United States Patent Office

2,893,993

Patented July 7, 1959

2,893,993

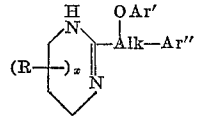
2-ARYLOXYARALKYL-1,4,5,6-TETRAHYDRO-PYRIMIDINES

Clinton A. Dornfeld, Glenview, Ill., assignor to G. D. Searle & Co., Chicago, Ill., a corporation of Delaware

No Drawing. Application June 17, 1958
Serial No. 742,476

9 Claims. (Cl. 260—251)

This invention relates to 2-aryloxyaralkyl-1,4,5,6-tetrahydropyrimidines and a process for the manufacture thereof. More particularly, this invention relates to compounds of the formula

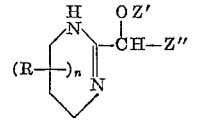


wherein R is a lower alkyl radical; x is 0 or a positive integer amounting to less than 8; Ar' and Ar'' are optionally alkylated, halogenated, and/or alkoxylated carbocyclic aromatic radicals; and Alk is a saturated acyclic hydrocarbon radical.

Illustrative of the lower alkyl radicals comprehended by R in the foregoing structural formula are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl, heptyl, and like alkyl groupings comprising fewer than 9 carbon atoms. As many as 7 such groupings can attach to the pyrimidine ring, subject only to the steric limitations inherent in disposing a plurality of molecular aggregates within a finite space. When no R substituents are present, the compounds represented are 2-aryloxyaralkyltetrahydropyrimidines otherwise non-alkylated; and x in the generic formula is seen to be 0.

The aryl radicals symbolized by Ar' and Ar'' in the formula include, for example, phenyl, benzyl, and naphthyl radicals, either or both of which can be nuclearly substituted by one or more lower alkyl radicals, halogen atoms, and/or lower alkoxy radicals. Those skilled in the art will appreciate that the term "alkoxy" refers to alkoxy groupings in which the alkyl constituent is of lower order.

Among the meanings assigned to Alk in the above formula, the simplest consists of a single carbon atom to which 1 hydrogen is bonded, the remaining valences being engaged by the pyrimidyl, aryloxy, and aryl radicals shown. Preferred compounds of this type, where the aryl moieties are of the benzene series, can be enformulated



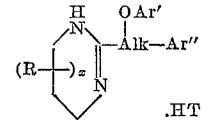
Z' and Z'' being selected from among phenyl, (lower alkyl)- phenyl, halophenyl, (lower alkoxy)phenyl, and benzyl radicals, and the expression $(R—)_n$ signifying the presence of 4 or fewer lower alkyl substitutents as shown.

The application for Letters Patent securing the invention herein described and claimed is a continuation-in-part of applicant's prior copending application, Serial No. 658,490, filed May 13, 1957, and now forfeited.

Compounds to which this invention relates are useful because of their valuable pharmacological properties. Especially, they are potent diuretic agents; and certain

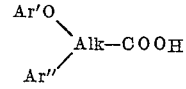
of the subject compounds additionally manifest spasmolytic, eurhythmic, anti-biotic, and/or anti-emetic activity.

Equivalent to the tertiary bases of this invention for the purposes disclosed are the non-toxic acid addition salts thereof, the composition of which may be depicted by



wherein R, x, Ar' Ar'', and Alk have the meanings hereinbefore assigned; and T is 1 equivalent of an anion—for example, chloride, bromide, iodide, nitrate, phosphate, sulfate, sulfamate, methyl sulfate, ethyl sulfate, benzene sulfonate, toluenesulfonate, acetate, lactate, succinate, malate, tartrate, citrate, gluconate, ascorbate, benzoate, cinnamate, or the like—which, in combination with the cationic portion of a salt aforesaid is neither pharmacologically nor otherwise undesirable in pharmaceutical dosage. Likewise adapted to the uses here set out are the N-acyl derivatives of the above compounds—particularly those in which the acyl substituent is a lower alkanoyl grouping.

The non-N-(alkylated or acylated) compounds of this invention are conveniently produced by condensing an appropriate 1,3-propanediamine having fewer than 7 lower alkyl substituents on the 3-carbon bridge with a suitable acid



Ar', Ar'', and Alk having the meanings assigned above, at temperatures of the order of 85° to 200° centigrade for periods of time ranging from a few hours to upward of several days, using an inert, organic, solvent reaction medium sufficiently high-boiling to permit operating at convenient pressures. Satisfactory media thus comprise such as toluene, xylene, ethylbenzene, cumene, cymene, and the like. In a preferred embodiment of the process of this invention, water formed during the course of the condensation is concurrently removed—for example, by means of a mechanical separator.

The N-(lower alkyl) derivatives of the compounds thus obtained are prepared therefrom by heating at 50–100° centigrade with an alkyl halide of choice, using a ketonic solvent as the reaction medium. The products are in the form of acid addition salts which, on alkalization, yield the tertiary base in each instance.

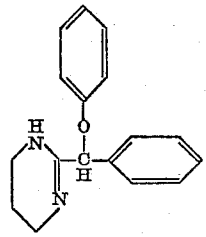
The N-acyl compounds hereinabove referred to are formed from the corresponding hydro derivatives by admixture with a selected acid chloride or anhydride in the presence of a basic catalyst, such as pyridine.

Conversion of the amine bases of this invention to corresponding acid addition salts is accomplished by simply contacting these bases with equivalent quantities of any of various inorganic and strong organic acids, the anionic portion of which conforms to T as hereinabove defined.

The following examples describe in detail certain compounds illustrative of the present invention and methods which have been devised for their preparation. However, the invention is not to be construed as limited thereby, either in spirit or in scope, since it will be apparent to those skilled in the art of organic synthesis that many modifications, both of materials and of methods, may be practiced without departing from the purpose and intent of this disclosure. In the examples hereinafter detailed, temperatures are given in degrees centigrade, pressures in millimeters of mercury, and relative amounts of materials in part by weight, except as otherwise noted.

