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3-CARBAMOYLOXY DERIVATIVES OF 5-(TERTIARYAMINOPROPYLIDENE) - 5H - DIBENZO[a,d] CYCLOHEPTENES

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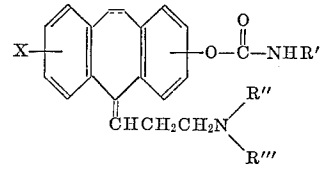
Int. Cl. C07c *125/06*

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ABSTRACT OF THE DISCLOSURE

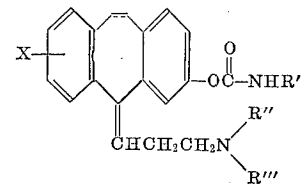
The new tranquilizer compounds disclosed herein include carbamoyloxy derivatives of 5-(tertiaryaminopropylidene)-5H-dibenzo[a,d]cycloheptenes, as well as the corresponding 10,11-dihydro derivatives thereof. These compounds are prepared from 2-(4-methoxyphenethyl) benzoyl chloride by reaction with stannic chloride to produce 3-methoxy-10,11 - dihydro - 5H - dibenzo[a,d] cyclohepten-5-one; converting said 5-keto compound to 3-hydroxy-5 - (3 - dimethylaminopropylidene) - 10,11-dihydro-5H-dizenzo[a,d]cycloheptene by reaction in either order with (1) dimethylaminopropyl magnesium chloride to form the 5-hydroxy-5-(3-dimethylaminopropyl) derivative followed by dehydration to the corresponding 5-(3-dimethylaminopropylidene) derivative and (2) cleavage of the 3-methoxy substituent (with pyridine hydrochloride in the case of the 10,11-unsaturated compound) to produce the desired 3-hydroxy compound and reaction of the 3-hydroxy-10,11-dihydro-5-(3-dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene with methyl isocyanate to produce the desired 3-carbamoyloxy derivative.

This invention relates to new chemical compounds and to a novel method for preparing them. In particular, this invention relates to new carbamoyloxy derivatives of dibenzo-cycloheptene compounds having the following general formula:



and nontoxic acid addition salts thereof wherein R' is a lower alkyl radical and R'' and R''', which can be similar or dissimilar, are each lower alkyl radicals, either straight or branched chain, having up to 6 carbon atoms and lower alkyl radicals linked together through an atom selected from the group consisting of carbon, nitrogen and oxygen to form a heterocyclic ring having from five to six atoms therein such as 1-piperidyl, 1-pyrrolidyl, 4-morpholinyl and 1-lower alkyl 4-piperazinyl and X is selected from the group consisting of hydrogen, an alkyl group having up to 6 carbon atoms, a perfluoroalkyl group having up to 4 carbon atoms, a phenyl or a substituted phenyl radical, a dialkylamino

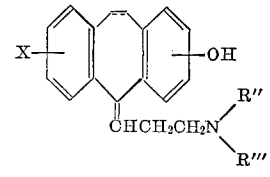
group having up to 4 carbon atoms, an acylamino group having up to 4 carbon atoms, a perfluoroacylamino group having up to 4 carbon atoms, an alkylsulfonylamino group having up to 4 carbon atoms, halogen (fluorine, chlorine, bromine or iodine), an alkoxyl group having up to 4 carbon atoms, a perfluoroalkoxyl group having up to 4 carbon atoms, cyano, carbamyl, an alkylcarbamyl group having up to 4 carbon atoms, a dialkylcarbamyl group having up to 8 carbon atoms, a carbalkoxy group having up to 6 carbon atoms, an alkylmercapto group having up to 4 carbon atoms, a perfluoroalkylmercapto group having up to 4 carbon atoms, an alkylsulfonyl group having up to 4 carbon atoms, a perfluoroalkylsulfonyl group having up to 4 carbon atoms, sulfamyl, an alkylsulfamyl group having up to 4 carbon atoms, or a dialkylsulfamyl group having up to 8 carbon atoms. Still more particularly it relates to compounds of the above general formula wherein the carbamoyloxy substituent is attached at the 3-position. Compounds of this type are included in the following general formula:



wherein R', R'' and R''' are as indicated above as well as the acid addition salts thereof.

The compounds of this invention have been found to be valuable particularly because of their tranquilizing properties. In addition, they are useful because of their antidepressant activity. They are also useful as antihistaminic agents. For administration to patients requiring either a tranquilizer or an antidepressant drug, the compounds are preferably administered as the acid addition salt. The particular acid used to prepare the acid addition salt is of little consequence provided only that it be nontoxic. The acid addition salts are considered to be essentially equivalent in activity to the free base from a therapeutic standpoint. The compounds may be administered in capsules, tablets, elixirs, or in other oral or parenteral dosage forms in amounts of from 20 to 1000 mg./day, perferably given in divided doses throughout the day. This invention also contemplates the amine oxides and quaternary salts of the subject compounds.

The process of our invention includes reaction of a compound having the following general formula:



wherein R'' and R''' are as defined above with an alkyl isocyanate to form the desired 5-(3-dialkylaminopropylidene) - 5H-dibenzo[a,d]cycloheptene having an N-alkyl carbamoyloxy substituent attached to one of the carbons of the benzenoid ring.

