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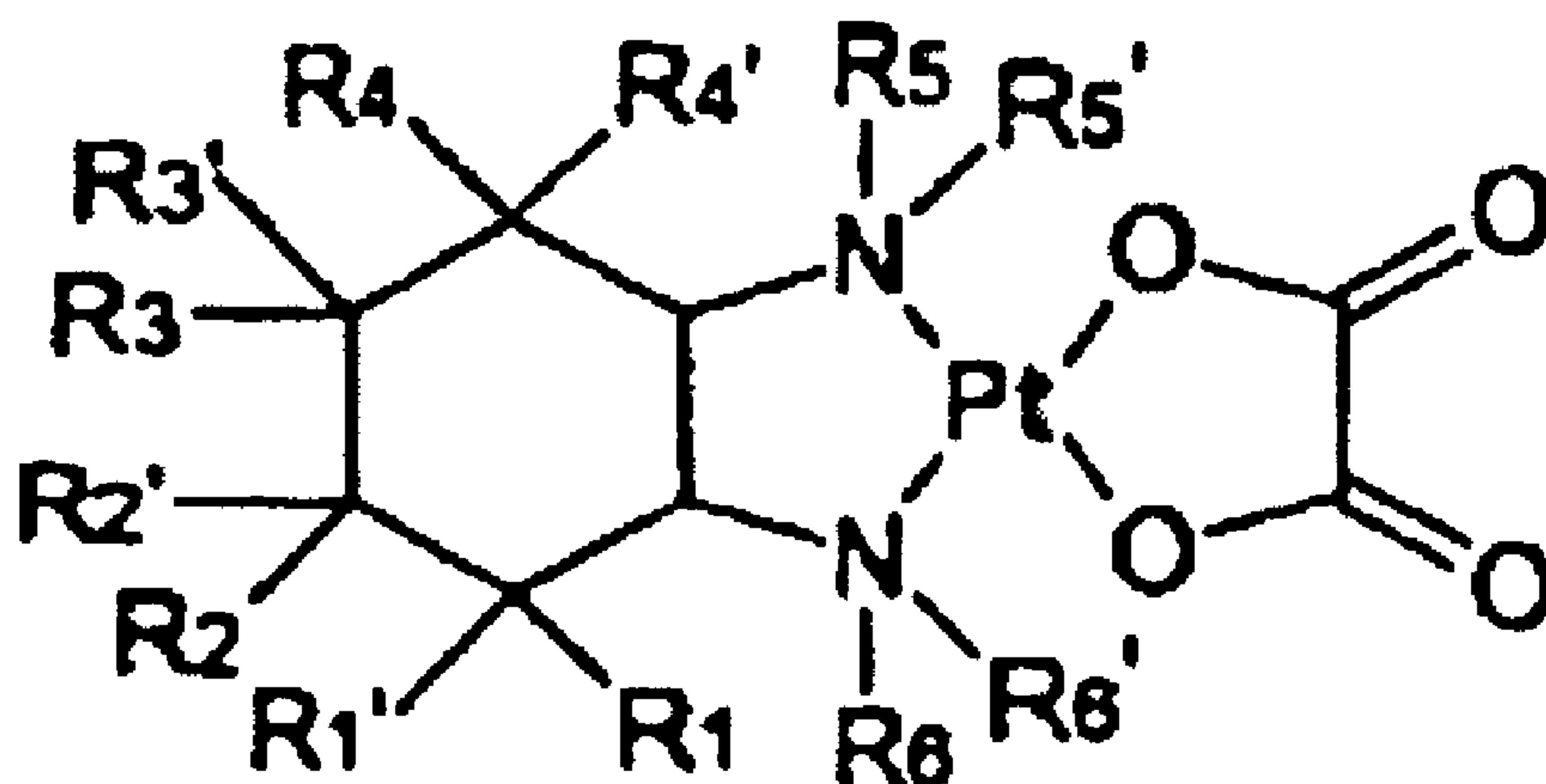
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(54) Titre : COMPLEXES PLATINE(II)-OXALATO INHIBITEURS DE TUMEURS

(54) Title: TUMOUR-INHIBITING PLATINUM (II) OXALATE COMPLEXES



(I)

(57) Abrégé/Abstract:

The invention relates to tumour-inhibiting platinum (II) oxalate complexes, the use thereof as a therapeutic agent, in particular as a tumour-inhibiting medicament. Particularly of interest are compounds of general formula (I), where the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ are independently selected from the group of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkenyl, unsubstituted or substituted aryl and unsubstituted or substituted alkylaryl groups, the substituents R^5 , $R^{5'}$, R^6 , and $R^{6'}$ are independently selected from the group of hydrogen, unsubstituted or substituted alkyl and unsubstituted or substituted alkenyl groups and optionally at least two of the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ can together form at least one unsubstituted or substituted alkenyl, unsubstituted or substituted alkenylene group or an unsubstituted or substituted aromatic ring and optionally at least one of the carbon atoms of the cyclohexane ring carrying the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ is replaced by a heteroatom and when the heteroatom is oxygen, the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ can additionally be hydroxy groups and the pharmaceutically acceptable salts thereof with the condition that at least one substituent R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , $R^{4'}$ is not hydrogen and the substituents R^1 or $R^{1'}$ and R^4 or $R^{4'}$ do not form an unsubstituted C_{1-2} alkylene group together.

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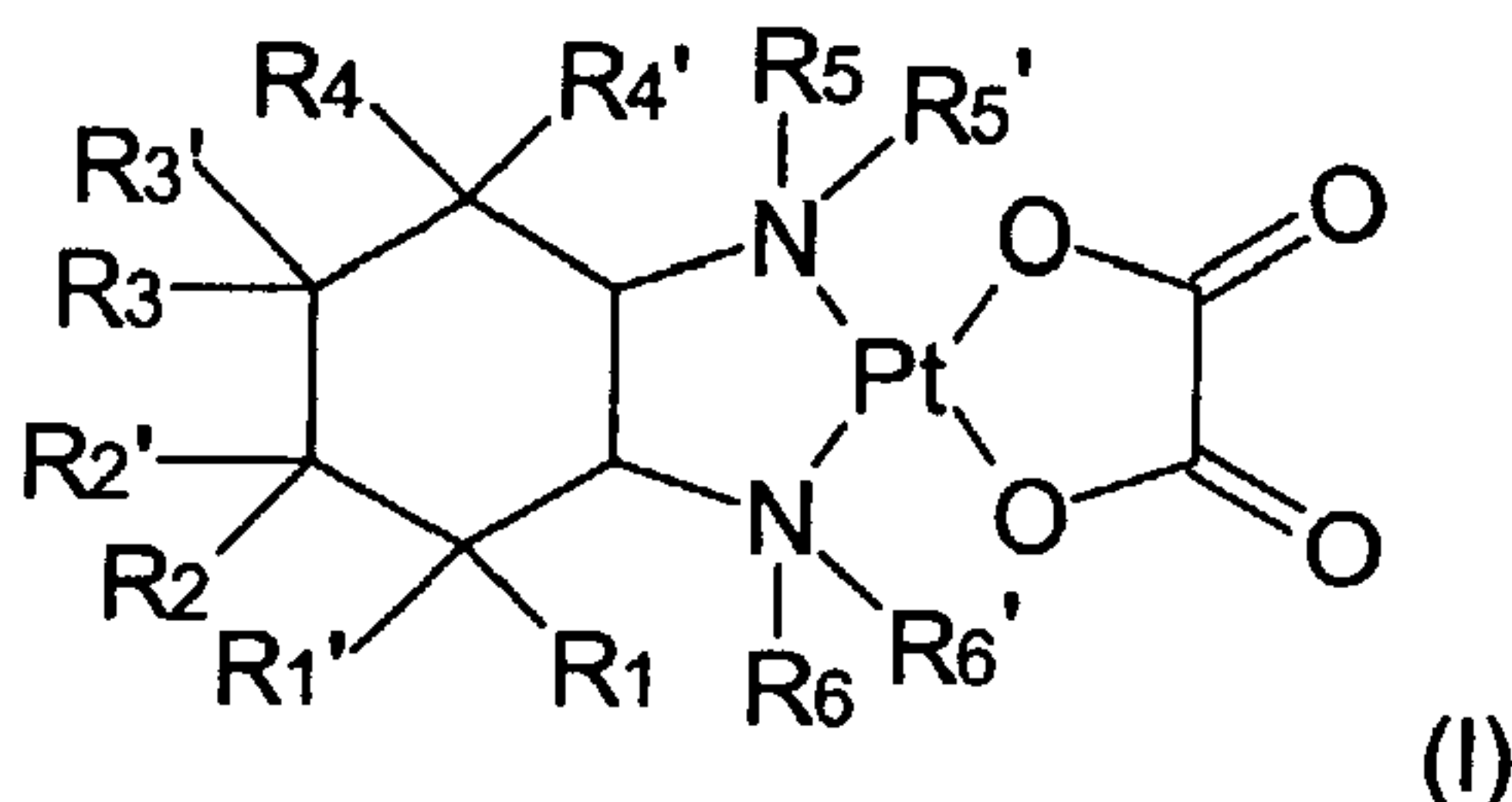
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(54) Title: TUMOUR-INHIBITING PLATINUM (II) OXALATE COMPLEXES

(54) Bezeichnung: TUMORHEMMENDE PLATIN(II)-OXALATO-KOMPLEXE

(57) Abstract: The invention relates to tumour-inhibiting platinum (II) oxalate complexes, the use thereof as a therapeutic agent, in particular as a tumour-inhibiting medicament. Particularly of interest are compounds of general formula (I), where the substituents R¹, R^{1'}, R², R^{2'}, R³, R^{3'}, R⁴, and R^{4'} are independently selected from the group of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkenyl, unsubstituted or substituted aryl and unsubstituted or substituted

tuted alkylaryl groups, the substituents R⁵, R^{5'}, R⁶, and R^{6'} are independently selected from the group of hydrogen, unsubstituted or substituted alkyl and unsubstituted or substituted alkenyl groups and optionally at least two of the substituents R¹, R^{1'}, R², R^{2'}, R³, R^{3'}, R⁴, and R^{4'} can together form at least one unsubstituted or substituted alkenyl, unsubstituted or substituted alkenylene group or an unsubstituted or substituted aromatic ring and optionally at least one of the carbon atoms of the cyclohexane ring carrying the substituents R¹, R^{1'}, R², R^{2'}, R³, R^{3'}, R⁴, and R^{4'} is replaced by a heteroatom and when the heteroatom is oxygen, the substituents R¹, R^{1'}, R², R^{2'}, R³, R^{3'}, R⁴, and R^{4'} can additionally be hydroxy groups and the pharmaceutically acceptable salts thereof with the condition that at least one substituent R¹, R^{1'}, R², R^{2'}, R³, R^{3'}, R⁴, R^{4'} is not hydrogen and the substituents R¹ or R^{1'} and R⁴ or R^{4'} do not form an unsubstituted C₁₋₂ alkylene group together.

(57) Zusammenfassung: Die Erfindung betrifft tumorhemmende Platin(II)-oxalato-Komplexe, deren Verwendung therapeutisches Mittel, insbesondere als tumorhemmendes Arzneimittel. Insbesondere betrifft die Erfindung Verbindungen der allgemeinen Formel (I), wobei die Substituenten R¹, R^{1'}, R², R^{2'}, R³, R^{3'}, R⁴, und R^{4'} unabhängig voneinander ausgewählt sind aus der Gruppe, bestehend aus Wasserstoff, unsubstituierten oder substituierten Alkyl-, unsubstituierten oder substituierten Alkenyl-, unsubstituierten oder substituierten Cycloalkyl-, unsubstituierten oder substituierten Cycloalkenyl-, unsubstituierten oder substituierten Aryl- und unsubstituierten oder substituierten Alkylarylresten, die Substituenten R⁵, R^{5'}, R⁶, und R^{6'} unabhängig voneinander ausgewählt sind aus der Gruppe, bestehend aus Wasserstoff, unsubstituierten oder substituierten Alkyl-, und unsubstituierten oder substituierten Alkenylresten, und wobei gegebenenfalls jeweils wenigstens zwei der Substituenten R¹, R^{1'}, R², R^{2'}, R³, R^{3'}, R⁴, und R^{4'} miteinander wenigstens einen unsubstituierten oder substituierten Alkylen-, unsubstituierten oder substituierten Alkenylenrest oder einen unsubstituierten oder substituierten aromatischen Ring bilden können, und wobei gegebenenfalls wenigstens eines der die Substituenten R¹, R^{1'}, R², R^{2'}, R³, R^{3'}, R⁴, und R^{4'} tragenden Kohlenstoffatome des Cyclohexanrings durch ein Heteroatom ersetzt ist, und falls das Heteroatom Sauerstoff ist, die Substituenten R¹, R^{1'}, R², R^{2'}, R³, R^{3'}, R⁴, und R^{4'} zusätzlich Hydroxyreste sein können, und pharmazeutisch verträglich Salze davon, mit der Massgabe, dass mindestens ein Substituent R¹, R^{1'}, R², R^{2'}, R³, R^{3'}, R⁴, R^{4'} ungleich Wasserstoff ist und die Substituenten R¹ oder R^{1'} und R⁴ oder R^{4'} miteinander keinen unsubstituierten C₁₋₂-Alkylenrest bilden.

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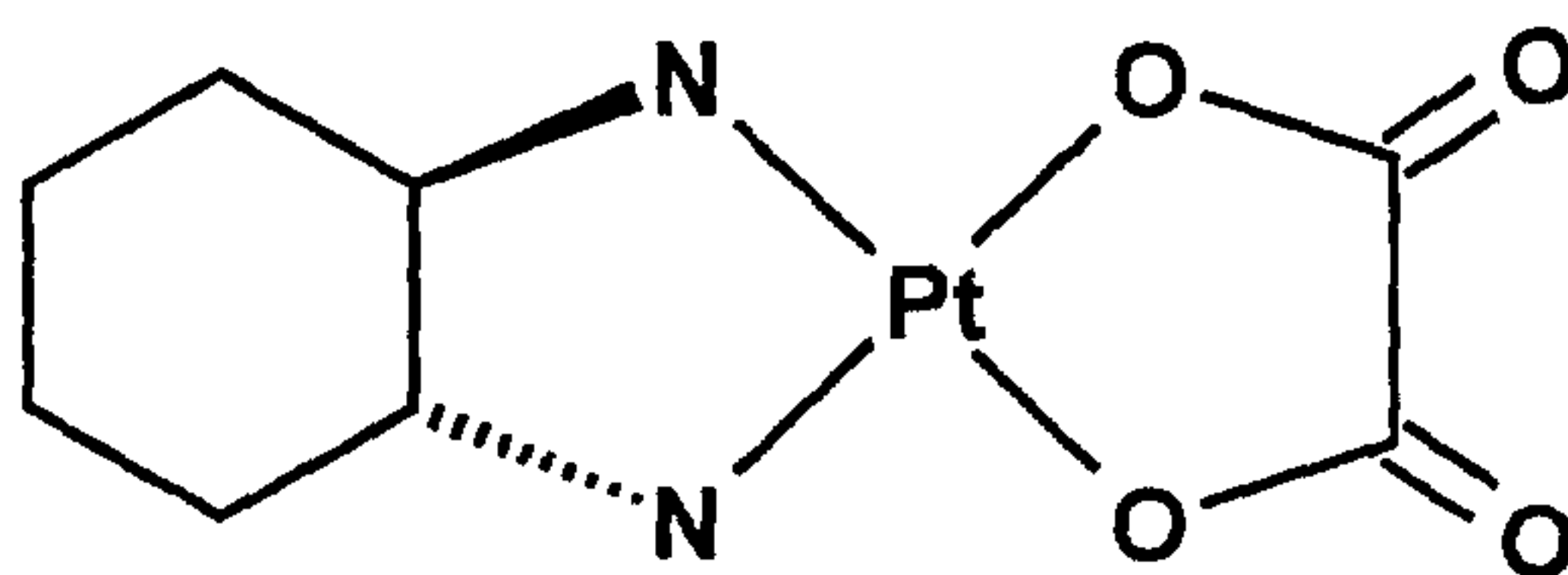
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Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

Tumour-inhibiting platinum (II) oxalate complexes

The invention relates to tumour-inhibiting platinum (II) oxalate complexes and their use as therapeutic agents, in particular as tumour-inhibiting medicaments.

It is known that some platinum complexes have tumour-inhibiting effects. Apart from cisplatinum, carboplatinum and oxaliplatinum with the following structure



represent the two most important known platinum active substances for combating tumours, whereby in oxaliplatin the leaving group of the complex with its use as an anti-tumour agent is oxalate. In particular, cisplatinum however has serious side-effects, such as renal toxicity, myelosuppression and ototoxicity.

Therefore, especially oxaliplatinum has, with a bidentate *trans-R,R*-1,2-diaminocyclohexane ligand and a similarly bidentate oxalato ligand with an effective spectrum deviating from the other two platinum (II) complexes, interesting properties as a cancer therapeutic agent. An advantage with the use of oxaliplatinum as an anti-tumour agent is particularly its lower toxicity in comparison to cisplatinum. However, oxaliplatinum has other undesirable side-effects, such as strong neuropathy.

So far, for the modification of this basic framework and the complex properties the leaving group of the complex was varied. Therefore, in US 4,168,846 *cis*-platinum (II) complexes with *trans-L*-1,2-diaminocyclohexane as the ligand without substituents on the cyclohexane ring are described, whereby the complexes, apart from oxalate, have as leaving group malonate and substituted derivatives of malonic acid.

The use of higher dicarboxylic acids or dicarboxylic acid derivatives as ligands in platinum (II) complexes, such as malonate or succinate, is, for example, also described in JP 61037794.

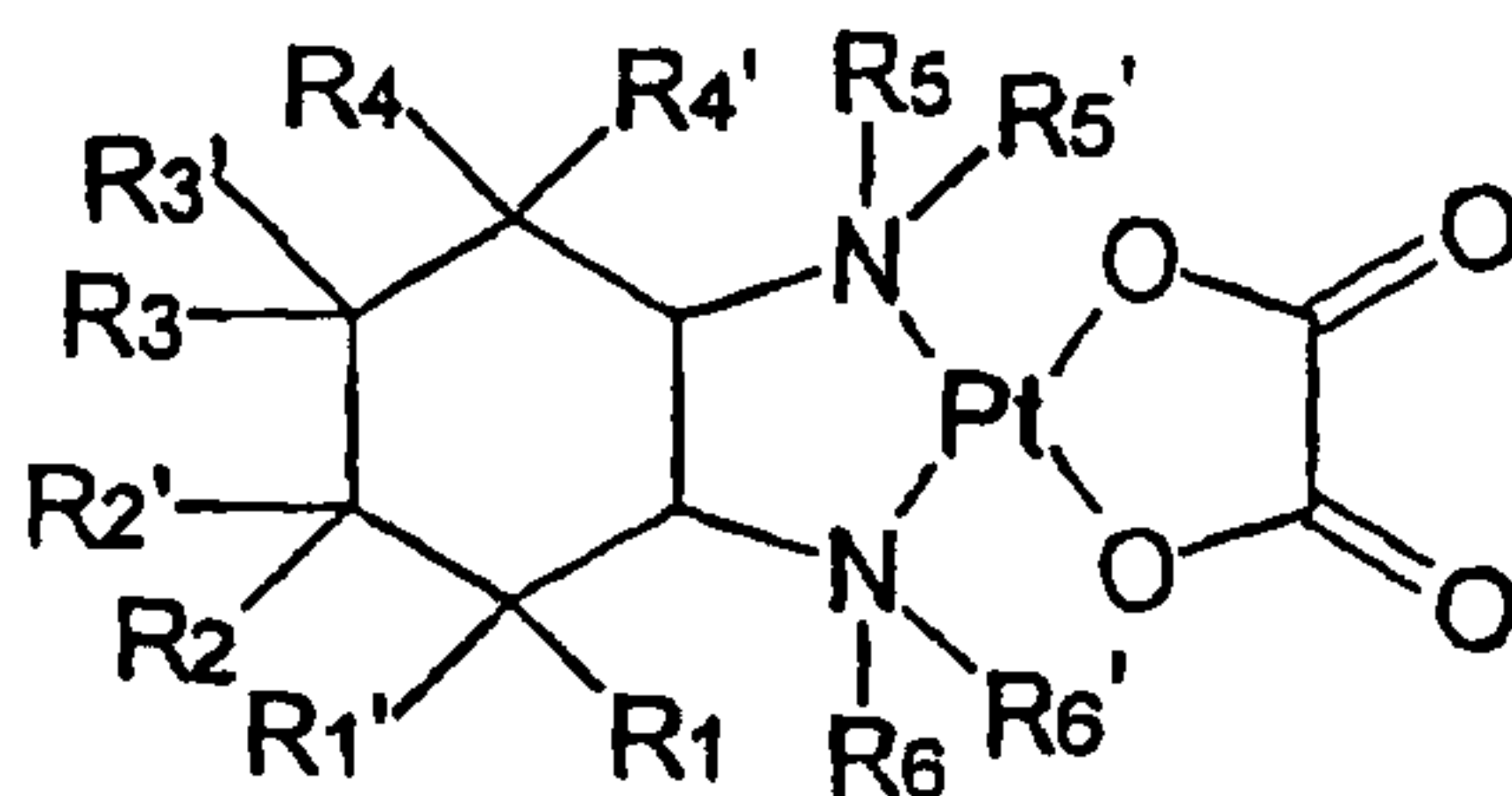
Furthermore, a range of platinum (II) complexes with monodentate anions, such as pyrophosphate, is described in US 4,234,500.

Also, platinum (II) complexes are known which have a modified diaminocyclohexane ligand. For example, in US 4,359,425 platinum (II) complexes are described, which have a special diaminocyclohexane ligand, which is bicyclic and is bridged on the two carbon atoms adjacent to the amino groups by a $(CH_2)_n$ bridge where $n = 1$ or 2. In US 4,670,458 dihydroxylised diaminocyclohexane derivatives are disclosed as diaminocyclohexane ligands.

10 In addition, substituted cyclohexane derivatives, which have pyrophosphate as the leaving group, are described in US 4,291,027.

The object of this invention is to provide further tumour-inhibiting platinum (II) oxalate complexes.

The object is solved by compounds of the general formula (I),



(I)

whereby the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ are independently of one another selected from the group consisting of hydrogen, branched or unbranched alkyl, branched or unbranched alkenyl, cycloalkyl, cycloalkenyl, aryl and alkylaryl radicals,

the substituents R^5 , $R^{5'}$, R^6 and $R^{6'}$ are independently of one another selected from the group consisting of hydrogen, branched or unbranched alkyl and branched or unbranched alkenyl radicals, and

whereby two or more of the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ optionally form with one another at least one alkylene or alkenylene radical or an aromatic ring, and

whereby at least one of the carbon atoms of the cyclohexane ring bearing the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ is optionally replaced by a heteroatom, and

10 if the heteroatom is oxygen, one or more of the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ can additionally be a hydroxy radical, and

its pharmaceutically compatible salts,

provided that

at least one substituent R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 or $R^{4'}$ is not hydrogen and the substituents R^1 or $R^{1'}$ and R^4 or $R^{4'}$ do not form an unsubstituted C_{1-2} -alkylene radical with one another.

20 In the invention as broadly disclosed but not claimed, the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , $R^{4'}$, R^5 , $R^{5'}$, R^6 and/or $R^{6'}$ can be substituted by halogens, in particular Cl, F or Br, hydroxyl, amino, nitro, CN, CF_3 , C_1 - C_4 -alkyl, in particular C_1 - C_3 -alkyl, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, in particular C_1 - C_3 -alkoxy, C_1 - C_4 -alkylthio, C_3 - C_7 -cycloalkyl, in particular C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkoxy, C_2 - C_4 -alkenyl, C_2 - C_4 -alkinyl, aryl, heteroaryl, NR_7R_8 , $COOR_7$, $CONR_7R_8$, NR_7COR_8 , $S(O)R_7$, SO_4R_7 , SO_3H ,

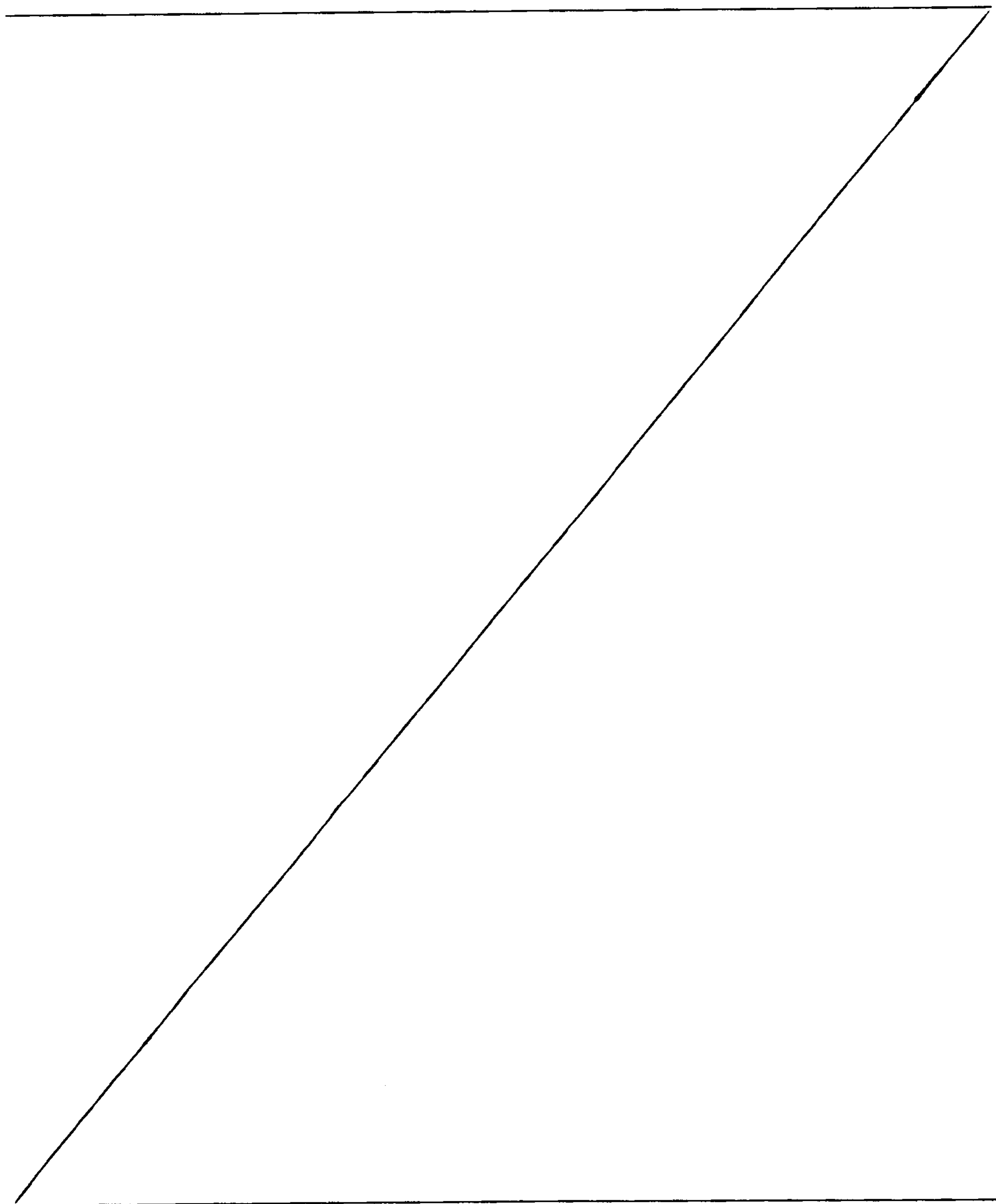
whereby

R^7 and R^8 signify independently H, C_1 - C_4 -alkyl, aryl or heteroaryl or can form a C_3 - C_7 -cycloalkyl ring or C_3 - C_7 -cycloalkenyl ring.

Preferably, the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ are selected independently of one another from the group consisting of hydrogen, C_1 - C_{15} -alkyl, C_2 - C_{15} -alkenyl, C_3 - C_{15} -cycloalkyl, C_3 - C_{15} -cycloalkenyl, C_6 - C_{14} -aryl and C_1 - C_{15} -alkyl- C_6 - C_{14} -aryl radicals.

3a

Particularly preferably the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ are selected independently of one another from the group consisting of hydrogen, C_1 - C_{10} -alkyl, C_2 - C_{10} -alkenyl, C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkenyl, C_6 - C_{10} -aryl and C_1 - C_{10} -alkyl- C_6 - C_{10} -aryl radicals;



in particular the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ are selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkenyl, C_6 - C_{10} -aryl and C_1 - C_6 -alkyl- C_6 - C_{10} -aryl radicals.

Particularly preferably the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , $R^{4'}$ are selected from the group consisting of hydrogen, C_1 - C_{10} -alkyl radicals, in particular methyl, ethyl, n-propyl, i-propyl, n-butyl, branched butyl radicals, n-pentyl, branched pentyl radicals, n-hexyl and branched hexyl radicals, C_3 - C_{10} -cycloalkyl radicals, in particular cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl radicals and C_6 - C_{14} -aryl radicals, in particular phenyl radicals.

The two substituents located on the same carbon atom R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, or R^4 , $R^{4'}$ can be the same or different.

Preferably one to three, more preferably one or two and especially preferably one of the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ are selected from the group consisting of unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkenyl, unsubstituted or substituted aryl and unsubstituted or substituted alkylaryl radicals and the remaining radicals are hydrogen atoms. The radicals are preferably as described above.

In a particularly preferred embodiment the substituents R^1 , $R^{1'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ are hydrogen and R^2 and $R^{2'}$ are selected from the group consisting of hydrogen, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_3 - C_6 -cycloalkyl, C_3 - C_6 -cycloalkenyl and C_6 - C_{10} -aryl radicals and provided that R^2 and $R^{2'}$ are not at the same time hydrogen.

Especially preferably, compounds are preferred whereby the substituents R^1 , $R^{1'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ are equal to hydrogen and the substituents R^2 or $R^{2'}$ are a C_1 - C_6 -alkyl radical, in particular methyl, ethyl, propyl or t-butyl radical or a C_6 - C_{10} -aryl radical, in particular phenyl radical, whereby optionally the other radical R^2 or $R^{2'}$ in each case is hydrogen.

Similarly especially preferably, compounds are preferred whereby the substituents R^1 , $R^{1'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ are equal to hydrogen and R^2 or $R^{2'}$ is a C_1 - C_6 -alkyl radical, in particular methyl, ethyl, propyl or t-butyl radical or a C_6 - C_{10} -aryl radical, in particular phenyl radical, whereby either R^2 or $R^{2'}$ is hydrogen.

In a further especially preferred embodiment the substituents R^1 , $R^{1'}$, R^4 , and $R^{4'}$ are equal to hydrogen, and R^2 , $R^{2'}$, R^3 and $R^{3'}$ are selected from the group consisting of hydrogen, C_1 - C_6 -alkyl and C_2 - C_6 -alkenyl radicals, and provided that R^2 , $R^{2'}$, R^3 and $R^{3'}$ are not at the same time hydrogen.

