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AMINOMETHYLDIBENZOBICYCLOALKENES

Eugene E. Galantay, Morristown, N.J., assignor to Sandoz Inc., Hanover, N.J.

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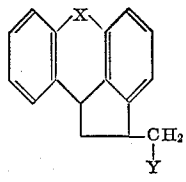
U.S. Cl. 260—293 10 Claims

ABSTRACT OF THE DISCLOSURE

The compounds are 2-aminomethyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulenes and 2-aminomethyl-1,2,6,7,8,12b - hexahydrocyclopenta[d,e]dibenzo[a,d]cyclooctenes, e.g., 2-methylaminomethyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene. The compounds are useful pharmaceutically.

This invention is directed to two series of pharmaceutically acceptable CNS (central nervous system) active aminomethyldibenzobycycloalkenes of the formula



I

wherein

X is either dimethylene (—CH_2—CH_2—), i.e. for one series, or trimethylene (—CH_2—CH_2—CH_2—), i.e. for the other series;

Y is either

e.g. primary amino (—HN_2), secondary amino (β-phenethylamino and isopropylamino) and tertiary amino (N-methyl-N-propylamino); lower alkyleneimino, e.g. ethyleneimino, propyleneimino, pyrrolidyl, piperidyl, hexahydroazepin-1-yl and octahydroazocin-1-yl; or saturated heteromonocyclic-imino, e.g. lower alkylpiperazinyl (ethylpiperazinyl), morpholino, thiomorpholino and pyrazolidino; and

each of

R and R° is, independently, either a hydrogen atom; lower alkyl, e.g. methyl, ethyl, propyl, isopropyl and butyl; or ar(lower)alkyl, e.g. benzyl;

to pharmaceutically acceptable acid addition salts thereof and to the intermediates in the preparation thereof. When X is dimethylene, compounds I are 2-aminomethyl-1,2,6,7 - tetrahydro-(11bH)-benzo[j]benz[c,d] - azulenes; When X is dimethylene, compounds I are 2-aminomethyl - 1,2,6,7,8,12b - hexahydrocyclopenta[d,e]dibenzo[a,d] cyclooctenes. The amino in both cases is defined by Y.

Compounds I have two asymmetric carbon atoms and, thus, four stereoisomeric forms. The intermediates with asymmetric carbon atoms also exist as chemical individuals. All of the stereoisomers are within the scope of the invention, even though some of the stereoisomeric pairs are preferably formed in the reactions described in the examples. As desired, single stereoisomers of compounds I or those of the intermediates are isolated by methods known to the art-skilled. Thus, the so-called geometric (cis- and trans-forms) or diastreoisomers are separated from each other by, e.g., fractional crystallization, where-

as single "racemates" are split into optical enantiomers by the process known as "resolution." It is understood that stereoisomeric forms of the same compound I may have quantitatively or qualitatively different physiological action.

Compounds I and pharmaceutically acceptable acid addition salts thereof are useful as tranquilizers. They are administered either orally or parenterally instandard dosage forms, e.g. tablets, capsules. The average daily dosage varies within the range from 20 to 100 milligrams.

Each of the pharmaceutically active compounds of this invention may be, e.g., incorporated, for oral administration, in a tablet as the sole active ingredient. A typical tablet is constituted by from 1 to 3 percent binder, e.g. tragacanth; from 3 to 10 percent disintegrating agent, e.g. corn starch; from 2 to 10 percent lubricant, e.g. talcum; from 0.25 to 1.0 percent lubricant, e.g. magnesium stearate; an average dosage of active ingredient; and q.s. 100 percent of filler, e.g. lactose; all percentages being by weight. Tablets are prepared according to standard tabletting techniques, which are well-known in the art, employing the necessary amounts of conventional granulating liquids, e.g. alcohol SD–30 and purified water. An exemplary tabletting formulation for the instant active compounds is:

	Parts
Title compound of Example 16	32
Tragacanth	2
Lactose	57.5
Corn starch	5
Talcum	3
Magnesium stearate	0.5

Alcohol SD–30, purified water, q.s.

Among the pharmaceutically acceptable acid addition salts are salts of organic acids, e.g. tartaric acid; inorganic acids, e.g. hydrochloric acid, hydrobromic acid and sulfuric acid; monobasic acids, e.g. an alkylsulfonic acid, such as methylsulfonic acid (H_3C—SO_3H) dibasic acids, e.g. tartaric acid and succinic acid; tribasic acids, e.g. phosphoric acid and citric acid; saturated acids, e.g. acetic acid; ethylenically unsaturated acids; e.g. maleic acid and fumaric acid; and aromatic acids, e.g. salicyclic acid and arylsulfonic acids, such as phenyl sulfonic acid. The only limitation on the acid selected is that the resulting acid addition salt be pharmaceutically acceptable; the acid does not nullify the therapeutic properties of compounds I. It is preferred, however, to select an acid so that the salt therewith is water-soluble; tartaric acid and succinic acid are preferred for this purpose.

