METHOD FOR CONTROLLING HYPERTENSION

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This invention relates to a novel process for controlling hypertension in humans and to novel medication compositions useful for such purpose.

The novel therapeutic process of this invention comprises the administration to humans of a hypertensive amine or a nontoxic pharmaceutically-acceptable acid addition salt thereof, said hypertensive amine being represented by the following formula:

\[
R_1-R_2-R_3
\]

wherein \( R_1 \) is a member of the group consisting of hydrogen, methyl, ethyl and propyl; \( R_2 \) is a member of the group consisting of alkyl and alkynyl radicals having from 1 to 7 carbon atoms, the sum of the carbon atoms in \( R_2 \) and \( R_3 \) being greater than 1, and \( R_2 \) and \( R_4 \) when taken together form a tetramethylene group; \( R_3 \) and \( R_4 \) are alkyl groups having from 1 to 4 carbon atoms, the sum of the carbon atoms in \( R_3 \) and \( R_4 \) being less than 8; \( R_3 \) is a member of the group consisting of lower alkyl, lower alkynyl and lower alkynyl radicals having from 2 to 4 carbon atoms, the acetyl radical and the \( \alpha \)-hydroxyethyl radical.

In the above formula, when \( R_3 \) is an alkyl or alkynyl radical having from 1 to 7 carbon atoms, it can be, illustratively, a methyl, ethyl, n-propyl isopropyl, t-butyl, n-butyl, t-amyl, sec-amyl, 3-ethyl-3-pentyl, 2-methyl-2-hexyl, allyl, methallyl, crotyl radical and the like. \( R_3 \) and \( R_4 \) can be, illustratively, a methyl, ethyl, n-propyl, isopropyl, t-butyl, isobutyl, sec-butyl or n-butyl radical. Illustrative groups which \( R_5 \) can represent include the ethyl, propyl, ethynyl, allyl, vinyl, \( \Delta^1 \)-butenyl, 1-butenyl, propynyl radicals and the like.

The nontoxic pharmaceutically-acceptable acid addition salts of the hypertensive amines represented by the above formula, can also be employed in the therapeutic process of this invention. Among the acids which are useful for forming these acid addition salts are both inorganic and organic acids, for example, hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid, maleic acid, cinnamic acid, benzoic acid, tartaric acid and the like.

Illustrative compounds including both amine bases and acid addition salts thereof useful in the therapeutic process and compositions of this invention include the following:

1. 3-isooxylamino-3-methylbutane maleate
2. 3-(2-methyl-2-pentylamino)-3-methyl-2-pentanol
3. isopropylamino-3-methyl-1-pentene sulfate
4. N-methyl-N-allyl-3-amino-3-methyl-2-pentanol
5. 3-t-butylinamino-3-methyl-1-butenetartrate
6. 3-t-amylamino-3-ethyl-2-butane
7. 3-ethylamino-3-methylhexane phosphate
8. N-ethyl-N-isopropyl-3-amino-3-methyl-2-butanol
9. 3-ethylamino-3-methyl-3,4-dimethyl-1-pentene hydrobromide
10. N-methyl-N-t-butyl-3-amino-3-methyl-2-butanone
11. 3-ethylamino-3-ethyl-4,4-dimethyl-1-pentene hydrochloride

In carrying out the novel therapeutic process of this invention, an amine represented by the above formula, or an acid addition salt thereof, is administered to a patient suffering from hypertension. The dosage level employed varies according to the need of the patient and is dependent upon both the type and severity of the hypertension. For most hypertensive patients, the daily administration of from 1 to 500 mg. of the amine base, usually in the form of a nontoxic pharmaceutically-acceptable acid addition salt, serves to control the hypertension by reducing the blood pressure to a safe level and maintaining it at that level. As is well understood, however, certain patients may require daily doses in excess of 500 mg. per day of an amine represented by the above formula for effective control of their hypertension. The daily dose also depends upon the particular compound used since the hypertensive amines coming within the scope of the above formula differs somewhat in their activity and in their length of action as well as in the incidence and type of side effects accompanying their administration. The compounds can be given by either the parenteral or oral route. The latter mode of administration is preferred because of its greater convenience.

The administration of hypertensive amines and amine salts according to the novel therapeutic process of this invention, effectively controls hypertension in humans suffering from that disease. Falls in both systolic and diastolic pressures are readily procured. For example, the administration of a single dose of 2.5 to 5 mg. of 3-t-butylinamino-3-methylbutane hydrochloride to a group of patients produced drops in systolic blood pressure which averaged about 26 mm., and drops in diastolic pressure which averaged about 9 mm. when the pressure was measured in the prone position, and average drops in systolic pressure of 34 mm., and diastolic pressure of 16 mm., when the pressure was measured in the standing position. In each instance, the measurements were made 3 hours after the administration of the drug. Repeated administration of 2.5 to 3 mg. of the drug 2 to 3 times every day for a period of three months maintained drops in both systolic and diastolic pressures of the above magnitude throughout the period.

Substantial blood pressure reductions have also been secured by the daily administration of 5 to 10 mg. dose amounts of 3-t-butylinamino-3-methyl-1-butenet hydrochloride.

A third compound, 3-t-butylinamino-3-methyl-1-butenet hydrochloride when administered to hypertensive patients in 20 or 25 mg. doses amounts 6 times a day, reduced the systolic pressure to about half of the pretreatment pressure and also produced substantial falls in diastolic pressure. Single doses of 5 mg. of the same drug gave decreases in both systolic and diastolic blood pressures in hypertensive patients in the standing and prone positions over a 5 hour period. Other patients maintained on a dosage of 10 or 15 mg. of 3-t-butylinamino-3-methyl-1-butenet in the form of the hydrochloride salts admini-
tered 3 times daily for periods of 1 to 2 weeks, have had substantial falls in systolic and diastolic pressures without any concomitant side effects attributable to the drug. The hypotensive amines useful in the therapeutic process of this invention are advantageously administered in the form of their nontoxic pharmaceutically-acceptable acid addition salts, since the salts are quite stable and are easily formulated into pharmaceutical compositions.

In carrying out the therapeutic process of this invention, a hypotensive amine, usually as an acid addition salt, is administered either orally or parenterally in a patient suffering from hypertension. The amines or their salts can be administered in any of the pharmaceutical forms commonly used for the administration of drugs, as for example, capsules, tablets, elixirs, suspensions, ampoules, enteric coated tablets, microencapsulations, adsorbates on ion-exchange resins, and the like. The above-mentioned pharmaceutical forms employ the common pharmaceutical extending media and excipients employed for the preparation of pharmaceutical forms of other amine salts.

The following examples illustrate the preparation of certain of the solid pharmaceutical forms of selected compounds useful in the therapeutic process of this invention. Any of the compounds of this invention, however, can be prepared for use in human therapy in a similar pharmaceutical form or as parenteral solutions, elixirs, suspensions and the like, as well understood in the art. The preparation of any of the pharmaceutically acceptable salts for purely illustrative purposes, it being understood that other pharmaceutically-acceptable salts can be substituted for the hydrochloride salts of the formulations.

The following specific compositions are illustrative of those useful in the therapeutic process of this invention.

Capsules containing 3-t-butylamino-3-methyl-1-butenyl hydrochloride were prepared by thoroughly mixing 0.125 g. of the hydrochloride salt with 54.875 g. of starch. The mixture was encapsulated in teasing gelatin capsules, with 0.22 g. of the mixture being placed in each capsule to provide an amount of 0.5 mg. of 3-t-butylamino-3-methyl-1-butenyl hydrochloride per capsule.

Capsules containing 3-t-butylamino-3-methyl-1-butenyl hydrochloride were also provided in a form suitable for administration to humans by thoroughly mixing 250 mg. of the salt with 74.75 g. of starch and then encapsulating the 0.3 g. of the mixture were placed in each of 750 teasing capsules so that each capsule contained 1 mg. of the active drug.

Capsules of 3-t-butylamino-3-methyl-1-butenyl hydrochloride suitable for administration to humans were prepared by thoroughly mixing 0.1375 g. of the salt with 44 g. of starch. The mixture was encapsulated after mixing so that each capsule contained 0.16 g. of the mixture to provide 0.5 mg. of the active drug. Capsules containing 1 mg. of the active drug per capsule were prepared in a similar fashion except that 0.275 g. of the salt was mixed with 44 g. of starch.

Capsules containing 3-t-butylamino-3-methyl-1-butenyl hydrochloride were prepared by thoroughly mixing 2.85 g. of the drug with 168.15 g. of starch and then filling 550 capsules each with about 0.3 g. of the mixture, thus providing in each capsule a 5 mg. dose amount of the hydrochloride. Capsules containing 10 and 20 mg. each of 3-t-butylamino-3-methyl-1-butenyl hydrochloride were prepared similarly.

3-t-butylamino-3-methylbutane hydrochloride was provided in a form suitable for administration to humans by mixing 0.0375 g. of the drug with 25.5 g. of starch and then encapsulating the mixture in suitably sized teasing gelatin capsules so that each capsule contained about 0.17 g. of the mixture and therefore about 0.25 mg. of the active drug. Capsules containing 0.5 mg. each of 3-t-butylamino-3-methylbutane hydrochloride were prepared in the same way except that 0.075 g. of the salt were mixed with 25.5 g. of starch. Capsules containing 1 and 3 mg. per capsule of 3-t-butylamino-3-methylbutane hydrochloride were prepared in similar fashion.

3-t-butylamino-3-methylbutane hydrochloride was prepared in tablet form for use in human therapy by mixing together 58 g. of active drug, 1.624 g. of milk sugar, 626 g. of starch and 12 g. of magnesium stearate. The mixture was granulated, and the granulation was pressed into scored tablets of such size that each contained about 2.5 mg. of active drug.

Pharmaceutical dosage forms containing the desired quantity or parenterally administered n-t-butyl-3-amino-3-methyl-1-butyne, 3-t-butylamino-3-methyl-2-butanone, N-methyl-N-t-butyl 3-amino-3-methyl-1-butyne in the form of their hydrochloride salts can be prepared in a fashion similar to those set forth above.

The compounds useful in the therapeutic process and compositions of this invention are prepared generally as follows: The secondary and tertiary amino acetylenes are synthesized by heating the corresponding chloroacetylene with a primary or secondary amine. The tertiary amino acetylenes can also be prepared by alkylation of the corresponding secondary amino acetylene. The amino ethylamines are prepared by the method of Hennion and Froning, J. Am. Chem. Soc. 62, 654 (1940). The preparation of 3-isopropyl-4-methyl-1-pentene-3-ol which follows, is typical of the procedure used for the synthesis of hydroxy acetylenes.

**PREPARATION OF HYDROXY ACETYLENES**

The procedure used to prepare the hydroxy acetylene intermediates useful as starting materials for preparing the compounds of this invention was patterned after that of Hennion and Froning, J. Am. Chem. Soc. 62, 654 (1940). The preparation of 3-isopropyl-4-methyl-1-pentene-3-ol which follows, is typical of the procedure used for the synthesis of hydroxy acetylenes.

**Example 1.—Preparation of 3-Isopropyl-4-Methyl-1-Pentyn-3-Ol**

46 g. of sodium in the form of small chunks were added with stirring to about 3 l. of liquid ammonia. After all the sodium had been added and the bluish color of sodium metal had disappeared, 228 g. of disobutyl ketone were added to the solution. The addition of the acetylene was maintained during the addition of the ketone and for about 4 hours thereafter. 1,000 ml. of ether were added and the reaction mixture was allowed to stand overnight during which time the liquid ammonia evaporated. 1,000 ml. of water were added and the ether layer which contained the 3-isopropyl-4-methyl-1-pentyn-3-ol formed in the above reaction, was separated and was dried. The ether was removed by evaporation in vacuo in the cold. Distillation of the resulting residue yielded purified 3-isopropyl-4-methyl-1-pentyn-3-ol boiling in the range 80-85°C. at a pressure of about 28 mm. of mercury; nD20=1.442.

Table 1 which follows lists new hydroxy acetylenes prepared by the above procedure as well as the known ketones from which they were prepared. In addition, Table I gives the boiling points and refractive indexes of the hydroxy acetylenes.
PREPARATION OF CHLOROACETYLENES

The procedure used to prepare the chloroacetylene intermediates useful in the synthesis of the compounds of this invention was patterned with certain modifications after that of Hennion and Maloney, J. Am. Chem. Soc. 73, 4735 (1951). The preparation of 3-chloro-3-methyl-1-butylene which follows is typical of the modified procedure used in preparing both the novel chloroacetylenes and those of the prior art useful as intermediates in preparing the amino acetylenes of this invention.

