Chemiluminescent substituted epidoxy-polycycloalkyl polycycloalkanes and process for preparing these compounds

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Polycycloalkylidene-polycycloalkanes, epidioxy derivatives thereof and method of preparation

Abstract:

PCT No. PCT/NL83/00014 Sec. 371 Date Dec. 7, 1983 Sec. 102(e) Date Dec. 7, 1983 PCT Filed Apr. 7, 1983 PCT Pub. No. WO83/03604 PCT Pub. Date Oct. 27, 1983.The invention relates to a process for preparing substituted polycyclo-alkylidene polycyclo-alkanes, such as substituted adamantylidene adamantanes, and the corresponding epidioxy compounds, in which polycyclo-alkylidene polycyclo-alkanes are halogenated with an N-halosuccinimide, tert.-butylhypohalite or sodium hypohalite/CH3COOH, the halogenation product is optionally subjected to a substitution reaction, and the substituted polycycloalkylidene polycyclo-alkanes are converted to the corresponding epidioxy compounds in a way known per se. Further, the invention relates to compounds of formula 44 in which A and B represent alkylene radicals, which alkylene radicals may be attached to each other via an alkylene radical C, and R1 represents a substituent, which, in case of 4-eq.-R1-2,2'-adamantylidene adamantane cannot be chloro, hydroxy, oxo, D or a group of formula 1: as well as to compounds of formula 45: in which A, B and C are as defined above, and R2 is a substituent which, in case of 4-eq.-R2-2,2'-epidioxy-2,2'-adamantyl adamantane cannot be chloro or hydroxy. Compounds of formula 45 are useful as thermochemiluminescent labels and probes in the study of biological processes and in immuno-assays.

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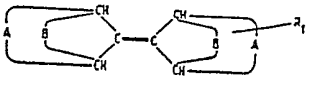

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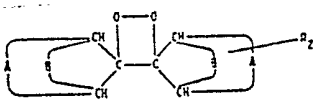

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(57) Abstract

Process for preparing substitued polycyclo-alkylidene polycyclo-alkanes, such as substituted adamantylidene adamantanes, and the corresponding epidioxy compounds, in which polycyclo-alkylidene polycyclo-alkanes are halogenated with an N-halosuccinimide, tert. -butylhypohalite or sodium hypohalite/CH_3COOH, the halogenation product is optionally subjected to a substitution reaction, and the substitued polycyclo-alkylidene polycyclo-alkanes are converted to the corresponding epidioxy compounds in a way known per se. Further, the invention relates to compounds of formula 44, in which A and B represent alkylene radicals, which alkylene radicals may be attached to each other via an alkylene radical C, and R_1 represents a substituent, which, in case of 4-eq.-R_1-2,2'-adamantylidene adamantane cannot be chloro, hydroxy, oxo, D or a group of formula (I), as well as to compounds of formula 45, in which A, B and C are as defined above, and R_2 is a substituent which, in case of 4-eq.-R_2-2,2'-epidioxy-2,2'-adamantyl adamantane cannot be chloro or hydroxy. Compounds of formula 45 are useful as thermochemiluminescent labels and probes in the study of biological processes and in immuno-assays.

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A process for preparing substituted polycyclo-alkylidene polycyclo-alkanes and the corresponding epidioxy compounds; as well as said substituted polycyclo-alkylidene polycyclo-alkanes and the corresponding epidioxy compounds.

The invention relates to a process for preparing substituted polycyclo-alkylidene polycyclo-alkanes and the corresponding epidioxy compounds, as well as to these substituted polycyclo-alkylidene polycyclo-alkanes and the corresponding epidioxy compounds.

The term "substituted polycyclo-alkylidene polycyclo-alkanes" as used herein comprises especially compounds of formula 44 of the formula sheet, in which A and B represent alkylene radicals, which alkylene radicals may be attached to each other via an alkylene radical C, and wherein R_1 represents a substituent which, in the case of 4-equatorially R_1-substituted 2.2'-adamantylidene adamantanes, cannot be chloro, hydroxy, oxo, D or a radical of formula 1 of the formula sheet. In preferred compounds of formula 44, alkylene radical A contains 2 to 5 carbon atoms, alkylene radical B 2 to 5 carbon atoms, and alkylene radical C, if present, 1 to 4 carbon atoms. Examples of compounds of formula 44 are 4-eq-R_1-2,2'-adamantylidene adamantanes, 4-eq-R_1-9,9'-bicyclo [3,3,1]-nonylidene-bicyclo[3,3,1]-nonanes, 2- or 7-R_1-8,8'-bicyclo[3,2,1]-octylidene-bicyclo[3,2,1]-octanes and 2- or 7-R_1-10,10'-bicyclo[4,3,1]-decylidene-bicyclo[4,3,1]-decanes, in which the two rings of each of the bicyclic radicals may be attached to each other via an alkylene bridge.

The corresponding epidioxy compounds - which contain a dioxetane ring - are especially compounds of formula 45, in which A, B and C, if present, have the above-mentioned meanings, and R_2 represents a substituent which, in the case of 4-eq-R_2-2,2'-epidioxy-2,2'-adamantyl adamantane cannot be chloro or hydroxy.

The invention relates to these compounds and to processes for the preparation thereof. Especially, the invention relates to a process for preparing substituted polycyclo-alkylidene polycyclo-alkanes, in which a corresponding non-substituted compound is subjected to a halogenation reaction, using a halogenating

agent in a solvent, and the halogenation product is recovered from the reaction mixture and/or, if desired, is subjected to a substitution reaction.

In Tetrahedron Letters 1970, 4579-82, J.H. Wieringa, J. Strating and H. Wynberg describe a process in which adamantylidene adamantane is reacted with chlorine in tetrachloromethane at a temperature of -20° to $+10^{\circ}C$ to form 4-eq.-chloroadamantylidene adamantane in addition to polychlorinated products. The chloro-substituted adamantane compound is the starting point for further reaction in the presence of $AgNO_3$ and THF/H_2O to form a mixture of the corresponding 4-hydroxy-adamantylidene adamantane compounds, which with the appropriate oxidant (Jones reagent: CrO_3, H_2SO_4, acetone) are finally converted into the corresponding ketone compound, in which the carbonyl group is in the 4-position.

It is an object of the invention to provide a process for preparing substituted polycyclo-alkylidene polycyclo-alkane compounds, in which these compounds are selectively produced in a high yield and in a simple manner and/or from which other substituted polycyclo-alkylidene polycyclo-alkane compounds can be selectively prepared in a high yield.

According to the invention, for this purpose, the process as defined above is carried out using as the halogenating agent N-halosuccinimide, tert.-butylhypohalite, or sodium hypohalite/CH_3COOH.

The invention is based on the surprising discovery that, with the halogenating agents mentioned, polycyclo-alkylidene polycyclo-alkanes which can be considered to be tetra-alkyl ethylene compounds, such as the adamantylidene adamantane, produce halogenation products with a structure, namely, the 4-eq.-halogen-substituted structure, which differs from the structure normally to be expected in reactions of these halogenating agents with mono-, di- and trialkylethylene compounds. Thus, in the process according to the invention, halogenation of the adamantylidene adamantane by means of N-chlorosuccinimide in boiling CCl_4 and in the presence of a radical initiator exclusively produces the 4-eq.-chloro-substituted compound. This halogenation reaction, carried out in CH_2Cl_2 at room temperature and in the absence of a radical initiator, produces the 4-eq.-

chloro-substituted compound in a quantitative yield in a smoothly proceeding reaction. The halogenation reaction also takes place in CCl_4, $CHCl_3$, or in a mixture of CH_2Cl_2/CH_3COOH, with the reaction velocity increasing with increasing polarity of the solvent.

It has been found that, in the presence of a radical inhibitor, for example hydroquinone, the halogenation reaction takes place at a high rate.

A further elaboration of the process according to the invention concerns causing the chlorine atom in the chloro-substituted compound formed to participate in a substitution reaction in a solvent in the presence of a silver salt, using as the substituting agent, in addition to the silver salt, a nucleophile, for example, an alcohol, a cyanide, a carbamate, or an isothiocyanate.

When, for example, 4-eq.-chloroadamantylidene adamantane is dissolved in an alcohol or a mixture of the alcohol and dioxane and $AgBF_4$ is added, a fast proceeding reaction takes place, in which the corresponding ether is formed without appreciable quantities of byproduct. In this reaction, the reaction components may be directly mixed with each other, whereby they react at room temperature or at a slightly elevated temperature. The degree of selectivity of the formation of a given ether is promoted by a careful preparation of the reaction components in the sense that they should be thoroughly dry.

In the reaction of 4-eq.-chloroadamantylidene adamantane with certain alcohols, for example, methanol, n-octanol-1 and hydroxy-acetone, these alcohols may themselves serve as the solvent, and hence be used in large excess. It has been found, however, that the yield of product ether did not decrease dramatically when a lower concentration of the alcohol component in the reaction mixture is selected.

When 4-eq.-chloroadamantylidene adamantane is reacted with a nitrile as the nucleophile in the presence of $AgBF_4$, taking care that the imminium ions formed are hydrolysed with water, there is produced N-(4-eq.-adamantylidene adamantyl)amide, albeit that, generally speaking, these reactions with a nitrile proceed

at a lower rate than with alcohols while the yield is also comparatively lower.

The reaction of, in particular, 4-eq.-chloroadamantylidene adamantane with alcohols to form ethers and with nitriles to form amides are the first steps on a route leading to diverse 4-eq.-substituted adamantylidene adamantanes, and via these compounds to the corresponding 1,2-dioxetanes, which will be entered into later.

In a preferred embodiment of the process according to the invention, the halogenating agent is a brominating agent, for example, N-bromosuccinimide, and, in accordance with the above, there is then produced the 4-eq.-bromo-substituted compound. When the starting point is, for example, the adamantylidene adamantane, heating for 12 hours at 40°C produces 4-eq.-bromoadamantylidene adamantane according to a fully completed reaction.

The 4-eq.-bromoadamantylidene adamantane has been found to have particularly advantageous and unexpected properties. Thus, unlike the corresponding 4-eq.-chloroadamantylidene adamantane, this compound permits carrying out substitution reactions by means of solvolysis without requiring an adjuvant such as an Ag^+ salt. It has moreover been found that certain substituents can be introduced in one step where this had not been possible before. The 4-eq.-bromoadamantylidene adamantane reacts with primary and secondary alcohols to form ethers, with carboxylic acids to form esters, with primary amines to form secondary amines, and with nitriles to form N-adamantylidene adamantyl amides. Furthermore it has been found to be possible to carry out halogen exchange reactions with this compound, for example, in a reaction with NaJ/acetone. Reaction of 4-eq.-bromoadamantylidene adamantane with H_2O/dioxane gives a quantitative yield of 4-eq.-hydroxyadamantylidene adamantane. The solvolysis reactions are carried out in the pure reagent as the solvent or together with dioxane or DMF as a co-solvent.

