United States Patent Office

3,130,227

Patented Apr. 21, 1964

3,130,227

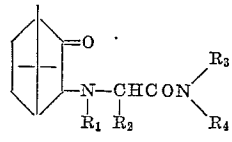
N-CAMPHORYL-AMINO ACETAMIDES

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No Drawing. Filed Aug. 2, 1960, Ser. No. 46,886
Claims priority, application Japan Aug. 27, 1959
13 Claims. (Cl. 260—557)

This invention relates to new camphor derivatives and to processes for the production of the same. The substances of the present invention show analgesic activity and may be used as a medicine.

According to the invention, the camphor derivatives are those in which alpha-amino aliphatic acid amide or its derivatives are introduced in the 3-position of the camphor molecule, and they are expressed with the following formula;



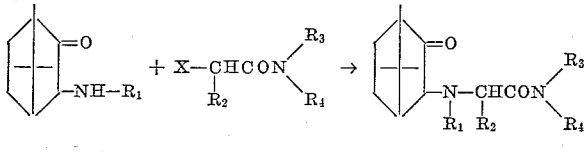
wherein R_1 stands for a hydrogen atom, lower alkyl or acetyl radical; R_2, R_3 and R_4 stand for a hydrogen atom or lower alkyl radical, respectively.

All of these compounds may form a salt such as hydrochloride etc.

The analgesic activity of these compounds may vary more or less, depending on a manner of selection of the radicals, R_1, R_2, R_3 and R_4, but it is always excellent and has low toxicity.

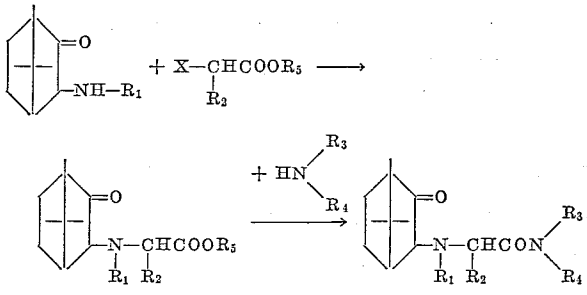
The compounds in the invention are produced by the following processes in which R_1, R_2, R_3 and R_4 stand for the same radicals as those defined above unless otherwise stated.

(A) A N—R_3, R_4 substituted-(alpha-halogeno aliphatic acid) amide is reacted with a N—R_1 substituted-3-aminocamphor, and this process is expressed by the following equation:



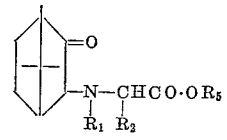
wherein X stands for a halogen atom.

(B) An alpha-halogeno aliphatic acid ester is reacted with a N—R_1 substituted-3-aminocamphor to form a N-camphoryl-(3)-α-amino aliphatic acid ester which is subsequently reacted with a R_3, R_4-substituted amine, and this process is expressed by the following equation:



wherein R_5 stands for a lower alkyl radical.

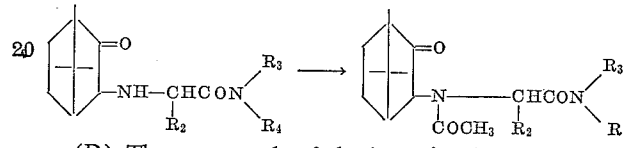
The compounds of the general formula:



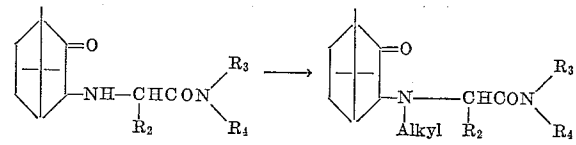
which are intermediately formed in the above process (B) are new compounds when the R_1 and R_2 do not stand for hydrogen simultaneously.

The substances of the invention may be prepared as stated above, but these substances are convertible from one to another as shown below.

(C) The compounds of the invention in which R_1 is hydrogen may be converted by acetylation into those in which R_1 is an acetyl radical, and this process is expressed by the following equation:



(D) The compounds of the invention in which R_1 is hydrogen may be converted by alkylation into those in which R_1 is an alkyl radical, and this process is expressed by the following equation:



These processes are the methods for the production of the camphor derivatives in accordance with the invention. All these compounds may form salts such as hydrochloride etc. by conventional methods, whereby liquid substances can be converted into solid, and (then), in general, water solubility can be increased.