Example 2—Preparation of 3-Chloro-3-Methyl-1-Butyne

167 g. of calcium chloride and 2 g. of copper bronze powder were mixed in a 11. r. round-bottomed flask. 168 g. of 3-methyl-1-butylene-3-ol were added and the resulting mixture was cooled to about 10°C. About 600 ml. of 12 N hydrochloric acid cooled to 0°C, were added in three 200 ml. portions with slight shaking. The reaction mixture was maintained at about 10-15°C. for about 15 minutes and was then allowed to warm up slowly to ambient room temperature. After a total reaction time of about one hour, the lower acetic acid layer was separated and was discarded. The organic layer was washed twice with 200 ml. portions of distilled water followed by a 100 ml. portion of a 10 percent sodium bicarbonate solution. The washes were all discarded. The organic layer was then steam distilled until about 90 percent of the organic layer had distilled. The aqueous portion of the distillate was separated and discarded. The organic layer containing 3-chloro-3-methyl-1-butyne formed in the above reaction was dried over solid anhydrous potassium carbonate and was then distilled through an electrically heated 60 cm. fractionating column. The fraction distilling in the range 77-77°C. at atmospheric pressure was collected. Redistillation of this fraction through the same column gave 105 g. of purified 3-chloro-3-methyl-1-butyne boiling in the range 74-76°C. at atmospheric pressure; nD20 = 1.416.

Table II which follows lists various chloroacetylenes prepared by following the above procedure. In addition, the table lists the hydroxyacetylene used as the starting material as well as the boiling point and refractive index of the chloroacetylene prepared therefrom.

PREPARATION OF ACETYLCYENIC AMINES

The acetylenic amines useful as active hypotensive agents in the therapeutic process and compositions of this invention can be prepared by the method of Hennion and Nilon, J. Am. Chem. Soc. 79, 2142 (1957). According to this procedure, an acetylenic chloride is reacted with a primary or secondary amine, preferably in aqueous solution and in the presence of a copper salt or of copper bronze powder. If no copper catalyst is used, the reaction between the acetylenic chloride and the primary or secondary amine takes considerable time even with heating. The use of the catalyst, however, greatly shortens the reaction time and in most instances, the reaction proceeds spontaneously without external heating.

In carrying out the reaction between an acetylenic chloride and an amine, an excess of the amine is customarily employed, the excess amine serving to react with the hydrogen chloride produced as a by-product in the reaction. A ratio of from 2 to 3 moles of amine per mole of acetylenic chloride is customarily employed. However, if the amine is difficult to obtain, an excess of a nonreacting basic substance can be employed in conjunction with an equivalent amount of the amine. For example, an inorganic base such as aqueous potassium hydroxide or sodium hydroxide can be used. In addition, organic bases which do not react with an acetylenic halide; e.g. tertiary amines such as triethyl amine or pyridine, can also be employed.

Two synthetic routes are also available for the preparation of acetylenic amines in which the acetylenic group is substituted with an alkyl group on the β-carbon atom of the acetylenic grouping. In one synthetic procedure, a compound of this type can be prepared by reacting the appropriately substituted acetylenic chloride with a primary or secondary amine, as set forth herein above. Alternatively, the active hydrogen on the β-carbon of the acetylenic group can be alkylated in liquid ammonia solution to yield the desired product employing an alkylating agent such as an alkyl halide.

Two synthetic routes are also available for the synthesis of the tertiary acetylenic amines. The first route as set forth above, comprises the direct reaction of the acetylenic halide with a secondary amine or the desired tertiary amine. The alternative method of preparation comprises the N-alkylation of a secondary acetylenic amine prepared by theamination of an acetylenic chloride with a primary amine. The alkylating agent can be any of those commonly employed, as for example, formaldehyde and formic acid or an alkyl halide, a dialkyl sulfate or sulfonate with or without the addition of a second basic substance.

The following specific examples more fully illustrate the preparation of the acetylenic amines of this invention.

Example 3—Preparation of 3-Isopropylamino-3-Methyl-1-Butyne

Five ml. portions of 44.3 g. of isopropylamine were added to about 23 ml. of water. 25.5 g. of 3-chloro-3-methyl-1-butylene were added to the aqueous amine and the resulting homogeneous solution was allowed to stand at ambient room temperature for about one week. The reaction mixture had by this time separated into two layers. The reaction mixture was poured into a mixture containing 200 ml. of water and 200 ml. of ether. The aqueous layer was separated and discarded. The ethereal layer containing 3-isopropylamino-3-methyl-1-butylene formed in the reaction was washed with two 100 ml. portions of water and was dried over solid potassium hydroxide. 3-isopropylamino-1-3-methyl-1-butylene was distilled and fractions boiling between 110-121°C. were collected. Redistillation of the combined fractions through a 30 cm. Vigreux column yielded purified 3-isopropylamino-3-3-methyl-1-butyne distilling in the range 115-118°C.; nD20 = 1.419. The distillate solidified upon standing.
and yielded crystalline 3-isopropylamino-3-methyl-1-butyne, melting at about 27° C.

Analysis.—Calc.: C, 76.74; H, 12.08. Found: C, 76.57; H, 12.19.

3-isopropylamino-3-methyl-1-butyne was converted to M the corresponding hydrochloride salt by dissolving the free base in ethanol and adding an excess of a solution of ethanol saturated with hydrogen chloride. The ethanol was evaporated in vacuo leaving the hydrochloride as a residue. Recrystallization of the residue from a mixture of ethyl acetate and isopropyl alcohol yielded 3-isopropylamino-3-methyl-1-butyne hydrochloride melting at about 204°-206° C.

Analysis.—Calc.: C, 59.43; H, 9.98; N, 8.66. Found: C, 59.30; H, 9.94; N, 8.55.

The sulfate salt of 3-isopropylamino-3-methyl-1-butyne can be prepared by adding an equivalent amount of 18 M aqueous sulfuric acid to an ethanol solution of the amine, and then isolating the sulfate salt by the procedure indicated above for the hydrochloride salt.

Example 4.—Preparation of 3-Ethylamino-3-Methyl-1-Butyne

A mixture was prepared containing 100 ml. of ether and 96 g. of ethylamine as a 70 percent aqueous solution. The mixture was placed in a 500 ml. round-bottomed flask equipped with a mechanical stirrer and dropping funnel. The flask had previously been flushed with dried nitrogen gas. About 0.3 g. of cuprous chloride were added to this mixture, followed by the dropwise addition of a mixture of 51 g. of 3-chloro-3-methyl-1-butyne and 50 ml. of ether. This last addition required about 40 minutes and during this time, the reaction temperature was maintained between 22°-25° C. by external cooling. The reaction mixture was stirred in an atmosphere of nitrogen for an additional 4½ hours and then was poured into a solvent mixture containing 200 ml. of ether and 100 ml. of water. The etheral layer containing 3-ethylamino-3-methyl-1-butyne formed in the above reaction was separated and was washed twice with 50 ml. portions of water. The washes were discarded. 200 ml. of a 10 percent aqueous hydrochloric acid solution were added and 3-ethylamino-3-methyl-1-butyne passed into the acidic aqueous layer as a hydrochloride salt. The etheral layer was separated and was discarded as were two further 100 ml. ether washes. 200 ml. of a 10 percent aqueous sodium hydroxide solution were then added to the acidic aqueous layer forming 3-ethylamino-3-methyl-1-butyne free base. The free base which was insoluble in the alkaline layer, was extracted with 200 ml. of ether. The aqueous layer was separated and was washed with two more 200 ml. portions of ether. The ether extracts were combined and were dried. The ether was removed by evaporation, and the resulting residue comprising 3-ethylamino-3-methyl-1-butyne was distilled. Fractions boiling in the range 100°-110° C. were collected. Redistillation of these fractions yielded about 23.5 g. of purified 3-ethylamino-3-methyl-1-butyne boiling at about 108°-109° C. The distillate which solidified upon standing melted at about 50.5° C.

Analysis.—Calc.: N, 12.60. Found: N, 12.02.

3-ethylamino-3-methyl-1-butyne hydrochloride was prepared by dissolving 5 g. of 3-ethylamino-3-methyl-1-butyne in 25 ml. of anhydrous ether. The solution was cooled to about 0° C. and a 10 percent excess of a saturated ethereal hydrogen chloride solution was added. 3-ethylamino-3-methyl-1-butyne hydrochloride precipitated and was separated by filtration. The precipitate was twice recrystallized from an ethanol-ethyl acetate solvent mixture. 3-ethylamino-3-methyl-1-butyne hydrochloride thus purified melted at about 183°-185° C.


The maleate salt of 3-ethylamino-3-methyl-1-butyne can be prepared by adding an ether solution containing one equivalent of maleic acid to an ether solution containing one equivalent of the base. The malonate salt can be isolated by the same procedure set forth above for the hydrochloride salt.

Example 5.—Preparation of 3-n-Propylamino-3-Methyl-1-Butyne

Following the procedure of Example 3, aqueous n-propylamine and 3-chloro-3-methyl-1-butyne were reacted to form 3-n-propylamino-3-methyl-1-butyne. The compound was isolated by the procedure of Example 3 and was purified by distillation. 3-n-propylamino-3-methyl-1-butyne boiled at about 125° C. at atmospheric pressure. The distillate crystallized and melted at about 32° C.


Following the procedure of Example 4, 3-n-propylamino-3-methyl-1-butyne was converted to the corresponding hydrochloride salt, which melted at about 171–173° C.

Analysis.—Calc.: C, 59.43; H, 9.98; N, 8.66. Found: C, 59.53; H, 9.94; N, 8.75.

Example 6.—Preparation of 3-Butylamino-3-Methyl-1-Butyne

Following the procedure of Example 3, aqueous n-butylamine and 3-chloro-3-methyl-1-butyne were reacted to form 3-n-butylamino-3-methyl-1-butyne. The compound was isolated by the procedure of Example 3 and was purified by distillation. 3-n-butylamino-3-methyl-1-butyne boiled at about 151° C. at atmospheric pressure. The maleate salt, which melted at about 181° C. was purified by recrystallization from water.

Analysis.—Calc.: C, 61.52; H, 10.33; N, 7.97. Found: C, 61.23; H, 10.34; N, 7.92.

Example 7.—Preparation of 3-Iso-butylamino-3-Methyl-1-Butyne

Following the procedure of Example 3, aqueous iso-butylamine and 3-chloro-3-methyl-1-butyne were reacted to form 3-isobutylamino-3-methyl-1-butyne. The compound was isolated by the procedure of Example 3 and was purified by distillation. 3-isobutylamino-3-methyl-1-butyne boiled at about 140–142° C. at atmospheric pressure. The maleate salt, which melted at about 19° C. was purified by recrystallization from water.

Analysis.—Calc.: N, 9.94. Found: N, 9.94.

Following the procedure of Example 4, 3-isobutylamino-3-methyl-1-butyne was converted to the corresponding hydrochloride salt, which melted at about 215–216° C.

Analysis.—Calc.: C, 61.52; H, 10.33. Found: C, 61.45; H, 10.46.

Example 8.—Preparation of 3-Sec.-Butylamino-3-Methyl-1-Butyne

Following the procedure of Example 3, 100 ml. of distilled water were added to 219 g. of sec-butylamine. 102.5 g. of 3-chloro-3-methyl-1-butyne were added to the aqueous amine solution and the reaction mixture was allowed to stand at ambient room temperature for 12 days. 3-sect-butylamino-3-methyl-1-butyne formed in the above reaction was isolated by the procedure of Example 3 and was purified by distillation through a Widdrington column. The compound boiled at about 72° C. at a pressure of about 67 mm. of mercury. The maleate salt, which melted at about 19° C. was purified by recrystallization from water.

Analysis.—Calc.: C, 61.52; H, 10.33; N, 7.97. Found: C, 61.78; H, 10.36; N, 7.86.
Example 9.—Preparation of 3-t-Butylamino-3-Methyl-1-Butyne

Following the procedure of Example 3, 700 ml of distilled water were added to 1,533 g of t-butylamine. 714.5 g of 3-chloro-3-methyl-1-butyne were added to the aqueous amine solution and the reaction mixture was allowed to stand at ambient room temperature for 11 days. 3-t-butylamino-3-methyl-1-butyne formed in the above reaction was isolated by the procedure of Example 3 and was purified by distillation through a Widmer column. The compound boiled at about 72-72.5°C at a pressure of about 84 mm of mercury; nD25 = 1.430. The distillate crystallized upon cooling to 0°C. It melted at about 24°C.

Analysis.—Calc.: N, 10.06. Found: N, 10.24.

Example 10.—Alternate Preparation of 3-t-Butylamino-3-Methyl-1-Butyne

290 ml of water were added to 1,050 g of t-butylamine. 294.8 g of 3-chloro-3-methyl-1-butyne were added to the aqueous amine solution followed by about 3 g of copper bronze powder. After about 10 minutes, a vigorous exothermic reaction took place with the temperature of the reaction mixture rising to about 65°C. The reaction mixture was cooled to about 50°C by means of an ice bath and was maintained at about that temperature until the initial vigorous reaction had subsided. The reaction mixture was heated at 40°C for another 16 hours. 3-t-butylamino-3-methyl-1-butyne thus formed was isolated and purified by the procedure of Example 4.


Example 11.—Preparation of N,N-di-n-Propyl 3-Amino-3-Methyl-1-Butyne

Following the procedure of Example 3, aqueous di-n-propylamine and 3-chloro-3-methyl-1-butyne were reacted, thus forming N,N-di-n-propyl 3-amino-3-methyl-1-butyne. The compound was isolated by the procedure of Example 3 and was purified by distillation. N,N-di-n-propyl 3-amino-3-methyl-1-butyne boiled at about 74°C at a pressure of about 19 mm of mercury; nD25 = 1.436.

