

4-*n*-Butoxy-3-methoxy- α -methylphenethylamine.—A solution of 12.6 g. (0.05 mole) of 4-*n*-butoxy-3-methoxyphenylacetone oxime in 150 cc. of glacial acetic acid was shaken with 0.25 g. of platinum oxide under 20 lb. pressure of hydrogen until reduction was complete. The mixture was filtered, the solvent was removed from the filtrate under vacuum, and the residue was treated with 100 ml. of 2 *N* hydrochloric acid. The acidic solution was washed with ether and made basic with 25% sodium hydroxide. The liberated amine was extracted with ether and distilled.

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77. Found: C, 70.74; H, 9.98.

Amides. By the Use of Acid Anhydrides.—The amine was dissolved in ten volumes of dry ether and treated with an equal weight of acetic, propionic or butyric anhydride. In most cases the crystalline amide soon precipitated. If it did not, the ether was removed and the residual oil was stirred with aqueous sodium hydroxide until the amide solidified, after which it was collected by filtration and washed with water.

By the Schotten-Baumann Reaction.—The amide was prepared from the amine and isobutyryl chloride or isovaleryl chloride in the usual manner, and was crystallized from aqueous alcohol.

***N*-Formyl- α -methyl-4-benzyloxy-3-methoxyphenethylamine.**—A mixture of 5 g. (0.02 mole) of 4-benzyloxy-3-methoxy- α -methylphenethylamine and 5 ml. of 100% formic acid was heated at 100° for 45 minutes. The resulting brown oil was poured into dry ether whereupon a solid formed which proved to be the formate salt of the amine. A sample after crystallization from alcohol and ether melted at 151°.

Anal. Calcd. for $C_{17}H_{21}NO_2 \cdot HCOOH$: C, 68.12; H, 7.30. Found: C, 68.29; H, 7.22.

This material was dissolved in 50 ml. of formic acid, and the mixture was allowed to reflux for 30 minutes in an oil-

bath at 165°. Then 25 ml. of distillate was removed and replaced by an equal volume of formic acid. The solution was heated for two more hours and was then concentrated under vacuum. The oily residue was treated with water and the mixture was shaken with ether. Evaporation of the dried ethereal extract gave a brown oil which partially dissolved in hot Skellysolve C. In the cooled decantate there separated crystals, m.p. 129–132°, and an oil which slowly crystallized. The total amount of solid thus obtained was small; therefore it was subjected to ring-closure without further purification.

***N*-Acetyl- α -methyl-4-*n*-butoxy-3-methoxyphenethylamine.**—The method applied to allylbenzene by Ritter and Kalish⁹ was followed using *O*-*n*-butyleugenol. The product did not solidify when the reaction mixture was made alkaline and was therefore extracted with ether. When the extract was evaporated a mixture of oil and crystals remained which was converted to the isoquinoline without further purification. The yield of amide was about 50%.

3,4-Dihydroisoquinolines.—A solution of 2 g. of amide in 15 ml. of dry chloroform was added dropwise with stirring to a solution of 4 g. of phosphorus pentachloride in 50 cc. of chloroform. The reaction flask was heated in an oil-bath at 48–50° during the addition and for one hour longer. The solvent was then removed under vacuum and the residual yellow solid was treated with 50 ml. of water. After the mixture had been warmed on a steam-bath for 30 minutes it was cooled and shaken with ether. The aqueous layer was made strongly basic with sodium hydroxide whereupon the dihydroisoquinoline separated. It was extracted with ether and the extract was dried over potassium hydroxide pellets. The product was obtained by evaporation, and, if solid, was recrystallized from Skellysolve B. The hydrochloride salts were prepared in ether, and were crystallized from a mixture of *n*-propanol and ether.

NORTH CHICAGO, ILL.

RECEIVED JUNE 4, 1951

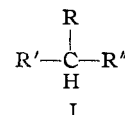
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

Histamine Antagonists. γ,γ -Disubstituted *N,N*-Dialkylpropylamines¹

BY NATHAN SPERBER, DOMENICK PAPA, ERWIN SCHWENK, MARGARET SHERLOCK AND ROSEMARIE FRICANO

A series of substituted dialkylaminoalkanes have been synthesized by various methods and tested as histamine antagonists. Two compounds, γ -phenyl- γ -(2-pyridyl)-*N,N*-dimethylpropylamine and γ -(*p*-chlorophenyl)- γ -(2-pyridyl)-*N,N*-dimethylpropylamine, have been found to be effective clinically. In general the most active compounds were derivatives of *N,N*-dimethylpropylamine, having a 2-pyridyl and a phenyl, para-substituted phenyl or heterocyclic group in the gamma position.

Following the preliminary clinical success of β -dimethylaminoethyl benzhydryl ether² and *N'*-benzyl-*N'*-(2-pyridyl)-*N,N*-dimethylethylenediamine³ as histamine antagonists, we undertook an extensive chemical program⁴ to establish whether antihistaminic activity was limited to compounds derived from ethanolamine and ethylenediamine.⁵ As part of our study, a new series of substituted dialkylaminoalkanes of general formula I, wherein



R is alkyl, cycloalkyl, aralkyl, heterocyclic, R' is heterocyclic, R'' is dialkylaminoalkyl or *N*-piperidinoalkyl were synthesized and a number of these compounds were found to be potent histamine antagonists.

One of the general methods for the synthesis of substituted dialkylaminoalkanes involved the preparation and conversion of tertiary nitriles V to I. When phenylacetone nitrile (II, R = phenyl) was alkylated with a dialkylaminoalkyl chloride and sodamide in toluene, the desired α -(β -dialkylaminoalkyl)-phenylacetone nitrile III was obtained in good yield⁶ (Method A). Upon further alkylation of III with 2-chloro- or 2-bromopyridine and sodamide in toluene, α -phenyl- α -(β -dialkylaminoalkyl)-2-pyridylacetone nitrile (V) was obtained. The synthesis

(1) Presented in abstract before the Division of Medicinal Chemistry at the Chicago Meeting of the American Chemical Society, April 21, 1948.

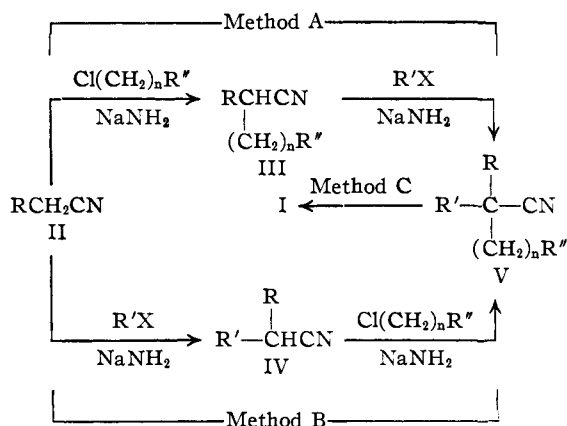
(2) E. R. Loew, M. E. Kaiser and V. Moore, *J. Pharmacol. Exptl. Therap.*, **83**, 120 (1945); E. R. Loew and M. E. Kaiser, *Proc. Soc. Exptl. Biol. and Med.*, **58**, 235 (1945); G. Rieveschl, Jr., U. S. Patent 2,421,714, June 3, 1947.

(3) C. P. Hutterer, C. Djerassi, W. L. Beears, R. L. Mayer and C. R. Scholz, *THIS JOURNAL*, **68**, 1999 (1946).

(4) N. Sperber and D. Papa, *ibid.*, **71**, 886 (1949); N. Sperber, D. Papa, E. Schwenk and M. Sherlock, *ibid.*, **71**, 887 (1949); D. Papa, N. Sperber and M. Sherlock, *ibid.*, **73**, 1279 (1951).

(5) Excellent discussions of histamine antagonists may be found in the reviews of C. P. Hutterer, *Enzymologia*, **13**, 277 (1948); *Experientia*, **5**, 53 (1949); F. Leonard and C. P. Hutterer, CBCC Review No. 3, National Research Council (1950) and B. Idson, *Chem. Revs.*, **47**, 307 (1950).

(6) O. Eisleb, *Ber.*, **74**, 1433 (1941); C. E. Kwartler and P. Lucas, *THIS JOURNAL*, **68**, 2395 (1946).



of V could also be effected by the reverse route (Method B), where α -phenyl-2-pyridylacetonitrile (IV) (prepared by the reaction of phenylacetonitrile with 2-chloro- or bromopyridine and two moles of sodamide⁷) could be further alkylated with a dialkylaminoalkyl halide and sodamide.