By selection of the appropriate starting material, there are formed as representative compounds of our invention

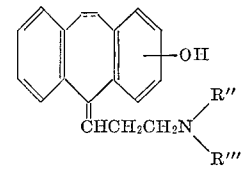
3-(N-methylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
7-chloro-3-(N-ethylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
7-methyl-3-(N-propylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
3-(N-butylcarbamoyloxy)-8-trifluoromethyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
3-(N-isopropylcarbamoyloxy)-7-phenyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
7-chloro-3-(N-isobutylmethylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
7-dimethylamino-3-(N-methylcarbamoyloxy)-5-(3-dipropylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
3-(N-methylcarbamoyloxy)-8-methylsulfonyl-5-(3-dibutylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
3-(N-methylcarbamoyloxy)-9-methylsulfamoyl-5-(3-diisopropylaminopropylidene)-5H-dibenzo[a,d,]cycloheptene;
7-chloro-3-(N-methylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d,]cycloheptene;
7-methyl-3-(N-methylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
7-ethyl-3-(N-methylcarbamoyloxy)-5-(3-dimethylaminoproylidene)-5H-dibenzo[a,d]cycloheptene;
3-(N-methylcarbamoyloxy)-7-trifluoromethyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
3-(N-methylcarbamoyloxy)-7-phenyl-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
7-dimethylamino-3-(N-methylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
7-methoxy-3-(N-methylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
7-methylsulfonyl-3-(N-methylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene;
7-chloro-3-(N-methylcarbamoyloxy)-5-[3-(1-methyl-4-piperazinyl)-propylidene]-5H-dibenzo[a,d]cycloheptene;
7-methyl-3-(N-methylcarbamoyloxy)-5-[3-(4-morpholinyl)propylidene]-5H-dibenzo[a,d]cycloheptene;
3-(N-methylcarbamoyloxy)-7-trifluoromethyl-5-[3-(1-piperidyl)propylidene]-5H-dibenzo[a,d]cycloheptene;
3-(N-methylcarbamoyloxy)-7-trifluoromethyl-5-[3-(1-pyrrolidyl)propylidene]-5H-dibenzo[a,d]cycloheptene.

The corresponding 10,11-dihydro compounds as, for example, 5-(3-dimethylaminopropylidene) - 3 - (N-methylcarbamoyloxy) - 10,11 - dihydro-5H-dibenzo[a,d]cycloheptene are likewise prepared in similar manner by selection of the appropriate 10,11-dihydro compound corresponding to the general formula hereinabove as starting material.

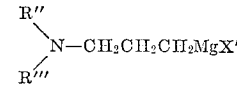
The reaction is preferably accomplished by mixing the 3-hydroxy-5-(3-dialkylaminopropylidene) - 5H - dibenzo [a,d]cycloheptene or the corresponding 10,11-dihydro derivative with an excess of the selected alkyl isocyanate at ambient temperature. The reaction proceeds readily and requires no added catalyst or solvent to prepare the desired compound in essentially quantitative yield, though a solvent having no active hydrogen may be used if desired. Thus, after mixing the reactants, the mixture is allowed to stand for up to about 1–5 hours at a temperature of from 0° to 100°. Preferably it is carried out at about room temperature (25° C.). The carbamoyloxy product formed in this manner is readily recovered by evaporation of excess reactant or added solvent leaving the free base

present as a residual amorphous solid. The solid base is preferably further purified by crystallization of the acid addition salt. To accomplish this purification it is only necessary to dissolve the product initially obtained in a solvent such as a lower alkanol, for example, isopropyl alcohol, methyl alcohol, or ethyl alcohol and mix the alcoholic solution with a chemically equivalent amount of the selected acid dissolved in the same solvent to form the desired salt. The salt is readily precipitated by the addition of ether to the alcohol solution and the crystalline acid addition salt is recovered by filtration.

In accordance with a further embodiment of our invention, the above-mentioned 3-hydroxy-5-(3-disubstituted-aminopropylidene) - 5H-dibenzo[a,d]cycloheptene of the formula

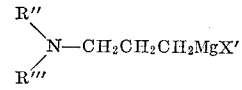


is prepared from the known 2-(4-alkoxyphenethyl)benzoyl chloride by reaction with stannic chloride to produce 10,11 - dihydro-3-alkoxy-5H-dibenzo[a,d]cycloheptene-5-one, contacting said 3 - alkoxydibenzocyclohepten-5-one with an N-bromo amide or an N-bromo imide to produce a mono-brominated derivative of 10,11-dihydro-3-alkoxy-5H-dibenzo[a,d]cyclohepten-5-one, dehydrobrominating said mono-brominated derivative by heating in the presence of a tertiary amine with consequent production of 3 - alkoxy-5H-dibenzo[a,d]cycloheptene-5-one and subsequently heating said 3-alkoxy compound with pyridine hydrochloride to convert said 3-alkoxy substituent to a 3-hydroxy substituent and produce 3-hydroxy-5H-dibenzo-[a,d]cyclohepten-5-one, condensing said 3-hydroxy compound with a tertiaryaminopropyl Grignard reagent of the formula