The pharmaceutically acceptable acid addition salts are prepared according to standard methods well known to the art-skilled.

In the preparation of compounds I and the intermediates therefor, the reactions are independent of whether X is dimethylene or trimethylene. Examples wherein X is dimethylene are thus equally illustrative of the preparation of the corresponding compounds wherein X is trimethylene. Reaction schemes for preparing compounds I follow on the next page.

Both compound II wherein X is dimethylene and compound II wherein X is thimethylene are known compounds.

Reaction A is a condensation of II with tertiary-butyl acetate in the presence of diethylamino magnesium bromide, following the general method of K. Sisido, H. Nozaki and O. Kurihara, JACS, 74, 6254 (1952), in diethylether, tetrahydrofuran or dioxane as solvent.

Reaction B is the Reformatsky Reaction with

$H_2C(Hal)$-CO-O-R'

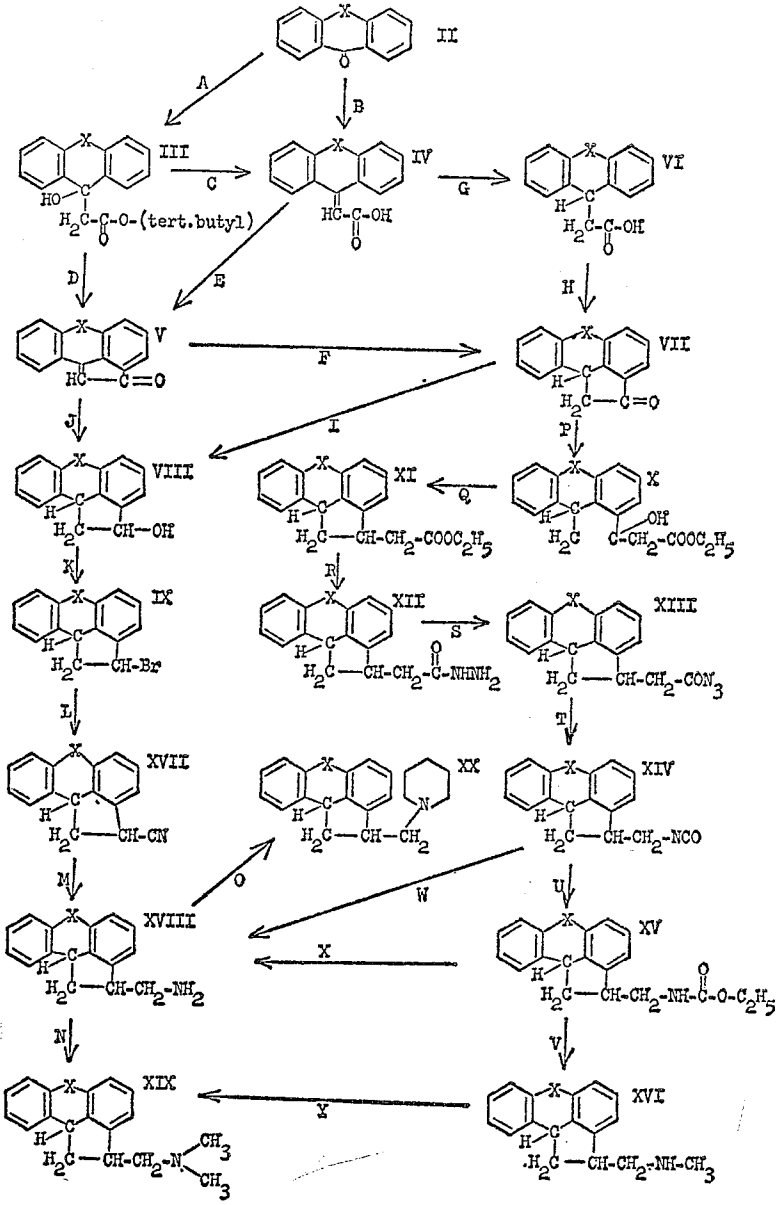
wherein

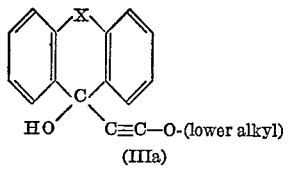
R' is lower alkyl, e.g. methyl, ethyl, propyl, isopropyl and butyl; and

Hal is preferably a bromine atom (—Br), but may be either a chlorine atom (—Cl) or an iodine atom (—I);

followed by saponification and dehydration.