Especially preferably, compounds are preferred whereby the substituents R^1 , $R^{1'}$, R^4 , and $R^{4'}$ are equal to hydrogen and the substituents R^2 , $R^{2'}$, R^3 and $R^{3'}$ are a C_1 - C_6 -alkyl radical, in particular methyl, ethyl, propyl or t-butyl radical, whereby optionally in each case the other radical R^2 or $R^{2'}$, resp. R^3 or $R^{3'}$ is hydrogen.

Similarly especially preferably, compounds are preferred whereby the substituents R^1 , $R^{1'}$, R^4 , and $R^{4'}$ are equal to hydrogen, R^2 or $R^{2'}$ and R^3 or $R^{3'}$ are a C_1 - C_6 -alkyl radical, in particular a methyl, ethyl, propyl or t-butyl radical, whereby R^2 or $R^{2'}$ and R^3 or $R^{3'}$ are hydrogen.

When at least two of the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ form with one another at least an unsubstituted or substituted alkylene, unsubstituted or substituted alkenylene radical or an unsubstituted or substituted aryl radical, then those that form them are preferably C_1 - C_{15} -alkylene radicals, C_2 - C_{15} -alkenylene radicals or C_6 - C_{14} -aryl radicals. Consequently, bi-, tri- or multi-cyclical radicals are obtained.

It is particularly preferable that in each case two radicals located on adjacent carbon atoms of the cyclohexane ring form with one another one of the previously described radicals. Furthermore, it is especially preferable that a C_6 - C_{14} -aryl radical, in particular a phenyl radical, is annelated via the carbon atoms of the cyclohexane ring bearing the substituents R^2 , $R^{2'}$ and R^3 , $R^{3'}$ to the cyclohexane ring.

Also, two radicals located on the same carbon atom of the cyclohexane ring can form together one of the previously described radicals, whereby the respective spiro-compounds are obtained. Especially preferably only two of the radicals together form respectively one of the previously described radicals, whereby a bicyclical system is obtained.

In a preferred embodiment the substituents R^5 , $R^{5'}$, R^6 , and $R^{6'}$ are selected independently of one another from the group consisting of hydrogen, C_1 - C_6 -alkyl or C_2 - C_6 -alkenyl radicals. The C_1 - C_6 -alkyl radicals are preferably methyl, ethyl, n-propyl or i-propyl radicals. The C_2 - C_6 -alkenyl

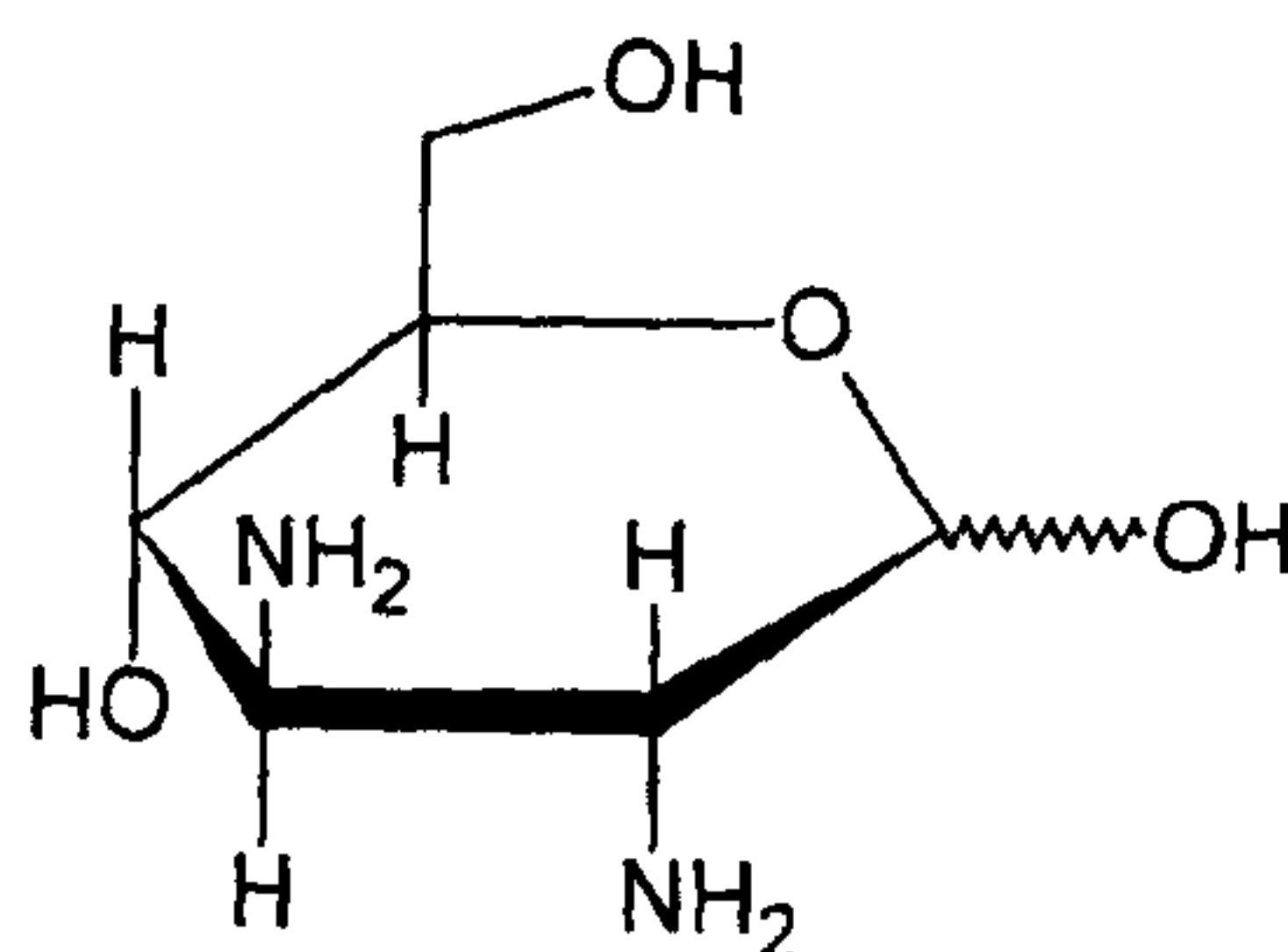
radicals are preferably ethenyl or propenyl radicals. Furthermore, the substituents R^5 , $R^{5'}$, R^6 , and $R^{6'}$ are preferably hydrogen. Preferably R^5 , $R^{5'}$, R^6 , and $R^{6'}$ are unsubstituted.

If at least one of the carbon atoms of the cyclohexane ring bearing the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ is replaced by a heteroatom, the heteroatom is preferably selected from the group consisting of oxygen, nitrogen and sulphur and it is preferable that one to three, in particular one or two, especially one heteroatom is present.

If one of the carbon atoms of the cyclohexane ring is substituted by a heteroatom, then depending on the binding of the heteroatom, less than two substituents can be bound to the heteroatom. Oxygen and sulphur are, for example, unsubstituted and nitrogen is simply substituted appropriate to the position in the heterocycle by one of the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , or $R^{4'}$.

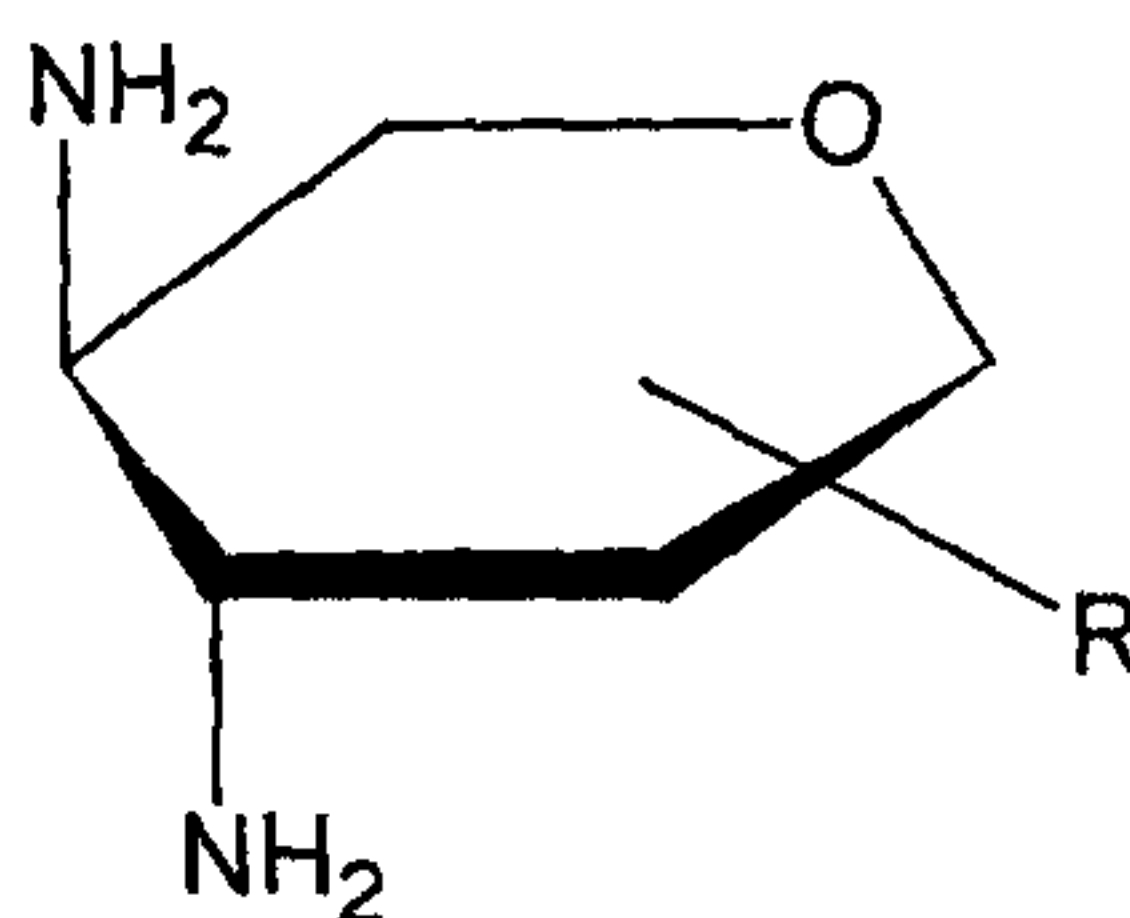
Preferably for the heteroatom, oxygen is involved which has been incorporated in place of the carbon atom in the cyclohexane ring bearing the R^3 and $R^{3'}$ or R^2 and $R^{2'}$, whereby at least one remaining substituent R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , or $R^{4'}$ is not equal to hydrogen.

If the heteroatom is oxygen, the appropriately modified cyclohexane ring can be an amino sugar, e.g. based on glucose.



The two amino groups on the cyclohexane ring in the compounds according to the invention can have a *cis*- or *trans*- arrangement relative to one another. Preferably they have a *trans* arrangement. The two carbon atoms of the cyclohexane ring, which bear the amino groups, can have an R,R, S,S, R,S or S,R configuration.

A possible arrangement of the two amino groups and of the heteroatom, oxygen, is illustrated in the following:



Furthermore, compounds are preferred with which the substituents R^5 , $R^{5'}$, R^6 , and $R^{6'}$ are hydrogen and optionally at least one of the carbon atoms of the cyclohexane ring bearing the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ is replaced by a heteroatom, and

if the heteroatom is oxygen, the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ are selected independently of one another from the group consisting of hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted cycloalkenyl, unsubstituted or substituted aryl and unsubstituted or substituted alkylaryl radicals.

In the sense of this description the terms "alkyl" or "alkenyl" always comprise unbranched or branched "alkyl" or "alkenyl".

The physiologically compatible salts of the compounds according to the invention are preferably selected from the group consisting of organic or inorganic addition salts, which in particular can be formed with the following described anions and cations.

The anions are preferably selected from the group consisting of halogens, such as chloride and bromide, pseudohalogens, phosphate, carbonate, nitrate, perchlorate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, benzoate, ascorbate, cinnamate, glycollate, methane sulphonate, formiate, malonate, naphthalin-2-sulphonate, salicylate and acetate.

The cations are preferably selected from the group consisting of H^+ , sodium and potassium cations.

The compounds according to the invention have a surprisingly good tumour-inhibiting effect.

The synthesis of the compounds according to the invention occurs according to known methods, for example, starting from $K_2[PtCl_4]$, whereby the two bidentate ligands are introduced

successively. To achieve this, first the tetrachloroplatinate (II) can be reacted with the suitably substituted diamine. The diamine (dichloro)platinum (II) complex can then be activated by reaction with silver nitrate or silver sulphate. The diaqua(diamine) or aqua(sulphato)diamine compound thus obtained can then be transformed into the corresponding compound according to the invention by ligand interchange with oxalic acid or sodium oxalate. For example, (SP-4-3)-(trans-cyclohexane-1,2-diamine-4-methyl)-oxalate platinum (II) can be made as described above.

The following schemes show, using the example of the 4-methyl substituted derivative, possible synthesis paths for the production of the compounds according to the invention.

For the production of (SP-4-3)-(trans-cyclohexane-1,2-diamine-4-methyl)-oxalate platinum (II), isomer mixtures of trans-4-methylcyclohexane-1,2-diamines can be made starting from 4-methylcyclohexanone according to Diagram 1. As can be seen in Diagram 1, after bromification and reaction with hydroxylamine, the dioxime obtained is reduced with sodium in absolute ethanol.

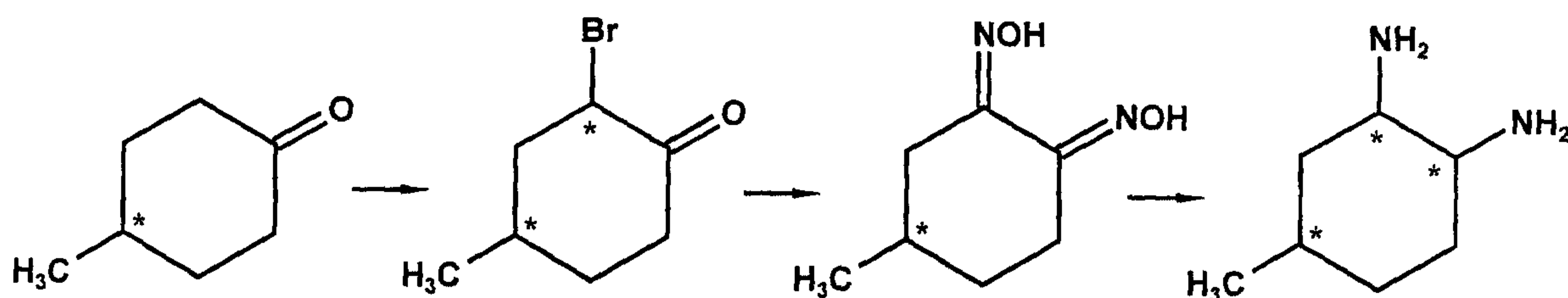


Diagram 1

For the production of the other compounds according to the invention the cyclohexanone in Diagram 1 can also be substituted by the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and / or R^4 , as described above. In particular the corresponding derivative can also be made analogously with an ethyl radical instead of a methyl radical. Alternatively, a suitably substituted cyclohexane-1,2-dion derivative, which can be transformed into the corresponding oxime directly as previously described by reaction with hydroxylamine, can be used instead of the substituted cyclohexanone.

Here, isomer mixtures of substituted trans-cyclohexane-1,2-diamine are obtained.

The substituted cyclohexane or cyclohexane-1,2-dione can also be substituted by the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and / or $R^{4'}$ as described above.

Alternatively, the suitably substituted cyclohexanone derivative is first reduced to alcohol and this can then be dehydrated to cycloalkene. By 1,2-addition of sodium azide to the C=C double bond the corresponding diazide is synthesised and it is then reduced to diamine using hydrogen on the Lindlar catalyst.

The diamine(dichloro)platinum (II) compounds obtained after the reaction of the previously described diaminocyclohexane ligands with $K_2[PtCl_4]$ can then be converted into the corresponding diaqua(diamine) or aqua(sulphato) compounds in each case by using silver nitrate or silver sulphate. After the addition of oxalic acid or sodium oxalate the compounds according to the invention are obtained as isomer mixtures as illustrated for example in the following Diagram 2.

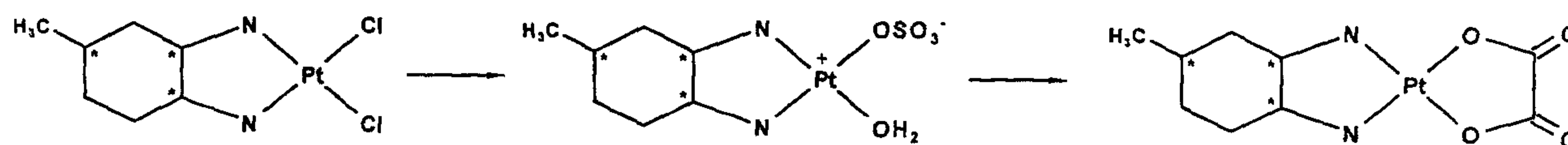


Diagram 2

Instead of substitution with methyl the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 , and $R^{4'}$ can also be present as described above.

After the production of the compounds according to the invention as isomer mixtures, they can be separated into the pure isomers according to known methods. The racemic compound splitting preferably occurs at the stage of the diamines according to a known method such as the formation of diastereomer salts with chiralic acids or column chromatography on the chiralic stationary phase.

The invention also relates to compounds of the formula (I) as therapeutic or prophylactic agents. In addition, the invention relates to the application of a compound of the formula (I) for the manufacture of a medicament for the treatment and / or prophylaxis of tumour diseases.

Furthermore, the object of this invention is solved by a medicament, in particular for the therapy and / or prophylaxis of tumour diseases, which comprises the compound according to the invention. One of the uses of the compound according to the invention is for the prophylaxis and / or treatment of cancer diseases.

In the following the medicament containing a compound according to the invention is described in more detail.

The medicament according to the invention is primarily administered intravenously, but also intramuscularly, intraperitoneally, subcutaneously or perorally. External application is also possible. Preferably, it is administered by intravenous injection or by intravenous infusion.

The medicament is manufactured according to known methods, whereby the compound according to the invention is used as such or in combination with suitable pharmaceutical carrier substances. If the medicament according to the invention contains pharmaceutical carrier substances as well as the active substance, the content of active substance in this mixture is 0.1 to 99.5, preferably 0.5 to 95% by weight of the total mixture.

The medicament according to the invention can be applied in any suitable formulation with the prerequisite that the establishment and maintenance of a sufficient level of active substance is ensured. This can, for example, be achieved by the oral or parenteral administration in suitable doses. Advantageously, the pharmaceutical preparation of the active substance is provided in the form of standard doses which are matched to the desired administration. A standard dose can, for example, be a tablet, a coated tablet, capsule, suppository or a measured volume of a powder, granulate, solution, emulsion or suspension.

A "standard dose" for the purposes of this invention is taken to mean a physically determined unit which contains an individual quantity of the active constituent in combination with a pharmaceutical carrier substance and its content of active substance corresponds to a fraction or multiple of a therapeutic single dose. A single dose preferably contains the quantity of active substance which is administered during an application and which normally corresponds to a whole, half, third or quarter of the daily dose. If only a fraction, such as half or quarter of the standard dose is needed for a single therapeutically administered dose, then the standard dose is advantageously divisible, e.g. in the form of a tablet with a dividing groove.

The medicaments according to the invention can, if the active substance is present in standard doses and is intended for application, e.g. on persons, contain about 0.1 to 500 mg, preferably 10 to 200 mg and particularly 50 to 150 mg of active substance.

Generally in human medicine, the active substance(s) are administered in a daily dose of 0.1 to 5, preferably 1 to 3 mg/kg of body weight, optionally in the form of a number, preferably 1 to 3, of single intakes for achieving the desired results. A single intake contains the active substance(s) in quantities of 0.1 to 5, preferably 1 to 3 mg/kg of body weight. With oral treatment similar dosages can be applied.

The therapeutic administration of the medicament according to the invention can occur 1 to 4 times daily at specified or varying time points, e.g. in each case before meals and / or in the evening. However, it may be necessary to deviate from the quoted dosages depending on the type, body weight and age of the individual to be treated, the type and severity of the disease, the type of preparation and the application of the medicament as well as the time period or interval within which the administration occurs. Consequently, in some cases it may be sufficient to use less than the amount of active substance mentioned above, whereas in other cases the above listed quantity of active substance must be exceeded. It may also be practicable to administer the medicaments only once or at intervals of a number of days.

The specification of the necessary optimum dosage and type of application of the active substance can be made by any specialist based on his specialist knowledge.

The medicaments according to the invention normally comprise the compounds according to the invention and non-toxic, pharmaceutically compatible medicament carriers, which as additive or dilution medium, are employed, for example, in solid, semi-solid or liquid form or as a means of enclosure, for example in the form of a capsule, a tablet coating, a bag or another container for the therapeutically active constituent. A carrier material may, for example, act as an intermediary for the ingestion of the medicament by the body, as a formulation medicament, sweetener, taste modifier, colorant or as a preservative.

For oral application, for example, tablets, coated tablets, hard and soft capsules, for example of gelatine, dispersible powder, granulate, aqueous and oily suspensions, emulsions, solutions and syrups can be employed.

Tablets may contain inert dilution agents, e.g. calcium carbonate, calcium phosphate, sodium phosphate or lactose; granulation and distribution agents, e.g. maize starch or alginates; binding agents, e.g. starches, gelatine or arabine; and lubricating agents, e.g. aluminium or magnesium stearate, talc or silicone oil. They can additionally be provided with a coating which is produced such that it causes delayed release and resorption of the medicament in the gastrointestinal tract, so that, for example, improved compatibility, assimilation or retardation is achieved. Gelatine capsules may contain the pharmaceutical substance mixed with a solid, e.g. calcium carbonate or kaolin or an oily dilution agent, e.g. olive, peanut or paraffin oil.

Aqueous suspensions may contain suspension agents, e.g. sodium carboxymethyl cellulose, methyl cellulose, hydroxypropyl cellulose, sodium alginate, polyvinyl pyrrolidon, traganth rubber or arabine; dispersant and wetting agents, e.g. polyoxyethylene stearate, heptadeca-ethylene-oxycatanol, polyoxyethylene sorbitol-monooleate, or lecithin; preservatives, e.g. methyl- or propylhydroxy-benzoate; taste modifiers; sweeteners, e.g. saccharose, lactose, sodium cyclamate, dextrose, invert sugar syrup.

Oily suspensions may contain, for example, peanut, olive, sesame, coconut or paraffin oil and thickening agents, such as bees wax, high melting point wax or cetyl alcohol; also sweeteners, taste modifiers and antioxidants.

Powder and granulates dispersible in water may contain the compound according to the invention in a mixture with dispersing, wetting and suspension agents, e.g. those mentioned above as well as with sweeteners, taste modifiers and colorants.

Emulsions may, for example, contain olive, peanut or paraffin oil as well as emulsifying agents such as arabine, traganth rubber, phosphatides, sorbitan monooleate, polyoxyethylene sorbitan monooleate and sweeteners and taste modifiers.

Aqueous solutions may contain preservatives, e.g. methyl- or propylhydroxybenzoates; thickening agents; taste modifiers; sweeteners, e.g. saccharose, lactose, sodium cyclamate, dextrose, invert sugar syrup as well as taste modifiers and colorants.

For the parenteral application of pharmaceutical substances sterile injectable aqueous solutions, isotonic salt solutions or other solutions can be used.

This invention also relates to a method for the prophylactic and / or therapeutic treatment of a mammal, which needs such a treatment, by administering a compound according to the invention. The mammal is selected from the group consisting of human beings and animals. Preferably the mammal requires treatment against a tumour disease as described above.

The invention will now be explained in more detail based on the following examples and accompanying drawings wherein:

FIG. 1 is a graphical representation of the cytotoxicity test results of the compounds of Examples 1 and 2 plotting the 41M cell line of living cells (T/C) [%] against concentration [μ M];

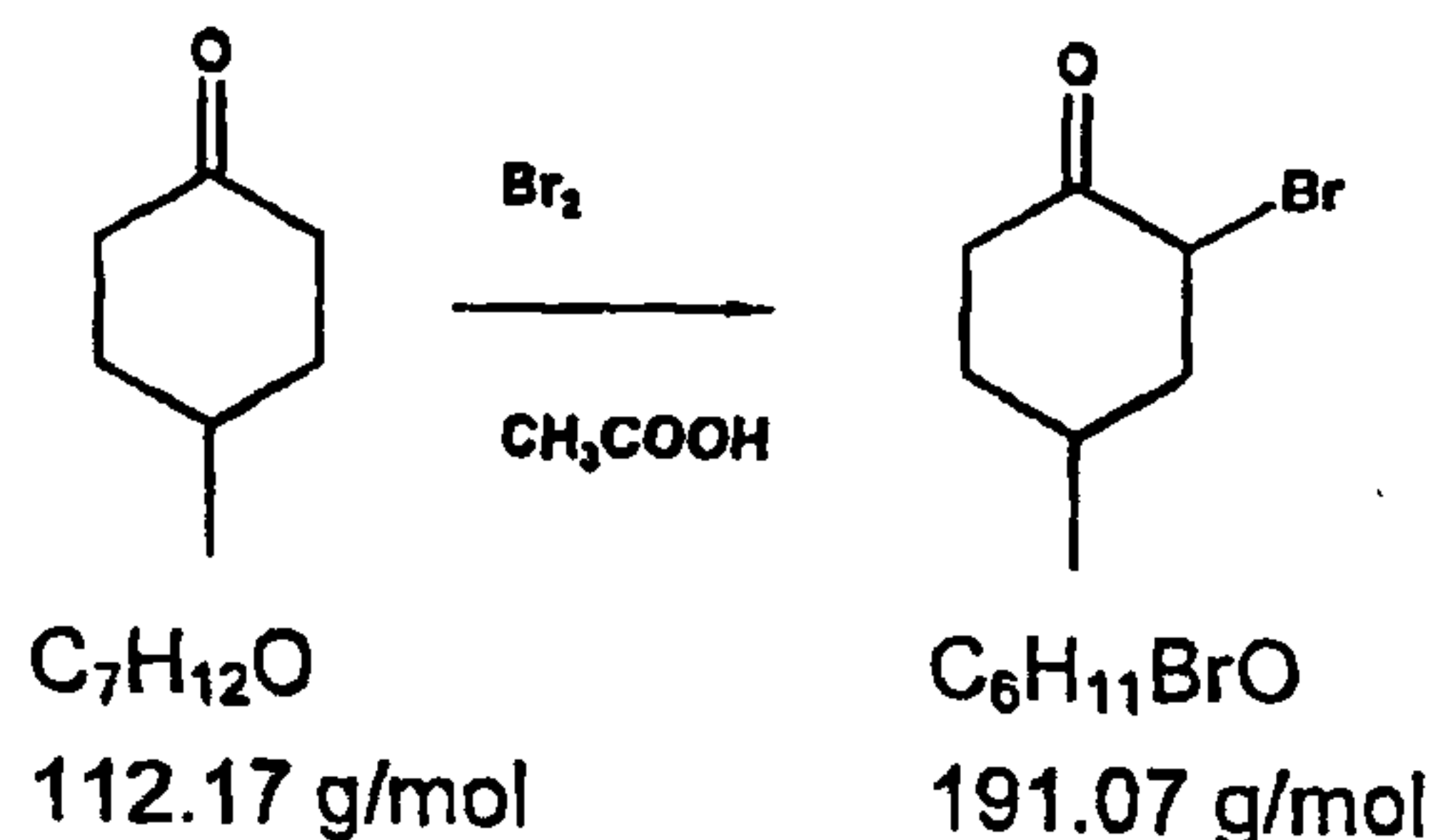
FIG. 2 is a graphical representation of the cytotoxicity test results of the compounds of Examples 1 and 2 plotting the CH1 cell line of living cells (T/C) [%] against concentration [μ M];

10 FIG. 3 is a graphical representation of the cytotoxicity test results of the compounds of Examples 1 and 2 plotting the SW480 cell line of living cells (T/C) [%] against concentration [μ M]; and

FIG. 4 is a bar graph of the results of the effectiveness of (4-methyl-trans-chxn)Pt(ox) in comparison to I-OHP in leukaemia L1210 in the mouse, plotting days of life against dosage.

Synthesis Example 1

2-bromine-4-methyl-cyclohexanone



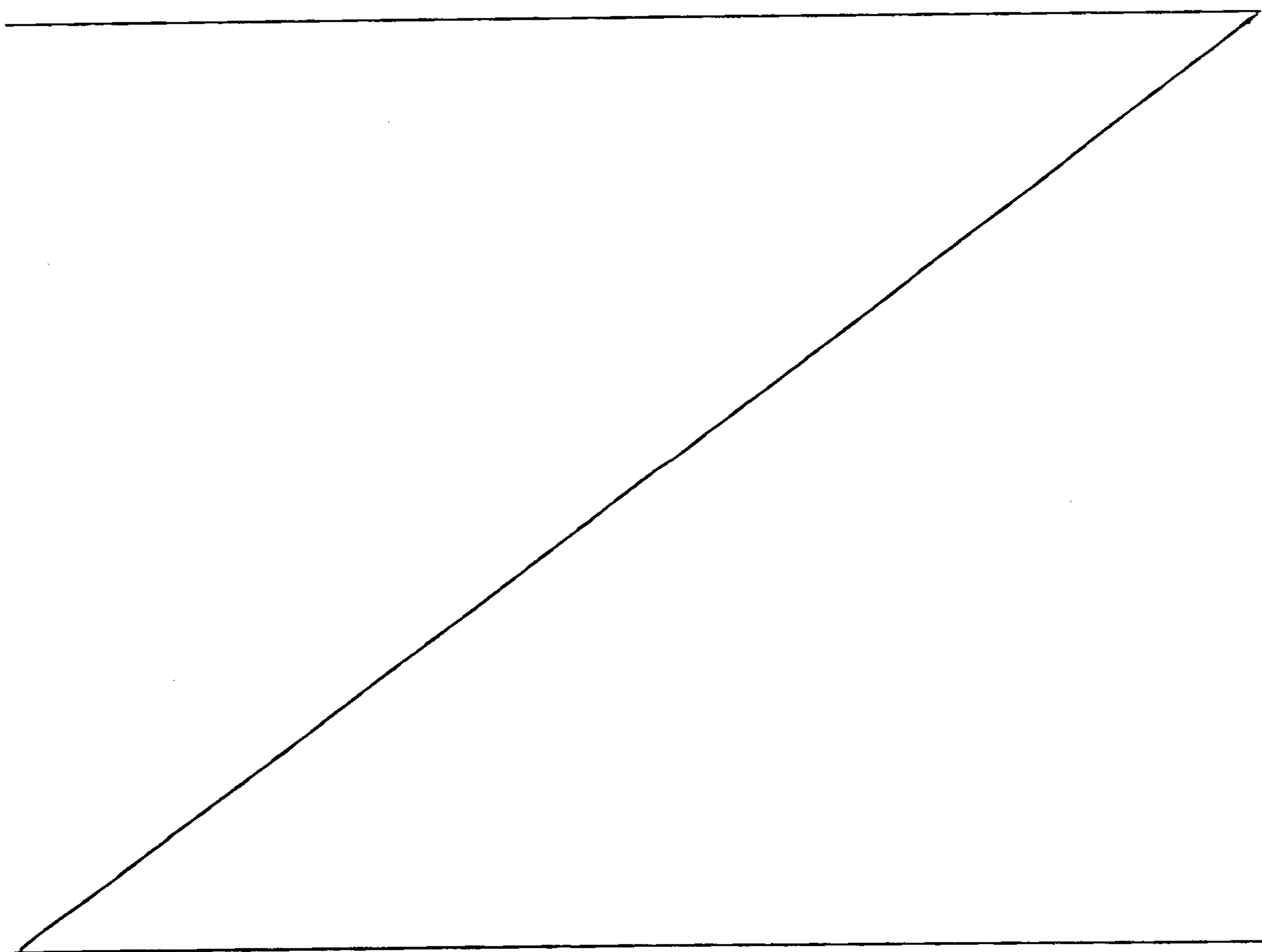
13a

Preparation: 50 g = 0.446 mmol 4-methylcyclohexanone
74 g = 0.463 mmol bromine
92 ml 99% acetic acid

50 g 4-methylcyclohexanone are put into a two-necked flask with a separating funnel and Liebig condenser with 120 ml water, 92 ml 99% acetic acid and 2 drops of bromine. The reaction mixture is heated to about 50°C until the reaction starts. Then 74 g bromine are added drop by drop over a period of 2 hours so slowly that the temperature remains at 35-40°C. Then the solution is neutralised with solid Na₂CO₃, so that the bromine ketone separates as a yellow oily liquid. The organic phase is washed with diluted Na₂CO₃ solution and then with water. The product is dried and filtered with Na₂SO₄.

