United States Patent Office 3,530,165 Patented Sept. 22, 1970

3,530,165

PHARMACEUTICALLY ACTIVE 4-PHENYLBICYCLO[2.2.2]-OCTANE AND OCT-2-ENE-1-CARBOXAMIDES AND DERIVATIVES THEREOF

Paul E. Aldrich, Wilmington, and Edward C. Hermann, Newark, Del., assignors to E. I. du Pont de Nemours and Company, Wilmington, Del., a corporation of Delaware

No Drawing. Filed Dec. 8, 1967, Ser. No. 688,998
Int. Cl. C07c *69/14, 69/30*
U.S. Cl. 260—479 3 Claims

ABSTRACT OF THE DISCLOSURE

This disclosure teaches that a new class of compounds, the 4-phenylbicyclo[2.2.2]octane and oct-2-ene-1-carboxamides and derivatives thereof are pharmaceutically useful as antifertility agents.

Compounds within the scope of this invention can be formulated into parenteral, oral or rectal dosage forms and when administered by the appropriate route, surprisingly prevent pregnancy in animals.

BACKGROUND OF THE INVENTION

This invention relates to a novel class of compounds, the 4-phenylbicyclo[2.2.2]octane and oct-2-ene-1-carboxamides and derivatives thereof. The term "phenyl" in the general description of the compounds of this invention is intended to include phenyl and substituted phenyl. In those compounds in which the phenyl group is substituted, the substituent is attached para to the point of attachment to the bicyclooctane cage structure. These subsituents can include groups such as H, OH, its alkyl carboxylic acid esters, OCH_3 and OC_2H_5.

It should further be stated that the term, carboxamides and derivatives thereof, is intended to include the carboxamides, hydrazides and hydroxamic acid derivatives which are more particularly defined below.

I have further discovered that this class of compounds can be used as antifertility agents in animals to prevent pregnancy.

This activity for the compounds of my invention is all the more startling when these compounds are compared in structure to contraceptive agents presently known to the medical art.

The agents which are known to be most effective for preventing pregnancy are compounds such as estrogens and progesterones.

Presently, the most widely accepted of these pharmaceutical agents are mixtures of steroidal estrogens progestins. When these agents are administered, a pseudopregnancy is established and ovulation is prevented. In order to induce this pseudopregnant condition, these agents are administered orally for about twenty days of the menstrual cycle. Although they are quite effective, this dosage regimen can result in side effects. The most commonly occurring side effects are similar to the symptoms observed during pregnancy. These side effects include nausea, occassional vomiting, dizziness, headache, breast enlargement and pigmentation of the nipples, and are most frequently observed during the first cycle in which these agents are administered.

The fact that these agents require a cyclic administration regimen also presents a problem. They must be administered without fail each day of the 20-day period or there is danger of breakthrough bleeding.

I have discovered that 4-phenylbicyclo[2.2.2]octane and oct-2-ene-1-carboxamides can be used in an entirely different manner to prevent pregnancy. Whereas the

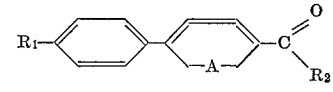
estrogenprogestin mixtures now most widely used must be taken for relatively long periods in anticipation of coitus, the 4-phenylbicyclo[2.2.2]octane and oct-2-ene-1-carboxamides can be administered after coitus to prevent pregnancy. Although the exact mechanism of action is not well understood, animal studies indicate that, most probably, nidation is in some manner prevented.

Therefore, in addition to the striking structural difference of the compounds of this invention over known contraceptive agents, it also appears that the compounds of this invention exhibit a mechanism of action that materially differs from presently employed contraceptive agents.

This new mechanism of action has numerous practical advantages such as ease of use, elimination of protracted periods of administration, elimination of a scheduled regimen of medication, and the avoidance of a continual state of pseudopregnancy which is responsible for many side effects.

SUMMARY OF THE INVENTION

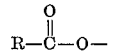
In summary, this invention relates to compounds of the formula



where

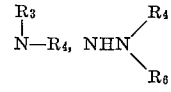
A is a single bond or a double bond

R_1 can be H, —OH, —OCH_3, —OC_2H_5, —OC_3H_7, —OC_4H_9 or



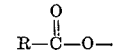
wherein R is an alkyl of from one through twelve carbons; and

R_2 can be —NH—NH_2, NHOH,



where each of R_3, R_4, R_5 or R_6 can be H, $CH_3C_2H_5$ or R_3 and R_4, and R_5 and R_6 can be taken together to form the following ring systems with the nitrogen, pyrrolidino, piperidino or morpholino.