Reaction B is alternatively effected with a (lower alkoxy) acetylene [e.g. methoxyacetylene, propoxyacetylene and butoxyacetylene, but preferably ethoxyacetylene], followed by rearrangement and saponification of the initial product





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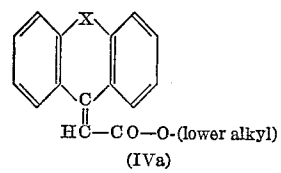


(IVa)

according to the general method described by G. F. Arens, "Advances in Organic Chemistry," vol. II, pages 157 to 161, Interscience Publishers, Inc., New York, New York, 1960.

Reaction C takes place in an inert solvent, such as benzene, toluene and xylene, at the boiling point of the reaction system in the presence of an acid catalyst, preferably para-toluenesulfonic acid, and advantageously in apparatus which permits azeotropic removal of water formed during the reaction.

Reactions D and E (cyclization) are best effected with a mixture of polyphosphoric acid and acetic acid, preferably with a 1:10 mixture, i.e. one part by volume of polyphosphoric acid with an 82% to 84% P_2O_5 content dissolved in ten parts by volume of glacial acetic acid, but mixtures with ratios from 1:1000 to 1:3 are useful for this purpose. At least one half mole of P_2O_5 for each mole of (IV) and 1.0 mole of P_2O_5 for each mole of (III) are advantageously employed. Reactions D and E are carried out at from 50° to 150° C. preferably in the range of from 100° to 120° C.

When other cyclization reagents are employed in reactions D and E, side products may be formed to a greater extent and/or the desired product may undergo further reactions, e.g. dimerization and condensation.

Reactions F and G are either chemical reductions or standard hydrogenations (preferred) at pressures from 1

to 500 atmospheres and temperatures from 0° to 150° C. in a solvent, such as dioxane, ethanol and ethyl acetate, preferably with palladium catalyst.

Reaction H (cyclization) is carried out preferably with polyphosphoric acid at a temperature from 40° to 200° C., but other methods, e.g. cyclization in liquid anhydrous hydrofluoric acid of Friedel-Crafts cyclization of the corresponding chloride, may also be used.

Reaction I is a reduction according to standard procedures. While reduction with lithium aluminum hydride is preferred, other complex hydrides, such as sodium and lithium borohydride, or other redutcion methods, such as the Meerwein-Ponndorf reduction or catalytic hydrogenation, may alternatively be employed.

Reaction J is either a chemical redutcion with a complex hydride, such as lithium aluminum hydride and sodium borohydride, or it is a catalytic hydrogenation.

Reaction K is with hydrogen bromide in benzene at a temperature from 4° to 30° C.

Reaction L is with a salt of hydrogen cyanide, preferably with sodium cyanide in dimethylformamide (DMF).

Reaction M is a reduction, preferably with lithium aluminum hydride—aluminum chloride complex.

Reaction N is an alkylation (Leuckart Reaction).

Reaction O is wtih 1,5-dibromopentane in toluene under reflux.

Reaction P is the Reformatsky Reaction.

Reaction Q is dehydration followed by hydrogenation.

Reaction R is hydrazinolysis.

Reaction S is with alkylnitrile, e.g. butylnitrile, in admixture with hydrogen chloride in glacial acetic acid/diethylether, or it is with sodium azide in glacial acetic acid.

Reaction T is the Curtius Rearrangement.

Reaction U is with absolute ethanol under reflux.

Reaction V is reduction with a complex hydride, e.g. lithium aluminum hydride.

Reaction W is an acid hydrolysis.

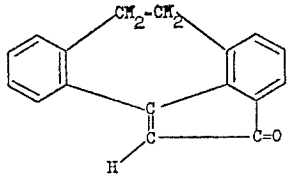
Reaction X is a hydrolysis with a strong base.

Reaction Y is an alkylation (Leuckart Reaction).

In the examples the parts and percentages are by weight unless otherwise specified, and the temperatures are in degrees Centigrade. The relationship between parts by weight and parts by volume is the same as that between the kilogram and the liter.

EXAMPLE 1

6,7-dihydro-2H-benzo[j]benz[c,d]azulen-2-one

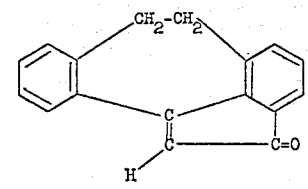


To a stirred solution of 40 parts commercial polyphosphoric acid in 400 parts by volume of glacial acetic acid, add in small portions 40 parts of 5-hydroxy-5-(carbotert.-butoxymethy) - 10,11-dihydro-5H-dibenzo[a,d]cycloheptane [1] and maintain the resulting red solution at 100° for 15 hours. Pour the reaction mixture onto ice, and dissolve the resulting orange precipitate in chloroform. Wash the obtained chloroform solution with 2N sodium hydroxide solution to separate 5-carboxymethylidene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene; then evaporate the remaining chloroform solution to give 17.5 parts of the crude 6,7-dihydro-2H-benzo[j]benz[c,d]azulen-2-one. Purify by chromatography on silica gel to separate the compound of this example from 5-methylidene-10,11-dihydro-5H - dibenzo[a,d]cycloheptene [1.8 parts, melting point (M.P.) 56°–58°]. The pure product is an orange solid, M.P. 66°–67°; oxime, M.P. 134°; dinitrophenylhydrazone, M.P. 258°.

