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CHEMICAL PROCESS AND PRODUCTS PRODUCED THEREBY

Norman L. Wendler, Summit, and David Taub, Metuchen, N.J., assignors to Merck & Co., Inc., Rahway, N.J., a corporation of New Jersey

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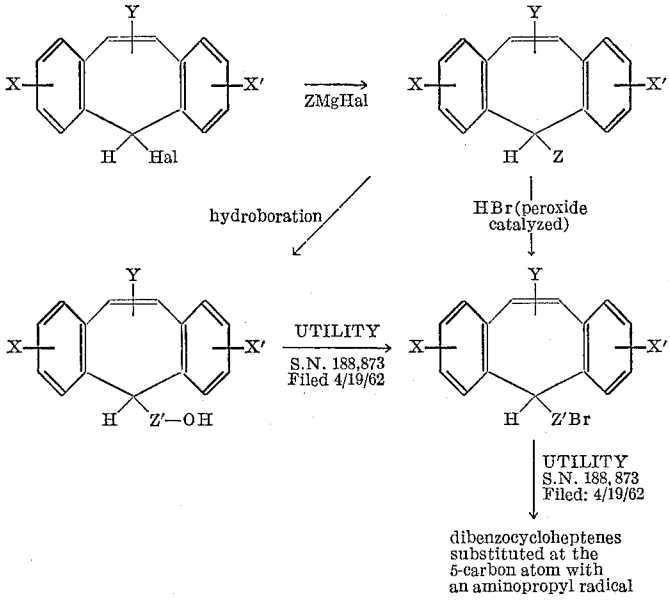
This invention relates to a process for making intermediates for the synthesis of 5H-dibenzo-[a,d]-cycloheptenes which are substituted at the 5-carbon atom with an aminopropyl radical. The invention also includes the synthesis of certain novel compounds produced by said process.

The aminopropyl compounds which are formed from the intermediates of the present invention are useful in the treatment of mental health conditions as they are antidepressants and serve as mood elevators or psychic energizers. These compounds are preferably administered in the form of their acid salts and these salts are included in the scope of this invention.

The process of the present invention may be represented by the following flow sheet.



in which Hal is a halogen, preferably chlorine or bromine; Y is a halogen or hydrogen; Z is allyl and a 1', 2' and 3'-alkyl-substituted allyl, Z' is propyl and alkyl substituted propyl, and X and X' are similar or dissimilar and are selected from the group consisting of hydrogen, an alkyl group having up to 6 carbon atoms, an alkenyl group having up to 6 carbon atoms, a perfluoroalkyl group having up to 4 carbon atoms, a phenyl or a substituted phenyl radical, an acyl group having up to 4 carbon atoms, a perfluoroacyl group having up to 4 carbon atoms, amino, an alkylamino group having up to 4 carbon atoms, a dialkylamino group having up to 8 carbon atoms, an acylamino group having up to 4 carbon atoms, a per-fluoroacylamino group having up to 4 carbon atoms, an alkylsulfonylamino group having up to 4 carbon atoms, halogen (fluorine, chlorine, bromine or iodine), hydroxyl, an alkoxyl group having up to 4 carbon atoms, a perfluoroalkoxyl group having up to 4

carbon atoms, cyano, carboxy, carbamyl, an alkylcarbamyl group having up to 5 carbon atoms, a dialkylcarbamyl group having up to 9 carbon atoms, a carbalkoxy group having up to 6 carbon atoms, mercapto, 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; more than one of these substituents may be on each benzenoid ring.

The starting compound, namely, the 5-halo-5H-dibenzo-[a,d]-cycloheptene, which may be substituted by X, X' and Y as defined above, may be made using the process described by G. Berti in the Gazz. Chim. Ital. 87, 293–309 (1957); F. J. Villani, C. A. Ellis, C. Teichman and C. Bigos, J. Med. Pharm. Chem., 5, 373 (1962); and M. Protiva et al., ibid, 4, 411 (1961), and the references cited therein. These compounds are, in turn, prepared from the known ketone, namely, 5H-dibenzo-[a,d]-cycloheptene-5-one, which may be prepared by using the process described by A. C. Cope et al., entitled, "Cyclic Polyolefins, XV, 1-methylene-2,3,6,7-dibenzocycloheptatriene," appearing in J.A.C.S., 73, 1673, 1678 (1951). Starting compounds for ketones having substituents on the benzene rings may be made by the following teachings of T. W. Campbell et al., in an article entitled, "Synthesis of 2'-acetamido-2,3:6,7-dibenzotropilidene and 2-acetamido-9,9-dimethylfluorene," appearing in Helv. Chem. Acta, 36, 1489 to 1499 (1953). Starting compounds where the Y substituent is a halogen may be made following the teachings of Villani in the above-cited reference.

As shown in the flow sheet above, the first step in the method of the present invention involves the condensation of a 5-halo-5H-dibenzo-[a,d]-cycloheptene with an allyl or a 1', 2' and 3'-alkyl substituted allyl magnesium halide to form the corresponding 5-allyl-5H-dibenzo-[a,d]-cycloheptene. In a typical run, 5-chloro-5H-dibenzo-[a,d]-cycloheptene is reacted with allyl magnesium bromide in dry diethyl ether under reflux to form 5-allyl-5H-dibenzo-[a,d]-cycloheptene.