These processes (A), (B), (C) and (D) are now further described as follows:

The process (A) may preferably be carried out using a solvent such as benzene, toluene etc., and by heating the reactants at 60–150° C. under normal pressure or under elevated pressure in a sealed tube.

The process (B) includes the first step in which the reaction may be preferably carried out at 100–150° C. using a solvent such as dimethylformamide etc. and conveniently in the presence of a catalytic quantity of an alkali in the reaction system; and the second step in which the reaction may preferably be carried out at 100–150° C. in a sealed tube using a solvent such as methanol or ethanol etc.

The process (C) may be performed by conventional procedure of acetylation.

The process (D) may be effected by conventional procedure using as alkylation agent, for example, alkyl halogenide, dialkyl sulfate or alkyl arylsulfonate etc.

Examples are now given to illustrate but do not restrict the processes for the production of the camphor derivatives according to the invention.

EXAMPLE 1

N-Camphoryl-(3)-Glycine Dimethylamide

2 mols. of 3-aminocamphor and 1 mol. of N,N-dimethylchloroacetamide are heated in benzene for 5 hours under reflux. After cooling, the precipitated crystals are filtered off and the benzene is distilled from the filtrate. When the residue is recrystallized from benzene and petroleum ether, there is obtained as colorless columnar

crystals N-camphoryl-(3)-glycine dimethylamide; melting point of 126° C. Yield 86%.

Analysis (as $C_{14}H_{24}O_2N_2$): Theoretical—C, 66.63%; H, 9.59%. Found—C, 66.77%; H, 9.86%.

When the resulting N-camphoryl-(3)-glycine dimethylamide is added to methanol/hydrochloric acid and distilled in vacuo to remove the methanol, a residue remains. When this is treated with an amount of ether, crystals are precipitated. Recrystallization from methanol and ether gives N-camphoryl-(3)-glycine dimethylamide hydrochloride as flaky crystals; M.P. 196° C. (decomposition).

Analysis (as $C_{14}H_{24}O_2N_2 \cdot HCl \cdot H_2O$): Theoretical—C, 54.80%; H, 8.87%. Found—C, 54.61%; H, 8.96%.

EXAMPLE 2

N-Camphoryl-(3)-Glycine Diethylamide

2 mols. of 3-aminocamphor and 1 mol. of N,N-diethylchloroacetamide are heated in benzene for 5 hours under reflux. After cooling, the precipitated crystals are filtered and the benzene is removed from the filtrate. The residue is distilled under reduced pressure, there is obtained N-camphoryl-(3)-glycine diethylamide as a pale yellow oil; B.P. 164–165° C./0.02 mm. Hg. Yield 79%.

N-camphoryl-(3)-glycine diethylamide hydrochloride are colorless needles of a melting point of 190° C.

Analysis (as $C_{16}H_{28}O_2N_2 \cdot HCl$): Theoretical—C, 60.64%; H, 9.22%. Found—C, 60.88%; H, 9.30%.

EXAMPLE 3

N-Methyl-N-Camphoryl-(3)-Glycine Amide

2 mols. of 3-methylaminocamphor and 1 mol. of chloroacetamide are heated in benzene in a sealed tube at 100° C. for 7 hours. After cooling, the reaction mixture is washed with water, dried over anhydrous sodium sulfate and distilled to remove the benzene. When the residue is recrystallized from benzene, there is obtained colorless N-methyl-N-camphoryl-(3)-glycine amide of a melting point of 139.5° C. Yield 63%.

Analysis (as $C_{13}H_{22}O_2N_2$): Theoretical—C, 65.51%; H, 9.31%. Found—C, 65.75%; H, 9.48%.

EXAMPLE 4

N-Methyl-N-Camphoryl-(3)-Alanine Amide

2 mols. of 3-methylaminocamphor and 1 mol. of α-bromopropionamide are treated similarly to Example 3. On recrystallization from ether, there is obtained N-methyl-N-camphoryl-(3)-alanine amide as colorless plates of a melting point of 109° C. Yield 54%.

