

PATENT SPECIFICATION

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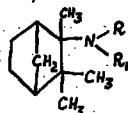
COMPLETE SPECIFICATION

Isocamphane Compounds and processes for preparing them

We, MERCK & CO., INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

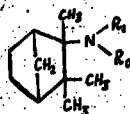
This invention is concerned with novel isocamphane compounds.

In brief, this invention provides new N-substituted derivatives of 3-aminoisocamphane having the general formula:



where R is a C₁₋₈ alkyl group and R₁ is a hydrogen atom or a C₁₋₈ alkyl group, and their acid-addition salts. The invention also provides quaternary ammonium salts of 3-aminoisocamphane. All these compounds are valuable ganglionic blocking agents, and the invention also provides pharmaceutical compositions containing a pharmaceutical carrier and, as active ingredients, one or more of the novel compounds.

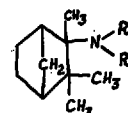
In accordance with the present invention, the new compounds of the above general formula may be obtained by reducing a compound having the general formula



in which R₁ is a hydrogen atom or a C₁₋₈ alkyl radical and R² is an acyl radical derived from a C₁₋₈ aliphatic carboxylic acid. The compound may be recovered in the form of an acid-addition salt.

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Also in accordance with the present invention, quaternary ammonium salts of 3-aminoisocamphane may be prepared by the reaction of a compound having the general formula



in which R and R₁ both represent C₁₋₈ alkyl groups, with an alkyl halide.

The invention also provides a process for resolving racemic forms of the new compounds of the invention having the above general formula, e.g. dl-3-(N-methylamino)isocamphane, by reacting them with an optically active acid such as d-camphor-sulphonic acid, separating the resulting salts and regenerating the compound by treatment with a base.

In accordance with one embodiment of the present invention 3-(N-methylamino)isocamphane is obtained by the reduction of 3-(N-formylamino)isocamphane, which compound forms part of the invention claimed in the specification of our copending application No. 2168/58 (Serial No. 804,880). The 3-(N-formylamino)isocamphane may be and preferably is prepared by treating camphene with hydrogen cyanide, in the presence of an acidic catalyst, this reaction being described in detail and claimed in the specification of our copending application No. 2168/58 (Serial No. 804,880).

A preferred method of reducing 3-(N-formylamino)isocamphane is by reaction with an alkali-metal aluminium hydride. This reaction is conveniently effected in a suitable anhydrous non-reactive solvent such as ethyl ether with an alkali-metal aluminium hydride such as lithium aluminium hydride or sodium aluminium hydride. In effecting the reaction, the aluminium hydride should be present in an amount equivalent to about 2 moles of hydride per mole of formamido compound.

Thus, the reduction is conveniently effected by dissolving lithium aluminium hydride in ethyl ether, adding to it a solution of 3-(N-formylamino)isocamphane in anhydrous ether and refluxing the resulting solution for about 4 to 6 hours. At this point the reduction of the formamido compound is substantially complete. The methylamino compound thus produced is recovered by adding water to the reaction mixture, filtering the resulting solution, and concentrating the filtrate to a small volume. The desired N-methyl compound is then conveniently recovered in the form of its chloride salt by adding a solution of ether saturated with HCl to the concentrate, whereupon the hydrochloride salt of 3-(N-methylamino) isocamphane precipitates in crystalline form and can be recovered and dried.

The formamido compound can be converted to 3-aminoisocamphane by reaction with a base and this process is described and claimed in the specification of copending application No. 2168/58 (Serial No. 804,880).

Pursuant to a further embodiment of this invention, N-methylamino isocamphanes are prepared by reacting 3-aminoisocamphane with formaldehyde and hydrogen in the presence of a hydrogenation catalyst of the platinum group. Thus, when a mixture of the hydrochloride salt of 3-aminoisocamphane, water, formaldehyde and a small amount of sodium acetate is reacted with hydrogen in the presence of palladium-on-charcoal and the reaction allowed to continue until the equivalent of about one mole of hydrogen per mole of 3-aminoisocamphane is absorbed, 3-(N-methylamino) isocamphane is produced. When the reaction is continued until about two mole equivalents of hydrogen are absorbed, 3-(N,N-dimethylamino)isocamphane is produced. The N-methyl derivatives so prepared can be readily recovered from the reaction mixture by removing the solvent under diminished pressure. The product so obtained can be further purified by dissolving it in water, adding alkali to the resulting solution to make it alkaline, extracting the alkaline solution with a water-immiscible solvent for the methylated amino isocamphane, such as ether, evaporating the solvent solution, and finally distilling the methyl derivative under diminished pressure.

In similar manner other N-(C₁₋₈ alkyl) derivatives of 3-aminoisocamphane can be prepared. Thus, when acetaldehyde is used in place of formaldehyde in the above-described process the corresponding N-ethylamino and N,N-diethylamino compounds are obtained.

In accordance with a further embodiment of this invention, other N-(C₁₋₈ alkyl) derivatives of 3-aminoisocamphane are produced by reducing the corresponding N-(C₁₋₈-carboxylic acyl)-amino compound, which may be obtained by reacting 3-aminoisocamphane with

a C₁₋₈ aliphatic carboxylic acid acylating agent. It should be noted that the acylation step is claimed in the specification of our copending application No. 2168/58 (Serial No. 804,880). For example, 3-(N-ethylamino) isocamphane is produced by reacting 3-aminoisocamphane with about one mole-equivalent of acetyl chloride in the presence of a base to produce 3-(N-acetylamino) isocamphane. The product is then reduced by reaction with an aluminium hydride following the procedures described above for the reduction of the formylamino compound.