[1] J. Org. Chem. 27, 230 (1962).

EXAMPLE 2

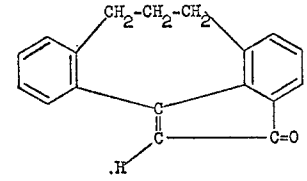
6,7-dihydro-2H-benzo[j]benz[c,d]azulen-2-one



Admix 40 parts of 5-carboxymethylidene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (see Example 1) with 60 parts of polyphosphoric acid in 600 parts of glacial acetic acid and reflux the resulting soltuion at 100° for 18 hours. Pour the reaction mixture onto ice, and dissolve the resulting orange precipitate in chloroform. Wash the obtained chloroform solution with 2N sodium hydroxide solution to separate any unreacted 5-carboxymethylidene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene; then evaporate the remaining chloroform solution to give 31 parts of the crude 6,7-dihydro-2H-benzo[j]benz[c,d]azulen-2-one. Purify by chromatography on silica gel to separate the compound of this example from 5-methylidene-10,11-dihydro - 5H-dibenzo[a,d]cycloheptene, M.P. 56°–58°. The pure product is an orange solid, M.P. 66°–67°.

EXAMPLE 3

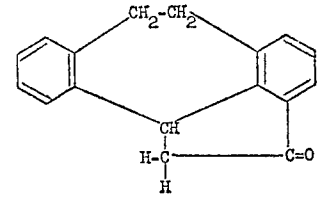
2,6,7,9-tetrahydrocyclopenta[d,e]dibenzo[a,d] cycloocten-2-one



React 50 parts of 5,10,11,12-tetrahydrodibenzo[a,d] cycloocten-5-one with the Grignard derivative of 15.75 parts of ethoxy-acetylene in tetrahydrofuran, following the general method described by Arens, G. F., vol. II, pp. 157 to 161, "Advances in Organic Chemistry," Interscience Publishers, Inc., New York, New York, 1960. Treat the crude product with acid, then saponify with alcoholic potassium hydroxide to isolate, after acidification, 5-carboxymethylidene - 5,10,11,12-tetrahydrodibenzo[a,d] cycloocetene, M.P. 170°–172°. Dissolve 40 parts of the foregoing product with 60 parts of polyphosphoric acid in 600 parts of glacial acetic acid, and heat the resulting solution under reflux for 30 minutes. Pour the reaction mixture onto ice, and dissolve the resulting orange precipitate in chloroform. Wash the obtained chloroform solution with 2N sodium hydroxide solution, with water and dry; then evaporate the remaining chloroform solution to obtain 53.2 parts of an orange oil, which consists of 85% of the desired 2,6,7,8-tetrahydrocyclopenta[d,e] dibenzo[a,d]cycloocten-2-one and 15% of side product, 5 - methylidene - 5,10,11,12 - tetrahydrodibenzo[a,d] cyclooctene. Separate the pure title compound by chromatography.

EXAMPLE 4

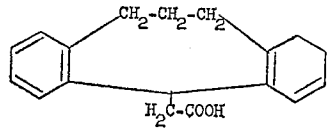
1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d] azulen-2-one



Shake a solution of 17.0 parts of crude 6,7-dihydro-2H-benzo[j]benz[c,d]azulen-2-one in 250 parts of 1,2-dimethoxyethane with 2.0 parts of palladium-charcoal (5%) catalyst in a hydrogen atmosphere of 50 pounds per square inch (p.s.i.g.) until the hydrogen consumption ceases. Filter the resultant mixture and extract the catalyst with boiling chloroform. Evaporate the filtrate and extracts. Isolate 3.0 parts of 1,2,6,7-tetrahydro-6(11bH)-benzo[j]benz[c,d]azulen-2-ol as side product.

EXAMPLE 5

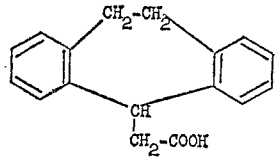
5-carboxymethyl-5,10,11,12-tetrahydrodibenzo[a,d]cyclooctene



Stir a mixture of 4.15 parts of 5-carboxymethylidene-5,10,11,12-tetrahydrodibenzo[a,d]cyclooctene (see Example 3), 0.2 part of 10% palladium-charcoal catalyst and 20 parts by volume of dioxane in a hydrogen atmosphere until the theoretical amount of hydrogen is absorbed. Filter the catalyst from the product, and evaporate the filtrate to obtain the title compound, M.P. 205°–206°, in quantitative yield.