Of the above compounds wherein R_1 is



those compounds are preferred wherein R is an alkyl of one through four carbons.

Most preferred of the compounds of this invention are those compounds of the above formula in which A can be a single bond or a double bond; R_1 can be HO—, H_3CO—, H_5C_2O— or CH_3CO_2—; and R_2 is NH_2.

DESCRIPTION OF THE INVENTION

The term 4-phenylbicyclo[2.2.2]octane and oct-2-ene-1-carboxamides is used as a generic term and includes 4-phenylbicyclo[2.2.2]octane-1-carboxamides, 4-(p-substituted phenyl)bicyclo[2.2.2]octane-1-carboxamide, 4-phenylbicyclo[2.2.2]octane-1-carbohydroxamic acids, 4-(p-substituted phenyl)bicyclo[2.2.2]octane-1-carboxylic acid hydrazides and the corresponding "bicyclo[2.2.2]-oct-2-ene" compounds. In this definition, the term "substituted phenyl" is intended to

include a phenyl having the para hydrogen replaced by groups such as —OH, —OCH_3, —OC_2H_5, —OC_3H_7, OC_4H_9 or

where R is an alkyl of from one through twelve carbons.

A convenient starting material for the compounds of this invention can be prepared beginning with acetophenone or a substituted acetophenone. The desired acetophenone is treated with diethylethoxymethylenemalonate in ethyl alcohol in the presence of sodium ethoxide under a nitrogen atmosphere. The intermediate thus formed is cyclized to a pyrone by treatment with anhydrous hydrogen fluoride.

The pyrone is dissolved in an inert solvent, such as benzene, and is heated with ethylene under pressure to give the corresponding 4 - phenylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid ethyl ester. This ester is then hydrolized to give the corresponding 4 - phenylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid.

The carboxamides of this invention can be prepared by heating a 4 - phenylbicyclo[2.2.2]octane or oct-2-ene-1-carboxylic acid at reflux with thionyl chloride and then adding this mixture to an aqueous solution of the appropriate amine resulting in the precipitation of the desired carboxamide. This carboxamide can be separated from the reaction system and purified using conventional techniques.

The hydroxamic acids of this invention can be prepared by treating a 4 - phenylbicyclo[2.2.2]octane or oct-2 - ene - 1 - carboxylic acid with thionyl chloride and stirring this mixture for one hour at room temperature. The solution is evaporated at reduced pressure and the residue is dissolved in pyridine. To this solution is added a solution of an hydroxylamine in pyridine. The resulting mixture is stirred for for 15 to 25 hours and the desired 4 - phenylbicyclo[2.2.2]octane or oct - 2 - ene-1-carbohydroxamic acid is precipitated by pouring the reaction mixture into an ice cold acid such as hydrochloric acid. This precipitate is then separated and purified using conventional techniques.

The carboxylic acid hydrazides of this invention can be conveniently prepared starting with the desired 4-phenylbicyclo[2.2.2]octane or oct - 2 - ene-1-carboxylic acid lower alkyl ester dissolved in a suitable inert solvent, such as amyl alcohol. The desired hydrazide is added to this solution and this mixture is refluxed for about 72 hours. The product is evaporated at reduced pressure and the hydrazide product in the residue is recrystallized from toluene.

For a more clear understanding of how the compounds

of this invention are obtained, the following examples are presented.

In the following examples parts are by weight unless otherwise indicated.

EXAMPLE 1

A mixture of 5 parts thionyl chloride and one part 4-phenylbicyclo[2.2.2]octane - 1 - carboxylic acid is heated at reflux for 15 minutes and is then cooled. This solution is poured into a cold, stirred, aqueous ammonium hydroxide. A precipitate forms and this precipitate is filtered off, is washed with water and is air-dried resulting in 4-phenylbicyclo[2.2.2]octane - 1 - carboxamide, M.P. 229.5–232° C.

EXAMPLES 2–7

The procedure of Example 1 is repeated substituting equivalent amounts of the indicated acid for the 4-phenylbicyclo[2.2.2]octane - 1 - carboxylic acid and an aqueous solution of the indicated amine for the ammonium hydroxide solution of Example 1 to obtain the indicated product.