Analysis (as $C_{14}H_{24}O_2N_2$): Theoretical—C, 66.63%; H, 9.95%. Found—C, 66.87%; H, 9.65%.

EXAMPLE 5

N-Methyl-N-Camphoryl-(3)-Glycine Dimethylamide

2 mols. of 3-methylaminocamphor and 1 mol. of N,N-dimethylchloroacetamide are heated in benzene for 5 hours under reflux. After cooling, the liquid reaction mixture is washed with water. When the residue is distilled under reduced pressure, there is obtained N-methyl-N-camphoryl-(3)-glycine dimethylamide as a pale yellow oil of a boiling point of 138–140° C./0.1 mm. Hg. Yield 68%.

Analysis (as $C_{15}H_{26}O_2N_2$): Theoretical—C, 67.63%; H, 9.84%. Found—C, 67.49%; H, 9.92%.

Infra-red absorption shows an absorption of five-membered carbonyl at 1740 $cm.^{-1}$.

N-methyl-N-camphoryl-(3)-glycine dimethylamide hydrochloride comprises short columnar crystals of a melting point of 174° C.

Analysis (as $C_{15}H_{26}N_2O_2 \cdot HCl$): Theoretical—C, 59.48%; H, 8.99%. Found—C, 59.72%; H, 9.17%.

EXAMPLE 6

N-Camphoryl-(3)-Alanine Dimethylamide

2 mols. of 3-aminocamphor and 1 mol. of N,N-dimethyl-α-chloropropionamide are heated in benzene for 6 hours under reflux. After cooling, the precipitated crystals are filtered and the benzene removed from the filtrate by distillation. When the residue is then recrystallized from petroleum ether, there is obtained as colorless plates N-camphoryl-(3)-alanine dimethylamide of a melting point of 98.5° C. Yield 65%.

Analysis (as $C_{15}H_{26}O_2N_2$): Theoretical—C, 67.63%; H, 9.84%. Found—C, 67.85%; H, 10.06%.

EXAMPLE 7

N-Methyl-N-Camphoryl-(3)-Alanine Dimethylamide

2 mols. of 3-methylaminocamphor and 1 mol. of N,N-dimethyl-α-bromopropionamide are heated in benzene in a sealed tube at 100° C. for 20 hours. After cooling, the insoluble matter is filtered and the filtrate has the benzene removed by distillation. The residue is then distilled under reduced pressure, there is obtained N-methyl-N-camphoryl-(3)-alanine dimethylamide as a pale yellow oil of a boiling point of 138–140° C./0.01 mm. Hg. Yield 62%.

N-methyl-N-camphoryl-(3)-alanine dimethylamide hydrochloride comprises colorless needles of a melting point of 200° C. (decomposition).

Analysis (as $C_{16}H_{28}O_2N_2 \cdot HCl$): Theoretical—C, 60.64%; H, 9.22%. Found—C, 60.89%; H, 9.45%.

EXAMPLE 8

N-Methyl-N-Camphoryl-(3)-Alanine Diethylamide

2 mols. of 3-methylaminocamphor and 1 mol. of N,N-diethyl-α-bromopropionamide are heated in toluene for 20 hours under reflux. After cooling, the insoluble matter is filtered and the toluene is removed from the filtrate by distillation. When the residue is distilled under reduced pressure, there is obtained N-methyl-N-camphoryl-(3)-alanine diethylamide as a pale yellow oil of a boiling point of 140° C./0.01 mm. Hg. Yield 34%.

Analysis (as $C_{18}H_{32}O_2N_2$): Theoretical—C, 70.09%; H, 10.46%. Found—C, 69.85%; H, 10.68%.

EXAMPLE 9

N-Methyl-N-Camphoryl-(3)-Glycine Ethylester

2 mols. of 3-methylaminocamphor and 1 mol. of ethyl chloroacetate are heated in dimethylformamide at 120° C. for 8 hours. After cooling, the solvent is distilled off in vacuo and the residue extracted with ether. After the ether is removed, the remainder is distilled under reduced pressure to give N-methyl-N-camphoryl-(3)-glycine ethylester as a pale yellow oil of a boiling point of 115–117° C./0.3 mm. Hg. Yield 68%.

