

ARYLVINYLAMINES OF PHARMACOLOGIC INTEREST

by
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the University of Maryland in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy

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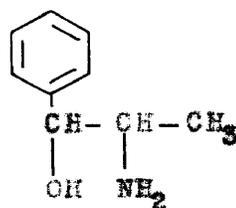
The author wishes to express his sincere appreciation to the following:

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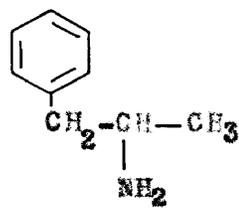
Alice F. Stahl, the author's wife, for her patience and encouragement while the work was in progress.

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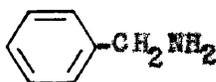
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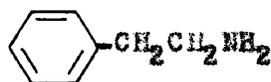
V

In either case, the nature of the substituents on the carbon adjacent to that which bears the amino group has a profound effect on the pharmacodynamic properties of the compound, i.e., the group X in compounds of type II is an important determinant of the pharmacodynamic properties of the compound. Such properties are also influenced, especially in a quantitative manner, by the nature and number of substituents on the amino group. These generalities have been deduced from consideration of such compounds as are tabulated in Table J.

A third generalization which concerns the relative positions of the group X and the amino group can be made with certain reservations from the above considerations. In the colamine or ethylamine derivatives, these groups are on adjacent carbon atoms, i.e., they are separated by an ethylene group. Such an arrangement is generally optimum for maximum pharmacodynamic activity. Barger and Dale (1) and Graham and Cortlund (2) observed maximum pressor activity in sympathomimetic phenylalkylamines when the phenyl group and the amino group were on adjacent carbon atoms (VI-VIII).



VI

1/1000¹

VII

1/300-1/500

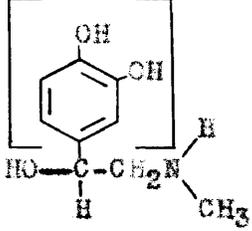
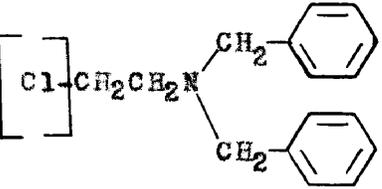
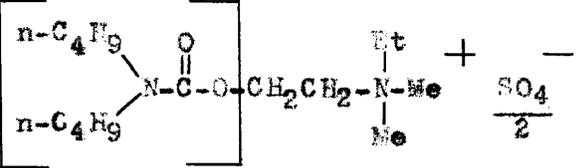
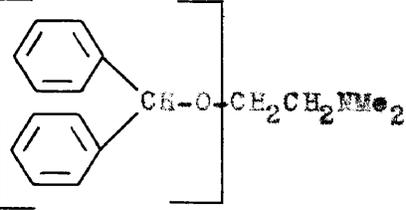
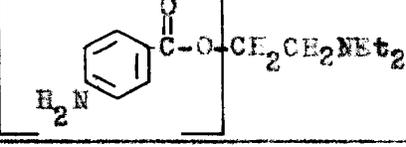
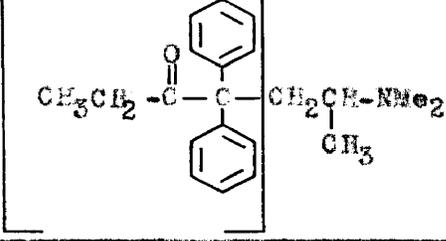


VIII

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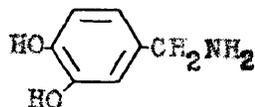
¹Pressor activity relative to that of epinephrine.

Table I
 Representative Pharmacologically Active Derivatives
 of Colamine or Ethylamine.*

Name	Compound Structural formula	Pharmacodynamic Classification
Epinephrine		Sympathomimetic
Dibenamine		Sympatholytic
Acetylcholine		Parasympathomimetic
Dibutoline Sulfate		Parasympatholytic
Diphenyl- hydramine		Histaminolytic
Procaine		Local anesthetic
Methadon		Analgesic

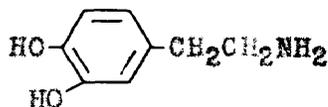
*The substituent X referred to above is indicated by brackets.