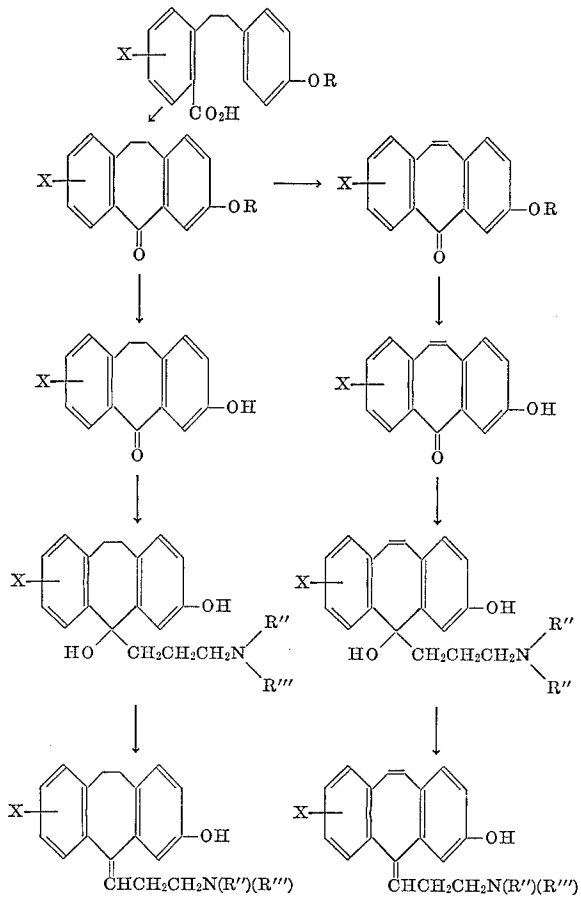
wherein R'' and R''' are as previously defined and X' is halo, followed by hydrolysis of the Grignard adduct obtained to produce the corresponding 3-hydroxy-5-tertiaryaminopropyl-5H-dibenzo[a,d]cyclohepten-5-ol and dehydrating this carbinol by means of an acidic dehydrating agent to produce the corresponding 5-tertiaryaminopropylidene-5H-dibenzo[a,d]cycloheptene.

The corresponding 10,11-dihydro-3-hydroxy-5-tertiaryaminopropyl - 5H - dibenzo[a,d]cyclohepten-5-ol compounds are prepared in accordance with an alternate process of our invention by heating 3-alkoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one with a hydrohalogen acid selected from hydrochloric, hydrobromic or hydriodic acid, to produce the corresponding 3-hydroxy-10,11 - dihydro-5H-dibenzo[a,d]cyclohepten-5-one, condensing said 3 - hydroxy-10,11-dihydrodibenzocyclohepten-5-one compound with a Grignard reagent of the formula:



wherein R'', R''' and X' are as previously described to produce 3-hydroxy-5-(3-tertiaryaminopropyl)-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol, dehydrating said intermediate 5-ol compound by heating in the presence of a strongly acidic reagent to produce the desired 3-hydroxy-5-(3-tertiaryaminopropylidene)-10,11dihydro-5H-dibenzo [a,d]cycloheptene. The processes of our invention as set

forth in the preceding broad description are outlined in the flow sheet which follows.



In the process outlined above a solution of 2-(4-alkoxyphenethyl)benzoic acid in an inert anhydrous non-polar organic solvent is mixed with an agent such as thionyl chloride or phosphorus trichloride to produce 2-(4-alkoxyphenethyl)benzoyl chloride. It is preferred to remove the excess reagent and the solvent by distillation under reduced pressure. The residue comprising 2-(4-alkoxyphenethyl)benzoyl chloride is then dissolved in an inert solvent such as an aromatic hydrocarbon as, for example, benzene, toluene, xylene and the like, and mixed with at least an equimolar amount of stannic chloride. The reactants are stirred together at a temperature of from 0° to 25° for a period of about 3 hours, following which the reaction mixture is treated with aqueous acid to liberate the product. The 3-alkoxy - 10,11 - dihydro-5H-dibenzo [a,d]cyclohepten-5-one formed is isolated by extraction with a solvent such as methylene chloride and purified by distillation.

The purified 3-alkoxy-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-one is then converted to the corresponding 3-hydroxy compound by heating in the presence of a concentrated hydrohalogen acid such as hydrobromic or hydrochloric acid for a period of several hours. We prefer to use hydrobromic acid since milder reaction conditions may be employed than with hydrochloric acid. In the case of hydrobromic acid, heating of the reaction mixture at the reflux temperature for a period of 1 to 10 hours, preferably 4 hours, is sufficient to accomplish the cleavage of the ether substituent in good yield. The reaction medium is preferably an inert, organic liquid as, for example, a lower aliphatic acid such as acetic acid. When the reaction is substantially complete, the product, 3-hydroxy-10,11-dihydro - 5H - dibenzo[a,d]cyclohepten-5-one, is isolated by dilution of the reaction mixture with water and extraction of the product with a water-immiscible solvent for the product such as methylene chloride. The product is obtained as a residue after evaporating the extraction solvent and can be further purified by crystallization from a suitable solvent.

