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3,422,141

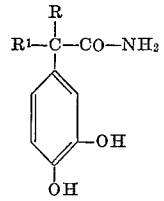
3,4-DIHYDROXYPHENYLALKANAMIDES

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No Drawing. Continuation of application Ser. No. 312,361, Sept. 30, 1963, which is a continuation-in-part of application Ser. No. 251,019, Jan. 14, 1963. This application Mar. 23, 1967, Ser. No. 625,557
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U.S. Cl. 260—559 9 Claims
Int. Cl. C07c *103/26*

ABSTRACT OF THE DISCLOSURE

The present invention discloses compounds having the following formula:

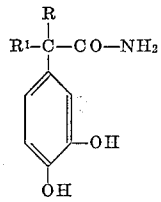


in which R is selected from the class consisting of hydrogen, lower alkyl, and alkoxy of at most 2 carbon atoms, and R^1 is selected from the class consisting of hydrogen and alkyl of at most 2 carbon atoms.

This application also discloses a method for producing such compounds by subjecting intermediate compounds to amidation reaction with the compound selected from the class consisting of ammonia and salts thereof, and thereafter converting any ether or ester groups directly attached to the benzene nucleus into the corresponding phenolic hydroxy groups. The application also discloses pharmaceutical compositions containing such compounds and the use of such compounds in inhibiting the action of certain enzymes which decompose adrenalin.

This invention relates to amides having useful pharmaceutical properties, their production, and pharmaceutical compositions containing them, and is a continuation of our application Ser. No. 312,361, filed Sept. 30, 1963, now abandoned, which in turn is a continuation-in-part of our application Ser. No. 251,019, filed Jan. 14, 1963, now abandoned.

The amides of the invention have the formula:

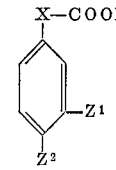


in which R represents a hydrogen atom, an alkyl group containing at most 6 carbon atoms or an alkoxy group containing at most 2 carbon atoms and R^1 represents a hydrogen atom or an alkyl group containing at most 2 carbon atoms. Especially useful compounds of the aforesaid formula are those in which R and R^1 each represent a hydrogen atom or an alkyl group of at most 2 carbon atoms and together contain not more than 2 carbon atoms, and also those in which R is an alkyl group containing from 3 to 6 carbon atoms or an alkoxy group

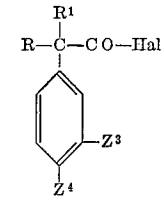
containing at most 2 carbon atoms and R^1 is a hydrogen atom.

These compounds exhibit an inhibiting action on certain enzymes which decompose adrenaline. The two most important methods of decomposing adrenaline and closely related catecholamines in the organisms of mammals consist in oxidative deamination by means of monoamino oxydase (MAO) and 3-O-methylation by the action of catechol-O-methyl-tranferase (COMT). The substance hitherto mostly employed for inhibiting COMT, pyrogallol, has pronounced toxic effects (inter alia methaemoglobinaemia), which greatly reduces its utility as a COMT inhibitor. Compounds of the aforesaid formula have a very useful inhibitory action on COMT, in many cases superior to that of pyrogallol, and are at the same time much less toxic than pyrogallol.

The amides of the aforesaid formula may be obtained by subjecting a compound of the formula:



(in which X, Z^1 and Z^2 are the same as or convertible into the corresponding groups in the desired product) or an amide-forming derivative thereof to an amidation reaction with ammonia or a salt thereof, and effecting such conversion of any of the groups X, Z^1 and Z^2 as may be necessary to give the product desired. Preferably a compound of the formula:



(in which R and R^1 are as defined above, and Z^3 and Z^4 which may be the same or different, each represent a hydroxy group or an ether or ester group of aliphatic, araliphatic or inorganic nature which is convertible into an hydroxy group and Hal represents a halogen atom) is reacted with ammonia or a salt thereof by methods known per se and any ether and ester groups directly attached to the benzene nucleus are converted into the corresponding phenolic hydroxy groups by hydrolysis or hydrogenolysis.