The conversion of V to I (Method C) was effected either by the hydrolysis of the nitrile to the corresponding acid with subsequent decarboxylation⁸ or by the direct removal of the nitrile group. In general, the nitrile was heated for several hours with three to five volumes of 70–80% sulfuric acid at 130–150° until the evolution of carbon dioxide ceased. Although this method was applicable to a large number of nitriles, it failed in the cases of α -(*p*-methoxyphenyl)- α -(β -dimethylaminoethyl)-2-pyridylacetonitrile and α -(α -naphthyl)- α -(β -dimethylaminoethyl)-2-pyridylacetonitrile. The decarboxylation products from these nitriles were soluble in sodium hydroxide solution and it was assumed that sulfonation had occurred. α -Benzyl- α -(β -dimethylaminoethyl)-2-pyridylacetonitrile was decarboxylated only at elevated temperatures. From a study of the hydrolysis and decarboxylation of a variety of nitriles, it was concluded that the best results were obtained when a heterocyclic group (such as 2- or 4-pyridyl, 2-thiazolyl or 2-pyrimidyl) and an aryl or heterocyclic group were attached directly to the carbon atom alpha to the nitrile group. An alternative method for effecting the conversion of V to I involved the elimination of the CN group by refluxing the nitrile with sodamide in toluene or xylene.⁹

In an attempt to prepare 4-phenyl-4-(2-pyridyl)-6-dimethylaminohexanone-3 by the reaction of ethylmagnesium bromide or ethyllithium and α -phenyl- α -(β -dimethylaminoethyl)-2-pyridyl-

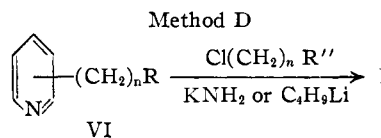
(7) L. Panizzon (*Helv. Chim. Acta*, **27**, 1748 (1944)) found that two moles of sodamide were necessary to obtain good yields of α -phenyl-2-pyridylacetonitrile. In a recent paper, R. A. Cutler, A. R. Surrey and J. B. Cloke (*THIS JOURNAL*, **71**, 3375 (1949)) reported on the preparation of substituted α -(4-quinolyl)-phenylacetonitriles by the alkylation of phenylacetonitrile with two moles of sodamide and 4,7-dichloroquinoline. Apparently the latter authors have overlooked the important paper of Panizzon, who carried out a number of similar reactions in the pyridine series.

(8) According to the procedure of L. Panizzon (ref. 7) for the conversion of α -phenyl-2-pyridylacetonitrile to 2-benzylpyridine.

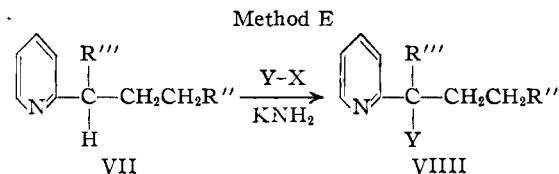
(9) Report No. 116, Item No. 24, British Intelligence Objective Subcommittee, August, 1945, page 50, describes the elimination of CN by sodamide from α -(β -N-piperidinoethyl)-diphenylacetonitrile.

acetonitrile,¹⁰ anomalous results were observed. The desired ketone could not be isolated and only γ -phenyl- γ -(2-pyridyl)- N,N -dimethylpropylamine and unreacted nitrile were obtained.

The alkylation of substituted 2-benzylpyridines¹¹ and α - and γ -picolines VI with potassium amide and dialkylaminoalkyl halides in liquid ammonia¹² (Method D) provided another alternate synthesis of I. The same reaction could be effected by sub-



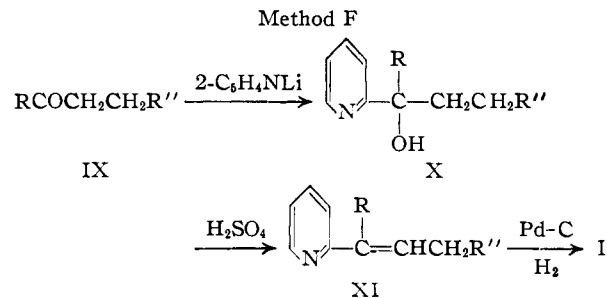
stituting butyllithium in ether for potassium amide in liquid ammonia, but the yields were lower and the products less pure than those obtained with potassium amide. Similarly, several compounds in this series have been prepared by the alkylation of γ -(2-pyridyl)- N,N -dimethylpropylamine (VII, $R'' = \text{dimethylamino}$, $R''' = H$) with certain alkyl, cycloalkyl and heterocyclic halides and potassium amide in liquid ammonia (Method E).



$R''' = H$ or R (of formula I); $Y = \text{alkyl, cycloalkyl or heterocyclic}$; $X = \text{chlorine or bromine}$

This method proved to be suitable for the preparation of γ -(2-pyridyl)- γ -(2-thiazolyl)- N,N -dimethylpropylamine (VIII, $R'' = \text{dimethylamino}$, $R''' = \text{hydrogen}$ and $Y = 2\text{-thiazolyl}$), although it failed when $Y-X$ was either 2-chlorothiophene or 2-chloropyrimidine. γ -Phenyl- γ -(2-pyridyl)- N,N -dimethylpropylamine was alkylated with ethyl bromide and potassium amide in liquid ammonia to yield γ -phenyl- γ -(2-pyridyl)- N,N -dimethylpropylamine (VIII, $R'' = \text{dimethylamino}$, $R''' = \text{phenyl}$ and $Y = \text{ethyl}$).

Another procedure for the preparation of examples of I employed the series of reactions



(10) α -Phenyl-2-pyridylacetonitrile (ref. 7) and 2,2-diphenyl-4-dimethylaminopentanenitrile (E. M. Schultz, C. M. Robb and J. M. Sprague, *THIS JOURNAL*, **69**, 2454 (1947); Office of the Publication Board, Department of Commerce, Report No. PB891, page 96-A) have been converted to the corresponding ketones with ethylmagnesium bromide.

(11) See N. Sperber, D. Papa, E. Schwenk and M. Sherlock, *THIS JOURNAL*, **73**, 3856 (1951), for the preparation of nuclear substituted 2-benzyl pyridines.

(12) Based on the procedure of F. W. Bergstrom, T. R. Norton and R. A. Seibert, *J. Org. Chem.*, **10**, 452 (1945).

When the Mannich base, β -dimethylamino-propionophenone IX ($R = \text{phenyl}$, $R'' = \text{dimethylamino}$), was treated with 2-pyridyllithium, there was obtained 1-phenyl-1-(2-pyridyl)-3-dimethylaminopropanol-1 (X). The dehydration of X with sulfuric acid yielded 1-phenyl-1-(2-pyridyl)-3-dimethylaminopropene-1 (XI); hydrogenation with palladium-on-charcoal in acetic acid gave I.¹³

Several attempts to prepare certain tertiary nitriles by the alkylation of ω -dialkylaminoalkane nitriles with heterocyclic and aralkyl halides produced anomalous results. When β -dimethylaminopropionitrile was alkylated with one mole of 2-bromopyridine and one mole of sodamide, the corresponding 2-pyridyl derivative was not obtained and a 7% yield of bis-(2-pyridyl)-acetonitrile¹¹ was isolated from the tarry reaction products. The formation of this compound may be explained by the initial alkylation of β -dimethylaminopropionitrile with two moles of 2-bromopyridine, followed by a cleavage of the dimethylaminomethyl group. The alkylation of β -dimethylaminopropionitrile with one mole of benzyl chloride and sodamide proceeded in a normal manner to yield α -dimethylaminomethyl- β -phenylpropionitrile; further alkylation with 2-bromopyridine and sodamide gave the desired α -dimethylaminomethyl- α -benzyl-2-pyridylacetonitrile. The latter could not be hydrolyzed and decarboxylated with sulfuric acid. Another anomalous alkylation product resulted when γ -dimethylaminobutyronitrile was alkylated with one mole of 2-bromopyridine and sodamide. Instead of the expected α -(2-pyridyl)- γ -dimethylaminobutyronitrile, there was obtained a 17% yield of γ -bis-(2-pyridyl)- N,N -dimethylpropylamine. The latter was formed, apparently, by the removal of the nitrile group from bis- α,α -(2-pyridyl)- γ -dimethylaminobutyronitrile by sodium amide. When γ - N,N -dimethylaminobutyronitrile was alkylated with 2-chlorothiazole and sodamide, bis- α,α -(2-thiazolyl)- γ - N,N -dimethylaminobutyronitrile was obtained in low yield.

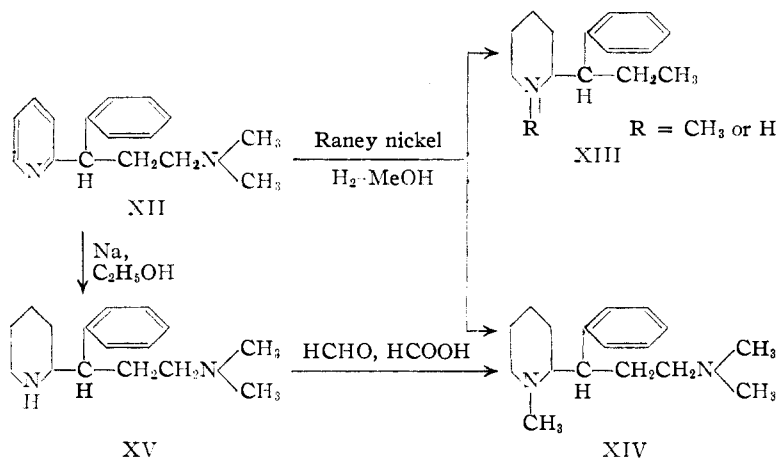
To evaluate the contribution of the 2-pyridyl group to the antihistaminic activity of γ -phenyl- γ -(2-pyridyl)- N,N -dimethylpropylamine (XII), the latter was hydrogenated with Raney nickel in methanol and separated into two fractions by distillation. The analysis of the lower boiling fraction XIII indicated hydrogenolysis of the dimethylamino group¹⁴ and reduction of the pyridine ring. From the analytical data, it was not possible to establish whether or not the ring nitrogen had been alkylated during the reduction. The higher boiling fraction analyzed for either γ -phenyl- γ -(N -methyl-2-piperidyl)- N,N -dimethylpropylamine (XIV) or γ -phenyl- γ -(2-piperidyl)- N,N -dimethyl

(13) After this work had been completed, D. W. Adamson and J. W. Billingham, *J. Chem. Soc.*, 1039 (1950), reported the preparation of several γ -aryl- γ -(2-pyridyl)- N,N -dialkylaminopropanes by the same series of transformations.