According to another elaboration of the process according to the invention, the symmetrical polycyclo-alkylidene polycycloalkane used as the starting point is adamantylidene adamantane.

Preferably the 4-eq.-substituted adamantylidene adamantane is subjected to a photo-oxigenation reaction to form the 4-eq.-substituted 1,2-dioxetane, as 1,2-dioxetanes have particularly advantageous properties, as will be explained in more detail hereinafter.

The invention also relates to substituted polycycloalkylidene polycycloalkanes, especially to compounds of formula 44 as defined above, and preferably to 4-eq.-R_1-substituted adamantylidene adamantane compounds, and in particular those in which R_1 is bromine, with the exception of the known per se 4-eq.-R_1-substituted adamantylidene adamantanes in which R is chlorine, hydroxyl, oxo, D or a group having the formula 1 of the sheet of formulae. A favourable property of adamantylidene adamantanes in general is that the 1,2-dioxetanes produced from them exhibit a good stability, as appears from a summary of a so-called "poster session" on bio- and chemiluminescence, published in June 1981 by Academic Press, New York.

1,2-dioxetanes themselves are stated in an article by T. Wilson in Int. Rev. Sci.: Phys. Chem. Ser. Two 9 (1976) 265 to be suitable as thermochemiluminescent compounds, with the possibility of controlling the chemiluminescence emitted by regulating the temperature of the system.

In accordance with the above, the invention accordingly also relates to chemiluminescent compounds of formula 45, in which A and B represent alkylene radicals, which alkylene radicals may be attached to each other via an alkylene radical C, and wherein R_2 represents a substituent which, in the case of 4-eq.-R_2-2,2'-epidioxy-2,2'-adamantyl adamantane cannot be chloro or hydroxy.

In preferred compounds of formula 45 the alkylene radical A contains 2 to 5 carbon atoms, the alkylene radical B 2 to 5 carbon atoms, and the alkylene radical C, if present, 1 to 4 carbon atoms. In particular, the invention relates to 4-eq.-R_2-2,2'-epidioxy-2,2'-adamantyl adamantanes in which R_2 represents a substituent, with the exception of chloro or hydroxy.

For example, the substituent R_2 may be chloro, bromo or iodo, a hydroxy group, an optionally substituted alkoxy, cyclo-

alkoxy or acyloxy group, or an amino, acylamino, isothiocyanato or isocyanato group, with the proviso that in case of 4-eq.-R_2-2,2'-epidioxy-2,2'-adamantyl adamantanes R_2 cannot be chloro or hydroxy.

In particular, the substituent R_2 represents a radical of a biologically active compound, such as of a fatty acid, a steroid, or a protein. In that case the compound of formula 45 is a biologically active substance labelled with a chemiluminescent 1,2-dioxetane.

It is true that it is known, within the framework of the analytical techniques used in biochemistry, clinical chemistry and biology for the qualitative and quantitative analysis and structural assay of biological materials to use luminescent labels and probes. The compounds having chemiluminescent properties, such as luminol and other phthalohydrazide derivatives used in these techniques, however, have the limitation that their chemiluminescence can only be generated by adding oxidants, for example hydrogen peroxide.

The novel chemiluminescent labels according to the present invention are suitable for use in immunochemical methods of determination, in particular immunoassay, and the study of steroids and membranes. Unlike known agents, such as luminol, the chemiluminescence is generated solely by heating.

To study, in particular, membranes, the thermo-chemiluminescent compounds according to the invention are modified to a label which exhibits chemiluminescence at a temperature of at least 150°C and up to approximately 250°C. By suitable substitution of the 1,2-dioxetane according to the invention, for example, by a long-chain fatty acid, the label is rendered compatible with the surroundings to be studied at the membrane.

A thermochemiluminescent fatty acid compound according to the invention is, for example, the compound of formula 28, in which the fatty acid radical is derived from arachidic acid. Such a compound has been found to have properties analogous to those of long-chain fatty acids, and to be suitable for use as a chemiluminescent label in membrane studies.

For chemiluminescence immunoassay based on a specific antibody-antigen reaction, a dioxetane compound according to the invention is modified to a "label", for example a protein label which is specific relative to certain functional groups in peptides.

Thus, for example, a protein may be marked at a free thiol group with a 4-eq.-substituted 2,2'-epidioxy-2,2'-adamantyl adamantane in which the substituent is α-iodoacetoxy of maleimido (formulae 29 and 42, respectively, of the sheet of formulae). The 1,2-dioxetane thus substituted may be reacted under standard conditions with, for example, Bovine Serum Albumine, which is a protein having 0.7 mole of free thio groups per mole of protein. Purification of the reaction product by chromatography over a Sephadex G-10 column, dialysis against distilled water, and freeze drying produces the chemiluminescent protein. This procedure may also be applied to other proteins and, for example, to glutathione.

For immunoassay on the basis of chemiluminescence for steroid investigation, the 1,2-dioxetane compound according to the invention may be attached to, for example, lithocholic acid (formula 31) or testosterone (formula 22).

The invention is illustrated in and by the following examples.

EXAMPLE I

In the examples, melting points were determined by means of a Mettler FP2 melting point apparatus. IR spectra were recorded with a Unicam (SP-200) spectrophotometer and ^{1}H NMR spectra with a Varian A-60 of Hitachi Perkin Elmer R-24 B at 60 Mc. ^{1}H chemical shifts are given in δ units (ppm) relative to TMS (tetramethylsilane).

^{13}CMR spectra were recorded at 25 Mc (Varian XL-100) and ^{13}C chemical shifts are indicated in δ units (ppm) relative to the solvent $CDCl_3$ and converted to δ TMS values using δ D KCl_3 = 76.9 ppm.

Mass spectra were recorded by means of a Perkin Elmer Polarimeter using a 10 cm cell.

All solvents were purified and dried according to standard conditions. Silver salts ($AgBF_4$; $AgClO_4$) were dried with P_2O_5 at 0.001 mm Hg for 10-20 hours.

The 4-eq.-chloroadamantylidene adamantane (formula 2 of the sheet of formulae) used in the examples can be characterized as follows: melting point 142-143°C. ^{13}C NMR ($CDCl_3$): 137.0; 130.8; 68.3; 39.4; 39.2; 38.8; 37.0; 35.6; 32.4; 32.1; 30.4; 30.4; 28.3; 27.6.

Preparation of 4-eq.-hydroxyadamantylidene adamantane (formula 3) and 4-eq.-, 4'-eq.-bisadamantylidene adamantyl ether (formula 4a in which R represents a group having formula 4b).

4-eq.-chloroadamentylidene adamantane having formula 2 (12.8 g; 40 mmoles) was dissolved in dioxane (160 cm^3) and distilled water (40 cm^3) was added. The mixtures was refluxed, and with stirring, $AgBF_4$ (10 g, 50 mmoles) was added in small quantities together with 120 cm^3 dioxane over a period of 75 minutes. Refluxing was continued for 15 minutes, whereafter the reaction mixture was cooled, filtered and concentrated. The residu was taken up in ether (120 cm^3), the ethereal solution was washed with water (3x100 cm^3), dried with $MgSO_4$, decolourized with 1 g activated charcoal, filtered and evaporated to yield 11.09 (97%) of the compound having formula 3 in the form of a white powder having a melting point of 211.5-213°C.

When the reaction was carried out in a dioxane/water (25/1) mixture and $AgBF_4$ was added all at once, after work-up and chromatography over Al_2O_3 (act. II/III) using CH_2Cl_2 as the eluent, the compound having formula 4a, in which R represents the group having formula 4b, could be isolated in a yield of 25%. Even after recrystallization (from n-hexane) a sharp melting point could not be obtained, probably because the compound having formula 4a consisted of a mixture of diastereo-isomers. ^1H NMR ($CDCl_3$) δ 3.33 (br, 2H); 3.05-2.55 (m, 8H); 2.50-1.1 (m, 44H). ^{13}C NMR (CDl_3): δ 135.2; 135.1; 131.6; 131.4; 80.7; 39.7; 39.5; 39.2; 37.2; 33.4; 32.3; 32.1; 31.4; 31.0; 28.5; 27.8: IR (KBr) 2900 (s), 1455 (m), 1080 (s), 1035 (m) and 975 (m) cm^{-1}. Mass: M^+ at m/e 550 (30%), 267 (100%) with metastable peak at 129.6. Exact mass: calculated for $C_{40}H_{54}O$: 550.417. Found 550.418.

EXAMPLE II

Preparation of 4-eq.-methoxyadamantylidene adamantane (formula 5).

The chloro-substituted compound having formula 2 (605 mg, 2 mmoles) was suspended in very dry MeOH (10 cm^3) under a nitrogen atmosphere and using a magnetic stirrer. Subsequently 600 mg (3 mmoles) $AgBF_4$ was added and the mixture was refluxed for 30 min. AgCl was filtered off and Et_2O (50 cm^3) was added. The solution was washed with H_2O (2x100 cm^3), dried with $MgSO_4$, filtered and concentrated at a reduced pressure to produce 520 mg (88%) spectroscopically pure compound having formula 5 in the form of a colourless oil. "Kugelrohr" distillation (170-180°/0.1 mm Hg) yielded 500 mg analytically pure material which solidified on standing: ^1H NMR ($CDCl_3$): δ 3.3 (br, 1H); δ 3.3-2.6 (br-5H); δ 2.3-2.1 (br, 22H). ^{13}C NMR ($CDCl_3$): 135.3, 130.8; 83.3; 54.9; 39.3; 39.0; 37.0; 36.7; 35.1; 32.6; 32.2; 31.8; 31.0; 30.8; 28.3; 24.5. Mass: M^+ at m/e 298 (100). IR (neat) 2900, 1450 and 1095 cm^{-1}. Analysis: calculated for $C_{21}H_{30}O$: 84.51, C; 10.13, H. Found: 84.81, C; 10.05, H.

EXAMPLE III

Preparation of 4-eq.-n-octyl-oxy-adamantylidene adamantane (formula 6).

The chloro-substituted compound having formula 2 (605 mg, 2 mmoles) was suspended in n-octanol-1 (5 cm^3). With stirring by means of a magnetic stirrer, $AgBF_4$ (600 mg, 3 mmoles) was added in 2 portions. The mixture was heated for 5 minutes at 100°C and then allowed to cool to room temperature while it was stirred for 3 hours. Ether (75 cm^3) was added and the solution was washed with water (2x100 cm^3), dried with $MgSO_4$, filtered and evaporated at 0.3 mm/100°C. Column chromatography over Al_2O_3 (act. II/III) using CH_2Cl_2 as the eluent produced 640 mg (81%) spectroscopically pure compound having formula 6 in the form of a colourless oil. ^1H-NMR ($CDCl_3$) δ 3.55-3.10 (3H, m); δ 3.10-2.60 (4H, m); δ 2.33-0.6 (37H). ^{13}C NMR ($CDCl_3$): δ 135.1; 131.2; 81.6; 67.3; 39.4; 39.1; 37.1; 36.8; 35.6; 32.9; 32.3; 31.9; 31.7; 31.0; 30.2; 29.4; 29.1; 28.4; 27.6; 26.2; 22.5; 13.8. Mass: M^+ at m/e 396, 267, 266, 41 (100%).