The group X in the starting material may, for example, contain unsaturated bonds. Conversion of such groups by reduction into the group



may be effected before or after conversion of groups Z^1 and Z^2 into hydroxy groups. However when the starting material contains ether groups which are to be converted into phenolic hydroxy groups in the final product, it is preferred to hydrogenate the group X and carry out hydrogenolysis of the ether groups simultaneously.

Methods known per se are applicable to the synthesis of the new amides. Preferably, hydroxy groups which occur in the starting material are protected, prior to amidation, by conversion into corresponding ether or ester groups which may ultimately be split off by catalytic hydrogenation, for example in the presence of palladized charcoal, or hydrolysis. Since amides having two or more

phenolic hydroxyl groups are sensitive to oxygen in solution, and since the very high water solubility of the reaction products renders their preparation difficult, it is advantageous to carry out catalytic hydrogenolysis of hydroxyl groups protected by conversion to an ether as the last stage of the reaction.

The active substances are preferably administered by injection, but they may be administered orally or percutaneously. Usually they will be administered in the form of compositions comprising the active substance in association with a pharmaceutical carrier. Compositions suitable for injection comprise the active substance dissolved or dispersed in a suitable sterile liquid. Water, preferably made isotonic with the blood and adjusted to a suitable pH value, is the preferred solvent but non-aqueous liquids may be employed. Injectable solutions will usually contain between 0.1 and 20%, for example between 0.5 and 5% of the active substance. For oral administration, the compositions may be solid or liquid, and will usually contain between 1 and 95%, for example between 5 and 50% of active substance. Orally administrable compositions may be in the form of a tablet, powder, pill, syrup or elixir, or alternatively may comprise the active substance enclosed in a capsule. Obviously the carrier employed will be compatible with the active substance.

The invention is illustrated by the following examples.

Example I

(a) 3,4-dibenzyloxyphenylacetyl chloride: 21.0 g. of 3,4-dibenzyloxyphenylacetic acid, 70 ml. of benzene and 30 ml. of thionyl chloride were heated under reflux for 3 hours. The residue obtained after evaporation in vacuo, an oil, was used for the next stage without further purification.

(b) 3,4-dibenzyloxyphenylacetamide: 20 g. of the acid chloride were dissolved in 50 ml. of benzene and the solution was shaken for 3 hours with 100 ml. of 15% aqueous ammonia solution. The solid product was filtered off and recrystallised from a mixture of methanol and water. The recrystallised product (18 g.) melted at 136° C.

(c) 3,4-dihydroxyphenylacetamide: 2.3 g. of 3,4-dibenzyloxyphenylacetamide were catalytically hydrogenated in 100 ml. of ethanol in the presence of 0.5 g. of palladized charcoal. After absorption of 2 moles of hydrogen, the mixture was filtered and evaporated. Recrystallisation of the residue from a mixture of acetone and benzene gave 1.1 of the amide (M.P. 147° C.).

Example II

(a) 3,4-diacetoxyphenylacetic acid: 2 g. of 3,4-hydroxyphenylacetic acid were dissolved in 10 ml. of anhydrous pyridine and 5 g. of acetic anhydride were added. After standing for 12 hours at room temperature, the solution was evaporated in vacuo at 20° C. The residue did not crystallise.

(b) 3,4-diacetoxyphenylacetyl chloride: 2 g. of 3,4-diacetoxyphenylacetic acid and 5 ml. of thionyl chloride were cooled in an ice bath and 3 drops of pyridine were added. After ½ hour at 0° C. and 3 hours at 20° C., the reaction mixture was evaporated in vacuo at 20° C. The residue was triturated with petroleum ether to remove thionyl chloride.

(c) 3,4-dihydroxyphenylacetamide: to 2 g. of 3,4-diacetoxyphenylacetyl chloride, cooled with ice, were added 7 ml. of concentrated NH_4OH and 0.1 g. of sodium sulphite. After 1 hour at room temperature, the solution was brought to a pH of 6 with 50% sulphuric acid and extracted four times with ethyl acetate. The ethyl acetate extracts were dried over sodium sulphate and evaporated. The residue was recrystallised from a mixture of acetone and benzene, giving 1.1 g. of product, M.P. 147° C.