(14) H. Adkins, "Reactions of Hydrogen," University of Wisconsin Press, 1937, p. 119, discusses the stabilizing influence of double bonds in the β - and γ -positions upon carbon to nitrogen linkages.

propylamine (XV). The problem was resolved by reducing XII with sodium and alcohol to XV and converting the latter to XIV with formic acid and formaldehyde. The picrate of XIV obtained by the Raney nickel-hydrogen-methanol procedure did not depress the melting point of the picrate of XIV (obtained by the sodium and alcohol reduction of XII followed by methylation with formic acid and formaldehyde). The picrate of XV, however, depressed the picrate of XIV obtained by the direct route XII to XIV.¹⁵

The compounds in Table II have been tested as histamine antagonists in guinea pigs by intravenous injection of lethal doses of histamine dihydrochloride one-half to one hour after the oral or subcutaneous administration of the test drug.¹⁶ In general, the most active compounds of formula I are those wherein R is phenyl (No. 1), para-substituted phenyl (No. 6, 7, 8, 11 and 14) or heterocyclic (No. 28, 29, 30 and 33), R' is 2-pyridyl, R'' is dimethylaminoethyl. γ -*p*-Chlorophenyl- γ -(2-pyridyl)- N,N -dimethylpropylamine (No. 11), the most active compound in the series, illustrates the marked increase in activity without increase in toxicity which results from *p*-chloro substitution of the phenyl ring of compound No. 1.^{16b} A de-



tailed pharmacological report will appear elsewhere.

Experimental¹⁷

Intermediates (1) Nitriles.—The requisite substituted acetonitriles were obtained either from commercial sources or were synthesized by standard procedures; *o*- and *p*-chlorophenylacetonitriles and *p*-methoxyphenylacetonitrile¹⁸ were obtained from the corresponding benzyl chlorides and potassium cyanide¹⁹; 2-thienylacetonitrile²⁰ from 2-thienylmethyl chloride and sodium cyanide.

3-Pyridylacetonitrile (a).—A mixture of 25 g. of 3-pyridylacetamide²¹ and 31 g. of phosphorus pentoxide was heated

(15) N. Sperber, D. Papa and E. Schwenk, *THIS JOURNAL*, **72**, 2012 (1950), obtained similar results with a different series of pyridine compounds.

(16) (a) A. La Belle and R. Tislow, *Federation Proc.*, **7**, 236 (1948); (b) R. Tislow, A. La Belle, A. J. Makovsky, M. A. Reed, M. D. Cunningham, J. F. Emele, A. Grandage and R. J. M. Roggenhofer, *ibid.*, **8**, 338 (1949); (c) R. Tislow, S. Margolin, M. T. Spoerlein and E. Volage, *ibid.*, **9**, 320 (1950).

(17) All melting points are corrected.

(18) R. L. Shriner and C. J. Hull, *J. Org. Chem.*, **10**, 228 (1945).

(19) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 107.

(20) F. F. Blicke and F. Leonard, *THIS JOURNAL*, **68**, 1934 (1946).

(21) M. Hartmann and W. Bosshard, *Helv. Chim. Acta*, **24**, 28E (1941).

to 360° at 15–20 mm. and the oil which distilled over at 145–210° was redistilled; yield 9 g. (42%) of a colorless oil, b.p. 101–109° (1.5 mm.), n_D^{20} 1.5216, lit. 107–108° (0.5 mm.).²²

Anal. Calcd. for $C_7H_8N_2$: N, 23.72. Found: N, 23.52.

(b).—A mixture of 45 g. of 3-pyridylacetamide, 30 g. of sodium chloride and 300 ml. of dry ethylene dichloride was stirred for 15 minutes and 26 ml. of phosphorus oxychloride was then added.²⁸ After stirring and refluxing for nine hours, the dark reaction mixture was decomposed with a dilute sodium hydroxide solution. The ethylene dichloride layer was dried, filtered, concentrated to a residue and distilled; yield 26.5 g. (68%), b.p. 92–100° (1 mm.), n_D^{20} 1.5249.

2-Pyridylacetoneitrile was prepared from 2-pyridylacetamide²⁴ as described for 3-pyridylacetoneitrile, yield 71.5%, b.p. 80–85° (0.5 mm.); n_D^{20} 1.5193. *Anal.* Calcd. for $C_7H_8N_2$: N, 23.72. Found: N, 23.93. 2-Pyridylacetamide with phosphorus pentoxide yielded only 12% of 2-pyridylacetoneitrile, b.p. 96–101° (2 mm.); n_D^{20} 1.5201.

(2) **Halogenated Heterocyclics.**—4-Chloropyridine,²⁶ 2-chloropyridine,²⁶ 2-bromopyridine,²⁷ 2-bromo-3-methylpyridine, 2-bromo-6-methylpyridine²⁸ and 2-chlorothiazole²⁹ were prepared by published procedures.

2-Chloropyrimidine.³⁰—To a stirred, cooled (–10°) solution of 19 g. of 2-aminopyrimidine in 100 ml. of concentrated hydrochloric acid, there was added over a period of one hour a solution of 25 g. of sodium nitrite in 40 ml. of water. The reaction mixture was allowed to reach 0° and was then made basic with gaseous ammonia. Upon cooling, a white solid separated; yield 12 g. (52%), m.p. 65–66° after recrystallization from benzene-petroleum ether, lit. m.p. 63.6–64.5°. *Anal.* Calcd. for $C_4H_5N_2Cl$: N, 30.96. Found: N, 30.70.

(3) **Dialkylaminoalkyl Halides.**—The hydrochlorides of β -diethylaminoethyl chloride, β -dimethylaminoethyl chloride, γ -dimethylaminopropyl chloride, 1-dimethylamino-2-chloropropane and β -(N-piperidinoethyl) chloride were secured by the action of thionyl chloride on the requisite amino alcohol.³¹ The crude amine hydrochlorides were placed in a stirred, cooled ether-water mixture and the free base liberated with an excess of 25% sodium hydroxide solution. The ether layer was dried over potassium carbonate, the solvent removed and the residue distilled.

General Procedures.—The di- and trisubstituted acetoneitriles of Table I were synthesized by methods A–C and are illustrated by the following specific examples: The preparation of α -*p*-chlorophenyl- α -(β -dimethylaminoethyl)-2-pyridylacetoneitrile (Table I, No. 24) will illustrate Method A. α -(β -Dimethylaminoethyl)-*p*-chlorophenylacetoneitrile (Table I, No. 2).—*p*-Chlorophenylacetoneitrile was alkylated with β -dimethylaminoethyl chloride as described for phenylacetoneitrile⁶ with the following modifications. Upon completion of the alkylation,³² the basic nitrile was separated from the toluene and the unreacted *p*-chlorophenylacetoneitrile by extraction with a 15% hydrochloric acid solution. The aqueous acid extracts were made basic with ammonia, the oil which separated was extracted with ether, the ether

extracts dried over sodium sulfate, and after removing the solvent, the residual oil was distilled *in vacuo*.

To a stirred, refluxing solution of 56 g. (0.25 mole) of α -(β -dimethylaminoethyl)-*p*-chlorophenylacetoneitrile and 41 g. (0.26 mole) of 2-bromopyridine in 300 ml. of toluene was added slowly a stirred suspension of sodamide (6.5 g. of sodium) in 100 ml. of toluene. A vigorous reaction ensued and the addition of the sodamide suspension was controlled to give a rapid rate of reflux. After refluxing and stirring for an additional four hours, the reaction mixture was cooled and decomposed with water. The toluene layer was separated and the aqueous layer extracted with benzene. The combined toluene-benzene solution was washed with water, the solvents removed *in vacuo* and the residue distilled.