Ex.	Acid	Amine	Product
2	4-(*p*-methoxyphenyl)-bicyclo[2.2.2]octane-1-carboxylic acid	Ammonia	4-(p-methoxyphenyl)-bicyclo[2.2.2]octane-1-carboxamide, 235.5–236° C.
3	do	Methylamine	N-methyl-4-(p-methoxyphenyl)-bicyclo[2.2.2]-octane-1-carboxamide, 204–240.5° C.
4	do	Dimethylamine	N,N-dimethyl-4-(p-methoxyphenyl)bicyclc-[2.2.2]octane-1-carboxamide, 138–140.5° C.
5	do	Pyrrolidine	N,N-tetramethylene-4-(p-methoxyphenyl)-bicyclo[2.2.2]octane-1-carboxamide.
6	do	Piperidine	N,N-pentamethylene-4-(p-methoxyphenyl)-bicyclo[2.2.2]-octane-1-carboxamide.
7	do	Morpholine	N,N-3'-oxa-pentamethylene-4-(p-methoxyphenyl)bicyclo-[2.2.2]octane-1-carboxamide.

EXAMPLE 8

Ten parts 4 - (p - ethoxyphenyl)bicyclo[2.2.2]oct-2-ene-1-carboxylic acid ethyl ester and 50 parts anhydrous ammonia are charged to an autoclave. The mixture is heated with shaking at 160° C. for 16 hours at autogenous pressure. The mixture is cooled and excess ammonia is evaporated having 4 - (p - ethoxyphenyl)bicyclo[2.2.2]oct-2-ene-1-carboxamide as the residue.

EXAMPLES 9 AND 10

The procedure of Example 8 is repeated, substituting an equivalent amount of the indicated ester and indicated amine respectively for the 4 - (p - ethoxyphenyl)bicyclo-[2.2.2]oct - 2 - ene - 1-carboxylic acid ethyl ester, and ammonia of Example 8 to obtain the indicated product.

Ex.	Acid	Amine	Product
9	4-(p-hydroxyphenyl)-bicyclo[2.2.2]octane-1-carboxylic acid methyl ester.	Ammonia	4-(p-hydroxyphenyl)-bicyclo[2.2.2]octane-1-carboxamide.
10	4-(p-hydroxyphenyl)bicyclo[2.2.2]oct-2-ene-1-carboxylic acid methyl ester.	Methylamine	N-methyl-4-(p-hydroxyphenyl)bicyclo[2.2.2]oct-2-ene-1-carboxamide.

EXAMPLE 11

To a solution of 0.010 mole of 4-(p-hydroxyphenyl) bicyclo[2.2.2]octane-1-carboxamide in 50 ml. of anhydrous pyridine is added at least one molar equivalent of acetic anhydride. The solution is allowed to stand for 16 hours. Then 5 ml. of water is added and the solution is allowed to stand for 4 hours. The solution is poured into a mixture of 200 g. of ice and 200 ml. of 6 N HCl. When the ice is melted, the precipitate is filtered off, is washed with water, is dried and is found to be 4-(p-acetoxyphenyl)bicyclo[2.2.2]octane-1-carboxamide.

EXAMPLES 12 and 13

The procedure of Example 11 is repeated substituting the indicated reactants for the 4-(p-hydroxyphenyl) bicyclo[2.2.2]octane-1-carboxamide and acetic anhydride of Example 11 to obtain the indicated product.

Ex.	Carboxamide	Acid chloride	Product
12	4-(p-hydroxyphenyl)bicyclo[2.2.2]octane-1-carboxamide	Propionyl chloride.	4-(p-propionoxyphenyl)bicyclo[2.2.2]octane-1-carboxamide.
13	N-methyl-4-(p-hydroxyphenyl)bicyclo[2.2.2]oct-2-ene-1-carboxamide.	Dodecanoyl chloride.	N-methyl-4-(p-dodecanolyoxyphenyl)bicyclo[2.2.2]oct-2-ene-1-carboxamide.

As is evident from the foregoing examples, when esterification of the phenolic p-hyroxyl group is desired, this can be accomplished using either the appropriate acid chloride or acid anhydride with equally satisfactory results.