In accordance with the above-described methods, the N-ethyl, N-propyl, N-butyl, N-hexyl, N-octyl, N-isopropyl, and N-isobutyl derivatives of 3-aminoisocamphane are obtained.

The N-(C₁₋₈ alkyl) derivatives of 2-aminoisocamphane may be converted to 3-[N,N-di-(C₁₋₈ alkyl)amino] isocamphane by reacting the mono alkyl derivative with a lower aliphatic acid acylating agent to obtain the corresponding acylated derivative as described and claimed in the specification of copending application No. 2168/58 (Serial No. 804,880), and then in accordance with the present invention, reducing this product. For example, 3-(N,N-diethylamino) isocamphane is produced by reacting 3-(N-ethylamino) isocamphane with acetic anhydride in the presence of a small amount of sulphuric acid to produce the N-acetyl derivative which on treatment with lithium aluminium hydride is reduced to the diethyl derivative. In similar manner, other dialkyl derivatives such as the dipropyl, dibutyl, dihexyl, diisopropyl, and the diisobutyl compounds are obtained. Alternatively, dialkyl derivatives in which the alkyl substituents are different such as the methyl-ethyl, ethyl-hexyl, and methyl-isopropyl, may also be prepared by this method.

The following experiments, which are examples of the invention claimed in the specification of our copending application No. 2168/58 (Serial No. 804,880) illustrate the preparation of various starting materials for the examples of the present invention given below.

EXPERIMENT 1.

Preparation of 3-(N-formylamino) isocamphane.

Into a three-necked flask which had been equipped with an agitator, thermometer, dropping funnel and reflux condenser through which water at 5-10° C. was circulated, 31.7 g. of *dl*-camphene was added and 58 cc. of glacial acetic acid. The mixture was stirred until all the solid had dissolved and then with stirring cooled to 10-12° C. At this point 20 cc. of liquid hydrogen cyanide was added while continuing the stirring. The solution was now cooled to 0° C. A slurry of white crystalline solid separated. With the maintenance of the reaction temperature at 0-2° C.

by outside cooling, the addition of a solution of 63.5 cc. of conc. H_2SO_4 in 58 cc. of glacial acetic acid was begun. After the addition of about 1—2 cc. of the sulphuric acid solution, the reaction mixture became very fluid and most of the solid dissolved. The acid was added over a period of two hours, during which time the reaction took on a yellowish colour. After all the acid was added the yellow-orange reaction mixture was stirred for an additional hour at 0—2° C. The cooling bath was removed and the reaction temperature was allowed to rise to 22° C. in 2 hours. The viscous reaction mixture was put under vacuum (25—35 mm.) for 15—30 minutes with stirring in order to remove most of the excess of hydrogen cyanide.

After most of the cyanide had been removed, the reaction was quenched by the slow addition of 500 cc. of cold water. The temperature of the reaction was maintained at 18—20° C. by external cooling. The resulting milky solution was extracted with 2 x 100 cc. of chloroform and 1 x 50 cc. of the same solvent. Care must be exercised at this point for the aqueous as well as the organic extracts contain hydrogen cyanide. The chloroform layer was washed with 2 x 100 cc. of water and then brought to a pH of 7—8 with a 10% solution of sodium bicarbonate, and finally washed with 150 cc. portions of water until the aqueous layer was free of cyanide.

After the final water wash, the chloroform layer was dried over 20 gm. of anhydrous sodium sulphate, filtered and concentrated on the steam bath in a vacuum of 25—35 mm. to dryness. When practically no more chloroform distilled, the yellow viscous residue was flushed with 100 cc. of *n*-heptane (Skellysolve C) at 25—35 mm. at 100° C. in order to remove the remaining chloroform. The residue was dissolved in 140 cc. *n*-heptane at 100° C. After all the residue had gone into solution, it was cooled slowly with agitation in order to allow slow crystallization. After 5 hours the temperature had fallen to 20—25° C. and a copious white precipitate had settled. The mixture was cooled with stirring to 5° C. for 8—10 hours, filtered and washed with cold *n*-heptane (3 x 10 cc.) and finally with 3 x 15 cc. of petroleum ether. The *dl*-3-(*N*-formylamino) isocamphane so obtained melted at 160—163° C.

EXPERIMENT 2.

Preparation of 3-(*N*-formylamino) isocamphane.

Into a 5-liter three-necked round-bottom flask equipped with stirrer, dropping funnel and thermometer, was added 325 ml. of glacial acetic acid. Then, portionwise, a total of 133 g. of sodium cyanide (granular, 2.6 mole) was added with a stirring while holding the temperature at 15° C. To the thick white slurry was added dropwise a previously prepared cold mixture of 325 ml. glacial acetic

acid and 360 ml. conc. sulphuric acid. After addition of a few ml. at 15° C., the thick slurry thins slowly and the remainder of the mixture of sulphuric and glacial acetic acids was added at 0—2° C. A total of about 2 hours was required for the addition. After addition, stirring was continued for 15 minutes. Then dropwise, over an hour, a solution of 178 g. (1.3 mole) of *dl*-camphene in 50 ml. of glacial acetic acid was added while keeping the temperature at about 0° C. ($\pm 3^\circ$).