Example 1

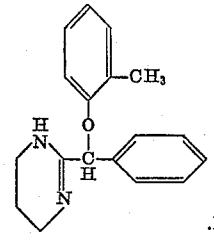
A. *1,4,5,6 - tetrahydro - 2 - (α-phenoxybenzyl)pyrimidine.*—A mixture of 23 parts of a α-phenoxyphenylacetic acid, 9 parts of 1,3-propanediamine, and 540 parts of xylene is heated at the boiling point under reflux while water formed in process is removed. After 20 hours, heating is stopped and the reaction mixture is extracted with dilute aqueous muriatic acid. The acid extract is filtered, washed with ether, and then made alkaline with caustic soda. The desired 1,4,5,6-tetrahydro-2-(α-phenoxybenzyl)pyrimidine is thrown down as an oil which crystallizes on separation and standing at room temperatures. The product melts at 104–106° and has the formula



B. *1,4,5,6 - tetrahydro - 2 - (α - phenoxybenzyl)pyrimidine hydrochloride.*—Approximately 3 parts of 1,4,5,6-tetrahydro-2-(α-phenoxybenzyl)pyrimidine in 25 parts of hot ethyl acetate is vigorously agitated while a slight excess of hydrogen chloride dissolved in isopropyl alcohol is introduced. An oily precipitate forms. Addition of butanone with continued agitation induces crystallization after a few minutes. The resultant mixture is chilled, following which the precipitate is removed by filtration and dried at 60°. The product thus obtained has a slight greenish tinge and melts at 223–224°. This material is 1,4,5,6-tetrahydro-2-(α-phenoxybenzyl)pyrimidine hydrochloride.

Example 2

1,4,5,6 - tetrahydro - 2 - [α - (o - tolyloxy)benzyl] - pyrimidine hydrochloride.—A mixture of 19 parts of α-(o-tolyloxy)phenylacetic acid and 6 parts of 1,3-propanediamine in 540 parts of xylene is heated at the boiling point under reflux for 21 hours, during which time water formed is concurrently removed. The reaction mixture is then cooled and extracted with dilute aqueous muriatic acid. From the acid extract, on standing, there is precipitated the desired 1,4,5,6 - tetrahydro - 2 - [α - (o - tolyloxy)benzyl]-pyrimidine hydrochloride. The product is filtered off, washed on the filter with a small amount of ether, and dried in vacuo. Slurrying in approximately 20 parts of hot butanone causes granulation of the previously somewhat amorphous material. The product melts at 217–218° and has the formula

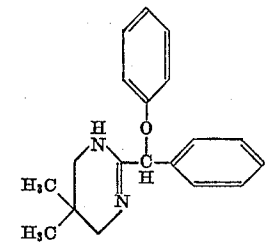


.HCl

Upon alkalization of an aqueous solution of the foregoing salt, the corresponding base is precipitated. Isolation is achieved by extraction into ether, drying of the ether extract over anhydrous sodium sulfate, and —finally—stripping of solvent via evaporation.

Example 3

A. *1,4,5,6 - tetrahydro - 5,5 - dimethyl - 2 - (α-phenoxybenzyl)pyrimidine.*—A mixture of approximately 25 parts of α-phenoxyphenylacetic acid, 10 parts of 2,2-dimethyl-1,3-propanediamine, and 540 parts of xylene is heated at the boiling point under reflux for 20 hours, water formed in process being concurrently removed. The reaction mixture is extracted with dilute aqueous muriatic acid, during which operation a small amount of insoluble material is thrown down. The acid extract is filtered, washed with ether, and finally made alkaline with caustic soda. Precipitation again occurs. The resultant mixture is extracted with chloroform, and the chloroform extract is dried over anhydrous sodium sulfate and ultimately stripped of solvent by evaporation. The crystalline residue is recrystallized from butanone, the product thus obtained being 1,4,5,6-tetrahydro-5,5-dimethyl-2-(α-phenoxybenzyl)pyrimidine, melting at 144–145°. The product has the formula



B. *1,4,5,6 - tetrahydro - 5,5 - dimethyl - 2 - (α - phenoxybenzyl)pyrimidine hydrochloride.*—To a hot solution of 31 parts of the base of the preceding Part A of this example in 145 parts of butanone is added, with agitation, 4 parts of anhydrous hydrogen chloride dissolved in 12 parts of isopropyl alcohol. Ether is then introduced just to the point of precipitation, following which the reaction mixture is let stand in the cold until crystallization is complete. The precipitated material is isolated by filtration, and dried is vacuo at 80°. The 1,4,5,6-tetrahydro-5,5 - dimethyl - 2 - (α - phenoxybenzyl)pyrimidine hydrochloride thus obtained melts at approximately 195°, there being preliminary alteration of physical structure in the range 182–185°.

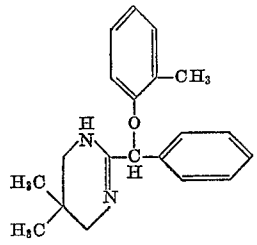
Example 4

A. *Ethyl α-(o-tolyloxy)phenylacetate.*—To 43 parts of sodium methylate in 1350 parts of xylene at the boiling point under reflux is added, with agitation during half an hour, 83 parts of o-cresol dissolved in 450 parts of xylene. In the ensuing hour, with the pot temperature in the neighborhood of 135°, approximately 25 parts of liquid is distilled off, following which a solution of 187 parts of ethyl α-bromophenylacetate in 450 parts of xylene is introduced during half an hour. The reactants are thereafter maintained at pot temperatures of the order of 125°, with agitation, overnight. Approximately 500 parts of water is next added and the aqueous phase thereupon made strongly alkaline with caustic soda. After thorough mixing, the xylene layer is removed and twice washed with dilute aqueous caustic. The xylene solution is then dried over anhydrous potassium carbonate and distilled. The fraction boiling at 116–128° under 0.06 mm. pressure is the desired ethyl α-(o-tolyloxy)phenylacetate.