EXAMPLE 6

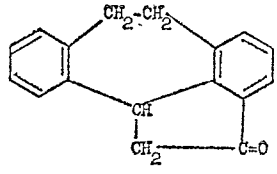
5-carboxymethyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene



Shake a suspension of 10.0 parts of 5-carboxymethylidene-10,11-dihydro-5H-dibenzo[a,d]cycloheptene in 100 parts by volume of dioxane with 0.85 parts of palladium-charcoal (10%) catalyst at 50° to 55° in a hydrogen atmosphere of 50 atmospheres until one mole of hydrogen is taken up. Filter the resultant mixture and extract the catalyst with boiling chloroform. Evaporate the filtrate and extracts to obtain 10.0 parts of title compound, M.P. 161°.

EXAMPLE 7

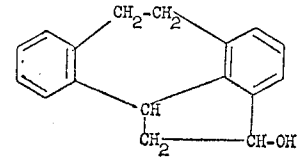
1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulen-2-one



To 1600 parts of commercial polyphosphoric acid (P_2O_5 content of 82% to 84%) vigorously stirred at 92° add, in one portion, 16 parts of 5-carboxymethyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene and maintain stirring between 90° and 93° for three hours. Pour produced mixture onto 4000 parts of ice, filter and wash separated solids with 2 N sodium carbonate solution to remove unchanged starting material. Rewash said solids with water, ethanol and diethylether. Recrystallize the thus-washed solids from 800 parts of boiling dimethylformamide to obtain about 90 parts of the pure title compound, M.P. 218°. Recover unchanged starting material from soda and aqueous washings by acidification.

EXAMPLE 8

1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulen-2-ol

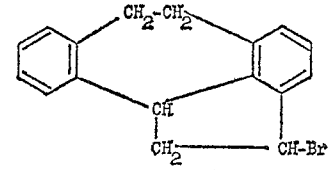


(a) Reflux for 3 hours a mixture consisting of 6.75 parts of 1,2,6,7 - tetrahydro-(11bH)-benzo[j]benz[c,d]azulen-2-one, 1 part of lithium aluminum hydride and 200 parts of dry diethylether. Decompose the excess lithium aluminum hydride with dilute sulfuric acid under cooling. Distill off the ether and obtain the title compound, M.P. 161°–163°, by filtration and recrystallization from either ethanol/diethylether or benzene.

(b) Admix 0.3 part of sodium borohydride with a solution of 1 part of 6,7-dihydro-(2H)-benzo[j]benz[c,d]azulen-2-one in 20 parts of ethanol (previously cooled to —70°), and warm the obtained mixture to room temperature over a period of three hours. After two more hours at room temperature, decompose excess borohydride with aqueous acetic acid and extract resultant with chloroform to obtain (after recrystallization of the chloroform extract from benzene) 0.9 part of title compound, M.P. 159°.

EXAMPLE 9

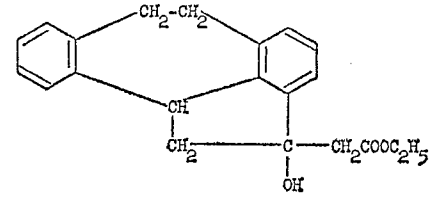
2-bromo-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene



Introduce hydrogen bromide gas for 2 hours into a suspension of 6.2 parts of 1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulen-2-ol in 150 parts of benzene. Wash the thus obtained solution with ice-cold water and sodium hydrocarbonate solution and evaporate the neutral, dry benzene solution to obtain 8.1 parts of crude 2-bromo - 1,2,6,7 - tetrahydro - (11bH - benzo[j]benz[c,d]azulene. Purify by crystallization with diethylether-petroleum ether to obtain the title compound, M.P. 117°–118°.

EXAMPLE 10

2-ethoxycarbonyl-2-hydroxy-1,2,-tetrahydro-(11bH-benzo[j]benz[c,d]-azulene

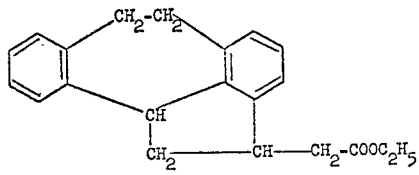


Add, to a refluxing mixture of 50.0 parts of 1,2,6,7-tetrahydro (11bH) - benzo[j]benz[c,d]azulen - 2 - one, 31.3 parts of activated zinc and 1500 parts per volume of benzene-toulene (1:1), over a period of 30 minutes, a solution of 80.0 parts of ethyl bromoacetate in 50 parts per volume of benzene. Continue refluxing for an additional 2.5 hours. Cool, decompose the complex with 500 parts per volume of saturated ammonium chloride solution. Work up the organic phase to obtain 76 parts of an oil; isolate 50.0 parts of the crude product (M.P. 98°–104°) by trituration with diisopropyl ether. The pure product,

after recrystallization from alcohol, has a M.P. of 104° to 105°.