Exact mass: calculated for $C_{28}H_{44}O$: 396,339. Found: 396,342.

EXAMPLE IV

Preparation of O-(4-eq.-adamantylidene adamantyl) lactamide (formula 7).

To a solution of 2.0 g l-lactamide (Merck) and 605 mg (2 mmoles) of chloro-substituted compound having formula 2 in 15 cm^3 dioxane, $AgBF_4$ (4 mmoles) was added with vigorous stirring at 70°C. The mixture was stirred at room temperature for 20 hours, diluted with ether (150 cm^3), washed with water, dried with $MgSO_4$, filtered and concentrated to produce 600 mg of a white material. Column chromatography using Al_2O_3/CH_2Cl_2 gave 200 mg non-reacted compound having formula 2 and then 330 mg of the compound having formula 7 (70%, based on converted compound having formula 2), which solidified when stripped with ether; melting point 133-135°C. ^{1}H-NMR ($CDCl_3$) 6.4 (br, 2H); 3.88 (q, J = 6.5 c.; 1H); δ 3.32 (m, 1H); δ 2.80 (m, 4H); 2.3-1.1 (m, 25H) with doublet at 1.39; J = 6.5 Hz. ^{13}C-NMR ($CDCl_3$): δ 177.4; 135.9; 130.0; 81.1; 80.8; 73.1 (br); 39.2; 38.6; 36.8; 36.5; 35.8; 32.8; 32.1; 31.8; 30.9; 30.5; 28.1; 27.2; 18.8; 18.5. IR (KBr): 3460, 3300, 2900, 1670, 1580, 1450, 1100, 1060 cm^{-1}. Mass: m^+ at m/e 355, 267, 137, 91. Exact mass: calculated for $C_{23}H_{33}NO_2$ 355.251. Found: 355.253.

EXAMPLE V

Preparation of N(4-eq.-adamantylidene adamantyl)-acetamide (formula 8).

A solution of 1.21 g (4 mmoles) of the compound having formula 2 in 20 cm^3 dry dioxane was added to a stirred solution of 1.2 g $AgBF_4$ in 20 cm^3 CH_3CN and 20 cm^3 dioxane in a period of 5 minutes and at reflux temperature. After completion of the addition, the whole was stirred for 1 hour and a half without further heating. Water (2 cm^3) was added and after stirring for 5 minutes the mixture was concentrated at a reduced pressure. To the residue, 300 cm^3 ether was added and after filtration over a glass filter, the ethereal solution was washed with water (3x300 cm^3), dried with $MgSO_4$, filtered and concentrated to produce 1.11 g of the crude compound having formula 8 in the form of a white foam. Column

chromatography over Cl_2O_3, using first hexane (150 cm^3) and then CH_2Cl_2 as eluents produced 0.86 g (66%) pure acetamide in the form of white crystals; melting point 159-161°C (from hexane). ^{1}H-NMR ($CDCl_3$): δ 5.75 (br, 1H); 3.9 (br, 1H); 2.88 (m, 4H); 2.4-1.3 (m, 25H, with peak for $-CH_3$ at 2.00). ^{13}C-NMR ($CDCl_3$): δ 169.0; 135.8; 130.5; 53.9; 39.3; 39.0; 38.8; 37.6; 37.1; 35.3; 33.2; 32.0; 31.7; 31.3; 30.6; 28.3; 28.2; 27.3; 23.5. IR (KBr) 3400, 2950, 1650, 1550, 1460 and 1090 cm^{-1}. Mass: M^+ at m/e 325, 213, 135, 79, 41. Exact mass: calculated for $C_{22}H_{31}NO$: 325.241. Found 325.240.

EXAMPLE VI

Preparation of N-(4-eq.-adamantylidene adamantyl)-3-hydroxy-propionamide (formula 9).

The chloro-substituted compound having formula 2 (605 mg, 2 mmoles), 3-hydroxypropionitrile (10 cm^3) and dioxane (50 cm^3) were mixed together under a nitrogen atmosphere at 70°C to produce a homogeneous solution. $AgBF_4$ (600 mg, 3 mmoles) was added and the mixture was stirred for 1 hour without heating. Ether (100 cm^3) was added, the ethereal solution was washed with water, dried with $MgSO_4$, filtered and evaporated to produce 485 mg (70%) spectroscopically pure compound having formula 9 in the form of a white solid. Melting point 172-174°C (from hexane). ^{1}H NMR ($CDCl_3$) δ 6.55 (1H); 3.8 (m, 3H); 2.85 (m, 4H); 2.4 (m, 2H); 2.1-1.2 (m, 22H). ^{13}C NMR ($CDCl_3$): δ 171.5; 135.9; 130.3; 58.7; 53.9; 39.4; 39.0; 38.2; 37.6; 37.0; 35.3; 33.2; 32.1; 32.0; 31.7; 31.2; 30.5; 28.2; 27.2. IR (KBr): 3500, 2920, 1650, 1550, 1455, 1100 cm^{-1}. Mass: M^+ at m/e 355 (100%); 266, 91,73. Exact mass: calculated for $C_{23}H_{35}NO_2$: 355.251; found 355.249.

EXAMPLE VII

Preparation of N-(4-eq.-adamantylidene adamantyl)-lactamide (formula 10).

The chloro-substituted compound having formula 2 (605 mg, 200 mmoles) and d,l-lactonitrile (9.2 g) were mixed under a nitrogen atmosphere, while $AgBF_4$ (600 mg, 3 mmoles) was added with stirring at 50°C. After 30 minutes, ether (110 cm^3) was added. The ethereal solution was washed with water (8x100 cm^3), dried with $MgSO_4$, filtered and evaporated to yield 440 mg (62%) of spectroscopically pure

compound having formula 10 in the form of a white powder. ^{1}H NMR ($CDCl_3$) δ 7.0 (br, 1H); 4.20 (q, J = 13 c, 1H); 3.85 (m, 1H); 2.9 (m, 4H); δ 2.1-1.0 (m, 26H with doublet J = 13 Hz at 1.40). ^{13}C NMR ($CDCl_3$): δ 174.0; 173.96; 135.9; 130.4; 68.1; 53.4; 39.3; 39.0; 37.6; 37.0; 35.2; 33.1; 32.1; 32.0; 31.6; 31.2; 30.5; 30.4; 28.3; 28.2; 27.3; 21.0: IR (KBr): 3450,2930, 1650, 1540, 1455, 1120 cm^{-1}. Mass: M^+ at m/e 355 (100%); 267, 266, 91.79. Exact mass: calculated for $C_{23}H_{33}NO_2$ 355.251; found 355.249.

EXAMPLE VIII

Preparation of N-(4-eq.-adamantylidene adamantyl)-acrylamide (formula 11)

To a stirred solution of the chloro-substituted compound having formula 2 (3.02 g, 10 mmoles), 100 mg hydroquinone, and 30 cm^3 acrylonitrile in 80 cm^3 dioxane, $AgBF_4$ (4.4 g) was added in 4 portions at 40°C under a nitrogen atmosphere in the course of 2 hours. After this period a further quantity of 10 cm^3 acrylonitrile was added to the yellow mixture, whereafter the whole was stirred at room temperature for 20 hours. The reaction mixture was filtered to remove precipitated AgCl, diluted with ether (200 cm^3), washed with water, dried with $MgSO_4$, filtered and evaporated to yield 2.7 g of a yellowish solid. Column chromatography over Al_2O_3 using CH_2CL_2/benzene (1/1) as the eluent and recrystallization from MeOH produced 1.81 g (54%) pure compound having formula 11: melting point 190.5-192°C. ^{1}H NMR ($CDCl_3$): δ 6.20-6.08 and δ 5.6-5.4 (complex ABC systems and -NH absorption, 4H), 3.9 (m, 1H); 2.85 (m, 4H); 2.1-1.3 (m, 22H). ^{13}C-NMR ($CDCl_3$): δ 164.6; 135.9 (s); 131.3 (d); 130.4 (s); 125.6 (t); 54.1; 39.4; 39.3; 38.9; 37.7; 37.0; 35.2; 33.1; 32.1; 32.0; 31.6; 31.2; 30.5; 28.3; 28.2; 27.3. IR (KBr): 3400, 2950, 660, 1630, 1535, 1460, 1220 cm^{-1}. Mass M^+ at m/e 337 (100%); 266 with a meta-stability at 210; 213; 91, 79. Exact mass: calculated for $C_{23}H_{31}NO$: 337.241. Found: 337.243.

EXAMPLE IX

Preparation of adamantylidene adamantan -4-one (formula 12).

A mixture of the chloro-substituted compound having formula 2 (10.1 g; 33 mmoles) and $AgClO_4$ (12 g) in 250 cm^3 DMSO was heated at 150-160°C under a nitrogen atmosphere for 25 hours.

After cooling and filtration, the product was extracted with n-hexane (4x15 moles). The hexane solution was washed with water, dried with $MgSO_4$, decolourized with 0.5 g activated charcoal, filtered and evaporated to produce 8.4 of the crude compound having formula 12. Chromatography over a short Al_2O_3 column, using CH_2Cl_2 as the eluent produced 7.15 g (76%) of the spectroscopically pure compound having formula 12 in the form of a white solid. All spectroscopic data were identical to those of the authentic sample. ^{13}C NMR ($CDCl_3$): δ 215.5; 138.0; 129.2; 51.7; 46.2; 41.4; 39.2; 39.1; 38.1; 38.7; 38.3; 37.7; 36.6; 32.7; 31.8; 31.6; 30.7; 28.1; 27.9; 27.5.

EXAMPLE X

Preparation of N(4-eq.-adamantylidene adamantyl)-ethylcarbamate (formula 13).

To a solution of 6.0 g (24 mmoles) $AgBF_4$ in 27 g ethylcarbamate, a solution of 6.05 g (20 mmoles) of the chloro-substituted compound having formula 2 in 250 cm^3 of dioxane was added at 60°C with stirring in the course of 15 minutes. The mixture was refluxed for a further period of 20 minutes, cooled, and concentrated at a reduced pressure. Ether (200 cm^3) was added, the etheral solution was washed with water (3 x 200 cm^3), dried with $MgSO_4$, filtered and evaporated. 100 cm^3 iso-octane was added and evaporated, and this was repeated three times to remove residual quantities of ethylcarbamate. Column chromatography over Al_2O_3 (10 cm path, dia. 5 cm) using $CHCl_3$ as the eluent produced 6.54 g pure compound having formula 13 (87%) in the form of a white solid. Melting point 158-159°C (from EtOH/H_2O). ^1H NMR ($CDCl_3$): δ 5.0 /br, 1H); 4.1 (q, J = 8 C, 2H); 3.65 (1H); 2.92 (m, 4H); 2.2-05 (25H) with triplet J = 8 Hz at 1.27 ppm. ^{13}C NMR ($CDCl_3$): δ 155.7; 135.8; 130.6; 60.3 (t); 55.4 (d); 39.4; 38.9; 37.7; 37.0; 35.7; 32.9; 32.1; 32.0; 31.1; 30.5; 28.3; 27.3; 14.4 IR (KBr): 3350, 2950, 1710, 1455, 1420, 1390, 1335 cm^{-1}. Mass : M^+ at m/e 355 (100%); 267, 91.79. Exact mass: calculated for $C_{23}H_{33}NO_2$ 355.251. Found: 355.248.