B. *α-(o-Tolyloxy)phenylacetic acid.*—A mixture consisting of 112 parts of the ester of the preceding Part A of this example, 20 parts of caustic soda, and 400 parts of approximately 95% alcohol is heated with agitation at the boiling point under reflux for 2 hours. The bulk of the alcohol is then removed by distillation, whereupon 900 parts of water is added to the distilland to dissolve the white solid thrown down. A substantially clear solution results. Addition of 50 parts of concentrated muriatic acid causes reprecipitation of a solid, together with a small amount of oil. The resultant mixture is extracted with ether. The ether extract, dried over finely divided calcium sulfate and stripped of solvent by evaporation, affords the desired α-(o-tolyloxy)phenylacetic acid as a

residue. The product melts at approximately 107°.

C. *1,4,5,6 - tetrahydro - 5,5 - dimethyl - 2 - [α - (o-tolyloxy)benzyl]pyrimidine.*—A mixture of 26 parts of α-(o-tolyloxy)phenylacetic acid and 10 parts of 2,2-dimethyl-1,3-propanediamine in 540 parts of xylene is heated at the boiling point under reflux during 2½ hours, water being removed as formed in process. On standing at room temperatures overnight, the reaction mixture is found to contain a white crystalline precipitate. The mixture is extracted with dilute aqueous muriatic acid. The acid extract is treated with decolorizing charcoal and thereupon filtered hot. Chilled, it is filtered again, and then made alkaline with caustic soda. Extraction of the resultant mixture with ether, followed by drying of the ether solution over calcium sulfate and evaporation of solvent, affords 1,4,5,6 - tetrahydro - 5,5, - dimethyl - 2-[α-(-o-tolyloxy)benzyl]pyrimidine as an oil which crystallizes on standing. The product, recrystallized from butanone, melts in the range, 116–119°. It has the formula



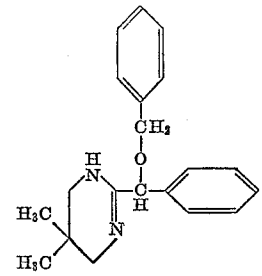
D. *1,4,5,6 - tetrahydro - 5,5 - dimethyl - 2 - [α - (o-tolyloxy)benzyl]pyrimidine hydrochloride.*—1,4,5,6-tetrahydro - 5,5 - dimethyl - 2 - [α - (o - tolyloxy)benzyl]pyrimidine is converted to the corresponding hydrochloric acid addition salt by neutralization in butanone solution with one equivalent of hydrogen chloride dissolved in isopropyl alcohol. Precipitation of the salt is induced by adding ether, and the product is isolated by filtration.

Example 5

A. *Ethyl α-(benzyloxy)phenylacetate.*—To a suspension of 11 parts of sodium hydride in 110 parts of xylene is cautiously added a solution of 75 parts of ethyl mandelate in 110 parts of xylene, vigorous agitation and temperatures in the range 50–60° being maintained throughout. As the last of the ethyl mandelate solution is introduced, the reaction mixture thickens and becomes difficult to work. This condition is alleviated by the addition of a further 225 parts of xylene. Agitation in the prescribed temperature range is maintained for 20 minutes longer, whereupon a solution of 58 parts of benzyl chloride in 90 parts of xylene is slowly added under the same conditions. The reactants are then heated to a high of 80° near the end of a still further 2-hour period of agitation. They are then allowed to stand at room temperatures overnight, at which point 250 parts of water is mixed in. The materials are allowed to layer out, whereupon the xylene phase is separated and dried over anhydrous potassium carbonate. Filtration of the dried solution is followed by distillation through a short column under high vacuum. The desired ethyl α-(benzyloxy)phenylacetate comes over at 145–155°/0.2 mm. pressure.

B. *α-(Benzyloxy)phenylacetic acid.*—A mixture of 37 parts of the ester of the preceding Part A of this example with 6 parts of caustic soda dissolved in 160 parts of alcohol is heated at the boiling point under reflux for 2 hours. The bulk of the alcohol is then removed by distillation at reduced pressures, following which the residue is taken up in approximately 500 parts of water. A small amount of insoluble matter is filtered out. The filtrate is treated with decolorizing charcoal and filtered again, using a filter aid. The clear solution which results is acidified with muriatic acid, throwing down an oil which is extracted into ether. The ether extract is dried over anhydrous calcium sulfate and then stripped of solvent by evaporation. The material which remains is α-(benzyloxy)phenylacetic acid.

C. *2-(α-benzyloxybenzyl)-1,4,5,6-tetrahydro - 5,5 - dimethylpyrimidine.*—A mixture of 15 parts of α-(benzyloxy)phenylacetic acid, 7 parts of 2,2-dimethyl-1,3-propanediamine, and 540 parts of xylene is heated at the boiling point under reflux and worked up in accordance with the technique set forth in Example 1A. The product is obtained as an oil which becomes substantially crystalline on standing at room temperatures. Recrystallization from hexane affords 2-(α-benzyloxybenzyl)-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine melting at 69–71°. The product has the formula



D. *2-(α-benzyloxybenzyl)-1,4,5,6-tetrahydro - 5,5 - dimethylpyrimidine hydrochloride.*—The base of the foregoing Part C of this example is converted to the corresponding hydrochloric acid addition salt in accordance with the procedure detailed in Example 1B. The 2-(α-benzyloxybenzyl)-1,4,5,6-tetrahydro-5,5 - dimethylpyrimidine hydrochloride thus obtained, upon drying in vacuo at 100° for 4 hours, has a melting point of approximately 200–200.5°.

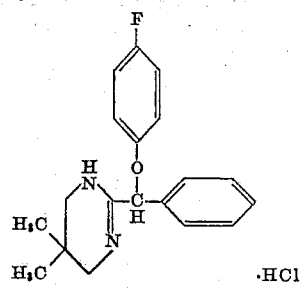
Example 6

A. *Ethyl α - (p - fluorophenoxy)phenylacetate.*—Using the procedure detailed in Example 4A above, but substituting p-fluorophenol for the o-cresol therein, 6 parts of sodium methylate, 500 parts of xylene, 20 parts of p-fluorophenol, and 36 parts of ethyl α-bromophenylacetate are reacted together to produce ethyl α-(p-fluorophenoxy)phenylacetate, which boils at 116–118° under 0.05 mm. pressure.