Analysis.—Calc.: N, 8.37. Found: N, 8.52.

Example 12.—Alternate Preparation of N,N-di-n-Propyl 3-Amino-3-Methyl-1-Butyne

51 ml of water, 152 g of di-n-propylamine and 500 mg of copper bronze powder were mixed with cooling. 51 g of 3-chloro-3-methyl-1-butyne were added dropwise to this mixture. The reaction mixture was kept below 40°C by cooling in an ice bath during the addition, and was stirred thereafter at ambient room temperature for about 18 hours. N,N-di-n-propyl 3-amino-3-methyl-1-butyne thus formed was isolated and purified by the procedure of Example 4.

Example 13.—Preparation of 3-Isopropylamino-3-Methyl-1-Pentyn
50 percent sodium hydroxide. 3-isopropylamino-3-ethyl-1-pentyne free base, being insoluble in the alkaline layer, was extracted with three 250 ml portions of ether. The ethereal layer was separated and was dried. The ether was removed by distillation through a Widmer column leaving as a residue 3-isopropylamino-3-ethyl-1-pentyne which was distilled through a Vigreux column. 3-isopropylamino-3-ethyl-1-pentyne boiled at about 97° C. at a pressure of about 25 mm. of mercury; \( n_\text{D}^20 = 1.433. \)


Following the procedure of Example 4, 3-isopropylamino-3-ethyl-1-pentyne was converted to the corresponding hydrochloride salt, which melted at about 222°-223° C.

**Analysis.**—Calc.: C, 63.30; H, 10.63; N, 7.38. Found: C, 63.58; H, 10.80; N, 7.40.

**Example 17.**—Preparation of 3-Ethylamino-3-Ethyl-1-Pentyne

Following the procedure of Example 3, 42 ml. of water were added to 193 g. of a 70 percent aqueous ethylamine solution. 130.5 g. of 3-chloro-3-ethyl-1-pentyne were added to the aqueous amine solution and the reaction mixture was allowed to stand at ambient room temperature for about 15 days. 3-ethylamino-3-ethyl-1-pentyne formed in the above reaction was isolated by the procedure of Example 3, and was purified by distillation through a glass helix-packed column. 3-ethylamino-3-ethyl-1-pentyne boiled at about 77°-79° C. at a pressure of 70 mm. of mercury; \( n_\text{D}^20 = 1.437. \)

**Analysis.**—Calc.: C, 60.96. Found: N, 9.89.

Following the procedure of Example 4, 3-ethylamino-3-ethyl-1-pentyne was converted to the corresponding hydrochloride salt, which melted at about 205°-207° C.

**Analysis.**—Calc.: C, 61.52; H, 10.32; N, 7.97. Found: C, 61.27; H, 10.13; N, 7.88.

**Example 18.**—Preparation of 3-Sec-Amylamino-3-Methyl-1-Butyne

Following the procedure of Example 3, 75 ml. of distilled water were mixed with 200 g. of sec-amylamine. 78 g. of 3-chloro-3-methyl-1-butyne were added to the aqueous amine solution and the reaction mixture was allowed to stand at ambient room temperature for 28 days. The reaction mixture was then heated to refluxing for about 24 hours and was cooled. 3-sec-amylamino-3-methyl-1-butyne formed in the above reaction was isolated by the procedure of Example 3. The compound was purified by distillation through a Widmer column. 3-sec-amylamino-3-methyl-1-butyne boiled at about 66° C. at a pressure of about 16 mm. of mercury; \( n_\text{D}^20 = 1.428. \)

**Analysis.**—Calc.: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.06; H, 13.13; N, 9.03.

3-sec-amylamino-3-methyl-1-butyne hydrochloride was prepared by adding an excess of ethanol saturated with hydrogen chloride to an ethereal solution of the free base. 3-sec-amylamino-3-methyl-1-butyne hydrochloride melted at about 133-135° C. after recrystallization from a mixture of ethyl acetate and isopropyl alcohol.

**Analysis.**—Calc.: N, 7.38. Found: N, 7.11.

**Example 19.**—Preparation of 3-Acrylamino-3-Methyl-1-Butyne

Following the procedure of Example 3, 100 ml. of water were mixed with 261 g. of t-amylamine. 102.5 g. of 3-chloro-3-methyl-1-butyne were added and the reaction mixture was allowed to stand at ambient room temperature for about 28 days. The reaction mixture was then refluxed for about 24 hours to bring the reaction nearly to completion. 3-acrylamino-3-methyl-1-butyne thus formed was isolated by the procedure of Example 3, and was purified by distillation through a Widmer column. 3-acrylamino-3-methyl-1-butyne boiled at about 51° C. at a pressure of 6 mm. of mercury; \( n_\text{D}^20 = 1.437. \)

**Analysis.**—Calc.: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.11; H, 12.52; N, 9.06.

3-acrylamino-3-methyl-1-butyne hydrochloride was prepared by adding an excess of ethanol saturated with hydrogen chloride to an ethereal solution of the free base. After isolation and purification the compound melted at about 167°-169° C.

**Analysis.**—Calc.: N, 7.38. Found: N, 7.17.

**Example 20.**—Preparation of 3-Acrylamino-3-Methyl-1-Butyne

Following the procedure of Example 3, 60 ml. of water were mixed with 98.3 g. of isopropylamine. 72.5 g. of 3-chloro-3-methyl-1-hexyne were added to the aqueous amine solution and the reaction mixture was allowed to stand at ambient room temperature for about 7 days. 3-isopropylamino-3-methyl-1-hexyne formed in the above reaction was isolated by the procedure of Example 3 and was purified by distillation through a Widmer column. 3-isopropylamino-3-methyl-1-hexyne boiled at about 73.5°-75.5° C. at a pressure of about 38 mm. of mercury; \( n_\text{D}^20 = 1.432. \)

Following the procedure of Example 18, 3-isopropylamino-3-methyl-1-hexyne was converted to the corresponding hydrochloride salt, which melted at about 167°-169° C. after recrystallization from a mixture of isopropanol and ethyl acetate.


**Example 21.**—Preparation of 3-t-Butylamino-3-Methyl-1-Butyne

Following the procedure of Example 3, 60 ml. of water were mixed with 121.7 g. of t-butyamine. 72.5 g. of 3-chloro-3-methyl-1-hexyne were added to the aqueous amine solution and the reaction mixture was allowed to stand at ambient room temperature for about 25 days. 3-t-butylamino-3-methyl-1-hexyne formed in the above reaction was isolated by the procedure of Example 3 and was purified by distillation through a Widmer column. 3-t-butylamino-3-methyl-1-hexyne boiled at about 50°-53° C. at a pressure of about 8 mm. of mercury; \( n_\text{D}^20 = 1.439. \)

**Analysis.**—Calc.: C, 78.97; H, 12.65; N, 8.37. Found: C, 79.01; H, 12.45; N, 8.15.

3-t-butylamino-3-methyl-1-hexyne hydrochloride was prepared by adding an excess of ethanol saturated with hydrogen chloride to an ethereal solution of the corresponding free base. The compound melted at about 175°-176° C.

**Analysis.**—Calc.: N, 6.88. Found: N, 6.65.

**Example 22.**—Preparation of 3-t-Butylamino-3-Ethyl-1-Hexyne

Following the procedure of Example 3, 60 ml. of water were mixed with 121 g. of t-butyamine. 79.8 g. of 3-chloro-3-ethyl-1-hexyne were added and the reaction mixture was allowed to stand at ambient room temperature for about 22 days. The reaction mixture was then heated to refluxing temperature for about 5 days in order to insure completion of the reaction. 3-t-butylamino-3-ethyl-1-hexyne formed in the above reaction was isolated by the procedure of Example 3 and was purified by distillation. 3-t-butylamino-3-ethyl-1-hexyne boiled at about 68° C. at a pressure of about 8 mm. of mercury; \( n_\text{D}^20 = 1.447. \)

Following the procedure of Example 18, 3-t-butylamino-3-ethyl-1-hexyne was converted to the corresponding hydrochloride salt, which melted at about 163°-164° C.

**Analysis.**—Calc.: N, 6.43. Found: N, 6.30.

**Example 23.**—Preparation of 3-t-Butylamino-3-Methyl-1-Hexyne

115 ml. of water were added to 253 g. of t-butyamine in a 1 l. externally cooled, 3-neck flask equipped with re-
13 flux condenser, mechanical stirrer and thermometer. 167.2 g. of 3-chloro-3-methyl-1-heptyne were added followed by 100 mg. of copper bronze powder. The temperature of the reaction mixture was 20° C. Initially and the temperature was allowed to rise to about 50° C., where it was maintained by heating while being stirred for about 14 hours. After cooling, the reaction mixture was poured into about 200 ml. of water and 400 ml. of ether. The organic layer was separated and the aqueous layer was extracted with two 150 ml. portions of ether. The ether extracts were combined and were cooled in an ice-water mixture. About 250 ml. of cold 12 N hydrochloric acid and 250 ml. of water were added, thus forming the hydrochloride salt of 3-t-butylaminom-3-methyl-1-heptyne. The hydrochloride salt dissolved in the aqueous layer. The organic layer was separated and discarded. The acidic aqueous layer was made alkaline to litmus by the addition of 50 percent sodium hydroxide. 3-t-butylaminom-3-methyl-1-heptyne base, being insoluble in the alkaline layer, separated and was extracted into 250 ml. of ether. The ether layer was separated and the alkaline layer was twice extracted with 250 ml. portions of ether. The ether extracts were combined and dried. The ether was removed by distillation at atmospheric pressure and the residue comprising 3-t-butylaminom-3-methyl-1-heptyne was purified by distillation in vacuum. 3-t-butylaminom-3-methyl-1-heptyne boiled at about 76° C. at a pressure of about 10 mm. of mercury; nD²⁰=1.441.

3-t-butylaminom-3-methyl-1-heptyne hydrochloride was prepared by adding an excess of ethanol saturated with hydrogen chloride to an ethanolic solution of the corresponding free base. The compound melted at about 144-146° C.

Example 26.—Preparation of 3-Butylaminom-3,4-Trimethyl-1-Heptyne

Following the procedure of Example 3, about 150 ml. of water were mixed with 221 g. of t-butylamine. 108 g. of 3-chloro-3,4,4-trimethyl-1-pentyne were added to the aqueous amine solution and the reaction mixture was allowed to stand at ambient room temperature for about 10 weeks. 3-t-butylaminom-3,4,4-trimethyl-1-pentyne formed in the above reaction was isolated by the procedure of Example 4 and was purified by distillation through an adiabatic glass helix-packed column. 3-t-butylaminom-3,4,4-trimethyl-1-pentyne boiled at about 110-111° C. at a pressure of about 25 mm. of mercury; nD²⁰=1.457.

Following the procedure of Example 18, 3-t-butylaminom-3,4,4-trimethyl-1-pentyne was converted to the corresponding hydrochloride salt, which disappeared on melting at about 238° C. It was recrystallized from a mixture of ethyl acetate and isopropanol.

Analysis.—Calc.: N, 6.47. Found: N, 6.35.

Example 27.—Preparation of 3-Isopropylaminom-3-Isopropyl-4-Methyl-1-Heptyne

Following the procedure of Example 3, 200 ml. of water were mixed with 535 g. of isopropylamine. About 270 g. of 3-chloro-3-isopropyl-4-methyl-1-pentyne were added to the aqueous amine solution followed by about 3 g. of copper bronze powder as a catalyst. The mixture was allowed to remain at ambient room temperature for about 17 days and then heated to refluxing temperature for about 18 hours. 3-isopropylaminom-3-isopropyl-4-methyl-1-pentyne formed in the above reaction was isolated by the procedure of Example 4 and was purified by distillation. 3-isopropylaminom-3-isopropyl-4-methyl-1-pentyne boiled in the range 110-118° C. at a pressure of about 52 mm. of mercury; nD²⁰=1.450.

Following the procedure of Example 18, 3-isopropylaminom-3-isopropyl-4-methyl-1-pentyne was converted to the corresponding hydrochloride salt, which melted at about 206-207° C.

Analysis.—Calc.: Cl, 16.28; N, 6.43. Found: Cl, 16.54; N, 6.38.

Example 28.—Alternate Preparation of 3-Isopropylaminom-3-Isopropyl-4-Methyl-1-Heptyne

163 g. of isopropylamine and about 35 g. of water were mixed. 89 g. of crude 3-chloro-3-isopropyl-4-methyl-1-pentyne were added to the aqueous amine solution and the resulting mixture was heated to refluxing temperature. About 1 g. of copper bronze powder was added and the refluxing was continued for about 6 days. 3-isopropylaminom-3-isopropyl-4-methyl-1-pentyne formed in the above reaction was isolated by the procedure of Example 4 and was purified by distillation.