Appearance: yellow oily liquid

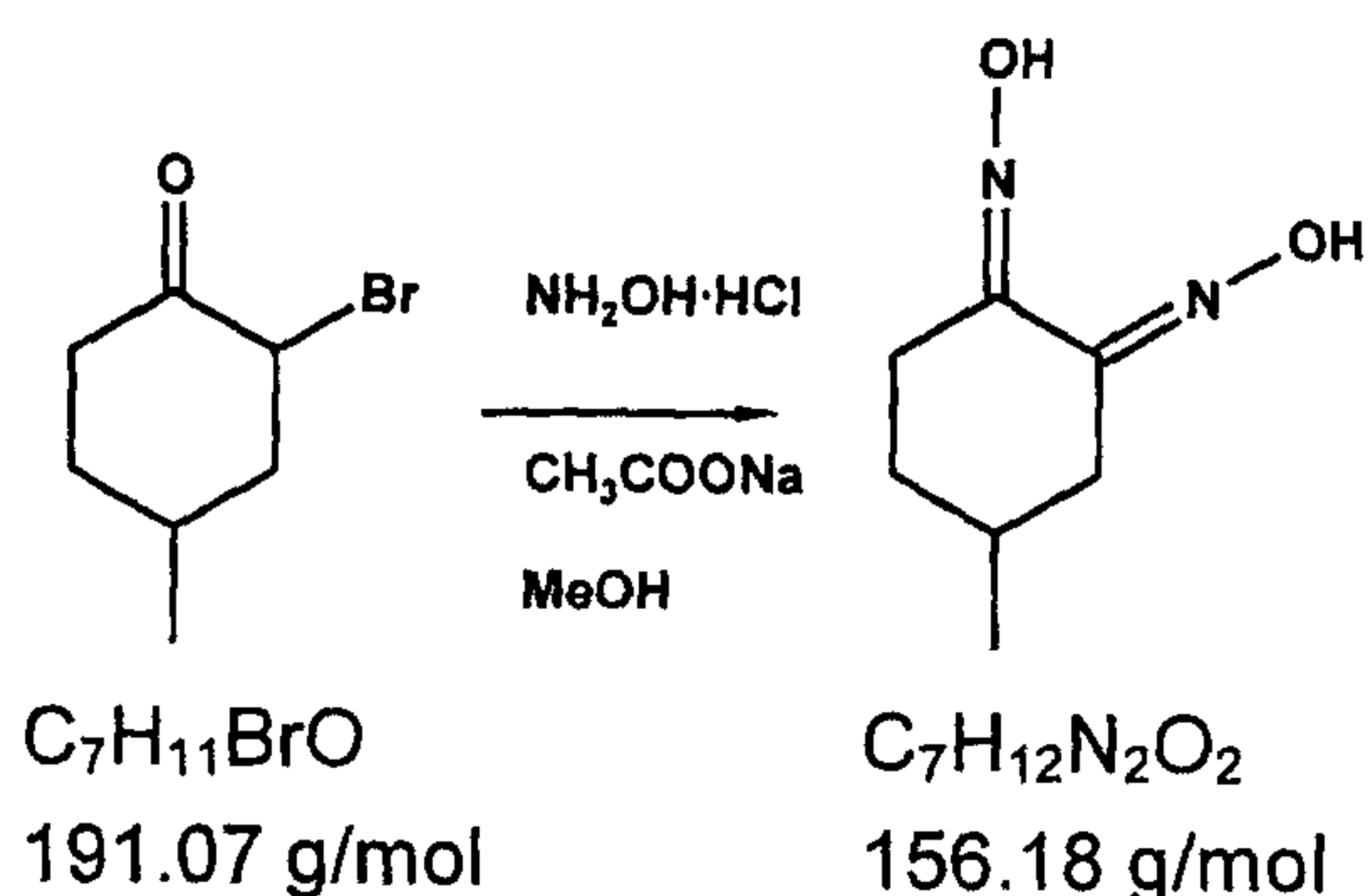
Yield: 33.3 g = 0.174 mmol = 39% (references: 78%)



α -bromine ketones decompose very easily during storage or heating, so that purification and characterisation were omitted. By-products do not affect the isolation of the dioxime.

Synthesis Example 2

4-methylcyclohexane-1,2-dioxime



Preparation: 33.2 g = 0.174 mol 2-bromine-4-methyl-cyclohexanone
 70.4 g = 1.01 mol hydroxylaminohydrochloride
 145.3 g sodium acetate trihydrate
 126 ml methanol

70.4 g hydroxylaminohydrochloride and 145.3 g sodium acetate trihydrate are heated to boiling point in 126 ml methanol and 146 ml water. 33.2 g 2-bromine-4-methyl-cyclohexanone are dropped into the boiling solution over a period of 1.5 hours. Then boiling takes place for one hour under reflux and then about 100 ml of methanol is distilled off until the remaining solution becomes turbid. The residue is cooled to room temperature and then extracted three times with 80 ml benzene in each case. The combined benzene phases are added to about 500 ml of petroleum ether (boiling point 40-60°C) and cooled for 2 days at 4°C. On the bottom a brown oil is deposited which after decanting the supernatant solution, recrystallises in water. Through the use of a continuous extraction apparatus, the yield could be increased to 14% with further preparations.

Appearance: white solid

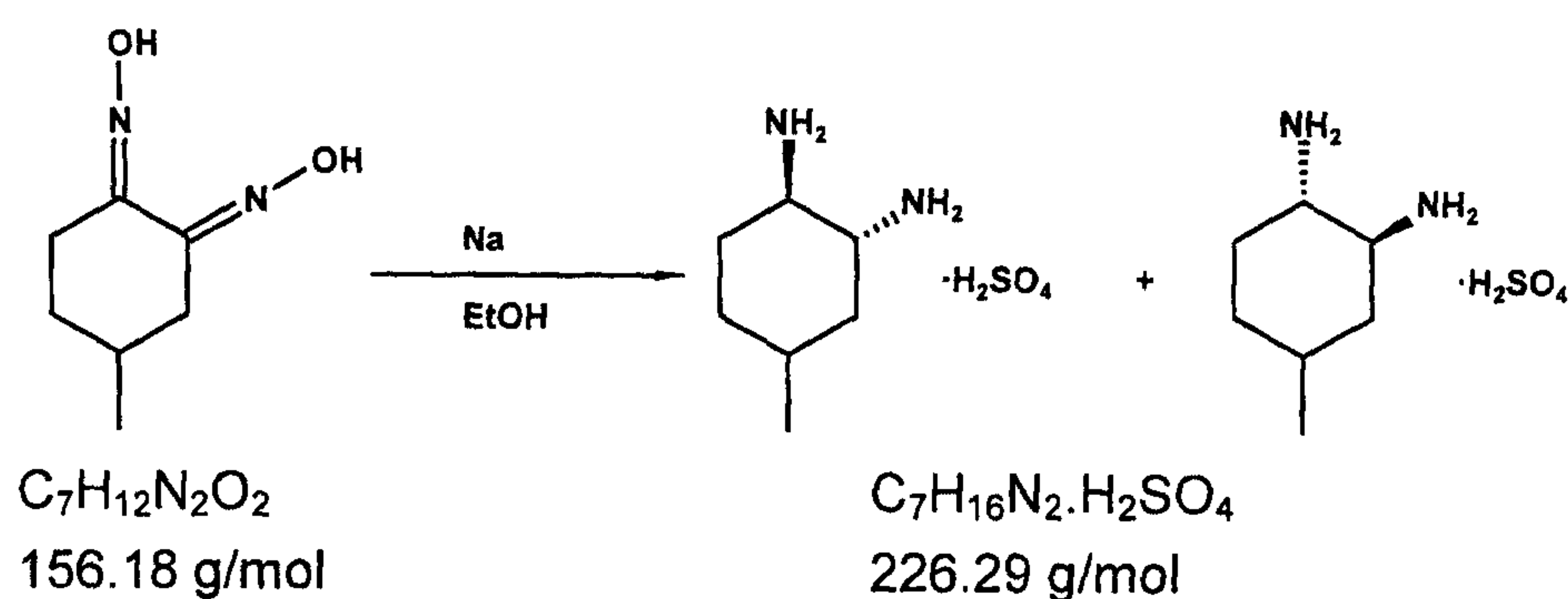
Yield: 2 g = 0.013 mol = 7.5% (references: 25%)

NMR spectra:**¹H-NMR spectrum** in methanol-d₄:

δ = 1.06 [d, 3H, CH₃, ³J_{H,H} = 6.53 Hz], 1.26 [m, 1H], 1.74 [m, 1H], 1.82 [m, 1H], 1.98 [m, 1H], 2.37 [m, 1H], 2.97 [m, 2H].

¹³C-NMR spectrum in methanol-d₄:

δ = 20.8 [CH₃], 23.9 [CH₂], 29.2 [CH], 30.4 [CH₂], 33.0 [CH₂], 153.1 [C=NOH], 153.1 [C=NOH].

Synthesis Example 3**4-methyl-*trans*-cyclohexane-1,2-diaminodihydrogensulphate**

Preparation: 4 g = 0.026 mol 4-methylcyclohexane-1,2-dioxime
 30 g = 1.305 mol sodium
 100 ml ethanol absolute

4 g 4-methylcyclohexane-1,2-dioxime are dissolved in a 1l three-necked flask with reflux condenser under N₂ atmosphere in 100 ml absolute ethanol and heated to boiling point. 30 g sodium are added in small pieces so that finally a large ball of molten sodium is formed on the liquid surface. A covering of sodium ethanolate on the surface of the ball is removed by further addition of absolute ethanol. The reaction mixture is boiled until all the sodium is dissolved. The solution is distilled with water vapour to first remove the alcohol and then to obtain the amine. The end of the distillation is reached when the distillate is no longer alkaline. The fraction containing the amine is acidified with 3 M sulphuric acid and evaporated to dryness on the

rotary evaporator. The pink coloured raw product is heated with 40 ml of ethanol under stirring to 50°C, the pink by-product dissolves and the white 4-methyl-*trans*-cyclohexane-1,2-diaminodihydrogensulphate is drawn off via a G4 filter crucible and dried in the air.

Appearance: white solid

Yield: 3.067 g = 0.013 mol = 52% = (references: 78%)

Elementary analysis: calculated for $C_7H_{16}N_2 \cdot H_2SO_4$ 226.29 g/mol

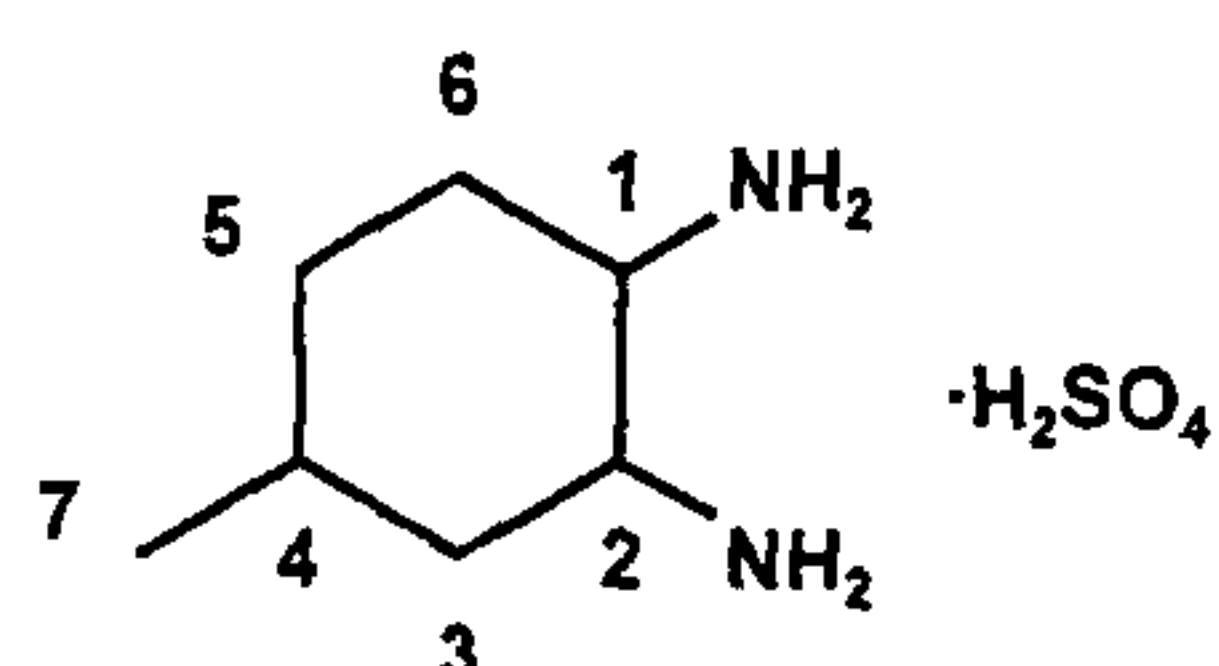
	C	H	N	O	S
calculated:	37.15	8.02	12.38	28.28	14.17
found:	37.27	7.80	12.17		

IR spectrum [370-7000 cm^{-1} , CsI], characteristic bands (in cm^{-1}):

in the range 2200-3300	$\nu(N-H)$
1651	$\delta(N-H)$
1550	$\delta(N-H)$

NMR spectra:

Two isomers were found. The isomer with the lower concentration is designated with '.



^1H -NMR spectrum in D_2O :

δ = 0.85 [d, 3H, H(7), $^3J_{H,H}$ = 6.53 Hz], 0.90 [d, 3H, H(7'), $^3J_{H,H}$ = 7.03 Hz], 0.99 [m, 1H, H(5)], 1.15 [m, 1H, H(3)], 1.42-1.55 [m, 2H, H(4), H(6)], 1.66-1.77 [m, 1H, H(5)], 1.99-2.10 [m, 2H, H(6) and H(3)], 3.23-3.39 [m, 2H, H(1) and H(2)], 3.50-3.60 [m, 2H, H(1') and H(2')].

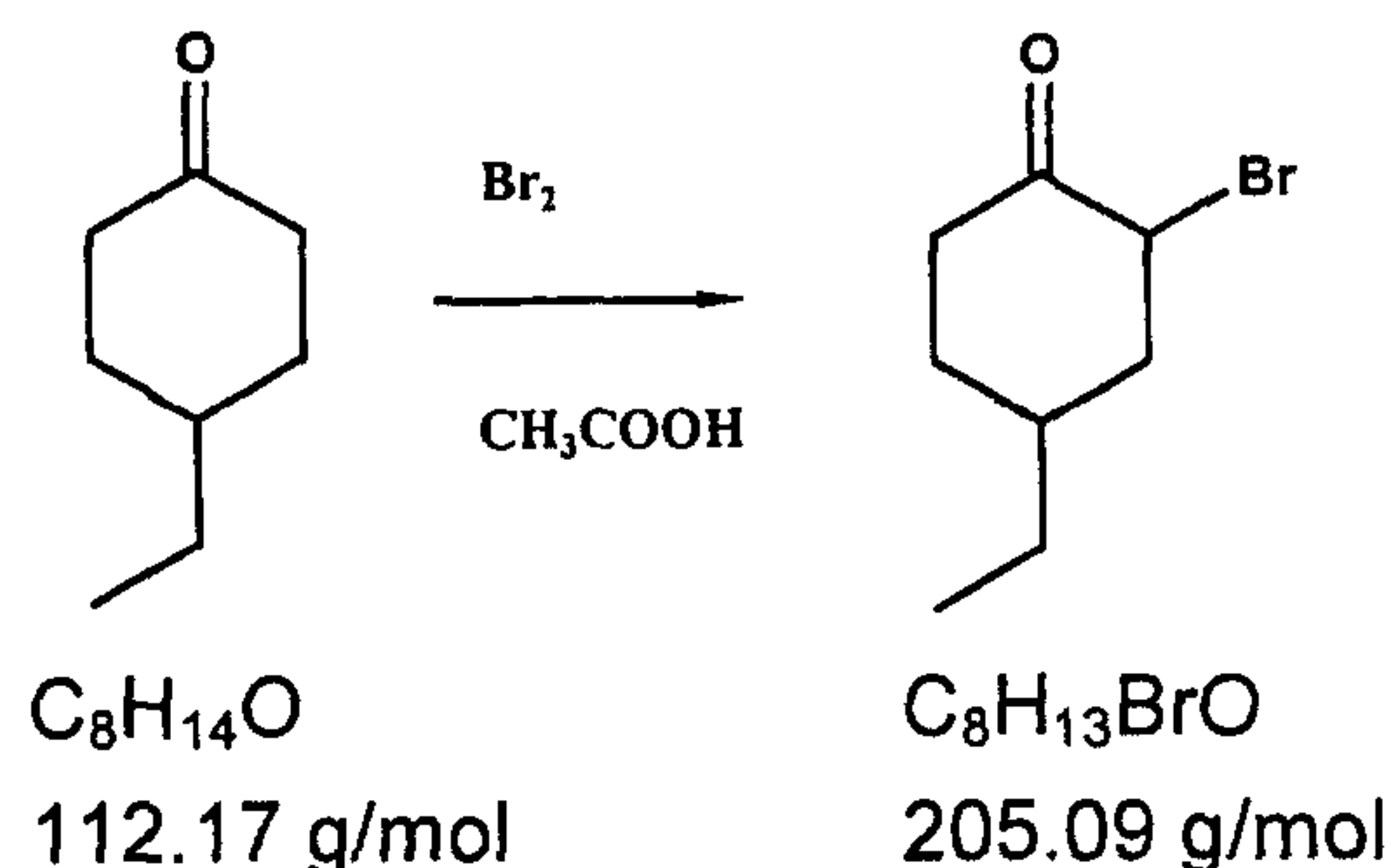
^{13}C -NMR spectrum in D_2O :

δ = 17.9 [C(7')], 20.7 [C(7)], 24.0 [C(6')], 25.8 [C(4')], 27.8 [C(5')], 29.5 [C(6)], 30.2 [C(4)], 31.5 [C(5)], 33.8 [C(3')], 37.6 [C(3)], 48.7 [C(1' or 2')], 51.2 [C(1' or 2')].

or 2')], 52.4 [C(1 or 2)], 52.5 [C(1 or 2)].

Synthesis Example 4

2-bromine-4-ethyl-cyclohexanone

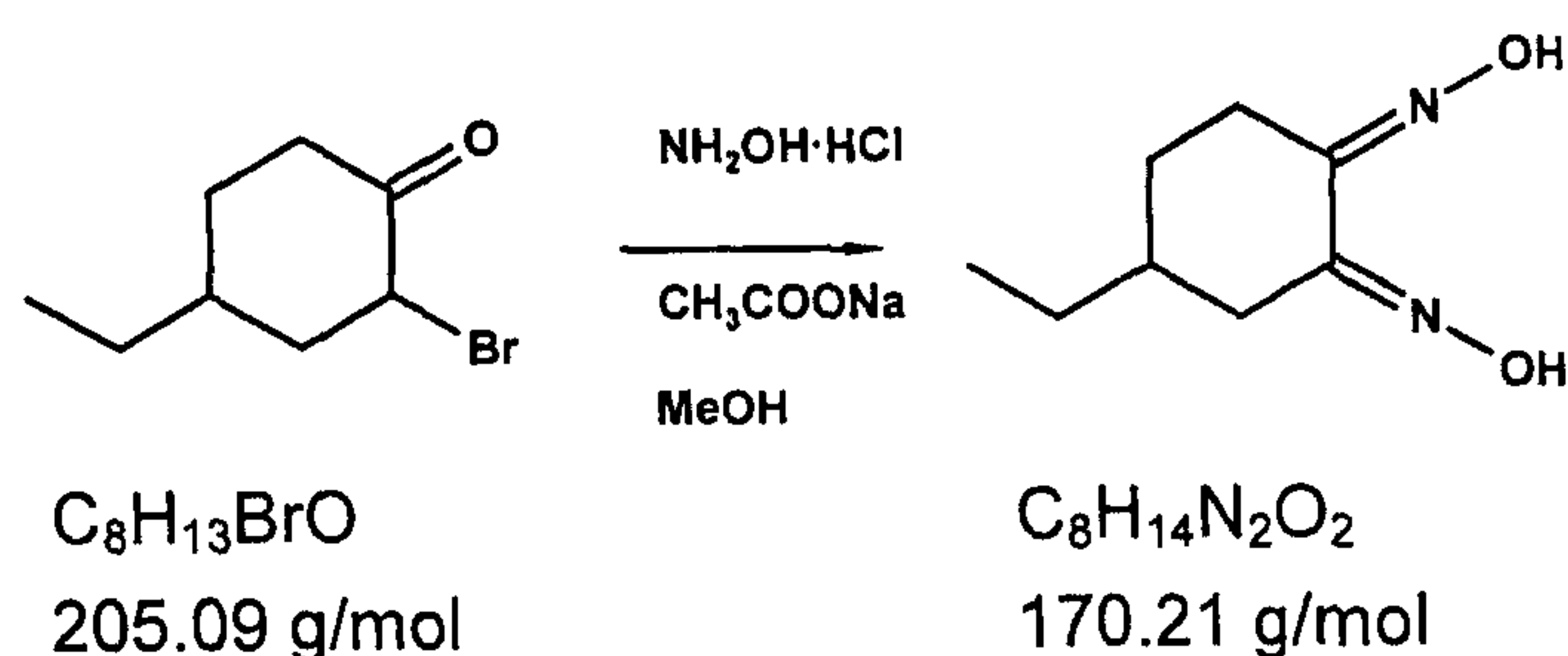


Preparation: 46 g = 0.36 mmol 4-ethylcyclohexanone
 66 g = 0.37 mmol bromine
 82 ml 99% acetic acid

46 g 4-ethylcyclohexanone are placed into a two-neck flask with separating funnel and Liebig condenser with 106 ml water, 82 ml 99% acetic acid and 2 drops of bromine. The reaction mixture is heated to about 50°C until the reaction starts. Then 59.2 g bromine are added drop by drop over a period of 1.5 hours so slowly that the temperature remains at 35-40°C. Then the solution is neutralised with solid NaCO_3 , so that the bromine ketone separates as a yellow oily liquid. The organic phase is washed with diluted NaCO_3 solution and then with water. The product is filtered over Na_2SO_4 .

Appearance: yellow liquid
Yield: 54 g = 0.263 mol = 73%

α -bromine ketones decompose very easily during storage or heating, so that purification and characterisation were omitted. By-products do not affect the isolation of the dioxime.

Synthesis Example 5**4-ethylcyclohexane-1,2-dioxime**

Preparation: 54 g = 0.263 mol 2-bromine-4-ethyl-cyclohexanone
 105.7 g = 1.52 mol hydroxylaminohydrochloride
 212 g sodium acetate trihydrate
 185 ml methanol

105.7 g hydroxylaminohydrochloride and 212 g sodium acetate trihydrate are heated to boiling point in 185 ml methanol and 185 ml water. 54 g 1-bromine-4-ethyl-cyclohexanone are dropped into the boiling solution over a period of one hour. Then boiling takes place for one hour under reflux and then distillation until the remaining solution becomes turbid. The residue is cooled to room temperature and then extracted with about 150 ml of benzene in a continuous extraction apparatus (in 4 portions of 100 ml, each for 2 hours). The benzene solution is topped up with petroleum ether (boiling point 40-60°C) to about 900 ml and cooled overnight at 4°C. On the bottom a brown oil is deposited which after decanting the remaining solution, is recrystallised in water repeatedly until the white 4-ethylcyclohexane-1,2-dioxime is obtained (4-5 times).

Appearance: white laminar shaped solid
Yield: 11.9 g = 0.0699 mol = 26.6%

NMR spectra:**¹H-NMR spectrum** in methanol-d₄:

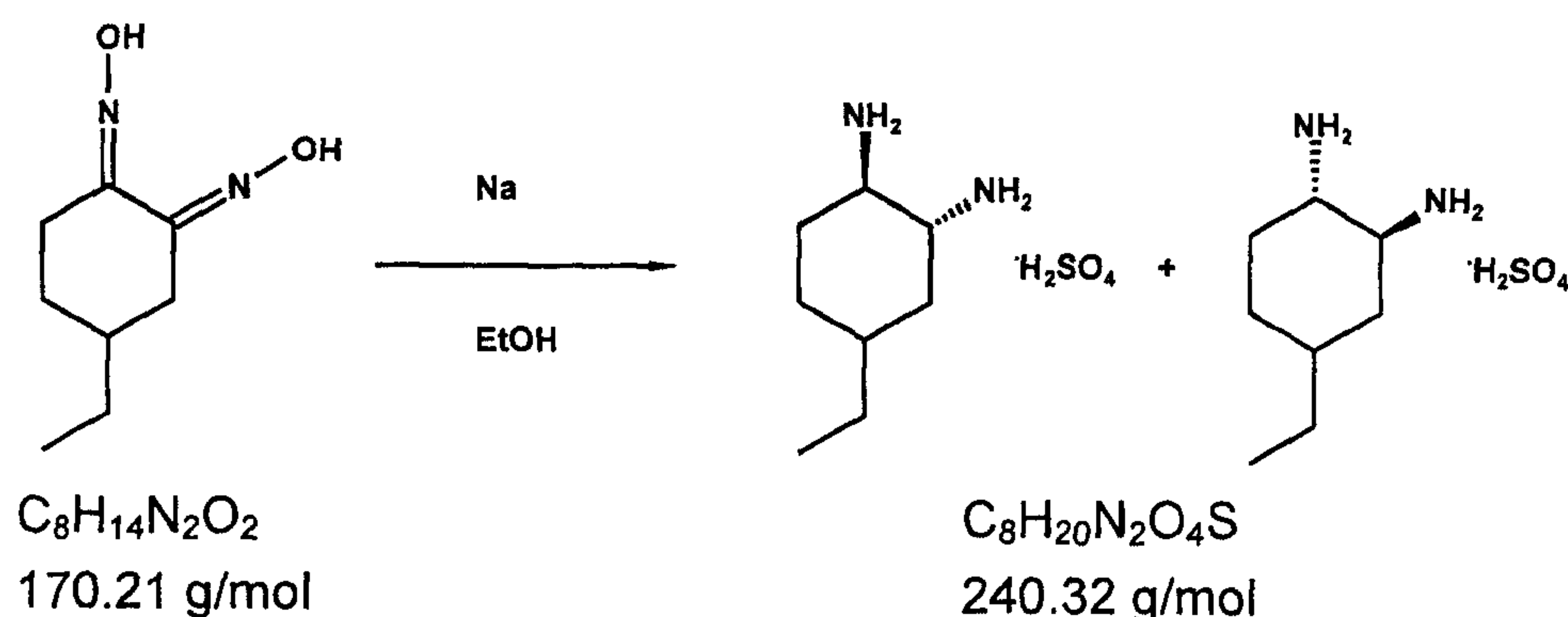
δ = 0.98 [t, 3H, CH₃, ³J_{H,H} = 7.53 Hz], 1.25 [m, 1H], 1.40 [m, 2H, CH₂CH₃], 1.50 [m, 1H], 1.88 [m, 1H], 2.03 [m, 1H], 2.37 [m, 1H], 2.96 [m, 2H].

¹³C-NMR spectrum in methanol-d₄:

δ = 10.73 [CH₃], 23.9 [CH₂], 27.9 [CH₂], 28.8 [CH₂], 30.8 [CH₂], 35.9 [CH], 153.3 [C=NOH], 153.5 [C=NOH].

Synthesis Example 6

4-ethyl-*trans*-cyclohexane-1,2-diaminodihydrogensulphate



Preparation: 9 g = 0.053 mol 4-ethylcyclohexane-1,2-dioxime
 50.05 g = 2.20 mol sodium
 280 ml ethanol absolute

9 g 4-ethylcyclohexane-1,2-dioxime are dissolved in a 1l three-necked flask with reflux condenser under N₂ atmosphere in 100 ml absolute ethanol and heated to boiling point. 50.5 g sodium are added in small pieces so that finally a large ball of molten sodium is formed on the liquid surface. A covering of sodium ethanolate on the surface of the ball is removed by further addition of absolute ethanol. The reaction mixture is boiled until all the sodium is dissolved. The solution is distilled with water vapour to first remove the alcohol and then to obtain the amine. The end of the distillation is reached when the distillate is no longer alkali. The fraction containing the amine is acidified with 3 M sulphuric acid and evaporated to dryness on the rotary evaporator. The pink coloured raw product is heated with 40 ml of ethanol under stirring to 50°C, the pink by-product dissolves and the white 4-ethyl-*trans*-cyclohexane-1,2-diaminodihydrogensulphate is drawn off via a G4 filter crucible and dried in the air.