B. *α - (p - Fluorophenoxy)phenylacetic acid.*—To 14 parts of ethyl α-(p-fluorophenoxy)phenylacetate is added 3 parts of caustic soda dissolved in 5 parts of water plus 60 parts of alcohol. The resultant solution is heated for 2½ hours at 90–100° under reflux, then allowed to cool and solidify. The solid mass is taken up in 500 parts of water. This solution is treated with decolorizing charcoal, then cooled below 10° and acidified. An oil is precipitated which crystallizes on standing. The material, α-(p-fluorophenoxy)phenylacetic acid, on recrystallization from a mixture of benzene and hexane melts at 123–124°.

C. *2-[α-(p-fluorophenoxy)benzyl]-1,4,5,6 - tetrahydro-5,5-dimethylpyrimidine hydrochloride.*—A mixture of 12 parts of α-(p-fluorophenoxy)phenylacetic acid and approximately 6 parts of 2,2-dimethyl-1,3-propanediamine in 450 parts of xylene is heated at the boiling point under reflux for 26 hours during which water is removed as formed in process. The reaction mixture is then extracted with dilute aqueous muriatic acid, and this extract in turn is made basic with aqueous caustic soda. The resultant mixture is extracted with ether. The ether extract is dried over anhydrous sodium sulfate, then thoroughly mixed with a slight excess of hydrogen chloride dissolved in isopropyl alcohol. The desired 2-[α-(p-fluorophenoxy)-benzyl]-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine hydro-

chloride oils out, but solidifies following vacuum distillation of the solvent. The product has the formula



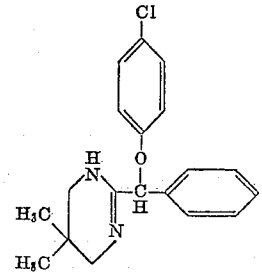
·HCl

Example 7

A. *Ethyl α-(p-chlorophenoxy)phenylacetate.*—A mixture of 51 parts of p-chlorophenol, 22 parts of sodium methylate, and 160 parts of absolute alcohol is heated at the boiling point under reflux with agitation for half an hour, whereupon a solution of 97 parts of ethyl α-bromophenylacetate in 80 parts of absolute alcohol is slowly added. The reaction mixture is maintained at the boiling point under reflux with agitation overnight, at which point alcohol is removed by vacuum distillation and the distilland is then extracted with ether. The ether extract is dried over anhydrous potassium carbonate and then distilled. The fraction boiling in the range 130–133° at 0.06 mm. pressure is ethyl α-(p-chlorophenoxy)phenylacetate.

B. *α-(p-Chlorophenoxy)phenylacetic acid.*—To a solution of 8 parts of caustic soda in 160 parts of approximately 95% alcohol at the boiling point under reflux is added, with agitation, 52 parts of ethyl α-(p-chlorophenoxy)phenylacetate dissolved in 80 parts of alcohol. A precipitate forms during the addition. Heating at the boiling point under reflux with agitation is continued for 30 minutes, whereupon approximately 25 parts of muriatic acid is cautiously introduced and the resultant mixture then stripped of alcohol by distillation. The distilland is extracted with ether and the ether extract dried over anhydrous sodium sulfate. Evaporation of ether leaves as a residue α-(p-chlorophenoxy)phenylacetic acid. The material is obtained first as an oil, which crystallizes on standing.

C. *2-[α-(p-chlorophenoxy)benzyl]-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine.*—A mixture of 26 parts of the acid of the preceding Part B of this example and 12 parts of 2,2-dimethyl-1,3-propanediamine in 540 parts of xylene is heated at the boiling point under reflux for 6 hours, during which time water is removed as formed. The reactants are allowed to stand at room temperatures overnight. A small amount of precipitate forms. The precipitate is filtered off and the filtrate is extracted with dilute muriatic acid. Upon alkalization of the extract thus obtained, a white precipitate is thrown down. This material is 2-[α-(p-chlorophenoxy)benzyl]-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine which, recovered on a filter and dried in vacuo at 100°, melts at 138–139°. The product has the formula



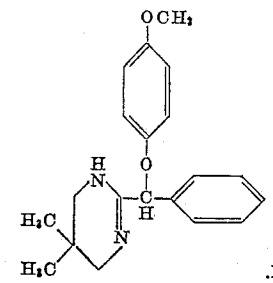
D. *2-[α-(p-chlorophenoxy)benzyl]-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine hydrochloride.*—Treatment of approximately 14 parts of 2-[α-(p-chlorophenoxy)-benzyl]-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine in 120 parts of hot butanone with one equivalent of hydrogen chloride dissolved in isopropyl alcohol, using the technique detailed in Example 3B, above, affords 2-[α-(p-chlorophenoxy)-benzyl]-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine hydrochloride, which is thoroughly dried by heating in vacuo at approximately 110° for upward of 2 hours. The vacuum drying operation is considered to remove volatile contaminants.

Example 8

A. *Ethyl α-(p-methoxyphenoxy)phenylacetate.*—Using the procedure detailed in Example 4A above, but substituting p-methoxyphenol for the o-cresol therein, 14 parts of sodium methylate, 540 parts of xylene, 31 parts of p-methoxyphenol, and 60 parts of ethyl α-bromophenylacetate are reacted together to produce ethyl α-(p-methoxyphenoxy)phenylacetate, which boils in the range 153–166° at 0.25 mm. pressure. The product is a viscous yellow oil.

