A process for preparing substituted polycyclo-alkylidene polycyclo-alkanes as well as said substituted polycyclo-alkylidene polycyclo-alkanes

EP0106863B1

Publication Title:

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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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 106 863**
B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **20.08.86**

(51) Int. Cl.⁴: **C 07 B 39/00**, C 07 C 23/38, C 07 D 321/00

(21) Application number: **83901235.8**

(22) Date of filing: **07.04.83**

(86) International application number:
PCT/NL83/00014

(87) International publication number:
WO 83/03604 27.10.83 Gazette 83/25

(54) A PROCESS FOR PREPARING SUBSTITUTED POLYCYCLO-ALKYLIDENE POLYCYCLO-ALKANES AS WELL AS SAID SUBSTITUTED POLYCYCLO-ALKYLIDENE POLYCYCLO-ALKANES.

(30) Priority: **07.04.82 NL 8201492**

(43) Date of publication of application:
02.05.84 Bulletin 84/18

(45) Publication of the grant of the patent:
20.08.86 Bulletin 86/34

(84) Designated Contracting States:
AT BE CH DE FR GB LI LU NL SE

(56) References cited:
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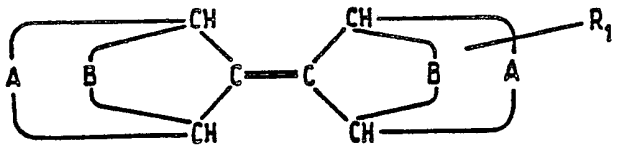
EP 0 106 863 B1

Courier Press, Leamington Spa, England.

Description

The invention relates to a process for preparing equatorial halogen substituted polycyclo-alkylidene polycyclo-alkanes, to these halogen substituted polycyclo-alkylidene polycyclo-alkanes and to a process for preparing substituted polycyclo-alkylidene polycyclo-alkanes by subjecting said halogen substituted compounds to a substitution reaction.

The term "halogen substituted polycyclo-alkylidene polycyclo-alkanes" as used herein comprises especially compounds of the formula



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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 chloro or bromo in the equatorial configuration, but in the case of 4-equatorially R_1-substituted 2.2'-adamantylidene adamantanes, cannot be chloro. In preferred compounds of formula 1, 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 1 are 4-eq-bromo-2.2'-adamantylidene adamantane, 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 invention relates to these compounds, to processes for the preparation thereof and to processes in which these compounds are subjected to a substitution reaction. Especially, the invention relates to a process for preparing equatorial halogen substituted polycycloalkylidene polycyclo-alkanes, in which a corresponding non-substituted compound is reacted with a halogenating agent in a solvent.

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°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 equatorial halogen substituted polycyclo-alkylidene polycycloalkane 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 the process as defined above is carried out by using sodium hypohalite in CH_3COOH, N-halosuccinimide, or tert.-butylhypohalite as the halogenating agent.

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 equatorial 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.

In a preferred embodiment of the halogenation 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 eq.-bromo-substituted compound. When the starting compound is, for example, the adamantylidene adamantane, heating for 12 hours at 40°C produces 4-eq.-bromoadamantylidene adamantane according to a fully completed reaction.

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

Preferably, the starting material used in the halogenation process according to the invention is adamantylidene adamantane.

In case of a chloro-substituted compound, this compound is reacted with a nucleophile in a solvent, in the presence of a silver salt, the nucleophile being, for example, an alcohol, a cyanide, a carbamate, or an isothiocyanate.

When, for example, 4-eq.-chloroadamantylidene adamantane is dissolved in an alcohol or in 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. The reaction components may be directly mixed with each other, and the reaction may be carried out 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 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 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 nucleophiles, such as water to form the corresponding hydroxy compound, 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 NaI/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.

The substituted polycycloalkylidene polycycloalkanes so prepared are useful as intermediates for the preparation of the corresponding 1,2-dioxetanes, which are chemiluminescent compounds. In view of this utility, particularly useful nucleophiles to be used in the substitution process of the invention are nucleophiles introducing residues of biologically important radicals, such as protein, a steroid or fatty acid radicals. As examples of such necleophiles may be mentioned a carboxylic acid comprising a protein radical, such as the bovine serum albumin radical, a cycloalkyl alcohol derived from a steroid, such as testosterone, or a hydroxy fatty acid, such as arachidic acid.

