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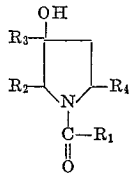
3,083,208

1-ACYL AND 1-CARBALKOXY-3-PYRROLIDINOLS

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This invention relates to 1-acyl and 1-carbalkoxy-3-pyrrolidinols and methods for the preparation of these compounds. More specifically, this invention relates to pyrrolidinols having the formula



wherein R_1 is selected from the group consisting of lower alkyl and lower alkoxy; R_2 is selected from the group consisting of hydrogen and lower alkyl; R_3 is selected from the group consisting of phenyl, diphenyl, halophenyl, dihalophenyl, hydroxyphenyl, lower alkyl phenyl, di lower alkyl phenyl, lower alkoxy phenyl, phenoxyphenyl, benzyloxyphenyl, halo lower alkyl phenyl, halobenzyl oxyphenyl, di lower alkyl methylene dioxyphenyl, lower alkyl thiophenyl, benzyl, halobenzyl and thienyl; and R_4 is selected from the group consisting of hydrogen, lower alkyl, phenyl, halophenyl, lower alkoxyphenyl, methylene dioxyphenyl, cyclohexyl and cyclohexenyl. The most preferred compounds are those in which R_1 is lower alkoxy, R_2 and R_4 are each selected from the group consisting of hydrogen and lower alkyl, and R_3 is selected from the group consisting of phenyl, halophenyl and di halophenyl. When lower alkyl is referred to it is intended to mean such alkyl radicals as methyl, ethyl, propyl, butyl, amyl and the like. Also by lower alkoxy it is intended to mean methoxy, ethoxy, propoxy, butoxy and the like.

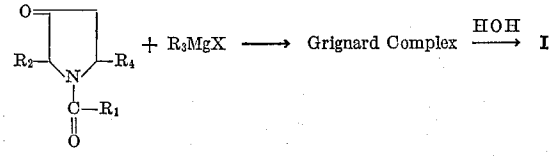
This application is a continuation-in-part of our application Serial No. 792,711, filed February 12, 1959, now abandoned.

The compounds of this invention are useful as therapeutic agents and have been found to have pronounced hypnotic activity. The compounds may be administered orally as tablets, wafers, capsules or the like, and to obtain the desired effect may be administered to mammals in an amount of from about 1.5 milligrams to 1500 milligrams per kilogram of body weight.

The compounds of this invention are particularly useful as intermediates in the preparation of certain 3-aryl-3-pyrrolidinols which are disclosed in Lunsford Patent No. 2,878,264 issued March 17, 1959, and in Wu, Feldkamp and Gould applications Serial No. 792,712, filed February 12, 1959 (now abandoned) and Serial No. 2571, filed January 15, 1960. The compounds disclosed in said applications also have therapeutic usefulness as set forth in those applications and are useful as intermediates in the preparation of certain 3-acyloxy-3-aryl-pyrrolidines as set forth in Wu, Feldkamp and Lobeck application Serial No. 792,713, filed on February 12, 1959. These pyrrolidines also have therapeutic usefulness as disclosed in the last mentioned application.

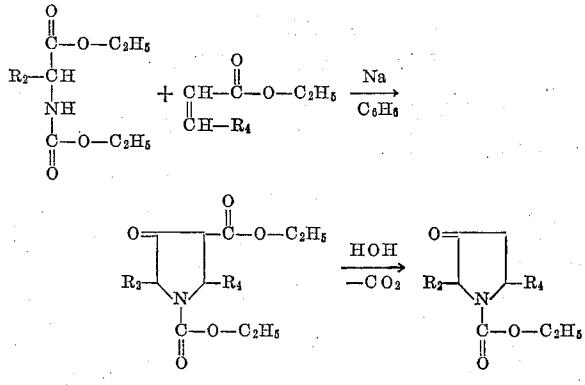
The compounds of this invention may be prepared by reacting a suitable 1-acyl or 1-carbalkoxy-3-pyrrolidinone with an appropriate Grignard reagent and hydrolyzing the resultant Grignard complex. Thus the generalized reac-

tion for preparing the compounds of this invention may be represented as follows:

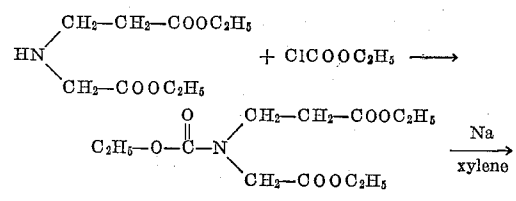


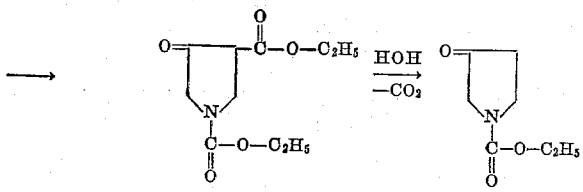
In the reaction indicated above, the values for R_1, R_2, R_3 and R_4 are the same as previously indicated and X is a halogen, such as bromine, chlorine or iodine, which is useful in forming Grignard reagents as is well known. In carrying out the reaction, the usual conditions of operation are observed where a Grignard reagent is reacted with a compound having a carbonyl grouping to form the Grignard complex. Thus the reaction is effected under anhydrous conditions in the presence of an organic solvent, such as an ether or tetrahydrofuran. Although temperatures are not particularly critical, reactions of this type are usually effected under reflux conditions. The complex is then hydrolyzed in the usual manner to form the corresponding alcohol.

The 1-carbalkoxy-3-pyrrolidinones that are reacted with the Grignard reagent to produce the compounds of this invention may be prepared by the method of Kuhn and Osswald, Chem. Ber., 89, 1423 (1956), which involves the reaction of N-carbethoxyglycine ethyl ester with esters of α,β-unsaturated carboxylic acids in the presence of metallic sodium and an inert solvent such as dry benzene to form the 1,4-dicarbalkoxy-3-pyrrolidinones which are partially hydrolyzed and decarboxylated. This prior are process may be generalized as follows:

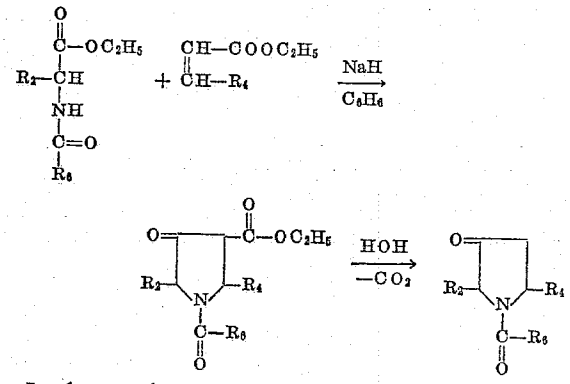


Also certain of the 1-carbalkoxy-3-pyrrolidinone starting materials may be prepared by the method of Miyamoto, Yakuzaku Zasshi, 77, 568 (1957), which comprises the condensation of ethyl chloroformate with ethyl N-carbethoxymethyl-β-amino propionate. The resulting condensation product is ring closed to form 1,4-dicarbethoxy-3-pyrrolidinone under the usual Dieckmann ring closure conditions and is thereafter partially hydrolyzed and decarboxylated to form the appropriate 3-pyrrolidinone derivative. This series of reactions may be indicated as follows:





In order to produce the 1-acyl-3-pyrrolidinone starting materials it has been found that the Kuhn and Osswald method above indicated can be extended to the ethyl esters of some N-acyl-α-amino acids. Thus ethyl aceturate condenses with ethyl acrylate in the presence of sodium hydride and dry benzene. The resulting product can then be partially hydrolyzed and decarboxylated to form the 1-acyl pyrrolidinone in accordance with the following generalized reaction:



In the reaction indicated immediately above, R_2 and R_4 have the values previously specified and R_6 is lower alkyl.