EXAMPLE XI

Preparation of 4-eq.-adamantylidene adamantane isothiocyanate (formula 14).

To a solution of $AgBF_4$ (2.4 g, 12 mmoles) and freshly distilled benzylthiocyanate in 40 cm^3 dioxane, a solution of the chloro-substituted compound having formula 2 (2.42 g, 8 mmol) in 40 cm^3 dioxane was added with stirring over a period of 45 minutes. After being stirred for another hour, the mixture was concentrated at a reduced pressure. Ether was added, the solution washed with water, dried with $MgSO_4$, filtered, and evaporated at a greatly reduced pressure. Column chromatography over Al_2O_3, using Ch_2Cl_2 as the eluent produced 1.6 g (61%) spectroscopically pure compound having formula 14 in the form of a white solid, melting point 180-181°C (from n-heptane). ^{1}H-NMR ($CDCl_3$): δ 3.75 (br, 1H), 3.12 (br, 1H); 2.87 (br, 3H); 2.3-1.2 (m, 22H). ^{13}C-NMR ($CDCl_3$): 137.6; 129.7; 128.8; 62.5; 39.4; 38.7; 37.3; 36.9; 36.8; 33.0; 32.3; 32.2; 31.2; 30.3; 28.2; 27.2: Ir (KBr): 2940, 2200, 1460, 1345, 1085, 765 cm^{-1}. Mass: M^+ at m/e 325, 267, 91, 79, 41. Exact mass: calculated 325.186. Found: 325.185.

EXAMPLE XII

Preparation of 4-eq-chloroadamantylidene adamantane (Formula 2).

To a solution of 1 mmol (268 mg) adamantylidene adamantane having the formula 19 in 20 cm^3 CH_2Cl_2, 1.05 mmols (140 mg) N-chlorosuccinimide was added. The reaction mixture was stirred at room temperature for 1 hour, diluted with CH_2Cl_2, and washed twice with water. The organic layer was dried with $MgSO_4$ and evaporated. The yield of 4-eq.-chloroadamantylideneadamantane was 300 mg (98%), melting point: 142-243°C. (literature: 144-145°C). ^{1}H NMR ($CDCl_3$): δ 4.15 (br s, 1H); 3.05 (br s 1H); 2.8 (br s, 3H); 2.6-1.15 (br m, 22H) ppm. When 0.1 mmol hydroquinone was added to the solution, exactly the same reaction occurred, and the product could be isolated in virtually the same quantitative yield.

EXAMPLE XIII

Preparation of 4-eq.-bromoadamantylideneadamantane (formula 16).

To a solution of 3 mmols (804 mg) adamantylideneadamantane in 40 cm^3 CH_2Cl_2, 6.6 mmols (1.175 g) N-bromosuccinimide was added. The reaction mixture was refluxed and stirred for 12 hours.

The reaction mixture was diluted with CH_2Cl_2 and washed twice with water and a saturated $Na_2S_2O_3$-solution. The organic layer was dried with $MgSO_4$ and evaporated. The yield of 4-eq.-bromo-adamantylideneadamantane having formula 20 was 1.05 g (97%). An analytically pure sample could be obtained by crystallization from acetone and sublimation (115°C/0.002 mm); melting point 130.5-131.5°C. ^1H NMR ($CDCl_3$); δ 4.4 (br s, 1H); 3.05 (br s, 1H); 2.8 (br s, 3H); 2.6-1.2 (br m, 22H); ^{13}C NMR ($CDCl_3$); δ 136.9 (s); 131.0 (s); 63.8 (d) and 12 signals between 39.9 and 27.6. Analysis, calculated: 69.16 C; 7.84 H; 23.01 Br; found: 69.21 C; 7.82 H; 22.99 Br. Mass m/e 346:348 (1:1).

EXAMPLE XIV

Preparation of 4-eq.-chlorobicyclo[3,3,1]-nonylidene-bicyclo[3,3,1]nonane (formula 18).

To a solution of 200 mg (0.82 mmol) of bicyclo [3,3,1] nonylidene-bicyclo[3,3,1]nonane (formula 17) in 20 cm^3 CH_2Cl_2, 115 mg (0.86 mmol) N-chlorosuccinimide was added. The reaction mixture was refluxed and stirred for 1 hour, and CH_2Cl_2 was added to dilute the reaction mixture. The organic layer was washed twice with water, dried with $MgSO_4$ and evaporated. The yield of 4-eq.-chlorobicyclo[3,3,1]nonylidene-bicyclo[3,3,1] nonane was 190 mg. Purification was effected via chromatography (hexane, Al_2O_3) and sublimation (45°C/0.01 mm), melting point 50.53°C, ^1H NMR ($CDCl_3$) δ 4.4-3.9 (m, 1H); 3.1 (br s, 1H): 2.85 (br s, 3H); 2.5-1.2 (br, 22H); ^{13}C NMR ($CDCl_3$) δ 136.8 (s); 129.7 (s); 66.0 (d) and lines between 39.7 and 21.7; mass m/e 278:280 (3:1); exact mass: calculated 278.180; found 278.182.

EXAMPLE XV

Preparation of 4-eq.-(2-chloroethoxy)-adamantylidene-adamantane (formula 19).

The bromo-substituted compound having formula 16 (220 mg, 0.58 mmol) was dissolved in dry dioxane (10 cm^3) and 2-chloro-ethanol (5 cm^3) was added. The mixture was refluxed for 18 hours, cooled, and concentrated at a reduced pressure. Water (50 cm^3) was added and the product was twice extracted with n-hexane, with the combined extracts being washed with brine. The hexane solution was dried with $MgSO_4$, filtered and concentrated at a

reduced pressure. Columnchromatography over Al_2O_3 (act. II/III), using hexane as the eluent, produced 180 mg (0.52 mmol, 89.7%) of pure compound having formula 23 in the form of a colourless oil. IR (neat) 2950 (s), 1455 (m), 1100 (s) and 785 cm^{-1} (s) ^{1}H-NMR (CCl_4, TMS): δ 3.6 (double triplet, 4H), 3.25 (m, 1H), 2.85 (m, 5H), δ 2.4-1.1 (m, 22H). ^{13}C-NMR ($CBCl_3$): δ 135.8; 130.8; 82.6 (d); 67.9 (t); 43.2 (t); 39.7; 39.6; 39.5; 39.1; 37.1; 36.8; 35.7; 33.0; 32.4; 32.1; 31.8; 31.0; 30.1; 28.4 and 27.6. Mass: M^+ at m/e 346 (100%). Exact mass: calculated for $C_{22}H_{31}ClO$: 346.206. Found 346.205.

EXAMPLE XVI

Preparation of 4-eq.-(3-bromopropyloxy-)-adamantylidene adamantane (formula 20).

The bromo-substituted compound having formula 16 (200 mg, 0.58 mmol) was dissolved in dry dioxane (10 cm^3) and 3-bromo-propanol-1 (5 cm^3) was added. The mixture was subsequently refluxed for 18 hours, and then concentrated at a reduced pressure. Water was added, and the product was extracted twice with n-hexane. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and evaporated substantially to dryness. Chromatography (see Example XV, the compound having formula 19) produced 195 mg (0.57 mmol, 85%) of the compound having formula 20 in the form of a colourless oil. IR (neat): 2900 (s), 1450 (m) and 1100 cm^{-1} (s). ^{1}H-NMR (CCl_4, TMS): δ 3.50 (t, J=6Hz, 4H); 3.2 (m, 1H), 2.9 (m, 4H); 2.4-1.1 (m, 24H). ^{13}C-NMR ($CDCl_3$): δ 135.6; 130.9; 82.0 (d); 68.2 (t); 64.6 (t); 39.7; 39.5; 39.4; 39.1; 37.2; 36.8; 35.7; 33.3; 33.0; 32.7; 32.3; 32.0; 31.7; 31.11; 31.08; 30.9; 30.4; 28.4; 27.6. Mass: M^+ at m/e 404/406 (1-1; 100%). Exact mass: calculated for $C_{23}H_{33}BrO$: 404.172. Found 404.171.

EXAMPLE XVIII

Preparation of 4-eq.-(L)-menthoxy-adamantylideneadamantane (formula 21).

The bromo-substituted compound having formula 16 (200 mg, 0.58 mmol) was dissolbed in dry DMF (1'cm^3), and L-menthol (1 g, 5.8 mmol) was added. The mixture was refluxed for 18 hours and concentrated at a reduced pressure. Chromatography (following the

procedure of Example XV, the compound having formula 19) produced the compound having formula 21 in the form of a colourless oil, yield 240 mg (98%). IR (neat): 2900 (s), 1450 (m), 1090 (s), 730 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): δ 3.6-2.8 (m, peaks at 3,5 and 3.0, 6H), 2.6-07 (m, 40H; peaks at δ1.9, 1.0, 0.9 and 0.75). ^{13}C-NMR (CDl_3): δ135.22; 135.13; 131.86; 131.70; 80.1; 79.3; 78.2; 76.9; 49.1; 48.9; 42.0; 41.7 (all pairs of both diastereomeric isomers) and 26 peaks between δ40 and 16. Mass: M^+ peak at m/e 422.267 (100%), 283, 135. Exact mass: calculated for $C_{30}H_{46}O$ 422.355. Found: 422.357.

EXAMPLE XVIII

Preparation of 17β-[4-eq.-adamantylideneadamantyloxy-]-testosterone (formula 22).

The bromo-substituted compound having formula 16 (200 mg, 0.58 mmol) was dissolved in dry DMF (10 cm^3). Testosterone (1 g, 3.5 mmols) was added and the mixture was refluxed for 18 hours. Evaporation of the solvent, and columnchromatography (Al_2O_3), activity II/III, using CH_2Cl_2 as the eluent, produced 240 mg of crude product in the form of a yellow oil. The pure compound having formula 22 was obtained after plate chromatography (Al_2O_3/CH_2Cl_2) as a white solid. The yield was 100 mg (30%). $[\alpha]^{rT}_{478}$= + 44.6 (c = 1.3; CH_2Cl_2). IR (KBr pellet): 2900 (s), 1680 (s), 1460 (m), 1090 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): δ 5.75 (br, 1H); 3.6-3.1 (m, 2H); 3.1-2.6 (m, 4H); 2.6-05 (m, 47H) with peaks at δ 1.8, 1.25, 1,2 and 0.85. ^{13}C-NMR ($CDCl_3$): δ 199.2; 171.1 (s); 135.0 (s); 131.2 (s); 123.6 (d); 85.4; 85.2; 80.4; 80.3; 53.9; 50.4; 42.6 and 27 peaks between δ 40 and 11.5. Mass: M^+ peak at m/e 554; 267 (100%). Exact mass calculated for $C_{29}H_{54}O_2$: 554.412. Found 554.411.

