03 mm); IR (neat) 3440–3380 cm^{-1} (OH); NMR δ ($CDCl_3$) 0.8–2.0 [m, 9, $(CH_2)_3CH_3$], 1.87 (s, 1, OH), 3.93 (s, 6, CH_3O), 4.5–4.8 (m, 1, benzyl), 6.8–7.1 (m, 3, aromatic). Anal. ($C_{13}H_{20}O_3$) C, H.

1-(3,4-Dimethoxyphenyl)-1-hexanol (13). Under conditions similar to the preparation of 10 and using 1.66 g (0.24 mol) of Li wire, 125 mL of Et_2O, 21.5 g (0.14 mol) of bromopentane, and 16.6 g (0.1 mol) of 9 in 100 mL of Et_2O was obtained 17.2 g (72.2%) of a clear oil, 13: bp 98–100 °C (0.06 mm); IR (neat) 3520–3380 cm^{-1} (OH); NMR δ ($CDCl_3$) 0.6–1.9 [m, 11, $(CH_2)_4CH_3$], 3.08 (s, 1, OH), 3.79 (s, 3, CH_3O), 4.3–4.7 (m, 1, benzyl), 6.6–6.9 (m, 3, aromatic). Anal. ($C_{14}H_{22}O_3$) C, H.

1-(3,4-Dimethoxyphenyl)-1-propene (14). A solution of 10 g (0.051 mol) of 10 in 250 mL of benzene containing 0.25 g (0.001 mol) of p-toluenesulfonic acid was allowed to reflux until H_2O no longer could be collected in a Dean-Stark trap. Upon cooling, the reaction mixture was washed with saturated $NaHCO_3$ solution and H_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The resultant yellow oil was distilled (Vigreux column), yielding 8.7 g (95.8%) of a colorless liquid: bp 78–82 °C (0.03 mm); NMR δ ($CDCl_3$) 3.79 (s, 3, CH_3O), 3.82 (s, 3, CH_3O), 6.6–7.0 (m, 3, aromatic), with calculated ABX_3 for CH=$CHCH_3$ exhibiting δ_A 6.36, δ_B 5.95, δ_X 1.83 (d) with J_{AB} = 15.5 Hz, J_{AX} = 0.0 Hz, J_{BX} = 5.0 Hz. Anal. ($C_{11}H_{14}O_2$) C, H.

1-(3,4-Dimethoxyphenyl)-1-butene (15) was prepared according to the procedure for 14 from 14 g (0.066 mol) of 11, affording 11.7 g (92.3%) of a colorless liquid: bp 86–90 °C (0.07 mm); NMR δ ($CDCl_3$) 1.07 (t, 3, CH_2CH_3), 3.81 (s, 3, CH_3O), 3.84 (s, 3, CH_3O), 6.6–7.0 (m, 3, aromatic), with calculated ABX_2 for $CH{=}CHCH_2$ exhibiting δ_A 6.37, δ_B 5.96, δ_X 1.9–2.5 (m) with J_{AB} = 15.5 Hz, J_{AX} = 0.0 Hz, J_{BX} = 5.0 Hz. Anal. ($C_{12}H_{16}O_2$) C, H.

1-(3,4-Dimethoxyphenyl)-1-pentene (16) was prepared according to the procedure for 14 from 15 g (0.067 mol) of 12 affording 12.7 g (92%) of a colorless liquid: bp 101–105 °C (0.03 mm); NMR ($CDCl_3$) δ 0.96 (t, 3, CH_2CH_3, J = 6.5 Hz), 1.51 (d of t, 2, $CH_2CH_2CH_3$, J = 7.0 and 14 Hz), 3.87 (s, 3, CH_3O), 3.90 (s, 3, CH_3O), 6.8–7.0 (m, 3, aromatic), with calculated ABX_2 for $CH{=}CHCH_2$ exhibiting δ_A 6.47, δ_B 6.06, δ_X 2.19 (d of t; deceptively simple q) with J_{AB} = 16.0 Hz, J_{AX} = 0.0 Hz, J_{BX} = 6.0 Hz. Anal. ($C_{13}H_{18}O_2$) C, H.