Bovet (3), citing the work of Tainter (4) and Tiffeneau (5), made a similar observation in the phenolic analogs (IX-XI) of the above compounds.



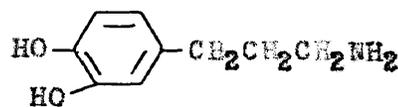
IX

1/800



X

1/65

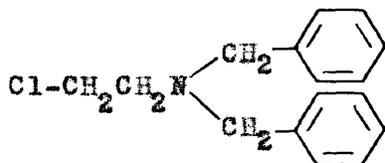


XI

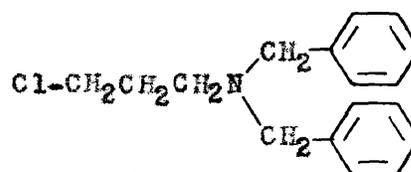
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The extensive studies of Nickerson and co-workers (6,7) of the pharmacodynamic properties of chloroalkylamines with adrenergic blocking activity (sympatholytic and adrenolytic), show that maximum activity depends on the adjacent orientation of the chlorine substituent and the amino group.

2-Chloroethyldibenzylamine (XII, Dibenamine) is active, while 3-chloropropyldibenzylamine (XIII) is inert.

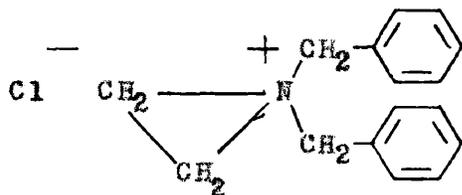
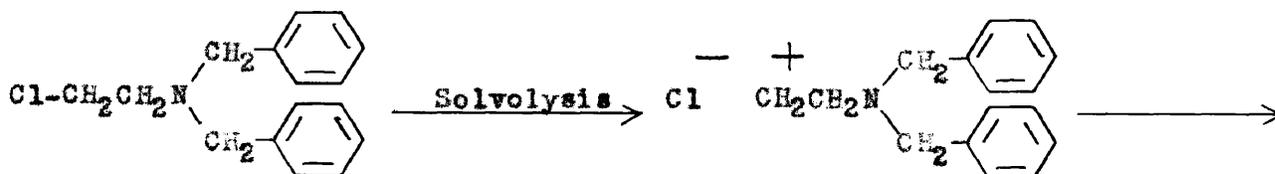


XII



XIII

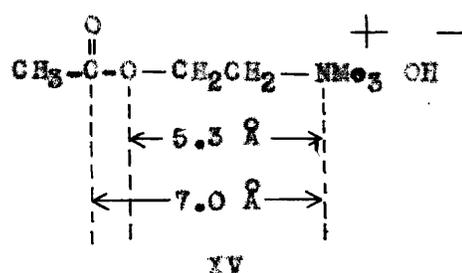
Considerable evidence is presented in support of the conclusion that the adjacent orientation is necessary to permit formation of an electrophilic ethylenimmonium ion (XIV) which reacts with a nucleophilic cell constituent that is required for an excitatory response to epinephrine (8,9).



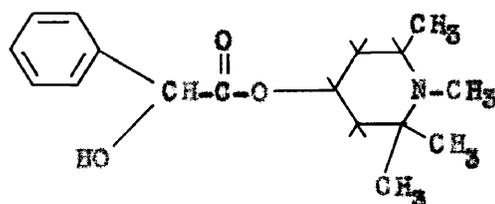
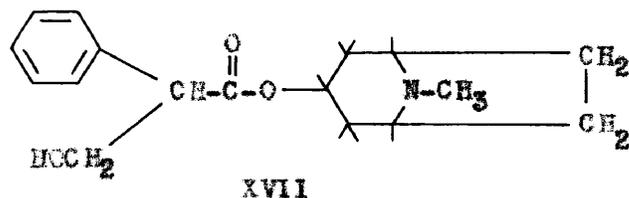
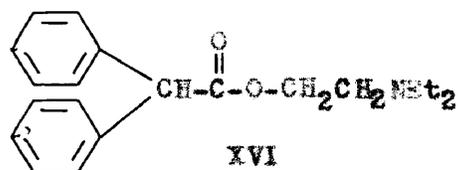
XIV

Nickerson cites the work of Gibbs and Marvel (10) in support of his idea that the analogous propylenammonium ion that would be formed in a similar way from XIII, has a much more stable cyclic structure and is, therefore, less reactive.