B. *α-(p-Methoxyphenoxy)phenylacetic acid.*—A mixture of 27 parts of the ester of the preceding Part A of this example, 5 parts of caustic soda, and 100 parts of alcohol is heated with agitation at the boiling point under reflux for 2½ hours. The alcohol is then distilled off under reduced pressures, and the residue taken up in 300 parts of water. This solution is treated with decolorizing charcoal, which is removed by filtration. The filtrate is made acid with muriatic acid. The mixture so produced is extracted with ether. The ether extract, in turn, is dried over anhydrous sodium sulfate, filtered, and stripped of solvent by evaporation under nitrogen. The brown residue is crystallized from a mixture of benzene and hexane to give pure white α-(p-methoxyphenoxy)-phenylacetic acid, the melting point of which is 111–113°.

C. *1,4,5,6-tetrahydro-2-[α-(p-methoxyphenoxy) - benzyl]-5,5-dimethylpyrimidine.*—A mixture of 15 parts of α-(p-methoxyphenoxy)phenylacetic acid, 6 parts of 2,2-dimethyl-1,3-propanediamine, and 540 parts of xylene is heated at the boiling point under reflux for 24 hours, water being removed as formed in process. The reaction mixture is then extracted with hot dilute aqueous muriatic acid, and the hot aqueous extract thereupon treated with decolorizing charcoal. Charcoal having been filtered out, the filtrate is made alkaline with aqueous caustic soda. The resultant mixture is extracted with ether. The ether extract is dried over anhydrous potassium carbonate, then filtered and stripped of solvent by evaporation. The residue, crystallized from ethyl acetate, melts at approximately 135°. This material is 1,4,5,6-tetrahydro-2-[α-(p-methoxyphenoxy)benzyl]-5,5-dimethylpyrimidine, of the formula



·HCl

D. *1,4,5,6-tetrahydro-2-[α-(p-methoxyphenoxy)benzyl]-5,5-dimethylpyrimidine hydrochloride.*—A solution of 13 parts of the base of the preceding Part C of this example in 90 parts of warm ethyl acetate precipitates on standing at room temperatures. The precipitate is redissolved by addition of a slight excess of hydrogen chloride dissolved in isopropyl alcohol. After prolonged standing in the cold, there is thrown down a white crystalline product, which is filtered off and dried at 80° in vacuo. This material is 1,4,5,6-tetrahydro-2-[α-(p-methoxyphenoxy)benzyl]-5,5-dimethylpyrimidine hydrochloride, melting in the range 125–130°.

Example 9

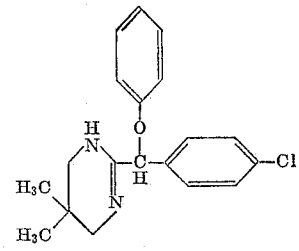
A. *Methyl p-chlorophenylacetate.*—To a solution of 536 parts of p-chlorophenylacetic acid in 900 parts of methyl alcohol is added 200 parts of concentrated sulfuric acid. The reaction mixture is heated at the boiling point under reflux for 2 hours, following which the bulk of the methyl alcohol is removed by distillation at atmospheric pressures. The residue is extracted with ether, and the ether extract is washed consecutively with water and aqueous 10% sodium bicarbonate. The extract is then dried over anhydrous potassium carbonate and stripped of solvent by distillation. There remains an oil which is distilled to give the desired methyl p-chlorophenylacetate, B.P. 102–103°/1.2–1.3 mm.

B. *Methyl α-bromo-p-chlorophenylacetate.*—A mixture of 537 parts of the ester of the preceding Part A of this example, 516 parts of N-bromosuccinimide, and 4000 parts of carbon tetrachloride is heated at the boiling point under reflux for 18 hours. Precipitated matter is filtered out and washed on the filter with carbon tetrachloride in three portions. These washings are combined with the filtrate and stripped of solvent at reduced pressures. The light yellow residual oil is distilled to give methyl α-bromo-p-chlorophenylacetate as a pale green oil boiling at 157–169°/19 mm.

C. *Methyl α-phenoxy-p-chlorophenylacetate.*—To a mixture of 84 parts of sodium methylate in 1350 parts of xylene is cautiously added a solution of 160 parts of phenol in 270 parts of xylene. Approximately 80 parts of methyl alcohol is distilled off, whereupon a solution of 386 parts of methyl α-bromo-p-chlorophenylacetate in 270 parts of xylene is cautiously added. The reaction mixture is then heated at the boiling point under reflux for 33 hours, at which point it is washed consecutively with dilute aqueous caustic soda and water, dried over anhydrous sodium sulfate, and stripped of solvent by distillation at reduced pressures. The brown oil which remains is distilled to give methyl α-phenoxy-p-chlorophenylacetate boiling in the range 152–159° at 0.3 mm. pressure.

D. *α-Phenoxy-p-chlorophenylacetic acid.*—A mixture of 187 parts of methyl α-phenoxy-p-chlorophenylacetate, 35 parts of caustic soda, 560 parts of alcohol, and 20 parts of water is heated at the boiling point under reflux for 2 hours. An additional 150 parts of water is then introduced, and the resulting amber solution is made acid with approximately 75 parts of muriatic acid plus 400 parts of water. The oil thrown down is extracted with ether. The ether extract, preliminarily dried over anhydrous sodium sulfate, is stripped of solvent by distillation; and the residual tan solid is crystallized from 360 parts of benzene. During the crystallizing operation, a small amount of material will not dissolve in the hot benzene solution and is discarded. The purified α-phenoxy-p-chlorophenylacetic acid obtained by this means is a colorless solid melting at 136–138°.