The next step in the method involves the addition of a molecule of water to the 5-allyl intermediate to form the corresponding 5-(γ-hydroxypropyl)-5H-dibenzo-[a,d]-cycloheptene. In accordance with the invention, the desired addition is accomplished by a process of hydroboration, which term denotes herein reaction with a suitable boron compound, subsequent oxidation and hydrolysis to form the desired hydroxy compound. For example, upon treatment of 5-allyl-5H-dibenzo-[a,d]-cycloheptene in ether solution with one mol equivalent of a borane, followed by oxidative hydrolysis, there is produced the corresponding 5-(γ-hydroxypropyl)-5H-dibenzo-[a,d]-cycloheptene.

Suitable boranes contain preferably at least one B-H bond in the molecule as, for example, amine boranes, alkyl boranes, aryl boranes, alkylaryl boranes, borane-aluminum oxides, and the like. A basic solution of hydrogen peroxide is a preferred hydrolysis medium, although others may be used as well.

Once the γ-hydroxy compounds are obtained, they are converted to the useful aminopropyl compounds by a process of halogenation with a hydrogen halide to produce the corresponding halide derivative, and amination with an amine to form the desired end product or 5-aminopropyl derivative. These steps are described in the copending application, Serial Number 188,873, filed April 19, 1962.

In an alternative route, the 5-allyl intermediate is converted to the 5-γ-bromopropyl intermediate by a peroxide-catalyzed addition of hydrogen bromine. The bromo intermediate then is converted to the aminopropyl end compound by direct amination according to the aforementioned copending application.

The examples which follow will more specifically illustrate the process of the present invention.

EXAMPLE 1

5-allyl-5H-dibenzo-[a,d]-cycloheptene

To a 125 ml., 3-neck flask (flamed out and cooled under dry nitrogen) equipped with a stirrer, addition funnel, and ether-type condenser are charged 4.8 g. of clean magnesium turnings and 15 ml. of dry ethyl ether. 17 g. of allyl bromide in 10 ml. of dry ethyl ether is added dropwise with stirring at a rate sufficient to maintain a gentle reflux. Stirring and refluxing is continued until all the metal is gone. The reaction mixture is then cooled below the point of reflux, but not so low as to cause the Grignard reagent to precipitate, and 10 g. of 5-chloro-5H-dibenzo-[a,d]-cycloheptene in 20 ml. of dry ether is added with stirring in 15 minutes. The reaction mixture is stirred and allowed to react at room temperature for ½ hour. The reaction mixture then is chilled in an ice bath and treated with 45 ml. of saturated ammonium chloride solution. The layers are separated and just enough water is added to dissolve the solid salts in the aqueous layer. The latter is extracted with 2 x 25 ml. of ether. The combined organic layers are washed with 25 ml. of saturated salt solution, dried over magnesium sulfate and the solvent removed in vacuo to yield the desired product as an oil. This oil is further purified by chromatography on alumina.

Following the procedure described in detail above and using starting compounds having X, X′ and Y substituents as presented above, there are produced the corresponding X, X′ and Y substituted 5-allyl-5H-dibenzo-[a,d]-cycloheptenes.

EXAMPLE 2

5-(γ-hydroxypropyl)-5H-dibenzo-[a,d]-cycloheptene

A solution of 0.5 g. of the 5-allyl intermediate produced in Example 1 in 15 cc. of dry ethyl ether is treated with 1 mol equivalent of bis-3-methyl-2-butyl borane at 0–5° C. for a period of 3 hours. At the conclusion of this period, 3 cc. of water is added, followed by 8 cc. of 2.5 N sodium hydroxide and the dropwise addition of 6–7 cc. of 30% hydrogen peroxide. The aqueous phase is then salted with potassium carbonate and the ether layer is separated, dried over magnesium sulfate, and the solvent is evacuated in vacuo. The residue is crystallized from pet. ether to give the desired γ-hydroxy compound.

Following the procedure described in detail above and using starting compounds having X, X′ and Y substituents as presented above, there are produced the corresponding X, X′ and Y substituted 5-(γ-hydroxypropyl)-5H-dibenzo-[a,d]-cycloheptenes.

EXAMPLE 3

5-(γ-bromopropyl)-5H-dibenzo-[a,d]-cycloheptene

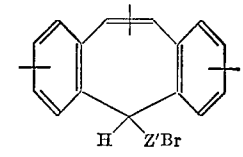
Hydrogen bromide gas is bubbled into a solution of 1.0 g. of 5-allyl-5H-dibenzo-[a,d]-cycloheptene and 50 mg. of benzoyl peroxide in 50 cc. of benzene at 25° for 2 hours. The solvent is removed under vacuum and the residue is crystallized from ether hexane to give the desired γ-bromopropyl compound.

EXAMPLE 4

Following the procedure described in detail in the above examples and using equivalent quantities of 1′, 2′ and 3′-methyl and ethyl substituted allyl bromides in place of allyl bromide in the above process, there are produced the corresponding propyl compounds substituted with α, β- and γ- methyl and ethyl groups.

What is claimed is:

1. A compound having the structural formula



wherein Z′ is selected from the group consisting of propyl and lower alkyl substituted propyl.

2. 5 - (γ - bromopropyl) - 5H - dibenzo - [a,d] - cycloheptene.

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LEON ZITVER, *Primary Examiner.*

M. B. ROBERTO, K. H. JOHNSON, K. V. ROCKEY, *Assistant Examiners.*