For a more complete understanding of this invention, reference will now be made to a number of specific examples for preparing various compounds that fall within the scope of this invention.

EXAMPLE 1

1-Carbethoxy-3-Pyrrolidinone

The procedure of Kuhn and Osswald was followed. 1-carbethoxy-3-pyrrolidinone distilled at 156–157° (36 mm.); N_D^{25} 1.4667.

1-Carbethoxy-3-Phenyl-3-Pyrrolidinol

An ethereal solution of phenylmagnesium bromide, prepared from 69 g. (0.44 mole) of phenylbromide, 11.7 g. (0.48 mole) of magnesium and 125 ml. of anhydrous ether, was added dropwise in one hour with stirring to 62.9 g. (0.4 mole) of 1-carbethoxy-3-pyrrolidinone in 100 ml. of anhydrous ether. A crystalline Grignard complex formed during the reaction. The mixture, after being stirred and refluxed for three hours, was poured into 600 g. of ice containing 30 g. of ammonium chloride. The ethereal layer was dried with anhydrous magnesium sulfate, filtered and concentrated. Fractional distillation in vacuo gave the crude product (37 g.) as a viscous oil, B.P. 132–180° (0.15 mm.). The oil was treated with a small amount of acetone and scratched with a glass rod. The pure crystalline product was filtered and dried at 60°; M.P. 87–89°; yield, 30 g. (31.9%).

EXAMPLE 2

1-Carbethoxy-3-p-Chlorophenyl-3-Pyrrolidinol

The process of Example 1 was repeated using p-chlorophenylbromide in place of the phenylbromide. The resulting crystalline product had a melting point of 95–97° C.

EXAMPLE 3

1-Carbethoxy-3-p-Anisyl-3-Pyrrolidinol

The process of Example 1 was repeated using p-anisylbromide in place of the phenyl bromide. The resulting crystalline product had a melting point of 77–79° C.

EXAMPLE 4

1-Carbethoxy-3-p-Tolyl-3-Pyrrolidinol

The process of Example 1 was repeated using p-tolylbromide in place of the phenyl bromide. The resulting crystalline product had a melting point of 74–76° C.

EXAMPLE 5

1-Carbethoxy-3-(2-Thienyl)-3-Pyrrolidinol

The process of Example 1 was repeated using 2-thienylbromide in place of the phenyl bromide. The resulting crystalline product had a melting point of 79–81° C.

EXAMPLE 6

1-Carbethoxy-3-p-Benzyloxyphenyl-3-Pyrrolidinol

The process of Example 1 was repeated using p-benzyloxyphenylbromide in place of the phenyl bromide. The resulting crystalline product had a melting point of 126–127° C.

EXAMPLE 7

N-Carbethoxy-D,L-Alpha-Alanine Ethyl Ester

A mixture of D,L-alpha-alanine (100 g., 1.12 moles), anhydrous hydrogen chloride (115.5 g., 3.20 moles) and 450 ml. of absolute ethanol was refluxed for five hours. The reaction mixture was evaporated at reduced pressure to nearly dryness. The syrupy residue was treated three times with 100 ml. portions of 95% ethanol. The ethanol was removed by distillation to leave a thick residue. Water (200 ml.) was added. The aqueous solution was cooled in an ice bath and neutralized with 116 ml. of 10 N sodium hydroxide. Ethyl chloroformate (128 g., 1.18 moles) was added dropwise with stirring in two hours. After being stirred for an additional hour, the mixture was stirred with 320 ml. of 20% sodium carbonate solution for ten minutes and extracted thoroughly with ether. The combined ethereal extract, after drying with anhydrous magnesium sulfate and filtering, was fractionated in vacuo. N-carbethoxyalanine ethyl ester was collected at 140.5–142° (27 mm.) as a colorless oil; N_D^{25} 1.4332; yield, 148.4 g. (70.0%).

1,4-Dicarbethoxy-2-Methyl-3-Pyrrolidinone

N-carbethoxyalanine ethyl ester (94.6 g. 0.5 mole) was added dropwise to a suspension of sodium hydride (53.8% pure, 22.3 g., 0.5 mole) in 375 ml. of dry benzene at such a rate that gentle refluxing was maintained. The addition took approximately one hour. After refluxing for an additional thirty minutes, the mixture was cooled to room temperature and treated with efficient stirring and dropwise with 50.1 g. (0.5 mole) of ethyl acrylate in thirty to forty minutes. The stirring was continued for an additional thirty minutes. To complete the reaction the mixture was refluxed for two hours. An equivalent amount of 3 N hydrochloric acid (167 ml.) was added. After thoroughly shaking, the benzene layer was decanted off and the aqueous layer extracted several times with chloroform. The combined benzene and chloroform solution was dried with anhydrous magnesium sulfate. After filtering and concentrating, the residue was distilled in vacuo to yield 83 g. (68.2%) of 1,4-dicarbethoxy-2-methyl-3-pyrrolidinone as a colorless oil, B.P. 106–125° (0.2 mm.), N_D^{25} 1.4652.

1-Carbethoxy-2-Methyl-3-Pyrrolidinone

A mixture of 1,4-dicarbethoxy-2-methyl-3-pyrrolidinone (83.0 g., 0.34 mole) and 300 ml. of water containing 3 ml. of concentrated hydrochloric acid was refluxed for fifteen hours. The resulting clear solution was saturated with sodium chloride and extracted with 250 ml. of chloroform in five portions. The combined chloroform extract was dried with anhydrous magnesium sul-

fate, filtered, concentrated and fractionated in vacuo to obtain 1-carbethoxy-2-methyl-3-pyrrolidinone as a colorless oil, B.P. 126–130° (14 mm.), N_D^{25} 1.4598. Yield 43.5 g. (74.8%).