EXAMPLE XIX

Preparation of 4-eq.-[isopropyloxy-]-adamantylideneadamantane (formula 23).

The bromo-substituted compound having formula 16 (200 mg; 0.58 mmol) was dissolved in isopropanol (10 cm^3) and the solution was refluxed for 18 hours and subsequently evaporated to leave the compound having formula 23 in the form of a colourless oil (0.55 mmol, 95%). IR (neat): 2900 (s), 1450 (m), 1080 (s) cm^{-1}.

^{1}H-NMR (CCl_4, TMS) : δ 3.6 (septet, J = 7C, 1H), 3.25 (m, 1H); 2.9 (m, 4H) and 2.5-1.0 (m, 28 H with sharp doublet at δ 1.15, J = 6C). ^{13}C-NMR ($CDCl_3$): δ 135.2; 131.4; 78.7; 67.4; 39.7; 39.6; 39.5; 39.4; 39.2; 37.2; 37.1; 36.1; 33.0; 32.5; 32.3; 32.1; 31.2; 31.0; 28.4; 27.2; 22.8; 22.6. Mass: M^+ peak at m/e 326 (100%); 268; 266; 135. Exact mass: calculated for $C_{23}H_{34}O$: 326.261. Found 326.263.

EXAMPLE XX.

Preparation of 4-eq.-[3-hydroxypropyloxy-]-adamantylidene adamantane (formula 24).

The bromo-substituted compound having formula 16 (200 mg, 0.58 mmol), dioxane (10 cm^3) and propanediol-1.3 (5 cm^3) were mixed, and refluxed for 18 hours. Dioxane was evaporated, and the residue dissolved in CH_2Cl_2 (50 cm^3). The solution was treated with H_2O (3x50 cm^3), dried with $MgSO_4$, filtered, and evaporated to produce 180 mg (91 %) spectroscopically pure compound having formula 24 in the form of a colourless oil. Analytically pure material was obtained after "Kugelrohr"distillation (250°C, 0.002 mm Hg). Analysis: calculated for $C_{23}H_{34}O_2$: 80.63% C 10.02% H. Found 80.52% C 9.95% H. IR (neat): 3400 (s), 2900 (s), 1450 (s), 1100 (br) cm^{-1}. ^{1}H-NMR (CCl_4, TMS): δ 3.6 (t, J = 7C, 2H), 3.5 (t, J = 7C, 2H); 3.2 (br, 1H); 2.9 (br, 4H); 2.3-1.0 (m, 25H). ^{13}C-NMR ($CDCl_3$): δ 135.4; 130.5; 82.1 (d); 66.6 (t); 61.8 (t); 39.2; 38.8; 36.9; 36.5; 35.2; 32.8; 32.0; 31.7; 31.3; 30.8; 30.6; 28.1; 27.3. Mass: M^+ peak m/e 342 (100%); 267; 135; 79.

EXAMPLE XXI

Preparation of 4-eq.-hydroxy-adamantylidene adamantane (formula 3).

The bromo-substituted compound having formula 16 (347 mg, 1 mmol) was dissolved in dioxane (15 cm^3) and H_2O (5 cm^3) was added. After refluxing for 0.5 hour, the solvents were removed by evaporation, and CH_2Cl_2 (100 cm^3) was added. After treating this solution with H_2O (2 x 100 cm^3) $MgSO_4$ was added, the solution was filtered and evaporated to produce the compound having formula 3 (280 mg, 99%) in the form of a white amorphous powder, melting point 211.5-213°C.

EXAMPLE XXII

Preparation of 4-eq.-acetoxy-adamantylidene-adamantane (formula 25).

A solution of the bromo-substituted compound having formula 16 (200 mg, 0.58 mmol) in acetic acid (10 cm^3) was refluxed for 36 hours. Evaporation of the solvent and fast chromatography over a short column of Al_2O_3 (activity II/III), using n-hexane as the first eluent and then CH_2Cl_2, produced the compound having formula 25 (140 mg, 74%) in the form of a colourless oil, which after standing for 1 day solidified. IR (neat): 2950 (s), 1715 (s), 1220 (s) cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): δ4.7 (br, 1H); 3.1-2.6 (br, 4H); 2.2-1.2 (m, 25H; with a peak at 2.05 for $-CH_3$). ^{13}C-NMR ($CDCl_3$): δ170.4; 136.7; 129.8; 77.1; 39.6; 39.5; 39.4; 39.0; 37.1; 36.9; 36.7; 35.6; 33.3; 32.4; 32.2; 31.6; 31.3; 30.6; 28.4; 28.3; 27.4; 21.4. Mass: M^+ peak at m/e 326. Exact mass: calculated for $C_{22}H_{30}O_2$ 326.22. Found 326.226.

EXAMPLE XXIII

Preparation of N-(4-eq.-adamantylidene adamantyl-)-3-hydroxy-propionamide (formula 26).

A mixture of the bromo-substituted compound having formula 16 (200 mg, 0.58 mmol), dioxane (10 cm^3) and cyanohydrine (5 cm^3) was concentrated at a reduced pressure, and dissolved in ether (50 cm^3). The ethereal solution was washed with H_2O (2x50 cm^3) and brine (1x50cm^3), dried with $MgSO_4$, filtered, and evaporated to produce 100 mg (49%) of pure compound having formula 26 in the form of a white solid. Melting point: 172-174°C (from hexane). IR (KBr pellet): 3300 (m, br), 2900 (s), 1640 (s), 1540 (m), 1450 (m) cm^{-1}. ^{1}H-NMR, ^{13}C-NMR and mass identical to the reaction with Ag^+.

EXAMPLE XXIV

Preparation of 4 eq.-iodo-adamantylidene adamantane (formula 27).

The bromo-substituted compound having formula 16 (347 mg, 1 mmol) was added to a solution of NaJ (4,5 g) in acetone (25 cm^3), and the whole was then refluxed for 20 hours. The solvent was evaporated, ether (50 cm^3) was added, whereafter the solution was treated with water (2 x 50 cm^3), concentrated $Na_2S_2O_3$ (1 x 50 cm^3) and water (1 x 50 cm^3). The ethereal solution was dried with $MgSO_4$, filtered and evaporated to produce 340 mg (86%) of pure compound having formula 27 in the form of a white solid. IR (KBr pellet): 2950 (s), 1450 (s), 1145 (m), 965 (m), 750 (m) cm^{-1}. ^{1}H-NMR ($CDCl_3$, TMS): δ 3.2-2.7 (m, 4H); 2.7-1.0

(m, 22H). ^{13}C-NMR ($CDCl_3$): δ 136.6; 131.2; 47.3; 41.1; 40.1; 39.5; 39.3; 37.5; 36.9; 34.3; 32.6; 32.3; 32.1; 30.7; 28.2; 27.9. Mass: M^+ peak at m/e 394; 267 (100%). Exact mass: calculated for $C_{20}H_{27}I$: 394.116. Found 394.114.

EXAMPLE XXV

Preparation of 4-eq.-bromo-2,2'-epidioxy-2,2'-adamantyl adamantane.

The bromo-substituted compound having formula 16 (1,5 mmol) was dissolved together with a pinch (approximately 12 mg) of methylene blue in 200 cm^3 of distilled CH_2Cl_2. This solution was transferred to a reactor 8, shown in the drawing, which was made mainly of glass.

In the apparatus 8 shown in the drawing, 10 designates the reaction vessel, in which a porous P-4 glass filter is provided. Placed on reaction vessel 10 is a spherical cooler 2 with a superjacent glass tube 3, approximately 1 m long. Placed on top of reaction vessel 8 is further a supply vessel for the solvent (in this case CH_2Cl_2). Reference numeral 5 designates an assembly of a sodium vapour lamp 6 (Philips SON 160 W) and a reflector 7.

Before the solution was transferred to the reaction vessel, oxygen (O_2) was passed through the reaction vessel in the manner shown in the drawing. When the solution was added to the reaction vessel, this oxygen stream became visible from the rising in the solution of finely divided bubbles.

The solution 9 present in the reaction vessel was irradiated with the sodium vapour lamp 6 + reflector 7, placed close to the reaction vessel, for 6 hours, with the liquid level being replenished from time to time with CH_2Cl_2 from the supply vessel. During the reaction the temperature of the solution rose to approximately 40 °C. The course of the reaction was followed by means of thin-layer chromatography (aluminum oxide/CH_2Cl_2 or n-hexane).

After completion of the reaction, the solution was poured out and decolorized with activated charcoal. The reaction product was purified by column chromatography to product 4-eq.-bromo-2,2'-epidioxy-2,2'-adamantyl adamantane.

EXAMPLE XXVI

Preparation of 4-eq.- [12-oxy-dodecanoic acid methyl ester]-adamantylidene adamantane (formula 32).

To a solution of 10 g 12-hydroxydodecanoic acid methyl ester having the formula 35 and 7 g $AgClO_4$ in 200 cm^3 1.4-dioxane, a solution of 5 g 4-eq.-chloroadamantylidene adamantane (formula 2) in 100 cm^3 dry 1.4-dioxane was added. The reaction mixture was stirred at room temperature for 40 hours, and subsequently poured into 500 cm^3 water and extracted with ether (3 x 200 cm^3). The combined organic layers were washed with water (7 x 150 cm^3), dried by means of $MgSO_4$, and evaporated, to produce 14.5 g crude mixture. The excess of compound having formula 35 was removed by means of column chromatography (Al_2O_3 act. II/III; CH_2Cl_2). Three crystallizations from methanol produced 2.98 g of the compound having formula 32. Gas chromatographic analysis showed, however, that approximately 15 % dodecane lactone (formula 36) was present.