EXAMPLE 14

A solution of 2.6 parts of 4-(p-methoxyphenyl) bicyclo[2.2.2]octane-1-carboxylic acid in 30 parts of benzene is treated with 5 parts of thionyl chloride and is stirred for 1 hour. The solution is evaporated at reduced pressure. The residue is dissolved in 20 parts of pyridine. A solution of 6.9 parts of hydroxylamine hydrochloride in 20 parts of pyridine is added, and the mixture is stirred for 16 hours. The mixture is poured into a mixture of 500 parts of 1 N HCl and 200 parts of ice. The precipitate is filtered off, is washed with water, and is dried. Recrystallization of the precipitate from nitromethane gives 4 - (p - methoxyphenyl)bicyclo[2.2.2]octane-1-carbohydroxamic acid, M.P. 217 (dec.). The crystals give a deep red color with ferric chloride in alcohol.

Analysis.—Calc'd for $C_{16}H_{21}NO_3$ (percent): C, 69.79; H, 7.69; N, 5.09. Found (percent): C, 69.48; H, 7.53; N, 5.04.

EXAMPLE 15

A solution of 8.64 parts of 4-(p-methoxyphenyl) bicyclo[2.2.2]octane-1-carboxylic acid ethyl ester and 9.6 parts of 99% hydrazine in 50 parts of amyl alcohol is refluxed together for 3 days. The product is evaporated at reduced pressure. The residue is recrystallized from toluene to give 4 - (p - methoxyphenyl)bicyclo[2.2.2] octane-1-carboxylic acid hydrazide, M.P. 196.5–198.5° C.

EXAMPLE 16

A solution of 0.010 mole of 4-(p-ethoxyphenyl)-bicyclo[2.2.2]oct-2-ene-1-carboxylic acid ethyl ester and 0.010 mole of methylhydrazine in 100 ml. of alcohol is heated at 150° C. in an autoclave at autogenous pressure for 16 hours. The mixture is cooled and evaporated to give N'-methyl-4-(p-ethoxyphenyl)bicyclo[2.2.2]oct-2-1-carboxylic acid hydrazide.

When the procedure of Example 16 is repeated, substistituting an equivalent amount of 4-(p-hydroxyphenyl) bicyclo[2.2.2]actane-1-carboxylic acid methyl ester and 1,1-dimethylhydrazine for the 4-(p-ethoxyphenyl)bicyclo [2.2.2]oct-2-ene-1-carboxylic acid ethyl ester and methylhydrazine, respectively, of Example 16, N',N'-dimethyl-4-(p-hydroxyphenyl)bicyclo[2.2.2]octane - 1 - carboxylic acid hydrazide is obtained.

EXAMPLE 17

A mixture of 2.88 parts of N',N'-dimethyl-4-(p-hydroxyphenyl)bicyclo[2.2.2]octane-1-carboxylic acid hydrazide, 54 parts of acetic anhydride, and 4 parts of anhydrous sodium acetate are refluxed for 1 hour. The mixture is cooled and 20 parts of water is added dropwise. The mixture is allowed to stand for 12 hours and then is evaporated at reduced pressure. The residue is treated with a mixture of 5% sodium bicarbonate solution and chloroform. The chloroform extract is washed with water, is dried with anhydrous sodium sulfate, and is evaporated to give N',N'-dimethyl-4-(p-acetoxyphenyl) bicyclo[2.2.2]octane-1-carboxylic acid hydrazide.

The compounds of this invention can be administered to prevent pregnancy according to the method of this invention by any suitable means. For example, administration can be parenterally, that is subcutaneously or intramuscularly. Alternatively administration can be by the oral or rectal route.

In most animals, these compounds are effective when given in single or divided doses for from 0 to 15 days after coitus.

It is preferred that these compounds be administered in a single dose after coitus, but before estimated time of implantation of the fertilized egg in the uterus.

The dosage administered will be dependent upon age, health and weight of the recipient and also upon the frequency of administration. Generally, from 0.001 to 50 mg./kg. per day of active ingredient for one or more days is effective to obtain the desired result. A dosage of from 0.005 to 10 mg./kg. per day is preferred with the most preferred dosage being in the range of from 0.01 to 5 mg./kg. per day.

These compounds have shown outstanding inhibition of pregnancy in rats as will be seen from the following example. Therefore, the method of this invention can be used in addition to, or as a replacement for, presently known rodent control methods.

