(12) UK Patent Application (19) GB (11) 2 134 103 A

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(21) Application No **8301602**
(22) Date of filing **21 Jan 1983**
(43) Application published
8 Aug 1984
(51) **INT CL³**
C07D 213/38 A61K 31/44
C07C 55/00 59/00
(52) Domestic classification
C2C 1530 20Y 215 246 247 250 251 25Y 292 29Y 308 30Y 321 322 32Y 351 355 360 361 366 367 36Y 37X 387 456 45Y 566 620 623 625 628 638 650 655 65Y 777 802 80Y AA CT CZ NL UV
U1S 1313 C2C
(56) Documents cited
None
(58) Field of search
C2C

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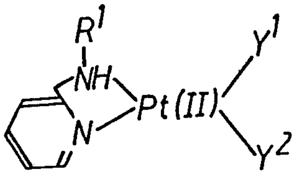
(54) Novel organic platinum complex and process for the preparation thereof

(57) A novel organic platinum complex of the formula:



[I]

wherein R^1 is hydrogen or methyl, Y^1 and Y^2 are the same or different and each is halogen, NO_3 or R^2—COO—, or y^1 and y^2 combine to form SO_4, PO_3OH or

$$—O—CO—(CHOH)_m—(CH_2)_n—CO—O—,$$

R^2 is a hydroxy-substituted lower alkyl or acetyl, and m and n are each 0, 1 or 2 with the proviso of $0 \leqq m+n \leqq 2$, and a process for the preparation thereof. The compound [I] has an excellent anti-tumor activity and is useful as an anti-tumor agent.

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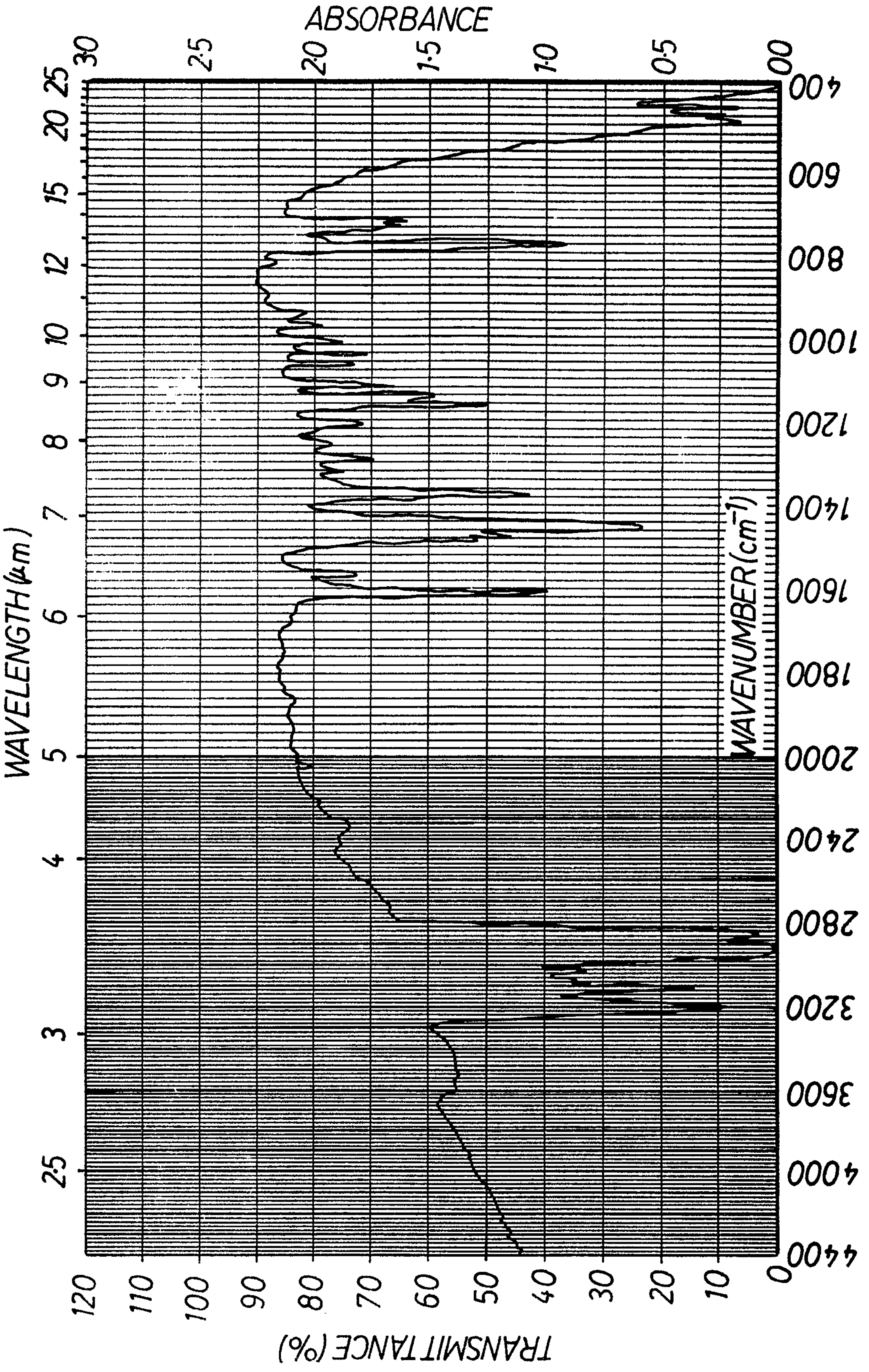
The chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

The drawings originally filed were informal and the print here reproduced is taken from a later filed formal copy.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2·0
1·5
1·0
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WAVELENGTH (μm)
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9
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WAVENUMBER (cm⁻¹)
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1600
1800
2000
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TRANSMITTANCE (%)
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Fig 1.

