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(19)

(54) N-(2-AMINOCYCLOALKYL) AMIDES

(71) We, THE UPJOHN COMPANY, a corporation organized and existing under the laws of the State of Delaware, United States of America, of 301 Henrietta Street, Kalamazoo, State of Michigan, 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 relates to novel N-(*trans*-2-aminocycloalkyl)aralkanoylamides, to processes for their preparation, and to compositions containing them.

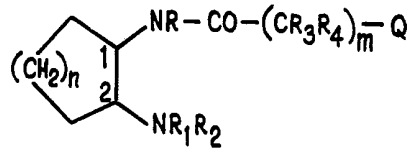
F. Winternitz *et al., Bull. Soc. Chim.,* (France), 382 (1956), disclose the compound N-(2-dimethylaminocyclohexyl)benzamide for the purpose of obtaining a solid derivative of a liquid diamino compound but that article contains no reference to biological data.

N. J. Harper *et al., J. Chem. Soc.* 4280 (1964), disclose some N-[2-(dimethylaminomethyl)cyclohexyl]benzamides. The stereochemistry of these compounds is not indicated with certainty. In a hot plate test. using pethidine (meperidine) as standard (activity = 1) the analgesic activity of N-[2-(dimethylaminomethyl)cyclohexyl]-*p*-chlorobenzamide was 0.22. In the electroshock test it was 35% as active as diphenylhydantoin, but all of the compounds disclosed lacked activity in the anti-amphetamine and antireserpine tests.

R. T. Brittain *et al., Brit. J. Pharm., 49,* 158P (1973) and N. J. Harper *et al., J. Med Chem., 17,* pp. 1188—1193 (1974), disclose some 1-amino-1-benzamidomethylcyclohexane analgesic compounds.

U.S. Patent Specification No. 3,510,492 discloses some 2-anilino- and 2-anilinomethyl-cycloalkylamines as antidiabetic drugs and some (2-aminocycloalkyl)carbonylanilides as intermediates in preparing the active compounds. U.S. Patent Specification No. 3,647,804 discloses some 2-aminocycloalkane-1-carboxamides and diamines which are said to be useful pharmaceutical drugs owing to their hypoglycemic, sedative and anti-inflammatory activities.

The novel compounds of this invention have the formula



I

wherein the 1- and 2-substituents are in the relative *trans*-configuration;

R is hydrogen or C_{1-3} alkyl;

either R_1 is hydrogen or C_{1-3} alkyl and R_2 is hydrogen, C_{1-6} alkyl, $-CH_2CF_3$, C_{3-6} alkenyl or C_{2-5} hydroxyalkyl (but is not alk-1-enyl or α-hydroxyalkyl), C_{3-6} cycloalkyl, (C_{3-4} cycloalkyl)methyl or phenyl (C_{1-3} alkyl) or NR_1R_2 is optionally 3-substituted azetidino, optionally 3-substituted pyrrolidino or optionally 3- or 4-substituted piperidino (in which any substituent is hydroxy, C_{1-3} alkoxy or C_{1-3} alkanoyloxy), imidazolino, tetrahydropyrimidino, piperazino, N-(C_{1-3} alkyl)-piperazine or a saturated 7-membered heterocyclic ring containing 5 carbon atoms and 2 isolated nitrogen atoms;

either m is one and $-CR_3R_4-$ is $-CH(CH_3)-$, $-C(CH_3)_2$ or 1,1-cyclopropylene or m is an integer of from one to 4 and $-CR_3R_4-$ is $-CH_2-$;

n is an integer of from one to 8; and

Q is 1-naphthyl; 2-naphthyl; phenyl; phenyl substituted by one azido, phenyl, trifluoromethyl or C_{1-3} alkoxy radical; or phenol substituted up to 3 times by substituents selected from fluorine, chlorine and bromine atoms and C_{1-3} alkyl radicals; provided that Q is not phenyl when R is hydrogen;

and include pharmaceutically acceptable salts thereof.

The compounds of this invention have been found to possess analgesic and narcotic antagonist properties while also having low apparent physical dependence liability. A pharmaceutical composition according to the invention comprises a compound of the invention in association with a pharmaceutically acceptable carrier. Such compositions may be provided in unit dosage form. They may be used for the relief of pain regardless of origin, for example, traumatic pain, bone pain, cancer pain, post-surgical pain, homotopic pain, menstrual pain and headache.

The compounds of formula I, including their acid addition salts, may be isolated in their crystallised state as solvates, i.e. with a discrete quantity of solvent such as water, ethyl acetate or methanol, physically associated therewith and thus removable without effective alteration of the chemical entity *per se*.

It will be appreciated that the compounds of the invention can exist in *trans-d*- or *trans-l*-stereoisomeric configuration, as well as *trans-dl*-configuration. Methods of preparing the various isomeric or racemic forms of the compounds are described below.

In this specification, "C_{1-3} alkyl" means methyl, ethyl, n-propyl or isopropyl. "C_{1-6} alkyl" includes the above alkyl groups as well as butyl, pentyl and hexyl groups and their various isomeric forms. "C_{3-6} alkenyl" includes allyl, 2- or 3-butenyl, (2,3 or 4)-pentenyl and (2,3,4 or 5)-hexenyl groups. "C_{3-6} cycloalkyl" means cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. "C_{1-3} alkoxy" means methoxy, ethoxy, propyloxy or isopropyloxy. "C_{1-3} alkanoyloxy" means formyloxy, acetoxy or propionoxy.

One preferred group of the compounds of this invention comprises those of formula I wherein R, R_1 and R_2 are each C_{1-3} alkyl; R_3 and R_4 are each hydrogen; n is 2; m is 1; Q is phenyl optionally substituted by an azido group or, preferably, by at least one fluorine, chlorine or bromine atom; including the pharmacologically acceptable salts thereof. Examples of compounds of this group include N-(*trans*-2-dimethylaminocyclohexyl)-N-methyl-*p*-bromophenylacetamide; N-(*trans*-2-dimethylaminocyclohexyl)-N-methyl-3',4'-dichlorophenylacetamide; and N-(*trans*-2-dimethylaminocyclohexyl)-N-methyl-*p*-azidophenylacetamide, and the pharmaceutically acceptable salts thereof.

Another preferred group of the compounds of the invention comprises those of formula I wherein R is C_{1-3} alkyl; NR_1R_2 is azetidino, pyrrolidino or piperidino; R_3 and R_4 are each hydrogen; n is 2; m is 1; and Q is phenyl substituted by an azido group or at least one fluorine, chlorine or bromine atom; including the pharmacologically acceptable salts thereof. Examples of compounds of this group include N-(*trans*-2-pyrrolidinocyclohexyl)-N-methyl-*p*-bromophenylacetamide, N-(*trans*-2-pyrrolidinocyclohexyl)-N-methyl-3',4'-dichlorophenylacetamide; and N-(*trans*-2-piperidinocyclohexyl)-N-methyl-*p*-azidophenylacetamide, and pharmacologically acceptable salts thereof.

Another preferred group of compounds of this invention comprises those of formula I wherein R is C_{1-3} alkyl; NR_1R_2 is azetidino, pyrrolidino or piperidino; R_3 is hydrogen; R_4 is methyl; n is 2; m is 1; and Q is phenyl substituted by an azido group or at least one fluorine, chlorine or bromine atom; including the pharmacologically acceptable salts thereof. Examples of compounds in this group include N-methyl-N-(*trans*-2-pyrrolidinocyclohexyl)-2-(3',4'-dichlorophenyl)-propionamide; N-methyl-N-(*trans*-2-pyrrolidinocyclohexyl)-2-(*p*-bromophenyl)propionamide; and N-ethyl-N-(*trans*-2-azetidinocyclohexyl)-2-(*p*-azidophenyl)propionamide; and the pharmacologically acceptable salt thereof.

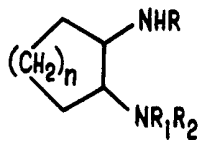
Another preferred group of compounds of formula I within this invention comprises those wherein R, R_1 and R_2 are each C_{1-3} alkyl; R_3 and R_4 are each hydrogen; n is 2; m is 1; and Q is phenyl substituted by at least one C_{1-3} alkyl radical, and preferably by 3 methyl groups. An example of such compounds is N-(*trans* - 2 - dimethylaminocyclohexyl) - N - methyl - 2',4',6' - trimethylphenylacetamide. Other compounds of the invention are N-(*trans*-2-diethylaminocyclohexyl)-3',5'-dimethylphenylacetamide and N-(*trans*-2-dipropylaminocyclohexyl)-*p*-propylphenylacetamide.

Preferred compounds of formula I which have larger ring systems include:

(A) those wherein Q is 1-naphthyl or 2-naphthyl; R, R_1 and R_2 are each C_{1-3} alkyl; R_3 and R_4 are each hydrogen; n is 2 and m is 1. Examples of compounds of this preferred group are N-(*trans*-2-dimethylaminocyclohexyl)-N-methyl-(1-naphthyl)acetamide; and N-(*trans*-2-dimethylaminocyclohexyl)-N-methyl-(2-naphthyl)acetamide; and

(B) those wherein n is 3 to 8, preferably 3 or 4; R, R_1 and R_2 are each C_{1-3} alkyl; R_3 and R_4 are each hydrogen; m is 1; and Q is phenyl substituted by an azido group or at least one C_{1-3} alkyl group or, preferably, with at least one fluorine, chlorine or bromine atom; including the pharmacologically acceptable salts thereof. Examples of these compounds include N-(*trans*-2-dimethylaminocycloheptyl)-N-methyl-*p*-bromophenylacetamide; N-(*trans*-2-dimethylaminocyclooctyl)-N-methyl-*p*-bromophenylacetamide; N-(*trans*-2-diethylaminocyclooctyl)-N-methyl-*p*-azidophenyl)acetamide; N-(*trans*-2-dipropylaminocyclododecyl)-N-methyl-3',4'-dichlorophenylacetamide; N-(*trans*-2-dimethylaminocycloheptyl)-N-methyl-*p*-trifluoromethylphenylacetamide, and the pharmacologically acceptable salts thereof.

In general, compounds of this invention can be prepared by reacting the appropriate 1,2-*trans*-cycloaliphatic diamine of formula II



II

wherein R, R_1, R_2 and n are as defined above, with a carbonyl compound of formula III

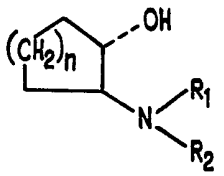
$$Z—CO—(CR_3R_4)_m—Q \qquad III$$

wherein R_3, R_4, m and Q are as defined above and Z is imidazolyl, chlorine or bromide, in an organic solvent for the reactants, preferably in a cyclic ether solvent such as tetrahydrofuran (THF) or dioxane, until the compound of this invention is produced. The reactants can be mixed in substantially equimolar proportions to effect formation of the desired product (I), but if one of the reactants is more expensive than the other, it is sometimes preferred to use a stoichiometric excess of the less expensive reactant to ensure that substantially all of the more expensive reactant is consumed in the reaction. The reaction will proceed at ambient temperature for most combinations of reactants, but for some combinations of reactants, variations from the initial to final reaction conditions may vary between −25°C. and reflux temperature of the mixture depending on, for example, the reactivity of the reactants, the desired reaction time, the solvent being used and the molar proportions.