N-methyl-N-camphoryl-(3)-glycine ethylester hydrochloride comprises colorless fine crystals of a melting point of 163–164° C.

Analysis (as $C_{15}H_{25}O_3N \cdot HCl$): Theoretical—C, 59.29%; H, 8.63%; N, 4.61%. Found—C, 59.39%; H, 8.67%; N, 4.89%.

EXAMPLE 10

N-Camphoryl-(3)-Alanine Methylester

7 g. of 3-aminocamphor, 7 g. of methyl α-bromopropionate and 2 g. of potassium carbonate are heated in 30 cc. of dimethylformamide at 120° C. for 20 hours. After cooling, the solvent is removed in vacuo and the residue is extracted with benzene. The extract is treated with diluted hydrochloric acid and extracted with benzene. This benzene layer is rendered alkaline with sodium carbonate and the benzene is again distilled off. When the residue is distilled under reduced pressure, there are obtained 6 g. of N-camphoryl-(3)-alanine methylester as a

pale yellow oil of a boiling point of 107–109° C./0.2 mm. Hg.

Analysis (as $C_{14}H_{23}O_3N$): Theoretical—C, 66.37%; H, 9.15%. Found—C, 66.65%; H, 9.38%.

EXAMPLE 11

N-Methyl-N-Camphoryl-(3)-Alanine Methylester

5 g. of 3-methylaminocamphor, 4.6 g. of methyl α-bromopropionate and 2 g. of potassium carbonate are heated in 25 cc. of dimethylformamide at 120° C. for 20 hours. After cooling, the solvent is removed in vacuo and the residue is subjected to distillation under reduced pressure to give 4.2 g. of N-methyl-N-camphoryl-(3)-alanine methylester as a pale yellow oil of a boiling point of 116° C./0.4 mm. Hg.

N-methyl-N-camphoryl-(3)-alanine methylester hydrochloride comprises colorless needles of a melting point of 176° C. (decomposition).

Analysis (as $C_{15}H_{25}O_3N \cdot HCl$): Theoretical — N, 4.61%. Found—N, 4.71%.

EXAMPLE 12

N-Camphoryl-(3)-Glycine Dimethylamide

1 mol. of N-camphoryl-(3)-glycine ethylester and an excess of 40% dimethylamine in methanol are heated in a sealed tube at 100° C. for 5 hours until the yellowish green contents become colorless.

After cooling, the methanol is distilled off. When the residue is recrystallized from benzene/petroleum ether, there is obtained N-camphoryl-(3)-glycine dimethylamide as colorless columnar crystals; melting point 126° C. Yield 90%.

Analysis (as $C_{14}H_{24}O_2N_2$): Theoretical—C, 66.63%; H, 9.59%. Found—C, 66.52%; H, 9.62.

The resulting N-camphoryl-(3)-glycine dimethylamide is added to methanol/hydrochloric acid and the methanol distilled off to leave a syrup which, on recrystallization from methanol/ether, gives N-camphoryl-(3)-glycine dimethylamide hydrochloride as flaky crystals; melting point 196° C. (decomposition).

Analysis (as $C_{14}H_{24}O_2N_2 \cdot HCl \cdot H_2O$): Theoretical—C, 54.80%; H, 8.87%. Found—C, 54.63%; H, 8.96%.

EXAMPLE 13

N-Camphoryl-(3)-Glycine Diethylamide

1 mol. of N-camphoryl-(3)-glycine ethylester and 1.2 mols. of diethylamine are heated in ethanol in a sealed tube at 100° C. for 5 hours. After cooling, the ethanol is distilled off and the residue is subjected to distillation under reduced pressure to give N-camphoryl-(3)-glycine diethylamide as a pale yellow oil of boiling point of 164–165° C./0.02 mm. Hg. Yield 87%.

N-camphoryl-(3)-glycine diethylamide hydrochloride are colorless needles of a melting point of 190° C.