Example 29.—Preparation of 3-Ethylaminom-3-Isopropyl-4-Methyl-1-Heptyne

Following the procedure of Henning and Teach, J. Am. Chem. Soc. 75, 4298 (1953), 3-chloro-3-isopropyl-4-methyl-1-pentyne was reacted with sodamide in liquid ammonia to form 3-amino-3-iso propyl-4-methyl-1-pentyne. Distillation of crude 3-amino-3-isopropyl-4-methyl-1-pentyne yielded a purified fraction boiling in the range of 68-81° C. at a pressure of about 15 mm. of mercury. 21 g. of 3-amino-3-isopropyl-4-methyl-1-pentyne were slowly added to 30.3 g. of ethyl p-toluene sulfonate in a round bottomed flask equipped with thermometer and condenser. The reaction mixture was heated to about 115° C. at which temperature a vigorous reaction took place. Heating was discontinued and the reaction mix-
ture was stirred for about 4 hours while slowly cooling. The mixture was again heated in the range 120-130° C. for about 2 hours and was again cooled. The cooled reaction mixture was treated with a mixture of 25 percent sodium hydroxide solution and ether. The ethereal layer containing 3-ethylamino-3-isopropyl-4-methyl-1-pentynne formed in the above reaction was separated and was dried. The ether was removed by distillation and the residue comprising 3-ethylamino-3-isopropyl-4-methyl-1-pentynne was distilled. Fractions boiling in the range 76-81° C. at a pressure of about 11 mm. of mercury were collected.

Following the procedure of Example 18, 3-ethylamino-3-isopropyl-4-methyl-1-pentynne was converted to the corresponding hydrochloride salt which was collected as a crystalline precipitate. Recrystallization of the precipitate from methyl ethyl ketone yielded a first fraction the hydrochloride salt of the starting compound 3-aminio-3-isopropyl-4-methyl-1-pentynne. Concentration of the filtrate by evaporation yielded crystals of 3-ethylamino-3-isopropyl-4-methyl-1-pentynne hydrochloride melting at about 179-181° C.

**Analysis.** Calc.: C, 64.84; H, 10.88; N, 6.88. Found: C, 64.55; H, 11.10; N, 7.03.

**Example 30.** Preparation of 4-t-Butylamino-3,4-Dimethyl-1-Pentynne

Following the procedure of Example 28, 133.6 g. of 3-chloro-3,4-dimethyl-1-pentynne were reacted with a mixture of 219 g. of t-butylamine and 102 ml. of water in the presence of copper bronze powder as a catalyst. 34-butylamino-3,4-dimethyl-1-pentynne was isolated and purified by the method of Example 28. It boiled at about 96.98° C. at a pressure of about 58 mm. of mercury; \( n_2^D = 1.400. \)

Following the procedure of Example 18, 3-t-butylamino-3,4-dimethyl-1-pentynne was converted to the corresponding hydrochloride salt, which melted above 280° C. after recrystallization from acetonitrile.

**Example 31.** Preparation of 3-Ethylamino-3,5-Dimethyl-1-Hexyne

Following the procedure of Example 3, 300 ml. of a 70 percent aqueous ethylamine solution were added to 73 g. of 3-chloro-3,5-dimethyl-1-hexyne. The reaction mixture was allowed to remain at ambient room temperature for about 72 hours. 3-ethylamino-3,5-dimethyl-1-hexyne formed in the reaction was isolated as a viscous oil by the procedure of Example 3. The hydrochloride salt was prepared by adding an excess of ethanol saturated with hydrogen chloride to an ethanol solution of the amine. The salt was isolated by evaporation of the ethanol solution to dryness. Recrystallization of the residue from a mixture of acetone and ethanol yielded 3-ethylamino-3,5-dimethyl-1-hexyne hydrochloride melting at about 204° C.

**Analysis.** Calc.: C, 63.30; H, 10.63. Found: C, 63.85; H, 10.59.

3-ethylamino-3,5-dimethyl-1-hexyne hydrobromide can be prepared according to the above procedure by using ethanol saturated with hydrogen bromide in place of ethanol saturated with hydrogen chloride.

**Example 32.** Preparation of 4-t-Butylamino-3,4-Methyl-2-Pentynne

Following the procedure of Hennion and Teach, J. Am. Chem. Soc. 75, 4297 (1953), 1,500 ml. of anhydrous liquid ammonia were placed in a 3 l. 3-neck flask equipped with inlet tube, a Dry Ice-acetone condenser and stirrer. 21 g. of sodium were added in chunks to the liquid ammonia together with a catalytic quantity of anhydrous ferric nitrate. The reaction mixture was stirred until all of the added sodium had been converted to sodamide, as evidenced by the discharge of a blue color in the liquid ammonia. 96.8 g. of 3-t-butylamino-3-methyl-1-butyne were added to the reaction mixture over a one-half hour period. The mixture was stirred for about 2 hours during which time the sodium salt of the acetylene was formed. 128 g. of methyl iodide was next added to the reaction mixture over a two-hour period, thus forming 4-t-buty1amino-3-methyl-2-pentynne. The reaction mixture was stirred for about 3½ hours after the addition of methyl iodide had been completed and was then allowed to remain overnight at ambient room temperature to allow evaporation of the ammonia. 1,000 ml. of water were added to the black flocculent residue, and the aqueous mixture was extracted with 300 ml. of ether. The ether extract was separated and the aqueous layer was extracted 3 more times with 125 ml. portions of ether. The ether extracts were combined and were dried. The ether was removed by distillation, leaving a residue comprising 4-t-buty1amino-3-methyl-2-pentynne. The residue was distilled in vacuo. 4-t-buty1amino-3-methyl-2-pentynne boiled at about 90-92° C. at a pressure of about 59 mm. of mercury; \( n_2^D = 1.440. \)

42.3 g. of 4-t-buty1amino-4-methyl-2-pentynne were dissolved in the minimal amount of ether and an excess of a cold saturated ethereal hydrogen chloride solution was added slowly with cooling. 4-t-buty1amino-4-methyl-2-pentynne hydrochloride was formed by this reaction. The hydrochloride, being insoluble in the ether solution, precipitated and was collected by filtration. Recrystallization of the precipitate from ethyl acetate yielded 4-t-buty1amino-4-methyl-2-pentynne hydrochloride melting at about 145-146° C.

**Analysis.** Calc.: C, 63.30; H, 10.63; N, 7.38. Found: C, 63.83; H, 10.25; N, 7.22.

The benzoate salt of 4-t-buty1amino-4-methyl-2-pentynne can be prepared by the above procedure by substituting an ethereal solution of benzoic acid for the ethereal hydrogen chloride solution.

**Example 33.** Preparation of 3-Allylamino-3-Methyl-1-Butyne

Following the procedure of Example 3, 3-chloro-3-methyl-1-butyn was added to an aqueous allylamine solution. 3-allylamino-3-methyl-1-butyn was formed was isolated by the procedure of Example 3 and was purified by distillation. 3-allylamino-3-methyl-1-butyn boiled at about 130° C. at atmospheric pressure.


The hydrochloride salt of 3-allylamino-3-methyl-1-butyn was prepared by the method of Example 3. It melted at about 194-195° C.

**Analysis.** Calc.: C, 60.18; H, 8.84; N, 8.77. Found: C, 60.62; H, 8.76; N, 8.85.

**Example 34.** Preparation of 3,4-Dimethyl-1-Hexyne

Following the procedure of Example 3, 195 g. of t-buty1amine and 90 ml. of water were mixed. 200 mg. of copper bronze powder were added followed by 129.3 g. of 3-chloro-3,4-dimethyl-1-hexyne. After the initial vigorous reaction had subsided, the reaction mixture was warmed at about 40° C. for 24 hours. 3-t-buty1amino-3,4-dimethyl-1-hexyne formed in the reaction was isolated by the procedure of Example 3 and was purified by distillation. 3-t-buty1amino-3,4-dimethyl-1-hexyne boiled at about 53° C. at a pressure of 6 mm. of mercury; \( n_2^D = 1.447. \)

**Analysis.** Calc.: N, 6.43. Found: N, 6.25.

The hydrochloride salt of 3-t-buty1amino-3,4-dimethyl-1-hexyne was prepared by the method of Example 4. It melted at about 174-175° C.

**Example 35.** Preparation of N-Methyl-N-Isopropyl-3-Amino-3-Methyl-1-Butyne

70.8 g. of N-methyl isopropylamine, 40 ml. of water and 0.5 g. of copper bronze powder were mixed and 41 g. of 3-chloro-3-methyl-1-butyn were added dropwise to
the mixture. After the addition of the chloroacetylene had been completed, the reaction mixture was heated at about 140° C. for about 18 hours. The reaction mixture was cooled and was poured into a mixture of water and ether. The ethereal layer containing N-methyl-N-isopropyl 3-amino-3-methyl-1-butyne formed in the above reaction was separated and was contacted with 250 ml. of a 20 percent aqueous hydrochloric acid solution. The ethereal layer was discarded. The aqueous layer containing the hydrochloride salt of N-methyl-N-isopropyl 3-amino-3-methyl-1-butyne was made basic to litmus by the addition of 50 percent sodium hydroxide. N-methyl-N-isopropyl 3-amino-3-methyl-1-butyne free base is insoluble in the alkaline layer and was extracted with chloroform. The chloroform layer was separated and was dried. The chloroform was removed by distillation and the N-methyl-N-isopropyl 3-amino-3-methyl-1-butyne which remained as a residue, was purified by distillation in vacuo. It boiled at about 96-98° C. at a pressure of about 135 mm. of mercury; nD²⁵=1.4352.

Following the procedure of Example 4, the hydrochloride salt of N-methyl-N-isopropyl 3-amino-3-methyl-1-butyne was prepared. It melted at about 184-186° C. after recrystallization from a mixture of ethyl acetate and isopropanol.

**Example 36.—Preparation of N-Methyl-N-t-Butyl 3-Amino-3-Methyl-1-Butyne**

33 g. of 3-t-butylamino-3-methyl-1-butyne hydrochloride were dissolved in water, and the aqueous solution was made basic to litmus with 40 percent sodium hydroxide. The 3-t-butylamino-3-methyl-1-butyne was insoluble in the alkaline layer, and was extracted with 200 ml. of ether. The ethereal layer was separated and was dried and the ether was removed by evaporation at atmospheric pressure. The residue, comprising 3-t-butylamino-3-methyl-1-butyne free base, was mixed with 40 g. of dimethyl sulfate and 10 g. of potassium carbonate. The reaction mixture was gradually heated with stirring to a temperature of about 95° C. During the heating period, about 20 g. more of potassium carbonate were added in small batches. The reaction mixture was cooled to about 40° C. and 100 ml. of water and 200 ml. of ether were added. The ethereal layer containing N-methyl-N-t-buty1 3-amino-3-methyl-1-butyne formed in the above reaction, was separated and was shaken with 200 ml. of 10 percent hydrochloric acid, thus forming the hydrochloride salt of N-methyl-N-t-buty1 3-amino-3-methyl-1-butyne. The salt dissolved in the aqueous layer; the ethereal layer was separated and discarded. The aqueous layer was neutralized with 40 percent sodium hydroxide, thus forming N-methyl-N-t-buty1 3-amino-3-methyl-1-butyne free base. The free base which was insoluble in the alkaline layer was extracted with 100 ml of ether. The ethereal layer was separated, was dried and the ether was removed by evaporation at atmospheric pressure, leaving a residue comprising N-methyl-N-t-buty1 3-amino-3-methyl-1-butyne. The residue was distilled yielding purified N-methyl-N-t-buty1 3-amino-3-methyl-1-butyne boiling in the range 115-116° C. at a pressure of about 130 mm. of mercury; nD²⁵=1.450.

N-methyl-N-t-buty1 3-amino-3-methyl-1-butyne was converted to the corresponding hydrochloride salt by dissolving the free base in ether and saturating the ethereal layer with anhydrous hydrogen chloride gas. N-methyl-N-t-buty1 3-amino-3-methyl-1-butyne hydrochloride was insoluble in ether and precipitated. The precipitate was separated by filtration and was recrystallized from a mixture of isopropanol and methyl ethyl ketone. N-methyl-N-t-buty1 3-amino-3-methyl-1-butyne hydrochloride thus prepared, melted at about 140-142° C.

**Example 37.—Alternate Preparation of N-Methyl-N-Isopropyl 3-Amino-3-Methyl-1-Butyne**

A mixture of 50 g. of 3-isopropylamino-3-methyl-1-butyne and 40 g. of dimethyl sulfate was stirred until an exothermic reaction took place. The N-methyl-N-isopropyl 3-amino-3-methyl-1-butyne thus formed was isolated by the procedure of Example 36 and was purified by distillation. N-methyl-N-isopropyl 3-amino-3-methyl-1-butyne boiled at about 96-98° C. at a pressure of 135 mm. of mercury; nD²⁵=1.4352.

Following the procedure of Example 36, N-methyl-N-isopropyl 3-amino-3-methyl-1-butyne hydrochloride was prepared. It melted at about 185-186° C. after recrystallization from a mixture of ethyl acetate and isopropanol.