When the reaction has proceeded to substantial completion, the product (I) can be recovered from the reaction mixture by known procedures. For example, the reaction mixture can be evaporated, under vacuum, if desired, to remove

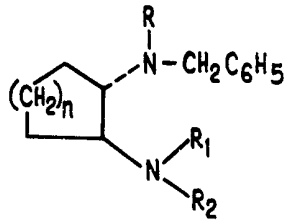
solvent and other volatiles, leaving the product, often as an oil, mixed with a small amount of solvent and any unreacted or unvolatilized starting materials. This residual mixture can be taken up in a solvent such as ethyl ether, washed with salt solution such as saturated sodium bicarbonate solution and with water, separated from the aqueous phases and dried over a water absorbent such as sodium sulfate or magnesium sulfate and then evaporated to leave the more pure product as an oil or crystalline material. Addition of hydrochloric acid (hydrogen chloride gas) or other economical acid such as sulfuric, maleic, naphthalene-sulfonic, *p*-toluene-sulfonic or oxalic acid in a suitable solvent, such as diethyl ether or methanol, converts the oil product to the corresponding salt form which crystallizes more readily than the free amine form of the product. The amine salt products can be recrystallized from solvent mixtures such as C_{1-3} alkanol/di(C_{1-3} alkyl)ether, e.g., methanol/diethyl ether, to give more easily handled crystalline forms of the product as the amine salts. Examples of such procedures are described in the detailed examples.

The diamines of formula II can be prepared by procedures known in the art. For example, amines of formula II in which R is C_{1-3} alkyl and R_1 and R_2 are as defined above, except that when R_1 and R_2 are taken separately, R_2 is not benzyl or C_{3-6} alkenyl can be prepared by reacting the respective 1,2-cycloalkane epoxide with the amine HNR_1R_2 wherein R_1 and R_2 are as defined immediately above to form the 2-aminocycloalkanol of the formula



(V)

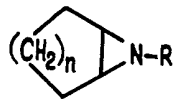
wherein n, R_1, and R_2 are as defined immediately above, and then reacting this aminocycloalkanol intermediate (V) first with a C_1 to C_6-alkanesulfonyl halide, e.g., with methanesulfonyl chloride, and then with a benzylamine of the formula $C_6H_5CH_2NHR$ where R is C_{1-3} alkyl, to form a compound of the formula



(VI)

wherein n, R_1 and R_2 are as defined immediately above, and then hydrogenolyzing this diamine (VI) with hydrogen in the presence of a palladium on charcoal catalyst and acid to remove the benzyl group.

Diamines of formula II may also be prepared by reacting a bicyclic aziridine of formula VII



VII

wherein R is C_{1-3} alkyl and n is as defined above, with an amine of the formula NHR_1R_2 wherein R_1 and R_2, or NR_1R_2, are as defined above. This synthesis is applicable whether the 2-amino group in the saturated cycloaliphatic ring is a tertiary, secondary or primary amino group, and is required when this 2-amino group is C_{3-6} alkenyl.

Processes for preparing the carbonyl compounds of formula III are known. See, for example, R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry* (1953), John Wiley and Sons, Chapter 17, p. 546 et seq. Compounds of formula III in which Z is imidazolyl can be prepared *in situ* by reacting carbonyldiimidazole with an acid of the formula

$$HOOC—(CR_3R_4)_{m-q}$$

wherein R_3, R_4, m and q are as defined above, in an organic solvent.

Acid addition salts of the invention can be prepared by reacting a Formula I free base with a stoichiometric amount of an acid, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, lactic acid, citric acid, succinic acid, benzoic acid, salicyclic acid, pamoic acid, cyclohexanesulfamic acid, methanesulfonic, naphthalenesulfonic, *p*-toluenesulfonic maleic, fumaric or oxalic acid. The reaction can be carried out in aqueous or organic liquid solvent such as diethyl ether or ethyl acetate. Non-aqueous media are preferred. When it is desired to obtain optically resolved products in crystalline form, it may be more convenient to form salts such as maleates, citrates or pamoates rather than the inorganic acid addition salts, such as the hydrochlorides. Also, whereas oxalic acid can be used to get the amino-amide product into a more easily handled solid form, it would preferably not be used as a pharmaceutically acceptable salt form of the amido-amide product.

Example of compounds within the scope of this invention, other than those given above, include the *trans*-isomers of the following compounds:

N - [2 - (N' - methyl - N' - (2 - phenylethyl)amino)cyclohexyl] - N - methyl - *p*-bromophenylacetamide;

N - (2 - dimethylaminocyclohexyl) - N - methyl - *p* - trifluoromethylphenylacetamide;

N - [2 - (N' - methyl - N' - cyclopropylmethylamino)cyclohexyl] - 2',4' - dibromophenylacetamide maleate;

N - [2 - (N' - allyl - N' - methylamino)cyclohexyl] - 2',4' - dibromophenylacetamide;

N-(2-dimethylaminocyclohexyl)-N-propyl-*m*-methoxyphenylacetamide;

N-(2-dimethylaminocyclohexyl)-2',4',6'-trimethylphenylacetamide;

N-(2-dimethylaminocyclohexyl)-N-methyl-*p*-methoxyphenylacetamide;

N-(2-dimethylaminocyclohexyl)-N-methyl-2-(*p*-chlorophenyl)propionamide;

N-(2-dimethylamino)cyclohexyl)-N-methyl-*p*-chlorophenylacetamide;

N-(2-dimethylaminocyclohexyl)-(2-naphthyl)acetamide;

N-(2-dimethylaminocyclohexyl)-(1-naphthyl)acetamide;

N - [2 - (N' - methyl - N' - benzylamino)cycloheptyl] - N - ethyl - *p* - bromophenylacetamide;

N-(2-di-n-propylaminocyclodecyl)-N-methyl-2-(p-azidophenyl)propionamide;

N-(2-piperidinocyclododecyl)-N-methyl-*p*-trifluoromethylphenylacetamide;

N-(2-(1-azetidinocyclonoyl)-N-methyl-3',4'-difluorophenylacetamide;

1 - (*p* - methoxyphenyl) - N - [2 - (N' - 3 - hydroxypropyl - N' - methylamino)cyclopentyl] - N - methylcyclopropanecarboxamide;

N-[2-(N'-cyclopropyl-N'-methylamino)cyclohexyl]-*p*-azidophenylacetamide;

N - [2 - (3 - acetoxypyrrolidino)cyclohexyl] - N - methyl - (3',4' - dichlorophenyl acetamide;

N - [2 - (3 - hydroxypyrrolidino)cyclohexyl] - N - methyl - 3',4' - dichlorophenyl amide;

N - [2 - [N' - (2 - hydroxyethyl) - N' - methylamino]cyclohexyl] - N - methyl - *p* - bromophenylacetamide;

N - [2 - (N' - butyl - N' - methylamino)cyclopentyl] - N - methyl - 3',4' - dichloro phenylacetamide;

N - [2 - (3 - hydroxyazetidino)cyclohexyl] - N - methyl - 3',4' - dichlorophenyl - acetamide;

N-[2-diethylaminocyclohexyl)-N-methyl-3',4'-dichlorophenylacetamide;

N - (2 - di - n - propylaminocyclohexyl) - N - methyl - 2',4',5' - trichlorophenyl - acetamide;

N-(2-diethylaminocyclohexyl)-N-methyl-3',4'-dichlorophenylacetamide;

N-[2-(4-methylpiperazino)cyclopentyl]-3',4'-dichlorophenylacetamide;

N-(2-dimethylaminocyclohexyl)-3',4'-dichlorophenylacetamide;

N-(2-dimethylaminocyclohexyl)-3',4'-dibromophenylacetamide;

N-(2-piperidinocycloheptyl)-N-ethyl-3',4'-difluorophenylacetamide;

N - [2 - [N' - methyl - N' - (2 - hydroxyethyl)amino]cyclohexyl] - 3 - (2',4',5' - trichlorophenyl)propionamide;

N - [2 - (N' - methyl - N' - cyclopropylamino)cyclopentyl] - 4 - (3,4 - dichlorophe butyramide; and

N - [2 - (N' - methyl - N' - cyclobutylmethylamino)cyclohexyl] - N - methyl - *p* - azidophenylpropionamide;

and the pharmaceutically acceptable salts thereof.

The pharmaceutical compositions of the invention are useful for local (topical) and systemic administration (oral, rectal and parenteral) in therapy for treating and

alleviating pain in humans and valuable animals, including dogs, cats and other commercially valuable and domestic animals.

The term "dosage unit form" as used in this specification and in the claims refers to physically discrete units suitable as unitary dosages for mammalian subjects, each unit containing a predetermined quantity of the essential active ingredient compound of this invention calculated to produce the desired effect, in combination with the required pharmaceutical means which adapt the said ingredient for systemic administration. Examples of suitable dosage unit forms in accordance with this invention are tablets, capsules and suppositories. Other suitable dosage forms include orally administered liquid preparations in suitable liquid vehicles, sterile preparations in suitable liquid vehicles for intramuscular and intravenous administration, and sterile dry preparations for the extemporaneous preparation of sterile injectable preparations in a suitable liquid vehicle. Suitable solid diluents or carriers for the solid oral pharmaceutical dosage unit forms are selected from lipids, carbohydrates, proteins and mineral solids, for example, starch, sucrose, lactose, kaolin, dicalcium phosphate, gelatin, acacia, corn syrup, corn starch and talc. Capsules, both hard and soft, are filled with compositions of these aminoamide active ingredients in combination with suitable diluents and excipients, for example, edible oils, talc, calcium carbonate and also calcium stearate. Liquid preparations for oral administration are prepared in water or aqueous vehicles which advantageous contain suspending agents, for example, methylcellulose, acacia, polyvinylpyrrolidone and polyvinyl alcohol. In the case of injectable forms, the injectable formulation must be sterile and must be fluid to the extent that easy syringeability exists. Such preparations must be stable under the conditions of manufacture and storage, and ordinarily contain in addition to the basic solvent or suspending liquid, preservatives in the nature of bacteriostatic and fungistatic agents, for example, parabens, chlorobutanol, benzyl alcohol, phenol and thimerosal. In many cases, it is preferable to include osmotically active agents, for example, sugars or sodium chloride in isotonic concentrations. Carriers and vehicles include vegetable oils, ethanol and polyols, for example, glycerol, propylene glycol and liquid polyethylene glycol. Any solid preparations for subsequent extemporaneous preparation of sterile injectable preparations are sterilized, preferably by exposure to a sterilizing gas, for example, ethylene oxide. The aforesaid carriers, vehicles, diluents, excipients, preservatives and isotonic agents constitute the pharmaceutical means which adapt the preparations for systemic administration.

The pharmaceutical dosage unit forms are prepared in accordance with the preceding general description to provide from 0.5 to 350 mg. of the essential active ingredient per dosage unit. The amount of the essential active ingredient provided in the pharmaceutical dosage unit forms is that amount sufficient to obtain analgesic and narcotic antagonist effects within the aforesaid effective non-toxic range. Expressed otherwise, when used systemically, an amount of the essential active ingredient is provided to a recipient within a range from 0.01 to 5 mg. per kg. of body weight of the recipient. Preferred dosages for most applications are 0.05 to 2.0 mg. per kg. of body weight. In a topical semi-solid ointment formulation the concentration of the active ingredient may be 0.1—10%, preferably 0.5—5% in a carrier, such as a pharmaceutical cream base.

The compounds of the invention have an advantage, to a great extent, depending upon the particular compound, of having lower physical dependence liability than known analgesic compounds such as morphone and methadone, as shown by evaluation of representative compounds and those standard analgesic drug compounds in various pharmacological test procedures which measure relative degrees of analgesic and the physical dependence liability of the test compounds in standard laboratory test animals.

