# United States Patent [19]

**Remy**

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[54] **2-PHENYLETHYNYL-BENZYL-AMINES**


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[52] **U.S. Cl.**.....**260/570.9**, 260/234 B, 260/247, 260/247.1, 260/247.5 R, 260/247.7 A, 260/268 R, 260/293, 260/293.4, 260/294, 260/294.7, 260/309.6, 260/326.3, 260/326.5 R, 260/326.8, 260/326.84, 260/326.85, 260/465 E, 260/465 F, 260/465 G, 260/465 D, 260/501.1, 260/501.18, 260/515 A, 260/515 M, 260/516, 260/518 R, 260/520, 260/52 R, 260/562 R, 260/570.8 R, 260/618 R, 260/649 R, 260/649 F, 424/330

[51] **Int. Cl.**.....**C07c 87/28**

[58] **Field of Search**.....260/570.8, 570.9, 501.21



[56] **References Cited**

UNITED STATES PATENTS

2,912,453 11/1959 Moffett.....260/570.9 X

OTHER PUBLICATIONS

Drefahl et al., "Chemical Abstracts," Vol. 55, pages 1523–1526, (1961).



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[57] **ABSTRACT**

This application discloses methods of preparing styrylaralkylamines and phenylethynylaralkyl-amines by the lithium aluminum hydride reduction of the corresponding cyanostilbenes and phenylethynylbenzonitriles. The produced alkylamines are converted to the corresponding N-alkyl and N,N-dialkyl derivatives thereof. The amines and their alkylated derivatives are useful as antiarrhythmics.


**5 Claims, No Drawings**

# 2-PHENYLETHYNYL-BENZYL-AMINES

This invention relates to unsaturated derivatives of aralkylamine compounds. More specifically, it relates to substituted and unsubstituted derivatives of styrylaralkylamines, phenylethynylaralkylamines and the corresponding N-substituted derivatives such as the N-alkyl and N,N-dialkyl derivatives thereof.

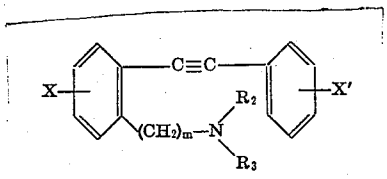
This invention also relates to the novel processes and the novel intermediates utilized in the production of new aralkylamines, to pharmaceutical formulations of the new aralkylamines and to methods of treating or preventing cardiac arrhythmias using the novel compounds and/or pharmaceutical formulations thereof, described hereinafter.

The new compounds of my invention are arylalkenylaralkylamines, arylalkynylaralkylamines, and the corresponding heterocyclic alkenyl (or alkynyl) aralkylamines represented by the following structural formula

$$Ar_1—C \equiv C—Ar_2$$

wherein $Ar_1$ is an aralkylamine substituent, particularly a substituted or unsubstituted phenyl-alkylamine substituent, $Ar_2$ is an aromatic or heteroaromatic substituent, particularly a substituted or unsubstituted phenyl radical and the dotted line represents dotted optional additional bond.

A preferred class of compounds of my invention are represented structurally as aralkyl-amines of the formula:

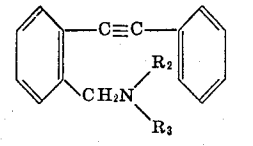



in which *m* is an integer varying from 1 to 4 inclusive; $R_2$ and $R_3$ are either similar or dissimilar and are either hydrogen, alkyl (preferably of from one to six carbon atoms), branched chain alkyl, alkenyl, alkynyl (each preferably containing one to six carbon atoms), and can be joined together or alternatively may be linked through an atom of carbon, nitrogen, oxygen, or sulfur to one of the methylene substituents bridging the aromatic ring and the amine radical to form a heterocyclic ring of from five to six atoms such as 1-piperidyl, 1-pyrrolidinyl, 1-morpholinyl, 4-thiomorpholinyl, or 1-loweralkyl-4-piperazinyl.