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 ^1H NMR spectra with a Varian A-60 of Hitachi Perkin Elmer R-24 B at 60 Mc. ^1H 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 0.13 Pa (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.-chloroadamantylidene 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 (3 × 100 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 ($CDCl_3$) 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 (MBr) 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 (2 × 100 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°/13.3 Pa (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}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-octyloxyadamantylidene adamantane (formula 6).

The chloro-substituted compound having formula 2 (605 mg, 2 mmoles) was suspended in n-octanol (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 (2 × 100 cm^3), dried with $MgSO_4$, filtered and evaporated at 40 Pa (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. ^{1}H-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 1-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 (3 × 300 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). ^1H 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, 1-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 (8 × 100 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. ^1H 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^3acrylonitrile 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. ^1H 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 dimethyl sulfoxide was heated at 150—160°C under a nitrogen atmosphere for 25 hours. After cooling and filtration, the product was extracted with n-hexane (4 × 15 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 ethyl N-(4-eq.-adamantylidene adamantyl)-carbamate (formula 13).

To a solution of 6.0 g (24 mmoles) $AgBF_4$ in 27 g ethyl carbamate, 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 × 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 ethyl carbamate. 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 benzyl thiocyanate 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 15 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-adamantylidene-adamantane having formula 20 was 1.05 g (97%). An analytically pure sample could be obtained by crystallization from acetone and sublimation [115°C/0:3 Pa (0.002 mm)]; melting point 130.5—131.5°C. ^{1}H 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/1.3 Pa (0.01 mm)], melting point 50.53°C, ^{1}H 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)-adamantylideneadamantane (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. Column chromatography 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 19 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-bromopropanol-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 XVII

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

The bromo-substituted compound having formula 16 (200 mg, 0.58 mmol) was dissolved 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 δ 1.9, 1.0, 0.9 and 0.75). ^{13}C-NMR (CDl_3): δ 135.22; 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 δ 40 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 dimethylformamide (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%). $[\alpha]_{478}^{rT}$ = +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), 1808 (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 (3 × 50 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, 0.3 Pa (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 × 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): δ 4.7 (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 ($CDCl_3$): δ 170.4; 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 (2 × 50 cm^3) and brine (1 × 50 cm^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 NaI (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 × 50 cm^3), concentrated $Na_2S_2O_3$ (1 × 50 cm^3) and water (1 × 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.-[11-methoxycarbonylundecyloxy]-adamantylidene adamantane (formula 28).

To a solution of 10 g 12-hydroxydodecanoic acid methyl ester having the formula 29 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 × 200 cm^3). The combined organic layers were washed with water (7 × 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 28. Gas chromatographic analysis showed, however, that approximately 15% dodecane lactone (formula 30) was present.

A suitable way of purifying the compound having formula 28 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 28 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 28 was isolated by Soxhlet extraction of the column chromatography material with 300 cm^3 methanol containing 0.5 g p-toluene sulphonic acid, followed by column chromatography (Al_2O_3 II, III, CH_2Cl_2). Ana analytically pure sample of the compound having formula 28 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 XXVI

Preparation of 3-O-(4-eq.-adamantylidene-adamantyl)-lithocholic acid methyl ester (formula 32).

To a stirred solution of 8 g of the compound having formula 31 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 32 was 4.5 g (95%). And 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 XXVII

Preparation of N-(4-eq.-adamantylidene adamantyl)-maleimide (formula 33).

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 34) (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.

Claims

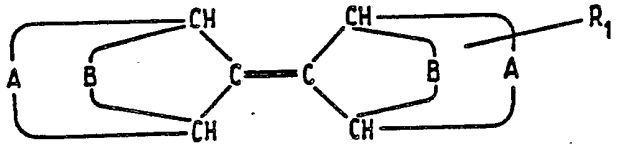
1. A process for preparing an equatorial halogen substituted polycyclo-alkylidene polycyclo-alkane, in which the corresponding non-substituted compound is reacted with a halogenating agent in a solvent, characterized by using as the halogenating agent sodium hypohalite in CH_3COOH, an N-halosuccinimide, or tert.-butyl-hypohalite.