1-Carbethoxy-2-Methyl-3-Phenyl-3-Pyrrolidinol

An ethereal solution of phenylmagnesium bromide (0.075 mole) in 100 ml. of anhydrous ether was prepared in the usual manner. With efficient stirring a solution of 1-carbethoxy-2-methyl-3-pyrrolidinone (8.6 g., 0.05 mole) in 30 ml. of anhydrous ether was added dropwise in thirty minutes. The reaction mixture after refluxing for one hour was poured into 400 g. of ice containing 20 g. of ammonium chloride. The whole was extracted thoroughly with ether. The combined ethereal extract was dried with anhydrous magnesium sulfate, filtered and concentrated. The thick residue was stirred with a small amount of n-heptane to separate 9.1 g. of crude 1-carbethoxy-2-methyl-3-phenyl-3-pyrrolidinol in white crystalline form, M.P. 91–94°. Crystallization from isopropyl ether raised the M.P. to 95–97°; yield, 7.2 g. (58.1%).

EXAMPLES 8, 9 AND 10

1-carbethoxy-2-methyl-3-o-tolyl-3-pyrrolidinol (an oil having a boiling point of 152–155° C. at 0.5 mm.), 1-carbethoxy-2-methyl-3-p-anisyl-3 - pyrrolidinol (crystalline solid having a melting point of 103–105° C.) and 1-carbethoxy-2-methyl-3-m-chlorophenyl - 3 -p yrrolidinol (crystalline solid having a melting point of 93–95° C.) were each prepared by essentially the same process as indicated in Example 7.

EXAMPLE 11

N-Carbomethoxyglycine Ethyl Ester

A solution of glycine ethyl ester hydrochloride (69.8 g., 0.5 mole) in 70 ml. of water was cooled in an ice bath and neutralized with 50 ml. of 40% sodium hydroxide. While the temperature was kept below 10°, methyl chloroformate (42.3 g., 0.5 mole) was added dropwise with stirring in two hours. After stirring for an additional thirty minutes, a second 50 ml. portion of 40% sodium hydroxide was added. The mixture was thoroughly extracted with ether. The combined ethereal extract was dried with anhydrous magnesium sulfate, filtered and concentrated. Fractional distillation in vacuo of the oily residue yielded 27.0 g. (33.5%) of N-carbomethoxyglycine ethyl ester as a colorless oil, B.P. 137–139° (17 mm.), N_D^{25} 1.4370.

1-Carbomethoxy-4-Carbethoxy-3-Pyrrolidinone

N-carbomethoxyglycine ethyl ester (27.0 g., 0.17 mole) was added dropwise to a suspension of sodium hydride (51.5% pure, 8 g., 0.17 mole) in 100 ml. of dry benzene at such a rate that gentle refluxing was maintained. The addition took approximately one hour. After refluxing for an additional thirty minutes, the mixture was cooled to room temperature and treated with efficient stirring and dropwise with 16.7 g. (0.17 mole) of ethyl acrylate in twenty minutes. To complete the reaction the mixture was refluxed for two hours. Fifty-five milliliters of 3 N hydrochloric acid was added. After shaking thoroughly the benzene layer was separated. The aqueous solution was extracted several times with chloroform. The combined benzene and chloroform extract was dried with anhydrous magnesium sulfate. After filtration and concentration the residue was distilled in vacuo to collect 20.0 g. (53.0%) of 1-carbomethoxy-4-carbethoxy-3-pyrrolidinone as a viscous oil, B.P. 105–110° (0.15 mm.).

1-Carbomethoxy-3-Pyrrolidinone

A mixture of 1-carbomethoxy-4-carbethoxy-3-pyrrolidinone (20.0 g., 0.09 mole) and 100 ml. of water containing 1 ml. of concentrated hydrochloric acid was refluxed for fifteen hours. The clear solution was saturated with sodium chloride and extracted thoroughly with chloroform. The combined chloroform extract was dried with anhydrous magnesium sulfate, filtered and concentrated. A crystalline solid separated. Crystallization from isopropyl ether yielded 8.1 g. (62.2%) of 1-carbomethoxy-3-pyrrolidinone, M.P. 59–63°.

1-Carbomethoxy-3-Phenyl-3-Pyrrolidinol

An ethereal solution of phenylmagnesium bromide (0.08 mole) in 100 ml. of ether was prepared in the usual manner. With efficient stirring 1-carbomethoxy-3-pyrrolidinone (8.1 g., 0.056 mole) in 30 ml. of anhydrous ether was added in thirty minutes. The reaction mixture after refluxing for two hours was poured into 400 g. of ice containing 20 g. of ammonium chloride. The whole was extracted thoroughly with ether. The combined ethereal extract was dried with anhydrous magnesium sulfate. After filtering and concentrating, the oily residue was distilled to produce 1-carbomethoxy-3-phenyl-3-pyrrolidinol as a thick oil, B.P. 150–155° (0.15 mm.); yield, 7.2 g. (58.1%). The oil was covered with 10 ml. of acetone and scratched with a glass rod to separate 4.3 g. (35.2%) of the pure product, M.P. 94–96°.

EXAMPLE 12

N-Carbisobutoxyglycine Ethyl Ester

A solution of glycine ethyl ester hydrochloride (139.6 g., 1 mole) in 140 ml. of water was cooled in an ice bath and treated with 100 ml. of 40% sodium hydroxide. While the temperature was kept below 10° an equivalent amount of isobutyl chloroformate (136.5 g., 1 mole) was added dropwise in two hours. After stirring for an additional thirty minutes the mixture was neutralized with 100 ml. of 40% sodium hydroxide. The whole was extracted thoroughly with ether. The combined ethereal extract was dried with anhydrous magnesium sulfate, filtered and concentrated. Fractionating the oily residue in vacuo yielded 120 g. (60.0%) of N-carbisobutoxyglycine ethyl ester as a colorless oil, B.P. 150–154° (17 mm.), N_D^{25} 1.4367.

1-Carbisobutoxy-4-Carbethoxy-3-Pyrrolidinone

N-carbisobutoxyglycine ethyl ester (120 g., 0.6 mole) was added dropwise to a suspension of sodium hydride (51.5% pure, 28 g., 0.6 mole) in 420 ml. of dry benzene at such a rate that gentle refluxing was maintained. The addition took approximately thirty minutes. After refluxing for an additional thirty minutes, the reaction mixture was cooled to room temperature and treated dropwise with 60 g. (0.6 mole) of ethyl acrylate in thirty minutes. The reaction was completed by refluxing for two hours. Two hundred ten milliliters of 3 N hydrochloric acid was added. After shaking thoroughly, the benzene layer was separated. The aqueous solution was extracted several times with chloroform. The combined benzene and chloroform extract was dried with anhydrous magnesium sulfate. After filtering and concentrating, the oily residue was distilled in vacuo to obtain 100.0 g. (65.0%) of 1-carbisobutoxy-4-carbethoxy-3-pyrrolidinone as a colorless oil, B.P. 135–243° (0.3 mm.), N_D^{25} 1.4676.