Representative examples of these formula I compounds, have ED_{50} values (± percent confidence limit) of less than 75 mg/kg s.c. (subcutaneous administration) in standard laboratory animal analgesic tests such as the tail flick, pinch, and writhing tests, and the more potent of them have ED_{50} values of less than 10 mg/kg (s.c.) in these tests, while at the same time giving quite high values (greater than 100 and often greater than 250 mg/kg s.c.) in the naloxone jumping test thus possessing only low to moderate apparent physical dependence liability as compared to commercial analgesics used as standards. The procedures used to determine these properties of these new compounds were essentially those of Way *et al* ("Simultaneous Quantitative Assessment of Morphine Tolerance and Physical Dependence", *J. Pharmacol. Exp. Ther.*, 167, pp. 1—8 (1969)) and Saalens *et al.*

("The Mouse Jumping Test — A Simple Screening Method to Estimate the Physical Dependence Capacity of Analgesics", *Arch. Int. Pharmacodyn.*, 190, pp. 213—218 (1971)). Statistical effective doses (ED_{50} values) and 95% confidence limits were calculated by the method of Spearman and Karber (Finney, D.J., "Statistical Methods in Biological Assay", Hafner Publ., (1952)).

Known analgesic drugs such as morphine and methadone exhibit analgesic ED_{50} values of less than 2 mg/kg., s.c., respectively, in these standard analgesic tail flick, pinch and writhing tests, but are known to have high apparent physical dependence liability effects, and this is confirmed by their having relatively low naloxone jumping ED_{50} values ranging from 12 to 30 mg/kg s.c. Although other representative compounds of this invention have analgesic potencies somewhat less than the preferred compounds (analgesic activity ED_{50} values up to 70 mg/kg s.c., in these standard tests) they still are characterized by having only low to moderate apparent physical dependence liability.

The following Preparations illustrated the preparation of diamines of formula II. All temperatures are in degrees Centigrade.

Preparation 1.

A. trans-2-methylaminocyclohexanol

Cyclohexene oxide (196.28 g., 2 mole) is added during 30 min. to 40% aqueous methylamine (466 ml., 6 moles) with stirring. The temperature is from 25° to 27° during this addition. During the following 45 min. the temperature rises to 55° and is kept at 50° to 58° by occasional cooling. It is stirred at room temperature for 18 hr., then heated on the steam bath for 2 hrs., cooled and saturated with solid sodium hydroxide (NaOH). The mixture is extracted well with ether, the extract dried over magnesium sulfate ($MgSO_4$) and evaporated through a 9" Vigreux. Distillation at 13 mm gives 241.9 g. (97% yield) of the title compound b.p. 100—101° nmr in $CDCl_3$ (100 MHz) is in accord; Mass spectrum M^+129.

This title compound was reported by Mousseron *et al.*, Bull. Soc. Chim, Fr., 850 (1947) by the reaction of cyclohexene oxide with methylamine for 2 hr. at 110°, b.p. 108—109° (17 mm); HCl salt, m.p. 114—115°.

B. N-Methyl-7-azabicyclo[4.1.0]heptane

Chlorosulfonic acid (162.9 g., 1.4 mole) is added dropwise during 70 min. to a solution of *trans*-2-methylaminocyclohexanol (179.7 g., 1.39 mole) keeping the temperature at 5 to 10°. The thick mixture is stirred for 1.5 hr. at room temperature (raising the stirrer made agitation possible). Ether is decanted, and the product washed once with 300 ml. of ether by decantation. It is then cooled in ice, treated with a solution of 206 g. sodium hydroxide in 1 liter of water (H_2O) (cautiously at first). The mixture is then distilled, while adding H_2O from a dropping funnel to keep the volume constant. About 600 ml. of distillate is collected during 4 hr. The distillate is saturated with solid sodium hydroxide and extracted with ether (8 x 100 ml.). The extract is dried (magnesium sulfate) and ether is distilled through a 9" glass helices column. The title product boils at 70—72° (97 mm); 73 g. (47% yield).

nmr (nuclear magnetic resonance) in $CDCl_3$ (100 MHz) is in accord, Mass spectrum: M^+111; ir (infrared): CH 2960, 2940, 2860; N-alkyl 2760; C—N 1110; other 760 $cm.^{-1}$.

This compound has been prepared by T. Taguchi and M. Eto, JACS 80, 4076 (1958) in 37% yield by the procedure of Paris and Fanta for the synthesis of 7-azabicyclo[4.1.0]heptane; D. E. Paris and P. E. Fanta JACS 74, 3007 (1951) used carbon tetrachloride (CCl_4) in the above-mentioned procedure and steam-distilled the product after refluxing with alkali for 2 hours.

C. trans-N,N-Dimethyl-1,2-cyclohexanediamine

The starting 7-azabicyclo[4.1.0]heptane is best prepared according to the procedure of D. E. Paris and P. E. Fanta, JACS, 74, 3007 (1952) from *trans*-2-aminocyclohexanol with chlorosulfonic acid, followed by heating with aqueous sodium hydroxide. For the reaction with dimethylamine the procedure described in *Bull. Soc. Chim*, France, 382 (1956) was followed.

A mixture of 7-azabicyclo[4.1.0]heptane (12 g., 0.124 mole), 40 ml. of aqueous dimethylamine and 0.2 g. of ammonium chloride (NH_4Cl) is stirred and heated on the steam bath for 18 hr. and partly evaporated at room temperature *in vacuo*. Sodium hydroxide (NaOH) is added and the mixture extracted with ether. The extract is dried ($MgSO_4$) and evaporated. Distillation at 16 mm gives 8.1 g. (46% yield) of the title compound as a colorless oil. nmr in $CDCl_3$ (100 MHz) is in accord. Mass spectrum: M^+142. B.p. 78—79.5° (13 mm Hg).

This compound is also prepared from *trans*-2-dimethylaminocyclohexanol by reaction with chlorosulfonic acid followed by ammonia, according to the procedure in *Helv. Chim. Acta*, 34, 1937 (1951).

Preparation 2.

A. trans-2-dimethylaminocyclohexanol

A mixture of cyclohexene oxide (196.28 g., 2 mole) and 40% aqueous dimethylamine (452 g., 4 mole) is stirred for two hours. An exothermic reaction occurs and the mixture is kept at 50—55° by occasional cooling. It is then stirred at room temperature for 20 hr., heated at 95° for 1 hour and then for additional 1 hour with the condenser in the horizontal position. The mixture is cooled, extracted twice with ether (800 ml., 300 ml.), the ether extract washed with saturated salt solution, dried ($MgSO_4$), and evaporated. Distillation at 15 mm gives 265.1 g. (93% yield), b.p. 82—83°; uv end absorption. ir: OH 3460; N-alkyl 2780; CH 1450; C—O/C—N 1300, 1270, 1185, 1120, 1085, 1060, 1035, 950, 875. nmr in $CDCl_3$ (100 MHz) confirms trans stereochemistry.

This compound was previously prepared from cyclohexene oxide and dimethylamine in benzene at room temperature for 14 days in 95% yield, b.p. 90° (20 mm): J. Chem. Soc., 4835 (1965); or in autoclave: C.A. *67*, 63899 d. Rocz. Chem. *41*, 541 (1967) b.p. 88° (14 mm); also Bull. Soc. Chim. France, 850 (1947): hydrochloride and resolution reported.

B. trans-N,N-dimethyl-1,2-cyclohexanediamine

A solution of *trans*-2-dimethylaminocyclohexanol (58 g., 0.405 mole) prepared in Part A in 80 ml. of THF is added during 10 min. to a suspension of NaH (17.05 g., 0.405 mole of 57% dispersion in mineral oil) in 240 ml. of THF and the mixture is refluxed for 3 hours. It is cooled to 10° and methanesulfonyl chloride (46.39 g., 0.405 mole) added dropwise during 30 min., keeping the temperature below 10°. Benzylamine (86.79 g., 0.81 mole) is then added during 5 min., the solvent evaporated, and heating continued at 95° for 16 hr. NaOH (500 ml. of 20% solution) is added and the mixture heated at 95° for 1 hr., cooled, and extracted with ether (5 × 100 ml.). The ether solution is extracted with 10% HCl (6 × 100 ml.) and backwashed once with ether (discard). The acid extract is cooled, basified with 20% NaOH, and extracted with ether. The ether solution is washed with H_2O, saturated salt solution, dried ($MgSO_4$) and evaporated. Distillation at 0.4 mm gives 61 g.(65% yield) of N,N-dimethyl-N'-benzyl-1,2-cyclohexanediamine, b.p. 112°. It is identical by tlc to the sample prepared by the reaction of benzylamine with *trans*-2-chloro-1-dimethylaminocyclohexane (Procedure III) in Preparation 3.

A solution of the benzylamino compound is hydrogenated in two batches, each containing 30.5 g (0.131 mole), 175 ml. EtOH, 3.4 g Pd-C and 56.5 g. (0.394 mole) of 70% $HClO_4$, at initial pressure of 51.5 p.s.i. for 19 hours. The two reduced batches are combined, filtered through Celite (registered Trade Mark) and evaporated *in vacuo* at 45°. The residue is cooled in ice, basified with 40% KOH to pH 11. The resulting thick suspension is extracted with ether (5 × 200 ml.), the ether extract dried ($MgSO_4$) and evaporated through a 9" Vigreux. The residue is distilled at 13 mm to give 32.5 g. (87% yield), b.p. 77—78.5°. ir and nmr are identical to those of the sample prepared by the reaction of 7-azabicyclo[4.1.0]heptane with dimethylamine (Preparation 1, Part C).

Preparation 3.

A. trans - N' - Benzyl - N,N - dimethyl - 1,2 - cyclohexanediamine, *p*-toluenesulfonate (1:2)

A mixture of *trans* - 1 - chloro - 2 - dimethylaminocyclohexane (56 g., 0.346 mole) and benzylamine (74.15 g., 0.692 mole) is heated at 95° for 17 hr. While still hot, it is poured into a solution of 85 ml. of conc. HCl and 425 ml. of H_2O, cooled, and extracted with ether (discard ether). The acidic solution is cooled in ice, basified with 40% NaOH, and extracted with ether. The ether extract is washed with H_2O, saturated salt solution, dried ($MgSO_4$) and evaporated. Distillation at 0.3 mm. gave 35.17 g. (44% yield). b.p. 114—116°.*uv*:sh 209 nm (ε 11,100); λmax 247 (430); 252 (418); 258 (386); 264 (263); sh 267 (165); sh 278 (49); sh 288 (33). *ir*:NH 3290; = CH 3020; CH 2920, 2850, 2820; N-alkyl 2780; C = C/NH def. 1600, 1585, 1495, 1455; (C—N 1030; aromatic 745, 735, 700. nmr in $CDCl_3$ is in accord. Mass spectrum M^+28(small).

The salt is prepared with 2 moles of p-TSA in ether and crystallized from MeOH-ether, m.p. 158—159°.*uv*;γmax 211 nm (ε 22,750); 219 (24,050); sh 222

(23,900); sh 252 (502); 256 (640); 261 (686); 267 (496); sh 271 (248). *ir.* $\overset{+}{N}H$ 3110—2600; $\overset{+}{N}H_2$/C=C 1590, 1520, 1495; SO_3—/C—N/other 2235, 1220, 1170, 1150, 1120, 1030, 1005, 685; aromatic 820, 750, 700. nmr in D_2O (100 MHz) is in accord. Mass spectrum M^+232.