A preferred group of such compounds includes derivatives in which one or more of the hydrogens of the benzene rings is replaced by substituents selected from the group consisting of hydrogen, an alkyl group having up to six carbon atoms, an alkenyl group having up to six carbon atoms, a perfluoroalkyl group having up to four carbon atoms, a phenyl or a substituted phenyl radical, amino, an alkylamino group having up to four carbon atoms, a dialkylamino group having up to four carbon atoms (halogen, particularly fluorine or chlorine), hydroxyl, an alkoxyl group having up to four carbon atoms, a perfluoroalkoxyl group having up to four carbon atoms, mercapto, an alkylmercapto group having up to four carbon atoms, a perfluoroalkylmercapto group having up to four carbon atoms. More than one of these substituents may be on each ring. These substituents are identified in the formula as X or X′.



An especially preferred group of compounds included within the scope of my invention is represented by the formula:




in which $R_2$ and $R_3$ are either hydrogen, alkyl (preferably of from one to six carbon atoms), alkenyl, alkynyl (each preferably of from one to six carbon atoms), and can be joined together through an atom of carbon, nitrogen, oxygen or sulfur to form a heterocyclic ring of from five to six atoms (such as 1-piperidyl, 1-pyrrolidinyl, 4-morpholinyl, 4-thiomorpholinyl or 1-loweralkyl-4-piperazinyl). The dotted line in the formula represents either an additional carbon to carbon single bond or two hydrogens attached to the adjacent carbons.

Illustrative of the compounds included within the scope of the invention are 2-(phenylethynyl)-benzylamine, 2-(4-methoxyphenylethynyl)-benzylamine, 2-(4-tolylethynyl)-benzylamine, 2-(4-fluorophenyl-ethynyl)-benzylamine, trans-2-styryl-benzylamine, trans-2-(4-methoxystryl)-benzylamine, the corresponding N-alkyl and the N,N-dialkyl derivatives thereof.

The compounds represented above, in either their free base or salt form, possess useful pharma-cological properties. In particular, they have been found to possess antiarrhythmic activity. It has been found that the administration of compounds of the present invention, depicted in the above formula, results in the prevention of arrhythmia in animals under conditions which ordinarily cause the development of arrhythmia in the animal 100 percent of the time.

It has further been found that administration of the compounds of the present invention will arrest an existing arrhythmia in the animal being treated and cause a resumption of normal cardiac rhythm. As anti-arrhythmic agents, these compounds may be administered orally or parenterally. The formulations for administration may be prepared in conventional manner, employing conventional pharmaceutical carriers and excipients.

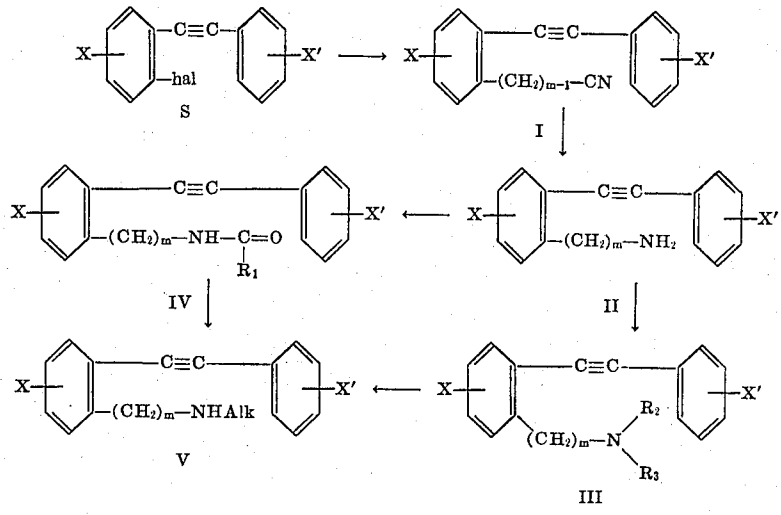
The non-toxic acid addition salts useful as components in the compositions provided by the present invention are salts formed by the reaction of an equivalent amount of the amine compound of the above formula and an acid which is pharmacologically acceptable in the intended doses. Salts of the above compound which are useful are salts of the amine with hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, fumaric acid, acetic acid, propionic acid, lactic acid, gluconic acid, maleic acid, succinic acid, tartaric acid, and the like. Salts of these acids with the amine base are useful as the active component of the compositions in the method of this invention.