**Example 38.—Preparation of N-Methyl-N-Isopropyl 3-Amino-3-Ethyl-1-Pentyl**

Following the procedure of Example 37, 3-isopropylamino-3-ethyl-1-pentyl and dimethyl sulfate were stirred together for several hours. N-methyl-N-isopropyl 3-amino-3-ethyl-1-pentyl formed in the reaction was isolated by the procedure of Example 36 and was converted to the hydrochloride salt by the procedure set forth in the same example. N-methyl-N-isopropyl 3-amino-3-ethyl-1-pentyl hydrochloride thus prepared melted at about 143-145° C. after recrystallization from methyl ethyl ketone.

**Example 39.—Preparation of N-Ethyl-N-Isopropyl 3-Amino-3-Methyl-1-Pentyl**

About 30 g. of potassium carbonate were added to 100 ml. of acetone in a round-bottomed flask equipped with stirrer and reflux condenser. 10 g. of 3-isopropylamino-3-methyl-1-pentyl, and 16 g. of ethyl p-toluene sulfonate were added and the resulting mixture was heated gradually until gentle refluxing took place. The heating was maintained for 6 hours. The reaction mixture was cooled and was filtered, the filter cake being discarded. The mother liquors were concentrated by evaporation. A second precipitate formed on cooling which was also removed by filtration and discarded. 50 ml. of ethanol saturated with hydrogen chloride were added to the filtrate, thus forming the hydrochloride salt of N-ethyl-N-isopropyl 3-amino-3-methyl-1-pentyl. N-ethyl-N-isopropyl 3-amino-3-methyl-1-pentyl formed in the above alkylation reaction. The ethanol solution was evaporated to dryness in vacuo leaving the hydrochloride salt as a residue. The residue was dissolved in water and the aqueous solution made alkaline to litmus by the addition of potassium carbonate. N-ethyl-N-isopropyl 3-amino-3-methyl-1-pentyl was insoluble in the alkaline layer and was extracted with ether. The ether layer was separated, was dried and the ether was removed by distillation at atmospheric pressure. Distillation of the residue comprising N-ethyl-N-isopropyl 3-amino-3-methyl-1-pentyl yielded a fraction from which a hydrochloric acid salt was prepared by dissolving the collected distillate in a small quantity of ether and bubbling in anhydrous hydrogen chloride gas. Fractional crystallization of the precipitate thus obtained yielded purified N-ethyl-N-isopropyl 3-amino-3-methyl-1-pentyl hydrochloride melting at about 177-179° C.

**Example 40.—Preparation of N-Methyl-N-Isopropyl 3-Amino-3,4-Dimethyl-1-Pentyl**

Following the procedure of Example 36, 12 g. of 3-isopropylamino-3,4-dimethyl-1-pentyl, 10 g. of dimethyl sulfate and 11 g. of potassium carbonate were heated with stirring at about 100° C. for one hour. N-methyl-
N-isopropyl-3-amino-3,4-dimethyl-1-pentyne was isolated as the free base by the procedure of Example 36 and was purified by distillation, boiling at about 73–75° C. at a pressure of about 20 mm. of mercury; $n_\infty^20=1.445$.

N-methyl-N-isopropyl-3-amino-3,4-dimethyl-1-pentyne was converted to the corresponding hydrochloride salt by the procedure of Example 4. N-methyl-N-isopropyl-3-amino-3,4-dimethyl-1-pentyne hydrochloride, melted with decomposition at about 198–200° C.

**PREPARATION OF ETHYLENYL AMINES**

The secondary ethenyl amines useful in the therapeutic process and compositions of this invention are best prepared by the catalytic semihydrogenation of the corresponding secondary or tertiary acetylenic amines. The semihydrogenation was carried out at low temperature and pressure, temperatures below 30° C. and pressures of 75 p.s.i. or less being entirely satisfactory. The catalytic semihydrogenation is usually carried out with the amine dissolved in a nonpolar solvent. The solvents customarily used are methycyclohexane, ether, benzene, pentane, hexane and the like. The preferred catalyst for this semihydrogenation is a noble metal catalyst such as palladium on activated charcoal, palladium on barium carbonate and the like. Raney nickel can also be used.

In carrying out the semihydrogenation, the reaction is interrupted after the theoretical quantity of hydrogen has been absorbed so as to minimize the production of the corresponding fully hydrogenated derivative.

Two synthetic routes are available for the synthesis of tertiary ethenyl amines. The first of these is, of course, the semihydrogenation of a tertiary acetylenic amine similar to that set forth above for the preparation of secondary ethenyl amines. The second route involves the direct alkylation of a previously prepared secondary ethenyl amine under similar reaction conditions to those employed for the preparation of tertiary acetylenic amines from secondary acetylenic amines, i.e., the use of an alkylation agent such as a dialkyl sulfate or an alkyl toluene sulfonate in the presence of excess base.

The following specific examples more fully illustrate the preparation of the ethenyl amines of this invention.

**Example 41.—Preparation of 3-Isopropyl-Amine-3-Methyl-1-Butene**

12.5 g. of 3-isopropylamino-3-methyl-1-butyne were dissolved in 50 ml. of hexane and about 0.01 g. of a 10 percent palladium on activated charcoal catalyst was added to the solution. The mixture was hydrogenated in a low pressure hydrogenation apparatus at an initial pressure of 41 p.s.i. After 5 hours and 10 minutes, the hydrogen pressure had dropped to about 8.8 p.s.i. After the pressure had remained stationary for 30 minutes, the hydrogenation mixture was removed from the hydrogenation apparatus, the catalyst was separated by filtration and the solvent was removed by distillation through a 30 cm. glass helix-packed column. The distillation residue comprising 3-isopropylamino-3-methyl-1-butenone formed in the above reaction was distilled through the same column. Fractions boiling in the range 100–122° C. at atmospheric pressure were collected, were dried and were redistilled. Purified 3-isopropylamino-3-methyl-1-butenone boiled at about 121–122° C.; $n_\infty^20=1.417$.

**Analysis.**

Calc.: C, 58.70; H, 11.08; N, 8.56. Found: C, 58.89; H, 11.13; N, 8.48.

Example 42.—Preparation of 3-Butylaminono-3-Methyl-1-Pentene

15.3 g. of 3-t-butylaminono-3-methyl-1-pentyne were dissolved in hexane and were hydrogenated using as a catalyst 0.075 g. of 5 percent palladium on barium carbonate. The semi-hydrogenation required only about 35 minutes to go essentially to completion, as evidenced by the drop in the hydrogen pressure from an initial reading of 43.8 p.s.i. to a steady reading of 8.4 p.s.i. The catalyst was separated by filtration and 3-t-butylaminono-3-methyl-1-pentene formed in the above hydrogenation, was purified by distillation. The compound boiled at about 67° C. at a pressure of 25 mm. of mercury; $n_\infty^20=1.437$.

**Analysis.**

Calc.: N, 9.02. Found: N, 9.05.

Following the procedure of Example 41, 3-t-butylaminono-3-methyl-1-pentene hydrochloride was prepared from the free base. It melted at about 164–166° C.

**Analysis.**

Calc.: C, 62.64; H, 11.57; N, 7.30. Found: C, 62.50; H, 11.59; N, 7.38.

Example 43.—Preparation of 3-Butylaminono-3-Ethyl-1-Pentene

8.35 g. of 3-t-butylaminono-3-ethyl-1-pentene were dissolved in 50 ml. of ethanol and were hydrogenated at low pressure using 2 g. of a heavy suspension of Raney nickel in ethanol as a catalyst. After the uptake of hydrogen had ceased, the hydrogenation mixture was removed from the apparatus and was filtered to remove the catalyst. 3-t-butylaminono-3-ethyl-1-pentene formed in the above reaction was isolated as the hydrochloride salt by adding cold 12 N hydrochloric acid dropwise to the filtrate until the filtrate became acid. Evaporation of the ethanol left the hydrochloride salt as a crystalline residue. Recrystallization of the residue from a mixture of ethyl acetate and isopropyl alcohol yielded 3-t-butylaminono-3-ethyl-1-pentene hydrochloride melting at about 183–184° C.

**Analysis.**

Calc.: C, 64.20; H, 11.76; N, 6.81. Found: C, 64.32; H, 11.50; N, 6.87.

The phosphate salt of 3-t-butylaminono-3-ethyl-1-pentene can be prepared by following the above procedure but substituting pyrophosphoric acid for 12 N hydrochloric acid.

3-t-butylaminono-3-ethyl-1-pentene hydrochloride was dissolved in water and the aqueous solution was made alkaline to litmus by the addition of cold 50 percent sodium hydroxide, thus forming 3-t-butylaminono-3-ethyl-1-pentene free base. The free base was insoluble in the alkaline layer, and was extracted into ether. The ether extract was separated and was dried. The ether was removed by distillation at atmospheric pressure, leaving a residue comprising 3-t-butylaminono-3-ethyl-1-pentene.

**Example 44.—Preparation of 3-Butylaminono-3-Methyl-1-Butene**

7 g. of 3-t-butylaminono-3-methyl-1-butyne were dissolved in 200 ml. of methyl cyclohexane. 30 mg. of 5 percent palladium on carbon were added as a hydrogenation catalyst. The mixture was placed in a low pressure hydrogenation apparatus and was semihydrogenated. After the theoretical quantity of hydrogen had been absorbed, the mixture was removed from the apparatus, washed with water, to remove the catalyst and any hydrogen chloride gas was bubbled into the filtrate. 3-t-butylaminono-3-methyl-1-butenone hydrochloride thus formed precipitated and was isolated by filtration. The precipitate which was
recrystallized from a mixture of ethyl acetate and isopropyl alcohol, melted at about 202-204°C. Analysis. — Calc.: N, 7.88. Found: N, 7.73.

Example 43. — Preparation of 3-Isopropylamino-3,4-Dimethyl-1-Pentene

7.6 g. of 3-isopropylamino-3,4-dimethyl-1-pentene hydrochloride were dissolved in water and the aqueous solution was made alkaline by the addition of solid potassium carbonate. 3-isopropylamino-3,4-dimethyl-1-pentene, being insoluble in the alkaline layer, separated and was extracted with methyl cyclohexane. The methyl cyclohexane was dried and the drying agent was removed by filtration. 40 mg. of 5 percent palladium on carbon were added to the filtrate and the resulting mixture was semi-hydrated on a low pressure hydrogenation apparatus. After the theoretical quantity of hydrogen had been absorbed, the mixture was removed from the apparatus and the catalyst was separated by filtration. Ethanol saturated with hydrogen chloride was added to the filtrate, thus forming the hydrochloride salt of 3-isopropylamino-3,4-dimethyl-1-pentene formed in the above reduction. The hydrochloride salt was insoluble in the solvent mixture and was separated by filtration. Recrystallization of the filtered salt from a mixture of ethyl acetate and methyl cyclohexane yielded 3-isopropylamino-3,4-dimethyl-1-pentene hydrochloride melting at about 101-105°C.

Analysis. — Calc.: N, 7.31; Cl, 18.49. Found: N, 7.52; Cl, 18.88.

Example 46. — Preparation of N-Methyl-N-Isopropyl 3-Amino-3-Methyl-1-Butene

Following the procedure of Example 44, 7 g. of N-methyl-N-isopropyl 3-amino-3-methyl-1-butene were dissolved in methyl cyclohexane and were hydrogenated at low pressure over a 5 percent palladium on carbon catalyst. N-methyl-N-isopropyl 3-amino-3-methyl-1-butene formed in the above reaction was isolated by the procedure of Example 43 and was purified by distillation. N-methyl-N-isopropyl 3-amino-3-methyl-1-butene boiled at about 76-80°C at a pressure of 107 mm. of mercury; nD^25 = 1.434.

N-methyl-N-isopropyl 3-amino-3-methyl-1-butene hydrochloride can be prepared from the free base by the process of Example 41.

Example 47. — Preparation of 3-Ethylamino-3-Methyl-1-Butene

Following the procedure of Example 42, 3-ethylamino-3-methyl-1-butene was semi-hydrated over a palladium on barium carbonate catalyst. After the uptake of hydrogen had ceased, the catalyst was separated by filtration and 3-ethylamino-3-methyl-1-butene formed in the above reaction was isolated and purified by the procedure of Example 42. 3-ethylamino-3-methyl-1-butene boiled at 110°C at atmospheric pressure; nD^25 = 1.416.

Analysis. — Calc.: N, 12.37. Found: N, 12.02. Following the procedure of Example 41, 3-ethylamino-3-methyl-1-butene hydrochloride was prepared from the free base and melted at about 138-140°C.

Analysis. — Calc.: C, 56.17; H, 10.78; N, 9.36. Found: C, 56.48; H, 10.54; N, 9.33.

Example 48. — Preparation of 3-Ethylamino-3-Methyl-1-Pentene

Following the procedure of Example 41, 3-ethylamino-3-methyl-1-pentene was semi-hydrated over a 5 percent palladium on activated charcoal as a catalyst. After the absorption of hydrogen had ceased, the catalyst was separated by filtration. 3-ethylamino-3-methyl-1-pentene formed in the above reaction was isolated and purified by the method of Example 41. 3-ethylamino-3-methyl-1-
acetylenic amine or of an ethylenic amine is prepared and is dissolved in an inert polar solvent such as ethanol. The solvent usually contains excess acid. It is, however, often convenient to prepare the acid addition salt in situ by adding an acid to an ethanolic solution of the free base. When Raney nickel is used as a catalyst, the amine itself can be hydrogenated also in a polar solvent.