The preparation of α -phenyl- α -(β -dimethylaminoethyl)-2-pyridylacetoneitrile (Table I, No. 15) will illustrate Method B. α -Phenyl-2-pyridylacetoneitrile was obtained by the alkylation of phenylacetoneitrile with 2-chloro- or 2-bromopyridine and two moles of freshly prepared sodamide.⁷ The tertiary nitrile, α -phenyl- α -(β -dimethylaminoethyl)-2-pyridylacetoneitrile was obtained as follows: To a solution of 87.6 g. (0.45 mole) of α -phenyl-2-pyridylacetoneitrile and 69 g. (0.64 mole) of β -dimethylaminoethyl chloride in 300 ml. of toluene, there was added slowly a stirred suspension of sodamide (11.3 g. of sodium) in 300 ml. of toluene. The dark brown reaction mixture was refluxed for two hours, cooled, and decomposed with water. The toluene layer was washed with water, dried, the solvent removed and the residue distilled *in vacuo*. In experiments where considerable amounts of tar were present, the toluene layer was extracted several times with a 15% hydrochloric acid solution and the aqueous acid extracts made basic with ammonia gas. The liberated oil was extracted with ether or benzene and the nitrile isolated as in Method A.

Removal of the CN Group. V. → I. (Method C) (1) Sulfuric Acid.³³—The conversion of α -phenyl- α -(β -dimethylaminoethyl)-2-pyridylacetoneitrile to γ -phenyl- γ -(2-pyridyl)-N,N-dimethylpropylamine (Table II, No. 1) will illustrate the general method. In a 1-l., three-necked flask, fitted with a stirrer, thermometer, dropping funnel and a condenser containing an outlet tube leading to a barium hydroxide solution, was placed 400 g. of a cooled 75% sulfuric acid solution and 100 g. (0.377 mole) of α -phenyl- α -(β -dimethylaminoethyl)-2-pyridylacetoneitrile was added slowly with stirring. After heating and stirring the solution at 130–140° for approximately one hour, the evolution of carbon dioxide started and heating was continued until no more carbon dioxide was evolved (six to ten hours). The reaction mixture was poured on ice, made basic with ammonia and the liberated oil extracted with ether. The combined ether extracts were washed with water, dried over sodium sulfate, the solvent removed and the residue distilled *in vacuo*.

(2) **Sodamide γ -(α -Naphthyl)- γ -(2-pyridyl)-N,N-dimethylpropylamine (Table II, No. 19).**—To a cold suspension of freshly prepared sodamide (4.6 g. of sodium) in 75 ml. of xylene, there was added 31.5 g. (0.1 mole) of α -(α -naphthyl)- α -(β -dimethylaminoethyl)-2-pyridylacetoneitrile in 100 ml. of xylene. The mixture was refluxed and stirred for 28 hours, cooled, decomposed with water, the xylene layer separated, the solvent removed *in vacuo* and the residue fractionated. When this method was applied to α -phenyl, α -(β -dimethylaminoethyl)-2-pyridylacetoneitrile, γ -phenyl, γ -(2-pyridyl)-N,N-dimethylpropylamine was obtained in a yield of 60%.

(3) **Ethyllithium.**—To a solution of ethyllithium³⁴ (from 31 g. (0.28 mole) of ethyl bromide and 4.14 g. (0.6 mole) of lithium shot) in 100 ml. of ether, cooled to –25°, there was added dropwise 26.5 g. (0.1 mole) of α -phenyl- α -(β -dimethylaminoethyl)-2-pyridylacetoneitrile. The deep red reaction mixture was stirred at room temperature for four hours and then decomposed with ice and dilute hydrochloric acid. The acid layer was separated, made alkaline with ammonia gas and the liberated oil extracted with ether. The ether extracts were dried, the solvent removed and the residue fractionated *in vacuo*; yield 15 g. (63%), b.p. 152–156° (5 mm.), n_D^{20} 1.5463.

(33) This procedure is based on the method described by L. Pannizon for the preparation of 2-benzylpyridine from α -phenyl-2-pyridylacetoneitrile (ref. 7).

(34) H. Gitman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller. *THIS JOURNAL*, **71**, 1499 (1949).

(22) Compare A. Burger and C. R. Walter, Jr., *THIS JOURNAL*, **72**, 1988 (1950).

(23) Compare "Organic Syntheses," Vol. 25, John Wiley and Sons, Inc., New York, N. Y., 1945, p. 63.

(24) D. B. Pattison and M. Carmack, *THIS JOURNAL*, **68**, 2033 (1946).

(25) J. P. Wibaut and F. W. Broekman, *Rec. trav. chim.*, **58**, 885 (1939); E. Koenigs, M. Miels and H. Gurlt, *Ber.*, **57**, 1179 (1924).

(26) W. Marckwald, *ibid.*, **27**, 1317 (1894); A. E. Chichibabin and M. D. Rjazancev, *J. Russ. Phys. Chem. Soc.*, **46**, 1571 (1915); *C. A.*, **10**, 2898 (1916).

(27) L. C. Craig, *THIS JOURNAL*, **56**, 231 (1934).

(28) R. P. Mariella and V. Kvinge, *ibid.*, **70**, 3126 (1948).


(29) J. McLean and G. D. Muir, *J. Chem. Soc.*, 383 (1942); K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 362 (1945); *C. A.*, **40**, 4059 (1946).

(30) After this work had been completed, K. L. Howard, U. S. Patent 2,477,409 (July 26, 1949), described essentially the same reaction.

(31) K. H. Slotta and R. Behnisch, *Ber.*, **68**, 754 (1935); F. F. Blicke and C. E. Maxwell, *THIS JOURNAL*, **64**, 428 (1942).

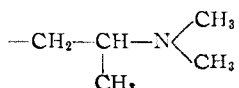
(32) A suspension of freshly prepared sodamide in toluene (M. T. Leffler, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 99) was superior to the commercial product.