The daily doses are based on the total body weight of the test animal and vary between about 1.00 and

100.00 mg./kg. for mature animals. Thus, a unit dose based on four-times-a-day administration is between 2.5 mg. and 250 mg. for a 10 kg. dog, and a total daily dose for a 10 kg. dog would vary between about 10 mg. and 1,000 mg. For larger animals, up to 100 kg. and above, proportional dosages are employed, based on the weight of the animal. Suitable dosage units provided for the administration of the compositions used in the method of the invention are tablets, capsules (which may be suitably formulated for either immediate or sustained release), syrups, elixirs, parenteral solutions, and the like. These dosage forms preferably contain per unit one or more multiples of the desired dosage unit in combination with the pharmaceutically acceptable diluent or carrier required for preparing the dosage unit.

The compounds represented by the above structural formulas may be prepared as illustrated below:

FLOW SHEET I




This step may include a homologation procedure involving initial replacement of the hal substituent by a carboxy substituent (i.e., treatment of the chloro compound with lithium followed by carbonation or treatment of bromo compound with magnesium followed by carbonation), followed by lithium aluminum hydride reduction of the acid to the primary alcohol derivative ($-CH_2OH$), conversion to ($-CH_2Br$) the next higher homolog of S.

wherein

$R_1$ is hydrogen or lower alkyl (preferably of from one to five carbon atoms);

$R_2$ and $R_3$ can be similar or dissimilar and are either hydrogen, alkyl (preferably of from one to six carbon atoms), aralkyl (preferably benzyl or phenethyl), alkenyl, alkynyl, and can be joined together or with one of methylene carbons bridging the amine substituent and the phenyl ring through an atom of nitrogen, oxygen or sulfur to form a heterocyclic ring of from five to six atoms (such as imidazolinyl, piperidyl, pyrrolidinyl, morpholinyl, thiomorpholinyl or loweralkyl piperazinyl;

X and X' are selected from the group consisting of hydrogen, halogen (chlorine or fluorine), alkyl (preferably of from one to six carbon atoms), alkoxy (preferably of from one to five carbon atoms), perfluoroalkyl (e.g., trifluoromethyl), alkylmercapto (preferably of from one to six carbon atoms);

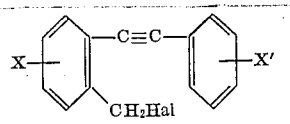
*m* is an integer selected from the group consisting of 1 to 4 inclusive; and

Alk is alkyl (preferably lower alkyl of from one to six carbon atoms).

In accordance with the process of my invention, a substituted or unsubstituted benzonitrile having a phenylethynyl or phenylethenyl substituent is reduced with an alkali metal hydride to form the corresponding benzylamine, e.g., 2-styryl benzylamine, (4'-methoxystyryl)-benzylamine, 2-(4-fluorophenylethynyl)-benzylamine, 2-(4-tolylethynyl)-benzylamine, 2-phenyl-ethynyl benzylamine, 2-(4-methoxyphenylethynyl)-benzylamine. The reduction is preferably effected by contacting the nitrile compound I in the structural formulas illustrating the process of my invention in the presence of a suitable inert organic solvent, such as tetrahydrofuran, ether or other solvents conventionally employed with lithium aluminum hydride. Preferably, this reduction is carried out in an either. The temperature at which the reduction is carried out is not critical but it is preferred to employ ambient temperatures and a rang of from 0°–50°C. is satisfactory. The resulting benzylamine compound is readily recovered employing conventional techniques.