1-Carbisobutoxy-3-Pyrrolidinone

A mixture of 1-carbisobutoxy-4-carbethoxy-3-pyrrolidinone (100 g., 0.39 mole) and 388 ml. of water containing 4 ml. of concentrated hydrochloric acid was refluxed for seventeen hours. The solution was saturated with sodium chloride and extracted thoroughly with chloroform. The combined chloroform extract was dried with anhydrous magnesium sulfate. The solvent was removed and the residue distilled to yield 57.6 g. (79.8%) of 1-carbisobutoxy-3-pyrrolidinone, B.P. 154–158° (15 mm.), N_D^{25} 1.4620. The oil solidified on standing, M.P. 25–35° C.

1-Carbisobutoxy-3-Phenyl-3-Pyrrolidinol

An ethereal solution of phenylmagnesium bromide (0.15 mole) in 100 ml. of anhydrous ether was prepared in the usual manner. With efficient stirring a solution of 1-carbisobutoxy-3-pyrrolidinone (20.4 g., 0.11 mole) in 30 ml. of anhydrous ether was added dropwise in thirty minutes. After refluxing for two hours the mixture was poured into 400 g. of ice containing 20 g. of ammonium chloride. The whole was extracted with ether several times. The combined ethereal extract was dried with anhydrous magnesium sulfate. The ether was removed and the residue distilled in vacuo to give 19.0 g. of crude 1-carbisobutoxy-3-phenyl-3-pyrrolidinol, B.P. 140–180° (0.4 mm.). Redistillation yielded 13.9 g. (48.3%) of pure material as a thick oil, B.P. 170–172° (0.4 mm.).

EXAMPLE 13

1-Carbisobutoxy-3-p-Chlorophenyl-3-Pyrrolidinol

Reaction of p-chlorophenylmagnesium bromide with 1-carbisobutoxy-3-pyrrolidinone by the process of Example 12 produced 1-carbisobutoxy-3-p-chlorophenyl-3-pyrrolidinol as a thick oil, B.P. 195–200° (0.2 mm.); yield; 60.1%.

EXAMPLE 14

1,4-Dicabethoxy-2,5-Dimethyl-3-Pyrrolidinone

N-carbethoxyalanine ethyl ester (94.5 g., 0.5 mole) was added dropwise to a suspension of sodium hydride (51.5% pure, 24.0 g., 0.5 mole) in 300 ml. of dry benzene at such a rate that gentle refluxing was maintained. The addition took approximately thirty minutes. After refluxing for an additional thirty minutes, the reaction mixture was cooled to room temperature and treated dropwise with efficient stirring with 57.0 g. (0.5 mole) of ethyl crotonate in thirty minutes. The reaction was completed by refluxing for two hours. 3 N hydrochloric acid (167 ml.) was added. After shaking thoroughly, the benzene layer was separated. The aqueous layer was extracted several times with chloroform. The benzene solution and the chloroform extracts were combined and the solvents removed by distillation. The residue was fractionated to obtain 71.4 g. (55.2%) of 1,4-dicarbethoxy-2,5-dimethyl-3-pyrrolidinone, B.P. 86–87° (0.2 mm.), N_D^{25} 1.4672.

1-Carbethoxy-2,5-Dimethyl-3-Pyrrolidinone

A mixture of 45.0 g. (0.175 mole) of 1,4-dicarbethoxy-2,5-dimethyl-3-pyrrolidinone and 200 ml. of water containing 2 ml. of concentrated hydrochloric acid was refluxed for twenty hours. The cooled hydrolysis mixture was extracted several times with chloroform and the combined chloroform extract concentrated to an oil residue by distillation. The residue was distilled in vacuo to give 29.2 (90.2%) of 1-carbethoxy-2,5-dimethyl-3-pyrrolidinone as a colorless oil, B.P. 130–132° (22 mm.), N_D^{25} 1.4550.

1-Carbethoxy-2,5-Dimethyl-3-Phenyl-3-Pyrrolidinol

An ethereal solution of phenylmagnesium bromide (0.15 mole) in 100 ml. of anhydrous ether was prepared in the usual manner. With efficient stirring a solution of 18.6 g. (0.1 mole) of 1 - carbethoxy-2,5-dimethyl-3-pyrrolidinone in 35 ml. of anhydrous ether was added dropwise. The addition took about thirty minutes. The reaction mixture was stirred and refluxed for an additional hour. The whole was poured into 400 g. of ice containing 20 g. of ammonium chloride. The ether layer was separated. The aqueous mixture was extracted several times with ether. The combined ethereal extract was dried with anhydrous magnesium sulfate. The residue obtained after filtration and concentration was distilled in vacuo. 1-carbethoxy-2,5-dimethyl-3-phenyl-3-pyrrolidinol was collected at 130–135° (0.2 mm.) as a viscous oil; yield, 13.3 g. (50.8%).

EXAMPLE 15

1-Acetyl-4-Carbethoxy-3-Pyrrolidinone

A solution of ethyl aceturate (370.1 g., 2.55 moles) in 660 ml. of dry benzene was added dropwise to a suspension of sodium hydride (45.8% pure, 133.6 g., 2.55 moles) in 2.64 liters of dry benzene. After one quarter of the solution was added, the mixture was gently heated to initiate the reaction. The heat was withdrawn once the reaction started. The rest of the solution was added at such a rate that gentle refluxing was maintained throughout the addition (approximately one hour). The reaction mixture was allowed to stand overnight at room temperature was occasional stirring. Ethyl acrylate (255.3 g., 2.55 moles) was added dropwise in thirty minutes with stirring. After stirring for an additional thirty minutes at room temperature and refluxing for two hours thereafter, the mixture was treated with 1.01 liters of 3 N hydrochloric acid. After shaking thoroughly, the benzene layer was separated. The aqueous solution was extracted with three 200 ml. portions of chloroform. The benzene solution and the chloroform extract were combined and the solvents removed by distillation. The oily residue was dissolved in one liter of carbon tetrachloride. On storing at 0° overnight, 1-acetyl-3-carbethoxy-3-pyrrolidinone separated as crystalline solid. It was filtered and air-dried; M.P. 55–57°; wt., 190.6 g. The filtrate was concentrated and then fractionated in vacuo to collect a fraction with B.P. 154–164° (0.5 mm.). The oil solidified on standing, M.P. 55–57° and amounted to 100.4 g., making the total yield 219.0 g. (57.3%) for the product.

1-Acetyl-3-Pyrrolidinone

A mixture of 291.0 g. (1.46 moles) of 1-acetyl-4-carbethoxy-3-pyrrolidinone and 1.3 liters of water containing 13 ml. of concentrated hydrochloric acid was refluxed for four hours. The resulting solution was concentrated to one-fourth of its original volume and extracted four times with 400 ml. portions of chloroform. The combined chloroform extract was dried with anhydrous magnesium sulfate. The oil obtained after filtering and removing the solvent was distilled in vacuo to yield 77.6 g. (41.7%) of 1-acetyl-3-pyrrolidinone as an oil, B.P. 120–123° (0.55 mm.); N_D^{25} 1.4978.