E. *2-(α-phenoxy-p-chlorobenzyl)-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine.*—A solution of approximately 26 parts of α-phenoxy-p-chlorophenylacetic acid and 11 parts of 2,2-dimethyl-1,3-propanediamine in 450 parts of boiling xylene is maintained at the boiling point under reflux for 24 hours. Water which forms during the heating period is separated and discarded. The xylene solution is extracted with dilute aqueous muriatic acid. The acid extract is made alkaline with aqueous caustic soda, and the resultant mixture is extracted with ether and with benzene. The ether and benzene extracts, in turn, are combined and dried over anhydrous sodium sulfate. Solvent is stripped by vacuum distillation, leaving a white solid which is recrystallized from isopropyl alcohol. 2-(α-phenoxy-p-chlorobenzyl)-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine comes down as white cottony needles which, dried in a vacuum oven at 70°, melt at approximately 162.5–163.5°. The product has the formula



F. *2-(α-phenoxy-p-chlorobenzyl)-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine hydrochloride.*—To a solution of 82 parts of the base of the preceding Part E of this example in 1000 parts of butanone is added 9 parts of hydrogen chloride as a solution in isopropyl alcohol. The resultant solution is precipitated by the addition of ether. The oil which comes down is isolated by decanting the supernatant solvents. Absolute alcohol is added and distilled off to remove residual moisture. Upon further drying in vacuo, the oil is converted to a white crystalline solid which melts in the range, 112–118°. This material is 2-(α-phenoxy-p-chlorobenzyl)-1,4,5,6-tetrahydro-5,5-dimethylpyrimidine hydrochloride.

Example 10

A. *Methyl p-methoxyphenylacetate.*—To a solution of 430 parts of p-methoxyphenylacetic acid in 730 parts of methyl alcohol is added approximately 170 parts of concentrated sulfuric acid. These materials are heated at the boiling point under reflux for 2 hours, whereupon the bulk of the alcohol is removed by distillation at atmospheric pressures. The residue is taken up in 700 parts of ether, and the resultant solution is consecutively washed with water and aqueous 10% sodium bicarbonate. After drying over anhydrous potassium carbonate, the ether solution is freed of solvent by distillation, leaving an oily residue which distills at 116–117°/1.2–1.3 mm. The product thus obtained is methyl p-methoxyphenylacetate.

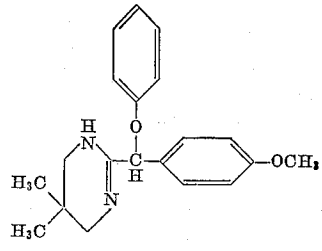
B. *Methyl α-bromo-p-methoxyphenylacetate.*—A mixture of 403 parts of the ester of the preceding Part A of this example, 399 parts of N-bromosuccinimide, and 3200 parts of carbon tetrachloride is heated at the boiling point under reflux for 18 hours. Worked up in accordance with the procedure set forth in the foregoing Example 9B, the reaction mixture yields the desired methyl α-bromo-p-methoxyphenylacetate as a pale green oil boiling in the range 119–136° under 0.3–0.5 mm. pressure.

C. *Methyl α-phenoxy-p-methoxyphenylacetate.*—To a mixture of 800 parts of xylene and 43 parts of sodium methylate is added a solution of 85 parts of phenol in 160 parts of xylene during 15 minutes. Approximately 30 parts of methyl alcohol is removed by distillation. At this point, 203 parts of methyl α-bromo-p-methoxyphenylacetate dissolved in 270 parts of xylene is introduced, and the reaction mixture thereupon heated at 136° under reflux for 26 hours. The resultant orange-red mixture is washed consecutively with aqueous caustic soda and water, then stripped of solvent by distillation at reduced pressures. The residual dark brown oil is distilled to give a heavy pink liquid boiling in the range 180–218°/0.4–0.8 mm. This material solidifies on standing, and melts in the range, 95–101°. The product thus obtained is methyl α-phenoxy-p-methoxyphenylacetate.

D. *α-phenoxy-p-methoxyphenylacetic acid.*—A mixture of 48 parts of methyl α-phenoxy-p-methoxyphenylacetate, 9 parts of caustic soda, 160 parts of alcohol, and 5 parts of water is warmed for 2 hours, then made acid with muriatic acid. The oil which separates is extracted with ether. The ether extract is dried over anhydrous sodium sulfate and then distilled to remove solvent,

The residual oil is crystallized from a mixture of benzene and hexane to give the desired α-phenoxy-p-methoxyphenylacetic acid, the melting point of which is 142–144°.

E. *1,4,5,6 - tetrahydro - 5,5 - dimethyl - 2 - (α - phenoxy-p-methoxybenzyl)pyrimidine.*—A mixture of 26 parts of α-phenoxy-p-methoxyphenylacetic acid, 11 parts of 2,2-dimethyl-1,3-propanediamine, and 450 parts of xylene is heated at the boiling point under reflux for 30 hours, during which time the water formed in process is concurrently removed. Following the prescribed heating period, the reaction mixture is extracted with dilute aqueous muriatic acid. The acid extract is made alkaline; and the alkaline extract, in turn, is extracted with ether and with benzene. The ether and benzene extracts are combined, dried over anhydrous sodium sulfate, and finally stripped of solvent by distillation. The residual deep brown oil is the desired 1,4,5,6-tetrahydro-5,5-dimethyl-2-(α-phenoxy-p-methoxybenzyl)-pyrimidine, of the formula



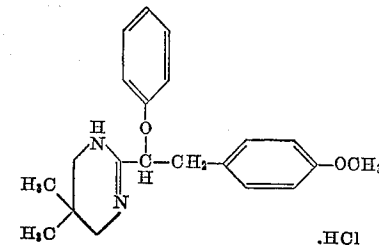
Example 11

A. *α-Phenoxy-p-methoxycinnamic acid.*—A mixture of 76 parts of phenoxyacetic acid, 68 parts of p-methoxybenzaldehyde, 51 parts of triethylamine, and 150 parts of acetic anhydride is heated for 45 hours at 120° under reflux in a vessel protected from moisture. The darkened reaction mixture is dumped onto ice and the oil extracted therefrom with ether. The ether extract is washed with water, then in turn extracted with aqueous 8% sodium carbonate. The carbonate extract is nearly neutralized with muriatic acid, then treated with decolorizing charcoal and filtered. The filtrate, chilled to 10°, is made acid with cold muriatic acid, precipitating a white powder which is recovered by filtration. This material is α-phenoxy-p-methoxycinnamic acid which, crystallized from alcohol, melts at 203–205°.