A suitable way of purifying the compound having formula 32 comprised the following procedure: the crude mixture was, after column chromatography (see supra), dissolved in 250 cm^3 methanol together with 0.5 g p-toluenesulphonic acid, and refluxed for 14 hours. After cooling the solvent was evaporated and the reaction mixture chromatographed over an Al_2O_3 (II,II), CH_2Cl_2 column to produce a mixture of the compound having formula 32 and 4-eq.-methoxyadamantylidene adamantane (formula 5). The latter compound was removed by hydrolysis of the compound having formula 32 with 2 g LiOH in ethanol, water (10:10 cm^3) at room temperature for 12 hours, followed by column chromatography (Al_2O_3 II,III; CH_2Cl_2) which produced the 4-eq.-methoxy compound. The pure compound having formula 32 was isolated by Soxhlet extraction of the column chromatography material with 300 cm^3 methanol containing 0.5 g p-toluenesulphonic acid, followed by column chromatography (Al_2O_3 II,III, CH_2Cl_2). An analytically pure sample of the compound having formula 32 was obtained by crystallization from methanol: melting point 44-48 °C, IR(Nujol): 2900, 1740, 1470, 1390, 1100 cm^{-1}; 1H-NMR ($CDCl_3$) δ 3.68 (s. 3H);

3.56-31. (br. 3H); 3.1-2.7 (br. 4H); 2.5-2.1 (br. 2H); 2.1-1.5 (br. adamantane); 1.5-1.15 (br. CH_2 chain). ^{13}C-NMR ($CDCl_3$): δ 174.2; 135.3; 131.2; 81.7; 67.4; 51.3 and 21 lines between 39.5-24.8. Mass spectrum m/e calc.: 496, 392; found 496, 393. Analysis: calc.: 79.79 C; 10.55 H; found: 79.87 C; 10.47 H.

EXAMPLE XXVII

Preparation of SYN and ANTI 4-eq.-[12-oxy-dodecanoic acid methyl ester]-adamantylidene-adamantane-1,2-dioxetane (formula 33).

A solution of 240 mg of the compound having formula 32 and 15 mg methylene blue in 200 cm^3 CH_2Cl_2 was irradiated with a high-pressure mercury lamp, while a slow stream of oxygen was passed through the solution. The UV light was filtered with a $K_2Cr_2O_7$ solution. The reaction was followed by gas chromatographic analysis. A reaction period of 7 hours was required for complete conversion of the olefin in the 1,2-dioxetane having formula 33. The dichloromethane was evaporated from the reaction mixture, which was then purified over an Al_2O_3 (II, III) column with CH_2Cl_2. The yield of compound having formula 33 in the form of a colourless oil was 240 mg (94%): IR neat: 2900, 1715, 1460 and 1100 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.60 (S 3H); 3.6-3.2 (br.m., 3H); 2.8-2.4 (br. m., 4H); 2.4-1.0 (br. m., 42H); ^{13}C NMR ($CDCl_3$): δ 174.1 (s); 96.4 (s); 960 (s); 95.6 (s); 95.5 (s); 76.0 (d); 67.9 (d); 67.7; 51.2 (q) and 24 lines between 37.0 and 24.8 ppm.

EXAMPLE XXVIII

Preparation of SYN and ANTI 4-eq.-[12-oxy-dodecanoic acid] adamantylidene-adamantane-1,2-dioxetane (formula 34).

To a solution of 240 mg of the compound having formula 33 in 15 cm^3 ethanol, a solution of 250 mg LiOH in 3 cm^3 water was added. The reaction mixture was stirred at room temperature for 12 hours. After acidification (pH = 4) with 0.1 N H_2SO_4, the reaction mixture was extracted with CH_2Cl_2 (2 x 30 cm^3). The organic layer was dried by means of $MgSO_4$, and concentrated. The yield of compound having formula 34 in the form of a colourless oil was 216 mg (92%): IR neat: 2900, 2500-3500, 1700, 1460, 1260, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.2-9.9 (s, 1H); 3.7-3.2 (br. m., 3H); 2.9-2.4 (br. m., 4H); 2.4-1.1 (br. m., 42H); ^{13}C NMR ($CDCl_3$): δ 179.7 (s); 95.8 (s); 95.4 (s); 95.3 (s); 75.9 (d); 75.7 (d); 67.8 (d); 67.5 (d) and 25 lines between 37.0 and 24.4 ppm.

EXAMPLE XXIX

Preparation of 3-0-(4-eq.-adamantylidene-adamantyl)-lithocholic acid methyl ester (formula 38).

To a stirred solution of 8 g of the compound having formula 37 and 3.5 g 4-eq.-chloroadamantylidene adamantane (formula 2) in 250 cm^3 p-dioxane under a nitrogen atmosphere, 4.4 g $AgBF_4$ was added. The reaction mixture was stirred at room temperature for 15 hours and diluted with ether. The organic layer was washed with water (six times), dried by means of $MgSO_4$, and concentrated. The crude product was thoroughly washed with methanol to remove the starting materials. The yield of compound having formula 38 was 4.5 g (95%). An analytically pure sample was obtained by crystallization from CH_2Cl_2/iso-propyl alcohol; melting point: 162.5-164°C; IR (Nujol): 1740, 1289, 1095 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.57 (s, 3H); 3.45-3.2 (br.m., 2H); 3.0-2.6 (br.m. 4H); 2.4-04 (br.m., 53H); 0.84 (s, 3H), 0.55 (s, 3H); ^{13}C NMR ($CHCl_3$): δ 174.0 (s); 134.9 (s); 131.2 (s); 78.2 (d), 75.2 (d), 56.1 (d), 55.7 (d); 50.9 (q) and 29 lines between 42.3 and 11.7 ppm; analysis $C_{45}H_{68}O_3$: calc.: 82.26% C; 10.43% H; found: 82.06% C; 10.44% H.

EXAMPLE XXX

Preparation of 3-0-(4-eq.-2,2'-epidioxy-2,2'-adamantyl adamantane)-lithocholic acid methyl ester (formula 39).

A solution of 2.5 g of the compound having formula 38 and 50 mg methylene blue in approximately 350 cm^3 CH_2Cl_2 was irradiated with a high-pressure mercury lamp, while a slow stream of oxygen was passed through the solution. The UV light was filtered by means of a $K_2CR_2O_7$ solution. Complete conversion required a reaction period of 20 hours The solvent was evaporated from the reaction mixture, and the residue was purified over an Al_2O_3 (act. II/III) column with CH_2Cl_2.
The yield of compound having formula 39, in the form of white crystals, was 2.0 g (76 %). An analytically pure sample was obtained by crystallization from iso-propylalcohol; melting point: 119-121°C; IR (nujol) 1740; 1160; 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.7-3.4 (br.m., 1H); 3.54 (s, 3H); 3.4-3.0 (br.m. 1H); 2.7-2.3 (br.m. 4H); 2.3-0.4 (br.m. 53H); 0.77 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 174.0 (s), 96.0 (s), 95.5 (s); 95.2 (s); 94.9 (s); 75.7 (d); 75.3 (d); 72.6 (d), 56.0 (d),

50.9 (q) and 28 lines between 42.3 and 11.6 ppm.; analysis $C_{45}H_{68}O_5$ calc.: 78.44%; 9.95% H; found 78.26% C; 9.99% H.

EXAMPLE XXXI

Preparation of 3-O-(4-eq.-2,2'-epidioxy-2,2'-adamantyl-adamantane)-lithocholic acid (formula 31).

To a solution of 200 mg of the compound having formula 39 in 25 cm^3 ethanol, 350 mg LiOH in 5 cm^3 water was added. The reaction mixture was stirred at room temperature for 12 hours. After acidification (pH = 4) with 0.1 N H_2SO_4, the reaction mixture was extracted with CH_2Cl_2. The organic layer was dried by means of $MgSO_4$ and concentrated. The yield of compound having formula 31 in the form of white crystals was 192 mg (98 %): melting point: 138-140°C; IR (Nujol): 3700-2700; 1705, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.8-3.3 (br.m, 1H); 3.6-3.0 (br.m. 1H); 2.8-2.3 (br.m., 4H); 2.5-94 (br.m., 53H); 0.8 (s, 3H); 0.55 (s., 3H) and 10.1-10.7 (br.s., 1H); ^{13}C NMR ($CDCl_3$): δ 180.3 (s); 96.4 (s); 59.9 (s); 95.7 (s); 95.5 (s); 75.7 (d); 75.4 (d); 72.9 (d); 56.2 (d); 55.8 (d) and 34 lines between 42.5 and 11.9 ppm.

EXAMPLE XXXII

Preparation of N-(4-eq.-adamantylidene adamantyl)-maleimide (formula 40).

Under a dry nitrogen atmosphere and with exclusion of light, a mixture of 6.05 g 4-eq.-chloroadamantylidene adamantane (formula 2), 200 cm^3 dry toluene, 20 mg hydroquinone and 5.2 g silver maleimide (formula 41) (from silver nitrate and maleimide) was boiled for 27 hours. After evaporation and addition of 100 cm^3 ether, a mixture of solids was obtained. Extraction by means of a Soxhlet apparatus, using ether as the solvent for 18 hours, and evaporation of the extract produced 6.0 g yellowish solid. Column chromatography over Al_2O_3 (act. II/III) with benzene as the eluent, evaporation and water with 20 cm^3 ether gave 2.7 g (37 %) pure maleimide; melting point: 199-202 °C. ^1H-NMR ($CDCl_3$, TMS): δ 6.52 (s, 2H); 3.9 (m, 1H); 3.5 (m, 2H); 2.9 (m, 4H); 2.7-1.0 (m, 20H). ^{13}C NMR ($CDCl_3$): δ 171.9; 135.9; 133.8; 130.9; 61.5; 39.4; 39.0; 37.1; 34.0; 32.3; 32.1; 31.9; 31.0; 30.2; 28.3; 26.9. IR (KBr): 2900 (s), 1700 (s), 1340 (m) cm^{-1}. Mass: M^+ peak at 363.

Exact mass: calc. 363.220. Found: 363.222.

EXAMPLE XXXIII

Preparation of 4-eq.-(maleimido)-2,2'-epidioxy-2,2'-adamantyl adamantane (2-isomers).

The olefin having formula 40 (500 mg) was subjected to photo-oxygenation in the manner specified before, except that the reaction period was 18 hours. Column chromatography over Al_2O_3 (act. III), using benzene as the eluent gave after a first fast travelling impurity the isomer having the formula 42a (75 mg) in the pure form and thereafter the isomer having formula 42b (60 mg) in the pure form, and both as white solids (together 25% yield).

Formula 42a:

^{1}H-NMR ($CDCl_3$, TSM): δ 6.5 (s, 2H), 4.2 (m. 1H), 3.4 (m, 1H), 2.9-2.5 (m, 4H), 2.4-1.0 (m, 21H). IR (KBr): 2950 (s), 1700 (s), 1365 (m), 1345 (m), 685 (m) cm^{-1}. ^{13}C-NMR ($CDCl_3$): δ 171.7; 133.9; 95.8; 55.8; 37.1; 35.2; 34.4; 33.9; 33.0; 32.2; 31.9; 31.3; 30.9; 29.5; 27.2; 26.5; 26.3; 24.9.