Examples III–V

The following compounds were prepared in a manner similar to that described above: 3,4-dihydroxyhydratropamide, M.P. 147° C.; α-3,4-dihydroxyphenylbutyramide, M.P. 139° C.; and α-3,4-dihydroxyphenylisobutyramide, M.P. 139° C.

The starting materials for Examples VI and VII were prepared by the following procedure.

(a) 3,4-dibenzyloxy-α-methoxy- and ethoxy-phenylacetic acids: 3,4-dibenzyloxybenzaldehyde (15.9 g.), bromoform (16 g.), methanol (50 ml.) and dioxane (50 ml.) were slowly mixed with stirring at below 20° C. with a solution of potassium hydroxide (14 g.) in methanol (55 ml.). After 12 hours at 20° C. sodium bromide which had separated was filtered off and solvent was removed by distillation in vacuo. The residue was dissolved in water (200 ml.), and the resulting aqueous solution was shaken with ether. After separation from the ether extract, the aqueous solution was acidified with concentrated hydrochloric acid. An oil, which slowly crystallised, was formed. Recrystallisation from a mixture of ethyl acetate and petroleum ether gave 13 g. of the acid in the form of colourless needles of melting point 160 C.

In a similar way 3,4-dibenzyloxy-α-ethoxy-phenylacetic acid was prepared by reacting 3,4-dibenzyloxybenzaldehyde (15.9 g.) and bromoform (16 g.) in ethanol (50 ml.) and dioxane (50 ml.) with potassium hydroxide (14 g.) in ethanol (70 ml.). 8.1 g. of the acid in the form of thin needles M.P. 100–101° C. was obtained after recrystallisation from a mixture of petroleum ether and ethyl acetate.

The acids may alternatively be prepared from the corresponding 3,4-dibenzyloxymandelic acids, as by the following procedure. 3,4-dibenzyloxymandelic acid (5 g.), methyl iodide (14.2 g.), silver oxide (23 g.) and dry acetone (200 ml.) were heated under reflux. After 2 hours further methyl iodide (15 g.) was added. After 12 hours the solution was filtered and evaporated. The ester was saponified by heating under reflux with potassium hydroxide (5 g.) in ethanol (100 ml.). After 2 hours the mixture was diluted with water (300 ml.) and acidified with concentrated hydrochloric acid. The acid crystallised and was isolated by filtration and dried. Recrystallisation from a mixture of ethyl acetate and petroleum ether gave 3.0 g. of the acid of M.P. 116° C., which was shown to be identical with acid obtained from 3,4-dibenzyloxybenzaldehyde by mixed melting point and I.R. spectrum determinations.

(b) 3,4-dibenyloxy-α-methoxy- and ethoxy-phenylacetyl chlorides: 3,4-dibenzyloxy-α-methoxy-phenyl acetic acid (10 g.) was heated with thionyl chloride (15 ml.) in chloroform (100 ml.) for 2 hours under reflux. After removal of the solvent and excess of thinoyl chloride in the reaction mixture, the acid chloride was obtained as an oil which was then used immediately in the next stage.

3,4-dibenzyloxy-α-ethoxy-phenylacetic acid (10 ml.) was mixed with thionyl chloride (50 ml.) while cooling with ice. Reaction was started by adding pyridine (0.1 ml.) and after allowing the reaction to continue for ½ hour at 0° C. and 3 hours at 20° C., excess of thionyl chloride was removed by distillation in vacuo at a temperature below 30° C. The residual oil was used immediately in the next step of the synthesis.

Example VI

(a) 3,4-dibenzyloxy-α-methoxy-phenylacetamide: 3,4-dibenzyloxy-α-methoxy-phenylacetyl chloride (10 g.) prepared as described above was dissolved in benzene (5 ml.) and then concentrated ammonium hydroxide (10 ml.) was added while shaking and cooling with ice. After one hour the amide which had formed was separated by filtration. Recrystallisation from a mixture of methanol and water gave 6.1 g. of white needles of melting point 124° C.