B. *β-(p-Methoxyphenyl)-α-phenoxypropionic acid.*—To a slurry of approximately 3 parts of palladium on charcoal catalyst in 40 parts of alcohol is added 15 parts of α-phenoxy-p-methoxycinnamic acid dissolved in 800 parts of alcohol. The resultant mixture is charged into a bomb under 42 pounds hydrogen pressure. After one hour during which vigorous agitation is maintained, the theoretical uptake of hydrogen is achieved, whereupon hydrogenation is stopped and the catalyst filtered out. The filtrate is stripped of solvent by distillation, and the residue is taken up in hot benzene. A small amount of insoluble material is filtered off. The benzene solution is precipitated with hexane, throwing down pure crystalline β-(p-methoxyphenyl)-α-phenoxy-propionic acid, the melting point of which is 96–98°.

C. *1,4,5,6 - tetrahydro - 5,5 - dimethyl - 2 - [1 -phenoxy - 2 - (p - methoxyphenyl)ethyl]pyrimidine hydrochloride.*—A mixture of 21 parts of β-(p-methoxyphenyl)-α-phenoxypropionic acid, 8 parts of 2,2-dimethyl-1,3-propanediamine, and 640 parts of xylene is heated at the boiling point under reflux for 24 hours during which water is removed as formed in process. The reaction mixture is then extracted with hot dilute aqueous muriatic acid and the acid extract filtered, using a filter aid. The filtrate is made basic with aqueous caustic soda.

1,4,5,6 - tetrahydro - 5,5 - dimethyl - 2 - [1 -phenoxy - 2-(p-methoxyphenyl)ethyl]pyrimidine precipitates and is taken up in ether. The ether extract is dried over anhydrous sodium sulfate and then precipitated with a slight excess of hydrogen chloride dissolved in isopropyl alcohol. Solvent is removed by vacuum distillation, leaving a residue which crystallizes on standing. This, the desired acid addition salt, is a colorless material of the formula

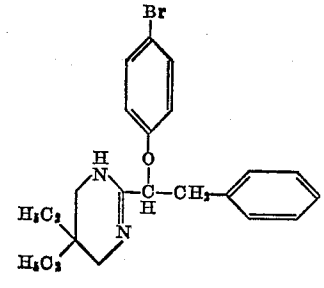


Example 12

A. *α-(p-Bromophenoxy)cinnamic acid.*—A mixture of 70 parts of p-bromophenoxyacetic acid, 32 parts of benzaldehyde, 31 parts of triethylamine, and 250 parts of acetic anhydride is heated at 120° for 48 hours. The reaction mixture is then dumped onto ice, and the brown oil which separates is extracted with ether. The ether extract, in turn, is extracted with aqueous 10% sodium carbonate. The carbonate extract is treated with decolorizing charcoal and filtered. Acidification of the filtrate produces a semi-solid precipitate which is crystallized from alcohol to give a white solid melting at 195–197°. This material is α-(p-bromophenoxy)cinnamic acid.

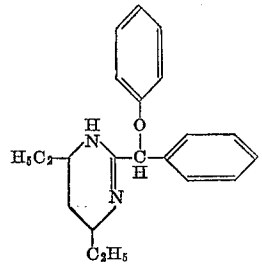
B. *α-(p-Bromophenoxy)-β-phenylpropionic acid.*—A solution of 12 parts of α-(p-bromophenoxy)cinnamic acid in 800 parts of alcohol is agitated in a pressure bomb with hydrogen, using approximately 2 parts of 5% palladium on charcoal as a catalyst. Hydrogenation is started at room temperatures and 40 pounds pressure. When the theoretical quantity of hydrogen is absorbed, hydrogenation is stopped and the catalyst filtered off. The filtrate is stripped of solvent by distillation, leaving as a residue the desired α-(p-bromophenoxy)-β-phenylpropionic acid.

C. *2 - [1 - (p - bromophenoxy) - 2 - phenylethyl] - 1,4, 5,6-tetrahydro--5,5-diethylpyrimidine.*—A mixture of 16 parts of α-(p-bromophenoxy)-β-phenylpropionic acid, 7 parts of 2,2-diethyl-1,3-propanediamine, and 540 parts of xylene is heated at the boiling point under reflux for 30 hours, during which time water is continuously separated and removed from the reaction mixture as formed. The mixture is then extracted with warm dilute aqueous muriatic acid. The acid extract, in turn, is treated with decolorizing charcoal and then filtered. The filtrate, made alkaline with aqueous caustic soda, is extracted with ether. The ether extract is dried over anhydrous potassium carbonate, and the solvent is thereupon removed by evaporation. There remains the desired 2-[1-(p-bromophenoxy)-2-phenylethyl]-1,4,5,6-tetrahydro - 5,5 - diethylpyrimidine, which has the formula



Example 13

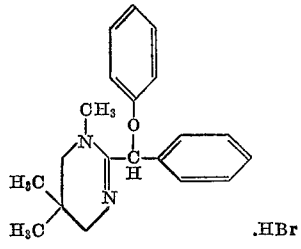
A. *4,6 - diethyl - 1,4,5,6 - tetrahydro - 2 - (α - phenoxybenzyl)pyrimidine.*—A mixture of approximately 23 parts of α-phenoxyphenylacetic acid, 14 parts of 3,5-heptanediamine, and 470 parts of p-cymene is heated at the boiling point under reflux for 9 hours, water formed in process being concurrently removed. The reaction mixture is then extracted with hot dilute aqueous muriatic acid; and the acid extract, in turn, is filtered, washed with ether, and finally made alkaline with aqueous caustic soda. The resultant mixture is extracted with ether, and the ether extract is dried over anhydrous sodium sulfate. Upon distillation of solvent, there remains as a residue the desired 4,6-diethyl-1,4,5,6-tetrahydro-2-(α-phenoxybenzyl)-pyrimidine. The product is obtained as a quite fluid oil. It has the formula



B. *4,6 - diethyl - 1,4,5,6 - tetrahydro - 2 - (α - phenoxybenzyl)pyrimidine hydrochloride.*—The base of the preceding Part A of this example is converted to the hydrochloric acid addition salt by dissolution in hot ethyl acetate and addition thereto of a slight excess of hydrogen chloride in isopropyl alcohol. The crystalline product which forms is filtered off and washed on the filter with ethyl acetate. Dried in vacuo at 80° overnight, the 4,6-diethyl-1,4,5,6-tetrahydro-2-(α-phenoxybenzyl)pyrimidine hydrochloride thus obtained is a colorless material melting at 207–209°.