1-Acetyl-3-Phenyl-3-Pyrrolidinol

An ethereal solution of phenylmagnesium bromide (0.2 mole) in 40 ml. of anhydrous ether was added dropwise in thirty minutes to a solution of 1-acetyl-3-pyrrolidinone (25.4 g., 0.2 mole) in 100 ml. of tetrahydrofuran. The reaction mixture was refluxed for five and one-half hours. The Grignard complex was decomposed with 50 ml. of saturated ammonium chloride solution. The whole was extracted several times with chloroform. The chloroform extract, after drying with anhydrous magnesium sulfate and filtering, was concentrated to a thick oil. Fractional distillation of this oil gave a fraction of 7.5 g. with B.P. 160–169° (0.15 mm.). Redistillation of this fraction yielded 43 g. (10.5%) of pure 1-acetyl-3-phenyl-3-pyrrolidinol as a viscous oil, B.P. 172–174° (0.1 mm.)

EXAMPLE 16

1-Acetyl-4-Carbethoxy-2-Methyl-3-Pyrrolidinone

A solution of N-acetylalanine ethyl ester (108.1 g., 0.67 mole) in 150 ml. of dry benzene was added dropwise with stirring to a suspension of sodium hydride (51.5% pure, 31.2 g., 0.67 mole) in 1.2 liters of dry benzene. After one-fourth of the solution was added, the mixture was gently heated to initiate the reaction. The heat was withdrawn once the reaction started. The rest of the solution was added dropwise at a rate to maintain the gentle refluxing. To the sodium salt thus formed was added ethyl acrylate (67.6 g., 0.67 mole) in thirty minutes. The mixture was then stirred and refluxed for one

and one-half hours and allowed to cool to room temperature Two hundred twenty-five milliliters of 3 N hydrochloric acid was stirred into the mixture. The benzene layer was separated and the aqueous layer was extracted several times with benzene. The combined benzene solution was concentrated. The residue was distilled to give 89.0 g. (62.3%) of 1-acetyl-4-carbethoxy-2-methyl-3-pyrrolidinone as a colorless oil, B.P. 105–107° (0.15 mm.), N_D^{25} 1.4830.

1-Acetyl-2-Methyl-3-Pyrrolidinone

A mixture of 1-acetyl-4-carbethoxy-2-methyl-3-pyrrolidinone (88.3 g., 0.41 mole) and 400 ml. of water containing 4 ml. of concentrated hydrochloric acid was refluxed for 17 hours. The product was extracted with chloroform and isolated in the usual manner. It distilled at 83–87° (0.15 mm.), N_D^{25} 1.4850. Yield: 31.9 g. (55.9%).

1-Acetyl-2-Methyl-3-Phenyl-3-Pyrrolidinol

An ethereal solution of phenylmagnesium bromide (0.36 mole) in 240 ml. of dry ether was prepared in the usual manner. To this Grignard reagent was added dropwise in one hour a solution of 1-acetyl-3-pyrrolidinone (34.9 g., 0.24 mole) in 80 ml. of anhydrous ether. The mixture, after being refluxed for one hour, was poured onto 300 g. of ice containing 15 g. of ammonium chloride. The ethereal solution was separated and dried over anhydrous magnesium sulfate. The residue after removing the solvent was distilled to obtain a fraction, weighed 11.0 g., with B.P. 155–170° (0.4 mm.). The distillate was dissolved in 100 ml. of acetone and charcoaled. On standing at 0° 1-acetyl-2-methyl-3-phenyl-3-pyrrolidinol crystallized out; weight after drying at 60°, 6.6 g. (12.5%) M.P. 143–145°.

EXAMPLE 17

3-Benzyl-1-Carbethoxy-2-Methyl-3-Pyrrolidinol

An ethereal solution of benzylmagnesium bromide (0.1 mole) in 125 ml. of anhydrous ether was prepared in the usual manner. To this Grignard reagent was added with stirring and dropwise an ethereal solution of 1-carbethoxy-2-methyl-2-pyrrolidinone (12.0 g., 0.07 mole) in 125 ml. of anhydrous ether in 30 minutes. The Grignard reaction mixture, after stirring and refluxing for one hour, was poured into a mixture of 200 g. of ice and 10 g. of ammonium chloride. The ethereal phase was separated and dried with anhydrous magnesium sulfate. The residue obtained after removal of ether was fractionally distilled to obtain 93 g. (50.7%) of 3-benzyl-1-carbethoxy-2-methyl-3-pyrrolidinol as a thick oil, B.P. 145–147° C. (0.15 mm.).

EXAMPLE 18

1-Carbethoxy-3,5-Diphenyl-3-Pyrrolidinol

1-carbethoxy-5-phenyl-3-pyrrolidinone was prepared according to the method of Kuhn and Osswald. A solution of 17.6 g. (0.075 mole) of 1-carbethoxy-5-phenyl-3-pyrrolidinone in 50 ml. of anhydrous ether was added dropwise to a stirred solution of 50 ml. (0.15 mole) 3 M phenylmagnesium bromide (0.15 mole) in 100 ml. of anhydrous ether. The reaction mixture was refluxed for 2 hours, cooled and hydrolyzed by pouring over ammonium chloride and ice. The ether layer was separated and the aqueous mixture extracted with 500 ml. of chloroform. The combined organic layers were evaporated to dryness. The solid residue was mixed with isopropyl ether and filtered; yield, 13.8 g. (60%); after two recrystallizations from isopropyl alcohol the product melted at 151–153°.

EXAMPLE 19

1-Carbethoxy-5-Methyl-3-Phenyl-3-Pyrrolidinol

To an ethereal solution of phenylmagnesium bromide (0.15 mole) in 50 ml. of anhydrous ether was added dropwise in two hours 100 ml. of an ethereal solution containing 17.1 g. (0.1 mole) of 1-carbethoxy-5-methyl-3-pyrrolidinone, prepared according to the procedure of Kuhn and Osswald. The mixture was stirred and refluxed for two hours. To decompose the Grignard complex, the mixture was poured into 50 ml. of ice-cold saturated ammonium chloride solution. The ethereal phase was separated and the aqueous phase extracted thoroughly with ethyl acetate. The ethereal solution and the extract were combined and the solvents removed. The crude 1-carbethoxy-5-methyl-3-phenyl-3-pyrrolidinol was recrystallized from anhydrous ethanol; yield, 7.7 g. (30.7%); M.P. 126–127°.