EXAMPLE 11

2-ethoxycarbonyl-1-1,2,6,7-tetrahydro-(11bH)-benzo[j] benz[c,d]azulene

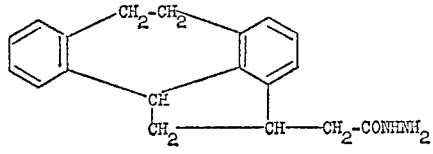


Reflux a mixture of 35 parts of 21ethoxycarbonyl-2-hydroxy - 1,2,6,7 - tetrahydro - (11bH) - benzo[j]benz [c,d]azulene, 1.3 parts of p-toluenesulfonic acid in 300 parts by volume of toluene under an azeotropic water separation trap until about (45 minutes) about 2 parts by volume of water are collected in the trap. Cool, wash the toluene solution with sodium hydrocarbonate solution and water, dry and evaporate to obtain 33.7 parts of an oil.

Hydrogenate the solution of the latter oil in 150 parts by volume of ethyl acetate in the presence of 1.0 part of palladium-carbon (10%) catalyst, under 50 p.s.i.g. of hydrogen pressure. After uptake of the calculated amount of hydrogen, filter the solution and evaporate same to obtain 33.7 parts of the product, M.P. 75° to 79°. [The pure product melts, after recrystallization from ethanol, at 78° to 80°.]

EXAMPLE 12

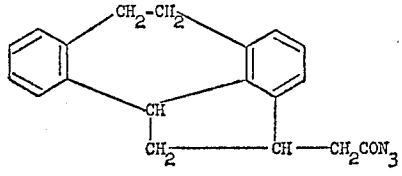
2-hydrazinocarbonyl-1-1,2,6,7-tetrahydro-(11bH)-benzo [j]benz[c,d]azulene



Reflux a mixture of 30.8 parts of 2-ethoxycarbonyl-1,2,6,7 - tetrahydro - (11bH) - bnezo[j]benz[c,d]azulene, 35.5 parts of hydrazine and 30 parts by volume of proponal for 5 hours. Cool the solution, filter and wash, with propanol and ether, solids separated yielding 25.2 parts, M.P. 202°–205°. The pure product (after recrystallization from propanol) has a M.P. of 203°–205°.

EXAMPLE 13

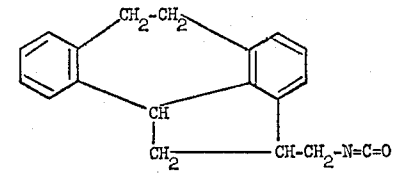
2-azidocarbonyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz [c,d]azulene



Dissolve 16.5 parts of 2-hydrazinocarbonyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene by heating in 125 parts by volume of glacial acetic acid. Cool, add thereto 125 parts by volume of ether and introduce hydrogen chloride gas. To the stirred suspension, at 5° and over a period of 45 minutes, add 34 parts by volume of butyl nitrite. Reduce the volume of the mixture to about its third by evaporation in vacuo, at temperatures not exceeding 20°. Filter off the product, wash thoroughly with cold water and dry at room temperature, yielding 15.3 parts of title compound, M.P. 91°–93°.

EXAMPLE 14

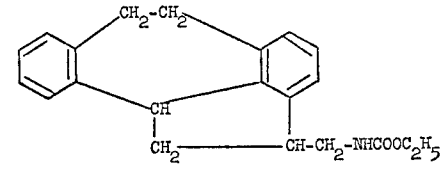
1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulenyl-2-methylisocyanate



Reflux a suspension of 15.3 parts of 2-azidocarbonyl-1,2,6,7 - tetrahydro - (11bH) - benzo[j]benz[c,d]azulene in 300 parts by volume of toluene for 60 minutes. Filter from a small amount of still undissolved solid and evaporate to obtain 15.2 parts of the oily product.