The purified 3-hydroxy-10,11-dihydro-5H-dibenzo[a,d] cyclohepten-5-one is then reacted in solution with a Grignard reagent prepared from a 3-dimethylaminopropyl halide and magnesium under anhydrous conditions. Following the reaction, the Grignard adduct obtained is hydrolyzed with water to produce 3-hydroxy-5-(3-dimethylaminopropyl) 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol and the thus-produced carbinol is then extracted with a suitable solvent and the solvent is evaporated, leaving the product as a residue. The carbinol is further purified, if desired, by recrystallization.

The purified product is then dehydrated using an acidic dehydrating agent. Typical of dehydrating agents which may be employed are strong mineral acids such as hydrochloric acid, trichloroacetic or trifluoroacetic acid, acetyl chloride, acetic anhydride or trifluoroacetic anhydride. The reaction is conducted at a temperature of from 25°–150° C. for a period of from a few minutes to several hours and gives the desired 5-tertiaryaminopropylidene-10,11 - dihydro-5H-dibenzo[a,d] cycloheptene which is purified by crystallization as an acid addition salt. In a typical method of carrying out the dehydration, the compound 10,11-dihydro-3-hydroxy-5-(3-dimethylaminopropyl)-5H-dibenzo[a,d]cyclohepten - 5-ol is heated in solution in trifluoroacetic anhydride with trifluoroacetic acid for a period of from 1 to 2 hours at a temperature of about 60°–80° C.

In preparing the corresponding 3-hydroxy-5-(tertiaryaminopropylidene)dibenzo[a,d]cycloheptene compound, the above-mentioned 3-alkoxy-10,11-dihydro-5H-dibenzo [a,d]cyclohepten-5-one is treated in solution with an N-bromo amide or N-bromo imide brominating agent such as N-bromosuccinimide, N-bromophthalide or N-bromoacetamide in the presence of a small amount of an organic per-acid. In carrying out this reaction, the 3-alkoxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one is heated with an equimolar amount of the N-bromo imide, whereby mono-bromination of either the 10 or 11-position of the dibenzocycloheptenone molecule is effected. The bromination proceeds rapidly at room temperature and may be carried out at any temperature between about 15°–200° C., preferably at about 100° C. for a period of about 2–4 hours. After removal of the excess reagent, the reaction mixture is washed with aqueous alkali to remove acidic by-products and evaporated under reduced pressure, whereby the product is obtained as a crude residue. The recovered product is then heated in contact with a tertiary amine such as trimethyl amine, triethyl amine, α-picoline, and the like, for a period of from 1–20 hours. Following the heating with the amine, the desired 3-alkoxy-5H-dibenzo[a,d]cyclohepten-5-one is obtained by extraction with a water-immiscible solvent and crystallized.

The crystalline 3-alkoxy-5H-dibenzo[a,d]cyclohepten-5-one is then heated with pyridine hydrochloride to effect ether cleavage and produce the corresponding 3-hydroxy compound. It has been found that pyridine hydrochloride is unique in effecting conversion of the 3-alkoxy to the 3-hydroxy compound in the 5H-dibenzo[a,d]cyclohepten-5-one series. When the ordinary reagents utilized for cleaving ethers to the corresponding alcohols, such as hydrogen bromide and the like, are employed, complicating side reactions take place which prevent the isolation of any pure product from the reaction mixture.

In the preferred method, an excess of pyridine hydrochloride and the 3-alkoxy-5H-dibenzo[a,d]cyclohepten-5-one are mixed together and heated to a temperature of from 150°–250° C. for a period of 10 minutes to 2 hours. When 3 - methoxy-5H-dibenzo[a,d]cyclohepten-5-one is used as the starting material, the reaction is preferably carried out at about 200° C. for half an hour. Following the reaction, the desired 3-hydroxy product is obtained by the addition of water and extraction of the prod-

uct. The product is then obtained from the extract after removal of the solvent.

The conversion of the thus-obtained 3-hydroxy-5H-dibenzo[a,d]cyclohepten-5-one to the desired 3-hydroxy-5-(3-tertiaryaminoalkylpropylidene) - 5H-dibenzo[a,d]cycloheptene is carried out in the same manner as in the case of the corresponding 10,11-dihydro compound, that is, by reaction with the appropriate Grignard reagent and dehydration of the carbinol obtained after hydrolysis of the Grignard adduct.

The new compounds of our invention, i.e., the carbamoyloxy derivatives of 5-(tertiaryaminopropylidene)-5H-dibenzocycloheptenes and the corresponding 10,11-derivatives are usually obtained as a mixture of geometric isomers. These isomers which constitute the cis and trans isomers are readily separated by fractional crystallization of the bases or the appropriate acid addition salts. The geometric isomers, when isolated in their pure form, may differ in biological activity.

The following examples are presented to illustrate the methods of carrying out the present invention.

EXAMPLE 1

3-(N-methylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene

(A) 3 - (p-methoxybenzlidene) - phthalide.—Phthalic anhydride (89.61 g., 0.605 mole), p-methoxyphenylacetic acid (100.52 g., 0.605 mole) and freshly fused sodium acetate (3.0 g.) are placed in a 500 ml. 3-necked flask provided with a thermometer and a condenser set for downward distillation. A few boiling chips are added and the flask is heated at 255° C. for one hour. Water starts to distill at approximately 220° C., and a total of 9.2 ml. is collected in a graduated cylinder used as a receiver. After cooling, the crystalline residue is pulverized in a mortar, dissolved in four liters of boiling absolute ethanol, filtered while hot and the filtrate is concentrated to approximately 2400 ml. After crystallizing overnight at room temperature, the product is collected and dried at 70° C. Concentration of the mother liquors to approximately 750 ml. affords additional product melting at 147°–149° C. An analytical sample from another experiment melts at 147.5°–148° C.