Anal. Calcd. for $C_{15}H_{24}N_2 \cdot 2pTSA$: C, 60.39; H, 6.99; N,4.86; S, 11.12.

Found: C, 60.39; H, 7.13; N, 4.79; S, 11.28.

B. *trans* - N',N' - dimethyl - 1,2 - cyclohexanediamine

The *p*-tolunenesulfonate salt from part A (above) is basified with aq. NaOH to give the free diamine base as an oil. A solution of this oil is hydrogenated over 10% Pd-C and 70% $HClO_4$ and further treated as in Preparation 7 to give the title diamine.

Preparation 4.

A mixture of N - methyl - azabicyclo[4.1.0]heptane (8.64 g., 0.078 mole), prepared as in Preparation 1, Part B, N - allyl - N - methylamine (11.05 g., 0.156 mole), 16.6 ml. of water, and 0.2 g. of ammonium chloride is stirred and heated in an oil bath maintained at 115—117° for 16 hr. The mixture is cooled, saturated with solid sodium hydroxide and extracted well with ether. The ether extract is dried ($MgSO_4$), evaporated through a Vigreux column, and the product residue of N,N - dimethyl - N - ethyl - *trans* - 1,2 - cyclohexanediamine distilled at 13 mm; b.p. 104—105°, 7.27 g. (15% yield).

nmr in $CDCl_3$ (100 MHz) is in accord. Mass spectrum: M^+182 (v. small).

Preparation 5.

A. trans - N - [2 - (dimethylamino)cyclohexyl]formamide

A solution of the diamine (5.12 g., 0.036 mole) and 100 ml. of ethyl formate (distilled over potassium carbonate) is refluxed for 17 hrs. and evaporated. The product is distilled at 0.1 mm, b.p. 104°, 5.2 g. (85% yield). ir:NH 3280, 3040, CH 2930, 2860, N-alkyl 2770, C=O 1670, amide II 1540, other 1450, 1385 cm^{-1}; Nmr in $CDCl_3$ (100 MHz) is in accord. Mass spectrum: M^+170.

B. N,N,N' - Trimethyl - 1,2 - cyclohexanediamine

A solution of the N - formyl compound prepared in A (above)(4 g., 0.0235 mole) in 50 ml. of ether is added during 5 min. to a solution of lithium aluminum hydride (LAH)(4 g.) in 250 ml. of ether and refluxed 17 hrs. It is cooled in ice and decomposed by successive addition of 4 ml. of H_2O, 4 ml. of 15% sodium hydroxide in water, 12 ml. of H_2O, and stirring 1 hr. at room temperature, followed by filtration. The filter cake is washed with ether, and the ether removed by distillation through a Vigreux column. The title product residue distills at 14 mm. b.p.86—87°, 3 g. (82% yield). ir:NH 3680 (very weak), 3320; CH 2940, 2820; N - alkyl 2780; CH1475, 1450, C—N/other 1270, 1155, 1145, 1125, 1060, 1045, 1005, 870, 805, 775 $cm.^{-1}$. Nmr in $CDCl_3$ (60 MHz) is in accord. Mass spectrum: M^+156.

Preparation 6.

A solution of *trans* - 2 - dimethylaminocyclohexanol (61.1 g., 0.427 mole) prepared as in Preparation 1, Part A, using dimethylamine instead of methylamine in 85 ml. of THF is added during 5 min. to a suspension of NaH (17.97 g., 0.427 mole of 57% dispersion in mineral oil) in 250 ml. of THF, and the mixture is heated at 95° for 2 hrs. It is cooled to 10° and treated dropwise with methanesulfonyl chloride (48.91 g., 0.427 mole) during 40 min. keeping the temperature at 15°. N - Methylbenzylamine (103.48 g., 0.854 mole distilled) is then added, THF is evaporated and heating is continued at 95° for 18 hr. The mixture is treated with 500 ml. of 20% NaOH, heated at 95°, cooled and extracted with ether (6 × 100 ml.). The ether solution is extracted with 10% HCl (6 × 100 ml), backwashed with ether (discard ether), cooled, basified with 20% NaOH and extracted with ether. The ether extract is washed with H_2O, saturated salt solution, dried ($MgSO_4$) and evaporated to give 48.6 g. of crude N,N,N' - trimethyl - N' - benzyl - 1,2 - cyclohexanediamine as an oil. A solution of this oil (46.6 g.) is hydrogenated in two portions, each in 130 ml. of EtOH, with 2.6 g of 10% Pd-C and 28.6 g. of 70% $HClO_4$ for 22 hrs. The mixture is filtered through Celite, the filtrate evaporated, cooled in

ice, and basified with 40% KOH. The resulting thick suspension is extracted with ether (4 x 200 ml.), the ether extract dried ($MgSO_4$) and evaporated. The product boils at 87—88° (16 min.). Vpc-mass spectrum showed that the first peak (3.4 min.) is N,N - dimethyl - 1,2 - cyclohexanediamine, and the second peak (4.1 min.) the desired N,N,N' - trimethyl - 1,2 - cyclohexanediamine.

A solution of the distillate (23.8 g.) in 50 ml. of ether is chromatographed on a column of Woelm neutral alumina (1200 g.) and eluted with 5% MeOH-ether. The center fractions (50 ml. each) give 18.68 g.(the impurity is retained on the column). Distillation at 13 mm gives 17 g., b.p. 81—82°. nmr in $CDCl_3$ (60 MHz) is identical to that of the compound prepared by Preparations 3 and 4.

Preparation 7.

A. trans - N - Benzyl - N - [2 - (dimethylamino)cyclohexyl]formamide *p* - toluenesulfonate (1:1)

A solution of *trans* - N - benzyl - N',N' - dimethyl - 1,2 - cyclohexanediamine (9.29 g., 0.04 mole) prepared as in Preparation 4, but using benzylamine instead of benzylmethylamine, in 40 ml. of formic acid is refluxed 20 hr., and poured into 200 g. of ice. It is basified with 15% NaOH and extracted well with ether. The extract is washed with H_2O and with saturated salt solution, is dried ($MgSO_4$) and evaporated. The residue is converted with 2 mole of *p* - TSA in ether. The resulting gum is crystallized from MeOH-ether to give 13.64 g. of title compound, m.p. 201—201.5°. The analytical sample melts at 202—203°. uv:sh 210 nm (ε 27,850); sh 222 (25,600); sh 227 (12,350); sh 243 (302); sh 248 (375); λmax 254 (472); 258 (556); 261 (562); 268 (399); sh 272 (175). ir:NH 2720, 2560; C=O 1670, 1650; C=C 1600, 1495; SO_3/other 1225, 1170, 1120, 1030, 1010, 815, 705, 685. nmr in D_2O (100 MHz) is in accord. Mass spectrum M^+260.

Anal. Calcd for $C_{16}H_{24}N_2O \cdot C_7H_7SO_3H$: C, 63.86; H, 7.46; N, 6.48; S, 7.41; Found: C, 64.04; H, 7.49; N, 6.34; S, 7.86.

The free base is prepared by basification of the ether-H_2O suspension of the above salt and extraction with ether; it is a colorless oil.

B. trans - N - Benzyl - N,N',N', - trimethyl - 1,2 - cyclohexanediamine *p* - toluenesulfonate (1:1)

A solution of the free base from Part A (above) (5.7 g., 0.0219 mole) in 100 ml. of ether is added to a solution of LAH (5.7 g.) in 300 ml. of ether during 10 min., and the mixture is refluxed overnight. It is cooled in ice, and decomposed in succession with 5.7 ml. H_2O, 5.7 ml. of 15% NaOH and 17.1 ml. of H_2O. The suspension is stirred at room temperature for 1 hr., filtered, and the cake washed with ether. The filtrate is dried ($MgSO_4$), and evaporated to give 5.6 g. of oil. The salt is prepared from 4.19 g. of the title amine base and 1 mole of *p* - toluenesulfonic acid monohydrate in ether. The resulting gum is crystallized from MeOH - ether; colorless needles of amine salt, 4.64 g., m.p. 143.5—145°. uv:λmax 206 nm (ε 16,400); sh 221 (13,350); sh 226.5 (8,600); sh 247 (359); sh 252 (407); 257 (463); 261 (446); 267 (298); sh 271.5 (138) ir:$\overset{+}{N}$H broad: =CH 3060, 3040, 3020; N - alkyl 2810; C=C 1605, 1495; SO_3^-/other 1215, 1175, 1145, 1050, 1030, 1010, 815, 740, 695, 680. nmr in D_2O (100 MHz) is in accord.

Anal. Calcd. for $C_{16}H_{26}N_2 \cdot CH_3C_6H_4SO_3H$: C, 65.99; H, 8.19; N, 16.69; S, 7.66; Found: C, 66.12; H, 8.04; N, 6.45; S, 7.69.

C. trans - N,N,'N' - trimethylcyclohexane - 1,2 - diamine

The *p* - toluenesulfonate salt from part B (above) is basified with aq. NaOH to give the free diamine base as an oil. A solution of this oil is hydrogenated over 10% Pd-C and 70% $HClO_4$ and further treated as in Preparation 4 to give the title diamine.

Examples of additional *trans* - cycloaliphatic diamines which have been prepared are summarized below:

8: N,N' - Dimethyl - N - cyclopropylmethyl - *trans* - 1,2 - cyclohexanediamine (b.p. 127—9°; 13 mm Hg)

9: *trans* - 2 - (4 - Methylpiperazino) - N - methylcyclohexamine (b.p. 143—5°; 15 mm Hg)

10: *trans* - 2 - Pyrrolidino - N - methylcyclohexamine (b.p. 118—9°; 13 mm Hg)

11: N,N' - Dimethyl - N - (β - hydroxyethyl) - *trans* - 1,2 - cyclohexanediamine (b.p. 158—60°; 14 mm Hg)

12: N,N' - Dimethyl - N - n - butyl - *trans* - 1,2 - cyclohexanediamine (b.p. 118—20°; 13 mm Hg)

13: *trans* - 2 - (3 - hydroxypyrrolidino) - N - methylcyclohexamine (b.p. 128—30°; 0.1 mm Hg)
14: N,N- Diethyl - N' - methyl - *trans* - 1,2 - cyclohexanediamine (b.p. 104—5°; 14 mm Hg)
15: *trans* - 2 - Pyrrolidino - N - methylcycloheptanamine (b.p. 148—151°; 0.1 mm Hg)
16: N,N,N' - Trimethyl - *trans* - 1,2 - cycloheptanediamine (b.p. 108—110°; 17 mm Hg)
17: N,N,N' - Trimethyl - *trans* - 1,2 - cyclooctanediamine (b.p. 113—115°; 13 mm Hg)

The compounds of Preparations 8 to 13 were prepared following the procedure of Preparation 4 (Preparations 9 and 10 using 4 equivalents of amine and Preparation 12 in a sealed bomb): those of Preparations 14, 16 and 17 following Preparation 5; and that of Preparation 15 following Preparation 6.

The following Examples (1 to 33) illustrate how compounds of the invention may be prepared. All temperatures are in degrees Centigrade unless otherwise noted. For brevity, in the above Preparations and in the Examples NaH means sodium hydride, DMF means N,N - dimethylformamide, THF means tetrahydrofuran, LAH means lithium aluminum hydride, MeI means methyl iodide, MeOH means methyl alcohol (methanol), $CHCl_3$ means chloroform, ether means diethyl ether, CH_2Cl_2 means methylene chloride, $CDCl_3$ means deuteriochloroform, HPLC means high pressure liquid chromatography, nmr means nuclear magnetic resonance, ir means infrared, and tlc means thin layer chromatograph, pTSA means *p* - toluenesulfonic acid, D_2O means deuterated water (or deuterium oxide), DMSO means dimethylsulfoxide and VPC means vapour phase chromatography.