Stirring was continued for two hours at 0° C. during which time a slight pinkish-yellow colour developed in the reaction mixture. The cooling bath was removed and the temperature allowed to rise to 15—20° C. in about 2—3 hours. The ice bath was then replaced and while holding the temperature at about 20° C., the mixture was gradually diluted with 3 liters of water while stirring vigorously. After an hour or two of good agitation at room temperature, the oily product was extracted with 2 x 500 ml. and 1 x 200 ml. of chloroform and the combined extracts washed with 2 x 500 ml. of water. The chloroform extract was then rendered neutral by stirring with 500 ml. water and gradually adding solid sodium bicarbonate to the mixture until the aqueous phase had a pH of about 7; required, approximately 88 g. of $NaHCO_3$. After separation the chloroform layer was washed with 2 x 500 ml. water, dried over calcium chloride, and after filtration the solvent was removed *in vacuo* on the steam bath. A solid somewhat sticky residue of 231.2 g. was obtained. After removal of last traces of chloroform by repeated swishing with petroleum ether, the cake was finally refluxed with about 500 ml. petroleum ether (b. 30—60° C.) until a thick crystalline slurry was obtained. After refrigeration for a day, the white crystalline mass was filtered by suction, washed with petroleum ether (2 x 125 ml.), then *n*-heptane (2 x 125 ml.) and again with petroleum ether (2 x 125 ml.). After air drying at room temperature to constant weight, 180.6 g. of the *dl*-3-(*N*-formylamino) isocamphane melting at 160—165° C. was obtained.

The combined petroleum ether and *n*-heptane washes were concentrated under diminished pressure and the residual oil dissolved in a minimum amount of hot petroleum ether (about 75 ml.). The resulting solution was placed in the refrigerator for two days. The precipitated *dl*-3-(*N*-formylamino) isocamphane was then recovered by filtration and washed with petroleum ether and *n*-heptane as described above. Obtained 12.6 g. of product having a melting point of 158—164° C.

The *dl*-3-(*N*-formylamino) isocamphane (193 g.) was dissolved in 1.9 liters of *n*-heptane by heating on a steam bath. After clarifying the

solution by filtration, the clear filtrate was allowed to stand at room temperature until crystallization was complete. The crystalline product is filtered by suction, washed with a little cold *n*-heptane and air dried. The *dl*-3-(N-formylamino)isocamphane melted at 169—174° C.

EXPERIMENT 3.

Preparation of 3-aminoisocamphane.

- 10 *dl*-3-(N-formylamino)isocamphane (21.75 g.) was dissolved in a mixture containing 70 g. of sodium hydroxide, 70 cc. water and 210 cc. methanol, and the resulting solution refluxed for about 16 hours. After removal of the bulk of methanol (*in vacuo* at about 50°), the alkaline liquor is steam-stripped until no more oil is collected. The distillate is saturated with sodium chloride and the amine extracted with ether. After drying (Na_2SO_4) and removal of the ether, the oily residue crystallizes to obtain the *dl*-3-aminoisocamphane as a waxy solid melting at 172—174° C. with softening at 171° C.

- 25 After subliming the product under diminished pressure the *dl*-3-aminoisocamphane melted at 173—175° C.

- 30 The amine is slightly soluble in water; the pH of the solution is about 10.5. For further identification it was converted to the hydrochloride which is obtained in quantitative yield and in a crystalline form by neutralizing the base with HCl and concentrating the solution.

- 35 Anal. Calcd. for $\text{C}_{10}\text{H}_{19}\text{N}\cdot\text{HCl}$ (189.73):
C, 63.30; H, 10.63; N, 7.38; Cl, 18.69
Found: C, 63.59; H, 10.79; N, 7.06; Cl, 18.83
The hydrochloride is quite soluble in water; it does not melt below 300° C.

- 40 The phosphate was obtained in a similar way.

- Anal. Calcd. for $\text{C}_{10}\text{H}_{19}\text{N}\cdot\text{H}_3\text{PO}_4$ (404.53):
C, 47.80; H, 8.83; N, 5.58; P, 12.30
Found: C, 47.84; H, 8.69; N, 6.70; P, 11.94

- 45 The phosphate is a white crystalline salt, soluble in water, but insoluble in ethanol. It melts at 281—283° C. with effervescence.

EXAMPLE 1.

Preparation of 3-(N-methylamino)isocamphane.

- 50 To 4.23 liters of anhydrous ether in a 12-liter three-necked flask fitted with a stirrer, reflux condenser and dropping funnel was quickly added 78 g. (2.05 mole) of lithium aluminium hydride. The mixture was gently refluxed with stirring until all hydride had dissolved which required several hours.