Analysis.—Calcd. for $C_{16}H_{12}O_3$ percent: C, 76.18; H, 4.80. Found (percent): C, 75.78; H, 5.00.

(B) 2 - (p-methoxyphenethyl)benzoic acid.—3-(p-methoxybenzylidene)phthalide (52.5 g., 0.21 mole) is dissolved in 1500 ml. of ethanol, six tablespoonsful of Raney nickel catalyst are added, and the mixture is hydrogenated at 25° and 40 p.s.i. After separating the catalyst by filtration, the filtrate containing the product is evaporated under reduced pressure to produce the product as a residual solid. The residue is heated on a steam bath for one hour with 400 ml. of saturated sodium bicarbonate solution, then diluted with 100 ml. of water and washed with three 200 ml. portions of methylene chloride. The aqueous solution is heated on a steam bath for 45 minutes to completely remove methylene chloride and the turbide solution is filtered through a mat of "Super-Cel." The clear filtrate is acidified with 3 N hydrochloric acid and the precipitated white solid product collected and washed with water. After drying at 65° the product melts at 116.5°–118.5°. Recrystallization from 100 ml. benzene and 25 ml. hexane yields product melting at 118°–119.5°. An analytical sample from another experiment melts at 119°–120.5°.

Analysis.—Calcd. for $C_{16}H_{16}O_3$ (percent): C, 74.98; H, 6.29. Found (percent): C, 74.63; H, 6.03.

(C) 3-methoxy-10,11 - dihydro-5H-dibenzo[a,d]cyclohepten-5-one.—A solution of dry ether, 48 ml., containing four drops of dry pyridine is cooled in an ice bath while thionyl chloride, 16 ml., and then 2-(p-methoxyphenethyl)-benzoic acid (28.9 g., 0.113 mole) are added. The mixture is stirred at room temperature for thirty minutes, and then refluxed on a steam bath for an additional fifteen minutes. The clear yellow solution is evaporated in a water bath below 40° under reduced pressure and the oily residue consisting of 2-(p-methoxyphenethyl)benzyl chloride is dissolved in 16 ml. of dry benzene. The solution is cooled in an ice bath and stirred while a solution of stannic chloride (30 ml., 0.26 mole) in 30 ml. of dry benzene is added over fifteen minutes. The brown reaction mixture is stirred in an ice bath for three hours, and then hydrolyzed with 96 ml. of concentrated hydrochloric acid. Two additional identical runs are made. The supernatent solutions from the three runs are decanted and combined. The black oily residues are mixed with methylene chloride (600 ml.) and water (225 ml.) and refluxed on a steam bath with stirring for approximately forty-five minutes. The methylene chloride layer is separated and the extraction is repeated with two additional 600 ml. portions of methylene chloride. The combined methylene chloride solutions then are used to extract the aqueous solutions which originally were decanted from the black oily residues. The organic extracts then are washed three times each with 3 N hydrochloride acid, water, saturated sodium bicarbonate solution and water. After drying over anhydrous magnesium sulfate, the solvent is removed under reduced pressure on a steam bath. The brown oily residue is distilled and the product boils as a yellow oil at 150°–155° C./0.08–0.1 mm.

(D) 3 - hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one.—3-methoxy - 10,11 - dihydro-5H-dibenzo-[a,d]cyclohepten-5-one (12.00 g., 0.050 mole) is dissolved in 80 ml. of glacial acetic acid, redistilled 48% hydrobromic acid, 20 ml., is added and the solution is refluxed for four hours under a stream of nitrogen. The reaction mixture is poured into 200 ml. of water and extracted three times with 100 ml. portions of methylene chloride. The combined extracts are washed twice with water, then extracted with 100 ml. and two 50 ml. portions of 5% sodium hydroxide solution. The basic extract is acidified with 6 N hydrochloric acid and extracted three times with methylene chloride. After washing the extracts with water and drying over anhydrous magnesium sulfate, the solvent is evaporated on a steam bath under reduced pressure. The solid residue is dissolved in 50 ml. of boiling absolute ethanol, treated with decolorizing charcoal for forty-five minutes and filtered. The filtrate is concentrated to approximately 30 ml., diluted to incipient turbidity with water (25 ml.) and the product crystallizes as a tan solid on standing at room temperature, M.P. 147.5°–148.3°. An analytical sample from another experiment melts at 147.5°–148.5°.

Analysis.—Calcd. for $C_{15}H_{12}O_2$ (percent): C, 80.33; H, 5.40. Found (percent): C, 80.57; H, 5.41.