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

3. The process according to claim 1, characterized in that the halogen atom in the halogenating agent is bromine.

4. The process according to claims 1—3, characterized in that a 4-eq. halogen substituted adamantylidene adamantane is prepared by using adamantylidene adamantane as the starting polycyclo-alkylidene polycyclo-alkane.

5. Compound of the formula



(1)

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 chloro or bromo in the equatorial configuration but, in case of 4-eq.-R_1-2,2'-adamantylidene adamantane cannot be chloro.

6. Compound according to claim 5 having formula 1, 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.

7. 4-eq.-bromo-2,2'-adamantylidene adamantane.

8. A process for preparing a substituted polycyclo-alkylidene polycyclo-alkane, characterized in that an equatorial halogen substituted compound obtained according to any of claims 1—4 is subjected to a substitution reaction.

9. The process according to claim 8, characterized in that a chloro substituted compound obtained according to any of claims 1, 2 and 4 is reacted with a nucleophile in the presence of a silver salt, in a solvent.

10. The process according to claim 9, characterized in that the silver salt is $AgBF_4$ or $AgClO_4$.

11. The process according to claim 8, characterized in that a bromo substituted compound obtained according to any of claims 1, 3 and 4 is reacted with a nucleophile, optionally in the presence of a cosolvent.

12. The process according to claim 11, characterized by using dimethylformamide or dioxane as the cosolvent.

13. The process according to claim 8, characterized in that a bromo substituted compound obtained according to any of claims 1, 3 and 4 is subjected to a halogen-exchanging reaction.

14. The process according to claim 13, characterized in that the halogen-exchanging reaction is carried out with NaI/acetone mixture to form the corresponding iodo-substituted compound.

15. The process of claim 9 or 10, characterized in that the nucleophile is an alcohol, a nitrile, a carbamate or an isothiocyanate.

16. The process of claim 11, in which the nucleophile is a carboxylic acid comprising a protein radical.
17. The process of claim 16, in which the protein radical is a radical of bovine serum albumin.
18. The process of claim 11 or 15, in which the nucleophile is an alcohol.
19. The process of claim 18, in which the nucleophile is a cycloalkyl alcohol derived from a steroid.
20. The process of claim 19, in which the steroid is testosterone or lithocholic acid.
21. The process of claim 11, in which the nucleophile is a hydroxy-fatty acid.
22. The process of claim 21, in which the hydroxy-fatty acid is arachidic acid.

Patentansprüche

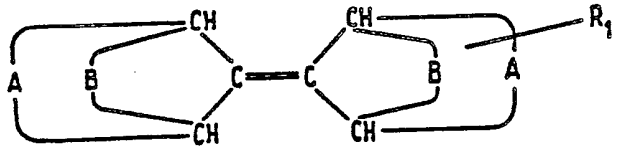
1. Verfahren zur Herstellung eines äquatorial halogensubstituierten Polycycloalkyliden-polycycloalkans, in dem die entsprechende nicht substituierte Verbindung mit einem Halogeniermittel in einem Lösungsmittel umgesetzt wird, gekennzeichnet durch die Verwendung von Natriumhypohalogenit in CH_3COOH, einem N-Halogensuccinimid oder tert.-Butylhypohalogenit als Halogeniermittel.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Halogenatom im Halogeniermittel Chlor ist.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Halogenatom im Halogeniermittel Brom ist.

4. Verfahren nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß ein 4-äquatorial halogensubstituiertes Adamantyliden-adamantan hergestellt wird durch Verwendung von Adamantyliden-adamantan als Ausgangspolycycloalkyliden-polycycloalkan.

5. Verbindung der Formel



(1)

worin A und B Alkylenreste darstellen, die miteinander über einen Alkylenrest C verbunden sein können, und R_1 Chlor oder Brom in äquatorialer Konfiguration sind, wobei es jedoch im Fall von 4-äquatorial-R_1-2,2'-Adamantyliden-adamantan nicht Chlor sein kann.

6. Verbindung nach Anspruch 5 der Formel 1, in der der Alkylenrest A 2 bis 5 Kohlenstoffatome enthält, der Alkylenrest B 2 bis 5 Kohlenstoffatome enthält und der Alkylenrest C, wenn vorhanden, 1 bis 4 Kohlenstoffatome enthält.

7. 4-äquatorial-Brom-2,2'-adamantyliden-adamantan.