As was the case with the preparation of tertiary acetylenic amines and tertiary ethylenic amines, two possible routes are available for the preparation of the tertiary saturated hypnotensive amines. The first of these methods involves the complete hydrogenation of the tertiary acetylenic or ethylenic amine by the method just described to yield the desired saturated tertiary amine. The second synthetic route is the direct alklylation of a secondary saturated amine with an alklylating agent such as a dialkyl sulfate or an alkyl p-toluene sulfonate.

The following examples more fully illustrate the preparation of secondary and tertiary saturated amines useful for the purposes of this invention.

**Example 52.—Preparation of 3-Ethylamino-3-Methylbutane**

11.1 g. of 3-ethylamino-3-methyl-1-butyne were dissolved in 50 ml. of 95 percent ethanol. About 2 g. of a heavy suspension of Raney nickel in ethanol were added and the mixture was placed in a low pressure hydrogenation apparatus and was hydrogenated. The hydrogen pressure initially was 39.8 p.s.i. After 2 hours and 11 minutes, the pressure had dropped about 22.4 p.s.i. The hydrogenation mixture was removed from the apparatus and the catalyst was separated by filtration. The filtrate, containing 3-ethylamino-3-methylbutane formed in the above hydrogenation, was cooled to about 15° C. and was then acidified to about pH 1 by the dropwise addition of 12 ml. of hydrochloric acid. The ethanol was removed in vacuo and the white crystalline residue of 3-ethylamino-3-methylbutane hydrochloride was dissolved in about 100 ml. of water. The water solution was extracted twice with 100 ml. portions of ether, and the extracts were discarded. The acid aqueous layer was cooled to about 15° C., was covered with about 100 ml. of ether and was made basic to litmus by the addition of 50 percent sodium hydroxide, added in 5 ml. portions with stirring. 3-ethylamino-3-methylbutane free base was formed. It was insoluble in the alkaline aqueous layer, and passed into the etheral layer. The alkaline aqueous layer was separated and was extracted twice more with 75 ml. portions of ether. The ether extracts were combined and were dried. The ether was removed by distillation through a 30 cm. glass helix-packed column and the residue, comprising 3-ethylamino-3-methylbutane, was distilled through a 30 cm. Vigreux column. Fractions boiling in the range 65-115° C. were collected and were redistilled through the same column. 3-ethylamino-3-methylbutane boiled at about 112-115° C.; n_\text{D}^{20}=1.405.


3-ethylamino-3-methylbutane hydrochloride was prepared by dissolving the free base in ether and adding an excess of a saturated ethereal hydrogen chloride solution. 3-ethylamino-3-methylbutane hydrochloride melted at about 160-161° C.

**Analysis.**—Calc.: C, 55.43; H, 11.96; N, 9.24. Found: C, 55.70; H, 11.85; N, 9.03

**Example 53.—Preparation of 3-4-Butylamino-3-Ethylpentane**

7.5 g. of 3-4-butylamino-3-ethyl-1-pentene were dissolved in about 200 ml. of ethanol containing 10 ml. of ethanol saturated with hydrogen chloride, thus forming the hydrochloride salt of 3-4-butylamino-3-ethyl-1-pentene. About 30 mg. of platinum oxide catalyst was added and the mixture was hydrogenated in a low pressure hydrogenation apparatus. After the hydrogenation had proceeded for about 4 hours, the catalyst was removed by filtration, 60 mg. of fresh platinum oxide catalyst were added and the mixture was hydrogenated for an additional 4 hours. The hydrogenation mixture was removed from the apparatus and the catalyst was separated by filtration. The filtrate containing 3-4-butylamino-3-ethylpentane hydrochloride formed in the above reaction was concentrated to a residue and the residue was recrystallized from ethyl acetate. 3-4-butylamino-3-ethylpentane hydrochloride thus purified melted with decomposition at about 172-173° C.

**Analysis.**—Calc.: C, 63.58; H, 12.61. Found: C, 63.24; H, 12.48.

3-4-butylamino-3-ethylpentane free base can be prepared by neutralizing an aqueous solution of the hydrochloride salt, extracting the liberated free base with ether and removing the ether by distillation, leaving the free base as a residue.

**Example 54.—Preparation of 3-4-Butylamino-3-Methylbutane**

28 g. of 3-4-butylamino-3-methyl-1-butyne were dissolved in ethanolic hydrochloric acid, thus forming the hydrochloride salt of the amine. 50 mg. of platinum oxide were added to the solution and the mixture was hydrogenated at low pressure as set forth in Example 53, yielding as a product 3-4-butylamino-3-methylbutane hydrochloride. After the uptake of hydrogen had ceased, the catalyst was removed by filtration and the hydrochloride salt was isolated as a residue by evaporation of the ethanol solvent. Recrystallization of the residue from a mixture of ethyl acetate and anhydrous ethanol yielded purified 3-4-butylnlamino-3-methylbutane hydrochloride, melting at about 218-219° C.

**Analysis.**—Calc.: C, 60.14; H, 12.34; N, 7.79. Found: C, 60.24; H, 12.26; N, 7.82.

3-4-butylamino-3-methylbutane free base was prepared by neutralizing an aqueous solution of the hydrochloride salt, extracting the liberated free base with ether, separating the ether extract and removing the ether by evaporation. The resulting residue comprising 3-4-butylamino-3-methylbutane was purified by distillation in vacuo. 3-4-butylamino-3-methylbutane boiled at 74° C. at 61 mm. of mercury; n_\text{D}^{20}=1.418.

3-4-butylamino-3-methylbutane was also prepared by hydrogenating 3-4-butylamino-3-methyl-1-butyne at low pressure using Raney nickel as a catalyst, and also by hydrogenating the hydrochloride salt with 5 percent palladium on carbon as a catalyst.

**Example 55.—Preparation of 3-Isopropylamino-3-Ethylpentane**

Following the procedure of Example 53, 7.7 g. of 3-isopropylamino-3-ethyl-1-pentene were dissolved in a mixture of 190 ml. of ethanol and 10 ml. of ethanol saturated with hydrogen chloride. The solution was hydrogenated in the presence of 40 mg. of platinum oxide catalyst. 3-isopropylamino-3-ethylpentane hydrochloride thus formed was isolated by the procedure of Example 53. It melted at about 217-218° C. after recrystallization from ethyl acetate.

**Analysis.**—Calc.: N, 7.27. Found: N, 7.14.

3-isopropylamino-3-ethyl-1-pentene was also hydrogenated as the hydrochloride salt in ethanol solution by the above procedure to yield 3-isopropylamino-3-ethylpentane hydrochloride. The 3-isopropylamino-3-ethylpentane free base, as in Example 54, can be prepared by neutralizing an aqueous solution of the hydrochloride salt, extracting the liberated free base with ether and removing the ether by distillation, leaving 3-isopropylamino-3-ethylpentane as a residue.

**Example 56.—Preparation of 3-Isopropylamino-3,4-Dimethylpentane**

7.6 g. of 3-isopropylamino-3,4-dimethyl-1-pentene hy-
8,067,101 25 drochloride were dissolved in a mixture of 195 ml. of ethanol and 5 ml. of ethanol saturated with hydrogen chloride. 40 mg. of platinum oxide were added and the mixture was hydrogenated at about 50 lb. hydrogen pressure in a low pressure hydrogenation apparatus. After the theoretical quantity of hydrogen had been absorbed, the mixture was removed from the hydrogenation apparatus and the catalyst was separated by filtration. The filtrate was evaporated to dryness leaving as a residue 3-isopropylamino-3,4-dimethylpentane hydrochloride. Recrystallization of the residue from a mixture of ethyl acetate and methyl cyclohexane yielded 3-isopropylamino-3,4-dimethylpentane hydrochloride, melting at about 183–184°C.

**Analysis.** Calc.: N, 7.23. Found: N, 7.53.

3-isopropylamino-3,4-dimethylpentane free base can be prepared as in Example 54 by neutralizing an aqueous solution of the hydrochloride salt, extracting the liberated free base into ether and removing the ether by distillation, leaving 3-isopropylamino-3,4-dimethylpentane as a residue.

**Example 57.—Preparation of 3-Isopropylamino-3,4,4-Trimethylpentane**

Following the procedure of Example 56, 10.2 g. of 3-isopropylamino-3,4,4-trimethyl-1-pentene hydrochloride were dissolved in 200 ml. of ethanol saturated with hydrogen chloride. The mixture was hydrogenated at low pressure using about 45 mg. of platinum oxide as a catalyst. 3-isopropylamino-3,4,4-trimethylpentane hydrochloride thus prepared was isolated by the method of Example 53. It melted at about 183–184°C after recrystallization from methyl ethyl ketone.

**Analysis.** Calc.: C, 63.58; H, 12.61; N, 6.74. Found: C, 63.74; H, 12.57; N, 6.72.

3-isopropylamino-3,4,4-trimethylpentane free base can be prepared as in Example 54 by neutralizing an aqueous solution of the hydrochloride salt, extracting the liberated free base into ether and removing the ether by distillation, leaving 3-isopropylamino-3,4,4-trimethylpentane as a residue.

**Example 58.—Preparation of 3-Sec-Butylamino-3-Methylbu tane**

4.7 g. of 3-sec-butylamino-3-methyl-1-butyne hydrochloride and 3.2 g. of 3-sec-butylamino-3-methyl-1-butyne free base were dissolved in a mixture of 190 ml. of ethanol and 10 ml. of ethanol saturated with hydrogen chloride. About 25 mg. of platinum oxide were added and the mixture was hydrogenated at low pressure. After the theoretical quantity of hydrogen had been absorbed, the mixture was removed from the hydrogenation apparatus and the catalyst was separated by filtration. The filtrate was evaporated to dryness leaving as a residue 3-sec-buty lamino-3-methylbutylhexane hydrochloride formed in the above reduction. Recrystallization of the residue from ethyl acetate yielded 3-sec-butylamino-3-methylbutylhexane hydrochloride melting at about 137–139°C.

**Analysis.** Calc.: N, 7.79. Found: N, 7.71.

3-sec-butylamino-3-methylbutane free base can be prepared as in Example 54 by neutralizing an aqueous solution of the hydrochloride salt, extracting the liberated free base into ether and removing the ether by distillation, leaving 3-sec-butylamino-3-methylbutane as a residue.

**Example 59.—Preparation of 3-Isopropylamino-3-Methylhexane**

4 g. of 3-isopropylamino-3-methyl-1-hexyne hydrochloride were dissolved in ethanol and were hydrogenated to form 3-isopropylamino-3-methylhexane hydrochloride. The procedure of Example 56 was followed except that no ethanolic hydrogen chloride was added to the hydrogenation mixture. 25 mg. of platinum oxide were used as a hydrogenation catalyst. 3-isopropylamino-3-methylhexane hydrochloride was isolated by the procedure of Example 53 and melted at about 113–115°C after recrystallization from ethyl acetate.

**Analysis.** Calc.: N, 7.23. Found: N, 7.00.

3-isopropylamino-3-methylhexane free base can be prepared as in Example 54 by neutralizing an aqueous solution of the hydrochloride salt, extracting the liberated free base into ether and removing the ether by distillation, leaving as a residue 3-isopropylamino-3-methylhexane.

**Example 60.—Preparation of 3-Ethylamino-3-Isopropyl-4-Methylpentane**

Following the procedure of Example 56, 4.6 g. of 3-ethylamino-3-isopropyl-4-methyl-1-pentene hydrochloride were dissolved in 200 ml. of ethanol and 45 mg. of platinum oxide were added to the mixture at low pressure yielded 3-ethylamino-3-isopropyl-4-methylpentane hydrochloride. The compound was isolated by the procedure of Example 53 and melted at about 195–196°C after recrystallization from a mixture of methyl ethyl ketone and ether.

**Analysis.** Calc.: C, 63.36; H, 12.61. Found: C, 63.58; H, 12.59.

3-ethylamino-3-isopropyl-4-methylpentane free base can be prepared as in Example 54 by neutralizing an aqueous solution of the hydrochloride salt, extracting the thus liberated free base with ether and removing the ether by distillation, leaving 3-ethylamino-3-isopropyl-4-methylpentane as a residue.

**Example 61.—Preparation of 3-Sec-Amylamine-3-Methylbutane**

Following the procedure of Example 56, 7.6 g. of 3-sec-amylamino-3-methyl-1-butyne hydrochloride in ethanol were hydrogenated at low pressure over a platinum oxide catalyst to yield 3-sec-amylamino-3-methylbutylhexane hydrochloride. The compound was isolated by the procedure of Example 53. 3-sec-amylamino-3-methylbutylhexane hydrochloride melted at about 142–144°C after recrystallization from benzene.

**Analysis.** Calc.: N, 7.23. Found: N, 7.04.

3-sec-amylamino-3-methylbutane free base can be prepared as in Example 54 by neutralizing an aqueous solution of the hydrochloride salt, extracting the liberated free base into ether and removing the ether by distillation, leaving 3-sec-amylamino-3-methylbutane as a residue.