Example 14

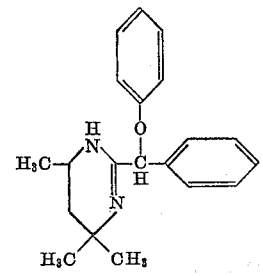
1,4,5,6 - tetrahydro - 1,5,5 - trimethyl - 2 - (α - phenoxybenzyl)pyrimidine hydrobromide.—A mixture of approximately 17 parts of 1,4,5,6-tetrahydro-5,5-dimethyl-2-(α-phenoxybenzyl)pyrimidine, 7 parts of methyl bromide, and 160 parts of butanone is maintained in a closed vessel at 60° for several days. Solution occurs after one hour, followed by precipitation starting 3 hours later. The precipitate is filtered off and dried at 60° in vacuo. The 1,4,5,6-tetrahydro-1,5,5-trimethyl-2-(α-phenoxybenzyl)pyrimidine hydrobromide thus obtained is a pure white solid melting at 239–241°. The product has the formula



.HBr

Example 15

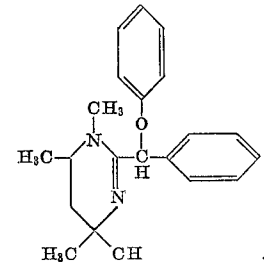
A. *1,4,5,6 - tetrahydro - 4,4,6 - trimethyl - 2 - (α - phenoxybenzyl)pyrimidine.*—A mixture of 23 parts of α-phenoxyphenylacetic acid, 14 parts of 2-methyl-2,4-phentanediamine, and 540 parts of xylene is heated at the boiling point under reflux for approximately 4 days, water being removed as formed in process. The reaction mixture is worked up as hereinbefore detailed to give the desired 1,4,5,6-tetrahydro-4,4,6-trimethyl-2-(α-phenoxybenzyl)pyrimidine in the form of an oil. The product has the formula



B. *1,4,5,6 - tetrahydro - 4,4,6 - trimethyl - 2 - (α-phenoxybenzyl)pyrimidine hydrochloride.*—To a solution of approximately 17 parts of the base of the preceding Part A of this example in 40 parts of hot ethyl acetate is added a slight excess of hydrogen chloride dissolved in isopropyl alcohol. A crystalline precipitate rapidly forms. The reaction mixture is chilled and the precipitate recovered on a filter. Dried at 60°, the material thus obtained melts at 261–262°. This product is 1,4,5,6-tetrahydro - 4,4,6 - trimethyl - 2 - (α - phenoxybenzyl) pyrimidine hydrochloride.

Example 16

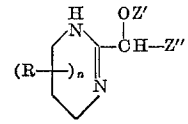
1,4,5,6 - tetrahydro - 1,4,4,6 - tetramethyl - 2 - (α-phenoxybenzyl)pyrimidine hydrobromide.—A solution of 3 parts of 1,4,5,6-tetrahydro-4,4,6-trimethyl-2-(α-phenoxybenzyl)pyrimidine, 1 part of methyl bromide and 50 parts of butanone is maintained in a closed vessel at 60° for 2 days. A precipitate forms as the reaction proceeds. This material, which is the desired 1,4,5,6-tetrahydro - 1,4,4,6 - tetramethyl - 2 - (α - phenoxybenzyl)pyrimidine hydrobromide, is separated by filtration. The product has the formula



.HBr

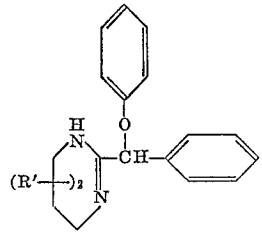
What is claimed is:

1. A compound of the formula



wherein R is a lower alkyl radical; *n* is selected from the group consisting of 0 and positive integers amounting to less than 5; and Z′ and Z″ are selected from the group consisting of phenyl, (lower alkyl)phenyl, halophenyl, (lower alkoxy)phenyl, and benzyl radicals.

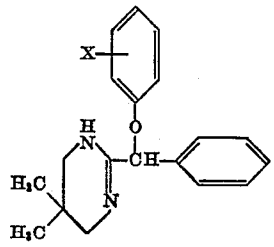
2. A compound of the formula



wherein R′ is a lower alkyl radical.

3. 1,4,5,6 - tetrahydro - 5,5 - dimethyl - 2 - (α - phenoxybenzyl)pyrimidine.

4. A compound of the formula



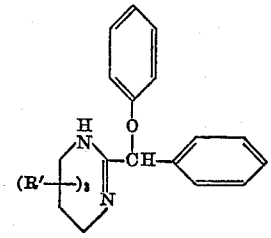
wherein X is halogen.

5. 2 - [α - (*p* - chlorophenoxy)benzyl] - 1,4,5,6 - tetrahydro-5,5-dimethylpyrimidine.

6. 1,4,5,6 - tetrahydro - 2 - [α(p - methoxyphenoxy)-benzyl]-5,5-dimethylpyrimidine.

7. 1,4,5,6 - tetrahydro - 2 - [α - (o - tolyloxy)benzyl]-pyrimidine.

8. A compound of the formula



wherein R′ is a lower alkyl radical.

9. 1,4,5,6 - tetrahydro - 4,4,6 - trimethyl - 2 - (α-phenoxybenzyl)pyrimidine.

No references cited.