8. Verfahren zur Herstellung eines substituierten Polycycloalkyliden-polycycloalkans, dadurch gekennzeichnet, daß eine äquatorial halogensubstituierte Verbindung, erhalten nach einem der Ansprüche 1 bis 4, einer Substitutionsreaktion unterworfen wird.

9. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß eine chlor-substituierte Verbindung, erhalten nach einem der Ansprüche 1, 2 und 4, mit einem nucleophilen Mittel in Gegenwart eines Silbersalzes in einem Lösungsmittel umgesetzt wird.

10. Verfahren nach Anspruch 9, dadurch gekennzeichnet, daß das Silbersalz $AgBF_4$ oder $AgClO_4$ ist.

11. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß eine brom-substituierte Verbindung, erhalten nach einem der Ansprüche 1, 3 und 4, mit einem nucleophilen Mittel, gegebenenfalls in Gegenwart eines Co-Lösungsmittels, umgesetzt wird.

12. Verfahren nach Anspruch 11, gekennzeichnet durch die Verwendung von Dimethylformamid oder Dioxan als Co-Lösungsmittel.

13. Verfahren nach Anspruch 8, dadurch gekennzeichnet, daß eine brom-substituierte Verbindung, erhalten nach einem der Ansprüche 1, 3 und 4, einer Halogenaustauschreaktion unterworfen wird.

14. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß die Halogenaustauschreaktion mit einem NaJ/Aceton-Gemisch zur Bildung der entsprechenden jod-substituierten Verbindung durchgeführt wird.

15. Verfahren nach Anspruch 9 oder 10, dadurch gekennzeichnet, daß das nucleophile Mittel ein Alkohol, ein Nitril, ein Carbamat oder ein Isothiocyanat ist.

16. Verfahren nach Anspruch 11, bei dem das nucleophile Mittel eine einen Proteinrest enthaltende Carbonsäure ist.

17. Verfahren nach Anspruch 16, bei dem der Proteinrest ein Rindeserumalbuminrest ist.

18. Verfahren nach Anspruch 11 oder 15, bei dem das nucleophile Mittel ein Alkohol ist.

19. Verfahren nach Anspruch 18, bei dem das nucleophile Mittel ein von einem Steroid abgeleiteter Cycloalkylalkohol ist.

20. Verfahren nach Anspruch 19, bei dem das Steroid Testosteron oder Lithocholsäure ist.

21. Verfahren nach Anspruch 11, bei dem das nucleophile Mittel eine Hydroxyfettsäure ist.

22. Verfahren nach Anspruch 21, bei dem die Hydroxyfettsäure Arachinsäure ist.

Revendications

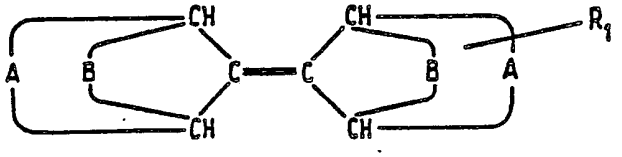
1. Procédé de préparation d'un polycycloalkylidène-polycycloalkane substitué par un halogène équatorial dans lequel le composé non substitué correspondant est mis en réaction avec un agent d'halogènation dans un solvant, caractérisé par l'utilisation comme agent d'halogénation d'hypohalite de sodium dans l'acide acétique, un N-halosuccinimide ou une tertio-butylhypohalite.

2. Procédé selon la revendication 1, caractérisé en ce que l'atome d'halogène de l'agent d'halogénation est le chlore.

3. Procédé selon la revendication 1, caractérisé en ce que l'atome d'halogène dans l'agent d'halogénation est du brome.

4. Procédé selon l'une des revendications 1 à 3, caractérisé en ce que l'adamantylidène-adamantane substitué par l'halogène 4-équatorial est préparé en utilisant l'adamantylidène-adamantane comme polycycloalkylidène-polycycloalkane de départ.

5. Composé de formule:



(1)

dans laquelle:

A et B représentent des radicaux alkylène, lesquels radicaux alkylène peuvent être attachés l'un à l'autre par un radical alkylène C; et

R_1 représente un atome de chlore ou de brome en configuration équatoriale, mais dans le cas du 4-équatorial-R_1-2,2'-adamantylidène-adamantane ne peut pas être un atome de chlore.