(E) 3-hydroxy - 10,11 - dihydro-5-(3-dimethylaminopropyl) - 5H - dibenzo[a,d]cyclohepten-5-ol.—Magnesium turnings (4.09 g., 0.168 g. atom) are placed in a 300 ml. 3-necked flask that is equipped with a Hershberg stirrer, reflux condenser and dropping funnel. An atmosphere of nitrogen is maintained throughout the reaction. The magnesium is covered with 20 ml. of dry, peroxide-free tetrahydrofuran and a crystal of iodine is added, followed by ethyl bromide (0.46 g., 0.0042 mole) and fifteen drops of a solution of 20.44 g., (0.168 mole) of 3-dimethylaminopropyl chloride in 68 ml. of tetrahydrofuran. The mixture is stirred and heated to refluxing until the reaction is initiated (approximately five minutes). Heat then is removed and the remainder of the 3-dimethylaminopropyl chloride solution is added dropwise at such a rate that gentle refluxing is maintained. When the addition is complete (30 minutes), stirring is continued and the mixture heated to refluxing for one hour on the steam bath. The solution is cooled in an ice-bath and stirred while a solution of 3-hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (9.44 g., 0.042 mole) in 28 ml. of tetrahydrofuran is added over fifteen minutes.

The red solution is stirred in the ice-bath for thirty minutes and then at room temperature for one hour. The bulk of the solvent is evaporated under reduced pressure below 35°. The residue is dissolved in 285 ml. of benzene and the Grignard adduct hydrolyzed by the dropwise addition of 64 ml. of water while cooling in an ice-bath. The benzene layer is decanted from the gelatinous precipitate which then is extracted with three 100 ml. portions of boiling benzene. The combined benzene extracts are washed twice with water, then extracted three times with 85 ml. portions of 0.5 M citric acid solution. After washing the benzene layer with water, the combined washings and acid extracts are carefully rendered alkaline, first by the addition of 25 ml. of 10 N sodium hydroxide solution and, finally, with 55 ml. of saturated sodium bicarbonate solution. The mixture is extracted with three 200 ml. portions of benzene, the combined extracts are washed with water and dried over anhydrous magnesium sulfate. The solvent is evaporated on the steam bath under reduced pressure and the solid residue is crystallized from 50 ml. of 95% ethanol-29 ml. of water. The product melts at 172°–173°. An analytical sample from another experiment melts at 171.5°–172.5°.

Analysis.—Calcd. for $C_{20}H_{25}NO_2$ (percent): C, 77.13; H, 8.09; N, 4.50. Found (percent): C, 77.50; H, 8.09; N, 4.72.

(F) 3-hydroxy-5-(3-dimethylaminopropylidene)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene.—3 - hydroxy-5-(3-dimethylaminopropyl) - 10,11 - dihydro-5H-dibenzo-[a,d]cyclohepten-5-ol (300 mg., 0.963 millimole) is dissolved in 3 ml. of trifluoroacetic acid, 1.5 ml. of trifluoroacetic anhydride is added and the solution is refluxed for one hour in a water-bath at 65°–70°. The solvent then is evaporated on the steam bath under reduced pressure, the oily residue is suspended in 25 ml. of saturated sodium bicarbonate solution and extracted three times with methylene chloride. The combined extracts are washed three times with water, dried over anhydrous magnesium sulfate and the solvent distilled in a water bath under reduced pressure until the residue attains constant weight and is recovered as an amorphous solid product.

(G) 3-(N - methylcarbamoyloxy)-5-(3-dimethylaminopropylidene) - 10,11 - dihydro-5H-dibenzo[a,d]cycloheptene-hydrogen oxalate ($\alpha+\beta$ isomers).—3-hydroxy-5-(3-dimethylaminopropylidene) - 10,11 - dihydro-5H-dibenzo[a,d]cycloheptene ($\alpha+\beta$ isomers) (264 mg., 0.900 millimole) is dissolved in 9 ml. of redistilled methyl isocyanate and the solution is stirred at room temperature for 20 hours. The solvent is evaporated in a water-bath below 40° under reduced pressure and the oil residue weighs 316 mg. (100%). A portion of the residue (293 mg., 0.836 millimole) is disolved in 5 ml. of isopropyl alcohol, a solution of 83 mg. (0.92 millimole) of oxalic acid in 5 ml. of isopropyl alcohol is added, the solution is concentrated to approximately 7 ml. and ether, 1.5 ml., is added to incipient turbidity. On standing at room temperature, the product crystallizes as a white solid melting with decomposition at 170.5°. An analytical sample melts at 167.2° with decomposition and shows a 46.4% slope on solubility analysis.

Analysis.—Calcd. for $C_{22}H_{26}N_2O_2 \cdot C_2H_2O_4$ (percent): C, 65.44; H, 6.41; N, 6.36. Found (percent: C, 65.08; H, 6.21; N, 6.42.