**Example 62.—Preparation of 3-Butylamino-3-Methylhexane**

Following the procedure of Example 56, 5.7 g. of 3-butylamino-3-methyl-1-hexyne hydrochloride were dissolved in 200 ml. of ethanol and were hydrogenated at low pressure using 25 mg. of platinum oxide catalyst. 3-butylamino-3-methylhexane hydrochloride thus prepared was isolated by the procedure of Example 53. It melted at about 142–144°C after recrystallization from a mixture of ethyl acetate and isopropyl ether.

**Analysis.** Calc.: N, 6.74; Cl, 17.06. Found: N, 7.00; Cl, 17.44.

3-butylamino-3-methylhexane free base can be prepared as in Example 54 by neutralizing an aqueous solution of the hydrochloride salt, extracting the liberated free base into ether and receiving the ether by distillation, leaving 3-butylamino-3-methylhexane as a residue.

**Example 63.—Preparation of 3-Amylamino-3-Methylbutane**

7.7 g. of 3-amylamino-3-methyl-1-butyne were dissolved in 200 ml. of ether and 0.5 g. of Raney nickel were added. The mixture was hydrogenated at low pressure. After about 70 percent of the theoretical quantity of hydrogen had been taken up, 40 mg. of platinum oxide were added and the mixture was again hydrogenated at low pressure until the theoretical quantity of hydrogen had been absorbed. The hydrogenation mixture was filtered to remove the catalyst and about 25 ml. of 12 N
hydrochloric acid were added to the filtrate, thus forming the hydrochloride salt of 3-amy lamino-3-methylbutane synthesized during the above hydrogenation. The filtrate was concentrated and was cooled. 3-α-amylino-3-methylbutane hydrochloride precipitated as a crystalline mass which was separated by filtration. Recrystallization of the precipitate from a benzene ether solvent mixture yielded 3-α-amylino-3-methylbutane hydrochloride melting at about 183–185°C.

Analysis.—Calc.: N, 7.33. Found: N, 7.45.

Example 64.—Preparation of N-Methyl-N-Isopropyl 3-Amino-3-Methylbutane

Following the procedure of Example 63, 17 g. of N-methyl-N-isopropyl 3-amino-3-methyl-1-butane were dissolved in 190 ml. of ethanol and 0.5 g. of a heavy suspension of Raney nickel in ethanol were added. The mixture was hydrogenated at low pressure, thus forming N-methyl-N-isopropyl 3-amino-3-methylbutane. The catalyst was separated by filtration and 100 ml. of ethanol saturated with hydrogen chloride were added to the filtrate, thus forming the hydrochloride salt of the amine. The filtrate was evaporated in vacuo leaving an oily residue comprising N-methyl-N-isopropyl 3-amino-3-methylbutane hydrochloride. The residue was dissolved in water. The acidic aqueous solution was made neutral to litmus by the addition of 50 percent sodium hydroxide and N-methyl-N-isopropyl 3-amino-3-methylbutane free base was being insoluble in the aqueous layer, separated and was extracted with chloroform. The chloroform extract was separated, was dried and the chloroform was removed by distillation. N-methyl-N-isopropyl 3-amino-3-methylbutane was purified by distillation in vacuo, boiling at about 90°C at a pressure of 110 mm. of mercury. The distillate was dissolved in ether and an excess of ethanol saturated with hydrogen chloride was added, thus forming N-methyl-N-isopropyl 3-amino-3-methylbutane hydrochloride. The hydrochloride salt, being insoluble in ether, precipitated and was collected by filtration. The precipitate was recrystallized from methyl ethyl ketone, and yielded purified N-methyl-N-isopropyl 3-amino-3-methylbutane hydrochloride, melting at about 142–144°C.

Analysis.—Calc.: N, 7.79. Found: N, 7.82.

Example 65.—Preparation of 3-Isopropylamino-3-Methylbutane

Following the procedure of Example 63, 25 g. of 3-isopropylamino-3-methyl-1-butane were hydrogenated at low pressure in ethanol solution using Raney nickel as a catalyst. 3-Isopropylamino-3-methylbutane was isolated and purified by distillation according to the procedure of Example 64. The compound boiled at about 78–80°C at a pressure of about 130 mm. of mercury; ν<sub>25</sub> = 1.408.

Analysis.—Calc.: N, 10.84. Found: N, 10.72.

The hydrochloride salt of 3-isopropylamino-3-methylbutane was prepared as in Example 63 by adding ethanolic hydrogen chloride to an ethanolic solution of the free base, and then evaporating the ethanol, leaving the hydrochloride salt as a residue. The residue was recrystallized yielding 3-isopropylamino-3-methylbutane hydrochloride melting at about 131–132°C.

Analysis.—Calc.: C, 57.98; H, 12.17; N, 8.45. Found C, 57.93; H, 11.85; N, 8.21.

Example 66.—Preparation of 3-Ethylamino-3-Methylpentane

Following the procedure of Example 53, 3-ethylamino-3-methyl-1-pentene was hydrogenated in ethanol solution to give 3-ethylamino-3-methylpentane, using Raney nickel as a catalyst. The compound was isolated by the procedure of Example 64 and was purified by distillation. 3-ethylamino-3-methylpentane boiled at about 81°C at a pressure of 110 mm. of mercury; ν<sub>25</sub> = 1.419.

Analysis.—Calc.: N, 10.84. Found: N, 11.12.

3-ethylamino-3-methylpentane hydrochloride was prepared by dissolving the free base in ether and adding thereto an excess of a saturated ethereal hydrogen chloride solution. 3-ethylamino-3-methylpentane hydrochloride melted at about 164–166°C.

Analysis.—Calc.: C, 57.98; H, 12.17; N, 8.45. Found: C, 57.61; H, 11.90; N, 8.44.

Example 67.—Preparation of 3-isopropylamino-3-Methylpentane

Following the procedure of Example 53, 3-isopropylamino-3-methyl-1-pentene was hydrogenated in ethanol solution to yield 3-isopropylamino-3-methylpentane, using Raney nickel as a catalyst. The compound was isolated by the procedure of Example 64 and was purified by distillation. 3-isopropylamino-3-methylpentane boiled at about 87°C at a pressure of 90 mm. of mercury; ν<sub>25</sub> = 1.421.


3-isopropylamino-3-methylpentane hydrochloride was prepared by dissolving the free base in ether and adding thereto an excess of a saturated ethereal hydrogen chloride solution. 3-isopropylamino-3-methylpentane hydrochloride melted at about 194–196°C.

Analysis.—Calc.: C, 60.14; H, 12.34; N, 7.79. Found: C, 60.36; H, 12.18; N, 7.84.

Example 68.—Preparation of 3-Butylamino-3-Methylpentane

Following the procedure of Example 53, 3-butylamino-3-methyl-1-pentene was hydrogenated in ethanol solution to yield 3-butylamino-3-methylpentane, using Raney nickel as a catalyst. The compound was isolated by the procedure of Example 64 and was purified by distillation. 3-butylamino-3-methylpentane boiled at about 70°C at a pressure of 25 mm. of mercury; ν<sub>25</sub> = 1.429.

Analysis.—Calc.: N, 8.91. Found: N, 9.33.

3-butylamino-3-methylpentane hydrochloride was prepared by dissolving the free base in ether and adding thereto an excess of a saturated ethereal hydrogen chloride solution. 3-butylamino-3-methylpentane hydrochloride melted at about 195–196°C.

Analysis.—Calc.: C, 61.99; H, 12.48; N, 7.23. Found: C, 62.06; H, 12.23; N, 7.43.

Example 69.—Preparation of 3-Ethylamino-3-Ethylpentane

Following the procedure of Example 53, 3-ethylamino-3-ethyl-1-pentene was hydrogenated in ethanol solution to yield 3-ethylamino-3-ethylpentane, using Raney nickel as a catalyst. The compound was isolated by the procedure of Example 64 and was purified by distillation. 3-ethylamino-3-ethylpentane boiled at about 88°C at a pressure of 70 mm. of mercury; ν<sub>25</sub> = 1.427.

3-ethylamino-3-ethylpentane hydrochloride was prepared by dissolving the free base in ether and adding an excess of an ethereal solution saturated with hydrogen chloride. 3-ethylamino-3-ethylpentane hydrochloride melted at about 189–191°C.

Analysis.—Calc.: C, 60.14; H, 12.34; N, 7.79. Found: C, 60.36; H, 12.44; N, 7.80.
Example 70.—Preparation of 2-t-Butylamino-2-Methylpentane

Following the procedure of Example 53, 9.45 g. of 4-t-butylamino-4-methyl-2-pentene were dissolved in a mixture of 190 ml. of anhydrous ethanol and 10 ml. of ethanol saturated with hydrogen chloride. The mixture was hydrogenated in the presence of 20 mg. of platinum oxide catalyst. 2-t-butylamino-2-methylpentane hydrochloride thus formed was isolated by the procedure of Example 53. It melted at about 136–138°C. After recrystallization from methyl ethyl ketone.

Analysis.—Calc.: N, 7.23; Cl, 18.30. Found: N, 7.03; Cl, 18.35.

2-t-butylamino-2-methylpentane free base was prepared by dissolving the hydrochloride salt in water, making the aqueous solution alkaline to litmus by the addition of solid sodium hydroxide, extracting the alkaline-insoluble free base with ether, separating and drying the ether solution, and distilling the dried solution. 2-t-butylamino-2-methylpentane thus prepared and purified boiled at about 90–91°C. at a pressure of 58 mm. of mercury; \( n_\text{D}^20 = 1.423 \).

PREPARATION OF AMINO KETONES

The secondary and tertiary amino ketones useful in the therapeutic process and compositions of this invention are readily prepared by the hydration of the corresponding acetylenic amine using aqueous sulfuric acid as the hydrating agent and mercuric oxide as a catalyst. Tertiary amino ketones can also be prepared by alkylating previously synthesized secondary amino ketones.

The following specific examples more fully illustrate the preparation of secondary and tertiary amino ketones useful for this invention.

Example 71.—Preparation of 3-t-Butylamino-3-Methyl-2-Pentanone

A mixture was prepared containing 49 g. of water, 49 ml. of methanol, 45 g. of 18 M sulfuric acid and 6 g. of mercuric oxide. The mixture was heated to about 70°C. and 30 g. of 3-t-butylamino-3-methyl-1-pentene were added. The reaction mixture was heated at 80°C. for about 3 hours, thus forming 3-t-butylamino-3-methyl-2-pentane. 100 g. of potassium carbonate and 200 ml. of a saturated sodium carbonate solution were added to the reaction mixture, thereby converting 3-t-butylamino-3-methyl-2-pentanone hydrochloride to the corresponding free base. The free base was insoluble in the alkaline solution and was extracted with 200 ml. of ether. The ether layer was separated and was dried. A slight excess of a solution of ethanol saturated with hydrogen hydrogen chloride was added, thus forming 3-t-butylamino-3-methyl-2-pentanone hydrochloride which precipitated. The precipitate was separated by filtration and was recrystallized from an ethyl acetate-acetone solvent mixture. 3-t-butylamino-3-methyl-2-pentanone hydrochloride thus prepared melted at about 152–154°C.


3-t-butylamino-3-methyl-2-pentanone free base can be prepared from the hydrochloride salt by dissolving the salt in water, making the acidic aqueous solution alkaline to litmus, extracting the liberated free base with ether, separating and drying the ether solution and purifying the free base by distillation.

Example 72.—Preparation of 3-Isopropylamino-3-Methyl-2-Pentanone

The procedure of Example 71 was followed except that 28 g. of 3-isopropylamino-3-methyl-1-pentene were employed in place of 3-t-butylamino-3-methyl-1-pentene. The ether extract containing 3-isopropylamino-3-methyl-2-pentanone free base formed when the acidic reaction mixture was contacted with potassium carbonate was separated and was dried. The ether was removed by evaporation at atmospheric pressure, leaving a residue comprising 3-isopropylamino-3-methyl-2-pentanone. The residue was distilled, and fractions boiling in the range 64–70°C. at a pressure of about 5 mm. of mercury were collected and combined. The combined fractions were dissolved in ethyl acetate and the resulting solution was saturated with anhydrous hydrogen chloride gas. 3-Isopropylamino-3-methyl-2-pentanone hydrochloride precipitated and was collected by filtration. 3-Isopropylamino-3-methyl-2-pentanone hydrochloride melted at about 99–101°C.

Analysis.—Calc.: N, 7.23. Found: N, 7.20.

Example 73.—Preparation of 3-Isopropylamino-3-Ethyl-2-Pentanone

30 g. of 3-isopropylamino-3-ethyl-1-pentene were hydrated by the procedure of Example 71 to yield 3-isopropylamino-3-ethyl-2-pentanone. The compound was isolated as a free base by adding potassium carbonate to the acidic hydration mixture as in Example 71. 3-Isopropylamino-3-ethyl-2-pentanone free base was insoluble in the alkaline layer and was extracted with ether. The ether layer was separated, and the ether was removed by evaporation in vacuo. The resulting residue comprising 3-isopropylamino-3-ethyl-2-pentanone was dissolved in ethyl acetate, and the ethyl acetate solution was saturated with anhydrous hydrogen chloride gas. The resulting precipitate of 3-isopropylamino-3-ethyl-2-pentanone hydrochloride was separated by filtration. Qualitative analysis of the precipitate showed the presence of mercury. The precipitate was dissolved in dilute hydrochloric acid and the acidic solution was saturated with hydrogen sulfide gas. The solution was filtered to remove mercuric sulfide thus formed and the filtrate was evaporated to dryness in vacuo. Recrystallization of the residue from ethyl acetate yielded 3-isopropylamino-3-ethyl-2-pentanone hydrochloride melting at about 135–136°C.