In preparing higher homologs of the benzyl-amine compound, the staring halo compound S is converted using conventional reaction methods to the next higher homolog in which the halogen substituent has been replaced by a halomethylene substituent ($-CH_2Br$). Thus, the aralkenyl (or alkynyl) aryl halide is treated with lithium followed by carbonation or with magnesium to form the Grignard reagent followed by carbonation to form the desired aralkenyl or (alkynyl) aryl carboxylic acid. The thus-obtained acid is then reduced using lithium aluminum hydride to produce the corresponding substituted benzyl alcohol which is recovered in accordance with conventional procedures and treated with thionyl chloride, phosphorus tribro-

mide or the like to form the corresponding benzyl halide



VI

wherein Hal is bromo or chloro. The thus-obtained product is purified using conventional techniques and subjected to treatment with potassium cyanide thereby completing the conversion of the intermediate benzonitrile (I) to the next higher homolog, the phenyl-ethenylphenylacetonitrile or phenylethynylphenylacetonitrile.

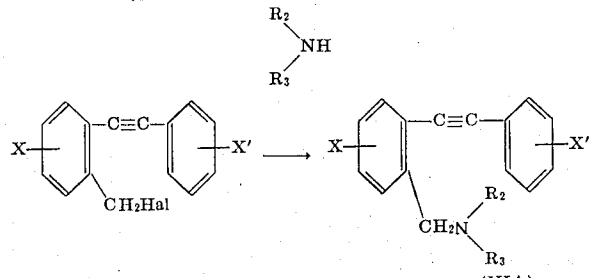
The corresponding N-(phenylethenyl or phenylethynylbenzyl)formamide (IV) or higher homologs thereof in which $R_1$ is hydrogen is prepared by formylation of the benzylamine compound (II) employing conventional conditions and reagents such as formic acid or esters thereof for this purpose. The resulting formamide derivative can be recovered in conventional manner. The N,N-dimethylamine (III), wherein $R_2$ and $R_3$ each represent methyl, is readily prepared by the treatment of the primary amine compound (II) with formaldehyde and formic acid in accordance with the known Eschweiler-Clarke modification of the Leuckart Reaction. Recovery of the N,N-dimethylamine is accomplished in conventional manner. The N-methylbenzylamine, represented by (V) wherein Alk is methyl, may be prepared by either reduction of the corresponding Ne(phenylethenyl or phenylethynylbenzyl)formamide (IV) or by monodealkylation of the corresponding N,N-dimethylamine (III) wherein $R_2$ and $R_3$ represent methyl. Reduction of the formamido-derivative (IV) is effected utilizing lithium aluminum hydride under the conditions set forth above for carrying out the reduction of the corresponding benzonitrile (I). Similarly, dealkylation of the N,N-dimethylamine (III) can be effected in known manner such as by treatment with cyanogen bromide followed by hydrolysis of the intermediate cyanamide or by treatment with a haloformate followed by hydrolysis of the resulting urethane intermediate. In each instance, the desired compound can be recovered employing conventional techniques.

The N-loweralkylamines and the N,N-dilower-alkylamines corresponding to compounds (V) and (III), respectively, are likewise prepared from the corresponding primary amine (II) by analogous reactions. Thus, the primary amine (II) is treated with a lower aliphatic acid halide or anhydride of from two to five carbon atoms, e.g., acetyl chloride, acetic anhydride, propionyl chloride, butyryl chloride or valeryl chloride to produce the N-alkanoyl amide corresponding to (IV) as, for example, the N-acetyl, N-propionyl, N-butyryl or N-valeryl amide. The thus-obtained amide is reduced to the corresponding N-loweralkyl benzylamine compound (V) by reduction in the manner described for the corresponding benzonitrile compound (I), i.e., by reduction with lithium aluminum hydride. The secondary amine compounds (V) produced in this manner are the N-loweralkyl derivatives of 2-(phenyl-ethenyl or phenylethynyl)benzylamines as, for example, the N-ethyl, N-propyl, N-butyl and the N-amyl derivatives. The corresponding tertiary amines (III), the N,N-dilower-alkyl derivatives, are prepared from the secondary amines by repeating the process employed in the preparation of the secondary amines. Thus, the amides of the secondary amines are prepared and reduced with lithium aluminum hydride to produce the corresponding tertiary amines as, for example, the corresponding N,N-diethyl, N-ethyl-N-methyl, N,N-dipropyl, N,N-dibutyl and the N,N-diamyl derivatives of substituted and unsubstituted phenyl-ethenyl or phenylethynyl benzylamine.