Example 1A.

N - Methyl - N - (2 - dimethylaminocyclohexyl) - *p* - bromophenylacetamide hydrochloride (using carbonyl diimidazole)

Carbonly diimidazole (0.811 g., 5 mmole) is added to a solution of *p* - bromophenylacetic acid (.106 g., 5 mmole) in 20 ml. dry THF and the solution stirred 1 hr. A solution of N,N,N' - trimethylcyclohexane - 1,2 - diamine (0.781 g., 5 mmole) is added during 10 min. and magnetically stirred 18 hrs. It is evaporated to dryness, taken up in 25 ml. ether, 20 ml. saturated aqueous sodium bicarbonate and the aqueous layer extracted once with ether. The combined ether extracts are washed with H_2O, saturated salt solution, dried over $MgSO_4$ and evaporated to give 1.8 g. of the title compound as an oil.

The crude oil is converted to the hydrochloride with ethereal HCl. Crystallization from methanol-ether gives the title compound C=C 1595, 1490; other/aromatic 1425, 1400, 1165, 1015, 960, 810, 790 $cm.^{-1}$. Mass spectrum: M^+352.

Anal. calcd: for $C_{17}H_{25}BrN_2O \cdot HCl$:

Calcd: C, 52.38; H, 6.72; Cl, 9.10; Br, 20.50; N, 7.19.

Found C, 52.25; H, 6.79; Cl, 8.94; Br, 20.69; N, 7.29.

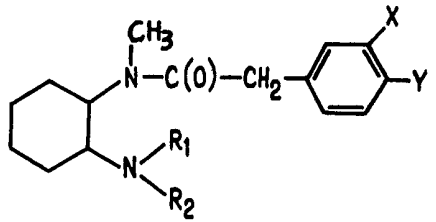
Example 1B.

N - Methyl - N - (2 - dimethylaminocyclohexyl - *p* - bromophenylacetamide hydrochloride (using acid chloride)

A solution of *p* - bromophenylacetyl chloride (1.17 g., 5 mmole) in 10 ml. of ether is added dropwise during 10 minutes to a solution of N,N,N' - trimethylcyclohexane - 1,2 - diamine (0.78 g., 5 mmole) in 50 ml. of ether containing triethylamine (0.505 g., 5 mmole), keeping the temperature at 20—25°. The resulting suspension is stirred 18 hrs. Saturated aqueous sodium bicarbonate solution (25 ml.) is added, the ether layer separated, and the aqueous layer extracted once with ether. The combined ether extracts are washed with H_2O, saturated salt solution, dried ($MgSO_4$), and evaporated to give 1.8 g. of the title compound as an oil.

The crude oil is converted to the hydrochloride with ethereal HCl. This title amine salt is crystallized from MeOH - ether, mp. 274—275° (60% yield). It is identical with the sample prepared in Example 1A, as shown by mixed mp. and nmr comparison.

The following table (Table 1) summarizes other *trans* - compounds of this invention, represented by the general formula



where $-NR_1R_2$, X and Y are as defined in Table 1. Any reference to a $C_4H_4O_4$ salt is to the maleate.

TABLE I

Example Number	R_1R_2N-	X	Y	M.P.	Formula	Anal. Calc.	Anal. Found	Preparation No. of Starting Diamine
2	$N(CH_3)_2$	H	CF_3	228–230	$C_{18}H_{25}F_3N_2O$ .HCl.$5H_2O$	C, 55.74 H, 7.02 Cl 9.14 F 14.70 N 7.22	C 56.06 H 6.49 Cl 9.46 F 14.71 N 7.49	5
3	N-cyclopropyl-methyl-N-methylamino	H	Br	145–147.5	$C_{20}H_{29}BrN_2O$.$C_4H_4O_4$	C 56.58 H 6.53 Br 15.69 N 5.50	C 56.94 H 6.51 Br 15.34 N 5.75	8
4	$N(CH_3)-CH_2CH=CH_2$	H	Br	162–3	$C_{19}H_{27}BrN_2O$.$CH_3C_6H_4SO_3H$	C 56.61 H 6.40 Br 14.49 N 5.08 S 5.81	C 56.99 H 6.40 Br 14.42 N 5.08 S 5.74	4
5	$N(CH_3)_2$	H	H	200–201	$C_{17}H_{26}N_2O$.$CH_3C_6H_4SO_3H$	C 64.54 H 7.67 N 6.27 S 7.18	C 64.20 H 7.83 N 6.12 S 7.18	5

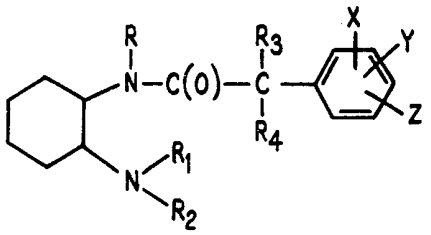
TABLE I – CONTINUED

Example Number	R_1R_2N-	X	Y	M.P.	Formula	Anal. Calc.	Anal. Found	Preparation No. of Starting Diamine
6	$N(CH_3)_2$	OCH_3	H	55–57.5	$C_{18}H_{28}N_2O_2$	C 71.01 H 9.27 N 9.20	C 70.90 H 9.39 N 9.32	5
7	$N(CH_3)_2$	H	CH_3	268–269	$C_{18}H_{28}N_2O$ .HCl	C 66.54 H 9.00 Cl 10.91 N 8.62	C 66.54 H 8.95 Cl 10.97 N 8.56	5
8	4-methylpiperazino	H	Br	257–9 dec.	$C_{20}H_{30}BrN_3O$ 1.5 H_2O	C 47.25 H 6.94 Br 15.72 Cl 13.95 N 8.26	C 47.05 H 6.94 Br Cl N	9
9	pyrrolidino	H	Br	213–214 dec.	$C_{19}H_{27}BrN_2O$ .5 H_2O	C 53.71 H 6.88 Br 18.81 Cl 8.35 N 6.60	C 53.86 H 6.96 Br 19.34 Cl 8.15 N 6.56	10
10	$N(CH_3)_2$	H	N_3	174–176 dec.	$C_{17}H_{25}N_5O$.$C_2H_2O_4$	C 56.28 H 6.71 N 17.17	C 55.97 H 6.71 N 17.24	5
11	$-N(CH_3)_2$	Cl	Cl	203–204	$C_{17}H_{24}Cl_2N_2O$.$CH_3C_6H_4SO_3H$	C 55.91 H 6.26 Cl 13.76 N 5.44 S 6.22	C 56.10 H 6.33 Cl 13.64 N 5.41 S 6.29	5
12	$-N(CH_3)_2$	H	C_6H_5	242–243	$C_{23}H_{30}N_2O$. HCl 0.5 H_2O	C 69.76 H 8.15 Cl 8.95 N 7.08	C 69.69 H 8.05 Cl 8.93 N 6.95	5

TABLE I – CONTINUED

Example Number	R_1R_2N–	X	Y	M.P.	Formula	Anal. Calc.	Anal. Found	Preparation No. of Starting diamine
13	$-N(CH_3)_2$	H	OCH_3	251–252 dec.	$C_{18}H_{28}N_2O_2$ .CHl	C 63.42 H 8.57 Cl 10.40 N 8.22	C 63.02 H 8.52 Cl 10.58 N 8.08	5
14	pyrrolidino	Cl	Cl	205–206	$C_{19}H_{26}ClN_2O$ .HCl $0.5H_2O$	C 55.01 H 6.80 Cl 25.64 N 6.75	C 54.87 H 6.81 Cl 25.43 N 6 66	10
14A	pyrrolidino	Cl	Cl	218–225	$C_{19}H_{26}ClN_2O$ .HCl	C 56.23 H 6.71 N 6.90 Cl 26.21	C 56.15 H 6.88 N 6.81 Cl 26.22	10
15	$N(CH_3)-CH_2CH_2OH$	Cl	Cl	115 effer.	$C_{18}H_{26}Cl_2N_2O_2$ .HCl $\frac{1}{3}H_2O$	C 51.99 H 6.71 Cl 25.58 N 6.74	C 52.03 H 6.90 Cl 25.16 N 6.50	11
16	$N(CH_3)-(CH_2)_3CH_3$	Cl	Cl	140.5–142	$C_{20}H_{30}Cl_2N_2O$.$C_4H_4O_4$	C 57.48 H 6.83 Cl 14.14 N 5.59	C 57.10 H 6.75 Cl 13.29 N 6.03	12
17	3-hydroxypyrrolidino	Cl	Cl	250–251	$C_{19}H_{26}Cl_2N_2O_2$ .HCl	C 54.10 H 6.45 Cl 25.22 N 6.64	C 54.15 H 6.49 Cl 25.33 N 6.72	13
18	$N(CH_2CH_3)$	Cl	Cl	160–161	$C_{19}H_{28}Cl_2N_2O$.$C_4H_4O_4$ $0.5H_2O$	C 55.64 H 6.70 Cl 14.28 N 5.64	C 55.74 H 6.56 Cl 13.92 N 5.62	14

The following *trans*- compounds of the invention satisfy the general formula



wherein R, — NR_1, R_2, R_3, R_4, X, Y and Z are defined in Table II.

TABLE II

Ex No.	R_1R_2N–	R	R_3	R_4	X	Y	Z	M.P.	Formula	Anal. Calcd.	Anal. Found
19	pyrrolidino (2)	CH_3	H	CH_3	H	3-Cl	4-Cl	124–125	$C_{20}H_{28}Cl_2N_2O$	C 62.66 H 7.36 Cl 18.50 N 7.31	C 62.32 H 7.38 Cl 18.40 N 7.04
20	$N(CH_3)_2$ (3)	CH_3	CH_3	CH_3	H	H	H	79.5–80.5	$C_{19}H_{30}N_2O$	C 75.45 H 10.00 N 9.26	C 74.97 H 9.83 N 9.21
21	$N(CH_3)_2$ [isomer I]	CH_3	H	CH_3	H	H	4-Cl	90–92	$C_{18}H_{27}ClN_2O$		
22	$N(CH_3)_2$ [isomer II] (3)	CH_3	H	CH_3	H	H	4-Cl	93–94	$C_{18}H_{27}ClN_2O$	C 66.95 H 8.43 Cl 10.98 N 8.68	C 66.83 H 8.36 Cl 11.02 N 8.51
23	$N(CH_3)_2$	H	H	H	2-CH_3	4-CH_3	6-CH_3	279–280 dec.	$C_{20}H_{32}N_2O$ .HCl	C 68.06 H 9.42 Cl 10.05 N 7.94	C 67.88 H 9.66 Cl 10.27 N 7.92
24	$N(CH_3)_2$	H	H	H	3-Cl	4-Cl	H	129–128	$C_{16}H_{22}Cl_2N_2O$	C 58.36 H 6.74 Cl 21.54 N 8.51	C 58.22 H 6.90 Cl 21.75 N 8.70

FOOTNOTES FOR TABLE II.

(1) – Crystallization solvent is methanol/ethyl ether (50:50 v/v)

(2) – Ethyl ether crystallization solvent

(3) – Petroleum ether crystallization solvent

The compounds whose properties are given in Table III below, are the following:

Example 25: 1 - (*p*-chlorophenyl) - N - (*trans* - 2 - dimethylaminocyclohexyl) - N - methyl - cyclopropanecarboxamide.