Formula 42b:

^{1}H-NMR ($CDCl_3$, TMS): δ 6.55 (s, 2H), 4.15 (m, 1H), 3.4 (m, 1H), 2.9-2.4 (m, 4H), 2.4-1.0 (m, 21H). IR (KBr): 2900 (s), 1700 (s), 1375 (m), 690 (m) cm^{-1}. ^{13}C-NMR ($CDCl_3$): δ 171.7; 133.9; 95.9; 55.3; 37.1; 34.5; 34.1; 33.7; 32.6; 31.9; 31.7; 31.5; 31.4; 31.1; 29.6; 28.8; 26.5; 26.3; 25.1.

EXAMPLE XXXIV

Preparation of 4-eq.-(α-iodoacetoxy)-2,2'-epidioxy-2,2'-adamantyl adamantane (formula 29) ("anti-isomer").

200 mg of the compound having formula 43, 284 mg pro-analysis iodo acetic acid and 150 mg pro-analysis pyridine were together dissolved in 30 cm^3 distilled CH_2Cl_2. After the solution had been cooled to 0 °C, brought under a nitrogen atmosphere, and sealed from light, a solution of 330 mg DCC (dicyclohexylcarbodiimide) in 2 cm^3 CH_2Cl_2 was injected by means of a glass syringe with stirring. Without further cooling, the mixture was stirred for three days. After evaporation, 50 cm^3 benzene was added, the

solution was filtered and the residue washed with benzene. The combined benzene solutions were washed with 5 % $Na_2S_2O_3$ solution (2 x 50 cm^3) and H_2O (1 x 50 cm^3), dried by means of $MgSO_4$, filtered, and evaporated. The yellow solid residue was dissolved in pro-analysis acetone and the solution was partially decolorized by means of decolorizing charcoal. After filtration, the solution was thickened to about 25 cm^3 volume, subsequently a little water was added, the solution was filtered and then allowed to stand for 18 hours at -40 °C for crystallization. Filtration and drying produced 140 mg pure product (42 %); melting point 137.2-137.9 °C ^{1}H-NMR ($CDCl_3$, TMS): δ 5.15 (br, 1H); 3.75 (s, 2H): 3.1-2.4 (m, 4H); 2.4-1.1 (m, 22H). IR (KBr): 2900 (s), 1720 (s) and 1265 (s) cm^{-1}. ^{13}C-NMR ($CDCl_3$): δ 167.9; 95.6; 95.2; 74.1; 36.9; 35.8; 34.7; 34.3; 32.9; 32.0; 31.8; 31.5; 31.4; 30.9; 30.5; 30.1; 26.5; 26.3; 25.3; -5.1.

The reaction to form 4-eq.-(α-iodoacetoxy)-2,2'-epidioxy-2,2'-adamantyl adamantane (formula 29) can also be carried out on a mixture of syn and anti hydroxydiadamantyl-1,2-dioxetane. There is then formed a mixture of syn and anti α-iodoacetoxy compounds in the same yield. The I.R.- and the ^{1}H-NMR-spectra are identical to those of the pure anti-isomer. ^{13}C-NMR($CDCl_3$): δ 167.9; 167.5; 95.5; 95.7; 95.2; 74.3; 74.1 and 27 peaks between 39.1 and 25; -41.9 and -5.1.

The syn- and anti- 4-eq.-hydroxy-1,2-dioxetanes needed for the above synthesis, can be prepared from 4-eq.-hydroxyadamantylidene adamantane <u>via</u> the photo-oxygenation method in a quantitative yield (after purification by column chromatography over Al_2O_3 (act. II/III) using ether as the eluent. The separation of syn- and anti-isomers is effected by means of plate chromatography with Al_2O_3 and CH_2Cl_2 as the eluent.

C L A I M S

1. A process for preparing a substituted polycyclo-alkylidene polycyclo-alkane, in which the corresponding non-substituted compound is subjected to a halogenation reaction, using a halogenating agent in a solvent, and the halogenation product is isolated from the reaction mixture and/or, if desired, is subjected to a substitution reaction, characterised by using as the halogenating agent an N-halosuccinimide, tert.-butyl-hypohalite or sodium hypohalite/CH_3COOH.

2. A process according to claim 1, characterised in that the halogen atom in the halogenating agent is chlorine.

3. A process according to claim 2, in which the chlorine atom in the chlorination product is caused to take part in a substitution reaction in a solvent in the presence of a silver salt, characterised by using as the substituting agent in addition to the silver salt, a nucleophile.

4. A process according to claim 3, characterised in that the silver salt is $AgBF_4$ or $AgClO_4$.

5. A process according to claim 1, characterised in that the halogen atom in the halogenating agent is bromine.

6. A process according to claim 1 and claim 5, in which the bromine atom in the bromination product is caused to take part in a substitution reaction in a solvent and in the presence of a substituting agent, characterised in that the solvent is the substituting agent, whether or not in the presence of a co-solvent, and is also a nucleophile.

7. A process according to claim 6, characterised by using as the co-solvent dimethylformamide or dioxane.

8. A process according to claim 5, characterised in that the bromination product is subjected to a halogen-exchanging reaction.

9. A process according to claim 8, characterised in that the halogen-exchanging reaction is carried out with NaJ/acetone mixture to form the corresponding iodo-substituted compound.

10. A process according to claims 1-9, characterised by using adamantylidene adamantane as the starting polycyclo-alkylidene polycyclo-alkane.

11. A process according to claim 1-10, characterised in that

the 4-eq.-substituted adamantylidene adamantane is subjected to a photo-oxygenation reaction to form the 4-eq.-substituted 2,2'-epidioxy-2,2'-adamantyl adamantane.

12. A process according to claim 11, characterised in that a previously prepared solution of 1-2 mmole 4-eq.-substituted adamantylidene adamantane and 10-15 mg methyleneblue in about 200 cm^3 CH_2Cl_2 is subjected to the photo-oxygenation reaction in a reaction vessel through which oxygen is passed, and with irradiation for 4-7 hours with a sodium lamp, after termination of the reaction the reaction solution is decolourized using activated charcoal and the product is recovered after purification with column chromatography.

13. Compound of formula 44, wherein A and B represent alkylene radicals, which alkylene radicals may be attached to each other via an alkylene radical C, and R_1 represents a substituent which, in case of 4-eq.-R_1-2,2'-adamantylidene adamantane cannot be chloro, hydroxy, oxo, D or a group of formula 1.

14. Compound according to claim 13 having formula 44, in which alkylene radical A contains 2 to 5 carbon atoms, alkylene radical B contains 2 to 5 carbon atoms, and alkylene radical C, if present, contains 1 to 4 carbon atoms.

15. 4-eq.-R_1-2,2'-adamantylidene adamantane in which R_1 represents a substituent, with the exception of chloro, hydroxy, oxo, D and the radical of formula 1.

16. Compound according to claim 13, 14 or 15, having formula 44, in which R_1 represents chloro, bromo or iodo, a hydroxy group, an optionally substituted alkoxy, cyclo-alkoxy or acyloxy group, or an amino, acylamino, isothiocyanato or isocyanato group, with the proviso that in the case of 4-eq.-R_1-2,2'-adamantylidene adamantane R_1 cannot be chloro, hydroxy, oxo, D or a group of formula 1.

17. Compound according to claim 16 having formula 44, in which R_1 represents an acyloxy group comprising a protein radical

18. Compound according to claim 17 having formula 44, in which the protein radical in R_1 is a radical of bovine serum albumine.

19. Compound according to claim 16 having formula 44, in which a cycloalkoxy radical R_1 is a steroid radical attached via oxygen.

20. Compound according to claim 19, in which the steroid radical is a testosterone or lithocholic acid radical.

21. Compound according to claim 16 having formula 44, in which R_1 is a radical of a fatty acid attached via oxygen.

22. Compound according to claim 21, wherein the fatty acid radical is a radical of arachidic acid.

23. Chemiluminescent compound of formula 45, in which A and B represent alkylene radicals, which alkylene radicals may be attached to each other via an alkylene radical C and R_2 represents a substituent which, in the case of 4-eq.-R_2-2,2'-epidioxy-2,2'-adamantyl adamantane cannot be chloro or hydroxy.

24. Compound according to claim 23 having formula 45, in which alkylene radical A contains 2 to 5 carbon atoms, alkylene radical B contains 2 to 5 carbon atoms, and alkylene radical C, if present, contains 1 to 4 carbon atoms.

25. 4-eq.-R_2-2,2'-epidioxy-2,2'-adamantyl adamantane in which R_2 represents a substituent with the exception of chloro and hydroxy.

26. Compound according to claim 23, 24 or 25 having formula 45, in which R_2 represents chloro, bromo or iodo, a hydroxy group, an optionally substituted alkoxy, cycloalkoxy or acyloxy group, or an amino, acylamino, isothiocyanato or isocyanato group, with the proviso that in the case 4-eq.-R_2-2,2'-epidioxy-2,2'-adamantyl adamantane R_2 cannot be chloro or hydroxy.

27. Compound according to claim 26 having formula 45, wherein R_2 represents an acyloxy group comprising a protein radical.

28. Compound according to claim 27, wherein the protein radical in R_2 is a radical of bovine serum albumine.

29. Compound according to claim 26 having formula 45, wherein a cycloalkoxy radical R_2 is a steroid radical attached via oxygen.

30. Compound according to claim 29, wherein the steroid radical is a testosterone or lithocholic acid radical.

31. Compound according to claim 26 having formula 45, wherein R_2 is a fatty acid radical attached via oxygen.

32. Compound according to claim 31, wherein the fatty acid radical is an arachidic acid radical.

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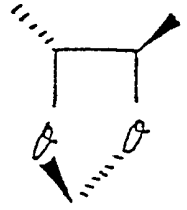

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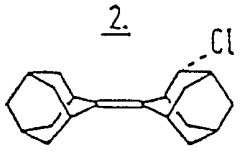

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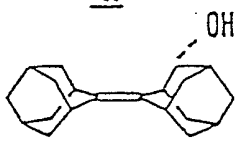

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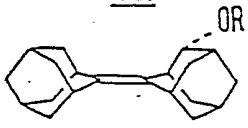

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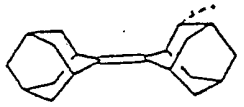

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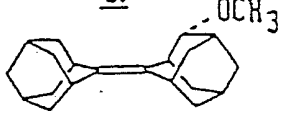

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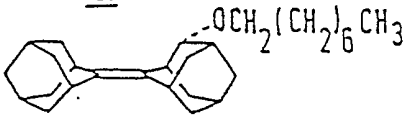

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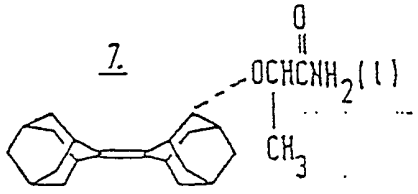

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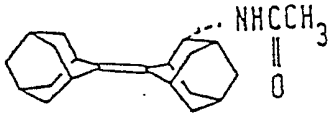

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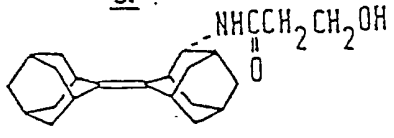