EXAMPLE 15

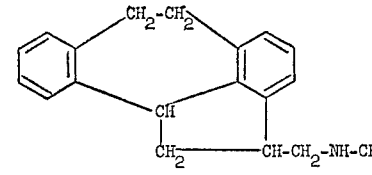
2-carbethoxyaminomethyl-1,2,6,7-tetrahydro-(11bH-benzo[j]benz[c,d]azulene



Reflux 15.2 parts of 1,2,6,7-tetrahydro-(11bH)-benzo [j]benz[c,d]azulenyl-2-methylisocyanate with 350 parts by volume of absolute ethanol for 15 minutes. Evaporate the resultant to obtain 15.9 parts of a solid, M.P. 90°–105°. The pure product, after chromatography and recrystallization from ether-petroleum ether, has a M.P. of 108°–110°.

EXAMPLE 16

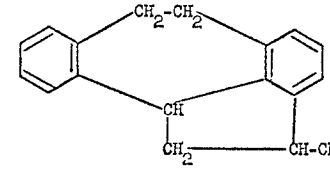
2-methylaminomethyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene



Add, to a suspension of 3.95 parts of lithium aluminum hydride in 100 parts by volume of tetrahydrofuran, a solution of 6.66 parts of 2-carbethoxylaminomethyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d] - azulene in 100 parts by volume of tetrahydrofuran. After 3 hours of reflux, decompose mixture with saturated sodium-potassium tartrate solution. Extract the basic product (5.73 parts) into chloroform and prepare hydrochloride salt (M.P. 220°–225° dec.) by introducing hydrogen chloride gas into the ether solution of former.

EXAMPLE 17

2-cyano-1,2,6,7-tetrahydro-(11bH)-benzo [j]benz[c,d]azulene

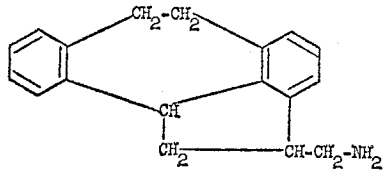


Add at room temperature, to a mixture of 23.6 parts of sodium cyanide and 150 parts by volume of dimethylformamide (previously heated to reflux and thereafter recooled) 32.8 parts of 2-bromo-1,2,6,7-tetrahydro-(11bH)-

benzo[j]benz[c,d]azulene, and stir mixture for 19 hours. Add 1000 parts by volume of water and extract the crude product (27.8 parts) with chloroform.

EXAMPLE 18

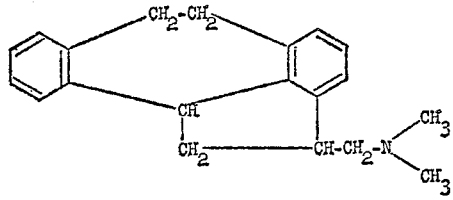
2-aminomethyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene



Admix 1.79 parts of lithium hydride and 6.28 parts of aluminum chloride under 700 parts by volume of dry ether. Add to the refluxing mixture, by the Soxhlet method, 10.50 parts of crude 2-cyano-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene and, after completing this addition, continue refluxing for 3 hours. Decompose the complex with 250 parts by volume of 25% potassium-sodium tartrate solution, decant ether phase. Add to the aqueous phase 100 parts by volume of 50% sodium hydroxide solution and maintain mixture at 80° for 12 hours. Cool the mixture and extract with ether. Into the unified and dried ethereal solution, introduce hydrogen chloride gas to obtain 9.33 parts of the cyanochloride of the product, M.P. after recrystallization from alcohol 263° to 268°.

EXAMPLE 19

2-dimethylaminomethyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene

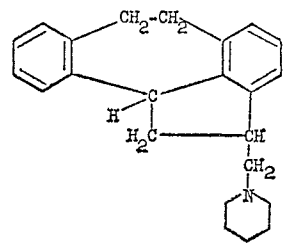


Heat a mixture of 8.9 parts of 2-aminomethyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene (free base), 10.1 parts of 80% formic acid and 7.9 parts of 40% formaldehyde solution to 100° until the evolution of carbon dioxide ceases. Add thereto 2 parts of concentrated hydrochloric acid and evaporate mixture in vacuo. The residue constitutes the crude produce in its hydrochloric acid salt form. Purification is achieved by liberating the free base with aqueous ammonia, extraction with ether and introduction of hydrogen chloride gas into the washed and dried ethereal solution, whereupon the hydrochloride of the product precipitates.

Reacting 2 - methylaminomethyl - 1,2,6,7 - tetrahydro - (11bH)-benzo[j]benz[c,d]azulene (free base) under the above conditions yields the same product.

EXAMPLE 20

2-N-piperidylmethyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene



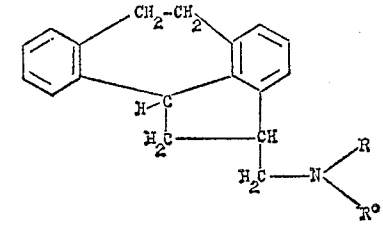
Admix 2.51 parts of the title compound of Example 18, 2.30 parts of 1,5-dibromopentane and 20 parts by volume of toluene and reflux the resultant for 3 hours. Add thereto 1.7 parts of sodium hydrocarbonate and 10 parts by volume of toluene and continue refluxing for an additional 15 hours. Cool the resultant to room temperature; add chloroform thereto; and wash the toluene/chloroform solution with water. Dry the above solution and precipitate the hydrochloride of the product by addition thereto of ethereal hydrogen chloride.