TABLE I

NITRILES OF THE FORMULA $R'-\overset{\overset{R}{ }}{\underset{\underset{R''}{ }}{C}}-CN$				Method	Yield, %	B.p., °C.	Mm.	Formula	Nitrogen, %	
No.	R	R'	R''						Calcd.	Found
1	<i>o</i> -ClC ₆ H ₄	H	CH ₂ CH ₂ N(CH ₃) ₂	A	58	140-142	2.0	C ₁₂ H ₁₅ N ₂ Cl	12.59	12.35
2	<i>p</i> -ClC ₆ H ₄	H	CH ₂ CH ₂ N(CH ₃) ₂	A	66	139-140	2.5	C ₁₂ H ₁₅ N ₂ Cl	12.59	12.29
3	<i>p</i> -CH ₃ C ₆ H ₄	H	CH ₂ CH ₂ N(CH ₃) ₂	A	79	124-125	3.0	C ₁₂ H ₁₅ N ₂	13.87	13.74
4	C ₆ H ₅ CH ₂	H	CH ₂ N(CH ₃) ₂	B	54	110-115	0.5	C ₁₂ H ₁₆ N ₂ ^a	14.88	15.37
5	C ₆ H ₅ CH ₂	H	CH ₂ CH ₂ N(CH ₃) ₂	A	31	115-120	0.5	C ₁₃ H ₁₈ N ₂	13.87	14.08
6	α -C ₁₀ H ₇	H	CH ₂ CH ₂ N(CH ₃) ₂	A	75	171-173	2.0	C ₁₆ H ₁₈ N ₂	11.76	11.51
7	C ₆ H ₁₁	H	CH ₂ CH ₂ N(CH ₃) ₂	A	59	103-106	0.5	C ₁₂ H ₂₂ N ₂	14.43	14.62
8	2-C ₄ H ₉ S	H	CH ₂ CH ₂ N(CH ₃) ₂	A	42	116-119	3.5	C ₁₀ H ₁₄ N ₂ S	14.42	14.33
9	2-C ₄ H ₉ SCH ₂	H	CH ₂ N(CH ₃) ₂	B	31	110-115	0.5	C ₁₀ H ₁₄ N ₂ S ^b	14.42	14.45
10	2-C ₆ H ₄ N	H	CH ₂ CH ₂ N(CH ₃) ₂	B	48	108-112	0.5	C ₁₁ H ₁₆ N ₃	22.21	21.79
11	3-C ₆ H ₄ N	H	CH ₂ CH ₂ N(CH ₃) ₂	A	40	112-116	1.0	C ₁₁ H ₁₆ N ₃	22.21	21.96
12	<i>o</i> -ClC ₆ H ₄	2-C ₆ H ₄ N	H	B	42	165-170	2.0	C ₁₃ H ₉ N ₂ Cl	12.25	12.35
13	<i>p</i> -ClC ₆ H ₄	2-C ₆ H ₄ N	H	B	73	163-167 ^c	2.5	C ₁₃ H ₉ N ₂ Cl	12.25	12.43
14	C ₆ H ₅	3-CH ₂ -2-C ₆ H ₃ N	H	B	68	162-170 ^d	0.5	C ₁₄ H ₁₂ N ₂	13.45	13.30
15	C ₆ H ₅	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	A	78	162-165	0.5	C ₁₇ H ₁₉ N ₂ ^e	15.85	16.42 ^{f,g}
				(B)	(74)					
16	C ₆ H ₅	2-C ₆ H ₄ N	CH ₂ CH ₂ N(C ₂ H ₅) ₂	B	92	162-164	0.3	C ₁₉ H ₂₃ N ₃	14.34	14.12
17	C ₆ H ₅	2-C ₆ H ₄ N	CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	B	82	168-170	1.0	C ₁₈ H ₂₁ N ₃	15.05	15.10
18	C ₆ H ₅	2-C ₆ H ₄ N	CH ₂ CH(CH ₃)N(CH ₃) ₂ ^h	A	63	179-184	3.5	C ₁₃ H ₂₁ N ₃	15.05	14.48
19	C ₆ H ₅	2-C ₆ H ₄ N	CH(CH ₃)CH ₂ N(CH ₃) ₂ ^h	A	48	159-165	0.5	C ₁₃ H ₂₁ N ₃	15.05	15.10
20	C ₆ H ₅	2-C ₆ H ₄ N	CH ₂ CH ₂ N 	B	89	175-180	1.0	C ₂₀ H ₂₃ N ₃	13.77	13.67
21	<i>p</i> -CH ₃ C ₆ H ₄	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	A	44	172-174	1.0	C ₁₈ H ₂₁ N ₃	15.05	15.75 ^{f,i}
22	<i>p</i> -CH ₃ OC ₆ H ₄	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	A	80	180-185	1.0	C ₁₈ H ₂₁ ON ₃	14.23	14.34
23	<i>o</i> -ClC ₆ H ₄	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	B	33	195-202	2.0	C ₁₇ H ₁₈ N ₃ Cl ^j		
24	<i>p</i> -ClC ₆ H ₄	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	A	67	183-188	3.0	C ₁₇ H ₁₈ N ₃ Cl	14.02	14.30
25	C ₆ H ₅	6-CH ₂ -2-C ₆ H ₃ N	CH ₂ CH ₂ N(CH ₃) ₂	A	74	173-178	2.5	C ₁₈ H ₂₁ N ₃	15.05	14.91
26	C ₆ H ₅	4-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	A	76	166-169	1.0	C ₁₇ H ₁₉ N ₃	15.85	15.49
27	C ₆ H ₅ CH ₂	2-C ₆ H ₄ N	CH ₂ N(CH ₃) ₂	B	46	147-152	0.5	C ₁₇ H ₁₉ N ₃	15.85	15.06 ^f
28	C ₆ H ₅ CH ₂	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	A	41	150-155	0.5	C ₁₈ H ₂₁ N ₃	15.04	15.10
29	α -C ₁₀ H ₇	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	A	76	205-220	1.5	C ₂₁ H ₂₁ N ₃	13.33	13.10
30	C ₆ H ₁₁	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	A	50	158-163	1.5	C ₁₇ H ₂₆ N ₃	15.51	16.22 ^f
31	2-C ₆ H ₄ N	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	B	78	167-173	0.5	C ₁₆ H ₁₈ N ₄ ^k		
32	2-C ₆ H ₄ N	3-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	A	35	172-180	1.0	C ₁₆ H ₁₈ N ₄ ^l		
33	2-C ₄ H ₉ S	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₃) ₂	A	36	150-158	1.0	C ₁₈ H ₁₇ N ₄ S	15.48	15.11
34	C ₆ H ₅	2-C ₄ H ₉ NS	CH ₂ CH ₂ N(CH ₃) ₂	A	83	153-159	1.5	C ₁₈ H ₁₇ N ₄ S	15.48	15.76
35	2-C ₆ H ₄ NS	2-C ₄ H ₉ NS	CH ₂ CH ₂ N(CH ₃) ₂	B	33	162-168	1.0	C ₁₂ H ₁₄ N ₄ S ^m		
36	C ₆ H ₁₁	C ₆ H ₅	CH ₂ CH ₂ N(CH ₃) ₂	A	82	156-160	1.5	C ₁₈ H ₂₈ N ₂ ⁿ		

^a Calcd. C, 76.53; H, 8.56. Found: C, 76.82; H, 8.50. ^b Calcd. C, 61.81; H, 7.26. Found: C, 61.69; H, 6.99. ^c M.p. 68-69° from benzene-petroleum ether. ^d M.p. 119-120° from benzene-petroleum ether. ^e Calcd. C, 76.92; H, 7.22. Found: C, 76.33; H, 7.52. ^f The analytical figures are slightly beyond the acceptable range. In the fractionation of these compounds, small amounts of the secondary nitrile could not be separated. ^g Picrate, m.p. 147-147.5°. *Anal.*

Calcd. for C₂₀H₂₂O₇N₆: N, 17.01. Found: N, 16.96. ^h The dialkylaminoalkyl residue is either $-\text{CH}-\text{CH}_2\text{N} \begin{matrix} \text{CH}_3 \\ | \\ \text{CH}_3 \end{matrix}$ or



or a mixture of both isomers; compare E. M. Schultz, C. M. Robb and J. M. Sprague, THIS JOURNAL,


69, 188 (1947); *ibid.*, 69, 2454 (1947). ⁱ Calcd. C, 77.36; H, 7.57. Found: C, 76.50; H, 7.72. ^j The extremely viscous nitrile was converted directly to the corresponding dialkylaminoalkane (Table II, No. 10). ^k Calcd. C, 72.20; H, 6.82. Found: C, 71.81; H, 6.63. ^l Calcd. C, 72.20; H, 6.82. Found: C, 72.20; H, 6.91. ^m Calcd. C, 51.76; H, 5.07. Found: C, 52.08; H, 5.03. ⁿ Calcd. C, 79.90; H, 9.67. Found: C, 79.61; H, 9.51.

(4) **Ethylmagnesium Bromide.**—To a Grignard solution of ethylmagnesium bromide (6 g. of Mg) in 100 ml. of redistilled anisole, there was added dropwise a solution of 53.5 g. (0.2 mole) of α -phenyl- α -(β -dimethylaminoethyl)-2-pyridylacetone nitrile in 100 ml. of anisole. The addition was made at a temperature of 50-60°. The solution was then heated and stirred for two hours at 60-70°, cooled, decomposed with ice and dilute hydrochloric acid, and the organic layer extracted several times with dilute hydrochloric acid. The combined acid extracts were made alkaline with ammonia and the oil extracted with ether. The ether extracts

were dried, the solvent removed and the residual oil fractionated; yield 17 g. (35%), b.p. 149-152° (3 mm.), n_D^{20} 1.5511. Twenty-three grams of unreacted nitrile was recovered, b.p. 149-165° (2 mm.). The former fraction was identified further by analysis. *Anal.* Calcd. for C₁₆H₂₀N₂: C, 79.98; H, 8.39; N, 11.66. Found: C, 80.07; H, 8.57; N, 11.86.

Mixed melting points of samples of the dipicrate of γ -phenyl- γ -(2-pyridyl)-N,N-dimethylpropylamine obtained by the reaction of the tertiary nitrile with sodamide, ethyllithium ethylmagnesium bromide, respectively, with the

TABLE II: COMPOUNDS OF THE FORMULA R—CR''H—R'