EXAMPLE 20

Ethyl N-Carbethoxy-D,L-α-Amino-n-Butyrate

A mixture of D,L-α-amino-n-butyric acid (100 g., 0.97 mole) anhydrous hydrogen chloride (100 g., 2.8 moles) and 500 ml. of absolute ethanol was refluxed for five hours. The reaction mixture was evaporated at reduced pressure to nearly dryness. The solid residue was treated three times with 100 ml. portions of 95% ethanol. The ethanol was removed by distillation. The solid residue was dissolved in 300 ml. of water. The aqueous solution was cooled in an ice bath and neutralized with 110 ml. of 10 N sodium hydroxide. Ethyl chloroformate (100 ml., 1.06 moles) was added dropwise with stirring over a period of two hours. After being stirred for an additional ninety minutes, the mixture was stirred with 320 ml. of 20% sodium carbonate solution for fifteen minutes and extracted thoroughly with ether. The combined ethereal extract, after drying with anhydrous magnesium sulfate and filtering, was fractionated in vacuo. Ethyl N-carbethoxy-D-α-amino-n-butyrate was collected at 144–146° (22 mm.); N_D^{25} 1.4365; yield 157.8 g. (80%).

1,4-Dicarbethoxy-2-Ethyl-5-Methyl-3-Pyrrolidinone

Ethyl N-carbethoxy-D,L-α-amino-n-butyrate (96.0 g., 0.47 mole) was added dropwise to a stirred suspension of sodium hydride (51.5% pure, 22.0 g., 0.47 mole) in 500 ml. of dry benzene at such a rate that gentle refluxing was maintained. After refluxing for an additional thirty minutes, a solution of 53.79 g. (0.47 mole) of ethyl crotonate in 75 ml. of dry benzene was added dropwise to the refluxing solution. The reaction was completed by refluxing for four hours. 3 N hydrochloric acid (157 ml.) was added. After shaking thoroughly, the benzene layer was separated. The aqueous layer was extracted several times with chloroform. The benzene solution and the chloroform extract were combined and the solvents removed by distillation. The residue was fractionated to obtain 61.3 g. (50%) of 1,4-dicarbethoxy-2-ethyl-5-methyl-3-pyrrolidinone, B.P. 101–105° (0.25 mm.), N_D^{25} 1.4684.

1-Carbethoxy-2-Ethyl-5-Methyl-3-Pyrrolidinone

A mixture of 61.3 g. (0.23 mole) of 1,4-dicarbethoxy-2-ethyl-5-methyl-3-pyrrolidinone and 600 ml. of water containing 6 ml. of concentrated hydrochloric acid was refluxed for twenty hours. The cooled mixture was extracted several times with chloroform and the combined chloroform extract was concentrated. The residue was distilled in vacuo to give 38.3 g. (85%) of 1-carbethoxy-2-ethyl-5-methyl-3-pyrrolidinone, B.P. 140°–141° (20 mm.); N_D^{25} 1.4557.

1-Carbethoxy-2-Ethyl-5-Methyl-3-Phenyl-3-Pyrrolidinol

An ethereal solution of phenylmagnesium bromide (0.3 mole) in 200 ml. of anhydrous ether was prepared in the usual manner. With efficient stirring, a solution of 38.3 g. (0.2 mole) of 1-carbethoxy-2-ethyl-5-methyl-3-

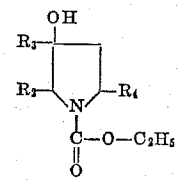
pyrrolidinone in 100 ml. of anhydrous ether was added dropwise to the Grignard solution. The reaction mixture was stirred and refluxed for two hours. The whole was poured into 500 g. of ice containing 50 g. of ammonium chloride. The ether layer was separated and the aqueous layer was extracted several times with ether. The combined ethereal extract was dried with anhydrous magnesium sulfate. The residue obtained after filtration and concentration was recrystallized from isopropyl ether. The precipitate was collected on a filter to yield 19.0 g. (37%) of 1-carbethoxy-2-ethyl-5-methyl-3-phenyl-3-pyrrolidinol, M.P. 111–116°.

The temperatures indicated in this specification are all expressed in degrees centigrade.

In the preceding examples there are shown represntative processes for preparing the compounds of this invention. A large number of additional compounds have also been prepared and they are specifically disclosed in the following table. As will be noted from that table, these compounds are all the 1-carbethoxy derivatives in which the radicals R_2, R_3 and R_4 are as indicated in the several columns for each example.

Generally speaking, the compounds listed in the table were prepared essentially by one of four procedures as