- 55 A solution of 168 g. (0.92 mole) of *dl*-3-(N-formylamino)isocamphane, prepared as described in Experiment 2, in 1.81 liters of anhydrous ether was then added during a period of about one hour with stirring. After addition, the mixture was refluxed for about 6 hours after which it was cooled slightly and 347 ml. of water added with stirring, hydro-

gen gas being evolved during the addition. 65
Stirring was continued until the precipitate had changed to a powder, which was filtered by suction and washed with ether (a total of about 2 liters). The combined filtrate and washes were concentrated to 1.6 liters and the concentrate containing the *dl*-3-(N-methylamino)isocamphane washed once with about 350 cc. water, and then dried over anhydrous sodium sulphate. The dried ether concentrate was then cooled in an ice-bath and with stirring a cold saturated ethereal hydrogen chloride solution was added slowly until acid to congo red; required about 440 ml. anhydrous ether saturated (at 0° C.) with HCl gas. After precipitation was complete, the white crystalline *dl*-3-(N-methylamino)isocamphane hydrochloride was filtered, and washed with anhydrous ether (about 1 liter) until the washes were neutral. 70
75

The *dl*-3-(N-methylamino)isocamphane hydrochloride was air dried at room temperature. Obtained, 156.5 g. of product melting with decomposition at 249° C. 80
85

The *dl*-3-(N-methylamino)isocamphane hydrochloride (156.5 g.) was dissolved in 1.5 liters of boiling isopropanol and then allowed to crystallize at room temperature for about 2 days. After filtration, the product was washed with a little cold isopropanol (2 x 70 ml.) and air-dried at room temperature. Obtained, 104 g. of product melting with decomposition at 249° C. 90
95

EXAMPLE 2.

Preparation of 3-(N,N-dimethylamino)isocamphane.

A mixture of 20 g. (0.105 mole) of the hydrochloride of *dl*-3-aminoisocamphane, 150 ml. of water, 34 ml. of 40% formalin, 1.0 g. of sodium acetate (anhydr.) and 2.0 g. of the catalyst (5% palladium on charcoal) was hydrogenated at room temperature and a pressure of 40 pounds per square inch for about 18 hours. After this time the equivalent of one mole of hydrogen was absorbed and the reaction had slowed down considerably. Then 2 grams of the palladium catalyst was added to the reaction mixture and hydrogenation continued (at room temperature and 40 p.s.i.) for 24 hours longer during which time another mole-equivalent of hydrogen was taken up. 100
105
110
115
After filtration of the catalyst, the clear colourless filtrate was concentrated *in vacuo* at about 40—50° C. and the residual oil flushed several times with water and ethanol to remove excess of formaldehyde. The partially crystalline residue was dissolved in 100 ml. water and the solution rendered alkaline with 45 ml. of 2.5 N NaOH with ice-cooling. The amine was then extracted with 1 x 100 ml. and 3 x 50 ml. of ether, the combined ether extracts washed with 1 x 100 ml. water, then dried over anhydrous magnesium sulphate. After removal of solvent the pale yellow oily residue is fractionally distilled *in vacuo*. Yield, 16.2 g. of 120
125

dl-3-(*N,N*-dimethylamino) isocamphane, b.p. 65–66° C. at 2 mm., n_D^{25} 1.4898.

The base was converted to the hydrochloride by dissolving the amine in 160 ml. anhydrous ether and precipitating with ethereal HCl solution using Congo red as an indicator. After filtration and washing with ether, 16.4 g. of the hydrochloride, melting at 166–169° C. with decomposition, was obtained.

Anal. Calcd. for $C_{12}H_{24}ClN$ (217.8):
C, 66.18; H, 11.11; N, 6.43; Cl, 16.28
Found: C, 66.17; H, 10.81; N, 6.54; Cl, 16.1

Crystallization of the hydrochloride salt from boiling methyl isobutyl ketone (1 g. compound per 17 ml.) gave a crystalline product, melting at 171–172° C. (dec.) A second crystallization raised the melting point to 173–174° C. (dec.).

EXAMPLE 3.

20 Preparation of 3-(*N*-ethylamino) isocamphane.

To 30 grams of *dl*-3-aminoisocamphane (m.p. 174°) was gradually added 120 ml. acetic anhydride with external cooling. After adding about one ml. of conc. sulfuric acid with good agitation a clear solution was obtained, which was allowed to age at room temperature for about 15 hours. The reaction mixture was then added slowly to 600 ml. of water with cooling and vigorous stirring. The white amorphous precipitate which formed gradually became crystalline with stirring. It was filtered by suction, well washed with water and air dried. The *dl*-3-acetamido isocamphane melted at 132–134° C.

35 Crystallization from hot Skellysolve (b. 95° C. 100°; 18 ml./g.) raised the m.p. to 133–135.5° C.

Anal. Calcd. for $C_{12}H_{23}NO$ (195.3):
C, 73.77; H, 10.83; N, 7.18
40 Found: C, 73.48; H, 10.58; N, 7.18

A solution of 4.0 g. of once-crystallized *dl*-3-acetamido isocamphane in 90 ml. of anhydrous ether, was added over a period of 25 minutes with stirring to a solution of 1.75 g. (0.046 mole) of lithium aluminium hydride in 100 ml. of absolute ether. After refluxing for 3 hours, the mixture was slightly cooled and with vigorous stirring 8.3 ml. water was added very cautiously. The white granular precipitate was filtered and washed with ether. The ether extracts were washed with 2 x 50 ml. water then dried over anhydrous sodium sulfate. After concentrating the ether extract to a small volume, ethereal HCl was added with cooling to a pH of about 3. The resulting white precipitate was filtered by suction, washed with ether (until free of HCl), then air dried. The *dl*-3-(*N*-ethylamino) isocamphane hydrochloride melted at 248° C.
60 Crystallization from boiling isopropanol (225 ml.) gave pure *dl*-3-(*N*-ethylamine) isocamphane hydrochloride, melting at 260–1° C. with decomposition.