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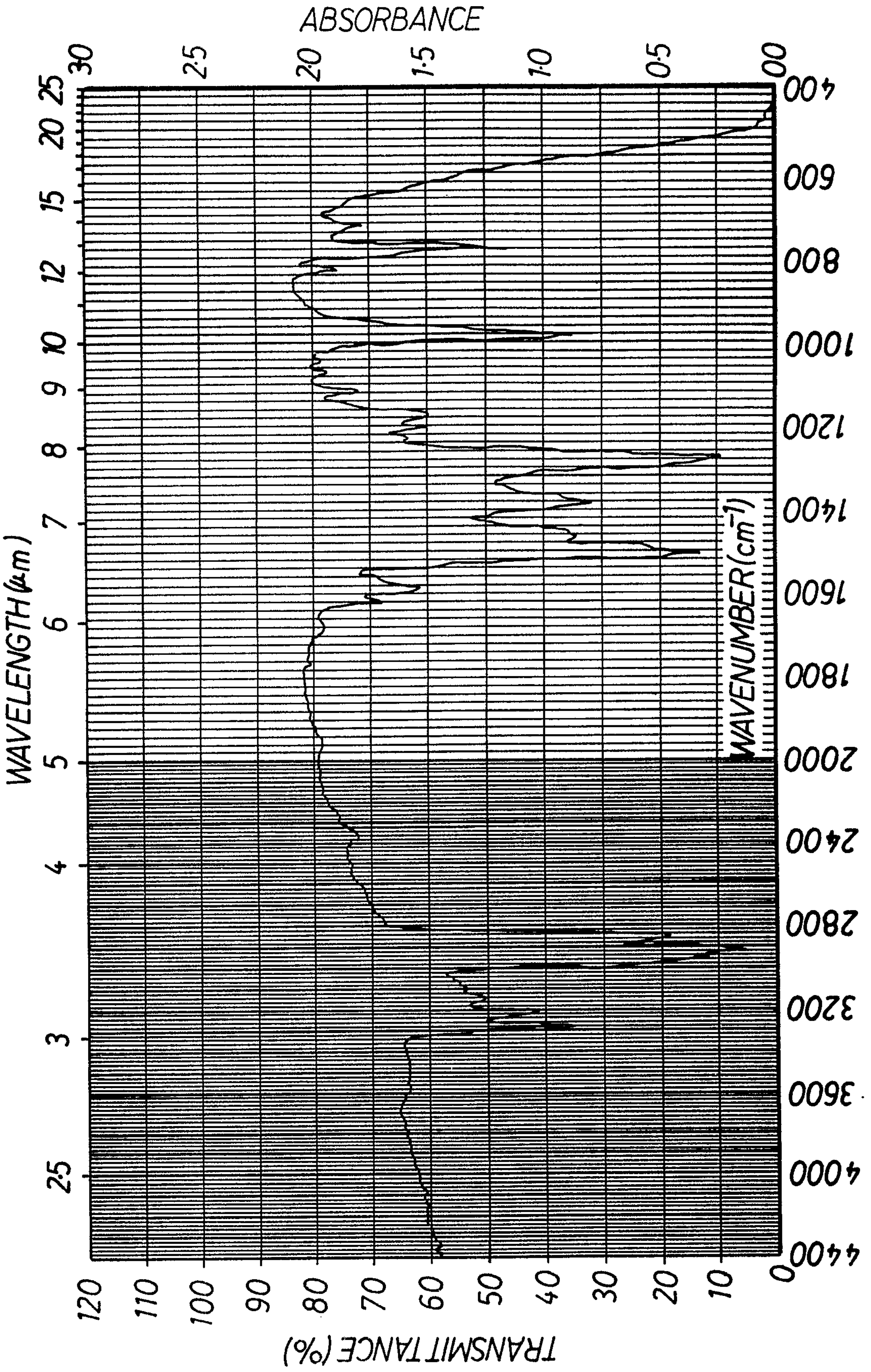

Fig 2.