EXAMPLE 2

3-(N-methylcarbamoyloxy)-5-(3-dimethylaminopropylidene)-5H-dibenzo[a,d]cycloheptene

(A) 3 - methoxy-5H-dibenzo[a,d]cyclohepten-5-one.—3-methoxy-10,11-dihydro - 5H - dibenzo[a,d]cyclohepten-5-one prepared as shown in Example 1(C) (19.43 g., 0.0815 mole) is dissolved in 167 ml. of carbon tetrachloride, N-bromosuccinimide (72.98 g., 0.41 mole) and then benzoyl peroxide, 295 mg., are added and the mixture is stirred and heated to refluxing cautiously. After approximately 15 minutes the reaction is initiated. The mixture is stirred at reflux for two hours, then cooled to room temperature and the succinimide separated by filtration. The combined filtrate and washings are extracted three times with 5% sodium hydroxide, washed with water and dried over magnesium sulfate. The solvent is distilled on the steam bath under reduced pressure, and triethylamine, 148 ml., is added to the yellow solid residue. The mixture is heated to refluxing with stirring for 16 hours. After cooling, the mixture is diluted with 200 ml. of benzene and washed three times with water. After filtering to remove some amorphous material, the benzene and triethylamine are distilled on the steam bath under reduced pressure. The residue is dissolved in 175 ml. of benzene and the solution is extracted with 3 N hydrochloric acid, washed with water and the solvent is evaporated under reduced pressure on the steam bath. The residue is sublimed at 135°/0.07 mm. The sublimate is crystallized from 35 ml. of cyclohexane and melts at 62°–65°. An analytical sample from another experiment melts at 68.2°–69.6°.

Analysis.—Calcd. for $C_{16}H_{12}O_2$ (percent): C, 81.33; H, 5.12. Found (percent): C, 81.68; H, 5.26.

(B) 3 - hydroxy-5H-dibenzo[a,d]cyclohepten-5-one.—Pyridine hydrochloride (57.78 g., 0.50 mole) is placed in a 200 ml. 3-necked flask equipped with a nitrogen inlet tube and drying tube. Under a slow stream of nitrogen, the flask is heated to 205° when 3-methoxy-5H-dibenzo-[a,d]cyclohepten-5-one (11.64 g., 0.049 mole) is added. The melt is heated at 207° for 30 minutes. After cooling to room temperature, the reaction mixture is distributed between 250 ml. of ethyl acetate and 200 ml. of water. The aqueous layer is separated and extracted with two 150 ml. portions of ethyl acetate. The combined ethyl acetate extracts are washed with water and the solvent is evaporated on the steam bath under reduced pressure. The solid residue is treated with 300 ml. of 1.5% sodium hydroxide solution and extracted with three 100 ml. portions of benzene. The alkaline solution is acidified with 3 N hydrochloric acid and extracted three times with 150 ml. of ethyl acetate. After washing with water, the solvent is evaporated on the steam bath under reduced pressure. The residue is dissolved in 1500 ml. of boiling benzene, filtered while hot and the filtrate concentrated to approximately 400 ml. On standing at room temperature, the product crystallizes as a yellow solid melting at 206.5°–207.5°. An analytical sample from another experiment melted at 206.6°–207.9°.

Analysis.—Calcd. for $C_{15}H_{10}O_2$ (percent): C, 81.06; H, 4.54. Found (percent): C, 80.78; H, 4.58.

(C) 3-hydroxy-5-(3-dimethylaminopropyl)-5H-dibenzo-[a,d]cyclohepten-5-ol.—Magnesium turnings (5.11 g., 0.21 g. atom) are placed in a 500 ml. 3-necked flask that is equipped with a Hershberg stirrer, reflux condenser and dropping funnel. An atmosphere of nitrogen is maintained throughout the reaction. The magnesium is covered with 23 ml. of dry, peroxide-free tetrahydrofuran and a crystal of iodine is added, followed by ethyl bromide (580 mg., 0.0053 mole) and 20 drops of a solution of 25.55 g. (0.21 mole) of 3-dimethylaminopropyl chloride in 82 ml. of tetrahydrofuran. The mixture is stirred and heated to refluxing on the steam bath until the reaction is initiated (approximately five minutes). Heat is removed and the remainder of the 3-dimethylaminopropyl chloride solution is added dropwise at such a rate that gentle refluxing is maintained. When the addition is complete (30 minutes), stirring is continued and the mixture heated to refluxing for one hour. The solution is cooled in an ice-bath and stirred while a solution of 3-hydroxy-5H-dibenzo[a,d]cyclohepten-5-one (11.66 g., 0.0525 mole) in 70 ml. of tetrahydrofuran is added over 15 minutes. The red solution is stirred in an ice-bath for 30 minutes and then at room temperature for one hour.

The bulk of the solvent is evaporated under reduced pressure below 35°. The residue is dissolved in 350 ml. of benzene and the Grignard adduct hydrolyzed by the dropwise addition of 82 ml. of water while cooling in an ice-bath. The benzene layer is decanted from the gelatinous precipitate which then is extracted with three 100 ml. portions of boiling benzene. The combined benzene extracts are washed twice with water, then extracted with 110 ml. and two 80 ml. portions of 0.5 M citric acid solution. After washing the benzene layer with water, the combined washings and acid extracts are carefully rendered alkaline, first by the addition of 80 ml. of 5 N sodium hydroxide solution, followed by 50 ml. of saturated sodium bicarbonate solution. The mixture is extracted with three 250 ml. portions of benzene followed by three 200 ml. portions of ethyl acetate. The combined extracts are washed with water and the solvent is evaporated on the steam bath under reduced pressure. The solid residue is crystallized from 35 ml. of 95% ethanol-2.5 ml. of water. The product melts at 200°–201° C. An analytical sample from another experiment melts identically.

Analysis.—Calcd. for $C_{20}H_{23}NO_2$ (percent): C, 77.64; H, 7.49; N, 4.53. Found (percent): C, 77.47; H, 7.41; N, 4.44.