6. Composé selon la revendication 5, ayant la formule 1, dans lequel le radical alkylène A contient 2 à 5 atomes de carbone, le radical alkylène B contient 2 à 5 atomes de carbone et le radical alkylène C, s'il est présent, contient 1 à 4 atomes de carbone.

7. 4-équatorial-bromo-2,2'-adamantylidène-adamantane.

8. Procédé de préparation d'un polycycloalkylidène-polycycloalkane substitué, caractérisé en ce qu'un composé substitué par un halogène en position équatoriale obtenu selon l'une quelconque des revendications 1 à 4 est soumis à une réaction de substitution.

9. Procédé selon la revendication 8, caractérisé en ce qu'un composé chloro-substitué obtenu selon l'une quelconque des revendications 1, 2 et 4 est mis en réaction avec un nucléophile en présence d'un sel d'argent dans un solvent.

10. Procédé selon la revendication 9, caractérisé en ce que le sel d'argent est $AgBF_4$ ou $AgClO_4$.

11. Procédé selon la revendication 8, caractérisé en ce qu'un composé bromo-substitué obtenu selon l'une quelconque des revendications 1, 3 et 4, est mis en réaction avec un nucléophile éventuellement en présence d'un cosolvant.

12. Procédé selon la revendication 11, caractérisé par l'utilisation de diméthylformamide ou de dioxanne comme cosolvant.

13. Procédé selon la revendication 8, caractérisé en ce qu'un composé bromo-substitué, obtenu selon l'une quelconque des revendications 1, 3 et 4, est soumis à une réaction d'échange d'halogène.

14. Procédé selon la revendication 13, caractérisé en ce que la réaction d'échange d'halogène est effectuée avec un mélange NaI/acétone pour former le composé correspondant iodo-substitué.

15. Procédé selon la revendication 9 ou 10, caractérisé en ce que le nucléophile est un alcool, un nitrile, un carbamate ou un isothiocyanate.

16. Procédé selon la revendication 11, dans lequel le nucléophile est un acide carboxylique comprenant un radical de protéine.

17. Procédé selon la revendication 16, dans lequel le radical de protéine est un radical de l'albumine de sérum de boeuf.

18. Procédé selon l'une quelconque des revendications 11 ou 15, dans lequel le nucléophile est un alcool.

19. Procédé selon la revendication 18, dans lequel le nucléophile est un alcool cycloalkylé dérivé d'un stéroïde.

20. Procédé selon la revendication 18, dans lequel le stéroïde est le testostérone ou l'acide lithocholique.

21. Procédé selon la revendication 11, dans lequel le nucléophile est un acide gras hydroxylé.

22. Procédé selon la revendication 21, dans lequel l'acide gras hydroxylé est l'acide arachidique.

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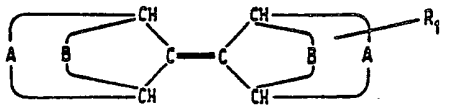

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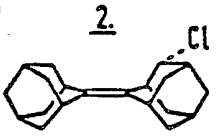

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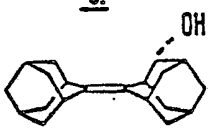

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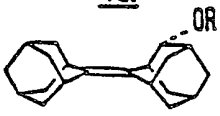

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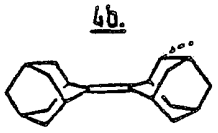

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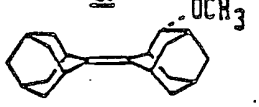

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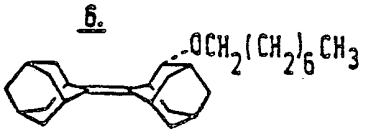

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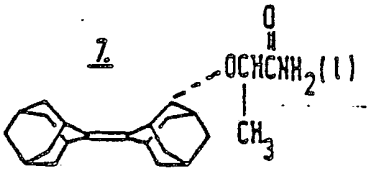

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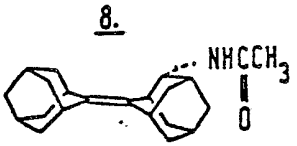

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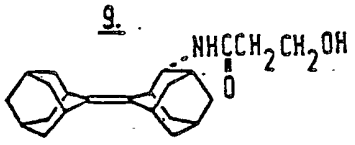