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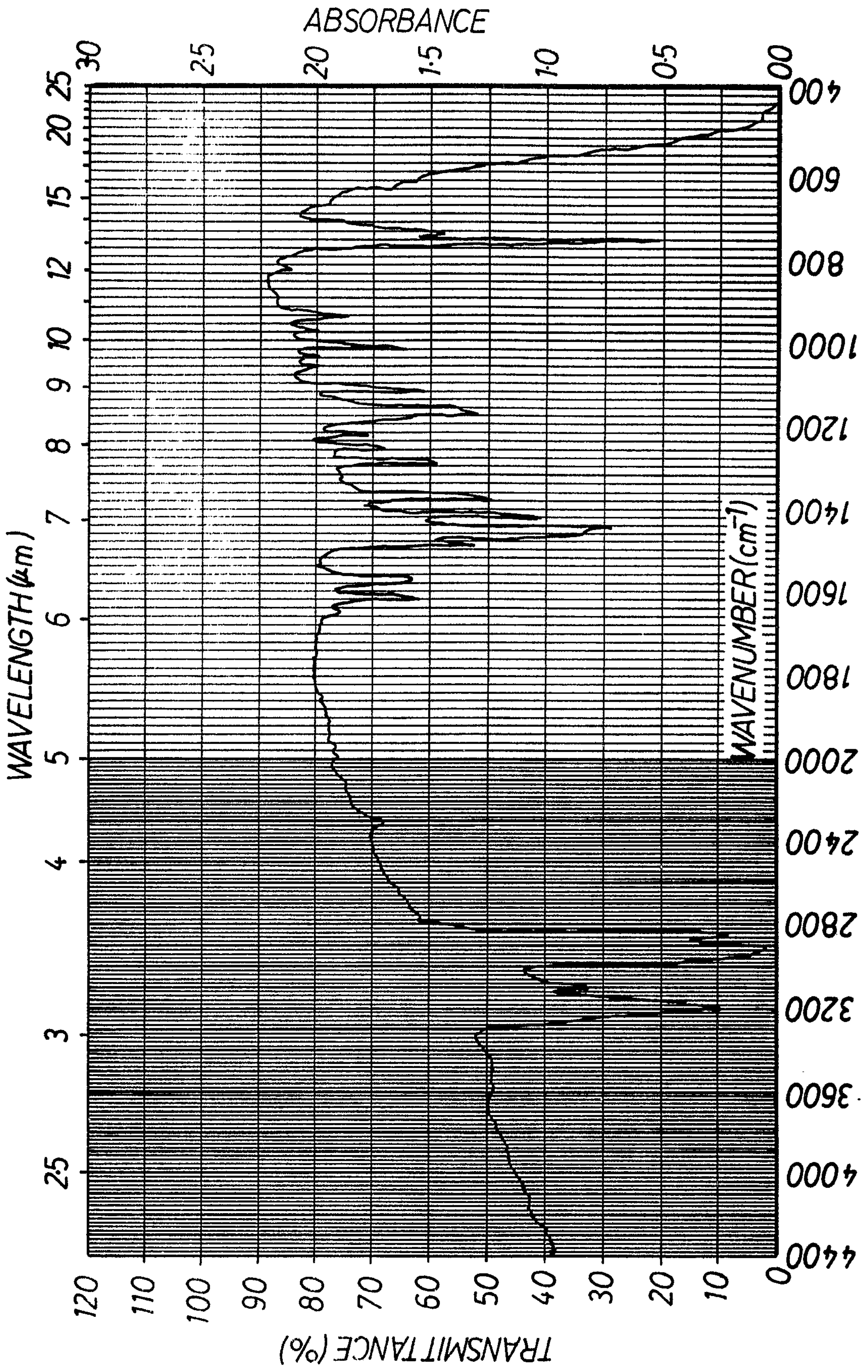
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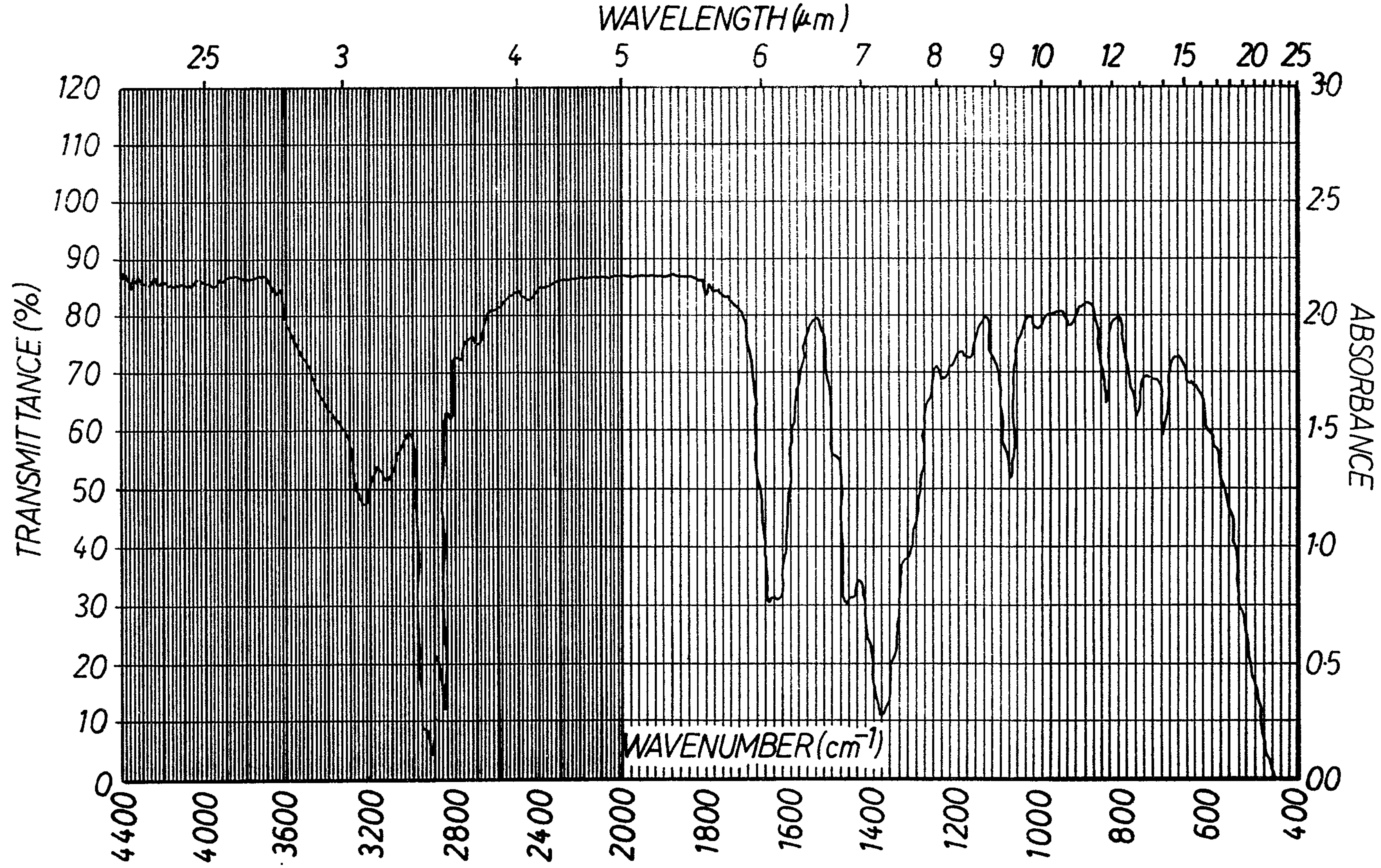
Fig 3.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TRANSMITTANCE (%)
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40
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ABSORBANCE
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2·0
1·5
1·0
0·5
0·0
WAVENUMBER (cm⁻¹)
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4000
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600
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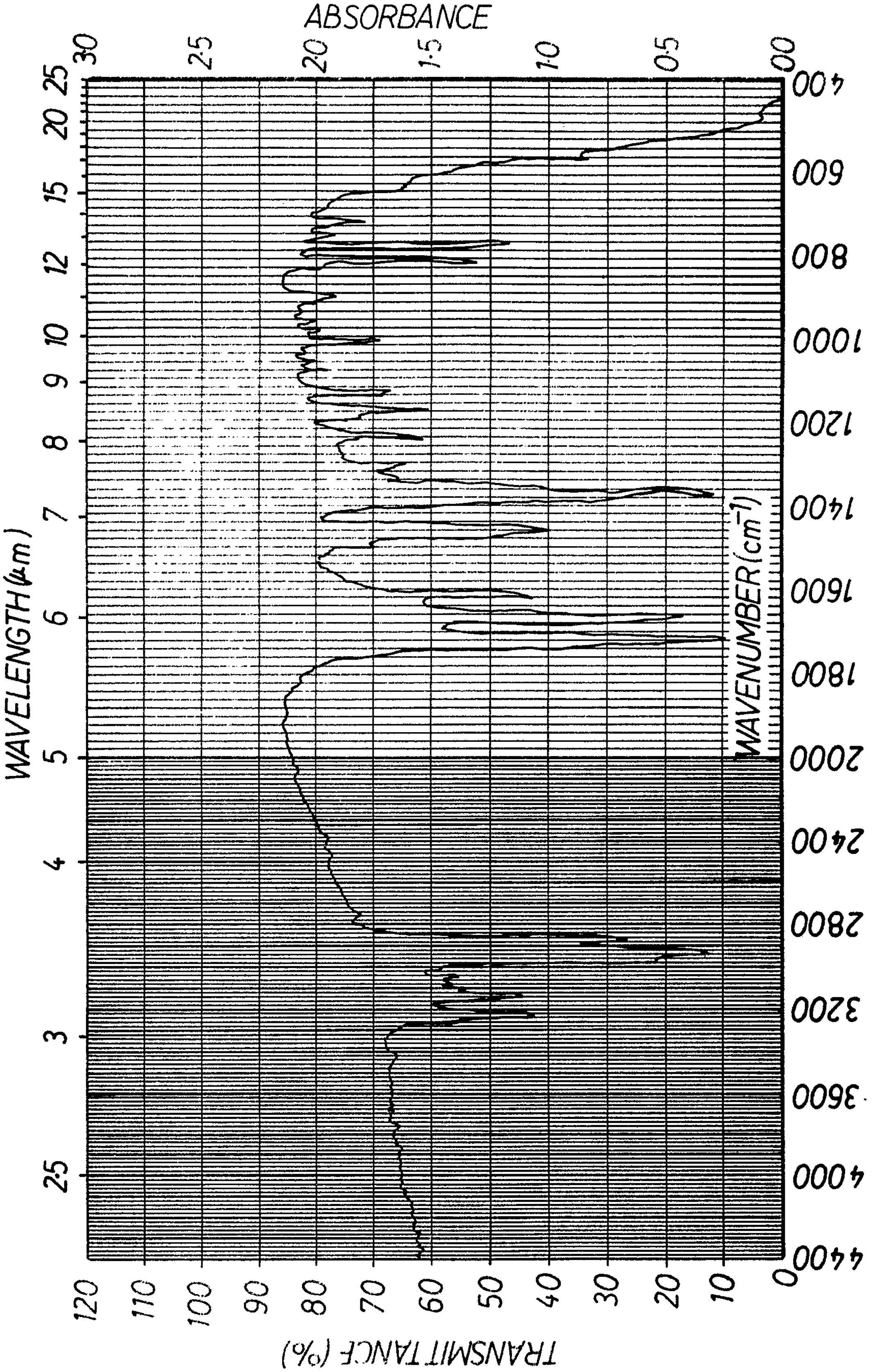
Fig 4.