20

Appearance: white solid
Yield: 3.055 g = 0.013 mol = 16%

Elementary analysis: calculated for $C_8H_{20}N_2 \cdot H_2SO_4$ 240.32 g/mol

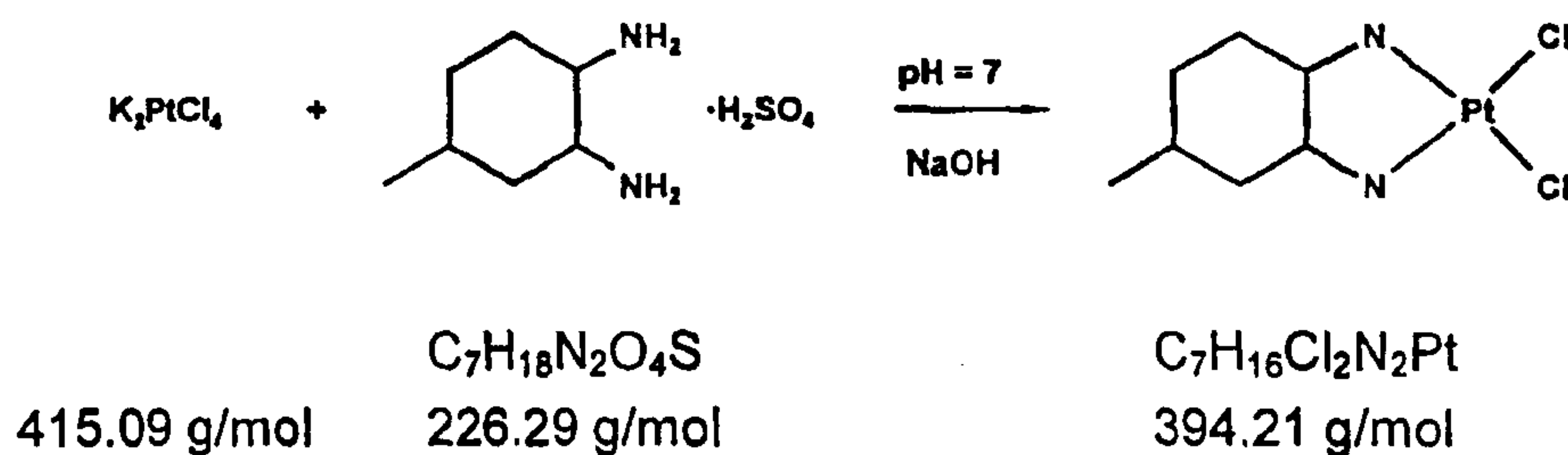
	C	H	N	O	S
calculated:	39.98	8.39	11.66	26.63	13.34
found:	40.11	8.10	11.64		

IR spectrum [$370\text{--}7000\text{ cm}^{-1}$, CsI], characteristic bands (in cm^{-1}):

10 in the range 2200-3300 $\nu(\text{N-H})$
 1637 $\delta(\text{N-H})$
 1546 $\delta(\text{N-H})$

Synthesis Example 7

(SP-4-3)-dichloro(4-methyl-*trans*-cyclohexane-1,2-diamine)platinum (II)



20 Preparation: 2.15 g = 9.50 mmol 4-methyl-*trans*-cyclohexane-1,2-diaminodihydrogensulphate
 3.944 g = 9.50 mmol K_2PtCl_4

3.944 g of K_2PtCl_4 are dissolved in 50 ml tridistilled water and suspended with 2.15 g 4-methyl-*trans*-cyclohexane-1,2-diaminodihydrogensulphate. Then the pH value is set to 7 with 0.5 M NaOH and maintained at this value with a 718 Stat Titrino* from Methrom with 0.1 M NaOH. The voluminous yellow precipitate is drawn off through a G3 filter crucible, washed twice each with ice-cold tridistilled water and ethanol and dried in the vacuum desiccator over phosphorus pentoxide.

* trademark

Appearance: yellow solid
Melting point: >310°C decomposition
Yield: 3.0 g = 7.6 mmol = 80%

Elementary analysis: calculated for $C_7H_{16}Cl_2N_2Pt$ 394.21 g/mol

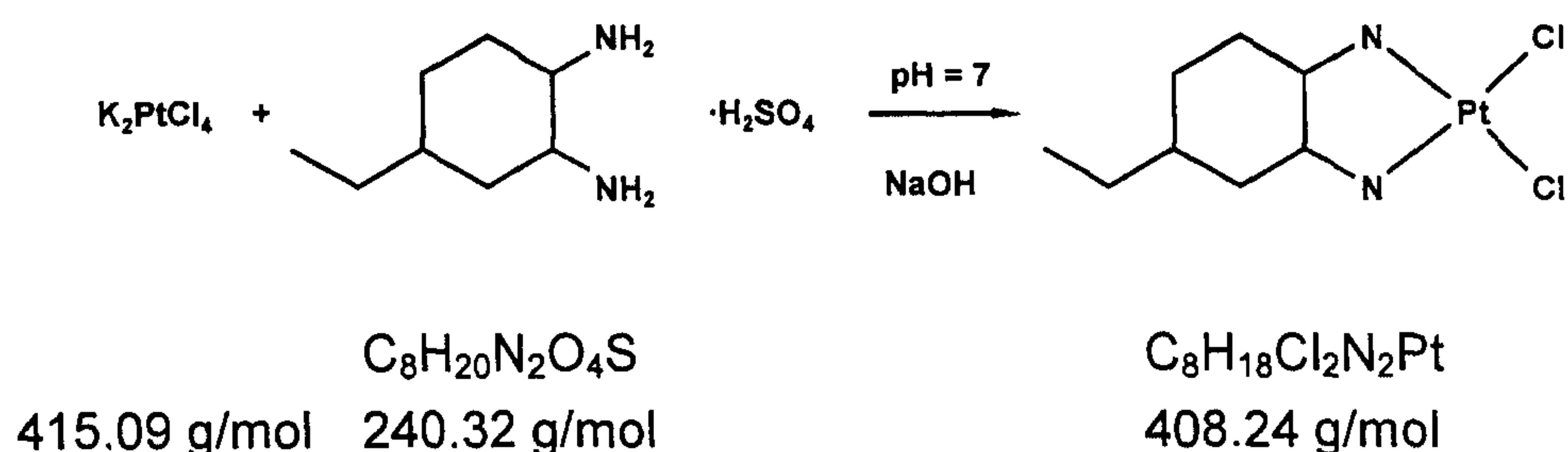
	C	H	N	Cl	Pt
calculated:	21.33	4.09	7.11	17.99	49.49
found:	21.44	3.80	7.00		

IR spectrum [370-7000 cm^{-1} , CsI], characteristic bands (in cm^{-1}):

3273, 3197	$\nu(N-H)$
2936, 2866	$\nu(C-H)$
1562	$\delta(N-H)$

Synthesis Example 8

(SP-4-3)-dichloro(4-ethyl-*trans*-cyclohexane-1,2-diamino)platinum (II)



Preparation: 2.000 g = 8.32 mmol 4-ethyl-*trans*-cyclohexane-1,2-diaminodihydrogensulphate
 3.454 g = 8.32 mmol K_2PtCl_4

3.454 g K_2PtCl_4 are dissolved in 50 ml tridistilled water and suspended with 2.000 g 4-ethyl-*trans*-cyclohexane-1,2-diaminodihydrogensulphate. Then the pH value is set to 7 with 0.5 M NaOH and maintained at this value with a 718 Stat Titrino from Methrom with 0.1 M NaOH. The voluminous yellow precipitate is drawn off through a G4 filter crucible, washed twice each with

ice-cold tridistilled water and ethanol and dried in the vacuum desiccator over phosphorus pentoxide.

Appearance: yellow solid
Melting point: >310°C decomposition
Yield: 3.238 g = 7.93 mmol = 95%

Elementary analysis: calculated for $C_8H_{18}Cl_2N_2Pt$ 408.24 g/mol

	C	H	N	Cl	Pt
calculated:	23.54	4.44	6.86	17.37	47.79
found:	23.52	4.18	6.63		

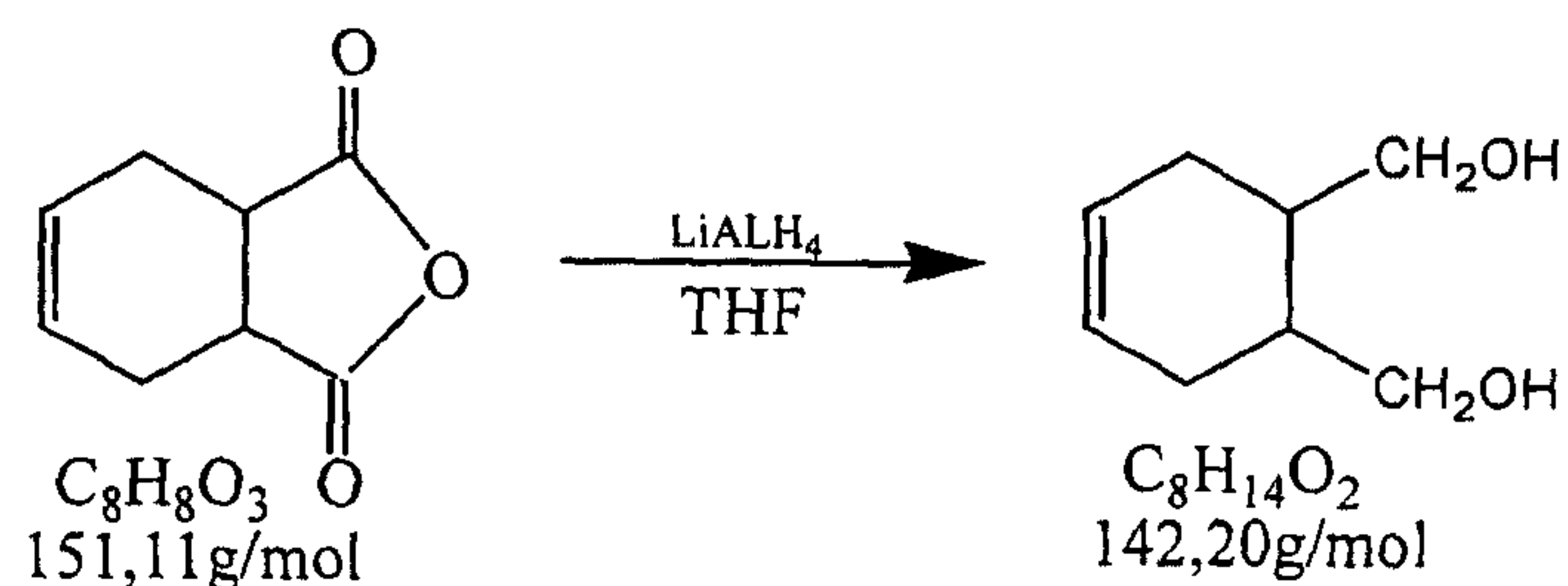
IR spectrum [370-7000 cm^{-1} , Csl], characteristic bands (in cm^{-1}):

3273, 3196	$\nu(N-H)$
2933, 2861	$\nu(C-H)$
1558	$\delta(N-H)$

Synthesis Example 9

4,5-dimethyl-1-cyclohexene (**2 ways: mesylate/tosylate**)

4,5-di(hydroxymethyl)cyclohexene



Preparation: 30 g = 0.2 mol cis-1,2,3,6-tetrahydrophthalic acid anhydride
 45 g = 1.2 mol $LiAlH_4$
 375 ml abs. tetrahydrofuran

30 g cis-1,2,3,6-tetrahydrophtalic acid anhydride in 150 ml abs. THF are added through a separating funnel to a solution of 45 g lithium aluminium hydride in 900 ml abs. THF and heated for 48 hours under reflux. Then the mixture is first cooled to room temperature and then in an ice-brine bath to about 15°C and the unused portion of the hydride is carefully broken down with water. Through the addition of diluted sulphuric acid the salts are dissolved and through the addition of diethylether the organic phase is separated from the aqueous phase.

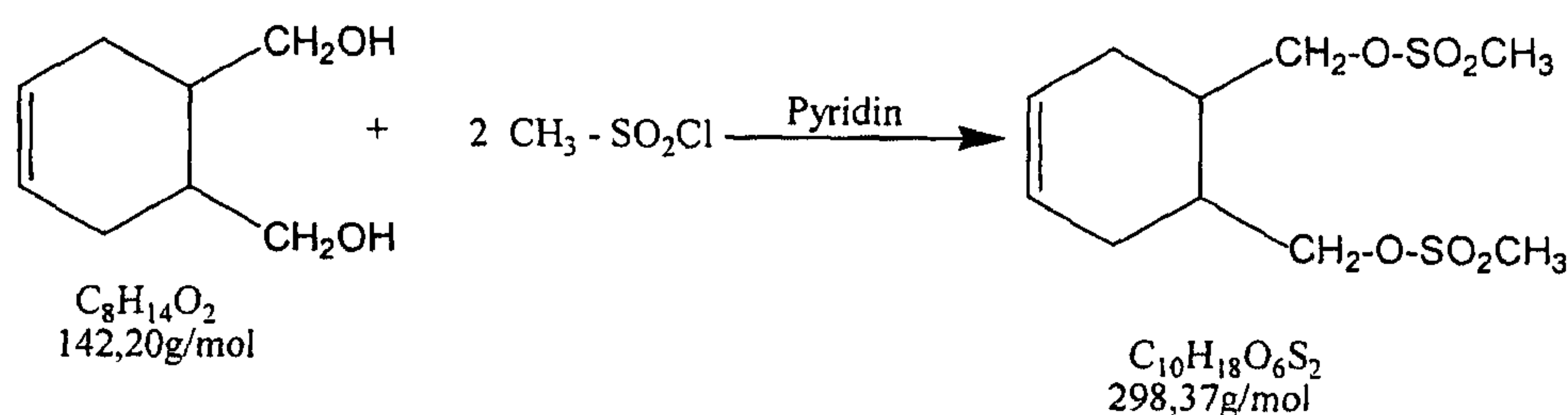
The organic phase is washed with a saturated Na₂CO₃ solution and dried with Na₂SO₄. The solvents, i.e. ether and THF are centrifuged off in a vacuum.

Appearance: yellow oily liquid

Yield: 27 g = 0.19 mol = 95.6%

Synthesis Example 10

4,5-di(methylsulphonate)cyclohexene



Preparation: 28 g = 0.19 mol 4,5-di(hydroxymethyl)-1-cyclohexene

46 g = 0.40 mol methane sulphonylchloride (Mr = 114.55)

330 ml abs. pyridine

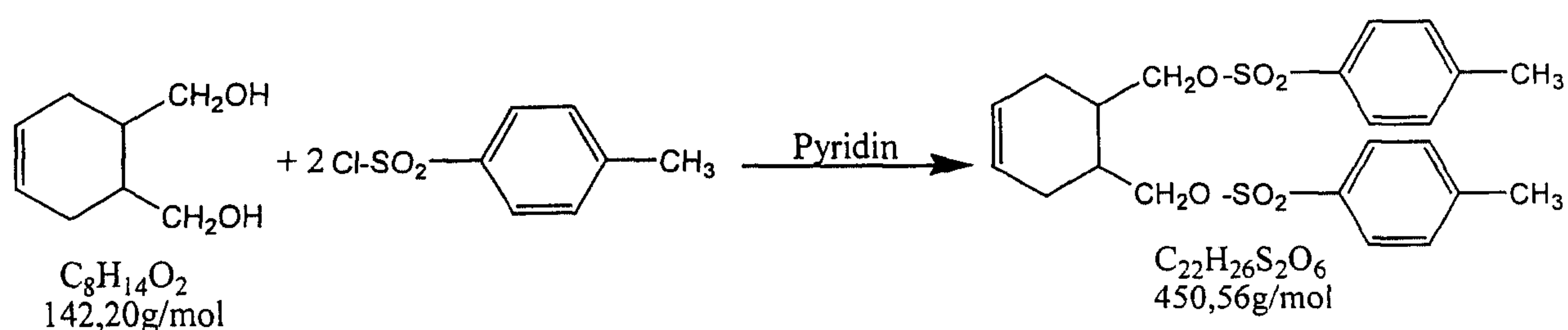
46 g methane sulphonylchloride are added in small portions to a cold solution of 28 g 4,5-di(hydroxymethyl)-1-cyclohexene in 200 ml abs. pyridine. The mixture is stirred for 4-5 hours at a temperature of 3-4°C and then stored for a further 24 hours at 2°C. After the addition of an excess of diluted hydrochloric acid, the solution is extracted with chloroform. The chloroform phase is washed with a saturated Na₂CO₃ solution and water, dried with Na₂SO₄ and the solvent centrifuged off in a vacuum. The product is then recrystallised out of methanol and petroleum spirit (40-60°C).

Appearance: colourless crystals
M.p.: 86-87°C
Yield: 39 g = 0.13 mol = 68.8%
Elementary analysis: calculated for C₁₀H₁₈S₂O₆

	C	H	O	S
calculated:	40.26	6.08	32.17	21.49
found:	40.17	6.08		21.42

Synthesis Example 11

4,5-di(methyltosylate)cyclohexene



Preparation: 30 g = 0.21 mol 4,5-di(hydroxymethyl)-1-cyclohexene
 84 g = 0.44 mol p-toluol-4-sulphochloride (Mr = 190.65)
 300 ml abs. pyridine

84 g p-toluol-4-sulphochloride in 200 ml pyridine are added in small portions to a cold solution of 30 g 4,5-di(hydroxymethyl)-1-cyclohexene in 60 ml abs. pyridine.

The mixture is stirred for 4-5 hours at a temperature of 3-4°C and then stored for a further 24 hours at 2°C. On the next day the mixture is mixed with 90 ml concentrated HCl and 180 ml ice, whereby a brown oil is formed. The aqueous phase is extracted twice with 50 ml ether. The ether phases and the ditosylate are washed once with water and then with a saturated NaHCO₃ solution and then again with water. The ether phase is dried with Na₂SO₄ and the solvent centrifuged off in a vacuum.

Appearance: colourless crystals
M.p.: 93-94°C

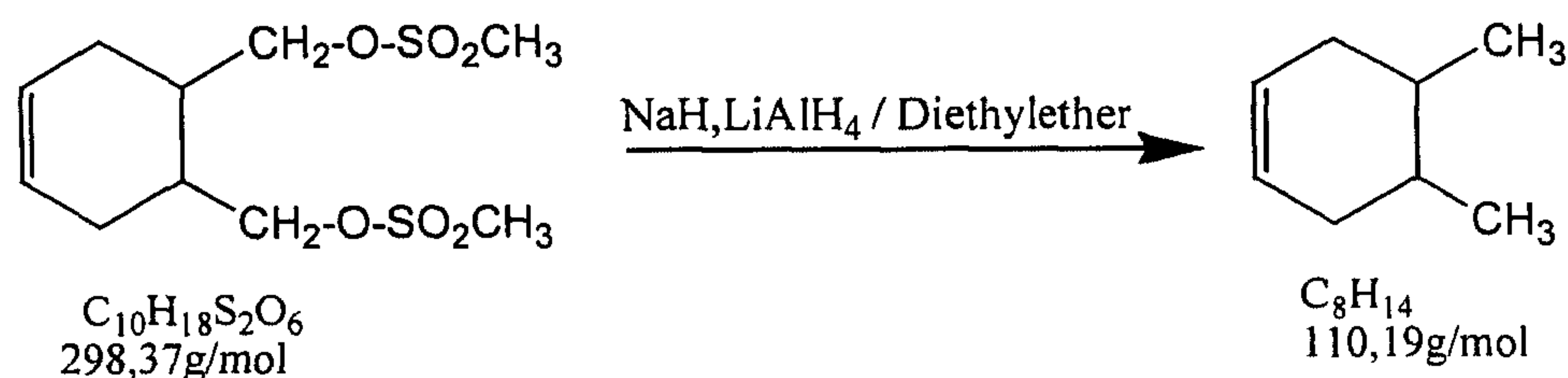
Yield: 49 g = 0.11 mol = 52.4%

Elementary analysis: calculated for $C_{22}H_{26}S_2O_6$

	C	H	O	S
calculated:	58.65	5.82	21.31	14.23
found:	58.06	5.84		13.91

Synthesis Example 12

4,5-dimethyl-1-cyclohexene from the di(methylsulphonate)



Preparation: 19.0 g = 0.064 mol 4,5-di(methane sulphonate)cyclohexene
 10.6 g = 0.28 mol $LiAlH_4$
 6.40 g = 0.27 mol NaH

11.2 g $LiAlH_4$ and 6.7 g NaH in 300 ml abs. ether are heated for 30 min. under reflux and then cooled to $-5^\circ C$. 19 g of the dimesylate are added in solid form and the temperature maintained at $-5^\circ C$ for one hour. Then the mixture is heated overnight under reflux.

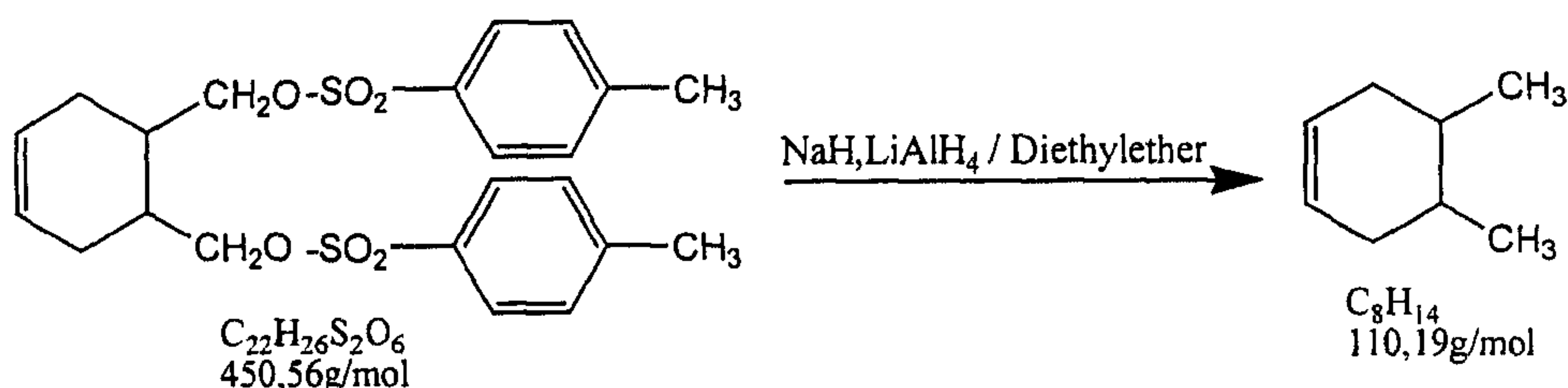
The hydride excesses are broken down by the addition of saturated ammonium chloride solution and the mixture is stirred for one hour. Then the solid is filtered off and washed with ether. The organic phase is dried with Na_2SO_4 and ether is centrifuged off. Then the product is distilled off at $123-125^\circ C$.

Appearance: colourless oily liquid

Yield: 2.3 g = 20.9 mmol = 32.6%

Synthesis Example 13

4,5-dimethyl-1-cyclohexene from the di(methyltosylate)



Preparation: 48.0 g = 0.1 mol 4,5-di(methyltosylate)cyclohexene
 17.0 g = 0.44 mol LiAlH_4
 10.0 g = 0.42 mol NaH

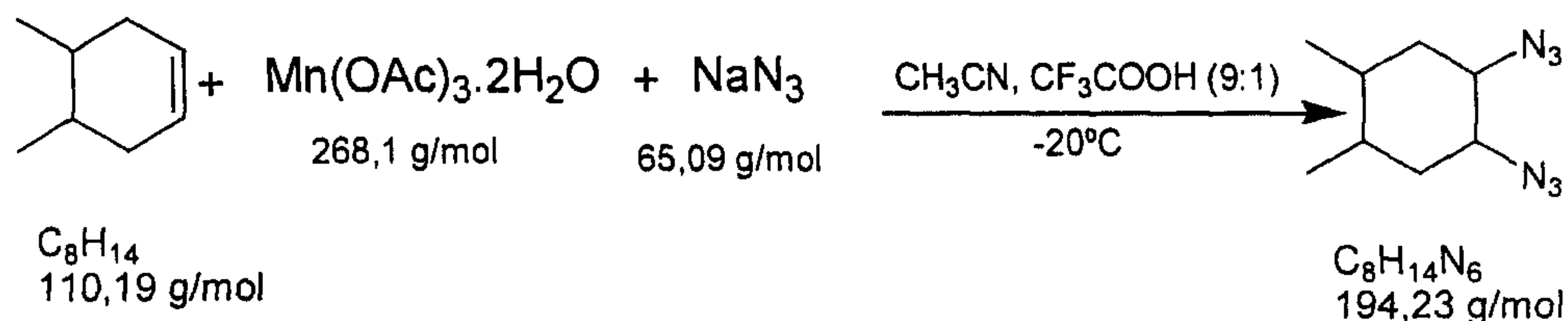
17 g LiAlH_4 and 10 g NaH in 500 ml abs. ether are heated for 30 min under reflux and then cooled to -5°C . 48 g of the ditosylate are added in solid form and the temperature maintained at -5°C for one hour. Then the mixture is heated overnight under reflux.

The hydride excesses are broken down by the addition of saturated ammonium chloride solution and the mixture is stirred for one hour. Then the solid is filtered off and washed with ether. The organic phase is dried with Na_2SO_4 and ether is centrifuged off. Then the product is distilled off at $123\text{--}125^\circ\text{C}$.

Appearance: colourless oily liquid
Yield: 2.3 g = 20.9 mmol = 20.9%

Synthesis Example 14

4,5-dimethyl-cyclohexane-1,2-diazide



Preparation: 1.90 g = 17.2 mmol 4,5-dimethyl-1-cyclohexene
 13.9 g = 51.6 mmol $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$
 5.60 g = 86.0 mmol NaN_3

1.9 g 4,5-dimethyl-1-cyclohexene and 20 ml TFA are added at -20°C and under a N_2 -atmosphere to a suspension of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ and NaN_3 in 200 ml acetonitrile. The mixture is stirred for 90 min. at -19 to -21°C and then diluted with a 10% NaHSO_3 solution. The solution is then extracted with 3 x 50 ml petroleum spirit (boiling point = 40 - 60°C).

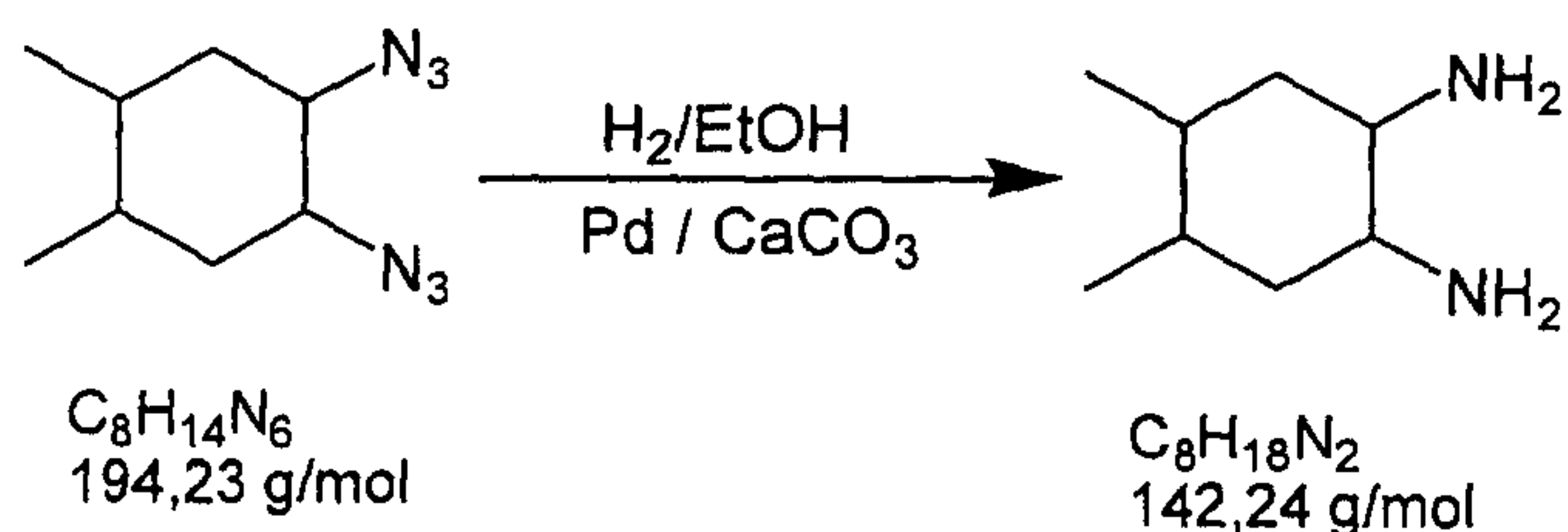
The organic phases are washed with saturated Na_2CO_3 solution and then washed with saturated NaCl solution and dried with Na_2SO_4 . The solution is then centrifuged off in a vacuum.

Yield: 2 g = 10.3 mmol = 60%

Appearance: colourless liquid

Synthesis Example 15

4,5-dimethyl-cyclohexane-1,2-diamine



Preparation: 1,9 g = 9.8 mmol 4,5-dimethyl-cyclohexane-1,2-diazide
 0.8 g $\text{Pd} / \text{CaCO}_3$

1.9 g 4,5-dimethyl-cyclohexane-1,2-diazide in 60 ml abs. ethanol are mixed with 0.8 g Lindlar catalyst and reduced to diamine over 45 hours in an autoclave at a H_2 pressure of 3-3.5 bar. At the end of the reduction the catalyst is filtered off and the ethanol is centrifuged off in a vacuum.

Yield: 1.34 g = 9.42 mmol = 96% 4,5-dimethyl-1,2-cyclohexanediamine

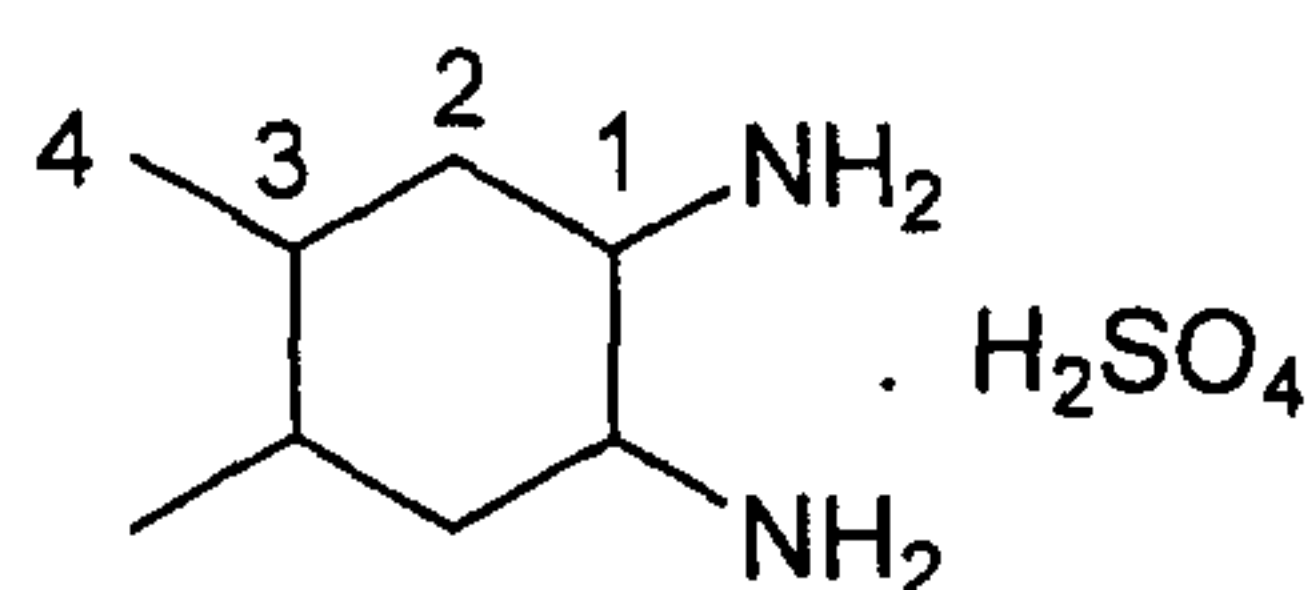
Characterisation as dihydrogen sulphate:

4,5-dimethyl-cyclohexane-1,2-diamine is acidified with sulphuric acid ($c = 3 \text{ mol/l}$). The precipitated solid is absorbed with ethanol and heated to 50°C . The impurities are dissolved and the white 4,5-dimethyl-1,2-diaminocyclohexane-dihydrogensulphate is drawn off via a G4 filter crucible and dried over phosphorus pentoxide in a vacuum.