1-(3,4-Dimethoxyphenyl)-1-hexene (17) was prepared ac-

cording to the procedure for **14** from 16 g (0.067 mol) of **13**, affording 13.8 g (93.6%) of a colorless liquid: bp 110–115 °C (0.03 mm); NMR ($CDCl_3$) δ 0.7–1.7 [m, 7, $(CH_2)_2CH_3$], 3.84 (s, 3, CH_3O), 3.87 (s, 3, CH_3O), 6.7–7.0 (m, 3, aromatic), with calculated ABX_2 for $CH{=}CHCH_2$ exhibiting δ_A 6.37, δ_B 6.02, δ_X 2.19 (d of t; deceptively simple q) with J_{AB} = 16.0 Hz, J_{AX} = 0.0 Hz, J_{BX} = 6.0 Hz. Anal. ($C_{14}H_{20}O_2$) C, H.

2-Methyl-3-(dimethylamino)-5,6-dimethoxy-1-indene hydrochloride (5) was prepared according to the method of Witiak et al.[2] for the preparation of methylenedioxy analogues **1–4** from 1-(3,4-dimethoxyphenyl)-1-propene (**14**; 9.0 g, 0.05 mol). The resulting dark mixture was not distilled[2] but dissolved in anhydrous Et_2O and acidified with gaseous HCl. The solid was filtered and recrystallized (Et_2O–EtOH), affording 6.2 g (45.1%) of white crystals: mp 156–157 °C; NMR δ ($CDCl_3$) 2.31 (s, 3, CH_3), 2.71 (d, 3, NCH_3, J = 5 Hz), 2.88 (d, 3, NCH_3, J = 5 Hz), 3.73 (s, 3, CH_3O), 3.76 (s, 3, CH_3O), 4.63 (s, 1, H_3), 6.61 (s, 1, H_1), 6.79 (s, 1, H_7), 7.82 (s, 1, H_4). Anal. ($C_{14}H_{20}O_2NCl{\cdot}0.5H_2O$) C, H, N.

2-Ethyl-3-(dimethylamino)-5,6-dimethoxy-1-indene hydrochloride (6) was prepared according to the procedure for **5** from **15** (10.0 g, 0.052 mol), affording 13.2 g (62.3%) of white crystals: mp 161–162 °C; NMR δ ($CDCl_3$) 1.28 (t, 3, CH_3, J = 7 Hz), 2.4–2.8 (m, 2, CH_2CH_3), 2.65 [s, 6, $(CH_3)_2N$], 3.90 (s, 3, CH_3O), 3.93 (s, 3, CH_3O), 4.71 (s, 1, H_3), 6.62 (s, 1, H_1), 6.81 (s, 1, H_7), 7.73 (s, 1, H_4). Anal. ($C_{15}H_{22}O_2NCl{\cdot}H_2O$) C, H, N.

2-Propyl-3-(dimethylamino)-5,6-dimethoxy-1-indene hydrochloride (7) was prepared according to the procedure for **5** from **16** (14.0 g, 0.068 mol), affording 13.4 g (66.2%) of white crystals: mp 153–154.5 °C; NMR δ ($CDCl_3$) 1.03 (t, 3, CH_2CH_3, J = 6.5 Hz), 1.4–2.0 (m, 2, $CH_2CH_2CH_3$), 2.4–3.0 [m, 8, $(CH_3)_2N$, $CH_2CH_2CH_3$], 3.91 (s, 3, CH_3O), 3.98 (s, 3, CH_3O), 4.65 (s, 1, H_3), 6.66 (s, 1, H_1), 6.83 (s, 1, H_7), 7.84 (s, 1, H_4). Anal. ($C_{16}H_{24}O_2NCl$) C, H, N, Cl.