In accordance with an alternative process for the preparation of the compounds of formula (III), wherein

represents 1-pyrrolidinyl, 1-piperidyl, 4-morpholinyl, 4-thiomorpholinyl or 1-loweralkyl-4-piperazinyl, the primary amine (II) is condensed with an $\alpha\omega$-dihalo compound such as tetramethylene bromide, pentamethylene bromide, $\beta,\beta'$-dichlorodiethyl ether, $\beta,\beta'$-dichlorodiethyl sulfide, or an N-alkyl-$\beta,\beta'$-dichlorodiethyl amine.

In accordance with a further alternative process for the preparation of the primary, secondary, and tertiary benzylamine products of my invention, a benzyl halide of Formula (VI) hereinabove is converted by reaction with ammonia or an amine to form the corresponding primary, secondary or tertiary amine (IIIA) as indicated below

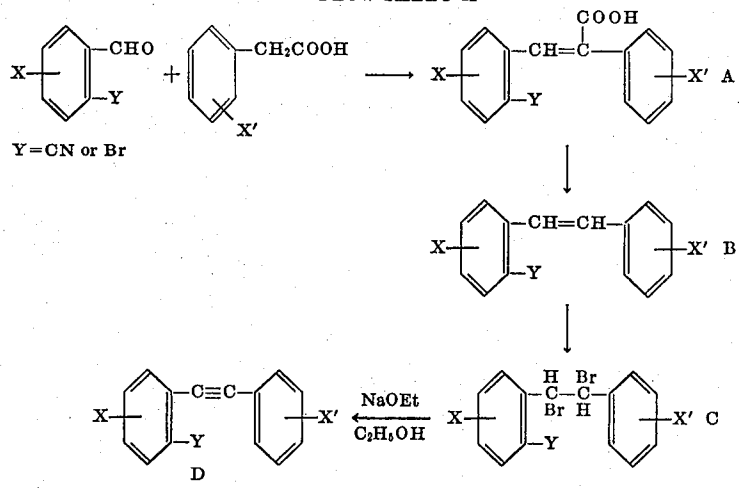


(VI) (IIIA)

wherein Hal, $R_2$, $R_3$, X, and X' have the significance previously indicated. In this manner, there is produced in addition to the N-alkyl and N,N-dialkyl derivatives of the substituted and unsubstituted phenylethenyl or phenylethynyl benzylamines or higher homologs thereof enumerated hereinabove, the corresponding compounds in which the amine nitrogen forms a part of a heterocyclic ring such as a piperidyl, pyrrolidinyl, morpholinyl, thiomorpholinyl or 1-loweralkyl-4-piperazinyl ring.

The starting compounds of the process of my invention, that is the aralkenylbenzonitrile and the aralkynylbenzonitriles containing X and X' substituents in the aromatic rings, are either known compounds or may be prepared from the corresponding halo substituted compounds by replacement of the halogen with cyanide through reaction with cuprous cyanide in pyridine. Other similarly substituted compounds may be prepared in accordance with the following flow sheet:

FLOW SHEET II




In this instance, a known cyano or bromo substituted benzaldehyde is condensed with a phenyl acetic acid to produce, as a first intermediate compound A, the appropriately substituted phenyl cinnamic acid. This, in turn, is converted to the desired stilbene intermediate B by decarboxylation. The stilbene compound B in the trans form is then brominated to produce Compound C, a stilbene dibromide which is then dehydrohalogenated with sodium methoxide in alcohol to produce the corresponding alkynyl compound D having a bromo substituent in the benzene ring. At any stage of the above-described process, the intermediates used in the preparation of the starting material wherein Y is bromo can be converted to the corresponding compound wherein y is cyano by treatment with cuprous cyanide. Compounds B and C can exist in two isomeric forms, the cis and trans isomers. These isomers have different physical characteristics and therefore are readily separable by conventional means as by crystallization.