Elementary analysis: calculated for $\text{C}_8\text{H}_{18}\text{N}_2\cdot\text{H}_2\text{SO}_4$

	C	H	N	O	S
calculated:	39.98	8.39	11.66	26.63	13.34
found:	39.15	8.55	11.23		13.43

NMR spectrum:



^1H -NMR in D_2O :

$\delta = 0.82\text{--}0.87$ [m, 3H, H(4) and H(4')], $^3J_{\text{H,H}}$, 1.68 [m, 1H, H(3) and H(3')], 1.95 [m, 2H, H(2) and H(2')], $3.34\text{--}3.4$ [m, 2H, H(1) and H(1')], $3.47\text{--}3.54$ [m, 2H, H(2) and H(2')].

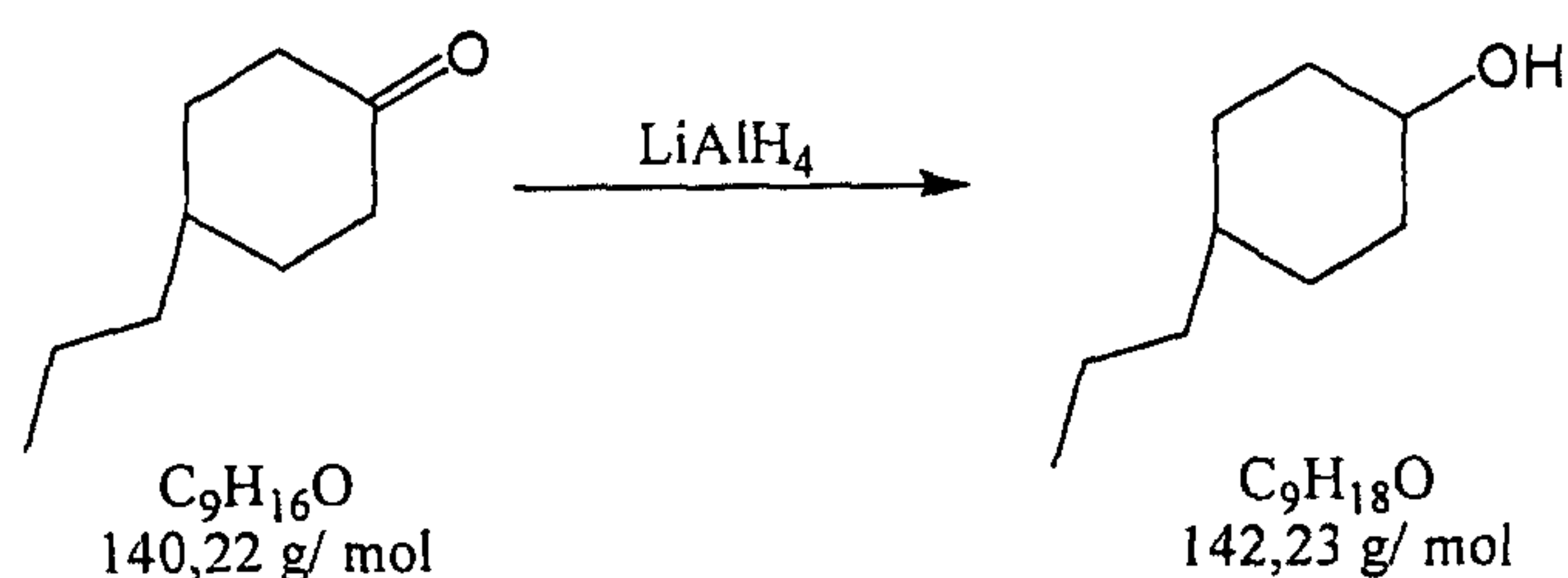
^{13}C -NMR spectrum in D_2O :

$\delta = 10.94$ [C(4')], 18.21 [C(4)], 31.61 [C(2')], 31.67 [C(3')], 32.65 [C(3)], 36.55 [C(2)], 48.71 [C(1')], 52.82 [C(1)].

Synthesis Example 16

4-propyl-1-cyclohexene

a) 4-propyl-1-cyclohexanol



Preparation: 20 g = 143 mmol 4-propyl-1-cyclohexanone
10 g LiAlH₄

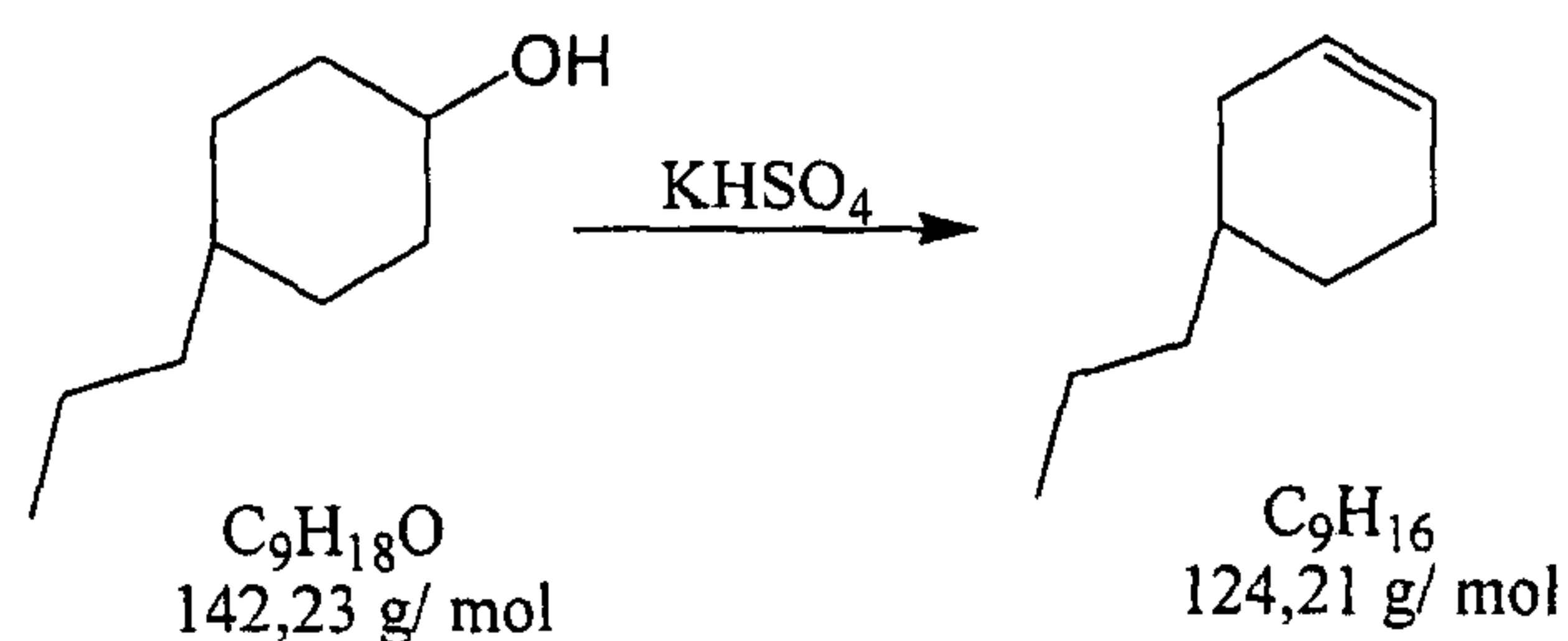
20 g 4-1-cyclohexanone are added slowly drop by drop through a separating funnel and under an argon atmosphere to a cooled solution of 10 g LiAlH_4 in 500 ml abs. THF.

After the end of the addition the mixture is heated to reflux and stirred for 48 hours at this temperature. After the end of the reduction 500 ml diethylether are added and the unreacted residues of LiAlH_4 are broken down by the drop-by-drop addition of dest. water. Then the mixture is mixed with 200 ml 10% sulphuric acid to dissolve the inorganic salts. The ether phase is then separated and the aqueous phase extracted twice with 50 ml of ether. The combined ether phases are dried with Na_2SO_4 , the ether and THF are centrifuged off.

Appearance: colourless oily liquid

Yield: 19.3 g = 135 mmol = 94%

b) 4-propyl-1-cyclohexene



Preparation: 19.0 g = 133 mmol 4-propylcyclohexanol
16.0 g KHSO₄

19 g 4-propyl-1-cyclohexanol are mixed with 16 g KHSO_4 and stirred for one week at 70°C . After the addition of ethylacetate KHSO_4 is filtered off. Ethylacetate is evaporated and the product obtained by fractional distillation.

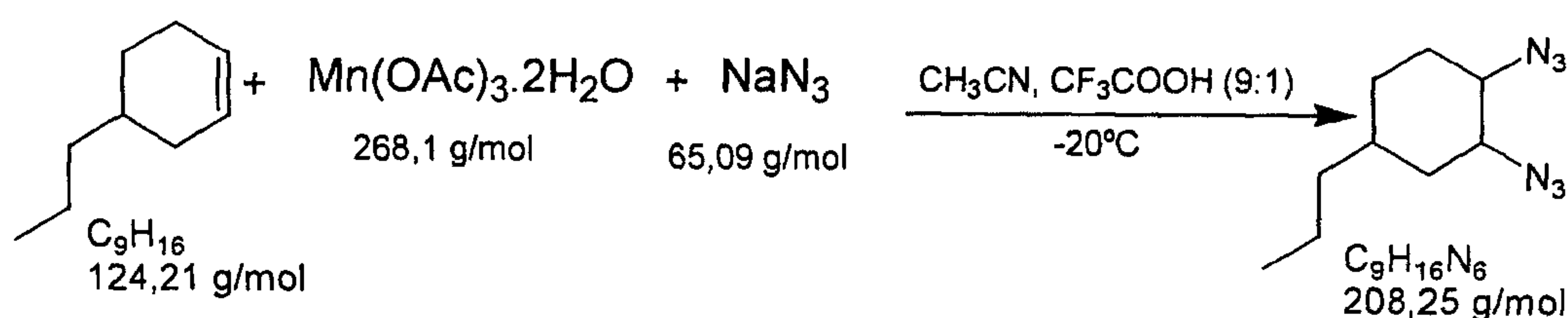
Yield: 13.7 g = 110 mmol = 83%

Appearance: colourless liquid

Boiling point = $151\text{--}153^\circ\text{C}$

Synthesis Example 17

4-propyl-cyclohexane-1,2-diazide



Preparation: 4.80 g = 38.6 mmol 4-propyl-1-cyclohexene

31.1 g = 116 mmol $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$

12.6 g = 196 mmol NaN_3

4.8 g 4-propyl-1-cyclohexene and 44 ml TFA are added at -20°C and under N_2 atmosphere to a suspension of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ and NaN_3 in 440 ml acetonitrile. The mixture is stirred for 3 hours at -19 to -21°C and then diluted with a 10% NaHSO_3 solution. The colourless solution is then extracted with 3 x 50 ml petroleum spirit (boiling point = $40\text{--}60^\circ\text{C}$).

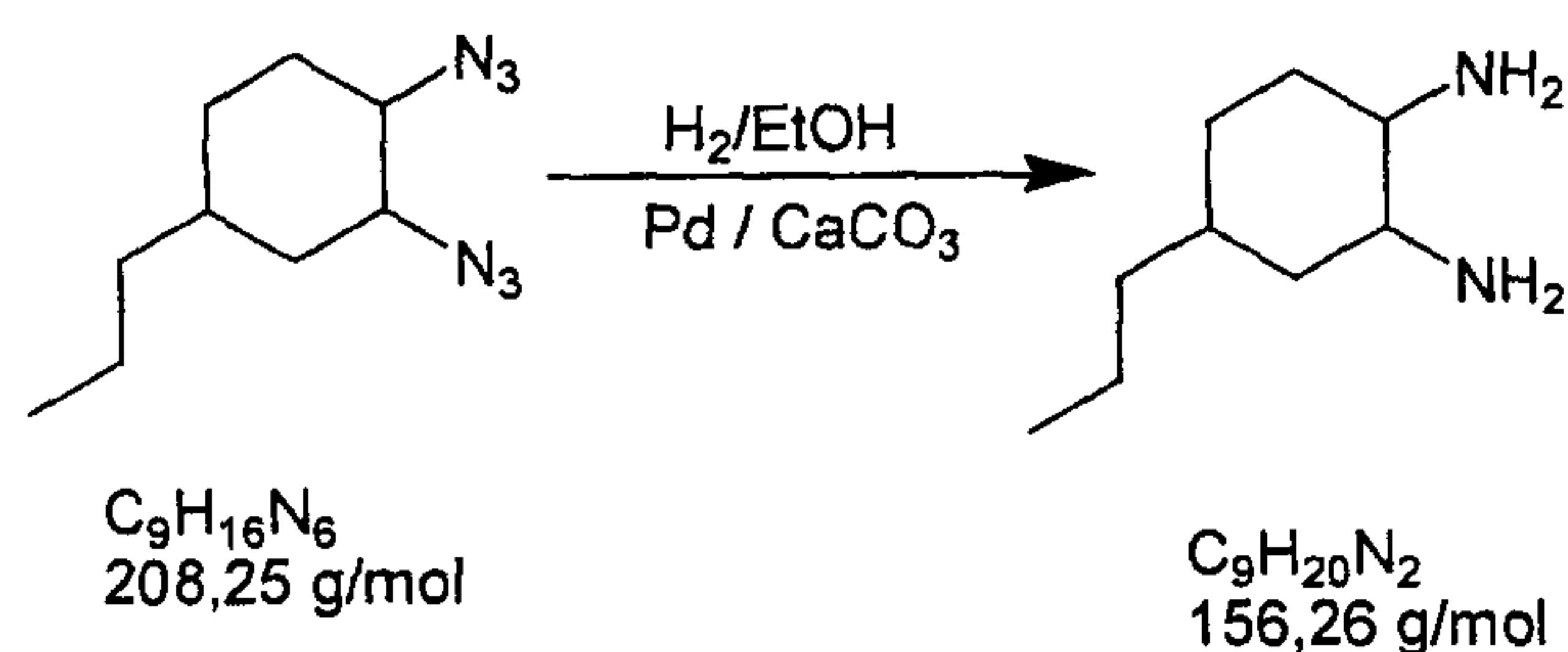
The organic phases are washed with saturated Na_2CO_3 solution and then with saturated NaCl solution and dried with Na_2SO_4 . The solution is then centrifuged off in a vacuum.

Yield: 29.4 g = 163 mmol = 78.5%

Appearance: colourless liquid

Synthesis Example 18

4-propyl-trans-cyclohexane-1,2-diamine



Preparation: 4 g = 19.2 mmol 4-propyl-cyclohexane-1,2-diazide
1.6 g Pd / CaCO₃

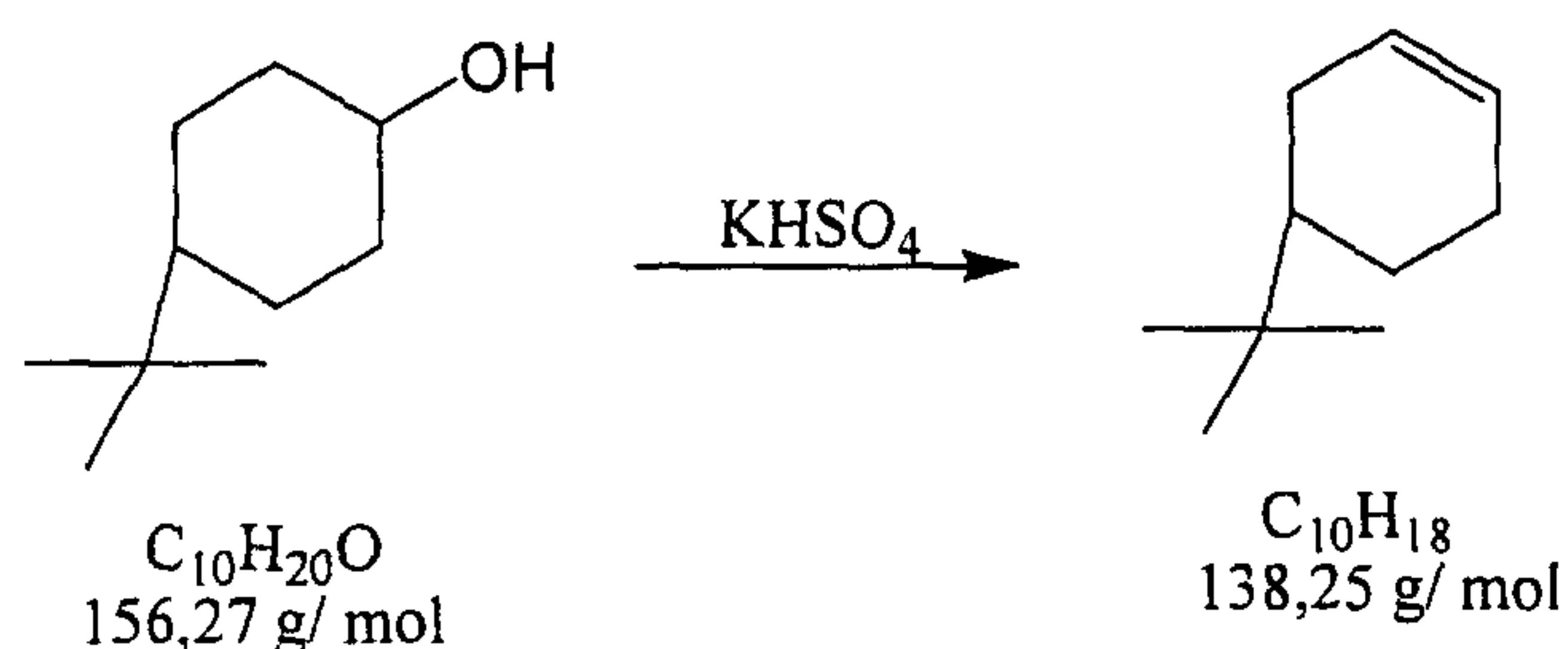
4 g 4-ethyl-cyclohexane-1,2-diazide in 60 ml abs. ethanol are mixed with 1.6 g Lindlar catalyst and reduced to diamine over 48 hours in an autoclave at a H₂ pressure of 3 bar. At the end of the reduction the catalyst is filtered off and the ethanol is centrifuged off in a vacuum.

Characterisation as dihydrogen sulphate:

4-propyl-1,2-diaminocyclohexane is acidified with sulphuric acid ($c = 3 \text{ mol/l}$). The precipitated solid is absorbed with ethanol and heated to 50°C . The impurities are dissolved and the white 4-propyl-cyclohexane-1,2-diamine-dihydrogensulphate is drawn off via a G4 filter crucible and dried over P_2O_5 in a vacuum.

Synthesis Example 19

4-t-butyl-1-cyclohexene



Preparation: 20.0 g = 120 mmol 4-propylcyclohexanol
17.0 g KHSO₄

20 g 4-t-butyl-1-cyclohexanol are mixed with 17 g KHSO_4 and stirred for one week at 95°C . After the addition of ethylacetate KHSO_4 is filtered off. Ethylacetate is evaporated and the product obtained by fractional distillation.

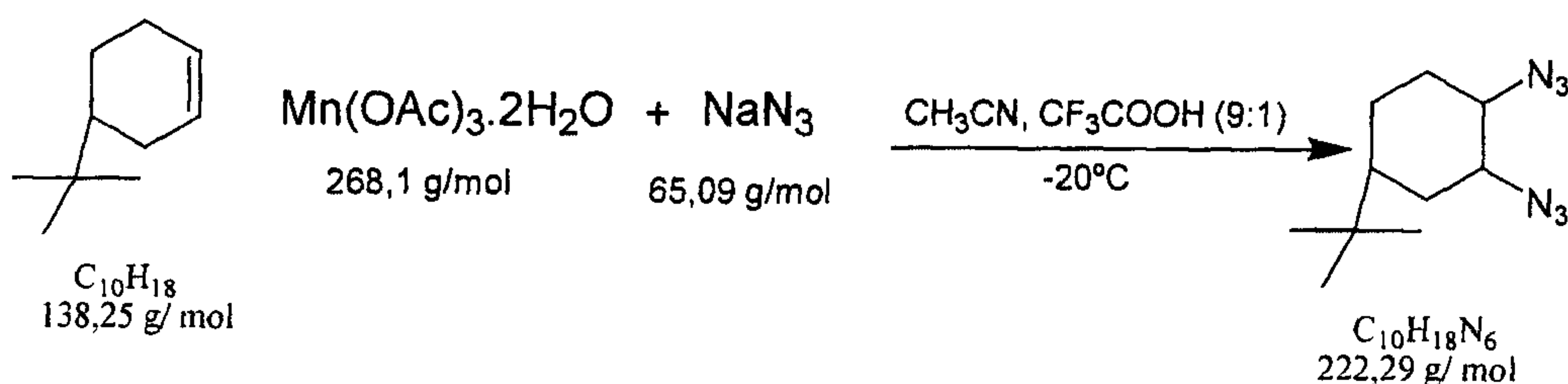
Yield: 11 g = 80 mmol = 65%

Appearance: colourless liquid

Boiling point = $168\text{--}171^\circ\text{C}$

Synthesis Example 20

4-t-butyl-cyclohexane-1,2-diazide



Preparation: 5.0 g = 36 mmol 4-t-butyl-1-cyclohexene

29 g = 108 mmol $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$

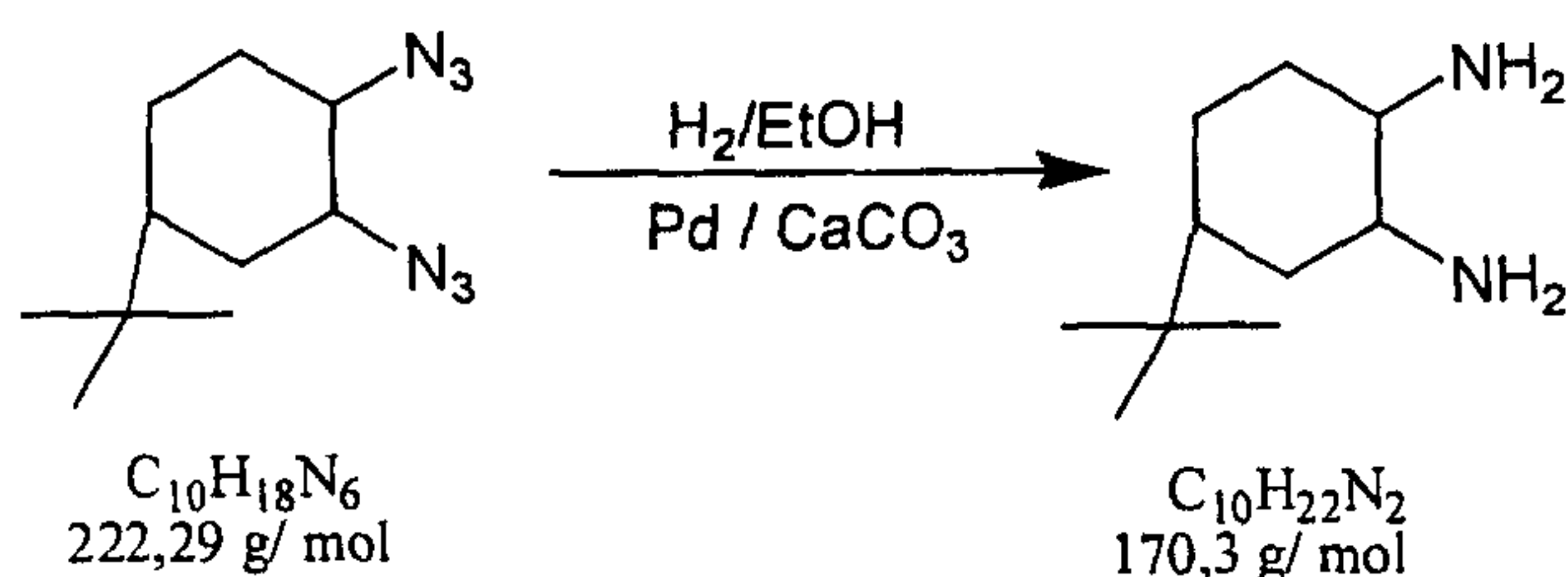
11.8 g = 180 mmol NaN_3

5 g 4-t-butyl-1-cyclohexene and 42 ml TFA are added at -20°C and under N_2 atmosphere to a suspension of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ and NaN_3 in 420 ml acetonitrile. The mixture is stirred for 3 hours at -19 to -21°C and then diluted with a 10% NaHSO_3 solution. The colourless solution is then extracted with 3 x 50 ml petroleum spirit (boiling point = $40\text{--}60^\circ\text{C}$).

The organic phases are washed with saturated Na_2CO_3 solution and then washed with saturated NaCl solution and dried with Na_2SO_4 . The solution is then centrifuged off in a vacuum.

Yield: 6.39 g = 28.7 mmol = 80%

Appearance: colourless liquid

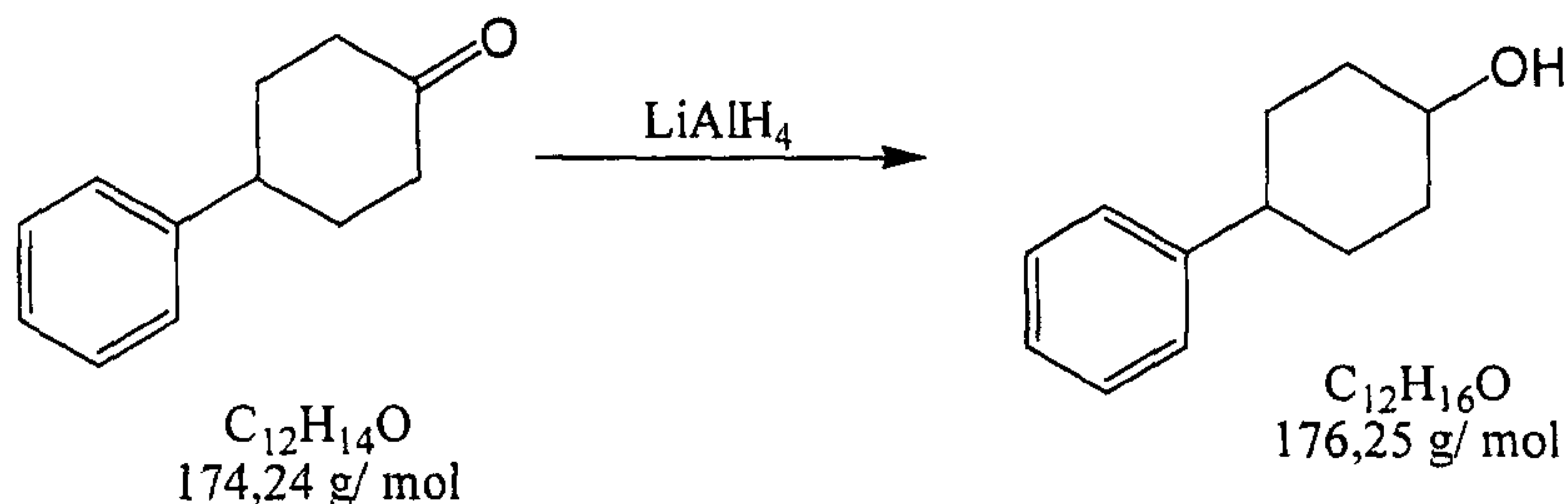
Synthesis Example 21**4-t-butyl-trans-cyclohexane-1,2-diamine**

Preparation: 4 g = 19.2 mmol 4-tert-butyl-cyclohexane-1,2-diazide
 1.6 g Pd / CaCO₃

4 g 4-ethyl-cyclohexane-1,2-diazide in 60 ml abs. ethanol are mixed with 1.6 g Lindlar catalyst and reduced to diamine over 48 hours in an autoclave at a H₂ pressure of 3 bar. At the end of the reduction the catalyst is filtered off and the ethanol is centrifuged off in a vacuum.

Characterisation as dihydrogen sulphate:

4-butyl-1,2-diaminocyclohexane is acidified with sulphuric acid ($c = 3 \text{ mol/l}$). The precipitated solid is absorbed with ethanol and heated to 50°C. The impurities are dissolved and the white 4-butyl-cyclohexane-1,2-diamine-dihydrogensulphate is drawn off via a G4 filter crucible and dried over P₂O₅ in a vacuum.

Synthesis Example 22**4-phenyl-1-cyclohexene****a) 4-phenyl-1-cyclohexanol**

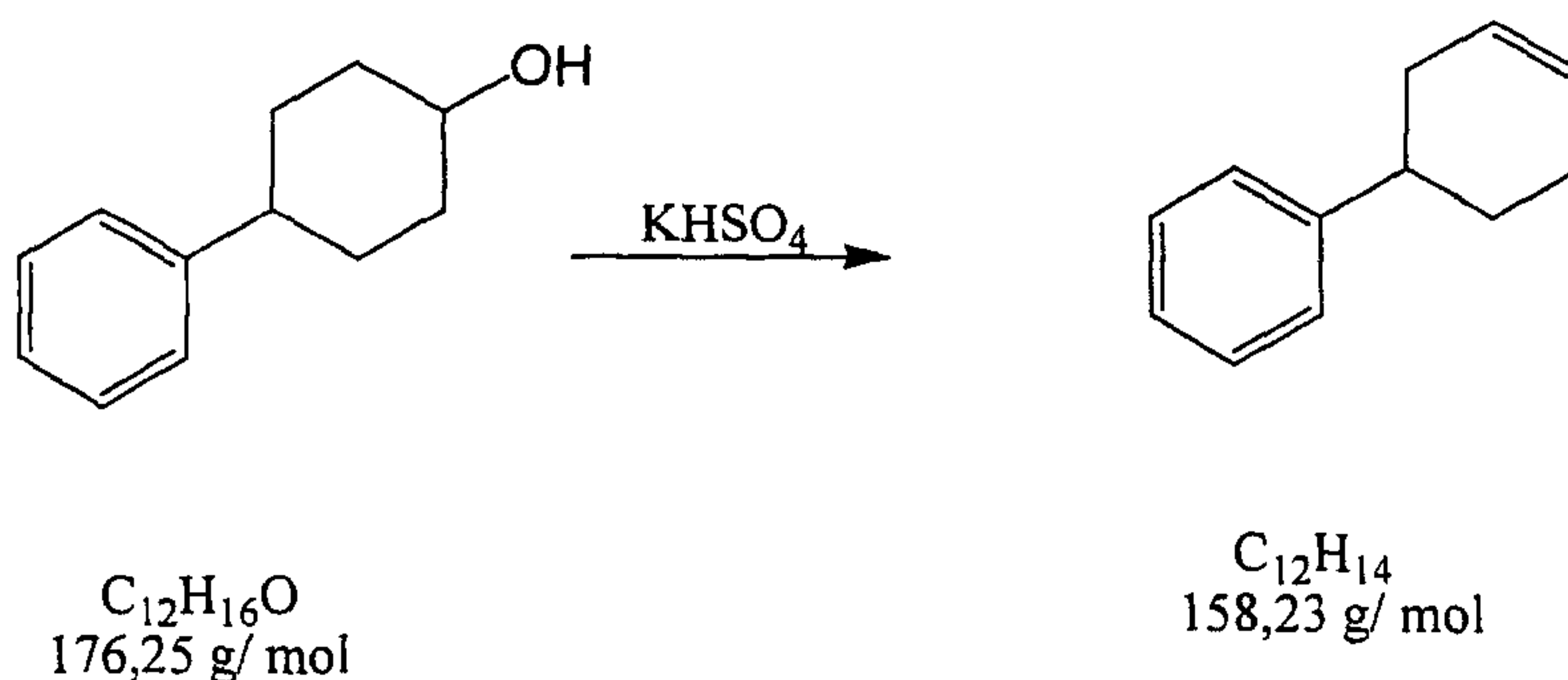
Preparation: 20 g = 115 mmol 4-phenyl-1-cyclohexanone
10 g LiAlH₄

20 g 4-phenyl-1-cyclohexanone are added slowly drop by drop through a separating funnel and under an argon atmosphere to a cooled solution of 10 g LiAlH₄ in 500 ml abs. THF.