(b) 3,4-dihydroxy-α-methoxy-phenylacetamide: 3,4-dibenzyloxy-α-methoxy-phenylacetamide (3.77 g.) prepared as described under (a) above was hydrogenated in etha-

nol (60 ml.) in the presence of palladized charcoal (0.5 g.). After absorption of 480 ml. (theoretical volume 482 ml.) of hydrogen the reduction came to a standstill. The reaction mixture was filtered and the residue obtained by evaporation of the filtrate recrystallised from a mixture of methanol and ethyl acetate. The resulting amide (1.69 g.) was in the form of prisms of M.P. 196° C. and contained ½ mole of water of crystallisation.

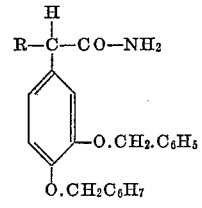
Example VII

(a) 3,4-dibenzyloxy-α-ethoxy-phenylacetamide: 3,4-dibenzyloxy-α-ethoxphenylacetyl chloride (10 g.) was treated in a manner analogous to that described in Example VI(a). On recrystallisation from a mixture of ethyl acetate and petroleum ether the product was obtained in the form of white needles (7.5 g.) of melting point 113° C.

(b) 3,4-dihydroxy-α-ethoxy-phenylacetamide: 3,4-dibenzyloxy-α-ethoxy-phenylacetamide (3.91 g.) was hydrogenated by a procedure analogous to that described in Example VI(b). On recrystallisation from a mixture of methanol and ethyl acetate, 1.91 g. of 3,4-dihydroxy-α-ethoxy-phenyl acetamide of melting point 159° C. were obtained.

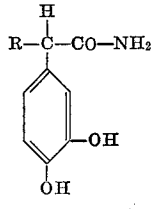
Example VIII–XIII

The following amides were prepared from the corresponding acid chlorides by a procedure analogous to that described in Examples VI and VII.



R:	Melting point, °C.
n-C_3H_7	146–147
iso-C_3H_7	142
n-C_4H_9	148–150
iso-C_4H_9	128–129
n-C_6H_{13}	82

On removing protecting groups by catalytical hydrogenation by a procedure analogous to that described in Examples VI and VII, the following compounds were obtained:



R:	Melting point
n-C_3H_7	° C.. 135
iso-C_3H_7	not cryst
n-C_4H_9	° C.. 132
iso-C_4H_9	° C.. 182
n-C_6H_{13}	° C.. 127

The compound 3,4-dihydroxy-α-methyl-α-ethyl-phenylacetamide was also prepared by an analogous procedure.

The substances specified in Examples I to V were tested as to their COMT-inhibiting action mainly in vivo on mice. The test substances were intraperitoneally injected in varying dosages. In the testing of the COMT-activity in the brain, a MAO inhibitor (nialamide, 100 mg./kg.) was first injected. After half an hour, the compound of the invention was injected, and after a further half an hour dopa (L-3,4-dihydroxyphenlalanine) was injected, usually in a dosage of 7.5 mg./kg. After a further hour, the animals were killed and their brains were analysed for the content of dopamine (3,4-dihydroxy-β-phenylethylamine), and its 3-0-methylated derivative, 3-methoxytyramine. A reduced 3-methoxytyramine content with an unchanged or increased dopamine content was regarded as a criterion of COMT-inhibiting activity.

It was found that, for example, 3,4-dihydroxyphenylacetamide has good activity and at the same time low toxicity. A dose of 2 g./kg. was well tolerated and gave a very powerful inhibition of the formation of 3-methoxytyramine. 500 mg./kg. was sufficient to give a significant effect (the content of 3-methoxytyramine in the brain was 0.2 μg./g. compared with 0.7 μg./g. in control animals). By comparsion, 3,4-dihydroxy-β-phenylpropionamide, although effective for inhibiting the action of COMT, was more toxic. In direct comparison, pyrogallol exhibited a substantially lower selective effect on COMT than 3,4-dihydroxyphenylacetamide. For a significant inhibition of the formation of 3-methoxythyramine in the brain of the mouse (corresponding to the action of 500 mg./kg. of 3,4-dihydroxyphenylacetamide), a dose of approximately 300 mg./kg. was necessary, but this produced in addition clear symptoms of toxicity.