EXAMPLE 18

Immature rats (28 days old) are induced into precocious puberty with a single dose of pregnant mouse' serum gonadotrophin and then are mated with normal males. A suspension of 4-(p-methoxyphenyl)bicyclo[2.2.2]octane-1-carboxylic acid hydrazide in sesame oil is administered orally daily for six days starting on the day of finding sperm or a vaginal plug. One week after mating, the animals are killed and their uteri are examined for implantation sites. If any are found, the animal is considered pregnant. Control animals have a mean of eight implantation sites. When a series of graded doses is administered, the dose at which fifty percent of the animals show no evidence of pregnancy, the ED_{50}, is found to be between 0.31 and 1.24 mg./kg.-day.

The test of Example 18 is repeated substituting 4-(p-methoxyphenyl) bicyclo[2.2.2]octane-1-carbohydroxamic acid for the compound used in the above test. The ED_{50} is found to be less than 1.24 mg./kg.-day.

The test of Example 18 is again repeated substituting 4-phenylbicycle[2.2.2]octane-1-carboxamide for the compound used in the above test. The ED_{50} is found to be between 1.25 and 4.99 mg./kg.-day.

The compounds of this invention can also be employed with equally satisfactory results to prevent pregnancy in other laboratory animals such as mice, guinea pigs, rabbits, monkeys and chimpanzees and are also effective in prevening pregnancy in domestic animals such as cows, sheep, swine and horses. In small animals, it is usually convenient to administer the compounds of this invention orally incorporated in a capsule, or incorporated in the feed of the animals. On the other hand, when these compounds are administered to large animals, it is often more convenient to administer them parenterally.

The active ingredient of this invention can be employed in useful compositions according to the present invention in such dosage forms as tablets, capsules, powder packets, or liquid solutions, suspensions, or elixirs, for oral administration or liquid solutions for parenteral use, and in certain cases, suspensions for parenteral use. In such compositions, the active ingredient will ordinarily always be present in an amount of at least 0.01% by weight based on the total weight of the composition and not more than 90% by weight.

Besides the active ingredient of this invention the composition will contain a solid or liquid non-toxic pharmaceutical carrier for the active ingredient.

In one embodiment of a pharmaceutical composition of this invention, the solid carrier is a capsule which can

be of the ordinary gelatin type. The capsule will be from about 0.1% to 75% by weight of a 4-phenylbicyclo [2.2.2]-octane and oct-2-ene-1-carboxamide or derivative thereof of this invention and 99.9–25% of a carrier. In another embodiment, the active ingredient is tableted with or without adjuvants. In yet another embodiment, the active ingredient is put into powder packets and employed. These capsules, tablets, and powders will generally constitute from about 0.5% to about 95% and preferably from 1% to 50% by weight of active ingredient. These dosage forms preferably contain from about 0.5 to about 250 milligrams of active ingredient, with from about 1 milligram to about 50 milligrams most preferred.

The pharmaceutical carrier can, as previously indicated be a sterile liquid such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, for example peanut oil, soybean oil, mineral oil, sesame oil, and the like. In general, water, saline, aqueous dextrose (glucose) and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are preferred liquid carriers, particularly for injectable solutions. Sterile injectable solutions such as saline will ordinarily contain from about 0.05% to 25%, and preferably about 0.1% to 5% by weight of the active ingredient.

As mentioned above, oral administration can be in a suitable suspension, syrup or elixer in which the active ingredient ordinarily will constitute from about 0.01 to 5% and preferably about 0.05 to 1% by weight. The pharmaceutical carrier in such composition can be an aqueous vehicle such as an aromatic water, a syrup or a pharmaceutical mucilage.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin, a well-known reference text in this field.

In addition to the exemplary illustrations above, the following examples further explain one aspect of the present invention.

EXAMPLE 19

A large number of unit capsules are prepared for oral administration by filling standard two-piece hard gelatin capsules with 10 milligrams of powdered 4-(p-acetoxyphenyl)bicyclo[2.2.2]oct-2-ene-1-carboxamide, 125 milligrams of lactose and 1 milligram of finely divided pyrogenic silica.

In addition to, or in place of, the lactose in the above formulation, fillers such as anhydrous lactose, kaolin, precipitated calcium carbonate, manitol, microcriptalline cellulose or the like can be substituted with satisfactory results.

If desired, lubricants and gliders such as talc, magnesium stearate, calcium stearate, corn starch, stearic acid, polyethylene glycol 4,000 or the like can be substituted for the pyrogenic silica of the formulation of Example 19 with satisfactory results.

EXAMPLE 20

A large number of unit capsules are prepared for oral administration by filling soft gelatin capsules with a solution of 4-(p-hydroxyphenyl)bicyclo[2.2.2]oct-2-ene-1-carboxamide in sesame oil.