TABLE



Example	R_2	R_3	R_4	Procedure	M.P., °C.	Solvent for recrystallization	B.P.(mm.), °C.
21	H	3-Cl—C_6H_4—	H	A	112–113	Isopropyl ether	
22	H	3-$C_6H_5CH_2OC_6H_4$—	H	B	94–96	Isopropyl alcohol	
23	H	3,4-$Cl_2C_6H_3$—	H	A	97–99	Isopropyl ether	
24	H	4-$ClC_6H_4CH_2$—	H	A	118–120	Ethyl alcohol—isopropyl ether.	
25	H	4-FC_6H_4—	H	A	79–82	Isopropyl ether	
26	H	4-BrC_6H_4—	H	A	111–113	do	150–160 (0.1)
27	H	4-$C_2H_3OC_6H_4$—	H	A	100–101	Skellysolve B	
28	H	3-$CF_3C_6H_4$—	H	A	80–81	Isopropyl ether	
29	H	4-$C_6H_5C_6H_4$—	H	B	162–163	Ethanol	
30	H	3-ClC_6H_4—	CH_3—	A	113–115	Isopropyl ether	
31	H	3,4-$Cl_2C_6H_3$—	CH_3—	A	100–101	do	
32	H	4-FC_6H_4—	CH_3—	A	128–130	do	
33	H	4-$C_6H_5CH_2OC_6H_4$—	CH_3—	B	142–144	Ethanol	
34	H	4-ClC_6H_4—	CH_3—	A	78–90	Isopropyl ether	
35	H	C_6H_5—	C_2H_5—	A	114–116	do	
36	H	4-ClC_6H_4—	C_2H_5—	A	117–119	Isopropyl ether—isopropyl alcohol.	
37	H	4-ClC_6H_4—	C_6H_5—	A	127–129	do	
38	H	3,4-$Cl_2C_6H_3$—	C_6H_5—	A	91–93	Isopropyl ether	
39	H	C_6H_5—	4-ClC_6H_4—	A	103–105	do	
40	H	C_6H_5—	4-$CH_3OC_6H_4$—	A	121–123	Isopropyl ether—isopropyl alcohol.	
41	H	C_6H_5—	3,4-$CH_2O_2C_6H_3$—[d]	A	131–133	do	
42	CH_3—	4-ClC_6H_4—	H	A	93–96	Isopropyl ether	
43	CH_3—	3-$CF_3C_6H_4$—	H	A	123–124	do	
44	CH_3—	4-$C_6H_5CH_2OC_6H_4$—	H	B	152–155	Isopropyl alcohol	
45	CH_3—	3-$C_6H_5CH_2OC_6H_4$—	H	B	112–115	Aqueous ethyl alcohol	
46	CH_3—	3,4-$Cl_2C_6H_3$—	H	A	122–124	Isopropyl ether	
47	CH_3—	4-$C_2H_3OC_6H_4$—	H	A	91–92	Skellysolve B	
48	CH_3—	4-$C_6H_5C_6H_4$—	H	A	115–117	Aqueous ethyl alcohol	
49	CH_3—	4-ClC_6H_4—	CH_3—	A	120–121	Isopropyl ether	145–170 (0.15)
50[a]	CH_3—	4-ClC_6H_4—	CH_3—	A			
51	CH_3—	C_6H_5—	C_6H_5—	A	163–165	Ethanol	
52	C_2H_5—	C_6H_5—	H	A	104–106	Isopropyl ether	
53	C_2H_5—	4-$C_6H_5CH_2OC_2H_4$—	H	B	115–117	Isopropyl ether—isopropyl alcohol.	
54	C_2H_5—	4-ClC_6H_5—	H	A	87–89	Isopropyl ether	
55[b]	C_2H_5—	C_6H_5—	CH_3—	A	80–82	Hexane	
56	CH_3—	4-$CH_3C_6H_4$—	H	A			150–155 (0.07)
57	H	2-ClC_6H_4—	H	A			157–160 (0.08)
58	C_2H_5—	4-ClC_6H_4—	CH_3—	A			165–175 (0.1)
59	H	2,5-$(CH_3)_2C_6H_3$—	H	A			150–155 (2)
60	H	C_6H_5—	C_6H_{11}—[c]	A			165–175 (0.7)
61	H	3-$CF_3C_6H_4$—	C_6H_5—	A			150–170 (0.08)
62	CH_3—	4-$C_6H_5OC_6H_4$—	H	B			180–200 (0.07)
63	H	C_6H_5—	$(CH_3)_2CH$—	A			120–150 (0.3)
64	H	4-BrC_6H_4—	CH	A			150–160 (0.7)
65	H	4-ClC_6H_4—	$(CH_3)_2CH$—	A			164–172 (0.1)
66	CH_3—	2,5-$(CH_3)_2C_6H_3$—	H	A			160–165 (2)
67	CH_3—	2-$CH_3OC_6H_4$—	H	A			110–120 (0.5)
68	H	4-ClC_6H_4—	3,4-$CH_2O_2C_6H_3$—[d]	A		(Purified by chromatography)	
69	H	C_6H_5—	C_6H_9—[e]	A			165–168 (0.3)
70	H	4-ClC_6H_4—	C_6H_9—[e]	A			160–200 (0.15)
71	H	2-$CH_3OC_6H_4$—	H	A			140–150 (0.08)
72	H	3,4-$[(CH_3)_2CO_2]C_6H_3$—	H	B	133–135	Aqueous ethyl alcohol	
73	CH_3—	4-$CH_3SC_6H_4$—	H	B			175–180 (0.2)
74	H	4-ClC_6H_4—	4-ClC_6H_4—	A	133–135	Isopropyl ether	
75	CH_3—	4-(4-$ClC_6H_5CH_2O$)C_6H_4—	H	D	144–146	Isopropyl alcohol	
76	H	2-ClC_6H_4—	CH_3—	A			150–165 (0.1)
77	CH_3—	2-ClC_6H_4—	H	A			140–155 (0.15)
78	CH_3—	4-$C_6H_5CH_2OC_6H_4$—	CH_3—	B	95–111	Isopropyl ether—Skellysolve B.	
79	CH_3—	4-HOC_6H_4—	H	C	123–127	Ether—Skellysolve B	
80	H	4-$C_6H_5CH_2OC_6H_4$—	4-ClC_4H_6—	B	135–136	Ethyl acetate—Skellysolve B.	
81	H	3,4-$[(CH_3)_2CO_2]C_6H_3$—	CH_3—	B	106–108		
82	CH_3—	3,4-$[(CH_3)_2CO_2]C_6H_3$—	H	D		(Purified by paper chromatography)	

[a] Diastereo isomer of compound of Example 50.
[b] Diastereo isomer of compound of Example 20.
[c] Cyclohexyl.
[d] 3,4-methylene dioxyphenyl.
[e] 3-cyclohexenyl.

noted. Essentially these processes were as follows for the several compounds:

PROCEDURE A (GENERAL)

A solution of 0.1 mole of a 1-carbalkoxy-3-pyrrolidinone in 50 ml. of anhydrous ether was added dropwise to 100 ml. of an ethereal solution of 0.15 mole of a Grignard reagent. After the addition was completed, the reaction mixture was refluxed for two to four hours. The mixture was cooled to room temperature and poured into 400 g. of ice containing 20 g. of ammonium chloride. The ether layer was separated. The aqueous layer was extracted with ether. The combined ethereal solutions were dried over anhydrous magnesium sulfate. The ether was removed by distillation. The residue was either fractionated under reduced pressure or recrystallized from a suitable solvent.

PROCEDURE B (GENERAL)

A solution of 0.1 mole of a 1-carbalkoxy-3-pyrrolidinone in 50 ml. of tetrahydrofuran was added dropwise to 100 ml. of a solution of 0.15 mole of a Grignard reagent in tetrahydrofuran. After the addition was completed, the mixture was refluxed for an additional two hours, cooled in an ice bath afterwards and treated dropwise with 50 ml. of a saturated aqueous ammonium chloride solution. The mixture was stirred for 15 minutes and the tetrahydrofuran solution was decanted. The aqueous mixture was stirred with several portions of tetrahydrofuran. The combined organic solutions were dried over anhydrous magnesium sulfate. The solvent was removed by distillation. The residue was recrystallized from a suitable solvent.

PROCEDURE C

1-Carbethoxy-3-(4-Hydroxyphenyl)-2-Methyl-3-Pyrrolidinol

A mixture of 9.0 g. (0.025 mole) of 3-(4-benzyloxyphenyl)-1-carbethoxy-2-methyl-3-pyrrolidinol, 5 ml. of glacial acetic acid, 250 ml. of absolute ethanol and 0.5 g. of 10% palladium-on-carbon was hydrogenated at 60 lbs. pressure and at room temperature until the calculated amount of hydrogen had been absorbed. The mixture was filtered and the filtrate was evaporated at reduced pressure. The residue was dissolved in 200 ml. of ether and washed with a saturated sodium bicarbonate solution to remove the acetic acid. The ethereal solution was then extracted with a 10% aqueous sodium hydroxide solution. The sodium hydroxide extract was washed with ether, cooled and acidified with 10% hydrochloric acid. The precipitated oily solid was dissolved in ether and the ethereal solution was dried over anhydrous magnesium sulfate, filtered and the ether removed at reduced pressure. The residue was mixed with 35 ml. of isopropyl ether, cooled and filtered; 5.0 g. (75%); M.P. 127–132°. After two recrystallizations from an ether-Skelly B mixture, the material melted at 123–127°.