ABSORBANCE
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2·0
1·5
1·0
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WAVELENGTH (μm)
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WAVENUMBER (cm⁻¹)
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2400
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3200
3600
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4400
TRANSMITTANCE (%)
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Fig 5

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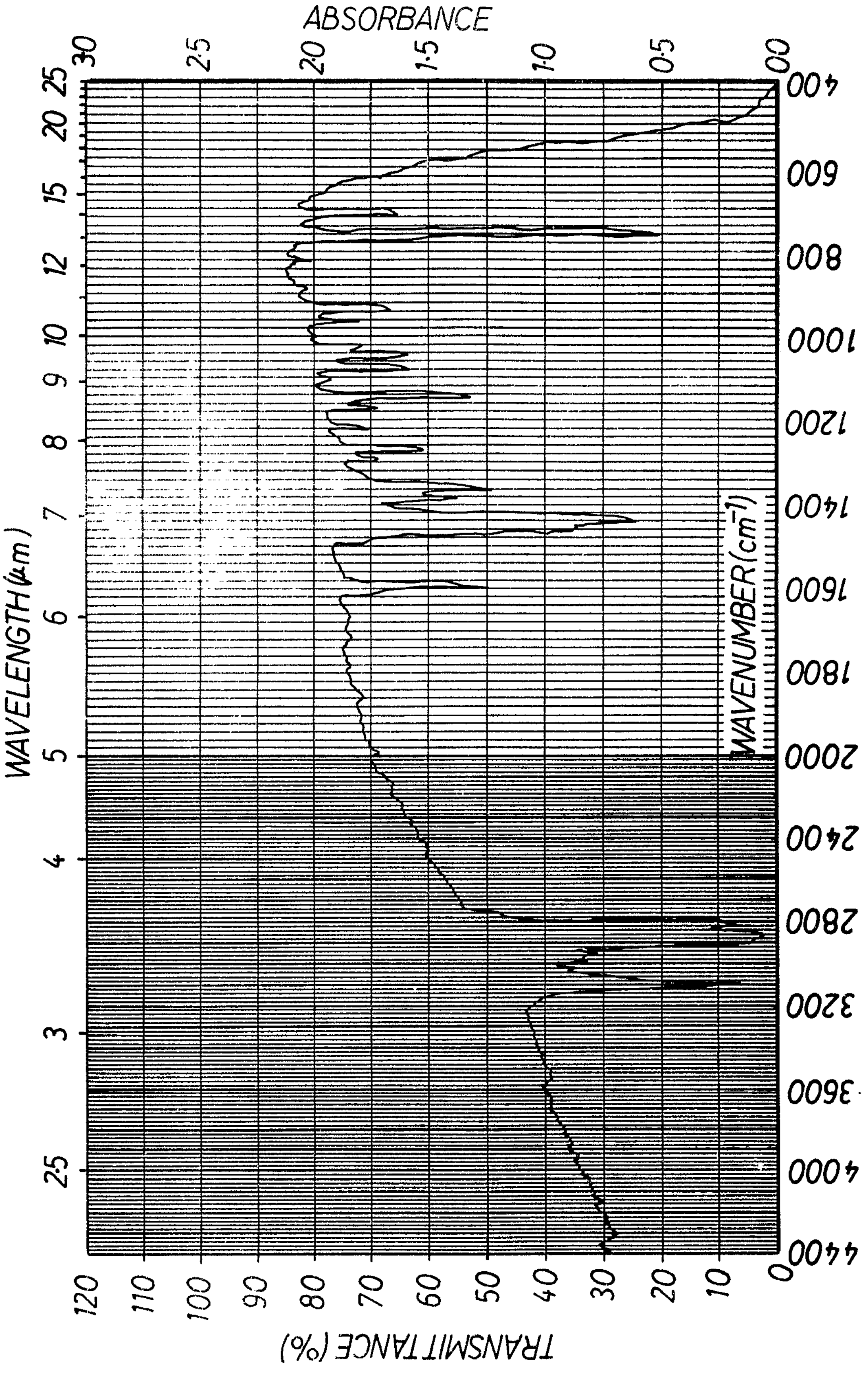
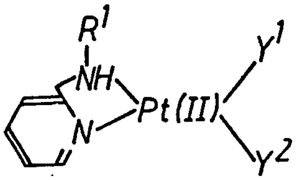


Fig 6.