An adjacent orientation of substituents (prosthetic groups) is also essential for maximum parasympatholytic (muscarinic) activity, and no data could be found concerning such activity in compounds of Types I and II, in which the substituents were otherwise oriented. Pfeiffer (11) has suggested that the intervening ethylene group provides proper intramolecular distances separating the prosthetic groups. Compounds (such as acetylcholine, XV) with such prosthetic groups and intramolecular dimensions are capable of interaction with similarly oriented chemo-receptors on the cell surface, thereby eliciting the response that usually results from parasympathetic stimulation.



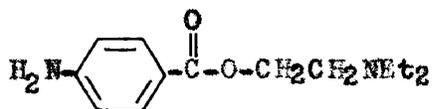
The necessity for similar orientation of prosthetic groups in compounds with parasympatholytic activity, has also been pointed out by Pfeiffer. Such an orientation results when the prosthetic groups are on adjacent carbon atoms of an ethylene group as in dibutoline sulfate (Table I) and trasentin (XVI) or in the 1- and 4- positions of a piperidine ring as in atropine (XVII) or eucatropine (XVIII).



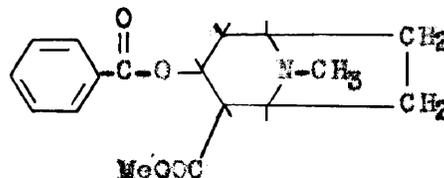
Pfeiffer has suggested that these compounds possess parasympholytic rather than parasymphomimetic activity, because the prosthetic groups are contained in the center of a large umbrella-like structure which may inactivate mechanically or electrostatically, adjacent receptors on the cell surface, thus preventing their interaction with acetylcholine or other parasymphomimetic agents.

The histaminolytic activity of ethers of amino alcohols is also maximum when the aralkyloxy and amino groups are on adjacent carbon atoms, as in diphenylhydramine (III), (12,13). In the other important series of histaminolytic agents, the ethylenediamine derivatives and related compounds, the substituents are again on adjacent carbon atoms.

Studies of structure-activity relationships of compounds with local anesthetic properties, reveal that maximum activity is not associated with an adjacent orientation of substituents, as in the structure of procaine (XIX), or the related 1,4- orientation in the piperidine derivative, cocaine (XX).



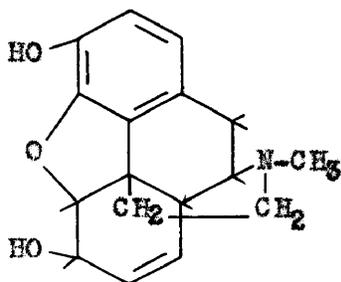
XIX



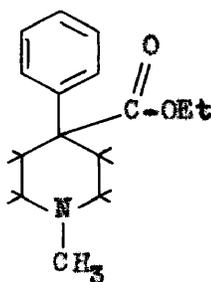
XX

Activity in this type of compound (XIX) has been found to increase as the length of the intervening alkylene group (14). The fact remains, nevertheless, that the adjacent orientation appears in the structures of a number of clinically-useful local anesthetics.

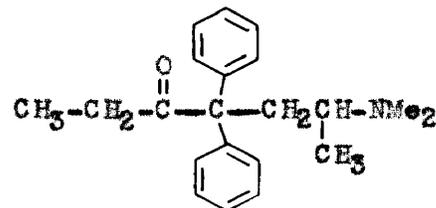
An ethylene group linking a tertiary amino group to a quaternary carbon is found in the three important classes of analgesics represented by morphine (XXI), meperidine (XXII) and methadon (XXIII).