(D) 3 - hydroxy - 5 - (3-dimethylaminopropylidene)-5H - dibenzo[a,d]cycloheptene.—3 - hydroxy - 5 - (3-dimethylaminopropyl) - 5H - dibenzo[a,d]cyclohepten-5 ol (4.00 g., 0.013 mole) is dissolved in 40 ml. of trifluoroacetic acid, 20 ml. of trifluoroacetic anhydride is added and the solution is refluxed for one hour in a water-bath at 65°–70°. The solvent is evaporated on the steam bath under reduced pressure, the residue suspended in 100 ml. of saturated sodium bicarbonate solution and extracted three times with 60 ml. portions of methylene chloride. The combined extracts are washed three times with water, dried over anhydrous magnesium sulfate and the solvent distilled on the steam bath under reduced pressure until the solid product attains constant weight.

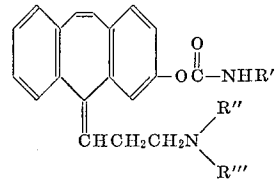
(E) 3 - (N - methylcarbamoyloxy) - 5 - (3-dimethylaminopropyldiene) - 5H - dibenzo[a,d]cycloheptene-hydrogen oxalate ($\alpha+\beta$ isomers).—3 - hydroxy-5-(3-dimethylaminopropylidene) - 5H - dibenzo[a,d]cycloheptene ($\alpha+\beta$ isomers) (968 mg., 0.00332 mole) is dissolved in 33 ml. of redistilled methyl isocyanate and the solution is stirred at room temperature for 2.5 hours. The solvent is evaporated in a water bath below 40° under reduced pressure and the amorphous solid residue weighs 1.118 g. (97%). A portion of the residue (1.007 g., 0.00289 mole) is dissolved in 4 ml. of absolute ethanol, a solution of 286 mg. (0.00318 mole) of oxalic acid in 4 ml. of absolute ethanol is added and ether, 9 ml., is added to incipient turbidity. On standing at room temperature, the product crystallizes as a white solid melting at 156° with decomposition. Concentration of the mother liquors to approximately 2 ml., followed by the addition of 12 ml. of ether to incipient cloudiness affords additional product melting at 157° with decomposition. On mixing, the two crops of product melt with decomposition at 155.5°.

Analysis.—Calcd. for $C_{22}H_{24}N_2O_2 \cdot C_2H_2O_4$ (percent): C, 65.74; H, 5.98; N, 6.39. Found (percent): C, 65.64; H, 6.11; N, 6.44.

In the preceding examples the designations α and β are used to designate the individual geometric isomers without regard to their configuration.

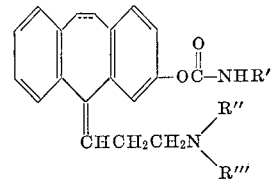
What is claimed is:

1. The compound having the formula



and the non-toxic acid addition salts and N-oxides thereof wherein R′ is a lower alkyl radical, R″ and R‴ are each lower alkyl radicals or when taken together with the nitrogen atom are either 1-pyrrolidyl, 1-piperidyl, 4-morpholinyl, or 1-loweralkyl-4-piperazinyl.

2. A compound in accordance with claim 1 having the formula:

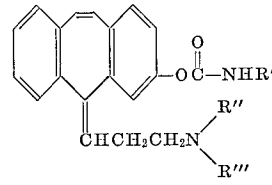


wherein R′, R″ and R‴ are each lower alkyl radicals, non-toxic acid addition salts and the N-oxides thereof.

3. A compound in accordance with claim 2 wherein R′ is defined as methyl.

4. A compound in accordance with claim 2 wherein R″ and R‴ are defined as methyl.

5. A compound in accordance with claim 1 having the general formula:



and a nontoxic addition acid salt and N-oxides thereof wherein R′, R″ and R‴ are each lower alkyl radicals.

6. A compound in accordance with claim 5 wherein R′ is defined as a methyl substituent.

7. A compound in accordance with claim 5 wherein R″ and R‴ are defined as methyl substituents.

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G. T. TODD, Assistant Examiner

U.S. Cl. X.R.

260—240, 247.1; 247.2, 247.5, 247.7 268, 293.4, 294, 294.3, 294.7, 326.3, 326.5, 465, 471, 516, 519, 520, 556, 559, 562, 570.8, 590; 424—248, 250, 267, 274, 311

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,547,980 Dated December 15, 1970

Inventor(s) Edward L. Engelhardt and Mark B. Freedman

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 3 line 61, insert after "material" -- in which th dotted line represents an optional additional bond --. Colur 4 line 26, delete "cycloheptene" and insert -- cyclohepten -- Column 5 line 30, righthand formula, delete the lower " R" " and insert -- R"' --. Column 7 line 60, delete "turbide" and insert -- turbid --. Column 8 line 5, delete "16" and insert -- 116 --; line 23, delete "hydrochloride" and insert -- hydr chloric --. Column 12 line 14, insert after "piperazinyl" -- in which the dotted line represents an optional additional bo

Signed and sealed this 29th day of June 1971.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

WILLIAM E. SCHUYLER,JR
Commissioner of Patent