SPECIFICATION

Novel organic platinum complex and process for the preparation thereof

The present invention relates to a novel organic platinum complex and a process for the preparation thereof. More particularly, it relates to a novel organic platinum complex of the formula:



[I]

wherein R^1 is a hydrogen atom or methyl group, Y^1 and Y^2 are the same or different and each is a halogen atom, NO_3 or a group of the formula: R^2—COO—, or Y^1 and Y^2 combine to form a group of the formula: $\supset SO_4$, $\supset PO_3OH$ or

$$-O-CO-(CHOH)_m-(CH_2)_n-CO-O-,$$

R^2 is a hydroxy-substituted lower alkyl or acetyl group, and m and n are each integers of 0, 1 or 2 with the proviso of $0 \leq m+n \leq 2$, and a process for the preparation of the organic platinum complex.

The organic platinum complex [I] of the present invention has an excellent anti-tumor activity and is useful as an anti-tumor agent.

There have hitherto been prepared many organic platinum complexes wherein various diamines are used as a ligand, and the anti-tumor activity of these compounds has also been studied (cf. Rosenberg et al, Nature, *222*, 385 (1969), etc.). However, these known compounds have toxicity to kidney and the organ of hearing [cf. A. W. Prestayko, Cancer and Chemotherapy, *3*, 133 (1981)].

As a result of extensive study by the present inventors, it has been found that a certain organic platinum complex containing 2-aminomethylpyridine or its derivative as a ligand has excellent anti-tumor activity without increasing the toxicity.

The organic platinum complex of the present invention is a compound of the formula [I] wherein, for example, R^1 is a hydrogen atom or methyl group, Y^1 and Y^2 are the same or different and each is a halogen atom such as for example chlorine, bromine or iodine, NO_3, or a group of the formula:

$HOCH_2COO-$,
$CH_3CH(OH)COO-$,
$HOCH_2CH(OH)COO-$,
$HOCH_2CH_2COO-$,
$(CH_3)_2CHCH(OH)COO-$

or

$CH_3COCOO-$,

or Y^1 and Y^2 combine to form a group of the formula:

$\supset SO_4$,
$\supset PO_3OH$,
$-O-CO-CO-O-$,
$-CO-CH_2CH_2-CO-O-$

or

$-O-CO-CH(OH)CH(OH)-CO-O-$.

Preferred compounds are a compound of the formula [I] wherein R^1 is a hydrogen atom or methyl group, Y^1 and Y^2 are the same or different and each is a chlorine atom, NO_3 or a group of the formula: $HOCH_2COO-$, or Y^1 and Y^2 combine to form a group of the formula: $\supset SO_4$,

$-O-CO-CO-O-$

or

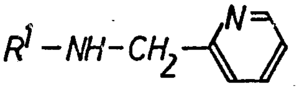
$-O-CO-CH_2-CO-O-$.

In the present specification, the term "a lower alkyl group" denotes an alkyl group having 1 to 4 carbon atoms.

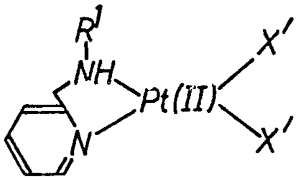
The organic platinum complex [I] of the present invention can be prepared for example by the following processes.

[Process A]:

A compound of the formula: $K_2Pt(II)X'_4$ or $Na_2Pt(II)X'_4$ (wherein X′ is a halogen atom) is reacted with a compound of the formula:


[II]

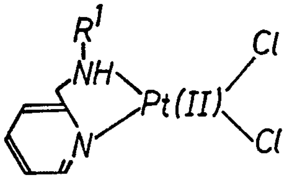
wherein R^1 is as defined above to give an organic platinum complex of the formula:


[I-a]

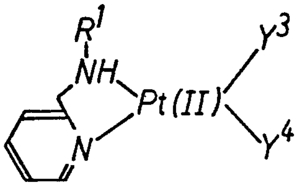
wherein R^1 and X′ are as defined above.

[Process B]:

A compound of the formula:


[III]

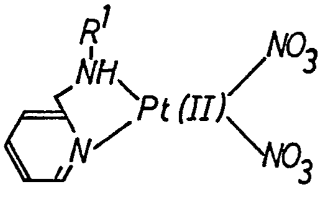
wherein R^1 is as defined above is reacted with silver sulfate or silver nitrate to give an organic platinum complex of the formula:


[I-b]

wherein Y^3 and Y^4 are the same each is NO_3, or Y^3 and Y^4 combine to form a group of the formula: ⊂ SO_4, and R^1 is as defined above.

[Process C]:

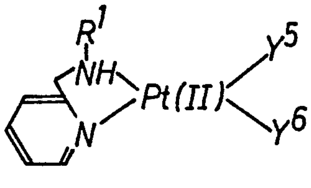
A compound of the formula:


[IV]

wherein R^1 is as defined above is reacted with an alkali metal bromide, an alkali metal iodide, di(alkali metal) phosphate, or a compound of the formula: R^2—COOM′ (wherein R^2 is as defined above and M′ is an alkali metal) or

$$M'—O—CO—(CHOH)_m—(CH_2)_n—CO—O—M'$$

(wherein m, n and M′ are as defined above) to give an organic platinum complex of the formula:


[I-c]

wherein Y^5 and Y^6 are the same or different and each is bromine, iodine, NO_3, or a group of the formula: R^2—COO— (R^2 is as defined above), or Y^5 and Y^6 combine to form a group of the formula $\subset PO_3OH$ or

$$—O—CO—(CHOH)_m(CH_2)_n—CO—O—$$

(m and n are as defined above), and R^1 is as defined above.

The procedure of the above processes is explained in detail below.

Process A: This process can be carried out by dissolving the compound of the formula: $K_2Pt(II)X'_4$ or $Na_2Pt(II)X'_4$ in an appropriate solvent and adding thereto a compound (II) and stirring the mixture. Examples of the starting $K_2Pt(II)X'_4$ and $Na_2Pt(II)X'_4$ are $K_2Pt(II)Cl_4$ and $Na_2Pt(II)Cl_4$ (i.e. X′ is chlorine). Examples of other starting compounds (II) are a compound of the formula (II) wherein R^1 is as defined above. The solvent is preferably water. The starting compound $K_2Pt(II)X'_4$ or $Na_2Pt(II)X'_4$ is preferably used in an amount of about 0.8 to about 1.0 mole to the compound (II), and the solvent is preferably used in an amount of about 5 to about 50 times as much as the amount of the starting $K_2Pt(II)X'_4$ or $Na_2Pt(II)X'_4$. The reaction is usually carried out at room temperature.