PROCEDURE D

1-Carbethoxy-3-[4-(4-Chlorobenzyloxy)Phenyl]-2-Methyl-3-Pyrrolidinol

A mixture of 4.4 g. (0.027 mole) of 4-chlorobenzyl chloride, 7.3 g. (0.027 mole) of 1-carbethoxy-3-(4-hydroxyphenyl)-2-methyl-3-pyrrolidinol, 3.75 g. (0.027 mole of anhydrous potassium carbonate and 10 ml. of acetone was stirred and refluxed for five hours. The mixture was allowed to stand overnight. The reaction mixture was transferred to a separatory funnel and 200 ml. of water and 200 ml. of ether were added. The ethereal layer was separated and washed with 50 ml. of 10% aqueous sodium hydroxide solution and then with water. The ethereal solution was filtered yielding 3.0 g. of white solid; M.P. 144–145.5°. The filtrate was dried over anhydrous magnesium sulfate, filtered and the ether was removed at reduced pressure. The residue was triturated with 25 ml. of cold ether and filtered; 4.5 g. M.P. 142–144°. Two recrystallizations from isopropyl alcohol yielded a sample melting at 144–146°.

As heretofore noted, the compounds of this invention have utility as intermediates in the preparation of certain 3-aryl-3-pyrrolidinols. Thus the compounds of this invention may be subject to hydrolysis to remove the acyl or carbalkoxy group attached to the nitrogen group in the 1 position and substitute a hydrogen on the nitrogen atom. As pointed out in Serial Nos. 792,712 and 2571, previously referred to, the hydrolysis may be readily effected in the presence of a base in aqueous or alcoholic solution. An example of such a process is as follows:

2-Methyl-3-Phenyl-3-Pyrrolidinol Hydrochloride

A mixture of 1-carbethoxy-2-methyl-3-phenyl-3-pyrrolidinol (3 g., 0.013 mole) and 25 ml. of 20% barium hydroxide solution was refluxed with stirring for thirty hours. The mixture was filtered and the solid washed with chloroform. The filtrate and the chloroform washings were mixed and thoroughly shaken. The chloroform layer was separated, dried with anhydrous magnesium sulfate and concentrated. The oily residue was distilled to collect 2.2 g. of a fraction with B.P. 140–160° (0.25 mm.) as a thick oil. Treating this oil in ethanol with anhydrous hydrogen chloride and diluting with anhydrous ether yielded 1.2 g. (52.2%) of 2-methyl-3-phenyl-3-pyrrolidinol hydrochloride, M.P. 195–197°.

Alternatively the compounds of this invention may be reduced by treatment with an alkali metal aluminum hydride to reduce the 1-acyl or 1-carbalkoxy group whereby to produce the corresponding 3-aryl-3-pyrrolidinol having a lower alkyl group attached to the nitrogen atom. An example of such a process is as follows:

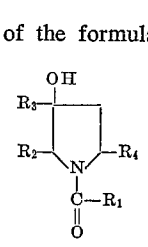
3-Benzyl-1,2-Dimethyl-3-Pyrrolidinol

To a slurry of 4.18 g. (0.11 mole) of lithium aluminum hydride in 75 ml. of tetrahydrofuran was added slowly (ca. one hour) a solution of 3-benzyl-1-carbethoxy-2-methyl-3-pyrrolidinol (13.9 g., 0.05 mole) in 75 ml. of tetrahydrofuran. After refluxing for four hours, the mixture was cooled and treated dropwise with efficient stirring with 6 ml. of water. The solid was filtered off and extracted with hot ethanol. The filtrate and the ethanol extract were mixed. Removal of the solvents yielded a light-colored solid. It was dissolved in isopropyl ether and decolorized with active carbon. On standing at 0°, 6.14 g. (59.7%) of 3-benzyl-1,2-dimethyl-3-pyrrolidinol crystallized in needles; M.P. 85–90°. The hydrochloride was prepared from the ethanol solution in 71.2% yield, M.P. 161–163°.

While several particular embodiments of this invention are shown above, it will be understood, of course, that the invention is not to be limited thereto, since many modifications may be made, and it is contemplated, therefore, by the appended claims to cover any such modifications as fall within the true spirit and scope of this invention.

We claim:

1. A pyrrolidinol of the formula



wherein R_1 is selected from the group consisting of lower alkyl and lower alkoxy; wherein R_2 is selected from the group consisting of hydrogen and lower alkyl; wherein R_3 is selected from the group consisting of phenyl, diphenyl, halophenyl, di halophenyl, hydroxyphenyl, lower alkyl phenyl, di lower alkyl phenyl, lower alkoxy phenyl, phenoxyphenyl, benzyloxyphenyl, halo lower alkylphenyl,

halobenzyl oxyphenyl, di lower alkyl methylene dioxyphenyl, lower alkyl thiophenyl, benzyl, halobenzyl and thienyl, and wherein R_4 is selected from the group consisting of hydrogen, lower alkyl, phenyl, halophenyl, lower alkoxyphenyl, methylene dioxyphenyl, cyclohexyl and cyclohexenyl.

2. The pyrrolidinol recited in claim 1 wherein R_1 and R_2 are lower alkyl, R_3 is phenyl and R_4 is hydrogen.

3. 1-carbethoxy-2-methyl-3-phenyl-3-pyrrolidinol.

4. The pyrrolidinol recited in claim 1 wherein R_1 is lower alkoxy, R_2 is lower alkyl, R_3 is phenyl and R_4 is hydrogen.

5. The pyrrolidinol recited in claim 1 wherein R_1 is lower alkoxy, R_2 is hydrogen, R_3 is halo phenyl and R_4 is phenyl.

6. The pyrrolidinol recited in claim 1 wherein R_1 is lower alkoxy, R_2 is hydrogen, R_3 is phenyl and R_4 is halo phenyl.

7. The pyrrolidinol recited in claim 1, wherein R_1 is lower alkoxy, R_2 is hydrogen, R_3 is dihalo phenyl and R_4 is phenyl.

8. The pyrrolidinol recited in claim 1, wherein R_1 is lower alkoxy, R_2 is hydrogen, R_3 is halo phenyl and R_4 is methyl.

9. The pyrrolidinol recited in claim 1, wherein R_1 is lower alkoxy, R_2 is hydrogen, R_3 is halophenyl and R_4 is cyclohexenyl.

10. 1-carbethoxy - 3 - (4-chlorophenyl)-5-(3,4-methylenedioxyphenyl)-3-pyrrolidinol.

11. 1-carbethoxy-3-(4 - chlorophenyl)-5-(3 - cyclohexenyl)-3-pyrrolidinol.

12. 1-carbethoxy-3-(4 - chlorophenyl)-5-methyl-3-pyrrolidinol.

13. 1-carbethoxy-3-(3,4 - dichlorophenyl)-5-phenyl-3-pyrrolidinol.

14. 1-carbethoxy-3-(4 - benzyloxyphenyl)-5-methyl-3-pyrrolidinol.

References Cited in the file of this patent

Kuhn et al.: "Angewandte Chemie," volume 69, page 60 (1957).