After the end of the addition the mixture is heated to reflux and stirred for 48 hours at this temperature. After the end of the reduction 500 ml diethylether are added and the unreacted residues of LiAlH₄ are broken down by the drop-by-drop addition of dest. water. Then the mixture is mixed with 200 ml 10% sulphuric acid to dissolve the inorganic salts. The ether phase is then separated and the aqueous phase extracted twice with 50 ml of ether. The combined ether phases are dried with Na₂SO₄, the ether and THF are centrifuged off.

Appearance: white solid
Yield: 18 g = 102 mmol = 89%
Melting point: 100.5-114.1°C

b) 4-phenyl-1-cyclohexene



Preparation: 18.0 g = 102 mmol 4-phenylcyclohexanol
16.0 g KHSO₄

19 g 4-propyl-1-cyclohexanol are mixed with 16 g KHSO₄ and stirred for one week at 125°C. After the addition of ethylacetate KHSO₄ is filtered off. Ethylacetate is evaporated and the product obtained by vacuum distillation.

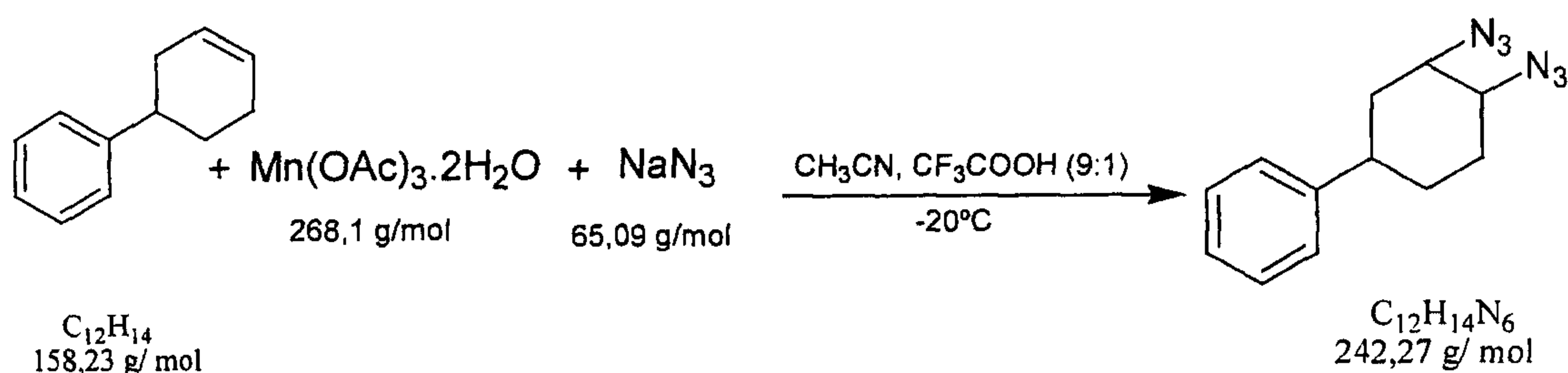
Yield: 12 g = 76 mmol = 75%

Appearance: colourless liquid

Boiling point = 56-59°C at 1.1-1.3 mbar

Synthesis Example 23

4-phenyl-cyclohexane-1,2-diazide



Preparation: 5.3 g = 33.5 mmol 4-phenyl-1-cyclohexene

27 g = 101 mmol $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$

11 g = 168 mmol NaN_3

5.3 g 4-phenyl-1-cyclohexene and 40 ml TFA are added at -20°C and under N_2 atmosphere to a suspension of $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$ and NaN_3 in 400 ml acetonitrile. The mixture is stirred for 3 hours at -19 to -21°C and then diluted with a 10% NaHSO_3 solution. The colourless solution is then extracted with 3 x 50 ml petroleum spirit (boiling point = 40 - 60°C).

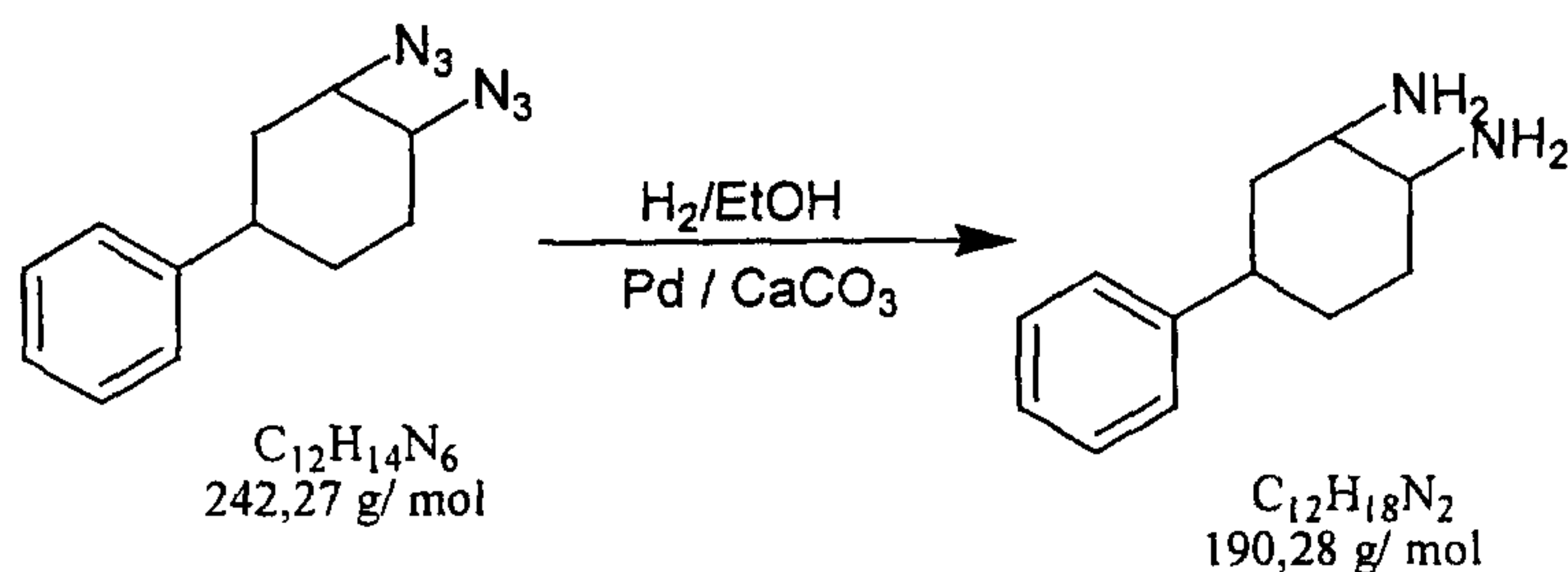
The organic phases are washed with saturated Na_2CO_3 solution and then with saturated NaCl solution and dried with Na_2SO_4 . The solution is then centrifuged off in a vacuum.

Yield: 6 g = 24.8 mmol = 74%

Appearance: colourless liquid

Synthesis Example 24

4-phenyl-trans-cyclohexane-1,2-diamine



Preparation: 4 g = 19.2 mmol 4-phenyl-cyclohexane-1,2-diazide
 1.6 g Pd / CaCO₃

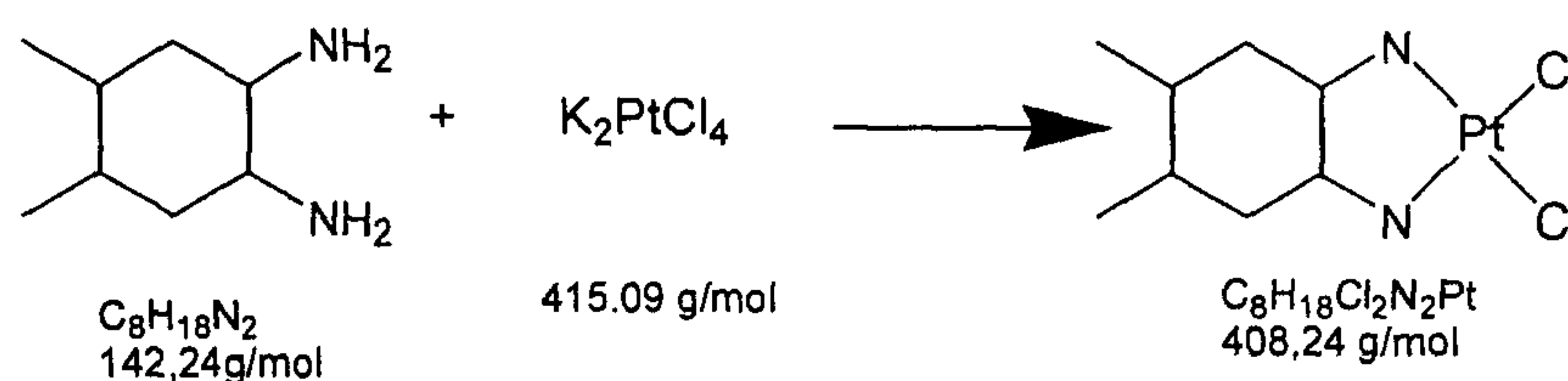
4 g 4-phenyl-cyclohexane-1,2-diazide in 60 ml abs. ethanol are mixed with 1.6 g Lindlar catalyst and reduced to diamine over 48 hours in an autoclave at a H₂ pressure of 3 bar. At the end of the reduction the catalyst is filtered off and the ethanol is centrifuged off in a vacuum.

Characterisation as dihydrogen sulphate:

4-phenyl-1,2-diaminocyclohexane is acidified with sulphuric acid (c = 3 mol/l). The precipitated solid is absorbed with ethanol and heated to 50°C. The impurities are dissolved and the white 4-phenyl-cyclohexane-1,2-diamine-dihydrogensulphate is drawn off via a G4 filter crucible and dried over P₂O₅ in a vacuum.

Synthesis Example 25

(SP-4-3)-dichloro(4,5-dimethyl-trans-cyclohexane-1,2-diamine)platinum (II)



Preparation: 0.60 g = 4.22 mmol 4,5-dimethyl-trans-cyclohexane-1,2-diamine
 1.75 g = 4.22 mmol K₂PtCl₄

1.75 g K_2PtCl_4 are dissolved in 30 ml tridistilled water and suspended with 0.6 g 4,5-dimethyl-trans-cyclohexane-1,2-diamine. The precipitate formed is drawn off gradually over a POR 4 glass filter crucible and dried in the desiccator over phosphorus pentoxide.

Appearance: yellow solid

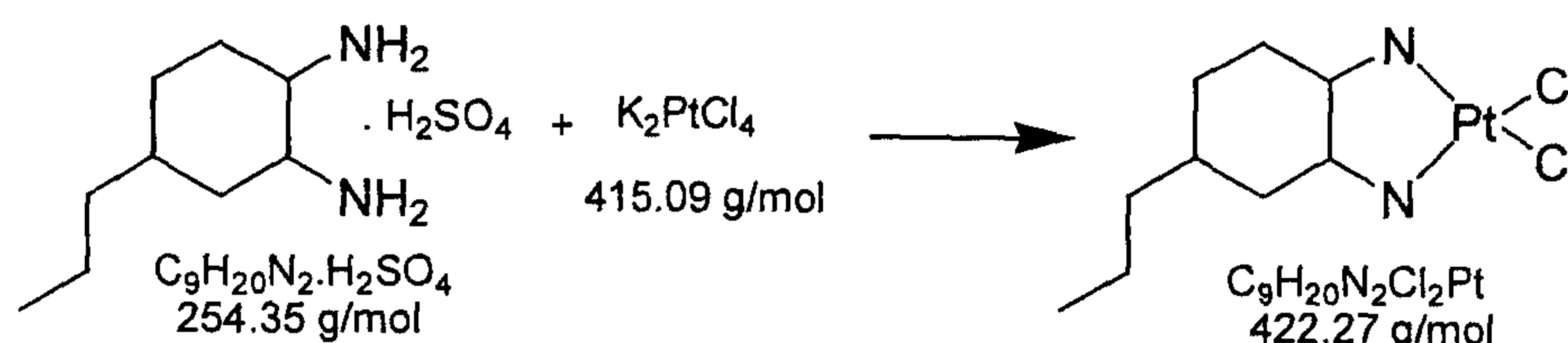
Yield: 1.12 g = 2.74 mmol = 65%

Elementary analysis: calculated for $\text{C}_8\text{H}_{18}\text{N}_2\text{Cl}_2\text{Pt}$ 408.24 g/mol

	C	H	N	Pt	Cl
calculated:	23.54	4.44	6.86	47.79	17.37
found:	23.32	4.39	6.59	47.00	16.81

Synthesis Example 26

(SP-4-3)-dichloro(4-propyl-trans-cyclohexane-1,2-diamine)platinum (II)



Preparation: 1.53 g = 6.02 mmol 4-propyl-trans-cyclohexane-1,2-diamine-dihydrogensulphate
2.50 g = 6.02 mmol K_2PtCl_4

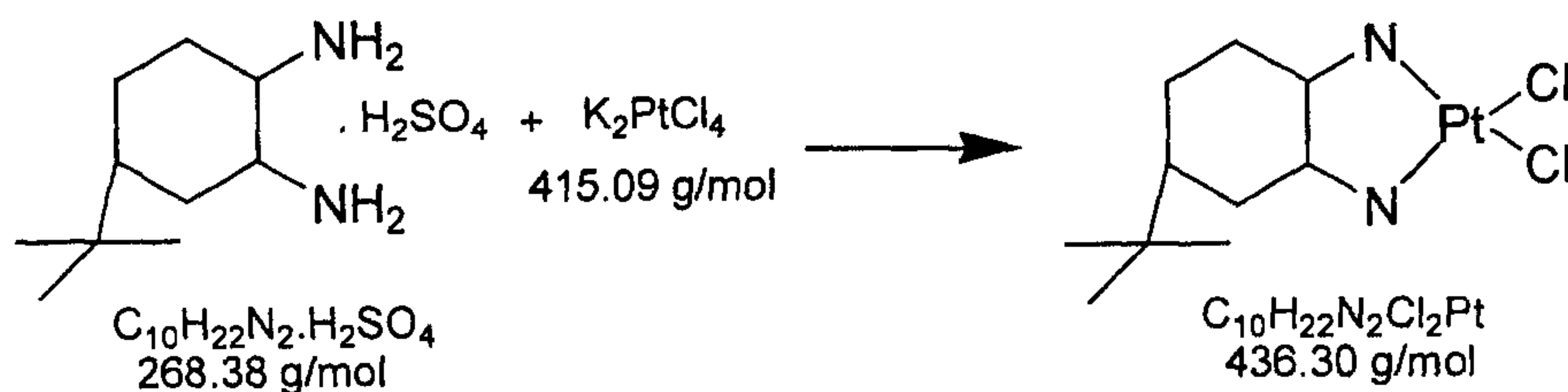
2.5 g of K_2PtCl_4 are dissolved in 40 ml tridistilled water and suspended with 1.53 g 4-propyl-trans-cyclohexane-1,2-diamine-dihydrogensulphate. Then the pH value is set to 7 with 0.5 N NaOH and maintained at this value with 0.1 N NaOH, whereby the pH value is continuously measured with a pH meter. The precipitate formed is drawn off gradually over a POR 4 glass filter crucible and dried in the desiccator over phosphorus pentoxide.

Appearance: yellow solid

Yield: 1.83 g = 4.33 mmol = 72%

Synthesis Example 27

(SP-4-3)-dichloro(4-t-butyl-trans-cyclohexane-1,2-diamine)platinum (II)



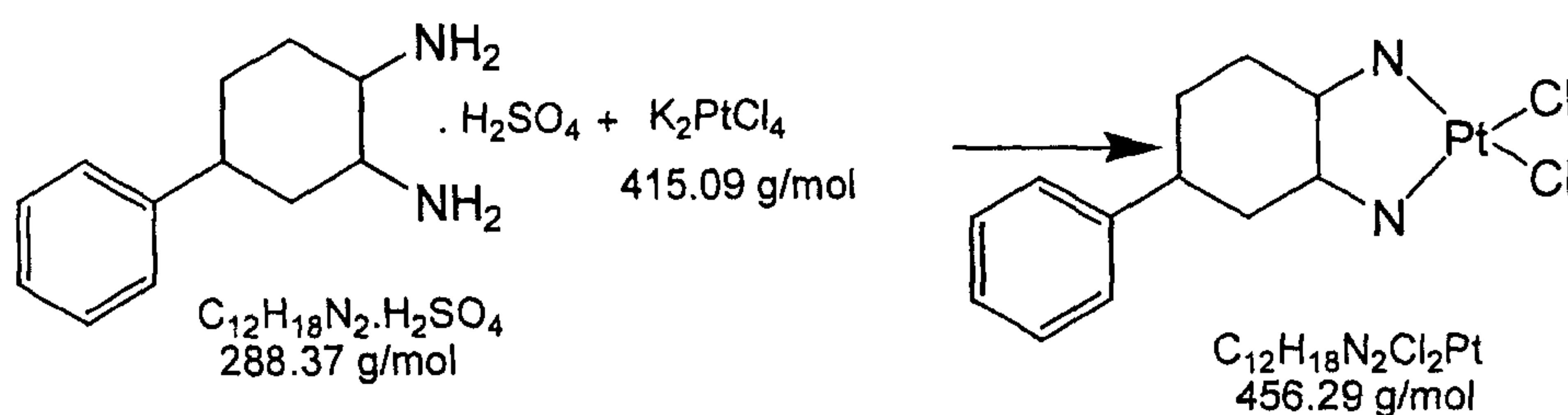
Preparation: 1.60 g = 6.02 mmol 4-t-butyl-trans-cyclohexane-1,2-diamine-dihydrogensulphate
 2.50 g = 6.02 mmol K_2PtCl_4

2.5 g of K_2PtCl_4 are dissolved in 50 ml tridistilled water and suspended with 1.6 g 4-t-butyl-trans-cyclohexane-1,2-diamine-dihydrogensulphate. Then the pH value is set to 7 with 0.5 N NaOH and maintained at this value with 0.1 N NaOH, whereby the pH value is continuously measured with a pH meter. The precipitate formed is drawn off gradually over a POR 4 glass filter crucible and dried in the desiccator over phosphorus pentoxide.

Appearance: yellow solid
Yield: 1.8 g = 4.12 mmol = 70%

Synthesis Example 28

(SP-4-3)-dichloro(4-phenyl-trans-cyclohexane-1,2-diamine)platinum (II)



Preparation: 1.4 g = 4.82 mmol 4-phenyl-*trans*-cyclohexane-1,2-diamine-dihydrogensulphate
2.0 g = 4.82 mmol K₂PtCl₄

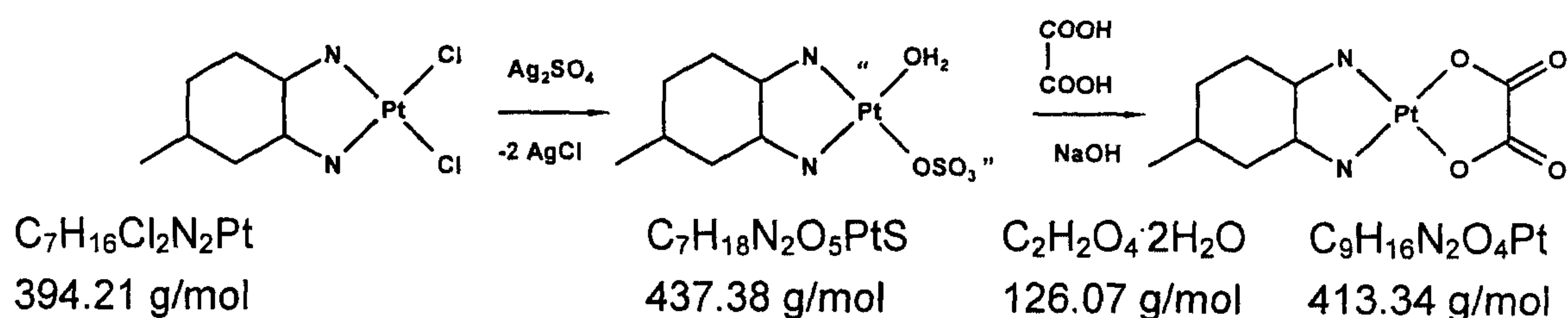
2.0 g of K₂PtCl₄ are dissolved in 40 ml tridistilled water and suspended with 1.4 g 4-phenyl-*trans*-cyclohexane-1,2-diamine-dihydrogensulphate. Then the pH value is set to 7 with 0.5 N NaOH and maintained at this value with 0.1 N NaOH, whereby the pH value is continuously measured with a pH meter. The precipitate formed is drawn off gradually over a POR 4 glass filter crucible and dried in the desiccator over phosphorus pentoxide.

Appearance: yellow solid

Yield: 1.2 g = 2.63 mmol = 55%

Example 1

(SP-4-3)-(4-methyl-*trans*-cyclohexane-1,2-diamine)oxalatoplatinum (II)



Preparation: 0.8036 g = 2.039 mmol (4-methyl-*trans*-dach)PtCl₂
0.623 g = 2.00 mmol Ag₂SO₄
0.193 g = 1.531 mmol oxalic acid dihydrate
3 ml 0.5 M NaOH

0.8036 g (4-methyl-*trans*-dach)PtCl₂ are well suspended in 30 ml tridistilled water. Then 0.6433 g Ag₂SO₄ are permanently added and the preparation stirred for 2 days with protection against light.

The precipitated AgCl is filtered off and the filtrate evaporated down to dryness on the rotary evaporator. From the residue 70 mg are taken for the elementary analysis and NMR spectroscopy. 0.193 g oxalic acid dihydrate and 3 ml 0.5 M NaOH are added to 669 mg = 1.53 mmol aqua(4-methyl-*trans*-cyclohexane-1,2-diamine)sulphatoplatinum (II) and stirred overnight. The white solid is filtered off over a G4 glass filter crucible and dried in the vacuum desiccator over phosphorus pentoxide.

Aqua(4-methyl-*trans*-cyclohexane-1,2-diamine)sulphatoplatinum (II)

Appearance: yellow solid

Yield: 0.739 g = 1.690 mmol = 85%

Elementary analysis: calculated for $C_7H_{18}N_2O_5PtS \cdot 0.2H_2SO_4$ 437.38 g/mol

	C	H	N	O	Pt	S
calculated:	18.40	4.06	6.13	20.31	42.69	8.52
found:	18.54	3.99	5.94			
found:	18.57	4.03	5.95			

(SP-4-3)-(4-methyl-*trans*-cyclohexane-1,2-diamine)oxalatoplatinum (II)

Appearance: white solid

Melting point: >270°C decomposition

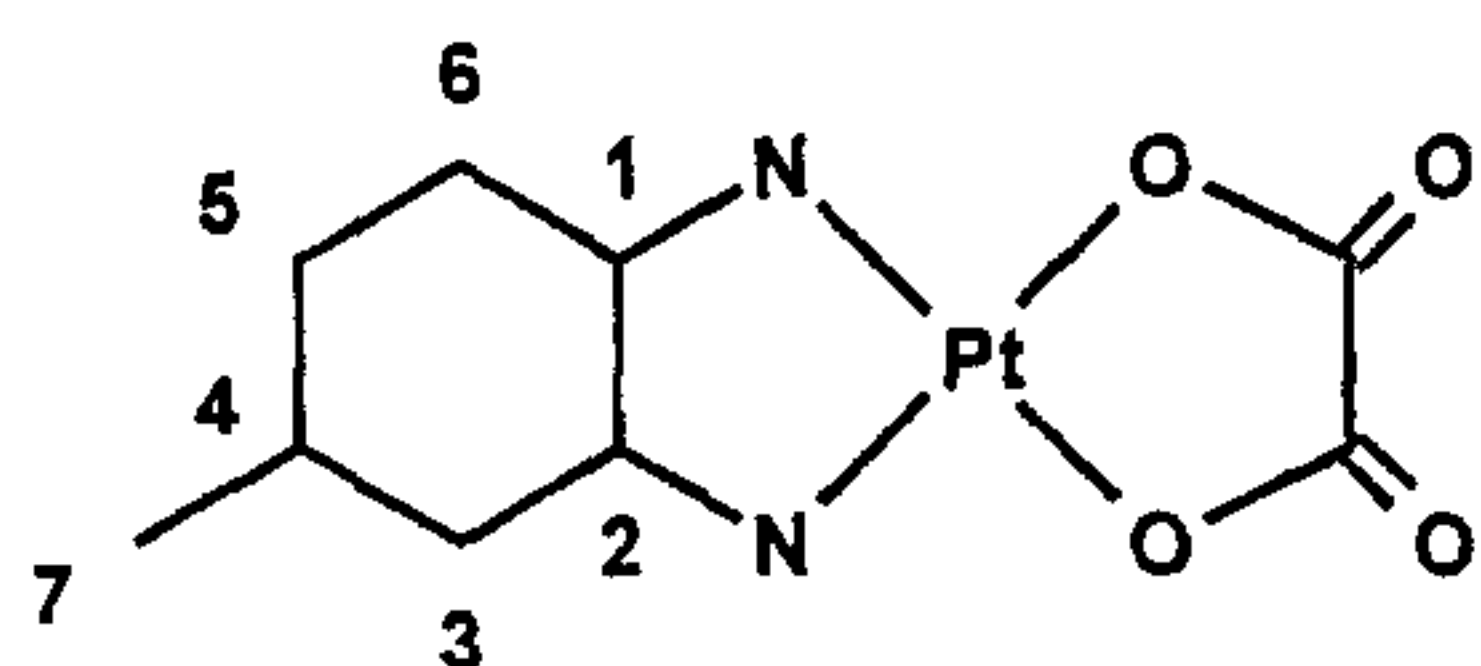
Yield: 0.310 g = 0.75 mmol = 50%

Elementary analysis: calculated for $C_9H_{18}N_2O_4Pt$ 411.33 g/mol

	C	H	N	O	Pt
calculated:	26.28	3.92	6.81	15.48	47.20
found:	26.33	3.67	6.62		
found:	26.30	3.70	6.60		

IR spectrum [370-7000 cm^{-1} , CsI], characteristic bands (in cm^{-1}):

3243	$\nu(N-H)$
2948, 2873	$\nu(C-H)$
1668	$\nu_{as}(C=O)$
1663	$\delta(N-H)$

NMR spectra:**¹H-NMR spectrum in H₂O/D₂O 9/1:**

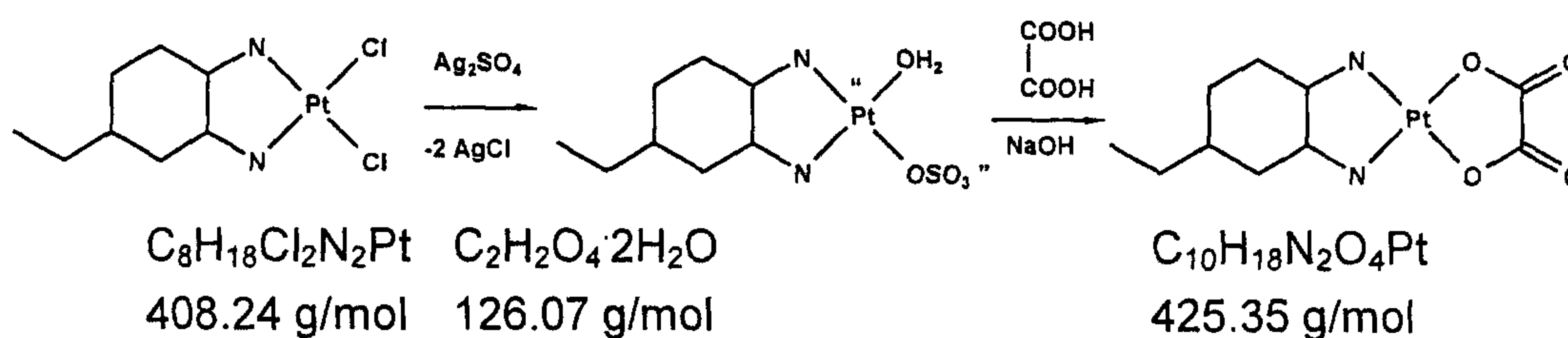
δ = 0.75-0.87 [mm, 1H, H(5)], 0.83 [d, 3H, H(7), $^3J_{H,H} = 6.60$ Hz], 0.88-0.99 [m, 1H, H(3)], 1.19-1.40 [m, 2H, H(4), H(6)], 1.41-1.51 [m, 1H, H(5)], 1.86-1.97 [m, 2H, H(6) and H(3)], 2.18-2.41 [m, 2H, H(1) and H(2)], 3.50-3.60 [mm, 2H, H(1') and H(2')], 5.03 NH₂, 5.73 NH₂.

¹³C-NMR spectrum in H₂O/D₂O 9/1:

δ = 17.1 [C(7')], 20.4 [C(7)], 26.9 [C(6')], 27.4 [C(4')], 29.7 [C(5')], 31.0 [C(6)], 31.3 [C(4)], 32.6 [C(5)], 39.8 [C(3')], 39.9 [C(3)], 62.4-62.4 [4C, C(1), C(2), C(1') and C(2')], 168.7 [2C, C=O].

¹⁵N signal from the ¹⁵N, ¹H-COSY spectrum in H₂O/D₂O 9/1:

δ = -34.58/5.73 [NH₂].

Example 2**(SP-4-3)-(4-ethyl-trans-cyclohexane-1,2-diamine)oxalatoplatinum (II)**

Preparation: 0.8052 g = 1.972 mmol (4-ethyl-*trans*-dach)PtCl₂
 0.584 g = 1.87 mmol Ag₂SO₄
 0.248 g = 1.972 mmol oxalic acid dihydrate
 4 ml 0.5 M NaOH

0.8052 g (4-ethyl-*trans*-dach)PtCl₂ are well suspended in 30 ml tridistilled water. Then 0.584 g Ag₂SO₄ are permanently added and the preparation stirred for 5 days with protection against light. The precipitated AgCl is filtered off and the filtrate evaporated down to dryness on the rotary evaporator. 0.248 g oxalic acid dihydrate and 4 ml 0.5 M NaOH are added to the residue and stirred overnight. The white solid is filtered off over a G4 glass filter crucible and dried in the vacuum desiccator over phosphorus pentoxide.