No.	R	R'	R''	Method	Yield, %	B.p., °C.	Mm.	Formula	Analyses, %					
									Carbon		Hydrogen		Nitrogen	
									Calcd.	Found	Calcd.	Found	Calcd.	Found
1	2-C ₆ H ₄ N	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂) ₂	C ₁ (D ₁)	88 (80)	127-129	1.0	C ₁₆ H ₂₀ N ₂ ^a	79.98	79.78	8.39	8.54	11.66	11.34
2	2-C ₆ H ₄ N	C ₆ H ₅	CH ₂ CH ₂ N(C ₂ H ₅) ₂	C ₁	85	156-157	1.0	C ₁₈ H ₂₄ N ₂	80.54	80.35	9.02	9.25	10.45	10.64
3	2-C ₆ H ₄ N	C ₆ H ₅	CH ₂ CH ₂ CH ₂ N(CH ₂) ₂	C ₁	89	148-150	2.0	C ₁₇ H ₂₂ N ₂					11.02	11.28
4	2-C ₆ H ₄ N	C ₆ H ₅	CH(CH ₃)CH ₂ N(CH ₂) ₂ ^b	C ₁	66	155-156	3.0	C ₁₇ H ₂₂ N ₂	80.25	79.80	8.72	8.68	11.02	11.11
5	2-C ₆ H ₄ N	C ₆ H ₅	CH ₂ CH ₂ N 	C ₁	68	176-177	3.5	C ₁₉ H ₂₄ N ₂					10.00	9.98
6	2-C ₆ H ₄ N	<i>p</i> -CH ₃ C ₆ H ₄	CH ₂ CH ₂ N(CH ₂) ₂	C ₁ (D ₁)	50 (76)	152-154	3.0	C ₁₇ H ₂₂ N ₂	80.25	80.25	8.72	8.60	11.02	11.30
7	2-C ₆ H ₄ N	<i>p</i> - <i>i</i> -C ₂ H ₇ C ₆ H ₄	CH ₂ CH ₂ N(CH ₂) ₂	D ₁	80	149-151	1.0	C ₁₉ H ₂₆ N ₂					9.92	10.03
8	2-C ₆ H ₄ N	<i>p</i> -CH ₃ OC ₆ H ₄	CH ₂ CH ₂ N(CH ₂) ₂	D	79	172-175	1.5	C ₁₇ H ₂₂ ON ₂					10.36	10.13
9	2-C ₆ H ₄ N	<i>p</i> -OHC ₆ H ₄	CH ₂ CH ₂ N(CH ₂) ₂ ^c		21	210-212	2.0	C ₁₆ H ₂₀ ON ₂	75.28	74.58	7.89	7.70		
10	2-C ₆ H ₄ N	<i>o</i> -ClC ₆ H ₄	CH ₂ CH ₂ N(CH ₂) ₂	C ₁ (D ₁)	63 (75)	155-157	1.0	C ₁₆ H ₁₉ N ₂ Cl ^d						
11	2-C ₆ H ₄ N	<i>p</i> -ClC ₆ H ₄	CH ₂ CH ₂ N(CH ₂) ₂	C ₁ (D ₁)	85 (82)	141-143	1.0	C ₁₆ H ₁₉ N ₂ Cl ^e						
12	2-C ₆ H ₄ N	<i>p</i> -ClC ₆ H ₄	CH ₂ CH ₂ N(C ₂ H ₅) ₂	D ₁	73	159-161	0.5	C ₁₈ H ₂₃ N ₂ Cl					9.25	9.20
13	2-C ₆ H ₄ N	3,4-Cl ₂ C ₆ H ₃	CH ₂ CH ₂ N(CH ₂) ₂	D ₁	53	168-175	1.5	C ₁₆ H ₁₈ N ₂ Cl ₂	62.13	62.86	5.86	5.82	9.06	9.32
14	2-C ₆ H ₄ N	<i>p</i> -(CH ₃) ₂ NC ₆ H ₄	CH ₂ CH ₂ N(CH ₂) ₂	D ₁	75	178-183	1.5	C ₁₉ H ₂₅ N ₂					14.83	14.42
15	2-C ₆ H ₄ N	C ₆ H ₅ CH ₂	CH ₂ CH ₂ N(CH ₂) ₂	C ₁ (D ₁)	55 (83)	136-138	1.5	C ₁₇ H ₂₂ N ₂ ^f	80.25	80.60	8.71	8.73	11.02	10.96
16	2-C ₆ H ₄ N	<i>p</i> -CH ₃ C ₆ H ₄ CH ₂	CH ₂ CH ₂ N(CH ₂) ₂	D ₂	41	137-140	1.0	C ₁₈ H ₂₄ N ₂ ^g	80.55	80.77	9.01	8.87	10.44	10.82
17	2-C ₆ H ₄ N	<i>p</i> -CH ₃ OC ₆ H ₄ CH ₂	CH ₂ CH ₂ N(CH ₂) ₂	D ₁	82	172-175	0.5	C ₁₈ H ₂₄ ON ₂ ^h	76.02	75.82	8.51	8.11		
18	2-C ₆ H ₄ N	<i>p</i> -OHC ₆ H ₄ CH ₂	CH ₂ CH ₂ N(CH ₂) ₂ ^c		40	215-230	3.0	C ₁₇ H ₂₂ ON ₂	75.55	75.05	8.20	7.93	10.37	10.74
19	2-C ₆ H ₄ N	<i>α</i> -C ₁₀ H ₇	CH ₂ CH ₂ N(CH ₂) ₂	C ₂	68	183-186	1.0	C ₂₀ H ₂₂ N ₂					9.65	9.96
20	2-C ₆ H ₄ N	C ₆ H ₁₁	CH ₂ CH ₂ N(CH ₂) ₂	D ₁	38	147-149	4.0	C ₁₆ H ₂₆ N ₂					11.38	10.92
21	2-C ₆ H ₄ N	C ₄ H ₉	CH ₂ CH ₂ N(CH ₂) ₂	D ₁	89	91-95	1.0	C ₁₄ H ₂₄ N ₂					12.71	12.70
22	6-CH ₃ -2-C ₆ H ₃ N	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂) ₂	C ₁	72	137-139	1.0	C ₁₇ H ₂₂ N ₂	80.25	80.44	8.72	8.72	11.02	11.20
23	3-CH ₃ -2-C ₆ H ₃ N	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂) ₂	D ₁	50	122-127	0.5	C ₁₇ H ₂₂ N ₂					11.02	10.83
24	4-C ₆ H ₄ N	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂) ₂	C ₁	82	150-151	1.0	C ₁₆ H ₂₀ N ₂					11.66	11.48
25	4-C ₆ H ₄ N	C ₆ H ₅ CH ₂	CH ₂ CH ₂ N(CH ₂) ₂	D ₁	27	142-147	0.5	C ₁₇ H ₂₂ N ₂					11.02	10.68
26	2-C ₆ H ₂ N ₂	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂) ₂	C ₁	20	127-130	0.5	C ₁₅ H ₁₉ N ₃	74.64	74.64	7.93	7.75		
27	2-C ₆ H ₂ NS	C ₆ H ₅	CH ₂ CH ₂ N(CH ₂) ₂	C ₁	92	124-126	1.0	C ₁₄ H ₁₈ N ₂ S ⁱ					11.37	11.68
28	2-C ₆ H ₄ N	2-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₂) ₂	C ₁	91	145-150	1.0	C ₁₆ H ₁₉ N ₃	74.64	74.13	7.93	7.42	17.41	17.02
29	2-C ₆ H ₄ N	3-C ₆ H ₄ N	CH ₂ CH ₂ N(CH ₂) ₂	C ₁	79	131-136	1.0	C ₁₅ H ₁₉ N ₃					17.41	17.42
30	2-C ₆ H ₄ N	2-C ₆ H ₄ S	CH ₂ CH ₂ N(CH ₂) ₂	C ₁	30	125-128	1.0	C ₁₄ H ₁₈ N ₂ S	68.25	68.85	7.36	7.30		
31	2-C ₆ H ₄ N	2-C ₆ H ₄ SCH ₂	CH ₂ CH ₂ N(CH ₂) ₂	D ₁	66	168-170	3.0	C ₁₅ H ₂₀ N ₂ S	69.16	69.32	7.74	7.64	10.76	10.33
32	2-C ₆ H ₄ N	5-ClC ₆ H ₃ SCH ₂	CH ₂ CH ₂ N(CH ₂) ₂	E	55	160-163	2.0	C ₁₅ H ₁₉ N ₂ ClS ^j						
33	2-C ₆ H ₄ N	2-C ₆ H ₂ NS	CH ₂ CH ₂ N(CH ₂) ₂	E	24	138-141	1.5	C ₁₃ H ₁₇ N ₂ S	63.12	63.38	6.93	6.63		

^a This compound is in clinical use under the registered trademark "Trimeton." Dipicrate, m.p. 203-204°. *Anal.* Calcd. for C₂₃H₂₅O₄N₃: N, 16.03. Found: N, 16.36. Oxalate, m.p. 152-152.5° from acetone (prepared by E. R. Dichter of our Pharmaceutical Development Dept.). *Anal.* Calcd. for C₁₈H₂₂O₄N₂: N, 8.48. Found: N, 8.85. Maleate, m.p. 107-108° from isopropyl acetate (prepared by W. S. Benica of our Pharmaceutical Development Dept.). *Anal.* Calcd. for C₂₀H₂₄O₄N₂: N, 7.86. Found: N, 7.57. ^b See footnote *h* in Table I. ^c For the demethylation procedure, see ref. 11. Dipicrate, m.p. 199-200°. *Anal.* Calcd. for C₂₃H₂₅O₄N₃: N, 15.69. Found: N, 15.41. ^d Calcd. Cl, 10.20. Found: Cl, 10.46. ^e Calcd. Cl, 10.20. Found: Cl, 10.23. Maleate, m.p. 132.5-133° from ethyl acetate. *Anal.* Calcd. for C₂₀H₂₂O₄N₂Cl: N, 7.17. Found: N, 7.40; in clinical use under the registered trademark "Chlor-Trimeton Maleate." ^f Dipicrate, m.p. 204-205°. *Anal.* Calcd. for C₂₃H₂₅O₄N₃: N, 15.72. Found: N, 15.88. ^g Dipicrate, m.p. 186-187°. *Anal.* Calcd. for C₂₆H₂₈O₄N₃: C, 49.59; H, 4.16. Found: C, 49.19; H, 4.35. ^h Dipicrate, m.p. 167-168°. *Anal.* Calcd. for C₂₀H₂₀O₄N₂: N, 15.08. Found: N, 15.10. ⁱ R. Dahlbom, *Acta Chem. Scand.*, **4**, 744 (1950), prepared this compound by the reaction of γ -dimethylamino- α -phenylthiobutyramide and chloroacetaldehyde hydrate, b.p. 150° (0.1 mm.); γ -phenyl- γ -(4-methyl-2-thiazolyl)-N,N-dimethylpropylamine was obtained by the alkylation of 2-benzyl-4-methylthiazole with β -dimethylaminoethyl chloride and sodamide and isolated as the picrate. ^j Calcd.: Cl, 12.03. Found: Cl, 11.94.

authentic dipicrate of the amine (prepared by the sulfuric acid method) were not depressed.