The test results given hereinafter are a summary of those obtained for the compounds of Examples VI to XIII which show that all have a powerful COMT-inhibiting effect.

The compounds were tested on mice by the procedure described above. Illustrative results obtained in these tests for the content of 3-methoxytyramine in the brains of mice are given in Table I.

TABLE I

	Dose, g./kg.	3-methoxytyramine content, μg./g.
Control	0	0.7–0.9
3,4-dihydroxy-α-methoxy phenylacetamide	0.5	0.57
	1	0.24
3,4-dihydroxy-α-ethoxy-phenylacetamide	0.5	0.23
	1	0.11
	2	0.08
3,4-dihydroxy-α-propyl-phenylacetamide	0.3	0.28
	0.5	0.11
3,4-dihydroxy-α-n-butyl-phenylacetamide	0.25	0.52
	0.5	0.12
3,4-dihydroxy-α-isopropyl-phenylacetamide	0.25	0.60
	0.5	0.18

The compounds have shown in vitro a higher COMT-inhibiting effect than those earlier described and may be effectively employed in doses as low as the doses for pyrogallol. The CNS-stimulating effect in the investigation with nialamide and 1-dopa is higher than with 3,4-dihydroxyphenylacetamide.

In addition, the compounds possess the unexpected effect that when once or repeatedly administered to mice they lower the content of catecholamines and of 5-hydroxytryptamine (principally noradrenaline and dopamine) in brain and heart by inhibiting their synthesis. This is illustrated by the following results obtained for contents of dopamine, noradrenalin, and 5-hydroxytryptamine.

TABLE II

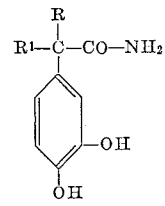
Substance	Content of substance in control animals (μg./g.)	Content of substance 3 hours after the administration of 1 g./kg. of 3,4-dihydroxy-α-ethoxy- or α-methoxy-phenylacetamide (μg./g.)
Dopamine	1.0	0.6
Noradrenalin	0.4	0.25
5-hydroxy-tryptamine	0.4	0.2

Tests carried out indicate the potential importance of the compounds in psychiatry. In the model psychosis in mice caused by injection of a MAO-inhibitor (nialamide 0.5 g./kg.), injection of 1 g./kg. of the compounds totally inhibits the development of characteristic symptoms similar to those of psychosis which are the consequence of accumulation of catecholamines and 5-hydroxytrypt-

amine in the brain. Mice injected with reserpine (15 mg./kg.) and nialamide (0.1 mg./kg.) show a powerful central stimulation which is greatly moderated when the compounds of Examples VI and VII are simultaneously administered in a dose of 1 g./kg.

We claim:

1. A compound of the formula:



in which R is selected from the class consisting of hydrogen, lower alkyl, and alkoxy of at most 2 carbon atoms, and R^1 is selected from the class consisting of hydrogen and alkyl of at most 2 carbon atoms.

2. A compound according to claim 1, wherein R and R^1 are individually selected from the class consisting of hydrogen and alkyl of at most 2 carbon atoms, and together contain at most 2 carbon atoms.

3. A compound according to claim 1 wherein R is selected from the class consisting of lower alkyl, and alkoxy of at the most 2 carbon atoms, and R^1 is hydrogen.

4. A compound according to claim 1, which is 3,4-dihydroxyphenylacetamide.

5. A compound according to claim 1, which is 3,4-dihydroxyhydratropamide.

6. A compound according to claim 1, which is α-3,4-dihydroxyphenylbutyramide.

7. A compound according to claim 1, which is α-3,4-dihydroxyphenylisobutyramide.

8. A compound according to claim 1, which is 3,4-dihydroxy-α-methoxyphenylacetamide.

9. A compound according to claim 1, which is 3,4-dihydroxy-α-ethoxy-phenylacetamide.

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