Appearance: white solid
Melting point: >290°C decomposition
Yield: 0.170 g = 1.48 mmol = 72%

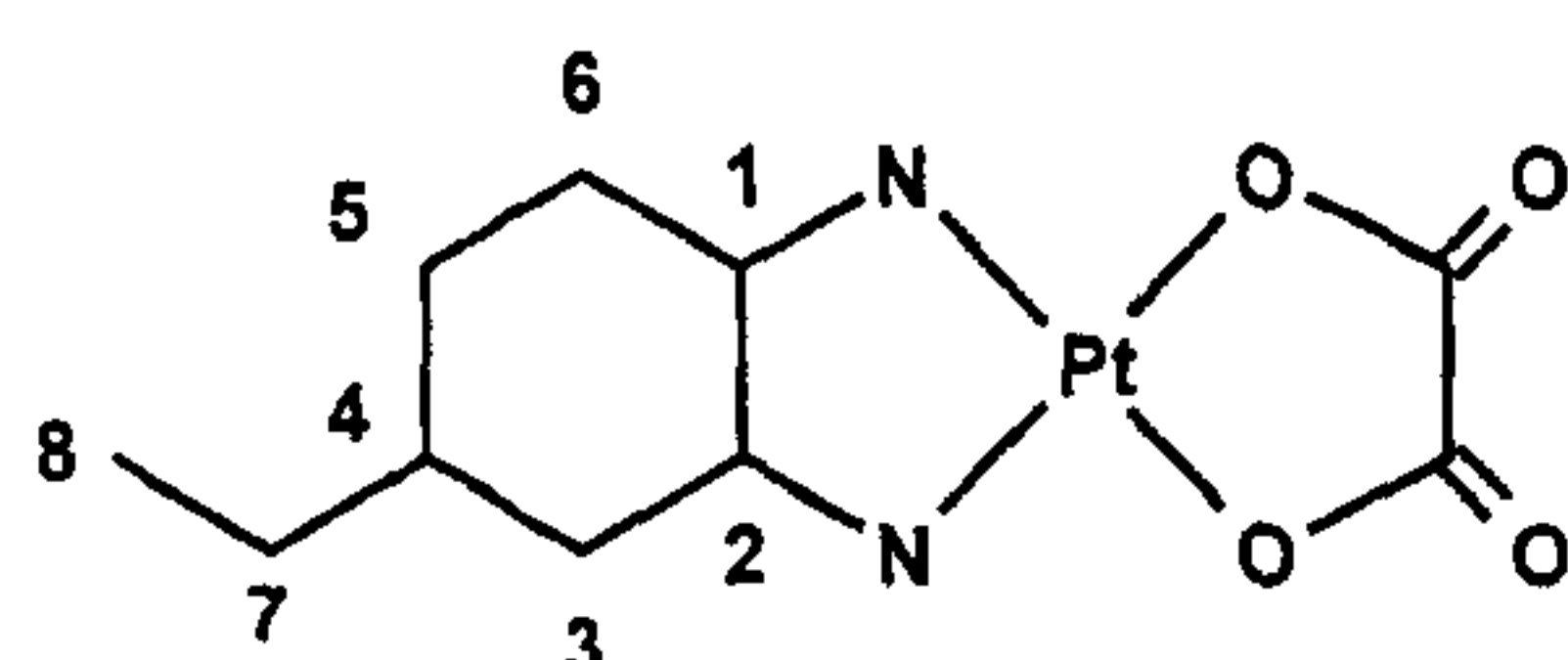
Elementary analysis: calculated for C₁₀H₁₈N₂O₄Pt 425.35 g/mol

	C	H	N	O	Pt
calculated:	28.24	4.27	6.59	15.05	45.87
found:	28.00	4.02	6.75		

IR spectrum [370-7000 cm⁻¹, Csl], characteristic bands (in cm⁻¹):

3100	v(N-H)
2960, 2934, 2861	v(C-H)
1706	v _{as} (C=O)
1665	δ(N-H)

NMR spectra:



^1H -NMR spectrum in $\text{H}_2\text{O}/\text{D}_2\text{O}$ 9/1:

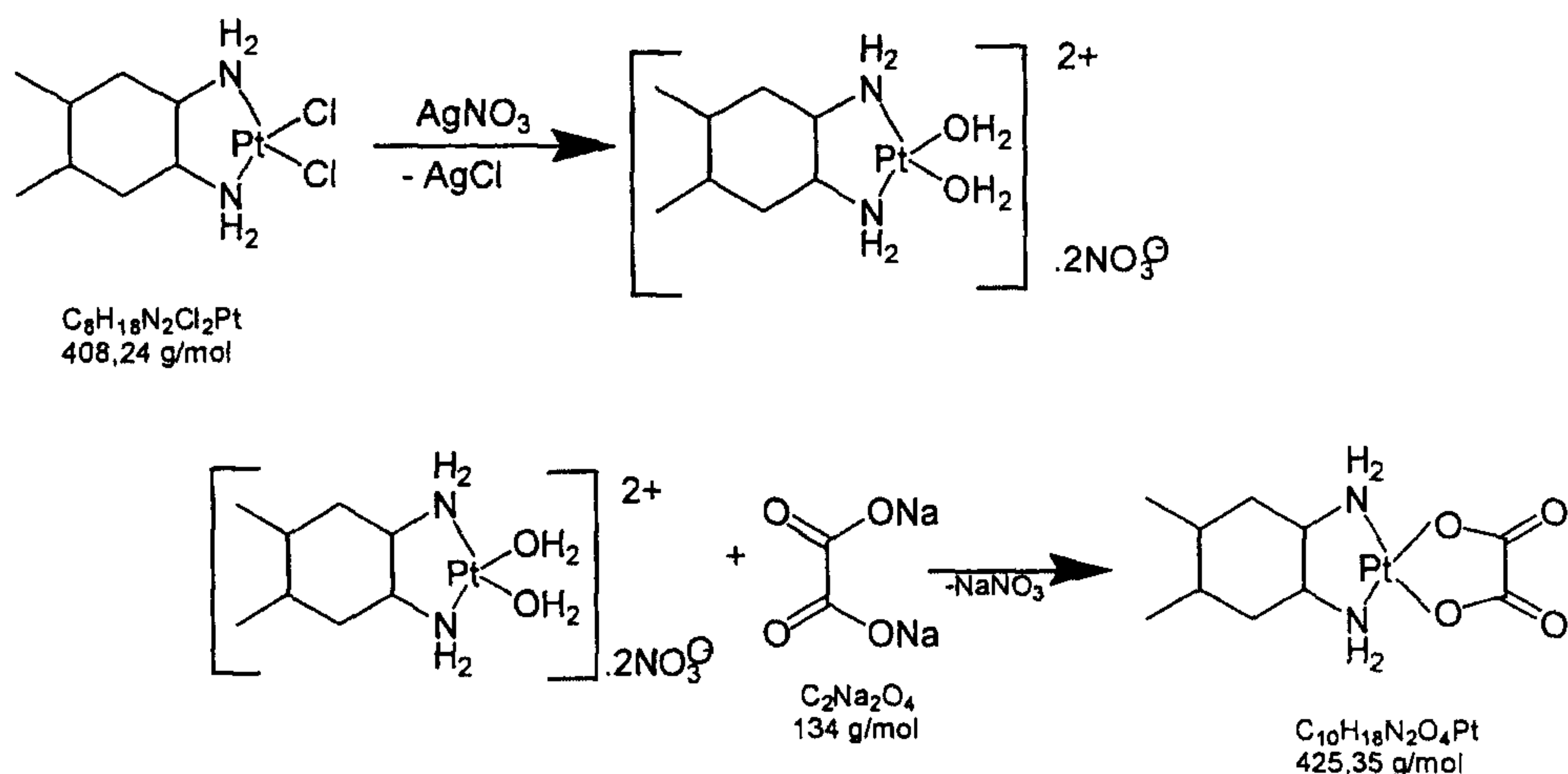
δ = 0.69-0.85 [m, 1H, H(5)], 0.75 [t, 3H, H(8), $^3J_{\text{H,H}} = 7.09$ Hz], 0.86-0.99 [m, 1H, H(3)], 1.07-1.31 [m, 4H, H(4), H(6), H(7)], 1.49-1.60 [m, 1H, H(5)], 1.89-2.03 [m, 2H, H(6) and H(3)], 2.21-2.41 [m, 2H, H(1) and H(2)], 5.75 NH_2 .

^{13}C signals from the ^{13}C , ^1H COSY NMR spectrum in $\text{H}_2\text{O}/\text{D}_2\text{O}$ 9/1:

δ = 11.1 [C(8)], 27.9 [C(7)], 30.1 [C(5)], 30.8 [C(6)], 37.5 [C(3)], 37.9 [C(4)], 62.5 [2C, C(1), C(2)].

Example 3

(SP-4-3)-(4,5-dimethyl-trans-cyclohexane-1,2-diamine)oxalatoplatinum (II)



Preparation:

600 mg = 1.47 mmol dichloro(4,5-dimethyl-cyclohexane-1,2-diamine)platinum (II)

480 mg = 2.82 mmol AgNO_3

127 mg = 1.41 mmol oxalic acid

2.80 ml = 2.80 mmol 1 N NaOH

600 mg dichloro(4,5-dimethyl-cyclohexane-1,2-diamine)platinum (II) are suspended in 70 ml of tridistilled water, 480 mg silver nitrate are added and stirred for one day at room temperature. The precipitated silver chloride is filtered off over a POR 4-glass filter crucible.

127 mg oxalic acid are dissolved in 2.8 ml NaOH and added to the above solution, which is reduced down to half. The mixture is stirred for 4 hours at room temperature. The ensuing

product is drawn off over a POR 4-glass filter crucible and dried over phosphor pentoxide in a vacuum.

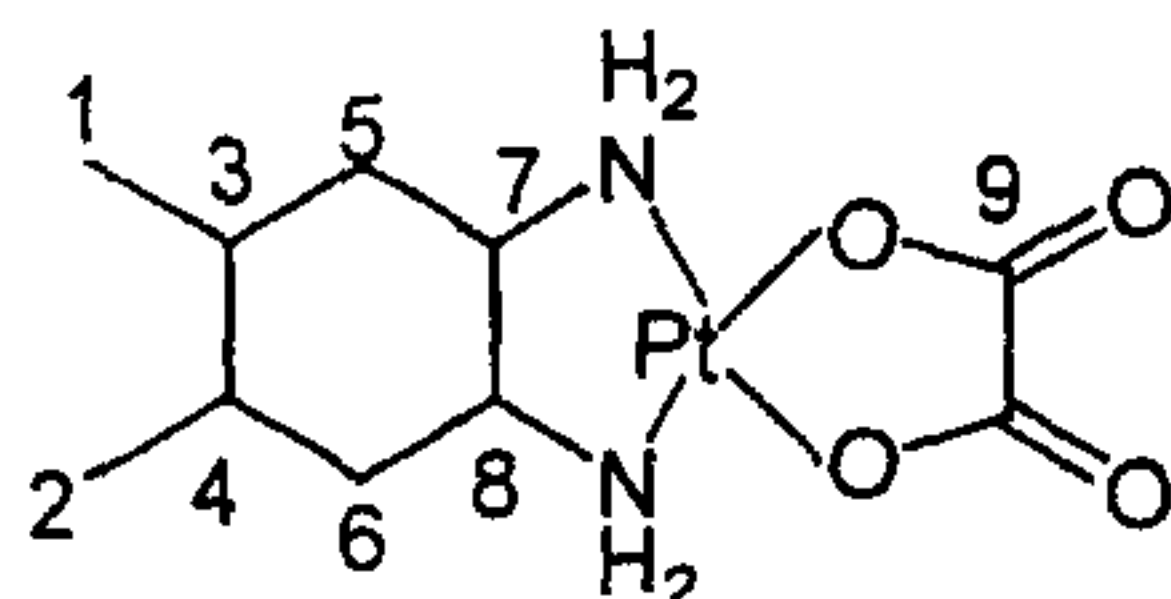
Appearance: white solid

Yield: 290 mg = 0.68 mmol = 48%

Elementary analysis: calculated for $C_{10}H_{18}N_2O_4Pt$ 425.35 g/mol

	C	H	N	O	Pt
calculated:	28.24	4.27	6.59	15.05	45.87
found:	28.11	4.02	6.41		

NMR spectrum:



^1H -NMR in D_2O :

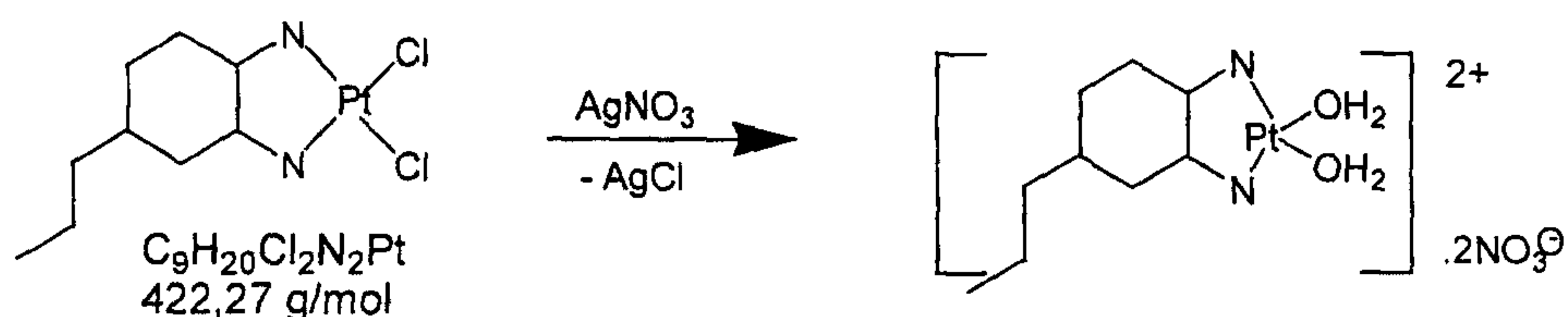
δ = 0.71-0.73 [d, 3H, H(1)], 0.8-0.82 [d, 3H, H(2)], 1.43-1.49 [m, 1H, H(3) and H(4)], 1.65-1.70 [m, 2H, H(5) or H(6)], 1.79-1.84 [m, 2H, H(5) or H(6)], 2.28-2.36 [m, 1H, H(7) or H(8)], 2.45-2.52 [m, 1H, H(8) or H(9)].

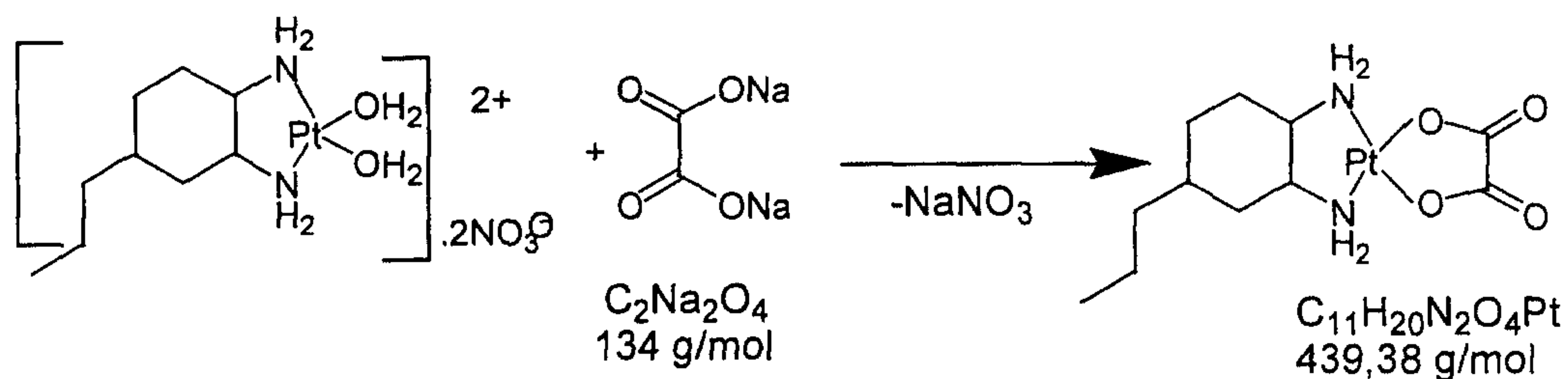
^{13}C -NMR in D_2O :

δ = 11.44 [(C1)], 17.94 [C(2)], 32.61 [(C3)], 33.85 [C(4)], 33.89 [(C5)], 38.25 [(C6)], 58.15 [C(7) and C(8)], 62.81 [C(7) and C(8)], 168.71 [C(9)].

Example 4

(SP-4-3)-(4-propyl-trans-cyclohexane-1,2-diamine)oxalatoplatinum (II)





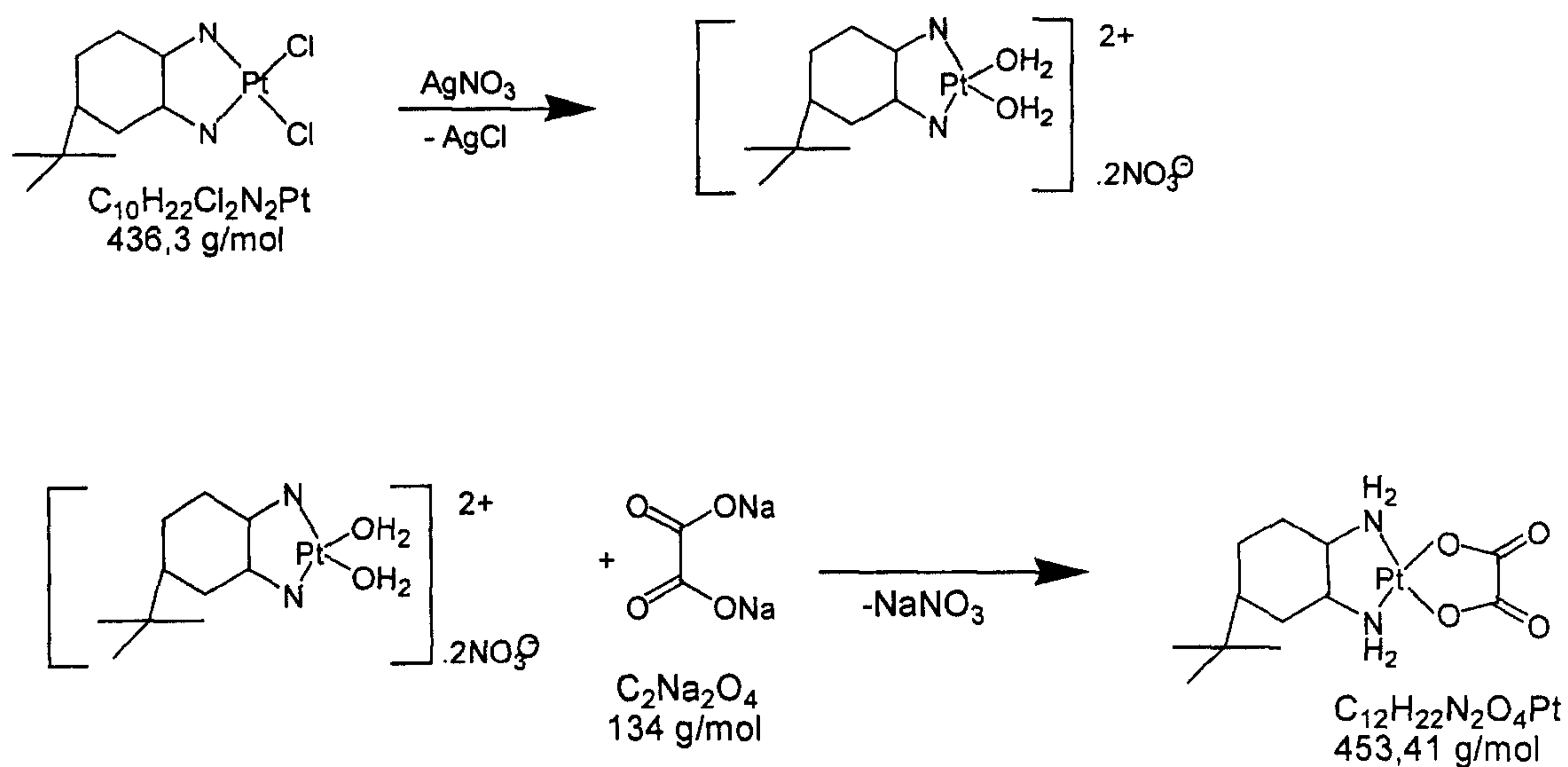
The synthesis occurs analogously to Example 3 from the dichloro complex.

Elementary analysis: calculated for $\text{C}_{11}\text{H}_{20}\text{N}_2\text{O}_4\text{Pt}$ 439.38 g/mol

	C	H	N
calculated:	30.07	4.59	6.37
found:	29.78	4.67	6.45

Example 5

(SP-4-3)-(4-t-butyl-trans-cyclohexane-1,2-diamine)oxalatoplatinum (II)



The synthesis occurs analogously to Example 3 from the dichloro complex.

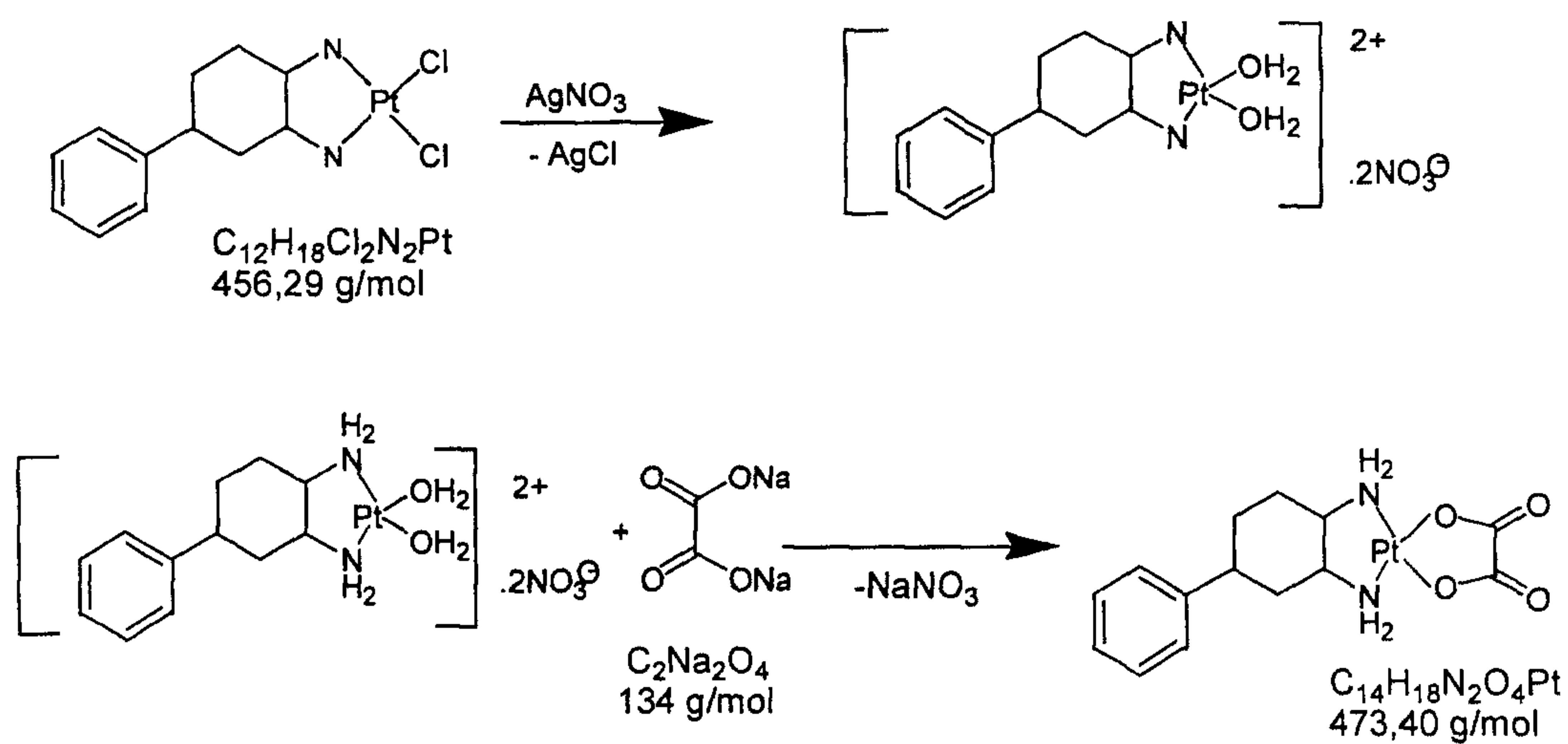
Elementary analysis: calculated for $C_{12}H_{22}N_2O_4Pt$

453.41 g/mol

	C	H	N
calculated:	31.79	4.89	6.18
found:	31.61	4.72	6.12

Example 6

(SP-4-3)-(4-phenyl-trans-cyclohexane-1,2-diamine)oxalatoplatinum (II)



The synthesis occurs analogously to Example 3 from the dichloro complex.

Elementary analysis: calculated for $C_{14}H_{18}N_2O_4Pt$

473.40 g/mol

	C	H	N
calculated:	35.52	3.83	5.92
found:	35.28	3.71	5.82

Carrying out the racemic compound splitting

The separation of the enantiomers of the diamines in the synthesis examples 3, 6, 15, 18, 21 and 24 can, for example, be carried out by forming the salts with tartaric acid. To do this, either (R,R)- or (S,S)-tartaric acid (depending on which enantiomer of the diamine is to be preferentially isolated) is dissolved in water and the diamine is added at a temperature of <70°C. After the complete addition of the diamine, glacial acetic acid is added and then the mixture is cooled to 5°C. The precipitated salt is filtered off and dried. By the addition of sodium hydroxide solution and the ensuing extraction with an organic solvent, it can be released and obtained.

Alternatively, O,O-dibenzoyl tartaric acid can be used instead of tartaric acid and then work proceeds in a water / acetone mixture.

The diamines obtained, clear of enantiomers, are then converted to the dichloroplatinum complexes analogously to the synthesis examples 7, 8, 25, 26, 27 and 28 and they can, after activation with silver nitrate or silver sulphate, be converted to the oxalato complexes with oxalic acid or sodium oxalate analogously to the examples 1-6.

Cytotoxicity tests

The cytotoxicity of the compounds according to Examples 1 and 2 was tested by using the following cell lines 41M, CH1 and SW480. In this respect the following method was selected:

The proliferation-inhibiting activity of oxaliplatin and its derivatives [(*trans*-S,S-chxn)Pt(ox)], [(4-methyl-*trans*-chxn)Pt(ox)] and [(4-ethyl-*trans*-chxn)Pt(ox)] was comparatively examined on 3 human tumour cell lines in the Microculture Tetrazolium Test (MTT assay) with continuous active substance exposition (96 h). In this regard, adherent monolayer cultures of the following cell lines were used: 41M (adenocarcinoma of the ovary), CH1 (adenocarcinoma of the ovary), SW480 (adenocarcinoma of the colon; primary resistance to cisplatin).

Culture conditions: The cells were kept in 75 cm² culture flasks at 37°C and moist atmosphere (5% CO₂). Minimal Essential Medium (MEM) was used as culture medium, with 2 mmol/l l-glutamine, 1 mmol/l sodium pyruvate, 50 IU/ml penicillin, 50 µg/ml streptomycin and 10% heat-inactivated foetal bovine serum.

Test execution: Cell suspensions were obtained from subconfluent cultures by treatment with trypsin and seeded in defined density in 96-well microculture plates. The initial density was selected such that for the complete test duration an exponential growth of the cultures was guaranteed. For the cell line 41M this was 4×10^4 cells/ml, for CH1 1.25×10^4 cells/ml and for SW480 1.5×10^4 cells/ml. The plates were incubated for 24 h under standard conditions to achieve cell establishment. Then the compounds to be tested were introduced in ten-staged concentration series in the culture medium (without addition of organic solvents or dissolving agents) into the plates and left for the complete test duration (96 h). Per experiment each concentration was tested on eight microcultures of the same cell line. At the end of the experiment the respective number of living cells in the microculture was determined spectrophotometrically (at 550 nm) using the MTT-dye reaction in relationship to the untreated control cultures. Equally, the number of living cells in microculture plates started in parallel was quantified at the start of the active substance exposition. The testing of [(*trans*-S,S-chxn)Pt(ox)] and the racemic compound was carried out once, all other experiments were carried out three times. The mean values were used for the evaluation.

Results with the cell line 41M

Compound	IC ₅₀	GL ₅₀	TGI	LC ₅₀
Oxaliplatinum	4.3 ± 1.4	0.67 ± 0.04	5.5 ± 2.8	17.7 ± 0.7
[(<i>trans</i> -S,S-chxn)Pt(ox)]	3.2	1.11	4.4	19.8
[(<i>trans</i> -chxn)Pt(ox)]	4.2	0.99	5.0	33.1
[(4-methyl- <i>trans</i> -chxn)Pt(ox)]	2.4 ± 0.5	0.91 ± 0.16	4.2 ± 2.6	17.9 ± 7.0
[(4-ethyl- <i>trans</i> -chxn)Pt(ox)]	2.4 ± 1.4	0.70 ± 0.32	3.0 ± 0.4	15.1 ± 5.1

Fig. 1 shows a schematic illustration of the results in dependence of the concentration and the living cells (T/C) [%].

Results with the cell line CH1

Substance	IC ₅₀	GI ₅₀	TGI	LC ₅₀
Oxaliplatinum	0.27 ± 0.22	0.42 ± 0.21	1.8 ± 0.4	3.6 ± 0.7
[(<i>trans</i> -S,S-chxn)Pt(ox)]	1.5	1.14	4.2	8.4

[(trans-chxn)Pt(ox)]	0.7	0.54	2.0	4.0
[(4-methyl-trans-chxn)Pt(ox)]	0.34 ± 0.10	0.22 ± 0.03	0.93 ± 0.22	1.9 ± 0.4
[(4-ethyl-trans-chxn)Pt(ox)]	0.30 ± 0.20	0.21 ± 0.14	0.98 ± 0.59	2.1 ± 1.1

Fig. 2 shows a schematic illustration of the results in dependence of the concentration and the living cells (T/C) [%].

Results with the cell line SW480

Substance	IC50	GI50	TGI	LC50
Oxaliplatinum	0.67 ± 0.28	0.17 ± 0.07	16.2 ± 2.7	230 ± 23
[(trans-S,S-chxn)Pt(ox)]	4.2	2.2	47.8	70.4
[(trans-chxn)Pt(ox)]	1.6	0.8	21.8	104.6
[(4-methyl-trans-chxn)Pt(ox)]	0.65 ± 0.07	0.31 ± 0.11	9.0 ± 2.9	73.3 ± 48.9
[(4-ethyl-trans-chxn)Pt(ox)]	0.61 ± 0.42	0.30 ± 0.23	9.1 ± 5.3	21.0 ± 5.0

Fig. 3 shows a schematic illustration of the results in dependence of the concentration and the living cells (T/C) [%].

As can be seen from the above results, in comparison to oxaliplatinum, the cytotoxicity of the isomer mixtures of the compounds according to Examples 1 and 2 is comparable or better. This is particularly surprising, because isomer mixtures generally have a lower cytotoxicity than pure trans-R,R-cyclohexane-1,2-diamine-platinum compounds.

In vivo experiments

Conducted efficacy studies show a clearly lower toxicity of the new derivatives compared to oxaliplatin itself. The use of oxaliplatin in the highest dosage leads to the death of all animals in the test group up to day 14, whereas in the groups, which have been administered the compounds according to the invention (4-methyl-trans-chxn)Pt(ox) and (4-ethyl-trans-chxn)Pt(ox) also in the highest dosage level, 4/6 animals ((4-methyl-trans-chxn)Pt(ox)) resp. 6/6 animals ((4-ethyl-trans-chxn)Pt(ox)) were still alive on day 14.