Example 26: N - (*trans* - 2 - dimethylaminocyclohexyl) - N - methyl - (2 - naphthyl)acetamide hydrochloride.

Example 27: N - (*trans* - 2 - dimethylaminocyclohexyl) - N - methyl - (1 - naphthyl)acetamide hydrochloride.

Example 28: N - (*trans* - 2 - dimethylaminocycloheptyl) - N - methyl - *p* - bromophenylacetamide maleate.

Example 29: N - (*trans* - 2 - dimethylaminocyclooctyl) - N - methyl - *p* - bromophenylacetamide napsylate.

Example 30: N - (*trans* - 2 - pyrrolidinocycloheptyl) - N - methyl - 3',4' - dichlorophenylacetamide hydrochloride.

TABLE III

Example No.	M.P.	Formula	Anal. Calcd.	Found
25	82.3	$C_{19}H_{27}ClN_2O$	C, 68.14; H, 8.13 Cl, 10.59; N, 8.37	C, 68.03; H, 8.21 Cl, 10.56 N, 8.39
26	227–8	$C_{21}H_{28}N_2O.HCl$ $.0.5H_2O$	C, 68.17; H, 8.17 Cl, 9.59 N, 7.57	C, 68.02 H, 8.06 Cl. 9.82 N, 7.42
27	251–2	$C_{21}H_{28}N_2O.HCl$ $1/3H_{20}$	C, 68.73; H, 8.15 Cl, 9.66; N, 7.64	C, 68.85; H, 8.04 Cl, 9.85; N, 7.60
28	174–5	$C_{18}H_{27}BrN_2O$ $.C_4H_4O_4$	C, 54.66; H, 6.46 Br, 16.53; N, 5.80	C, 54.61; H, 6.58 Br, 16.11; N, 5.86
29	191–2	$C_{19}H_{28}BrN_2O$ $C_{10}H_8SO_3$	C, 59.07; H, 6.33 Br, 13.55; N, 4.75 S, 5.44	C, 58.97; H, 6.40 Br, 13.26 N, 4.93 S, 5.25
30	134–6	$C_{20}H_{28}Cl_2N_{20}$ $.HCl.½H_2O$	C, 56.01; H, 7.05 Cl, 24.80; N, 6.53	C, 56.07; H, 6.98 Cl, 24.96; N, 6.36

The compound of Examples 14 and 14A, viz. N - *trans* - 2 - pyrrolidinocyclohexyl) - N - methyl - 3',4' - dichlorophenyl acetamide hydrochloride was prepared as follows:

A 5.62 g. (0.0274 mole) portion of 3,4 - dichlorophenylacetic acid is dissolved in 100 ml, of tetrahydrofuran (THF). To this solution is added 4.4 g. 4.4 g. (0.0274 mole) of 1,1' - carbonyldiimidazole (CDI) and the reaction mixture stirred for 2 hours at room temperature. Then 5.0 g. (0.027 mole) of *trans* - 2 - (N - pyrrolidinyl)cyclohexyl - N - methylamine in 25 ml. of the THF is added and the resulting mixture stirred for 20 hours at room temperature. The mixture is evaporated to dryness, the residue is taken up in ether and mixed with a saturated aqueous sodium bicarbonate solution. The ether layer is separated from the aqueous layer, washed well with water and dried over magnesium sulfate ($MgSO_4$) to give a residue which is dissolved in methanol. To the resulting methanol solution is added 1N ethereal hydrogen chloride solution (hydrogen chloride in ether) to lower the pH of the mixture to less than 7; then ether is added to the point of cloudiness. The produced crystalline hydrochloride salt (solvate hemihydrate) is collected in 84.5% yield (9.4 g.), m.p. 205—206°C. See Table II (Example 14) for its elemental analysis. Drying the solvate for 18 hr. at 65° and 0.1 mm Hg. gives the non-solvated hydrochloride salt. See Table II for elemental analysis (Example 14A).

Example 14B.

A 5 gr. portion of the product of Example 14A was converted to its free base form with 20% sodium hydroxide aqueous solution, and the mixture was extracted with chloroform. The chloroform extracts were dried with anhydrous magnesium sulfate and evaporated to dryness to leave 4.3 g. of colorless amino-amide oil which was then converted to the maleic acid salt as follows:

The 4.3 g. of amino-amide oil was dissolved in methanol and 1.35 g. (0.0116 mole) of maleic acid in ether was added. Additional ether was introduced to the solution to the point of cloudiness; on standing crystallization occurred to give 4.6 g. of the N - (*trans* - pyrrolidinocyclohexyl) - N - methyl - 3',4' - dichlorophenylacetamide maleate salt (colorless rods), m.p., 191—192°. The crystals were dried at 65° (0.1 mm 18 hrs.). The ir spectrum was consistent with the named structure.

Anal. $C_{19}H_{26}N_2OCl_2 \cdot C_4H_4O_4$

Calcd.:	C, 56.91;	H, 6.23;	N, 5.77;	Cl, 14.61
Found:	C, 56.92;	H, 6.35;	N, 5.72;	Cl, 14.80

The maleate salt form of some of these amino-amide compounds has been found particularly useful for resolving the *d*- and l- isomers of these compounds, for further specific study in the pharmacology of these drug compounds.

Preliminary pharmacological testing of the separated trans-*d*- and trans-*l*- isomers of the compound of Example 14B indicates that the analgesic activity of these compounds resides in the 1-isomer, but analgesic activity is also shown by the trans-dl-isomer mixtures thereof, and such mixtures are included within this invention.

Example 31.

N - [*trans* - 2 - (3 - acetoxypyrrolidino)cyclohexyl) - N - methyl - 3',4' - dichlorophenylacetamide hydrochloride hemihydrate.

Following the procedure of Example 14, but substituting *trans* - N - [2 - (3 - hydroxypyrrolidino)cyclohexyl] - N - methylamine for the *trans* - 2 - pyrrolidino)cyclohexyl - N - methylamine, N - [*trans* - 2 - (3 - hydroxypyrrolidino)cyclohexhyl) - N - methyl - 3',4' - dichlorophenylacetamide is obtained as the hydrochloride.

Then, in a nitrogen atomosphere, a mixture of 0.9 g. (0.002 mole) of the above product and 5 ml. of acetic anhydride is heated on a steam bath for 4 hours. Then 10 ml. of water is added and the mixture is further heated on the steam bath for 30 minutes. The resulting solution is cooled in ice and basified to pH 7—8 by addition of solid sodium bicarbonate. This resulting reaction mixture is extracted well with ether, the ether extracts are combined and washed well with water and saturated aqueous sodium chloride solution, dried over $MgSO_4$ and evaporated to dryness. A

brown oil (0.562 g.) is obtained. This oil is converted to the hydrochloride salt in ether with ethereal HCl. Crystallization of the title compound from a methanol-ether mixture gives 0.325 g. of off-white needles, m.p. 161—162°C. The mass spectrum analysis shows an M^+426 ion.

Anal. for $C_{21}H_{28}Cl_2N_2O_3HCl \cdot H_2O$:

Calcd.:	C, 53.24;	H, 6.40;	Cl, 22.50;	N, 5.93
Found:	C, 53.23;	H, 6.25;	Cl, 22.54;	N, 5.92

If desired, the compounds of this invention can be resolved into their respective *d*- and *l*- optical isomers by methods known in the art. In this case, the optical resolution can be done by at least two different routes. The resolving agents by either route are any of the known resolving agents such as optically active camphorsulfonic acid, bis - *p* - toluyl - tartaric acid, tartaric acid, and diacetyl tartaric acid which are commercially available and which are commonly used for resolution of amines (bases), as for example in *Organic Syntheses*, Coll. Vol. V., *p* 932 (1973), resoluton of *d*-(+) and 1 - (−) - α - phenylethylamine with (+)-tartaric acid.

By the first method for resolving the compounds of this invention, for example, one of the amino amide compounds can be converted into its optically active diasterecisomeric salts by reaction with an optically active acid—mentioned above—in a manner standard in the isomer resolution art. These diasterecisomeric salts can then be separated by conventional means such as differential crystallization. Diastereoisomeric salts have different crystallization properties, which are taken advantage of in this separation. On neutralization of each diastereoisomeric salt with aqueous base the corresponding optically active enantiomers of the free amino amide can be obtained, each of which can subsequently and separately be converted as previously described in the examples to the desired acid addition salt.

By the second method, which in the case of some of these compounds is preferred, the formula I compounds can be made into their respective *d*- and *l*- isomers by first resolving each unsymmetrically substituted diamine of formula II into its respective *d*- and *l*-isomers by treatment with the resolving agent, crystallization, separation and regeneration of the respective *trans-d*-diamine or *trans-l*-diamine, and then reacting the respective resolved diamine starting material with the desired compound of formula III to form the respective *d*- or *l*- compound of formula I, which can then be converted to any desired pharmaceutically acceptable acid addition salt by procedures exemplified above.

The following Preparation illustrates the synthesis of formula II diastereoisomers.

Preparation 18

Part A—Preparation of trans-d and 1 - N - methyl - (2 - pyrrolidinocyclohexyl)amine hydrochloride

Di - *p* - toluyl - *d* - tartaric acid is dissolved in 100 ml. of methanol; this solution is added to a solution of *trans* - N - methyl - N - [2 - (1 - pyrollidinyl)cyclohexyl]amine (4 g., 0.022 mole) in 100 ml. of methanol and the combined mixture is allowed to stand for 50 min. to crystallize. The suspension is filtered. The residue is washed with methanol and dried at 50° to give 6.01 g. of solid A (m.p. 194—196°). The filtrate is saved. 0.5 gram of solid A (acid addition salt) is converted to the free base with 20% NaOH in water and is then extracted into chloroform. The organic phase is dried over $MgSO_4$, evaporated to dryness and converted to the hydrochloride salt in ethereal HCl. Recrystallization from CH_3OH gives 95 mg. of colourless crystals (m.p. 236—239°) of *d*-amine hydrochloride $[\alpha]_D^{22°}+17°$ (C=16.52 mg/2 ml chloroform).

Further refinements in the isolation of optically pure *d* amine hydrochloride: The remaining 5.5 g. of solid A is dissolved in 600 ml. CH_3OH, concentrated to 200 ml. and the concentrate is allowed to crystallize overnight. 3.7 g. of solid is collected (m.p. 197—198°). 0.5 gram of this solid is converted to the free base with 20% NaOH/$CHCl_3$, the organic layer is washed with water and saturated sodium chloride solution, dried over $MgSO_4$ and evaporated to dryness. Conversion to the hydrochloride salt in etheral HCl and crystallization from CH_3OH gives colorless needles of the *trans*-diamine HCl, which are dried at 50° *in vacuo* (m.p.

247.5—248.5°) $[\alpha]_D^{22°}$+30° (C=19.49 mg/2 ml $CHCl_3$).

The filtrate (from original filtration of Solid A above) is evaporated to dryness; this results in a pale tan solid B (5.77 g.). 0.5 gram of solid B is converted to the free base in 20% NaOH in water and extracted into chloroform. The organic ($CHCl_3$) phase is dried over $MgSO_4$ and evaporated to give 150 mg. of oil. This oil is converted to the hydrochloride salt in ethereal HCl; crystallisation in CH_3OH/ether gives 100 mg. of *trans-l*-diamine (m.p. 240—242° $[\alpha]_D^{22°}$ –28° (C=15.84 mg/2 ml. chloroform.