## EXAMPLE 1

2-(Phenylethynyl)-bromobenzene

To a solution of 9.2 g. (0.4 mole) of sodium dissolved in 150 ml. of absolute ethanol is added 15.0 g. (0.036 mole) of trans-2-bromostilbene dibromide. The mixture is stirred and is heated under reflux for one hour. The bulk of the ethanol is removed by evaporation, and the residue is diluted with 1 liter of water. The oil that precipitates is extracted with ether. Evaporation of the ether after drying over magnesium sulfate gives 8.30 g. of clear oil, 2-(phenylethynyl)-bromo-benzene, that is, 95 percent pure by GLC.

## EXAMPLE 2

2-(Phenylethynyl)-benzylamine

A. 2-(phenylethynyl)-benzonitrile

A mixture of 8.30 g. (0.0323 mole) of 2-(phenylethynyl)-bromobenzene, 3.18 g. (0.036 mole) of cuprous cyanide and 2.81 g. (0.036 mole) of pyridine is stirred and is heated under reflux for 3 hours. The residue is partitioned between ether and 3N hydrochloric acid and then filtered. The ether phase is separated and is washed with 3N hydrochloric acid (3 × 100 ml.), water (2 × 200 ml.) and dried over magnesium sulfate. Evaporation of the ether gives a dark oil. Fractional distillation of this oil gives 2-(phenylethynyl)-benzonitrile, 2.16 g., b.p. 127°–129°C. (0.1 mm.).

When the above process is repeated using trans-2-cyanostilbene dibromide as the starting material, the product formed is 2-(phenylethynyl)-benzonitrile, b.p. 127°–129°C. (0.1 mm.).

B. 2-(Phenylethynyl)-benzylamine hydrochloride

A solution of 0.69 g. (0.0182 mole) of lithium aluminum hydride in 15 ml. of ether is cooled in an ice bath. To this solution is added dropwise over 30 minutes, a solution of 2.16 g. (0.0165 mole) of 2-(phenylethynyl)-benzonitrile in 25 ml. of ether. The mixture is stirred for 1 hour at 0°C. A solution of 5N sodium hydroxide is added dropwise until a clear ether phase is obtained. The ether is decanted, and the red gelatinous residue that remains is extracted with five 50 ml. portions of ether. The combined ether phases are dried over magnesium sulfate. The magnesium sulfate is removed by filtration and the ether filtrate containing 2-(phenylethynyl)-benzylamine is treated with gaseous hydrogen chloride. The crystalline precipitate is removed by filtration and is recrystallized from isopropyl alcohol and ether to give 2-(phenylethynyl)-benzylamine hydrochloride, m.p. 187°–188°C.

Anal. Calcd. for $C_{15}H_{13}N \cdot HCl$: C, 73.92; H, 5.78; Cl, 14.55. Found: C, 73.60; H, 5.73; Cl, 14.35.

## EXAMPLE 3

2-(4-Methoxyphenylethynyl)-benzylamine

A. Trans-2-cyano-4'-methoxystilbene dibromide

A mixture of o-cyanobenzaldehyde and 4-methoxyphenylacetic acid in approximately equimolar proportions is refluxed in a mixture of acetic anhydride and triethyl amine for 1.5 hours. The reaction mixture is diluted with water and the formed trans α-(4-methoxyphenyl)-2 cyano-cinnamic acid is precipitated and filtered from the diluted reaction mixture.

The trans α-(4-methoxyphenyl)-2 cyano-cinnamic acid is added portion-wise over a period of 10 minutes to redistilled quinoline containing a catalytic amount of copper-chromium oxide catalyst at a temperature of 225°–230°C. in the proportion of approximately 1 g. of acid of to 2.5 ml. of quinoline. When carbon dioxide evolution ceases the reaction mixture is cooled, decanted from the catalyst, distilled under reduced pressure and the distillate poured into dilute aqueous

hydrochloric and the formed cis 2 cyano-4'-methoxystilbene recovered by extraction into methylene chloride. The methylene chloride extract of product is washed to remove acid and after removal of the solvent by evaporation under reduced pressure the product is further purified by distillation.