Method D. Alkylation of Substituted α - and γ -Picolines. (1) **With Potassium Amide.**¹² γ -(*p*-Methylphenyl)- γ -(2-pyridyl)-*N,N*-dimethylpropylamine (Table II, No. 6).—To a stirred solution of potassium amide (from 27 g. of potassium) in two liters of liquid ammonia was added 115 g. of *p*-methylbenzyl-2-pyridine. After ten minutes, 75 g. (0.7 mole) of β -dimethylaminoethyl chloride was added followed by one liter of dry ether. The reaction mixture was stirred at room temperature for 20 hours and then decomposed with water. The ether layer was separated, dried, the ether distilled and the residue fractionated. The product distilled as a red oil which gradually became yellow upon exposure to light.

With sodamide, 60% of 2-benzylpyridine was recovered and only 34% of γ -phenyl- γ -(2-pyridyl)-*N,N*-dimethylpropylamine was obtained.

(2) **With Butyllithium** δ -Phenyl- γ -(2-pyridyl)-*N,N*-dimethylbutylamine (Table II, No. 15).—To a cold solution (0–10°) of butyllithium in an atmosphere of nitrogen from 3.1 g. of lithium, 18.5 g. of dry *n*-butyl chloride and 120 ml. of ether was added slowly 36.8 g. (0.2 mole) of α -dihydrostilbazole. The reaction mixture was refluxed and stirred for one hour and 22 g. (0.2 mole) of β -dimethylaminoethyl chloride was added dropwise. The reaction mixture was stirred for 18 hours, decomposed with water and processed in the usual manner.

The preparation of γ -(2-pyridyl)- γ -(2-thiazolyl)-*N,N*-dimethylpropylamine (Table II, No. 33) illustrates Method E. The intermediate γ -(2-pyridyl)-*N,N*-dimethylpropylamine was prepared in the following manner: To a solution of potassium amide (from 39 g. of potassium) in 1500 ml. of ammonia, there was added dropwise 104 g. (1.12 moles) of α -picoline. The solution was stirred for 20 minutes and 107.5 g. (1 mole) of β -dimethylaminoethyl chloride was added slowly. After stirring for eleven hours, the ammonia was allowed to evaporate and the residue was decomposed with a saturated solution of potassium carbonate. The oil which separated was extracted with benzene, the solvent removed, and the residue distilled; yield 111 g. (60%), b.p. 105–107° (10 mm.), n_D^{20} 1.4968. *Anal.* Calcd. for $C_{10}H_{16}N_2$: N, 17.06. Found: N, 17.24. The condensation was also effected in yields of 50–60% by the reaction of α -picoline, β -dimethylaminoethyl chloride and sodamide in refluxing benzene over a period of 24–40 hours.³⁵

To a solution of potassium amide (from 6.2 g. of potassium) in 500 ml. of liquid ammonia was added 25 g. of γ -(2-pyridyl)-*N,N*-dimethylpropylamine. After stirring for 15 minutes, 22 g. (0.185 mole) of 2-chlorothiazole was added to the deep red solution resulting in a vigorous reaction and the slow discharge of the red color. Three hundred milliliters of dry ether was added and the stirring continued for an additional four hours. The reaction mixture was decomposed with water, and processed in the usual manner.

γ -(Phenyl)- γ -(2-pyridyl)-*N,N*-dimethylpropylamine.—To a solution of potassium amide (from 4.2 g. of potassium) in 500 ml. of liquid ammonia, there was added a solution of 24 g. (0.1 mole) of γ -phenyl- γ -(2-pyridyl)-*N,N*-dimethylpropylamine in 250 ml. of anhydrous ether. After the reaction mixture had been stirred for one-half hour, 15 g. (0.137 mole) of ethyl bromide in 50 ml. of ether was added and stirring was continued until all of the ammonia had evaporated. The reaction mixture was decomposed with water, the ether layer separated, washed with water, dried, concentrated and the residue fractionated; yield 23 g. (90%), b.p. 152–155° (1.5 mm.). The oil crystallized upon standing, m.p. 53–54°. *Anal.* Calcd. for $C_{18}H_{24}N_2$: N, 10.44. Found: N, 10.54.

2-Pyridyllithium on Mannich Bases (Method F). 1-Phenyl-1-(2-pyridyl)-3-dimethylaminopropanol-1.—To a stirred suspension of 4.2 g. (0.61 mole) of lithium shot in 200 ml. of ether, in an atmosphere of nitrogen, there was added dropwise 41 g. (0.3 mole) of *n*-butyl bromide keeping the temperature at –10°. After stirring for one hour, the reaction mixture was cooled to –40° and 47.4 g. (0.3 mole) of 2-bromopyridine was added dropwise. The deep-red reaction mixture was stirred for an additional 30 minutes and 53 g. (0.3 mole) of β -dimethylaminopropiophenone³⁶ was

added dropwise. The mixture was stirred at room temperature for several hours, decomposed with ice and dilute hydrochloric acid and the aqueous acid layer made basic with ammonia. The oil was extracted with ether, the ether layer dried, the solvent removed and the residue distilled; yield 38 g. (50%), b.p. 145–150° (1.5 mm.). The oil slowly solidified and upon recrystallization from ligroin (70–90°) a white solid melting at 101–102°¹³ was obtained. *Anal.* Calcd. for $C_{18}H_{26}ON_2$: C, 74.94; H, 7.86; N, 10.94. Found: C, 74.73; H, 7.80; N, 10.85.

1-Phenyl-1-(2-pyridyl)-3-dimethylaminopropane-1.—A solution of 20 g. (0.078 mole) of 1-phenyl-1-(2-pyridyl)-3-dimethylaminopropanol-1 in 100 ml. of 80% sulfuric acid was stirred and heated at 160° for ten minutes. The dark mixture was poured on ice, made alkaline with cold, dilute sodium hydroxide solution, ether extracted, the ether layer washed with water, dried, concentrated and distilled; yield 15 g. (80%), b.p. 138–140° (1.0 mm.).¹³ *Anal.* Calcd. for $C_{18}H_{26}N_2$: N, 11.78. Found: N, 11.28.

γ -Phenyl- γ -(2-pyridyl)-*N,N*-dimethylpropylamine.—A solution of 5 g. of 1-phenyl-1-(2-pyridyl)-3-dimethylaminopropane-1 in 100 ml. of glacial acetic acid was shaken with 2.5 g. of 5% palladium-on-charcoal catalyst and hydrogen at 60 p.s.i. The theoretical amount of hydrogen was absorbed in 30 minutes. The catalyst was removed by filtration, the filtrate concentrated *in vacuo*, the residue treated with 100 ml. of 10% sodium hydroxide and the liberated oil extracted with ether. The ether layer was washed with water, concentrated and the residue converted to the dipicrate in ethanol in a yield of 70%. After two recrystallizations from ethanol, a sample of the dipicrate melted at 199–200°. A mixed melting point with an authentic sample of γ -phenyl- γ -(2-pyridyl)-*N,N*-dimethylpropylamine dipicrate (m.p. 201–202°) gave no depression.

Alkylation of Dialkylaminoalkanenitriles. Formation of Bis-(2-pyridyl)-acetonitrile by the Alkylation of β -Dimethylaminopropionitrile with 2-Bromopyridine.—To a stirred, refluxing solution of 158 g. (1 mole) of 2-bromopyridine and 98 g. (1 mole) of β -dimethylaminopropionitrile³⁷ in 400 ml. of toluene was added a suspension of sodamide (from 26 g. of sodium) in 300 ml. of toluene. The reaction mixture was refluxed and stirred for four hours, cooled, decomposed with water and the organic layer separated from the tars. The toluene was removed *in vacuo* and the residue fractionated; yield 13 g. (7%), b.p. 171–185° (3.5–4 mm.). The oil solidified and after two recrystallizations from benzene-petroleum ether melted at 138–139°. *Anal.* Calcd. for $C_{12}H_{18}N_3$: N, 21.53. Found: N, 21.22.

Formation of Bis- γ -(2-pyridyl)-*N,N*-dimethylpropylamine (Table II, No. 28) by the Alkylation of γ -Dimethylaminobutyronitrile with 2-Bromopyridine.—To a stirred, warm (60°) solution of 28 g. (0.25 mole) of γ -dimethylaminobutyronitrile³⁸ and 40 g. (0.25 mole) of 2-bromopyridine in 200 ml. of toluene, there was added in portions a suspension of sodamide (prepared from 12 g. of sodium) in 250 ml. of toluene. The reaction mixture was stirred and refluxed for six hours, decomposed with water, and the product isolated and distilled; yield 10.2 g. (17%), b.p. 145–150° (2 mm.). *Anal.* Calcd. for $C_{18}H_{26}N_3$: N, 17.41. Found: N, 17.33. The bis- γ -(2-pyridyl)-*N,N*-dimethylpropylamine resulted, apparently, from bis- α -(2-pyridyl)- γ -dimethylaminobutyronitrile by the removal of the CN group with sodamide.