Example 32.

Preparation of *trans* - d - 2 - (3,4 - dichlorophenyl) - N - methyl - N - [2 - (1 - pyrrolidinocyclohexyl]acetamide maleate.

Following the procedure of Example 14 but substituting the *trans* - 1 - 2 - (N - pyrrolidinyl)cyclohexyl - N - methylamine for the *trans*-diamine of Example 14 there is obtained a yellow oil, 50 mg. of which (0.14 millimole) is dissolved in ethyl ether; to this is added 15.7 mg. (0.14 millimole) of maleic acid dissolved in ether. The gummy oil which comes out is washed with distilled ether and crystallized in CH_3OH to give 31 mg. of colorless well-defined rods (the title product). Dried at 65° *in vacuo* for 3 hr. m.p. 199—200° (dec.). $[\alpha]_D^{22°}$ + 83° (C=18.65 mg/2 ml. chloroform).

Example 33.

Preparation of trans - 1 - 2 - (3,4 - dichlorophenyl)N - methyl - N - [2 - 1 - pyrrolidinyl) - cyclohexyl]acetamide maleate.

Following the procedure of Example 14 but substituting the *trans* - d - 2 - (N - pyrrolidinyl)cyclohexyl - N - methylamine for the *trans*-diamine of Example 14 there is obtained a yellow oil which is further purified by high pressure liquid chromatography on a Merck (registered Trade Mark) micro-packed silica gel column, eluting with 5% MeOH—$CHCl_3$·v/v. The center fractions are collected, as they contain the desired product (TLC determination) and are evaporated to give a yellow oil, 50 mg. of which (0.14 millimole) is dissolved in ether. The maleate acid addition salt is prepared by addition of 15.7 mg (0.14 millimole) of maleic acid in ether. Crystallization from CH_3OH gives the titled compound as a solid; this solid is dried *in vacuo* at 65° for 3 hrs. (38 mg; m.p. 199—200°). $[\alpha]_D^{22°}$–84° (C=15.46 mg/2 ml. $CHCl_3$).

The following Examples illustrate the preparation of pharmaceutical compositions containing the compounds of this invention.

Example 34.

One thousand tablets for oral use, each containing 40 mg. of *trans* - N - methyl - N - [2 - (3 - hydroxypyrrolidinyl) - cyclohexyl] - 3',4' - dichlorophenylacetamide hydrochloride as the essential active ingredient are prepared from the following ingredients:

Essential active ingredient	40 gm.
Dicalcium phosphate	150 gm.
Methylcellulose, U.S.P. 15 cps)	6.5 gm.
Talc	20 gm.
Calcium Stearate	2.0 gm.

The essential active ingredient and dicalcium phosphate are mixed well, granulated with 7.5% aqueous solution of methylcellulose, passed through a No. 8 screen and dried carefully. The dried granules are passed through No. 12 screen, mixed with the talc and stearate and compressed into tablets. These tablets are useful in the treatment of pain in adult humans at a dose of 1 tablet 1 to 4 times a day as needed.

Example 35.

One thousand two-piece hard gelatin capsules for oral use, each capsule containing 20 mg. of *trans* - N - methyl - N - [2 - (N - pyrrolidinyl)cyclohexyl] - 3',4' - dichlorophenylacetamide hydrochloride as the essential active ingredient are prepared from the following ingredients:

Essential active ingredient	20 gm.
Lactose, U.S.P.	100 gm.
Starch, U.S.P.	10 gm.
Talc, U.S.P.	5 gm.
Calcium stearate	1 gm.

The finely powdered materials are mixed thoroughly, then filled into hard gelatin capsules of appropriate size.

One capsule 4 times a day is useful for the treatment of pain in adult humans.

Example 36.

One-piece soft elastic capsules for oral use, each containing 100 mg. of *trans* - N - methyl - N - [2 - (N - pyrrolodinyl) - cyclohexyl] - 2 - (*p* - chlorophenyl)propionamide as the essential active ingredient are prepared in the usual manner by first dispersing the powdered active material in sufficient corn oil to render the material capsulatable.

One capsule 2 times a day is useful in the treatment of pain in adult humans.

Example 37.

An aqueous oral preparation containing in each teaspoonful (5 ml.) 80 mg. of *trans* - N - methyl - N - [2 - (3 - acetoxy - 1 - pyrrolidinyl)cyclohexyl] - 3',4' - dichlorophenylacetamide hydrochloride as the essential active ingredient is prepared from the following ingredients:

Essential active ingredient	160 gm.
Methylparaben, U.S.P.	7.5 gm.
Propylparaben, U.S.P.	2.5 gm.
Saccharin Sodium	12.5 gm.
Glycerin	3,000 ml.
Tragacanth powder	10 gm.
Orange oil flavor	10 gm.
Orange II	7.5 gm.
Deionized water, q.s. to	10,000 ml.

The foregoing aqueous preparation is useful in the treatment of adult pain at a dose of 1 teaspoonful 4 times a day.

Example 38.

One thousand tablets for oral administration, each containing 10 mg. of *trans* - N - methyl - N - (2 - pyrrolidinocyclohexyl) - 3',4' - dichlorophenylacetamide hydrochloride as the essential active ingredient and 16.2 mg. of phenobarbital are prepared from the following ingredients:

Essential active ingredient, micronized	10 gm.
Phenobarbital	16.2 gm
Lactose	150 gm.
Starch	15 gm.
Magnesium stearate	1.5 gm.

The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a screen and the resulting granules are then compressed into tablets.

These tablets are useful in reducing post-surgical pain in dogs at a dose of 1 to 3 tablets depending on the weight of the animal and its condition.

Example 39.

A sterile aqueous suspension suitable for intramuscular injection and containing in each milliliter 50 mg. of the compound of Example 35 as essential active ingredient is prepared from the following ingredients:

Essential active ingredient	5 gm.
Polyethylene glycol 4000, U.S.P.	3 gm.
Sodium chloride	0.9 gm.
Polysorbate 80 U.S.P.	0.4 gm
Sodium metabisulfite	0.1 gm.
Methylparaben, U.S.P.	0.18 gm.
Propylparaben, U.S.P.	0.02 gm.
Water for injection, q.s. to	100 ml.

The preceding sterile injectable is useful in the treatment of pain at a dose of ½ to 2 ml.

Example 40.

One thousand suppositories, each weighing 2.5 gm. and containing 50 mg. of N - methyl - N - (2 - dimethylaminocyclohexyl) - *p* - bromophenylacetamide as the essential active ingredient, are prepared from the following ingredients:

Essential active ingredient	150 gm.
Propylene glycol	165 gm.
Polyethylene glycol 4000 q.s.	2,500 gm.

The essential active ingredient is added to the propylene glycol and the mixture milled until uniformly dispersed. The PEG 4000 is melted and the propylene glycol dispersion added. The suspension is poured into molds and allowed to cool and solidify.

These suppositories are useful in the treatment of post-surgical pain at a dose of 1 suppository rectally twice a day.

The following examples illustrate pharmaceutical compositions containing the aminoamide compounds of this invention in combination with other drug compounds.

Example 41.

One thousand hard gelatin capsules for oral use, each containing 20 mg. of the compound of Example 35 as essential active ingredient and 40 mg. ketazolam are prepared from the following ingredients:

Essential active ingredient, micronized	20 gm.
Ketazolam	40 gm.
Starch	125 gm.
Talc	25 gm.
Magnesium stearate	1.5 gm.

One capsule 4 times a day is useful in the relief of pain in adult humans.

Example 42.

Ten thousand scored tablets for oral use, each containing 80 mg. of N - methyl - N - (2 - dimethylaminocyclohexyl) - 3',4' - dichlorophenylacetamide tosylate as the essential active ingredient and 32 mg. of caffeine are prepared from the following ingredients:

Essential active ingredient, micronized	800 gm.
Caffeine	320 gm.
Lactose	1,500 gm.
Corn Starch	500 gm.
Talc	500 gm.
Calcium Stearate	25 gm.

The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a number 16 screen. The resulting granules are then compressed into tablets each containing 80 mg. of the acetamide derivative essential ingredient and 32 mg. of caffeine.

This combination of active materials is effective in reducing pain in adult humans. The dose is one-half of two tablets 3 times a day, depending on the severity of the condition.

Example 43.

Ten thousand tablets for oral use, each containing 60 mg. of *trans* - N - methyl - N - [2 - (3 - acetoxy - N - pyrrolidinyl) - cyclohexyl]3,4 - dichlorophenyl - acetamide hydrochloride as the essential active ingredient and 0.5 mg. of methylprednisolone are prepared from the following ingredients using the procedure described in Example 38.

Essential active ingredient, micronized	600 gm.
Methylprednisolone	5 gm.
Lactose	1,000 gm.
Corn Starch	500 gm.
Talc	500 gm.
Calcium Stearate	25 gm.

These tablets are useful in treating adult humans suffering from arthritic pain by administering 1 tablet 3 times a day.

Example 44.

Ten thousand tablets for oral use, each containing 5 mg. of *trans* - N - methyl - N - (2 - pyrrolidinocyclohexyl) - 3',4' - dichlorophenylacetamide hydrochloride as the essential active ingredient and 320 mg. acetaminophen, are prepared from the following ingredients and using the procedure of Example 38.

Essential active ingredient, finely powdered	50 gm.
Acetaminophen, finely powdered	3,200 gm.
Corn starch	500 gm.
Talc	500 gm.
Calcium stearate	50 gm.

This tablet is useful in treating homotopic pain or headache in an adult patient

by administering one or two tablets 3 times a day depending on the severity of the condition.

In similar formulations the acetaminophen can separately be replaced by aspirin (320 mg./tablet) or Phenacetin-Aspirin-Caffeine (P-A-C) compound (390 mg./tablet).

Example 45.

One thousand tablets for oral use, each containing 110 mg. of N - methyl - N - (2 - dimethylaminocyclohexyl) - 3',4' - dichlorophenylacetamide maleate as an essential active ingredient and 400 mg. of chlorophenesin carbamate (Maolate) are prepared from the following ingredients:

Essential active ingredient, micronized (the maleate salt)	110 gm.
Maolate	400 gm.
Lactose	50 gm.
Starch	15 gm.
Magnesium stearate	1.5 gm.

The ingredients are thoroughly mixed and slugged. The slugs are broken down by forcing through a screen and the resulting granules are then compressed into tablets.

These tablets are useful in reducing pain and muscle spasms at a dose of 1 tablet one to 3 times per day, depending upon the severity of the condition.

Example 46.

One thousand grams of ointment for topical use, each gram containing 20 mg. of N - methyl - N - (2 - pyrrolidinocyclohexyl) - 3',4' - dichlorophenylacetamide hydrochloride as the essential active ingredient is prepared from the following ingredients:

Essential active ingredient	20 gm.	
Spermaceti	115 gm.	
White wax	110 gm.	
Mineral oil	560 gm.	
Sodium borate	5 gm.	
Purified water q.s.	1,000 gm.	(190 ml.)

Apply to site of pain 5 to 6 times daily.

Following the procedures of the preceding Examples 34 to 46, similar dosage forms of other formula I compounds can be prepared by substituting an equivalent amount of the following compounds as the essential active ingredients; it is understood that these compounds can be the optically active or racemic *trans* stereoisomers.