Analysis (as $C_{16}H_{28}O_2N_2 \cdot HCl$): Theoretical — C, 60.64%; H, 9.22%. Found: C, 60.51%; H, 9.39%.

EXAMPLE 14

N-Methyl-N-Camphoryl-(3)Glycine Dimethylamide

2 g. of N-methyl-N-camphoryl-(3)-glycine ethylester and an excess of 40% dimethylamine in methanol are heated in a sealed tube at 100° C. for 10 hours.

After cooling, the reaction mixture is treated similarly to Example 13 to give 1.6 g. of N-methyl-N-camphoryl-(3)-glycine dimethylamide as a pale yellow oil of a boiling point of 143–145° C./0.2 mm. Hg.

N-methyl-N-camphoryl-(3)-glycine dimethylamide hydrochloride as short columnar crystals of a melting point of 174° C.

Analysis (as $C_{15}H_{26}O_2N_2 \cdot HCl$): Theoretical — C, 59.48%; H, 8.99%. Found—C, 59.59%; H, 9.15%.

EXAMPLE 15

N-Camphoryl-(3)-Alanine Dimethylamide

2 g. of N-camphoryl-(3)-alanine methylester and an excess of 40% dimethylamine in methanol are heated in a sealed tube at 100° C. for 10 hours.

After cooling, the methanol is distilled off. When the residue is recrystallized from petroleum ether, 1.5 g. of N-camphoryl-(3)-alanine dimethylamide is obtained as colorless plates of a melting point of 98° C.

Analysis (as $C_{15}H_{26}O_2N_2$): Theoretical—C, 67.63%; H, 9.84%. Found—C, 67.51%; H, 9.98%.

EXAMPLE 16

N-Methyl-N-Camphoryl-(3)-Alanine Dimethylamide

2 g. of N-methyl-N-camphoryl-(3)-alanine methylester and an excess of 40% dimethylamine in methanol are heated in a sealed tube at 100° C. for 12 hours. After cooling, the solvent is distilled off and the residue is subjected to distillation to give 1.4 g. of N-methyl-N-camphoryl-(3)-alanine dimethylamide as a pale yellow oil of a boiling point of 145° C./0.1 mm. Hg.

N-methyl-N-camphoryl-(3)-alanine dimethylamide hydrochloride are colorless needles of a melting point of 200° C. (decomposition).

Analysis (as $C_{16}H_{28}O_2N_2 \cdot HCl$): Theoretical — C, 60.64%; H, 9.22%. Found—C, 60.73%; H, 9.40%.

EXAMPLE 17

N-Acetyl-N-Camphoryl-(3)-Glycine Dimethylamide

1 g. of N-camphoryl-(3)-glycine dimethylamide is dissolved in 10 cc. of acetic anhydride and the solution is heated up on a boiling water bath for 3 hours. After cooling, the acetic anhydride is distilled off in vacuo and impurities are removed from the residue by chromatography with an alumina column using chloroform as the solvent. On recrystallization from benzene/ether, there is obtained N-acetyl-N-camphoryl-(3)-glycine dimethylamide as colorless needles; melting point 131° C. Yield is almost quantitative.

Analysis (as $C_{16}H_{26}O_3N_2$): Theoretical—C, 65.28%; H, 8.90. Found—C, 65.57%; H, 9.08%.

EXAMPLE 18

N-Acetyl-N-Camphoryl-(3)-Glycine Diethylamide

1 g. of N-camphoryl-(3)-glycine diethylamide is dissolved in 10 cc. of acetic anhydride and the solution is warmed over a boiling water bath for 5 hours. After cooling, the acetic anhydride is distilled off. When the residue is recrystallized from ether/petroleum ether, there is obtained N-acetyl-N-camphoryl-(3)-glycine diethylamide as colorless needles; melting point 62° C. Yield is quantitative.

Analysis (as $C_{18}H_{30}O_3N_2 \cdot \frac{1}{2}H_2O$): Theoretical—C, 65.23%; H, 9.43%. Found—C, 65.68%; H, 9.41%.