Process B: This process is preferably carried by adding the compound (II) which is prepared by Process A to an appropriate solvent, adding thereto silver sulfate or silver nitrate and stirring the mixture. The solvent is preferably water. Silver nitrate is preferably used in an amount of about 2 moles to 1 mole of the compound (III), and silver sulfate is preferably used in an approximately equimolar amount to the compound (III). The solvent is preferably used in an amount of about 20 to about 500 times as much as the amount of the compound (III). The reaction is usually carried out at a room temperature. The reaction of the compound (III) and silver salt is preferably carried out in the absence of light.

Process C: This process is preferably carried out by adding the compound (IV) which is prepared by Process B to an appropriate solvent, adding thereto an alkali metal bromide, an alkali metal iodide, di(alkali metal) phosphate or a compound of the formula: R^2—COOM′ (R^2 and M′ are as defined above) or

$$M'—O—CO—(CHOH)_m—(CH_2)_n—CO—O—M'$$

(M′, m and n are as defined above), and stirring the mixture. Examples of the alkali metal bromide are sodium bromide and potassium bromide, and of the alkali metal iodide are sodium iodide and potassium iodide. Examples of the di(alkali metal) phosphate are Na_2HPO_4 and K_2HPO_4. Examples of the compounds of the formula R^2—COOM′ are compounds wherein R^2 is a hydroxy-substituted lower alkyl group such as for example the hydroxymethyl, 1-hydroxyethyl, 1,2-dihydroxyethyl, 2-hydroxyethyl and 1-hydroxy-2-methylpropyl groups or an acetyl group, and M′ is an alkali metal such as for example sodium or potassium. Examples of the compounds of the formula

$$M'—O—CO—(CHOH)_m—(CH_2)_n—CO—O—M'$$

are the disodium or dipotassium salt of oxalic acid, malonic acid, hydroxymalonic acid, d,1-malic acid, d,1-tartaric acid or succinic acid. The solvent is preferably water. The alkali metal bromide, alkali metal iodine and the compound of the formula R^2—COOM′ are preferably used in an amount of about 1 or 2 moles to 1 mole of the compound (IV), and di(alkali metal) phosphate and the compound of the formula

$$M'—O—CO—(CHOH)_m—(CH_2)_n—CO—O—M'$$

are preferably used in an approximately equimolar amount to the compound (IV). The solvent is preferably used in an amount of about 10 to about 200 times as much as the amount of the compound (IV). The reaction is usually carried out at room temperature. The dissolution of the compound (IV) in a solvent is preferably done with heating.

The desired compound [I] prepared by the above processes can be isolated from the reaction mixture, by, for example, a conventional method, e.g. by filtering the resulting precipitate. If required, prior to said filtration the reaction mixture may be concentrated or it may be subjected to a column chromatography, followed by concentration. When silver chloride is produced as a by-product in the above reactions, it is preferable to separate off the silver chloride by filtration, to add in portions a 5% aqueous potassium chloride solution to the filtrate and filter in order to remove the unreacted silver compound in the form of silver chloride, and then to subject the resulting filtrate to the above isolation procedure.

The organic platinum complex [I] thus obtained shows potent anti-tumor activity against various tumor cells such as, for example, Ehrlich carcinoma, sarcoma 180, leukemia L-1210, Lewis lung carcinoma, Yoshida sarcoma and rat ascites hepatoma. It may be useful to prolong the survival time of warm-blood aminals, including human, afflicted with tumors and/or minimize the growth of tumors in said animals. For example, according to experiments on anti-leukemia L-1210 activity (wherein the test compound was intraperitoneally administered for 5 days to mice grafted intraperitoneally with leukemia L-1210 cells) and experiments on activity against Ehrlich ascites carcinoma, cis-oxalate(2-aminomethylpyridine) platinum (II) shows an increase of more than 745% in life span (i.e. the ratio of the average survival days in the treated animals and in the control animals) in anti-leukemia L-1210 activity in a dose of 50 mg/kg/day, and 100% inhibition of Ehrlich ascites carcinoma (i.e. the ratio of the amount of ascites carcinoma in the treated animals and in the control animals) in a dose of 3 to 50 mg/kg/day. The compounds of the present invention are also useful for the treatment of various other tumors such as, for example, prostate tumor, orchis tumor, ovary tumor, malignant lymphoma, leukemia and breast cancer. The compound [I] of the present invention shows potent anti-tumor activities and has a low toxicity, and hence, can be used as an anti-tumor agent with a high safety index.

The organic platinum complex [I] of the present invention can be used for pharmaceutical use in the form of a pharmaceutical preparation suitable for either oral or parenteral administration, preferably for parenteral administration. The compound [I] may also be used in conjunction or admixture with a pharmaceutical excipient. The excipient selected should be one which does not react with the compound [I]. Examples of suitable excipients are gelatin, lactose, glucose, sodium chloride, starch, magnesium stearate and talcum. Other known medicinal excipients may be employed. The pharmaceutical preparation may be solid dosage from such as for example, a tablet, a coated tablet, a pill or a capsule; or a liquid dosage form such as for example, a solution, a suspension or an emulsion. Further, the compound [I] may be used together with an isotonic agent such as for example, mannitol, sodium chloride, glucose, sorbitol, glycerol, xylitol, fructose, mannose, or the like. The pharmaceutical preparation may be sterilized and/or may contain auxiliaries such as for example preserving and stabilizing agents. The dose of the compound [I] for pharmaceutical use depends on route of administration; the age, weight and condition of the host; and the particular disease to be treated. In general, it may be used for pharmaceutical use at a dose of about 20 to about 1000 mg/m^2, especially 50 to 500 mg/m^2, per day.

A dosage of 50 mg/m^2 is roughly equal to 1.5 mg/kg which in turn is roughly equal to 75 mg/patient weighing 50 kg.

Practical and presently-preferred embodiments of the present invention are illustratively shown in the following Examples.

Example 1

2-Aminoethylpyridine (1.20 g) is added to a solution of potassium tetrachloroplatinate (II) (4.15 g) in water (50 ml), and the mixture is stirred at room temperature overnight. The precipitated crystal is separated by filtration, washed with a small amount of cold water and dried to give cis-dichloro(2-aminomethylpyridine) platinum (II) (3.19 g) as brownish yellow crystals.