N - methyl - N - (2 - dimethylaminocyclohexyl) - *p* bromophenylacetamide hydrochloride;

N - methyl - N - (2 - dimethylaminocyclohexyl) - *p* - trifluoromethylphenylacetamide hydrochloride;

N - methyl - N - [2 - (N' - methyl - N' - cyclopropylmethyl)cyclohexyl] - *p*-bromophenylacetamide maleate;

N - methyl - N - (2 - dimethylaminocyclohexyl) - *m* - methoxyphenylacetamide;

N - methyl - N - (2 - dimethylaminocyclohexyl) - *p* - tolylacetamide hydrochloride;

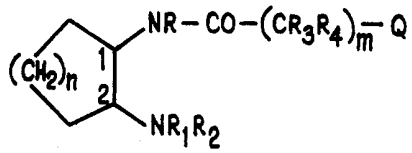
N - methyl - N - (2 - pyrrolidinocyclohexyl) - *p* - bromophenylacetamide hydrochloride;

N - methyl - N - (2 - dimethylaminocyclohexyl) - *p* - azidophenylacetamide;
N - methyl - N - (2 - dimethylaminocyclohexyl) - 3',4' - dichlorophenylacetamide tosylate;
N - methyl - N - (2 - dimethylaminocyclohexyl) - *p* - methoxyphenylacetamide hydrochloride;
N - methyl - N - [2 - [N' - (2 - hydroxyethyl) - N' - methylamino] - cyclohexyl] - 3',4' - dichlorophenylacetamide hydrochloride;
N - methyl - N - [2 - (N' - butyl - N' - methylamino)cyclohexyl] - 3',4' - dichlorophenylacetamide maleate;
N - methyl - N - (2 - diethylaminocyclohexyl) - 3',4' - dichlorophenylacetamide maleate;
N - methyl - N - (2 - dimethylaminocyclohexyl) - 2',4',6' - trimethylphenylacetamide hydrochloride;
1 - (*p* - chlorophenyl) - N - (2 - dimethylaminocyclohexyl) - N - methylcyclopropanecarboxamide;
N - methyl - N - (2 - dimethylaminocyclohexyl) - (2 - naphthyl)acetamide hydrochloride;
N - methyl - N - (2 - dimethylaminocyclohexyl) - (1 - naphthyl)acetamide hydrochloride;
N - methyl - N - (2 - dimethylaminocycloheptyl) - *p* - bromophenylacetamide maleate;
N- methyl - N - (2 - dimethylaminocyclooctyl) - *p* - bromophenylacetamide napsylate,
or other equivalent pharmaceutically acceptable salts thereof.

If desired, additional active ingredients can be incorporated in the present pharmaceutical dosage unit forms as desired. For example, each pharmaceutical dosage unit form may contain therein an amount within the following non-toxic effective ranges: tranquilizers, anti-psychotic and anti-anxiety agents, such as chlorpromazine (5 to 50 mg.), thioridazine (5 to 200 mg.), haloperidol (0.5 to 5 mg.), meprobamate (100 to 400 mg.), chlordiazepoxide (5 to 50 mg.), diazepam (2 to 15 mg.), trazolam (·25—1 mg.), ketazolam (5—300 mg.) and ectylurea (100 to 300 mg.); barbiturates, such as phenobarbital (8 to 60 mg.), butabarbital (8 to 60 mg.), and amobarbital (16 to 120 mg.); analgesics, anti-pyretics-anti-inflammatories, such as aspirin 150 to 600 mg.), flurbiprofen (20 to 200 mg.), ibuprofen (2 to 400 mg.), naproxen (20 to 200 mg.), indomethacin (20 to 200 mg.) and acetaminophen (150 to 600 mg.); and anti-depressants, such as amitriptyline hydrochloride (10 to 50 mg.), methylphenidate hydrochloride (5 to 20 mg.), *d*-amphetamine (5 to 20 mg.), *d*-amphetamine sulfate (2 to 15 mg.), methamphetamine hydrochloride (2 to 15 mg.), depending upon the condition being treated.

WHAT WE CLAIM IS:—

1. A compound of the formula



wherein the 1- and 2-substituents are in the relative *trans*-configuration;

R is hydrogen or C_{1-3} alkyl;

either R_1 is hydrogen or C_{1-3} alkyl and R_2 is hydrogen, C_{1-6} alkyl, $—CH_2CF_3$, C_{3-6} alkenyl or C_{2-5} hydroxyalkyl (but is not alk-1-enyl or α-hydroxyalkyl), C_{3-6} cycloalkyl, (C_3-cycloalkyl)methyl or phenyl)(C_{1-3} alkyl) or NR_1R_2 is optionally 3-substituted azetidino, optionally 3-substituted pyrrolidino or optionally 3- or 4-substituted piperidino (in which any substituent is hydroxy, C_{1-3} alkoxy or C_{1-3} alkanoyloxy), imidazolino, tetrahydropyrimidino, piperazino, N-(C_{1-3} alkyl)piperazino or a saturated 7-membered heterocyclic ring containing 5 carbon atoms and 2 isolated nitrogen atoms;

either m is one and $—CR_3R_4—$ is $—CH(CH_3)—$, $—C(CH_3)_2$ or 1,1-cyclopropylene or m is an integer of from one to 4 and $—CR_3R_4—$ is $—CH_2—$;

n is an integer of from one to 8; and

Q is 1-naphthyl; 2-naphthyl; phenyl; phenyl substituted by one azido, phenyl, trifluoromethyl or C_{1-3} alkoxy radical; or phenyl substituted up to 3 times by

substituents selected from fluorine, chlorine and bromine atoms and C_{1-3} alkyl radicals; provided that Q is not phenyl when R is hydrogen;
or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein R, R_1 and R_2 are each C_{1-3} alkyl; m is one; $-CR_3R_4-$ is $-CH_2-$; n is 2; and Q is phenyl substituted by at least one fluorine, chlorine or bromine atom.

3. N - (*trans* - 2 - dimethylaminocyclohexyl) - N - methyl - *p* - bromophenylacetamide or a pharmaceutically acceptable salt thereof.

4. N - (*trans* - 2 - dimethylaminocyclohexyl) - N - methyl - 3',4' - dichlorophenylacetamide or a pharmaceutically acceptable salt thereof.

5. A compound as claimed in claim 1 wherein R is C_{1-3} alkyl; NR_1R_2 is azetidino, pyrrolidino or piperidino; m is one; $-CR_3R_4-$ is $-CH_2-$; n is 2; and Q is phenyl substituted by an azido group or at least one fluorine, chlorine or bromine atom.

6. N - (*trans* - 2 - pyrrolidinocyclohexyl) - N - methyl - *p* - bromophenylacetamide or a pharmaceutically acceptable salt thereof.

7. N - (*trans* - 2 - pyrrolidinocyclohexyl) - N - methyl - 3',4' - dichlorophenylacetamide or a pharmaceutically acceptable salt thereof.

8. N - (*trans* - 2 - pyrrolidinocyclohexyl) - N - methyl - 3',4' - dichlorophenylacetamide hydrochloride.

9. A compound as claimed in claim 1 wherein R is C_{1-3} alkyl; NR_1R_2 is azetidino, pyrrolidino or piperidino; m is one; $-CR_3R_4-$ is $-CH(CH_3)-$; n is 2; and Q is phenyl substituted by an azido group or at least one fluroine, chlorine or bromine atom.

10. N - (*trans* - 2 - pyrrolidinocyclohexyl) - N - methyl - 2 - (3',4' - dichlorophenyl)propionamide or a pharmaceutically acceptable salt thereof.

11. A compound as claimed in claim 1 wherein R, R_1 and R_2 are each C_{1-3} alkyl; m is one; $-CR_3R_4-$ is $-CH_2-$; n is 2; and Q is phenyl substituted by at least one C_{1-3} alkyl radical.

12. A compound as claimed in claim 11 wherein Q is phenyl substituted by 3 methyl groups.

13. A compound as claimed in claim 1 wherein R, R_1 and R_2 are each C_{1-3} alkyl; m is one; $-CR_3R_4-$ is $-CH_2-$; n is 3; and Q is phenyl substituted by at least one fluorine, chlorine or bromine atom.

14. N - (*trans* - 2 - dimethylaminocycloheptyl) - N - methyl - *p* - bromophenylacetamide or a pharmaceutically acceptable salt thereof.

15. A compound as claimed in claim 1 wherein R, R_1 and R_2 are each C_{1-3} alkyl; m is one; $-CR_3R_4-$ is $-CH_2-$; n is 4; and Q is phenyl substituted by at least one fluorine, chlorine or bromine atom.

16. N - (*trans* - 2 - dimethylaminocyclooctyl) - N - methyl - *p* - bromophenylacetamide or a pharmaceutically acceptable salt thereof.

17. A compound as claimed in claim 1 wherein R, R_1 and R_2 are each C_{1-3} alkyl; m is one; $-CR_3R_4-$ is $-CH_2-$; n is 2; and Q is 1-naphthyl or 2-naphthyl.

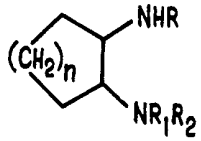
18. N - [*trans* - 2 - (3 - hydroxypyrrolidino)cyclohexyl] - N - methyl - 3,4 - dichlorophenylacetamide or a pharmaceutically acceptable salt thereof.

19. N - (*trans* - 2 - dimethylaminocyclohexyl) - N - methyl - 2',4',6' - trimethylphenylacetamide or a pharmaceutically acceptable salt thereof.

20. N - (*trans* - 2 - dimethylaminocyclohexyl) - N - methyl - (1 - naphthyl)-acetamide or a pharmaceutically acceptable salt thereof.

21. N - [*trans* - 2 - (3 - acetoxypyrrolidino)cyclohexyl] - N - methyl - 3',4' - dichlorophenylacetamide or a pharmaceutically acceptable salt thereof.

22. A process for the preparation of a compound as claimed in claim 1 which comprises reacting a diamine of the formula



wherein R, R_1, R_2 and n are as defined in claim 1, with a carbonyl compound of the formula

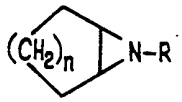
$$Z—CO—(CR_3R_4)_m—Q$$

wherein $-CR_3R_4-$, m and Q are as defined in claim 1 and Z is imidazolyl, chlorine or bromine, in an organic solvent.

23. A process for the preparation of a compound as claimed in claim 1 wherein R_2 is C_{3-6} alkenyl which comprises (a) reacting an amine of the formula

$$NHR_1R_2$$

wherein R_1 is as defined in claim 1 and R_2 is as defined above, with a bicyclic aziridine of the formula



wherein R and n are as defined in claim 1, to form a diamine as defined in claim 22 wherein R_2 is as defined above; and (b) reacting the diamine with a carbonyl compound as defined in claim 22.

24. A process for the preparation of a compound as claimed in claim 1 substantially as herein described with reference to any of Examples 1 to 33.

25. A compound as claimed in claim 1 when prepared by a process according to any of claims 22 to 24.

26. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 21 and 25 in association with a pharmaceutically acceptable carrier.

27. A composition according to claim 26 in which the compound is as claimed in claim 5.

28. A composition according to claim 26 in which the compound is as claimed in claim 7.

26. A compound as claimed in claim 1 or claim 25 wherein Q is not phenyl and, when R is hydrogen, Q is not monohalo- or monoalkyl-substituted phenyl.

27. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 21, 25 and 26 in association with a pharmaceutically acceptable carrier.

28. A composition according to claim 27 in which the compound is as claimed in claim 5.

29. A composition according to claim 27 in which the compound is as claimed in claim 7.

30. A composition according to claim 27 substantially as described in any of Examples 34 to 46.

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