The cis 2-cyano-4'-methoxystilbene is isomerized to trans 2-cyano-4'-methoxystilbene by heating with iodine in nitrobenzene. Removal of the iodine and nitrobenzene gives the crystalline trans stilbene derivative.

The dibromide of the trans-2-cyano-4-methoxy stilbene is prepared by treatment with an equimolar amount of bromine in carbon tetrachloride and crystallizes readily from the reaction mixture.

B. 2-(4-Methoxyphenylethynyl)-benzylamine

The dibromide prepared in Part A of this example is treated in accordance with the procedure of Examples 1 and 2 to produce 2-(4-methoxyphenyl-ethynyl)-benzylamine, m.p. 206.5°–208°C.

## EXAMPLE 4

2-(p-Tolylethynyl)-benzylamine hydrochloride

The procedure of Example 3 is repeated using as the starting material p-tolylacetic acid and o-bromobenzaldehyde to produce trans-2-bromo-4'-methylstilbene dibromide.

The resulting dibromide is treated with sodium methoxide dissolved in ethanol in accordance with the procedure described in Example 1 to produce 2-(p-tolylethynyl)-bromobenzene.

The 2-(p-tolylethynyl)-bromobenzene is then converted in accordance with the procedures set forth in Example 2 to produce 2-(p-tolylethynyl)-benzylamine hydrochloride, m.p. 205°–207°C.

## EXAMPLE 5

2-(p-Fluorophenylethynyl)-benzylamine hydrochloride

The procedure of Example 3 is repeated using as starting materials approximately equimolar portions of p-fluorophenylacetic acid and o-cyanobenzaldehyde to produce 2-(p-fluorophenylethynyl)-benzylamine hydrochloride, m.p. 172°–174°C.

## EXAMPLE 6

Trans-2-styrylbenzylamine hydrochloride

To a solution of 0.86 g. (0.023 mole) of lithium aluminum hydride in 30 ml. of ether is added dropwise over 40 minutes a solution of 2.83 g. (0.0138 mole) of trans-2-cyanostilbene in 70 ml. of ether. The mixture is stirred for 1.5 hours at room temperature and under reflux for 1 hour. Water (10 ml.) is added dropwise until a thick paste separates and a clear ether phase is obtained. The ether is decanted and the solid residue is washed with either. The combined ether phases are placed in a separatory funnel and shaken with 3N hydrochloric acid. A voluminous white crystalline precipitate forms. This precipitate is removed by filtration, washed with ether and water, and is recrystallized from water to give trans-2-styrylbenzylamine hydrochloride 0.25 $H_2O$, m.p. 213°–214°C.

Anal. Calcd. for $C_{15}H_{15}N \cdot HCl \cdot 0.25\ H_2O$: C, 71.99; H, 6.24; Cl, 14.17. Found: C, 71.94; H, 6.36; Cl, 14.18; $H_2O$, 0.22 mole.

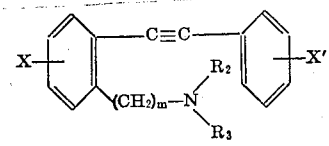
## EXAMPLE 7

Trans-2-(4'-methoxystyryl)-benzylamine hydrochloride

The procedure of Example 6 is repeated utilizing as the starting material the intermediate trans-2-cyano-4'-methoxystilbene prepared in accordance with the procedures of Example 3A herein-above to produce trans-2-(4'-methoxystyryl)-benzyl-amine hydrochloride, m.p. 204°–205°C.

We claim:

1. A compound represented by the formula



wherein X and X' are selected from the group consisting of hydrogen, chlorine, fluorine, loweralkyl and loweralkoxy; and $R_2$ and $R_3$ are hydrogen or loweralkyl.

2. A compound in accordance with claim 1 consisting of 2-(phenylethynyl)-benzylamine.

3. A compound in accordance with claim 1 consisting of 2-(4-methoxyphenylethynyl)-benzylamine.

4. A compound in accordance with claim 1 consisting of 2-(4-tolylethynyl)-benzylamine.

5. A compound in accordance with claim 1 consisting of 2-(4-fluorophenylethynyl)-benzylamine.

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