EXAMPLE 21

A large number of tablets are prepared by conventional procedures so that the dosage unit is 5 milligrams of active ingredient, 82.9 milligrams of anhydrous lactose, 2 milligrams of magnesium stearate and 10 milligrams of microcrystalline cellulose and 0.1 milligram of pyrogenic silica. Slow release tablets can also be prepared by applying appropriate coatings. In other tablet formulations from 1 to 7% of the total weight of the dosage form can be comprised of a lubricant or glidant such as talc, stearic acid, magnesium stearate or the like in place of the pyrogenic silica of the above formulation.

Other binders which can be substituted for the anhydrous lactose of the above formulation include starch, ethylcellulose polyethylene glycol 4,000 or the like.

Other fillers which can be substituted for the microcrystalline cellulose of the above formulation include lactose, manitol or the like.

In some formulations, it is also preferred to include a typical disintegrating agent such as methylcellulose, veegum, starch, microcrystalline cellulose or the like.

EXAMPLE 22

A parenteral composition suitable for administration by injection is prepared by stirring 0.5% by weight of 4-(p-ethoxyphenyl)bicyclo[2.2.2]octane - 1 - carboxamide in sterile mineral oil.

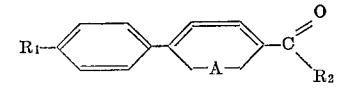
EXAMPLE 23

Suppositories suitable for rectal administration can be prepared by stirring 0.25% by weight of 4-(p-methoxyphenyl)bicyclo[2.2.2]oct-2-ene-1-carboxamide in melted theobroma oil and molding the mass into two-gram suppositories.

A large variety of compositions according to this invention can thus readily be made by substituting other compounds for this invention, and including specifically but not limited to compounds for this invention that have specifically been named hereinbefore. The compounds will be used in the amounts indicated in accordance with procedures well known and described in the Martin text mentioned above.

Since many different embodiments of the invention can be made without departing from the spirit and scope thereof, it is to be understood that the invention is not limited by the specific illustrations except to the extent defined in the following claims.

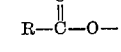
1. A compound of the formula



where

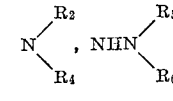
A is selected from the group consisting of a single bond and a double bond;

R_1 is selected from the group consisting of H, OH, OCH_3, OC_2H_5 and



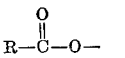
wherein R is an alkyl of from one through twelve carbons; and

R_2 is selected from the group consisting of —NH–NH_2, NHOH,



where each of R_3 and R_4 or R_5 and R_6 can be the same or different and are selected from the group consisting of hydrogen, methyl and ethyl and R_3 and R_4 or R_5 and R_6 can be taken together to form a ring system selected from the group consisting of pyrrolidino, piperidino and morpholino.

2. A compound of claim 1 wherein R_1 is selected from the group consisting of H, OH, OCH_3, OC_2H_5 and



wherein R is an alkyl of one through four carbons and R_2 and H are as defined in claim 1.

3. A compound of claim 1 selected from the group consisting of 4-(p-hydroxyphenyl)bicyclo[2.2.2]octane-

1 - carboxamide; 4 - (p - hydroxyphenyl)bicyclo[2.2.2] oct - 2 - ene - 1 -carboxamide; 4-(p-methoxyphenyl) bicyclo[2.2.2]octane - 1 - carboxamide; 4-(p-methoxyphenyl)bicyclo[2.2.2]oct - 2 - ene - 1 - carboxamide; 4-(p-ethoxyphenyl)bicyclo[2.2.2.]octane - 1 - carboxamide; 4-(p-ethoxyphenyl)bicyclo[2.2.2]oct - 2 - ene - 1 - carboxamide; 4 - (p - acetoxyphenyl)bicyclo[2.2.2]octane-1-carboxamide and 4 - (p-acetoxyphenyl)bicyclo[2.2.2] oct-2-ene-1carboxamide .

References Cited

C. A. Chem. Abstracts, vol. 67 (1967), page P5387*a*.

JAMES A. PATTEN, Primary Examiner

U.S. Cl. X.R.

260—247.2, 247.7, 293.4, 294.3, 326.3, 326.5, 343.5, 410.5, 469, 473, 515, 558; 424—248, 267, 274 311, 324