Elementary analysis for $C_6H_8N_2Cl_2Pt$:

Found (%):	C, 19.26;	H, 2.15;	N, 7.48
Calcd. (%):	C, 19.41;	H, 2.22;	N, 7.44

$IR\nu_{max}^{Nujol}$ (cm^{-1}): 3240, 3200, 3110, 1635.

The IR spectrum of the above compound is shown in the accompanying Figure 1.

Example 2

A solution of silver nitrate (3.40 g) in water (40 ml) is added to a suspension of cis-dichloro(2-aminomethylpyridine) platinum (II) (3.74 g) prepared as in Example 1 in water (200 mg), and the mixture is stirred in the absence of light at room temperature over two nights. The precipitated silver chloride is filtered off, and a 5% aqueous potassium chloride solution is added in portions to the filtrate to convert the unreacted silver nitrate into silver chloride which is removed by filtration. The resulting filtrate is concentrated to dryness under reduced pressure and then dried to give cis-dinitrato(2-aminomethylpyridine) platinum (II) (3.9 g) as a pale yellow powder.

Elementary analysis for $C_6H_8N_4O_6Pt$:

Found (%):	C, 16.86,	H, 1.87;	N, 13.11
Calcd. (%):	C, 16.95;	H, 1.76;	N, 12.96

$IR\nu_{max}^{Nujol}$ (cm^{-1}): 3280, 3220, 3150, 1620, 1510, 1280.

The IR spectrum of the above compound is shown in accompanying Figure 2.

Example 3

Cis-dinitrato(2-aminomethylpyridine) platinum (II) (0.43 g) prepared as in Example 2 is dissolved in water (40 ml) with heating, potassium bromide (0.71 g) is added and the mixture is stirred at room temperature overnight. The precipitated crystals are separated by filtration and dried to give cis-bromo(2-aminomethylpyridine) platinum (II) (0.43 g) as a brownish yellow powder.

Elementary analysis for $C_6H_8H_2Br_2Pt$:
Found (%): C, 15.55; H, 1.73; N, 6.05
Calcd. (%): C, 15.73; H, 1.68; N, 6.28
IRν_{max}^{Nujol} (cm^{-1}): 3220, 3180, 3100, 1615.

The IR spectrum of the above compound is shown in the accompanying Figure 3.

Example 4

Cis-dichloro(2-aminomethylpyridine) platinum (II) (0.37 g) prepared as in Example 1 is added to a solution of silver sulfate (0.31 g) in water (100 ml), and the mixture is stirred in the absence of light at room temperature over two nights. The reaction mixture is treated in the same manner as described in Example 2 to give cis-sulfato(2-aminomethylpyridine) platinum (II) (0.32 g) as a pale yellowish white powder.

Elementary analysis for $C_6H_8N_2O_4SPt$:
Found (%): C, 18.04; H, 2.00; N, 7.01
Calcd. (%): C, 17.88; H, 1.93; N, 6.85
IRν_{max}^{Nujol} (cm^{-1}): 3250, 3210, 1610, 1120, 1030.

Example 5

Cis-dinitrato(2-aminomethylpyridine) platinum (II) (0.43 g) prepared as in Example 2 is dissolved in water (40 ml) with heating, sodium glycolate (0.20 g) is added, and the mixture is allowed to stand at room temperature for 7 days. The reaction mixture is concentrated under reduced pressure to give cis-diglycolato(2-aminomethylpyridine) platinum (II) (0.35 g) as a white powder.

Elementary analysis for $C_{10}H_{14}N_2O_6Pt$:
Found (%): C, 26.49; H, 3.09; N, 6.18
Calcd. (%): C, 26.35; H, 3.26; N, 6.01
IRν_{max}^{Nujol} (cm^{-1}): 3240, 3130, 1640, 1620.

The IR spectrum of the above compound is shown in the accompanying Figure 4.

Examples 6 to 9

In the same manner as described in Example 5, the following compounds are prepared by using cis-dinitrato(2-aminomethylpyridine) platinum (II) and the sodium salt of an organic carboxylic acid.

(6) Cis-dipyruvinato(2-aminomethylpyridine) platinum (II), pale yellow powder, yield: 75%.

Elementary analysis for $C_{12}H_{14}N_2O_6Pt$:
Found (%): C, 30.18; H, 2.93; N, 5.87
Calcd. (%): C, 30.14; H, 2.78; N, 5.69
IRν_{max}^{Nujol} (cm^{-1}): 3300, 3210, 1760, 1640.

(7) Cis-oxalato(2-aminomethylpyridine) platinum (II), colourless crystalline powder, yield: 90%.

Elementary analysis for $C_8H_8N_2O_4Pt$:
Found (%): C, 24.55; H, 2.04; N, 7.16
Calcd. (%): C, 24.72; H, 2.31; N, 6.98
IRν_{max}^{Nujol} (cm^{-1}): 3220, 3130, 1720, 1660, 1610.

The IR spectrum of the above compound is shown in the accompanying Figure 5.

(8) Cis-malonato(2-aminomethylpyridine) platinum (II), white powder, yield: 82%.

Elementary analysis for $C_9H_{10}N_2O_4Pt$:
Found (%): C, 26.66; H, 2.46; N, 6.91
Calcd. (%): C, 26.78; H, 2.28; N, 7.12
IRν_{max}^{Nujol} (cm^{-1}): 3220, 3140, 1640.

(9) Cis(glycolato) (nitrato) (2-aminomethylpyridine) platinum (II), pale yellow powder, yield: 70%.

Elementary anslysis for $C_8H_{11}N_3O_6Pt$:
Found (%): C, 21.81; H, 2.50; N, 9.54
Calcd. (%): C, 21.73; H, 2.33; N, 9.71
IRν_{max}^{Nujol} (cm^{-1}): 3210, 3120, 1600.

Example 10

(1) A mixture of pyridine-2-aldehyde (5.4 g), methylamine hydrochloride (0.5 g) and methanolic methylamine (3 g in 100 ml) is hydrogenated in the presence of Pd/C catalyst to give 2-(methylaminomethyl)pyridine (4.5 g), b.p. 79—81°C/14 mmHg.

IRν_{max}^{Nujol} (cm^{-1}): 3340, 1590, 1570
Mass m/e: 121 (M^+—1), 92 (M^+—30 ($NHCH_3$))
NMR ($CDCl_3$) δ: 2.47 (3H, s, NCH_3), 2.20 (1H, s, NH), 3.87 (2H, s, CH_2), 7.05—7.80 (3H, m, proton at pyridine ring), 8.56 (1H, d, J=3.7 Hz, proton at pyridine ring).