Analysis.—Calc.: N, 6.74. Found: N, 6.36.

3-Isopropylamino-3-ethyl-2-pentanone free base can be prepared from the hydrochloride salt by dissolving the salt in water, making the acidic aqueous solution alkaline to litmus, extracting the liberated free base with ether, separating and drying the ether solution and purifying the free base by distillation.

Example 74.—Preparation of 3-t-Butylamino-3-Methyl-2-Butanone

40 g. of 3-t-butylamino-3-methyl-1-butene were hydrated according to the process of Example 71 by adding the acetylene to a mixture containing 55 g. of 18 M sulfuric acid, 60 ml. each of water and methanol, and 7.5 g. of mercuric oxide. The addition of the 3-t-butylamino-3-methyl-1-butene required 1.5 hours. During the addition, the temperature of the reaction was maintained at about 70°C. Another 7.5 g. of mercuric oxide were added and the heating was maintained for an additional 1.5 hours. The reaction mixture was cooled and was made alkaline to litmus with 50 percent aqueous sodium hydroxide. 3-t-Butylamino-3-methyl-2-butanone, being insoluble in the alkaline solution, separated and was extracted with 200 ml. of ether. The ether extract was contacted with 130 ml. of 10 percent aqueous hydrochloric acid, thus forming 3-t-butylamino-3-methyl-2-butane hydrochloride which passed into the aqueous layer. The acidic aqueous layer was decolorized with activated charcoal. The charcoal was removed by filtration and the filtrate was made alkaline to litmus with 50 percent aqueous sodium hydroxide. 3-t-Butylamino-3-methyl-2-butane separated from the alkaline filtrate and oil acetic acid was extracted with 200 ml. of ether. The ether extract was separated and was dried over solid potassium carbonate. The ether was removed by evaporation in vacuo, leaving a residue comprising 3-t-Butylamino-3-methyl-2-butane which was distilled. 3-t-Butylamino-3-methyl-2-butane boiled at about 104°C. at 58 mm. of mercury; \( n_\text{D}^20 = 1.434 \).
Following the procedure of Example 71, an ethereal solution of the free base was mixed with ethanolic hydrogen chloride, thus forming an insoluble precipitate of 3-t-butylamino-3-methyl-2-butane hydrochloride. The precipitate was separated by filtration and was recrystallized from a mixture of isopropanol and ethanol. 3-t-butylamino-3-methyl-2-butane hydrochloride thus purified melted at about 208° C.

Example 75.—Preparation of 3-t-Butylamino-3-Ethyl-2-Pentanone

Following the procedure of Example 71, 50 g. of 3-t-butylamino-3-ethyl-1-pentane were hydrated to yield 3-t-butylamino-3-ethyl-2-pentanone. The compound was isolated and converted to the hydrochloride salt by the procedure of Example 71. 3-t-butylamino-3-ethyl-2-pentanone hydrochloride melted at about 173-175° C. after recrystallization from a mixture of ethyl acetate and isopropanol.

Analysis.—Calc.: C, 59.57; H, 10.91; N, 6.32. Found: C, 59.87; H, 11.02; N, 6.30. 3-t-butylamino-3-ethyl-2-pentanone free base can be prepared from the hydrochloric salt by the procedure set forth in Example 71.

Example 76.—Preparation of 3-Isopropylamino-3-Methyl-2-Butanone

Following the procedure of Example 71, 3-isopropylamino-3-methyl-1-butane was hydrated to yield 3-isopropylamino-3-methyl-2-butanone. The compound was isolated and converted to the hydrochloride salt by the procedure set forth in Example 71. 3-isopropylamino-3-methyl-2-butanone hydrochloride melted at about 131-133° C. 3-isopropylamino-3-methyl-2-butanone free base can be prepared from hydrochloride salt by the procedure set forth in Example 71.

PREPARATION OF AMINO ALCOHOLS

The amino alcohols useful in the therapeutic process and medicaments of this invention are readily prepared by reducing the corresponding secondary and tertiary amino ketones. The reduction is most conveniently carried out with sodium borohydride in alcoholic solution or by lithium aluminium hydride in ethereal solution. Low pressure catalytic hydrogenation of the ketone can, of course, also be employed with equal success.

The preparation of the secondary and tertiary amino alcohols of this invention is more fully illustrated by the following specific examples:

Example 77.—Preparation of 3-Isopropylamino-3-Ethyl-2-Pentanol

12 g. of 3-isopropylamino-3-ethyl-2-pentanone hydrochloride were dissolved in water. The acidic aqueous solution was made basic to litmus by the addition of solid potassium carbonate. 3-isopropylamino-3-ethyl-2-pentanone was insoluble in the alkaline solution and was extracted with 150 ml. of ether. The etheral layer was separated, washed and dried to a majority of the ether was removed by evaporation on a steam bath at atmospheric pressure. The resulting concentrate, containing some residual ether, was dissolved in 100 ml. of ethanol and 2.3 g. of sodium borohydride were added to the solution. The reaction mixture was allowed to remain overnight at ambient room temperature. 200 ml. of water were added and the mixture was extracted with 250 ml. of ether. The etheral layer containing 3-isopropylamino-3-ethyl-2-pentanol formed in the above reaction, was separated and washed. Anhydrous hydrogen chloride gas was bubbled into the dried etheral solution, thus forming 3-isopropylamino-3-ethyl-2-pentanol hydrochloride. The solvent was removed by distillation in vacuo. Recrystallization of the resulting residue from a mixture of ethyl acetate and isopropanol yielded 3-isopropylamino-3-ethyl-2-pentanol hydrochloride melting at about 126-127° C.

Analysis.—Calc.: N, 6.68. Found: N, 6.54. 3-Isopropylamino-3-ethyl-2-pentanol free base can be prepared from the hydrochloride salt by dissolving the salt in water, making the aqueous solution alkaline to litmus, extracting the liberated free base with ether, separating and drying the ethereal solution and purifying the free base by distillation.

Example 78.—Preparation of 3-Butylamino-3-Ethyl-2-Pentanol

Following the procedure of Example 77, 5.4 g. of 3-Butylamino-3-ethyl-2-pentanone hydrochloride was converted to the corresponding free base which was obtained in ether solution. A majority of the ether was removed by evaporation in vacuo. The resulting residue, comprising 3-Butylamino-3-ethyl-2-pentanone free base was dissolved in ethanol and reduced with 2.2 g. of sodium borohydride in ethanolic solution as in Example 77. 3-Butylamino-3-ethyl-2-pentanol formed in the above reaction was isolated as the free base. It was converted by the procedure of Example 77 to the hydrochloride salt. 3-Butylamino-3-ethyl-2-pentanol hydrochloride melted at about 141-142° C. after recrystallization from a mixture of ethyl acetate and isopropanol alcohol.


Example 79.—Preparation of 3-Butylamino-3-Methyl-2-Pentanol

Following the procedure of Example 77, 3-Butylamino-3-methyl-2-pentanone hydrochloride was converted to the corresponding free base which was obtained as an ethereal solution. A majority of the ether was evaporated in vacuo and the resulting residue comprising 3-Butylamino-3-methyl-2-pentanone free base was dissolved in ethanol and reduced with sodium borohydride as set forth in Example 77. 3-Butylamino-3-methyl-2-pentanol formed in the above reaction was isolated as the free base and the free base was converted to the corresponding hydrochloride salt by the procedure of Example 77. 3-Butylamino-3-methyl-2-pentanol hydrochloride thus prepared was recrystallized from ethyl acetate. It melted at about 126-127° C.

Analysis.—Calc.: N, 6.68. Found: N, 6.43.

Example 80.—Preparation of 3-Butylamino-3-Methyl-2-Butanol

Following the procedure of Example 77, 10 g. of 3-Butylamino-3-methyl-2-butane were dissolved in 50 ml. of methanol. 1 g. of sodium borohydride was added to the solution of the ketone with stirring, thereby forming 3-Butylamino-3-methyl-2-butanol by reduction. The butanol was isolated as the free base and was converted to the corresponding hydrochloride salt by the procedure of Example 77. 3-Butylamino-3-methyl-2-butanol hydrochloride thus prepared melted at about 154-156° C.

Analysis.—Calc.: C, 55.22; H, 11.33; N, 7.16. Found: C, 55.68; H, 11.22; N, 7.23.

Example 81.—Preparation of 3-Pyrrolidino-3-Methyl-2-Butanol

Following the procedure of Example 77, 3-Pyrrolidino-3-methyl-2-butane was dissolved in ethanol and reduced with sodium borohydride. 3-Pyrrolidino-3-methyl-2-butanol thus formed was isolated as the free base and was purified by distillation. 3-Pyrrolidino-3-methyl-2-butanol boiled at about 99° C. at a pressure of 17 mm. of mercury; nD°=1.465. 3-Pyrrolidino-3-methyl-2-butanol hydrochloride can be prepared by the procedure set forth in Example 77.

Example 82.—Preparation of 3-Isopropylamino-3-Methyl-2-Butanol

Following the procedure of Example 77, 3-isopropyl-
amino-3-methyl-2-butanol was dissolved in ethanol and reduced with sodium borohydride to yield 3-isopropylamino-3-methyl-2-butanol which was isolated as the free base. The free base was converted to the corresponding hydrochloride salt by the procedure of Example 77. 3-isopropylamino-3-methyl-2-butanol hydrochloride melted at about 125–127°C.

Example 83.—Preparation of Salts

Salts of secondary and tertiary amino acetylens, ethylenes, ketones and alcohols as well as salts of the secondary and tertiary saturated amines can be prepared by dissolving the free base in a solvent and adding thereto a solution containing an equivalent amount of the acid. If ether is used as a solvent, the acid salt of the amine is usually insoluble therein and can be isolated by filtration. If, on the other hand, a solvent such as ethanol is used in which the amine salt is usually soluble, the salt is isolated by evaporation of the solvent. As is well known in the art, salts of acids which can be obtained in gaseous form such as hydrogen chloride can also be prepared by bubbling the gaseous acid into a solution of the amine. The resulting salt is, as before, isolated according to whether it is soluble or insoluble in the solvent employed.

We claim:

1. The process of controlling hypertension which comprises administering to humans in unit dosage form from about 1 to about 500 mg. per day of a member of the group consisting of a hypotensive amine and its nontoxic pharmaceutically-acceptable acid addition salts, said amine being represented by the formula

\[
R_1 R_2
\]

wherein \( R_1 \) is a member of the group consisting of hydrogen, methyl, ethyl and propyl; \( R_2 \) is a member of the group consisting of alkyl radicals having from 1–7 carbon atoms and alkenyl radicals having from 2 to 7 carbon atoms, the sum of the carbon atoms in \( R_1 \) and \( R_2 \) being greater than 1, and \( R_1 \) and \( R_2 \) when taken together form a tetramethylene group; \( R_3 \) and \( R_4 \) are alkyl groups having from 1 to 4 carbon atoms, the sum of the carbon atoms in \( R_3 \) and \( R_4 \) being less than 8; and \( R_5 \) is a member of the group consisting of lower alkyl, lower alkenyl, and lower alkylnyl radicals having from 2 to 4 carbon atoms, the n-octyl radical and the \( \alpha \)-hydroxyethyl radical.

2. The process of claim 1 wherein the amine is 3-butylamino-3-methyl-1-butyne.

3. The process of claim 1 wherein the amine is 3-butylamino-3-methyl-1-butene.

4. The process of claim 1 wherein the amine is 3-butylamino-3-methylbutane.

5. The process of claim 1 wherein the amine is 3-butylamino-3-methyl-2-butanone.

6. The process of claim 1 wherein the amine is 3-butylamino-3-methyl-2-butanol.

7. The process of claim 1 wherein the amine is N-methyl-N-t-buty1 3-amino-3-methyl-1-butyne.

8. The process of controlling hypertension which comprises administering in unit dosage form from about 1 to about 500 mg. per day of a member of the group consisting of a tertiary alkyl amine and its nontoxic pharmaceutically-acceptable acid addition salts, said amine being represented by the formula

\[
\text{methyl} \quad \text{t-buty1-} \quad \text{NH} \quad \text{–} \quad \text{X} \quad \text{–} \quad \text{H}
\]

wherein \( X \) is a divalent radical of the group consisting of

\[
\text{–} \quad \text{CH} \quad \text{–} \quad \text{CH} \quad \text{–} \quad \text{C} \quad \text{–} \quad \text{C} \quad \text{–} \quad \text{–} \quad \text{CHOH} \quad \text{–} \quad \text{CH} \quad \text{–}
\]

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