Anal. Calcd. for $C_{12}H_{24}NCl$ (217.78);

C, 66.18; H, 11.11; N, 6.43; Cl, 16.28
65 Found: C, 66.04; H, 11.16; N, 6.16; Cl, 16.12

When the *N*-ethyl compound so obtained is treated with acetic anhydride in the presence of a small amount of sulfuric acid as described in Example 6, the acylated derivative is obtained. The acylated ethyl derivative is then reduced with lithium aluminium hydride following the method described in the foregoing example to obtain 3-(*N,N*-diethylamino) isocamphane. 75

EXAMPLE 4.

Preparation of 3-(*N*-*n*-butylamino) isocamphane.

Normal butyryl chloride (16 ml.) was added in portions with ice cooling to 8.0 g. of *dl*-3-aminoisocamphane, followed by the gradual addition of 80 ml. of 20% sodium hydroxide solution. The mixture was vigorously agitated until reaction had ceased and then diluted with 150 ml. water. After extraction of the reaction mixture with 3 x 80 ml. of benzene, the combined extracts were washed with 2.5N NaOH (75 ml.), water (2 x 100 ml.), 2.5N HCl (75 ml.) and again with 3 x 100 ml. of water. After drying the extract and removing the solvent, *dl*-3-(*N*-butylamino) isocamphane, melting point 75–76.5° C. was obtained. 80

Anal. Calcd. for $C_{14}H_{27}NO$ (223.35):

C, 75.28; H, 11.28; N, 6.27

Found: C, 75.49; H, 11.01; N, 6.33 95

To a solution of 2.62 g. (0.069 mole) of $LiAlH_4$ in 150 ml. absolute ether was added with stirring 7.0 g. (0.031 mole) of *dl*-3-(*N*-butylamino) isocamphane dissolved in 60 ml. of dry ether. After gently refluxing overnight, the mixture was treated with 13 ml. of water, and the powdery metal hydroxide mixture which formed was filtered and washed with ether. After washing the ether extract with water (3 x 50 ml.), it was dried (anhydr. $MgSO_4$), and concentrated to a volume of about 30 ml. The hydrochloride salt was then precipitated with an ethereal HCl solution (about 8 ml.; pH 3) and the product filtered and washed with ether until free of acid. Upon crystallizing the product from 400 ml. methylisobutylketone pure *dl*-3-(*N*-*n*-butylamino) isocamphane hydrochloride melting at 212.5–213.5° C. was obtained. 100

Anal. Calcd. for $C_{14}H_{27}N.HCl$ (245.83):

C, 68.40; H, 11.48; N, 5.70; Cl, 14.43

Found: C, 68.75; H, 11.72; N, 5.96; Cl, 14.1 105

EXAMPLE 5.

Preparation of 3-(*N*-3,3-dimethylbutylamino) isocamphane. 120

To 6.0 g. of *dl*-3-aminoisocamphane cooled in ice-water was added a total of 12.0 ml. *t*-butylacetylchloride in 3 ml. portions with swirling over a period of about 10 minutes. To the thick slurry was then gradually added a total of 60 ml. of 20% NaOH with good agitation. After shaking for 2–3 hours, the reaction mixture was diluted with 200 ml. 125

water and extracted with 3 x 60 ml. benzene. The benzene extracts were washed with 2.5N NaOH (50 ml.) water (2 x 80 ml.) 2.5N HCl (50 ml.) and finally with 4 x 70 ml. water.

- 5 After drying over magnesium sulfate and removing the solvent, the crystalline *dl*-3-(N-3,3-dimethylbutyrylamino) isocamphane melting at 106–8° C. was obtained.

- 10 Crystallization from hot Skellysolve C (b.p. 95–100° C.) gave pure product, melting at 107–108.5° C.

Anal. Calcd. for $C_{16}H_{29}NO$ (251.40):

C, 76.44; H, 11.63; N, 5.57

Found: C, 76.13; H, 11.48; N, 5.59

- 15 To a mixture of 6.1 g. (0.16 mole) of lithium aluminium hydride in 350 ml. absolute ether was added 6.77 g. (0.027 mole) of *dl*-3-(N-3,3-dimethylbutyrylamino) isocamphane dissolved in 80 ml. ether. After refluxing for about 19 hours, the reaction mixture was de-
- 20 composed by the gradual addition of 30 ml. water and the inorganic salts filtered and washed with ether. The ether filtrate was washed with water (3 x 100 ml.) and dried over magnesium sulphate. After concentrating
- 25 to a small volume the hydrochloride salt was precipitated by the addition of a cold saturated ethereal hydrogen chloride solution (ca. 10 ml.) until acid to Congo paper. The precipitated
- 30 *dl*-3-(N-3,3-dimethylbutylamino) isocamphane was filtered and washed with ether. After crystallizing from hot methylisobutyl ketone the product was found to melt at 233–4° C. with decomposition.

- 35 Anal. Calcd. for $C_{16}H_{29}N.HCl$ (273.89):

C, 70.16; H, 11.78; N, 5.12

Found: C, 70.25; H, 11.86; N, 5.31

EXAMPLE 6.

- 40 Preparation of trimethylammonium iodide of 3-aminoisocamphane.