Bis- α , α -(2-thiazolyl)- γ -*N,N*-dimethylaminobutyronitrile (Table I, No. 35).—To a stirred solution of 51 g. (0.43 mole) of 2-chlorothiazole and 22.4 g. (0.2 mole) of γ -*N,N*-dimethylaminobutyronitrile in 150 ml. of toluene was added dropwise a stirred suspension of sodamide (from 8 g. of sodium) in 150 ml. of toluene. The solution became deep red in color and considerable foaming occurred. After the reaction mixture had been refluxed and stirred for four hours, it was cooled and decomposed with water. The organic layer was separated, concentrated to dryness and the residue distilled.

α -Dimethylaminomethyl- α -benzyl-2-pyridylacetoneitrile (Table I, No. 27).—The requisite α -dimethylaminomethyl- β -phenylpropionitrile (Table I, No. 4) was prepared in the following manner: To a stirred, hot solution (85°) of 25 g. (0.255 mole) of β -dimethylaminopropionitrile in 100 ml. of

(35) Compare F. Brody and M. T. Bogert, *THIS JOURNAL*, **65**, 1075 (1943).

(36) "Organic Syntheses," Vol. 23, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 30.

(37) Prepared by the procedure of F. C. Whitmore, *et al.*, *THIS JOURNAL*, **66**, 725 (1944); compare C. A., **42**, 3723 (1948).

(38) W. Huber, R. O. Clinton, W. Boehme and M. Jackman, *THIS JOURNAL*, **67**, 1618 (1945).

toluene, was added dropwise a mixture of sodamide (from 6.2 g. sodium) and 32.2 g. (0.255 mole) of benzyl chloride in 200 ml. of toluene. The mixture was refluxed and stirred for an additional seven hours, cooled, decomposed with water and the toluene layer separated. The aqueous layer was extracted with benzene and the combined benzene-toluene solutions were extracted several times with a 10% hydrochloric acid solution. The aqueous acid extracts were made basic with ammonia, processed in the usual manner and distilled.

To a warm, stirred suspension of sodamide (from 2.6 g. of sodium) in 200 ml. of dry xylene was added 20 g. (0.106 mole) of α -dimethylaminomethyl- β -phenylpropionitrile, followed by the cautious addition of 20 g. (0.127 mole) of 2-bromopyridine. A violet reaction occurred with the addition of each increment of 2-bromopyridine. The reaction mixture was stirred and refluxed for eight hours, cooled, decomposed with water, the organic layer separated, the solvent removed and the residue distilled. Attempts to hydrolyze and decarboxylate this nitrile with 80% sulfuric acid at 140–150° were unsuccessful.

Reduction of γ -Phenyl- γ -(2-pyridyl)-N,N-dimethylpropylamine (XII) (a) Raney Nickel in Methanol. γ -Phenyl- γ -(N-methyl-2-piperidyl)-N,N-dimethylpropylamine (XIV).—A solution of 24 g. (0.1 mole) of γ -phenyl- γ -(2-pyridyl)-N,N-dimethylpropylamine was reduced in methanol with Raney nickel catalyst and hydrogen for four hours at an initial pressure of 1,000 p.s.i. and a temperature of 170°. The catalyst was filtered, washed with methanol, the combined filtrates and washings concentrated *in vacuo* and the residue distilled to give two fractions; fraction I, wt. 8.2 g., b.p. 105–121° (1 mm.), n_D^{20} 1.5292; fraction II, wt. 12 g., b.p. 126–132° (1 mm.), n_D^{20} 1.5196. Fraction II was redistilled and boiled at 122–125° (0.5 mm.), n_D^{20} 1.5193. *Anal.* Calcd. for $C_{17}H_{23}N_2$: C, 78.38; H, 10.84; N, 10.84. Found: C, 78.61; H, 11.09; N, 10.88. The picrate (m.p. 200–204°) depressed the melting point of the picrate of γ -phenyl- γ -(2-pyridyl)-N,N-dimethylpropylamine (m.p. 203–204°).

Fraction I, upon redistillation, boiled at 100–105° (0.5 mm.), n_D^{20} 1.5299. *Anal.* Calcd. for $C_{15}H_{23}N$: C, 82.87; H, 10.67; N, 6.45; and for $C_{14}H_{21}N$: C, 82.68; H, 10.42;

N, 6.89. Found: C, 82.42; H, 10.08; N, 6.79. On the basis of the analyses, it is apparent that the dimethylamino group had been lost.

(b) **Sodium and Alcohol. γ -Phenyl- γ -(2-piperidyl)-N,N-dimethylpropylamine (XV).**—To a solution of 24 g. (0.1 mole) of XII in 190 ml. of ethanol (dried over sodium) was added 27.4 g. of sodium metal (in cubes) as rapidly as possible. After the vigorous reaction had subsided, an additional 90 ml. of alcohol was added and the solution was refluxed on the steam-bath until all the sodium had dissolved. Upon vacuum concentration, the contents of the flask solidified and water was added until an oil appeared. The latter was extracted with ether, the ether layer washed with water, dried, the solvent removed and the residue distilled. After a forerun (5.2 g.), b.p. 100–125° (0.5 mm.), the main fraction, yield 14.2 g. (58%), b.p. 127–130° (0.5 mm.), n_D^{20} 1.5244, was obtained. Redistilled for analysis, b.p. 117–120° (0.1 mm.), n_D^{20} 1.5249. *Anal.* Calcd. for $C_{16}H_{26}N_2$: C, 78.00; H, 10.64. Found: C, 77.44; H, 10.26.

γ -Phenyl- γ -(N-methyl-2-piperidyl)-N,N-dimethylpropylamine (XIV).—To 6 ml. of cooled, 90% formic acid was added 8.5 g. of γ -phenyl- γ -(2-piperidyl)-N,N-dimethylpropylamine (XV). Six ml. of 37% formalin solution was then added and the reaction mixture heated on the steam-bath overnight. Twenty ml. of 10% hydrochloric acid solution was added and the solution was vacuum concentrated to a residue, made basic with sodium hydroxide solution and the oil extracted with ether. The ether layer was washed with water, dried, the solvent removed and the residue distilled; yield 7 g. (78%), b.p. 127–134° (1 mm.), n_D^{20} 1.5231. *Anal.* Calcd. for $C_{17}H_{23}N_2$: C, 78.42; H, 10.84. Found: C, 78.63; H, 10.60.

The picrate melted at 204–205° and when mixed with the picrate of γ -phenyl- γ -(N-methyl-2-piperidyl)-N,N-dimethylpropylamine (m.p. 202–204°), obtained from the reduction of γ -phenyl- γ -(2-pyridyl)-N,N-dimethylpropylamine with Raney nickel and hydrogen in methanol, melted at 203–204°. However, a mixed melting point with the picrate of γ -phenyl- γ -(2-piperidyl)-N,N-dimethylpropylamine (m.p. 204–205°) was depressed, m.p. 192–193°.

BLOOMFIELD, NEW JERSEY

RECEIVED JUNE 9, 1951

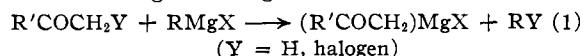
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

The Displacement of the Allyl Group in the Reaction between Phenylmagnesium Bromide and α -Allylisobutyromesitylene

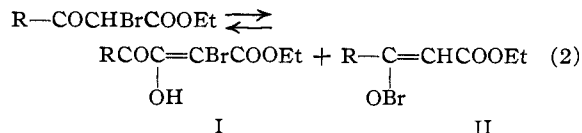
BY T. A. GEISSMAN AND ROBERT M. HOROWITZ

α -Allylisobutyromesitylene is cleaved by phenylmagnesium bromide in ethyl ether solution at 125–135° to yield allylbenzene and isobutyromesitylene. In isoamyl ether at 125° but in the presence of traces of metallic magnesium the reaction takes a different course and appears to proceed with the intervention of free-radical intermediates.

The "enolization" of carbonyl compounds and the removal of halogen from α -halocarbonyl compounds by the action of Grignard reagents are well-known reactions¹ which appear to be closely related. Equation (1) represents the general reaction, which appears to involve a nucleophilic displacement on hydrogen or halogen by the group R of the Grignard reagent



The details of this reaction are obscure. It has been suggested² that the actual species upon which the displacement occurs are in the case of an α -bromo- β -keto ester, the enol form (I) and the analogous hypobromite form (II)



Since, however, Grignard reagents can "enolize" carbonyl compounds which contain no detectable amount of enol,³ and replace active hydrogen in compounds such as acetylenes, sulfones, indene, etc.,⁴ there appears to be no reason to dismiss the more general alternative that hydrogen and halogen may be displaced from carbon directly.

It is convenient to correlate reactions of this kind with certain other reactions involving Grignard reagents, for which "cyclic mechanisms"

(1) See F. Runge, "Organo-Metallverbindungen," Stuttgart, 1944, Edwards Bros., Inc., Ann Arbor, Mich., 1945, p. 383.

(2) B. W. Howk and S. M. McElvain, *THIS JOURNAL*, **55**, 3375 (1933).

(3) D. Ivanov and A. Spasov, *Bull. soc. chim.*, [4] **49**, 375 (1931); [5] **1**, 1419 (1934).

(4) H. Güman, "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 499.