2-Butyl-3-(dimethylamino)-5,6-dimethoxy-1-indene hydrochloride (8) was prepared according to the procedure for **5** from **17** (15.0 g, 0.068 mol), affording 13.2 g (62.3%) of white crystals: mp 157–158 °C; NMR δ ($CDCl_3$) 0.96 (t, 3, CH_2CH_3, J = 6.5 Hz), 1.2–1.9 [m, 4, $(CH_2)_2CH_3$], 2.4–2.9 [m, 8, $(CH_3)_2N$, $CH_2(CH_2)_3CH_3$], 3.90 (s, 3, CH_3O), 3.93 (s, 3, CH_3O), 4.62 (s, 1, H_3), 6.62 (s, 1, H_1), 6.80 (s, 1, H_7), 7.82 (s, 1, H_4). Anal. ($C_{17}H_{26}O_2NCl$) C, H, N, Cl.

Pharmacology. Methods employed were similar to those described previously by Rahwan et al.[3] Briefly, female albino rats (200–250 g) were sacrificed by cervical dislocation and sections of the ileum were prepared for isotonic contraction recordings under 500 mg of tension in 10-mL tissue baths containing a bathing solution (37 °C) having the following composition (g/L): NaCl (8.086); KCl (0.20); $CaCl_2{\cdot}2H_2O$ (0.52); $MgCl_2{\cdot}2H_2O$ (0.42); $NaH_2PO_4{\cdot}H_2O$ (0.10); $NaHCO_3$ (1.0); dextrose (1.0). Recordings were made with an isotonic MK II myograph transducer and a Physiograph 4 recorder (E & M Instrument Co., Houston, TX). The bathing solution was aerated with 5% CO_2 in O_2. A 30-min equilibration time was allowed prior to all experiments.

In each experiment a control response to $PGF_{2\alpha}$ (3×10^{-7} M bath concentration) or acetylcholine (AcCh; 10^{-6} M bath concentration) was obtained, and the bath was then washed three times prior to incubation of the tissue with any of the test compounds, **5–8**. The test compound was added to the bath and left in contact with the ileum for 3 min. $PGF_{2\alpha}$ (3×10^{-7} M) or AcCh (10^{-6} M) was then added to the bath and the contractions were recorded. After 5 min the bath was washed three times and the control response to $PGF_{2\alpha}$ or AcCh regained. All values were calculated as percent of the control responses to $PGF_{2\alpha}$ or AcCh. A separate ileum strip was used for each compound and each concentration. The tissues did not demonstrate any potentiation or tachyphylaxis upon repeated exposure to $PGF_{2\alpha}$ or AcCh alone.

References and Notes

(1) Support of this work by U.S. Public Health Service Grant HL-21670 from the National Heart, Lung and Blood Institute is gratefully acknowledged.
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Antitumor Activity of 1,2-Diaminocyclohexane–Platinum Complexes against Sarcoma-180 Ascites Form

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Platinum complexes derived from three isomers of 1,2-diaminocyclohexane have been synthesized and their antitumor activities were evaluated against ascites Sarcoma-180. All the platinum complexes had high antitumor activity. Platinum complexes derived from *cis*-1,2-diaminocyclohexane were more effective than those derived from *trans-l*- and *trans-d*-1,2-diaminocyclohexane. Among the platinum complexes tested, oxalato(*cis*-1,2-diaminocyclohexane)platinum had a remarkably high therapeutic index. Modification of the nonleaving group as well as that of the leaving group is important in order to find better antitumor platinum complexes.

Since the discovery of antitumor activity of (*cis*-dichlorodiammine)platinum,[1] a great number of new platinum complexes were synthesized and tested. Among them, (dichloro-1,2-diaminocyclohexane)platinum, which was synthesized and tested by Connors et al.,[2] Cleare and Hoeschele,[3] Gale et al.,[4] and Speer et al.,[5] had a high antitumor activity against various tumor systems. Unfortunately, its therapeutic index was disappointingly low. Modification of the leaving group was attempted to find better complexes having higher values of therapeutic indices, and malonato- and sulfato(1,2-diaminocyclohexane)platinum[6-9] were consequently prepared. Both the

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