- To a solution of 4.68 g. (0.021 mole) of *dl*-3-(N,N-dimethylamino)-isocamphane hydrochloride in 100 ml. water was added with ice cooling 8.4 ml. of 2.5N NaOH and the free amine extracted from the mixture
- 45 with 4 x 50 ml. benzene. After washing the combined benzene extracts with a small amount of water (25 ml.) and drying over anhydrous magnesium sulphate, solvent was removed *in vacuo*. The free amine so obtained
- 50 was dissolved in 10 ml. absolute ethanol and 3 ml. of methyl iodide and 3 ml. of a 1% solution of sodium ethylate in ethanol (freshly prepared) were added. The mixture was re-
- 55 fluxed on the steam bath for about 18 hours and the white crystalline precipitate filtered, washed with ethanol (4 x 1 ml.) and then ether. After air-drying the crude solid was triturated with chloroform (10 x 10 ml.). Evap-
- 60 oration of the chloroform extract yielded the quaternary salt, the trimethylammonium iodide of *dl*-2-aminoisocamphane melting at 181–182° C. with decomposition.

- 65 This product crystallizes from water in stout needles.

EXAMPLE 7.

Preparation of *d*-3-(N-methylamino) isocamphane and *l*-3-(N-methylamino) isocamphane.

To a cold solution of 25.0 grams of *dl*-3-(N-methylamino) isocamphane hydrochloride in 200 ml. of water was added 50 ml. of 2.5N sodium hydroxide. The free base was extracted with 2 x 100 ml. portions of ether. The ether solution was dried over sodium sulphate to yield 21.0 grams of free amine.

A solution of the amine (21.0 g.) so obtained in 210 ml. of acetone was mixed with a solution of 26.5 grams of *d*-camphor-sulphonic acid in 200 ml. of acetone. The first crop of crystals was filtered after standing at room temperature for two hours. The *d*-3-(N-methylamino)-isocamphane-*d*-camphor-sulphonate so obtained melted at 213–214° C. and had a rotation, $[\alpha]^{25}_D = +31.2$ (C=2% in absolute ethanol). Recrystallization failed to increase the specific rotation or the melting point of the salt.

The *d*-(3-N-methylamino) isocamphane hydrochloride was prepared by treating the *d*-camphor sulphonic acid salt with an equivalent of 2.5 N sodium hydroxide, extracting the free base with ether, and treating the dried ethereal solution with a solution of hydrogen chloride in ether. The *d*-3-(N-methylamino) isocamphane hydrochloride after two recrystallizations from isopropanol had a rotation $[\alpha]^{25}_D = +20.6$ (C=1.57 chloroform) and melted at 262–264° C., dec.

The *l*-3-(N-methylamino) isocamphane-*d*-camphor sulfonate can be recovered from the mother liquors from which the *d* form was separated by evaporating these liquors under diminished pressure. Conversion of the salt to the free base and treatment of the free base with a solution of hydrogen chloride in ether afforded the *l*-3-(N-methylamino) isocamphane hydrochloride which can be purified further by recrystallization from isopropanol to obtain a product having a rotation of about –20°.

The N-alkyl derivatives of 3-aminoisocamphane and their acid salts as well as the quaternary ammonium salts of the tertiary amines, are useful new chemical compounds having valuable pharmacological properties. Thus, 3-(N-methylamino) isocamphane has been found to be a valuable ganglionic blocking agent which inhibits the transmission of nerve impulses through both the sympathetic and parasympathetic ganglia of the autonomic nervous system. This compound was found to be about twice as active on a mg./kg. basis and substantially longer in duration of action than is hexamethonium bromide based on studies in the anaesthetized bilaterally vagotomized dog making use of (1) stimulation of the peripheral end of the cut vagus, (2) carotid occlusion and, (3) the response to the injection of nicotine.

The N-alkyl derivatives of 2-aminoisocamphane in amounts ranging from about 10—50 mgs. per day can be administered both orally and by injection for use as a ganglionic blocking agent. The following are examples of pharmaceutical compositions containing compounds of the invention.

EXAMPLE 8.

- For oral administration the novel compounds of this invention can be administered in suitable forms such as tablets or capsules containing suitable extenders and excipients which can be prepared in accordance with procedures well known in the art. For example, tablets containing about 10 mg. each of 3-(N-methylamino) isocamphane hydrochloride can be prepared as follows:

105 g. 3-(N-methylamino) isocamphane hydrochloride
291.9 g. lactose
115.5 g. dicalcium phosphate
31.5 g. starch
10.5 g. accacia gum
10.5 g. talc
2.1 g. magnesium stearate

- The isocamphane compound, lactose, dicalcium phosphate, starch and accacia gum were mixed and passed through a No. 60 bolt. After adding the talc and magnesium stearate to the bolted material, the mixture was slugged to form granules. The granules were then passed through a No. 12 and then a No. 18 sieve, and the fines reslugged to form granules of the desired size. The granules were then compressed into tablets.

EXAMPLE 9.

- Solutions of the N-alkylated amines suitable for parenteral injection are also prepared in accordance with procedures well known in the art. For example, the following are formulations of suitable solutions:

(a) 10% Solution
10% 3-(N-methylamino) isocamphane hydrochloride

0.9% sodium chloride
q.e.s. pyrogen-free water pH-5.45

(b) 1% Solution
1% 3-(N-methylamino) isocamphane hydrochloride

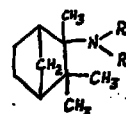
0.57% sodium chloride
0.15% methylparaban
0.02% propylparaban
q.e.s. pyrogen-free water pH-5.35

- In the above described formulations, the 3-(N-methylamino) isocamphane hydrochloride can be replaced by other acid salts of the isocamphane, or by other alkylated derivatives of 3-aminoisocamphane. Alternatively, quaternary ammonium salts of the tertiary aminoisocamphane compounds, such as methane halide salts, for example, the methyl chloride or methyl bromide, or the methosulfate can be used. Examples of such quaternary ammonium salts that might be mentioned are the methiodide of 3-(N,N-dimethylamino)

isocamphane, the methochloride of 3-(N,N-diethylamino) isocamphane, and the methosulphate of 3-(N,N-diisopropylamino) isocamphane.