Examples 17 to 20 illustrate a reaction scheme alternative to that illustrated by Examples 10 to 16. The latter is longer, but stereospecific. The shorter process yields the diastereoisomers which are separated into chemical individuals by known methods.

The invention will be understood from the foregoing description. Various changes may be made in the processes, the intermediates and the final products without departing from the spirit or scope of the invention or sacrificing its material advantages. The processes, the novel intermediates and the final products hereinbefore described are merely illustrative embodiments of the invention.

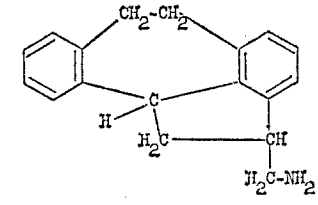
What is claimed is:

1. A pharmaceutically acceptable compound which, in free base form, is of the formula



wherein each of R and R° is a member selected from the group consisting of a hydrogen atom, alkyl having from 1 to 4 carbon atoms, benzyl and phenethyl.

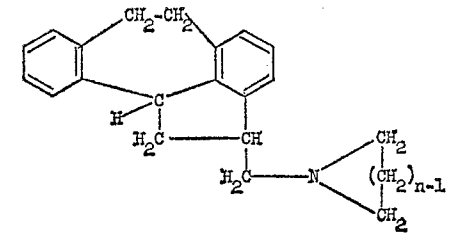
2. The compound of the formula



3. 2 - methylaminomethyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene.

4. 2 - dimethylaminomethyl - 1,2,6,7 - tetrahydro-(11bH)-benzo[j]benzo[c,d]azulene.

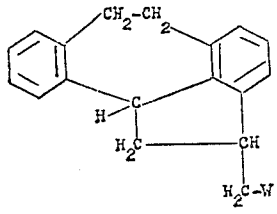
5. A pharmaceutically acceptable compound which, in free base form, is of the formula



wherein *n* is an integer from 1 to 6, inclusive.

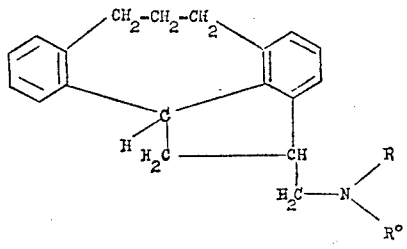
6. 2 - N - piperidylmethyl-1,2,6,7-tetrahydro-(11bH)-benzo[j]benz[c,d]azulene.

7. A pharmaceutically acceptable compound which, in free base form, is of the formula



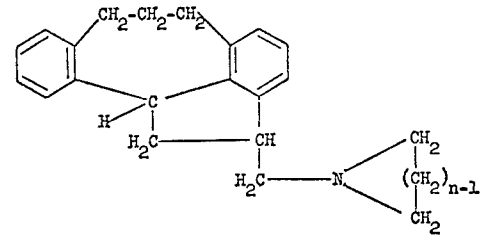
wherein W is a member selected from the group consisting of alkylpiperazinyl having from 1 to 4 carbon atoms in the alkyl portion, morpholino, thiomorpholino and pyrazolidino.

8. A pharmaceutically acceptable compound which, in free base form is of the formula



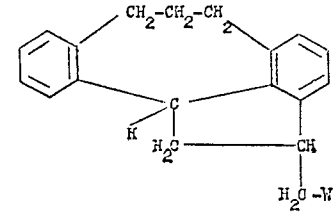
wherein each of R and R° is a member selected from the group consisting of a hydrogen atom, alkyl having from 1 to 4 carbon atoms, benzyl and phenethyl.

9. A pharmaceutically acceptable compound which, in free base form, is of the formula



wherein *n* is an integer from 1 to 6, inclusive.

10. A pharmaceutically acceptable compound which, in free base form, is of the formula



wherein W is a member selected from the group consisting of alkylpiperazinyl having from 1 to 4 carbon atoms in the alkyl portion, morpholino, thiomorpholino and pyrazolidino.

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HENRY R. JILES, *Primary Examiner.*

H. I. MOATY, *Assistant Examiner.*

U.S. Cl. X.R.

260—140, 239, 243, 247, 268, 310, 326.81, 349, 453, 465, 473, 469, 471, 515, 558, 570.8, 570.9, 590, 611, 618, 649; 424—244, 246, 248, 250, 267, 269, 274, 330