EXAMPLE 19

N-Acetyl-N-Camphoryl-(3)-Alanine Dimethylamide

1 g. of N-camphoryl-(3)-alanine dimethylamide is dissolved in 15 cc. of acetic anhydride and the solution heated over a boiling water bath for 6 hours. After cooling, the acetic anhydride is distilled off and the residue is freed from impurities by chromatography with an alumina column using chloroform as the solvent. On recrystallization from benzene, there is obtained N-acetyl-N-camphoryl-(3)-alanine dimethylamide as a colorless columnar crystal; melting point 215° C. Yield is quantitative.

Analysis (as $C_{17}H_{28}O_3N_2$): Theoretical—C, 66.20; H, 9.15%. Found—C, 66.24; H, 9.29%.

EXAMPLE 20

N-Methyl-N-Camphoryl-(3)-Glycine Dimethylamide

2 g. of N-camphoryl-(3)-glycine dimethylamide is dis-

solved in methanol and the solution is mixed with 1.5 g. of methyl iodide and (then) with an excess of potassium carbonate. The mixture is subsequently heated in a sealed tube at 100° C. for 5 hours. After cooling, the solvent is distilled off and the residue extracted with ether. When the ether layer is distilled under reduced pressure, there is obtained 1.8 g. of N-methyl-N-camphoryl-(3)-glycine dimethylamide as a pale yellow oil of a boiling point of 145° C./0.4 mm. Hg.

N-methyl-N-camphoryl-(3)-glycine dimethylamide hydrochloride shows a melting point of 174° C.

EXAMPLE 21

N-Methyl-N-Camphoryl-(3)-Glycine Dimethylamide

2 g. of N-camphoryl-(3)-glycine dimethylamide is suspended in 50% methanol and 2 g. of dimethyl sulfate are slowly added to the suspension drop-by-drop with stirring while caustic soda is added so as to keep a slight alkalinity.

After standing for 3 hours with stirring, the reaction mixture is extracted with ether. When the ether layer is distilled under reduced pressure, there is obtained 1.3 g. of N-methyl-N-camphoryl-(3)-glycine dimethylamide as a pale yellow oil of a boiling point of 139–141° C./0.1 mm. Hg.

EXAMPLE 22

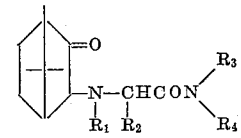
N-Methyl-N-Camphoryl-(3)-Glycine Dimethylamide

2 g. of N-camphoryl-(3)-glycine dimethylamide is added to 1.2 g. of formic acid and 1.2 g. of 35% aqueous formaldehyde solution and then the solution is heated at 100–110° C. for 5 hours. After cooling, sodium bicarbonate is added to make the reaction mixture alkaline, which is then extracted with ether. When the ether layer is distilled under reduced pressure, there are obtained 1.5 g. of N-methyl-N-camphoryl-(3)-glycine dimethylamide as a pale yellow oil of a boiling point of 139–141° C./0.1 mm. Hg.

Analysis (as $C_{15}H_{26}O_2N_2$): Theoretical—C, 67.63%; H, 9.84%. Found—C, 67.52%; H, 9.93%.

What we claim is:

1. A compound of the following Formula I:



wherein R_1 is a member selected from the group consisting of hydrogen, lower alkyl and acetyl; R_2, R_3 and R_4 are members selected from the group consisting of hydrogen and lower alkyl.

2. N-camphoryl-(3)-glycine dimethylamide.
3. N-camphoryl-(3)-glycine diethylamide.
4. N-methyl-N-camphoryl-(3)-glycine amide.
5. N-methyl-N-camphoryl-(3)-alanine amide.
6. N-methyl-N-camphoryl-(3)-glycine dimethylamide.
7. N-camphoryl-(3)-alanine dimethylamide.
8. N-methyl-N-camphoryl-(3)-alanine dimethylamide.
9. N-methyl-N-camphoryl-(3)-alanine diethylamide.
10. N-acetyl-N-camphoryl-(3)-glycine dimethylamide.
11. N-acetyl-N-camphoryl-(3)-glycine diethylamide.
12. N-acetyl-N-camphoryl-(3)-alanine dimethylamide.
13. A pharmaceutically acceptable addition salt of a compound of the Formula I as defined in claim 1.

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