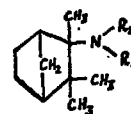
WHAT WE CLAIM IS:—

1. A compound having the formula:



where R is a C_{1-8} alkyl group and R_1 is a C_{1-8} alkyl group or a hydrogen atom.

2. A 3-[N-(C_{1-8} alkyl)-amino] isocamphane.
3. 3-(N-methylamino) isocamphane.
4. 3-(N,N-dimethylamino) isocamphane.
5. 3-(N-n-butylamino) isocamphane.
6. 3-(N-3,3-dimethylbutylamino) isocamphane.
7. 3-(N-ethylamino) isocamphane.
8. 3-(N,N-diethylamino) isocamphane.
9. d-3-(N-methylamino) isocamphane.
10. l-3-(N-methylamino) isocamphane.
11. An acid-addition salt of a compound as claimed in any one of claims 1—10.
12. The hydrochloride of a compound as claimed in any one of claims 1—10.
13. A quaternary ammonium salt of 3-aminoisocamphane.
14. The trimethylammonium iodide of 3-aminoisocamphane.
15. The process that comprises reducing a compound having the general formula:



in which R_1 is a hydrogen atom or a C_{1-8} alkyl radical and R_2 is an acyl radical derived from a C_{1-8} aliphatic carboxylic acid, to produce a compound as claimed in claim 1.

16. A process as claimed in claim 15 in which the reduction is effected by means of an alkali-metal aluminium hydride.
17. A process as claimed in claim 16 in which the reduction is effected by means of lithium aluminium hydride.
18. A process as claimed in claim 16 or 17, in which about 2 moles of the aluminium hydride are used to every mole of the isocamphane starting material.
19. A process as claimed in any one of claims 15—18, in which the reduction is carried out in solution in ethyl ether.
20. A process as claimed in any one of claims 15—19 in which the compound as claimed in claim 1 is recovered in the form of an acid-addition salt.
21. A process as claimed in any one of claims 15—20 in which the starting material

The N-alkyl derivatives of 2-aminoisocamphane in amounts ranging from about 10—50 mgs. per day can be administered both orally and by injection for use as a ganglionic blocking agent. The following are examples of pharmaceutical compositions containing compounds of the invention.

EXAMPLE 8.

For oral administration the novel compounds of this invention can be administered in suitable forms such as tablets or capsules containing suitable extenders and excipients which can be prepared in accordance with procedures well known in the art. For example, tablets containing about 10 mg. each of 3-(N-methylamino) isocamphane hydrochloride can be prepared as follows:

105 g. 3-(N-methylamino) isocamphane hydrochloride

291.9 g. lactose

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31.5 g. starch

10.5 g. accacia gum

10.5 g. talc

2.1 g. magnesium stearate

The isocamphane compound, lactose, dicalcium phosphate, starch and accacia gum were mixed and passed through a No. 60 bolt. After adding the talc and magnesium stearate to the bolted material, the mixture was slugged to form granules. The granules were then passed through a No. 12 and then a No. 18 sieve, and the fines reslugged to form granules of the desired size. The granules were then compressed into tablets.

EXAMPLE 9.

Solutions of the N-alkylated amines suitable for parenteral injection are also prepared in accordance with procedures well known in the art. For example, the following are formulations of suitable solutions:

(a) 10% Solution

10% 3-(N-methylamino) isocamphane hydrochloride

0.9% sodium chloride

q.e.s. pyrogen-free water pH-5.45

(b) 1% Solution

1% 3-(N-methylamino) isocamphane hydrochloride

0.57% sodium chloride

0.15% methylparaban

0.02% propylparaban

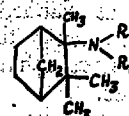
q.e.s. pyrogen-free water pH-5.35

In the above described formulations, the 3-(N-methylamino) isocamphane hydrochloride can be replaced by other acid salts of the isocamphane, or by other alkylated derivatives of 3-aminoisocamphane. Alternatively, quaternary ammonium salts of the tertiary aminoisocamphane compounds, such as methane halide salts, for example, the methyl chloride or methyl bromide, or the methosulfate can be used. Examples of such quaternary ammonium salts that might be mentioned are the methiodide of 3-(N,N-dimethylamino)

isocamphane, the methochloride of 3-(N,N-diethylamino) isocamphane, and the methosulphate of 3-(N,N-diisopropylamino) isocamphane.

WHAT WE CLAIM IS:

1. A compound having the formula:



where R is a C₁₋₃ alkyl group and R₁ is a C₁₋₃ alkyl group or a hydrogen atom.

2. A 3-[N-(C₁₋₃ alkyl)-amino] isocamphane.

3. 3-(N-methylamino) isocamphane.

4. 3-(N,N-dimethylamino) isocamphane.

5. 3-(N-n-butylamino) isocamphane.

6. 3-(N-3,3-dimethylbutylamino) isocamphane.

7. 3-(N-ethylamino) isocamphane.