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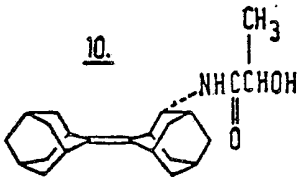

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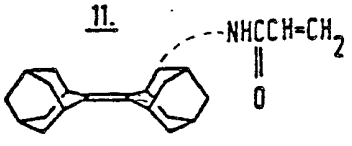

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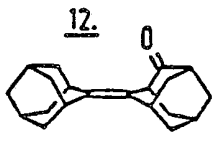

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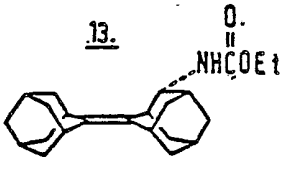

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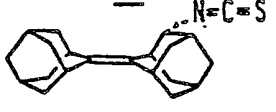

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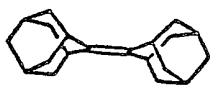

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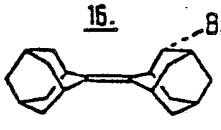

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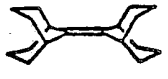

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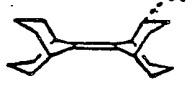

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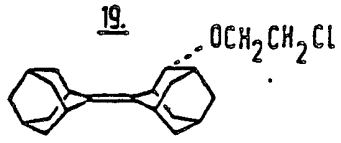

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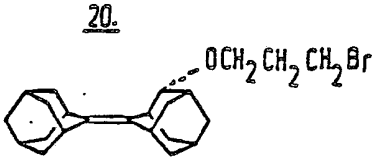

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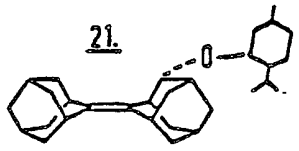

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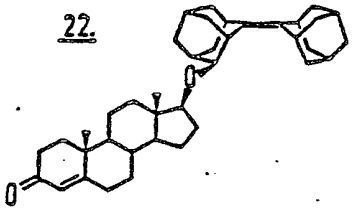

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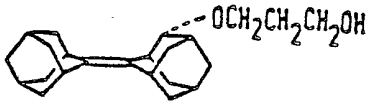

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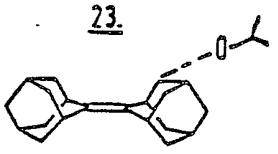

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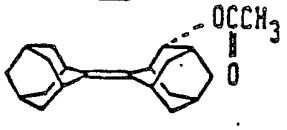

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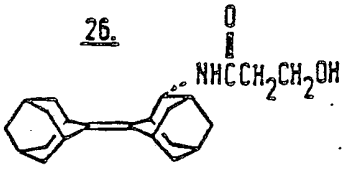

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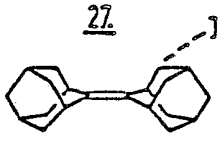

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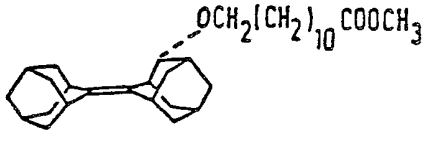

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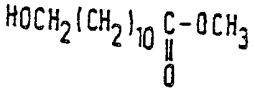

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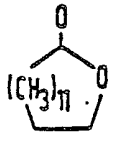

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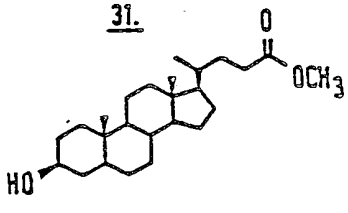

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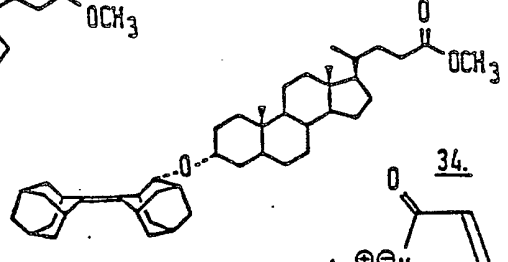

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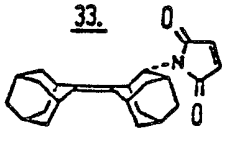

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