Schedule: Qd x 5

Female, tumour-bearing B6D2F1 mouse, day 14 after tumour transplantation.

Substance	Dose mg/kg	Survivors/total number
(4-methyl-trans-chxn)Pt(ox)	1.30	6/6
	2.60	5/6
	5.20	4/6
(4-ethyl-trans-chxn)Pt(ox)	1.34	5/6
	2.68	6/6
	5.35	6/6
Oxaliplatin	1.25	5/6
	2.50	6/6
	5.00	0/6

The effectiveness of the compounds according to the invention in the i.m. transplanted murine Lewis lung carcinoma was, despite the significantly better compatibility, comparable with the effect of oxaliplatin.

L1210 leukaemia in the mouse

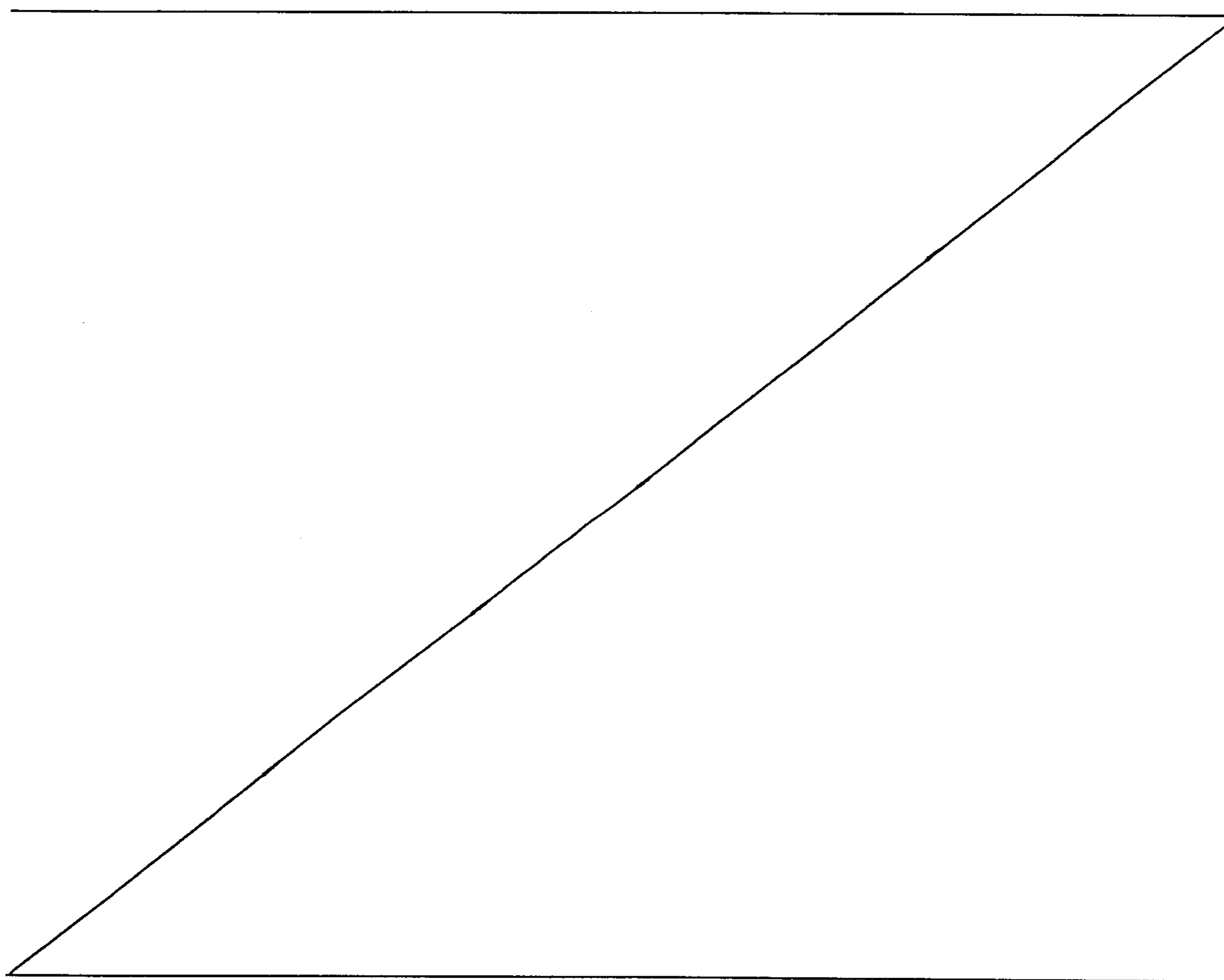
In this experiment the new compound (4-methyl-trans-chxn)Pt(ox) showed in mouse leukaemia both a better tolerance at high dosage (24 mg/kg) and also a better effectiveness in the region of 3 mg/kg and 6 mg/kg (all animals survived the experiment to the end), whereas in the group treated with I-OHP deaths already occurred.

L1210 survivors in dependence of the dosage

Fig. 4: illustrates the results of the effectiveness of (4-methyl-trans-chxn) Pt(ox) in comparison to I-OHP in leukaemia L1210 in the mouse in an experiment terminated in 21 days.

MTD study

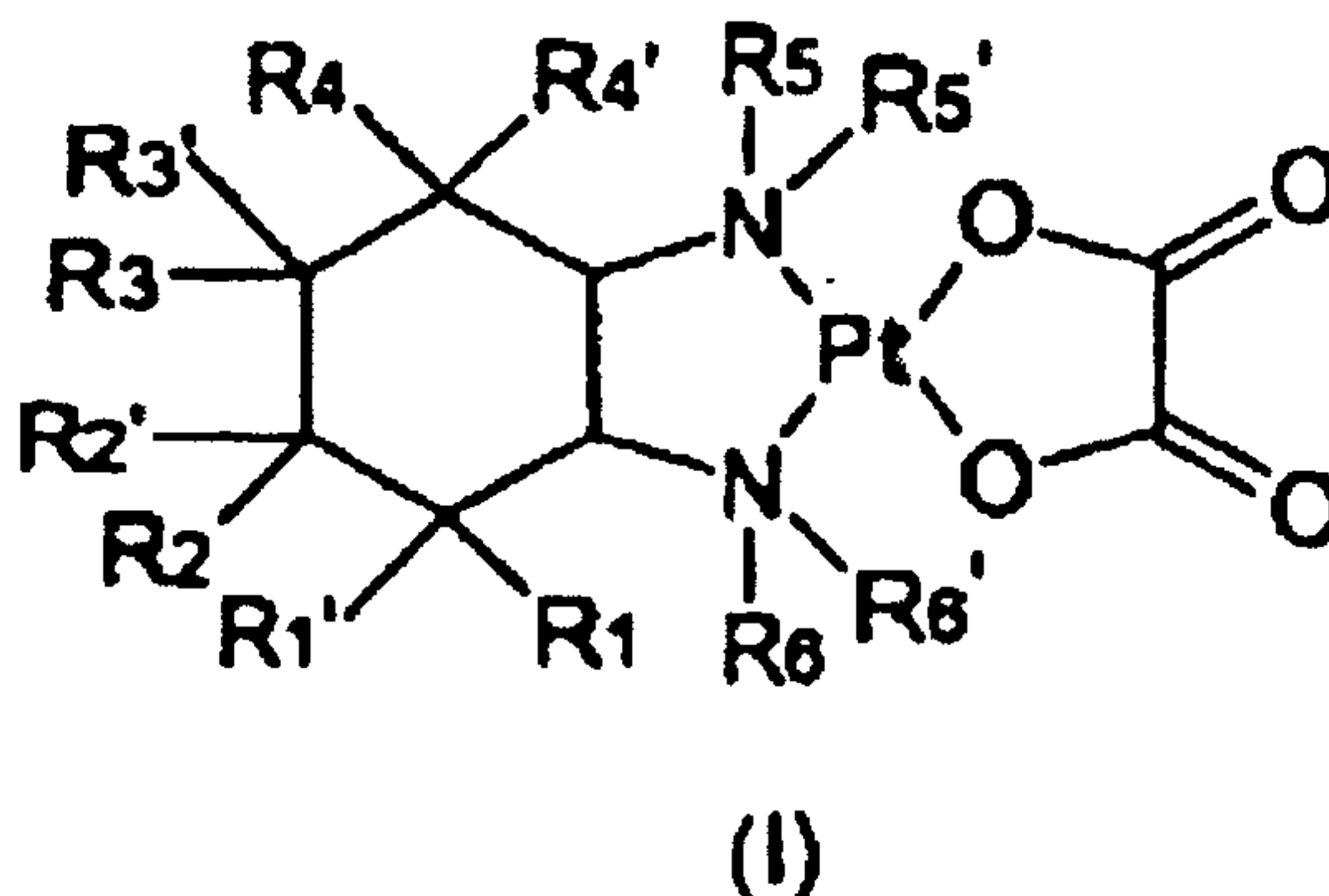
In this study on animals free of tumours the two new derivatives (4-methyl-trans-chxn)Pt(ox) and (4-ethyl-trans-chxn)Pt(ox) show a clearly better tolerance than can be found for oxaliplatin (MTD in both cases 10 mg/kg Qd x 5, weight loss 5% on day 5, in comparison: oxaliplatin MTD = 5 mg/kg with the same schedule).



Consequently, a better tolerance of the new derivatives according to the invention is found compared to the established oxaliplatinum in animal tests.

WHAT IS CLAIMED IS:

1. A compound of the general formula (I),



whereby the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ are independently of one another selected from the group consisting of hydrogen, branched or unbranched alkyl, branched or unbranched alkenyl, cycloalkyl, cycloalkenyl, aryl and alkylaryl radicals,

- 10 the substituents R^5 , $R^{5'}$, R^6 and $R^{6'}$ are independently of one another selected from the group consisting of hydrogen, branched or unbranched alkyl and branched or unbranched alkenyl radicals, and

whereby two or more of the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ optionally form with one another at least one alkylene or alkenylene radical or an aromatic ring, and

- whereby one or more of the carbon atoms of the cyclohexane ring bearing the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ is optionally replaced by a
 20 heteroatom, and

if the heteroatom is oxygen, one or more of the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ can additionally be a hydroxy radical, and

its pharmaceutically compatible salts,

provided that

at least one substituent R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 or $R^{4'}$ is not hydrogen and the substituents R^1 or $R^{1'}$ and R^4 or $R^{4'}$ do not form an unsubstituted C_{1-2} -alkylene radical with one another.

10 2. The compound according to claim 1, whereby the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ are independently of one another selected from the group consisting of hydrogen, C_1 - C_{15} -alkyl, C_2 - C_{15} -alkenyl, C_3 - C_{15} -cycloalkyl, C_3 - C_{15} -cycloalkenyl, C_6 - C_{14} -aryl and C_1 - C_{15} -alkyl- C_6 - C_{14} -aryl radicals.

3. The compound according to claim 1 or 2, whereby the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ are selected from the group consisting of hydrogen, C_1 - C_{10} -alkyl, C_3 - C_{10} -cycloalkyl and C_6 - C_{14} -aryl radicals.

20 4. The compound according to any one of claims 1 to 3, whereby the substituents R^1 , $R^{1'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ are equal to hydrogen and one of the substituents R^2 or $R^{2'}$ is a C_1 - C_6 -alkyl radical or a C_6 - C_{14} -aryl radical and the other one is a hydrogen atom.

5. The compound according to claim 4, whereby one of the substituents R^2 or $R^{2'}$ is a methyl, ethyl, propyl, t-butyl or phenyl radical and the other is a hydrogen atom.

6. The compound according to claim 1, whereby the substituents R^5 , $R^{5'}$, R^6 , and $R^{6'}$ are hydrogen and optionally at least one of the carbon atoms of the cyclohexane ring bearing the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ is replaced by a heteroatom, and

if the heteroatom is oxygen, the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ are independently of one another selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl and alkylaryl radicals.

7. The compound according to claim 1, whereby one or two of the substituents R^1 , $R^{1'}$, R^2 , $R^{2'}$, R^3 , $R^{3'}$, R^4 and $R^{4'}$ are selected from the group consisting of alkyl, alkenyl, cycloalkenyl, aryl and alkylaryl radicals and the remaining radicals are hydrogen atoms.

10

8. The compound according to claim 7, whereby the alkyl radicals are methyl radicals.

9. The compound according to claim 1, selected from the group consisting of (SP-4-3-)-(4-methyl-trans-cyclohexane-1,2-diamine)oxalatoplatinum(II) and (SP-4-3-)-(4,5-dimethyl-trans-cyclohexane-1,2-diamine)oxalatoplatinum(II).

10. Use of a compound according to any one of claims 1 to 9 for combating and/or the prophylaxis of tumour diseases.

20

11. Use of a compound according to any one of the claims 1 to 9 for the production of a medicament for combating and/or the prophylaxis of tumour diseases.

12. A medicament comprising a compound according to any one of the claims 1 to 9 and at least one pharmaceutically acceptable carrier.

1/4

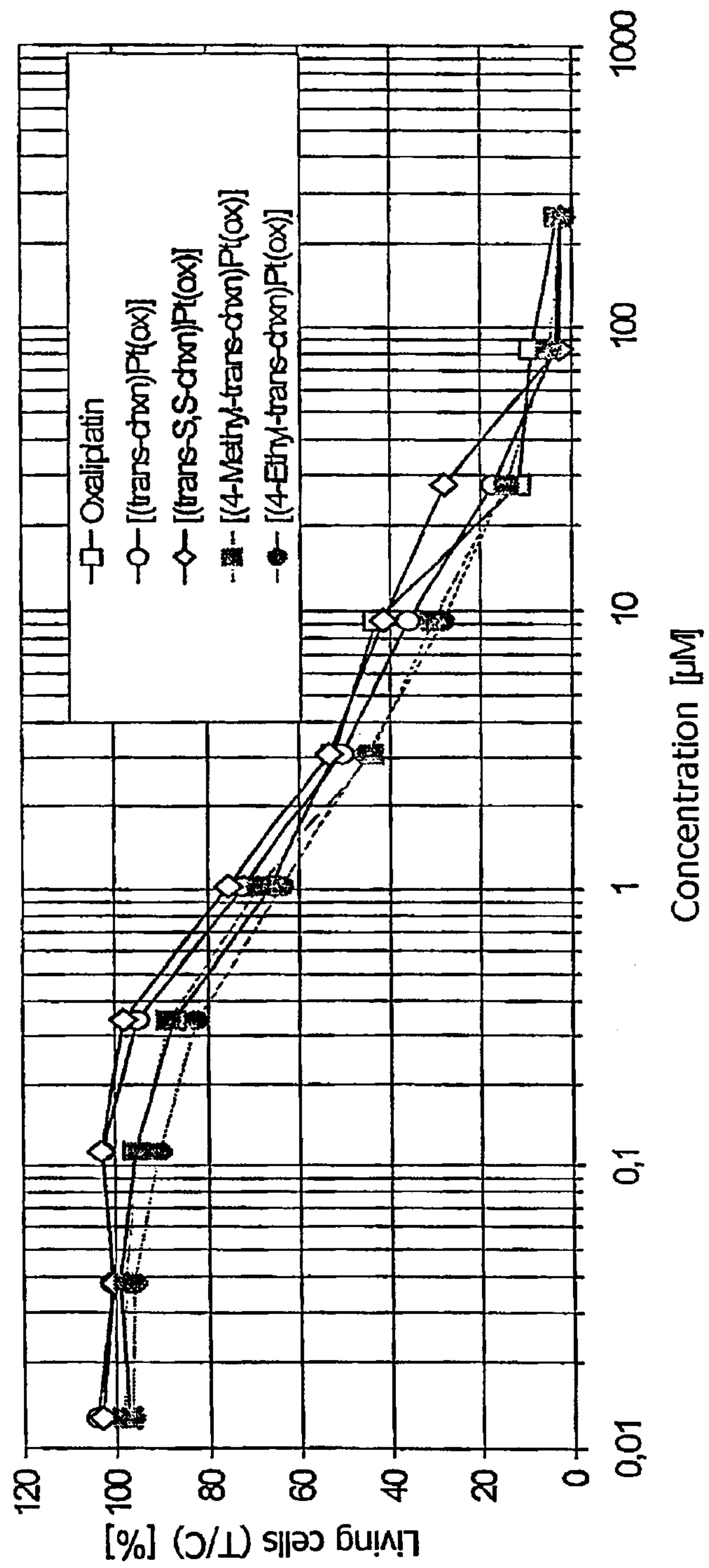


FIG. 1

2/4

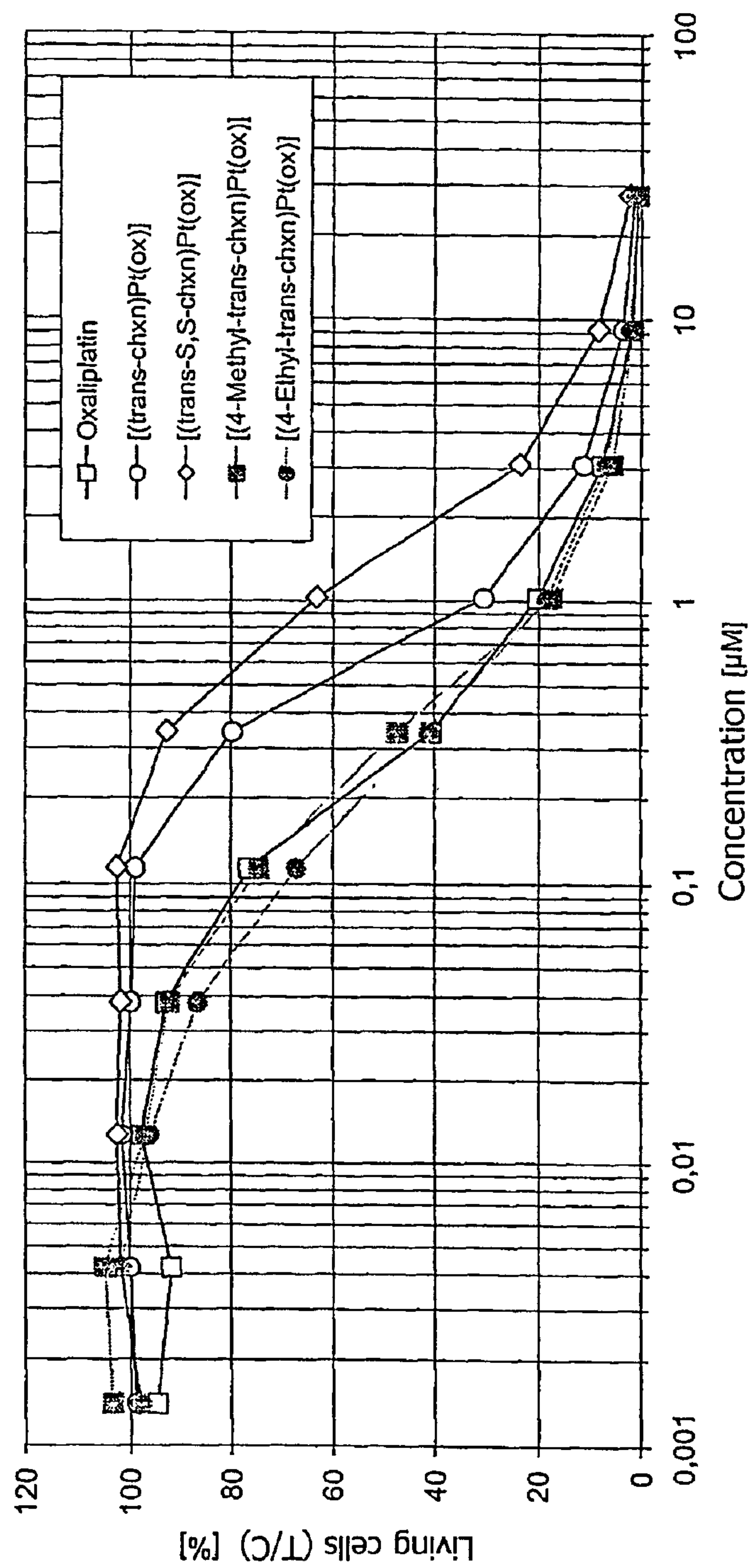


FIG. 2

3/4

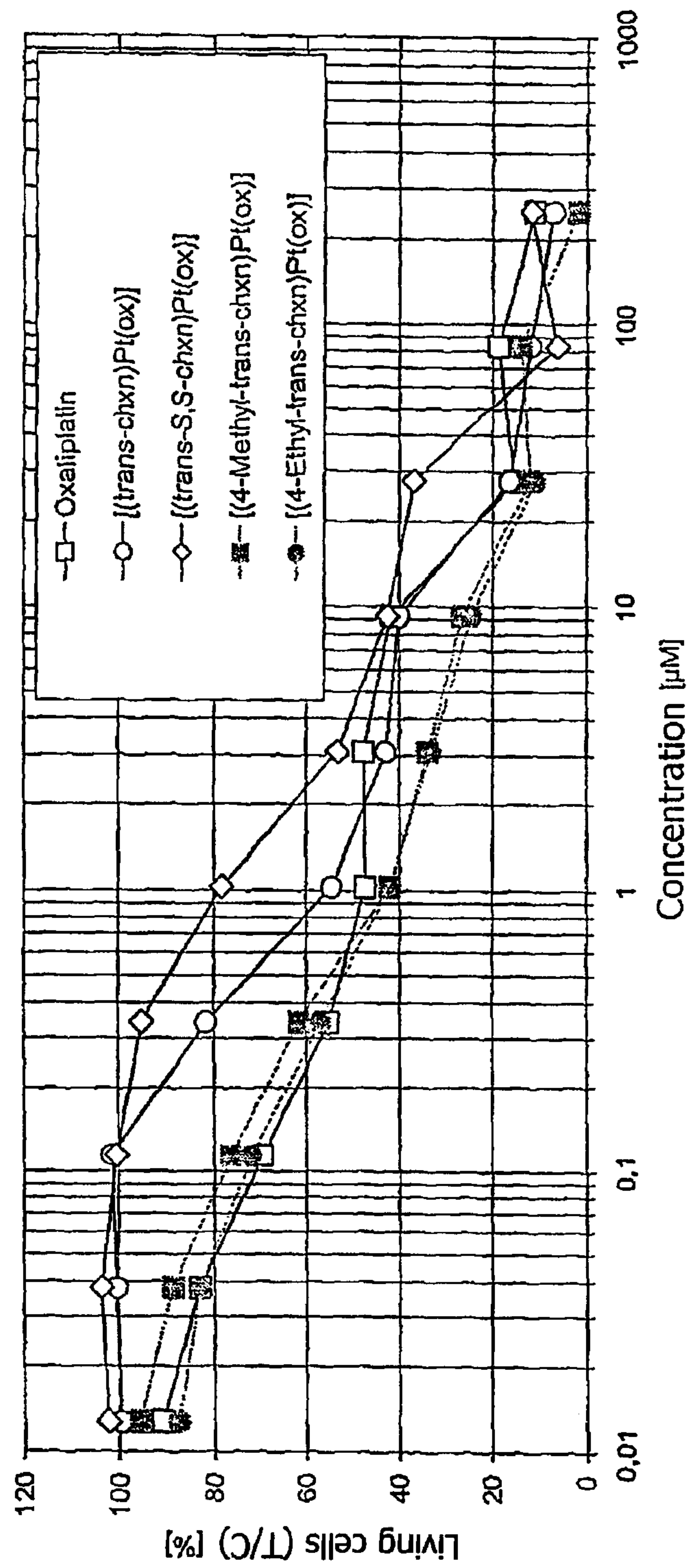


FIG. 3

4/4

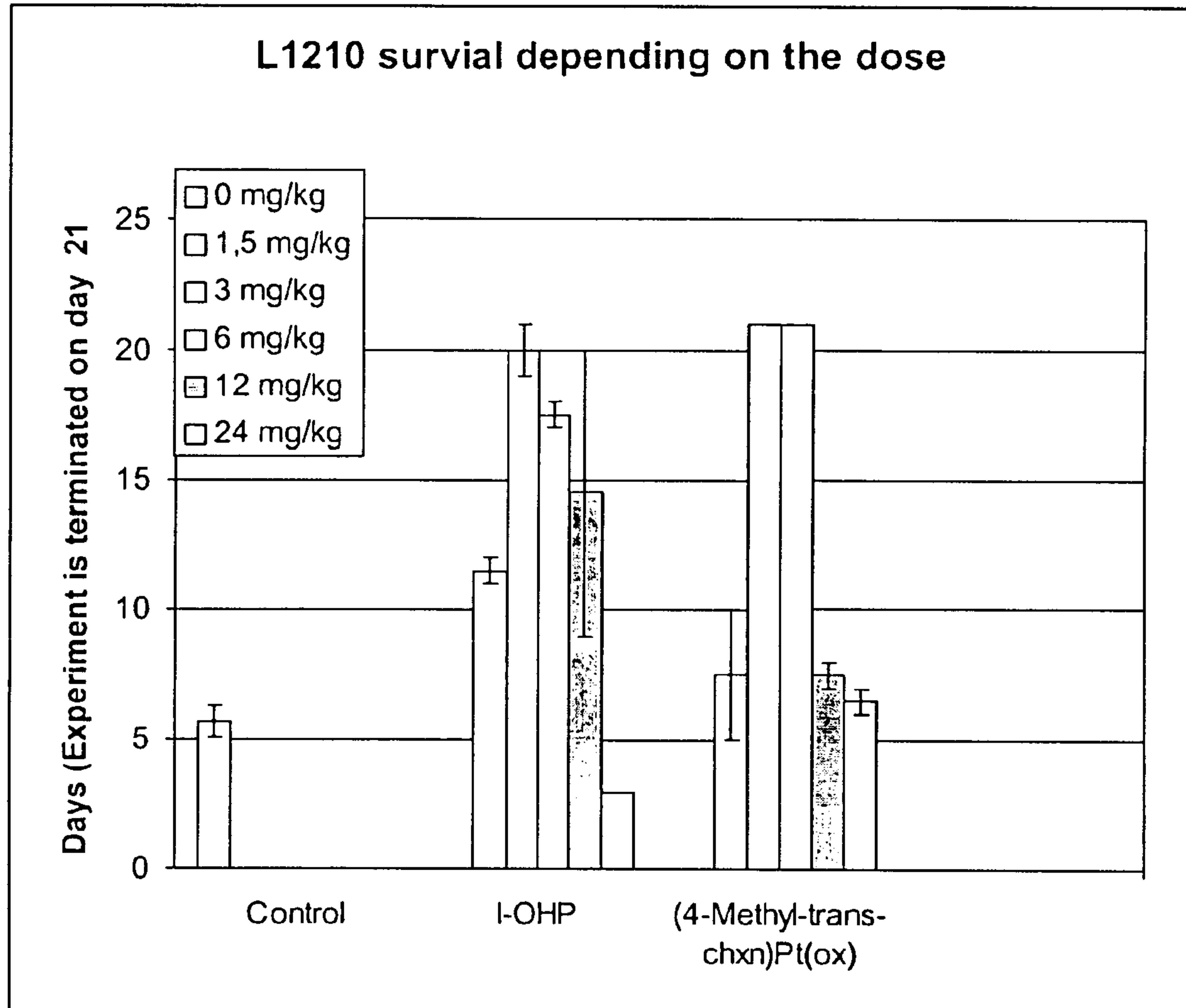
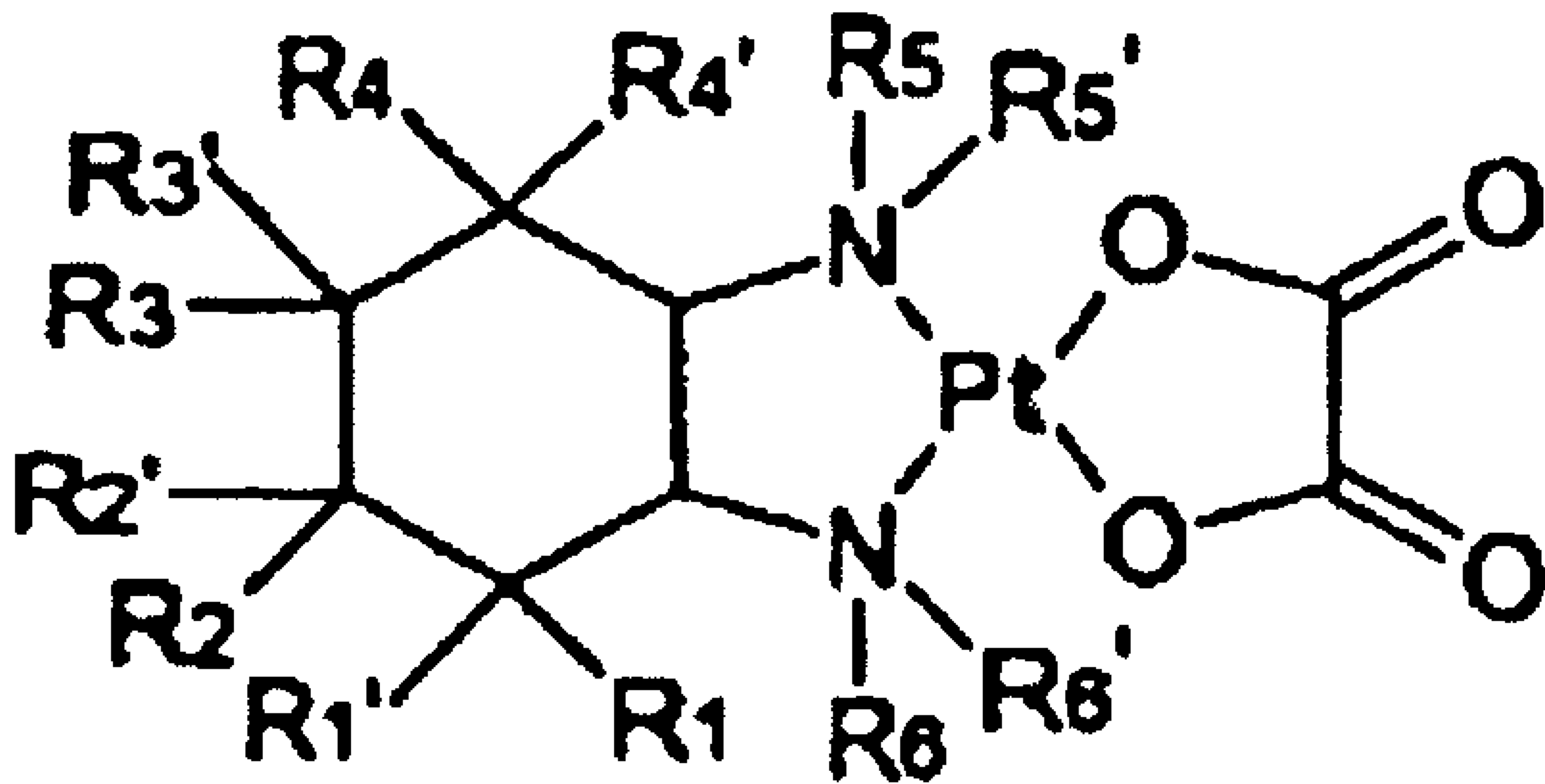


FIG. 4



(I)