8. 3-(N,N-diethylamino) isocamphane.

9. d-3-(N-methylamino) isocamphane.

10. l-3-(N-methylamino) isocamphane.

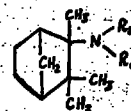
11. An acid-addition salt of a compound as claimed in any one of claims 1—10.

12. The hydrochloride of a compound as claimed in any one of claims 1—10.

13. A quaternary ammonium salt of 3-aminoisocamphane.

14. The trimethylammonium iodide of 3-aminoisocamphane.

15. The process that comprises reducing a compound having the general formula:



in which R₁ is a hydrogen atom or a C₁₋₃ alkyl radical and R^o is an acyl radical derived from a C₁₋₃ aliphatic carboxylic acid, to produce a compound as claimed in claim 1.

16. A process as claimed in claim 15 in which the reduction is effected by means of an alkali-metal aluminium hydride.

17. A process as claimed in claim 16 in which the reduction is effected by means of lithium aluminium hydride.

18. A process as claimed in claim 16 or 17, in which about 2 moles of the aluminium hydride are used to every mole of the isocamphane starting material.

19. A process as claimed in any one of claims 15—18, in which the reduction is carried out in solution in ethyl ether.

20. A process as claimed in any one of claims 15—19 in which the compound as claimed in claim 1 is recovered in the form of an acid-addition salt.

21. A process as claimed in any one of claims 15—20 in which the starting material



has been prepared by a process claimed in the specification of our copending application No. 2168/58 (Serial No. 804,880).

22. A process as claimed in any one of claims 15—21, involving the conversion of 3-(N-formylamino)-isocamphane to 3-(N-methylamino)-isocamphane.

23. A process as claimed in any one of claims 15—21, involving the conversion of 3-(N-acetylamino)-isocamphane to 3-(N-ethylamino)-isocamphane.

24. A process as claimed in any one of claims 15—21, involving the conversion of 3-(N-butylamino)-isocamphane to 3-(N-butylamino)-isocamphane.

25. A process as claimed in any one of claims 15—21, involving the conversion of 3-(N-3,3-dimethylbutylamino)-isocamphane to 3-(N-3,3-dimethylbutylamino)-isocamphane.

26. A process as claimed in any one of claims 15—21, involving the conversion of 3-(N-ethyl-N-acetylamino)-isocamphane to 3-(N-diethylamino)-isocamphane.

27. A process as claimed in claim 15, substantially as described in Examples 1, 3, 4 or 5 hereinbefore.

28. The process that comprises reacting 3-aminoisocamphane with a C_{1-8} aliphatic aldehyde and hydrogen in the presence of a hydrogenation catalyst to produce a compound as claimed in claim 1, in which R_1 is hydrogen and R contains the same number of carbon atoms as the aldehyde.

29. A process as claimed in claim 28 in which the reaction is continued for a sufficient period to produce a compound as claimed in claim 1 in which R and R_1 are both alkyl groups containing the same number of carbon atoms as the aldehyde.

30. A process as claimed in claim 28 or 29 in which the 3-aminoisocamphane has been prepared by a process described and claimed in the specification of our copending application No. 2168/58 (Serial No. 804,880).

31. A process as claimed in any one of claims 28—30 in which the hydrogenation catalyst is of the platinum group.

32. A process as claimed in claim 31, in which the catalyst is palladium on charcoal.

33. A process as claimed in any one of claims 27—32, in which the reaction is carried out in the presence of water.

34. A process as claimed in any one of claims 28—33 in which the aldehyde is formaldehyde.

35. A process as claimed in claim 28, sub-

stantially as described in Example 2 hereinbefore.

36. The process that comprises reacting a compound as claimed in claim 1 in which both R and R_1 are C_{1-8} alkyl groups with an alkyl halide to produce a quaternary ammonium salt of 3-aminoisocamphane.

37. The process that comprises reacting 3-(N,N-dimethylamino)-isocamphane with methyl iodide to produce the trimethylammonium iodide of 3-aminoisocamphane.

38. A process as claimed in claim 36, substantially as described in Example 6 hereinbefore.

39. The process that comprises resolving a racemic form of a compound as claimed in claim 1 by reacting it with an optically active acid; separating the salts so produced, and regenerating the compound by treatment with a base.

40. The process that comprises reacting 3-(N-methylamino)-isocamphane with *d*-camphorsulphonic acid, separating the salts so produced and forming *d*-3-(N-methylamino)-isocamphane and *l*-3-(N-methylamino)-isocamphane from the salts by treatment with a base.

41. A process as claimed in claim 39 substantially as described in Example 7 hereinbefore.

42. A compound as claimed in claim 1, when prepared by a process in accordance with any one of claims 15—35 or an obvious chemical equivalent of such a process.

43. A compound as claimed in claim 13, when prepared by a process in accordance with any one of claims 36—38 or an obvious chemical equivalent of such a process.

44. An optically active form of a compound as claimed in claim 1, when prepared by a process in accordance with any one of claims 39—41 or an obvious chemical equivalent of such a process.

45. A pharmaceutical composition containing, as active ingredient, a compound as claimed in any one of claims 1—14 and 42—44, together with a pharmaceutical carrier.

46. A composition as claimed in claim 45, in orally administrable form.

47. A composition as claimed in claim 45, in a form suitable for parenteral injection.

48. A composition as claimed in claim 45, substantially as described in Example 3 or 9(a) or 9(b) hereinbefore.

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