(2) In the same manner as described in Example 1, potassium platinate chloride (4.15 g) is reacted with 2-(methylaminomethyl)pyridine (1.34 g) to give cis-dichloro(2-methylaminomethyl)-pyridine) platinum (II) (3.3 g) as pale yellow crystals.

Elementary analysis for $C_7H_{10}N_2Cl_sPt$:
Found (%): C, 21.65; H, 2.59; N, 7.21
Calcd. (%): C, 21.59; H, 2.59; N, 7.19
IRν_{max}^{Nujol} (cm^{-1}): 3160, 1620.

The IR spectrum of the above compound is shown in the accompanying Figure 6.

Example 11

In the same manner as described in Example 2, cis-dichloro(2-(methylaminomethyl)pyridine) platinum (II) (0.39 g) prepared as in Example 10 is reacted with silver nitrate (0.34 g) to give cis-dinitrato(2-(methylaminomethyl)pyridine) platinum (II) (0.40 g) as a pale yellow powder.

Elementary analysis for $C_7H_{10}N_4O_6Pt$:
Found (%): C, 19.04; H, 2.26; N, 12.69
Calcd. (%): C, 19.26; H, 2.41; N, 12.81
IRν_{max}^{Nujol} (cm^{-1}): 3190, 1620, 1520, 1280.

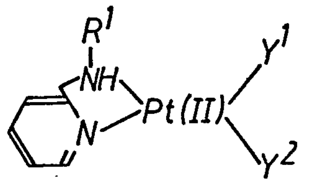
Example 12

In the same manner as described in Example 5, cis-dinitrato(2-(methylaminomethyl)pyridine) platinum (II) (0.44 g) prepared as in Example 11 is reacted with sodium oxalate (0.13 g) to give cis-oxalato(2-(methylaminomethyl)pyridine) platinum (II) (0.37 g) as a white powder.

Elementary analysis for $C_9H_{10}N_2O_4Pt$:
Found (%): C, 26.66; H, 2.46; N, 6.91
Calcd. (%): C, 26.52; H, 2.61; N, 6.78
IRν_{max}^{Nujol} (cm^{-1}): 3160, 1720, 1650.

Claims

1. An organic platinum complex of the formula:



[I]

wherein R^1 is a hydrogen atom or methyl group, Y^1 and Y^2 are the same or different and each is a halogen atom, NO_3 or a group of the formula: R^2—COO—, or Y^1 and Y^2 combine to form a group of the formula: ⊂ SO_4, ⊂ PO_3OH or

$$—O—CO—(CHOH)_m—(CH_2)_n—CO—O—,$$

R^2 is a hydroxy-substituted lower alky or acetyl group, and m and n are each integers of 0, 1 or 2 with the proviso of $0 \leqq m+n \leqq 2$.

2. Complex according to claim 1, wherein Y^1 and Y^2 are the same or different and each is a chlorine atom, NO_3 or a group of the formula: $HOCH_2COO$— or Y^1 and Y^2 combine to form a group of the formula: ⊂ SO_4,

$$—O—CO—CO—O—$$

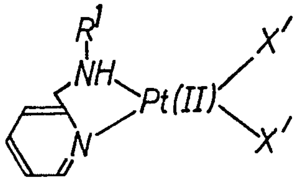
or

$$—O—CO—CH_2—CO—O—.$$

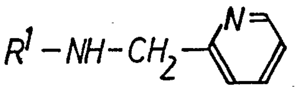
3. Complex according to claim 1 which is cis-oxalato(2-aminomethylpyridine) platinum (II).

4. Organic platinum complexes of formula (i) substantially as herein described with reference to and as illustrated in any of the Examples.

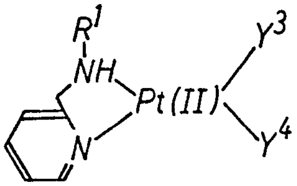
5. A process for preparing an organic platinum complex of the formula:


[I-a]

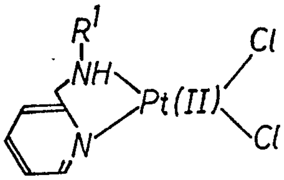
wherein R^1 is a hydrogen atom or methyl group, and X′ is a halogen atom, which comprises reacting a compound of the formula: $K_2Pt(II)X'_4$ or $Na_2Pt(II)X'_4$ with a compound of the formula:


[II]

6. A process for preparing an organic platinum complex of the formula:

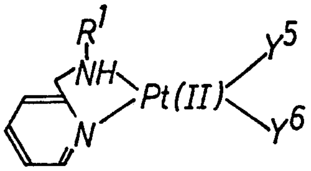

[I-b]

wherein R^1 is a hydrogen atom or methyl group, and Y^3 and Y^4 are the same and each is NO_3, or Y^3 and Y^4 combine to form a group of the formula: $\subset\!\supset SO_4$, which comprises reacting a compound of the formula:


[III]

with silver sulfate or silver nitrate.

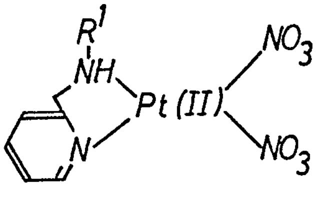
7. A process for preparing an organic platinum complex of the formula:


[I-c]

wherein R^1 is a hydrogen atom or methyl group, Y^5 and Y^6 are the same or different and each is bromine, iodine, NO_3, or a group of the formula: R^2—COO—, or Y^5 and Y^6 combine to form a group of the formula: $\subset\!\supset PO_3OH$ or

$$—O—CO—(CHOH)_m—(CH_2)_n—CO—O—,$$

R^2 is a hydroxy-substituted lower alkyl group or acetyl group, and m and n are each integers of 0, 1 or 2 with the proviso of $0 \leq m+n \leq 2$, which comprises reacting a compound of the formula:


[IV]

with an alkali metal bromide, an alkali metal iodide, silver sulfate, or a compound of the formula: R^2—COOM′ (M′ is an alkali metal) or

$$M'—O—CO—(CHOH)_m—(CH_2)_n—CO—O—M'.$$

8. A process for preparing an organic platinum complex of formula (I) substantially as herein described with reference to and as illustrated in any of the Examples.

9. A pharmaceutical composition, which comprises as an essential active ingredient an organic platinum complex as claimed in any of claims 1 to 4 in admixture with a pharmaceutically acceptable carrier or diluent.

10. A pharmaceutical composition according to claim 9 for use as an anti-tumor agent.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1984. Published by the Patent Office,
25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.