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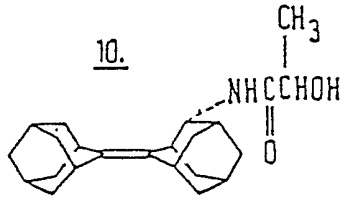

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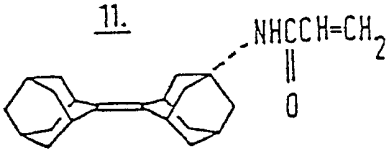

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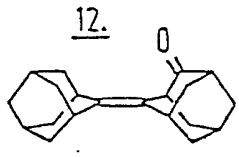

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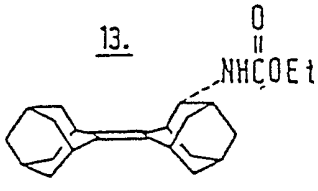

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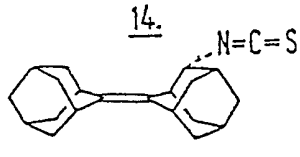

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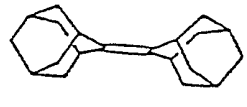

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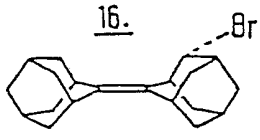

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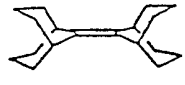

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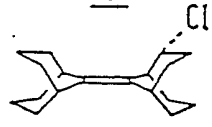

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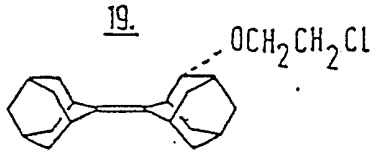

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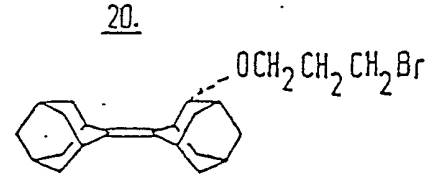

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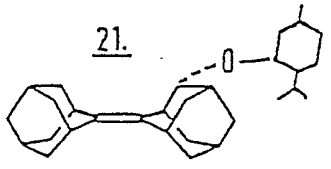

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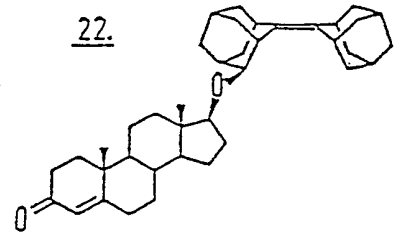

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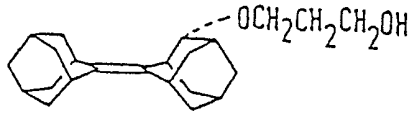

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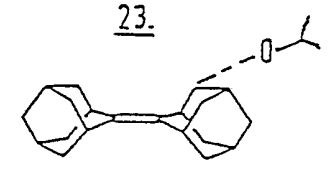

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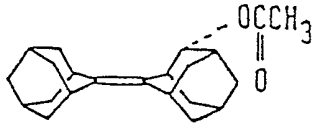

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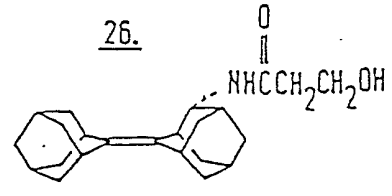

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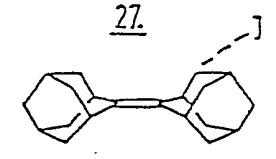

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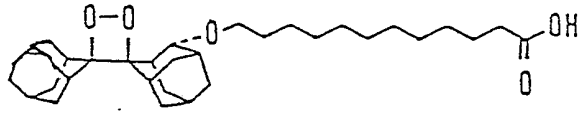

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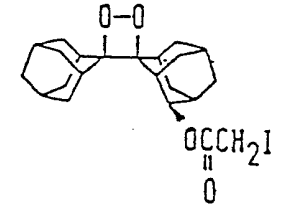

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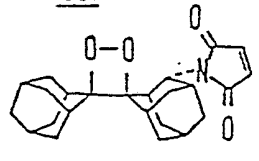

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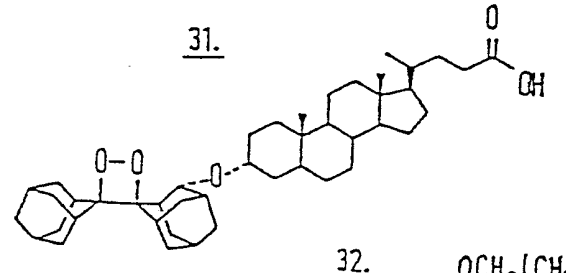

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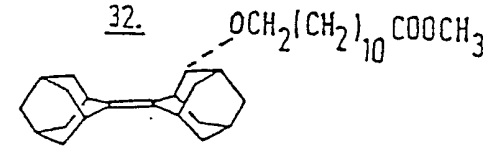

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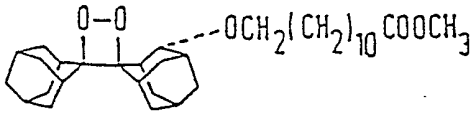

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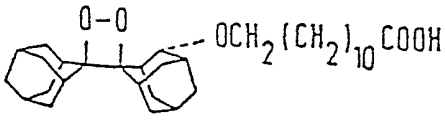

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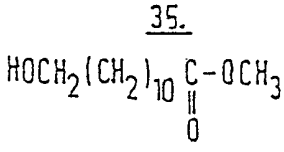

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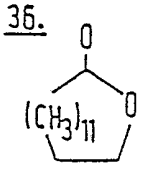

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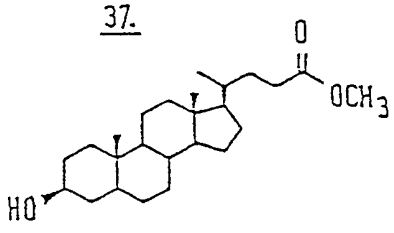

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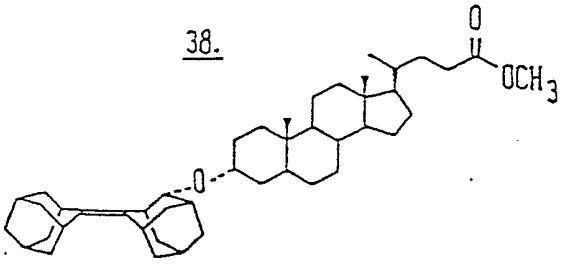

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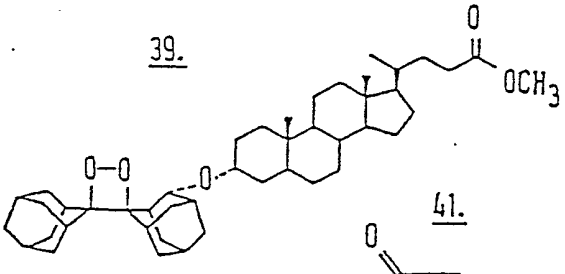

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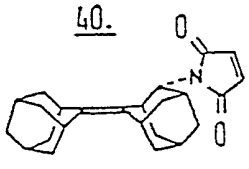

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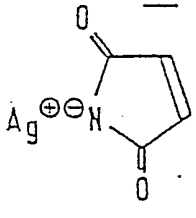

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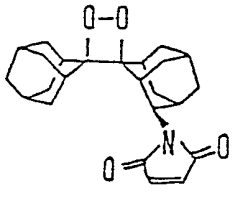

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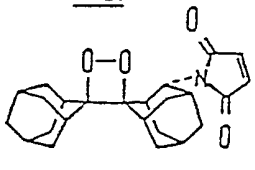

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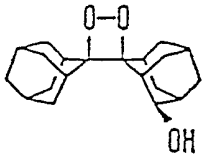

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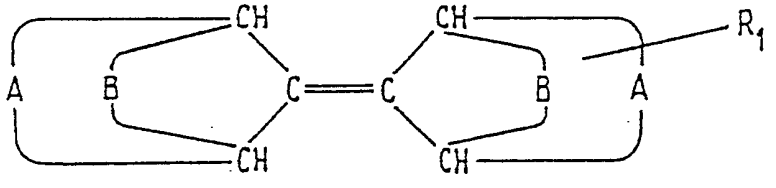

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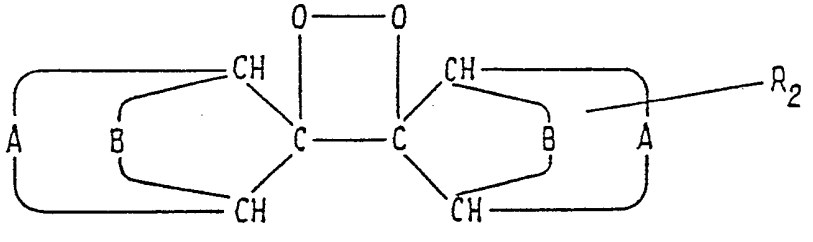

INTERNATIONAL SEARCH REPORT

International Application No PCT/NL-83/00014

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[3]: C 07 B 9/00; C 07 C 23/38; C 07 D 321/00

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC[3]	C 07 C 23/00; C 07 C 17/00; C 07 B 9/00; C 07 D 321/00; C 07 C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	Tetrahedron Letters, published 1970 (Oxford, GB) J.H. Wieringa et al.: "The reaction of chlorine with adamantylidenadamantane", see pages 4579-4582 (cited in the application)	1-3,10
Y	Houben-Weyl: "Methoden der organischen Chemie", 4th edition, vol. V/3 "Halogenverbindungen", 1962, Georg Thieme Verlag (Stuttgart, DE) see pages 765,780,800	1-2
Y	Houben-Weyl: "Methoden der organischen Chemie", 4th edtion, vol. V/4 "Halogenverbindungen", 1960, Georg Thieme Verlag (Stuttgart, DE) see pages 23,24,30	1,5
Y	Tetrahedron Letters, published 1972, (Oxford, GB) J.H. Wieringa et al. "Adamantylideneadamantane peroxide, a stable 1,2-dioxetane", see pages ./.	1,10-12

* Special categories of cited documents: [16]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [3]	Date of Mailing of this International Search Report [3]
7th June 1983	01 JUIL. 1983
International Searching Authority [1]	**Signature of Authorized Officer [20]**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

FURTHER INFORMATION CONTINUED FRO A THE SECOND SHEET

169-172

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ..... because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. [X] Claim numbers °°), because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

°°) claims not searched : 17-24, 27-32
claims searched incompletely: 1-9, 13-14, 16, 26 (in so far as related to claims 10-12, 15, 25)

Reason: Formulation of the claims is not clear and concise enough. It is not clear in what the invention consists: the halogenation; the following conversion; the products per se.

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.