XXI



XXII



XXIII

Such a group is considered by Eddy (15) to be essential for analgesic activity.

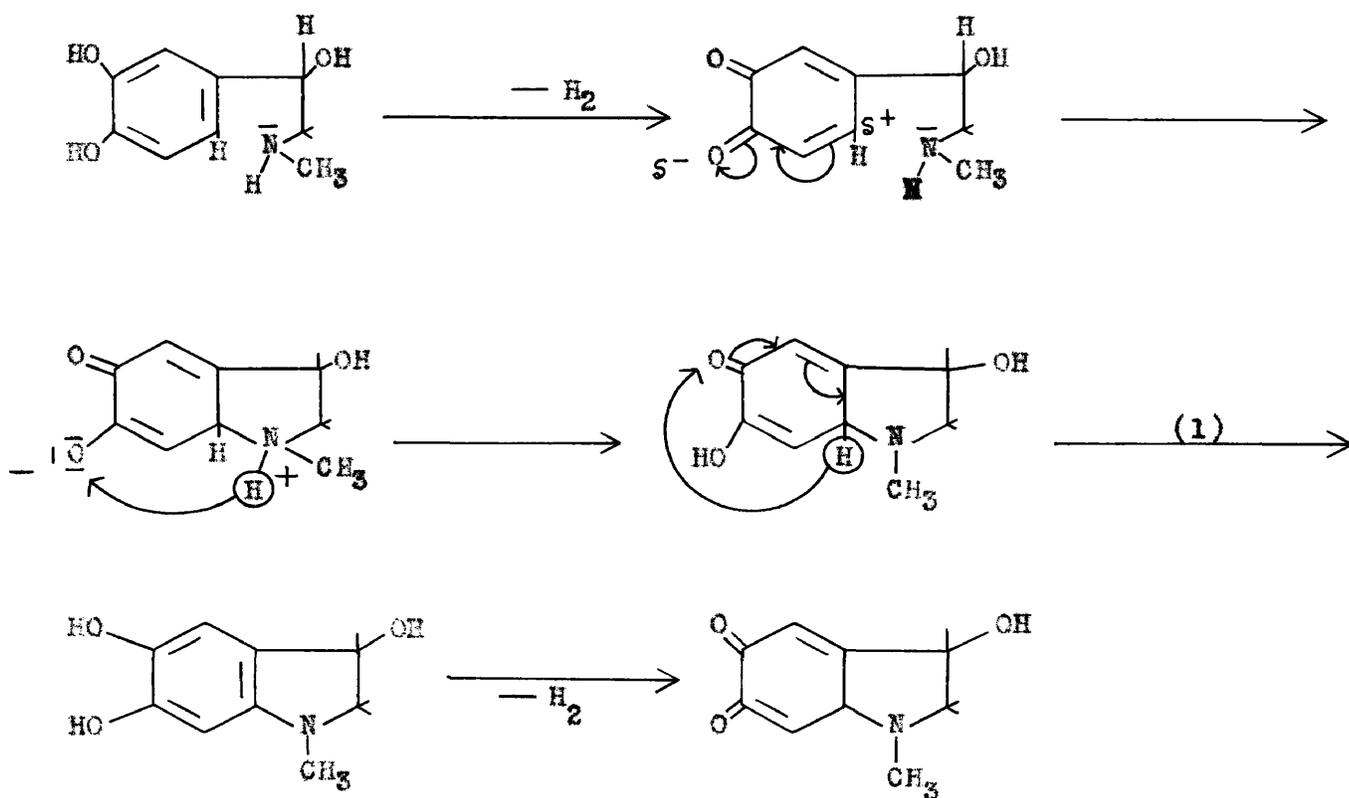
OBJECT OF THE INVESTIGATION

The necessity for an adjacent orientation of a substituent X (Formula II) and an amine function in compounds with maximum pharmacodynamic properties of various types, has been well established empirically. Theoretical considerations in the effort to explain the necessity for this structural feature have been advanced for the adrenergic-blocking agents (Nickerson, q.v.) and for the muscarinic and cholinergic-blocking agents (Pfeiffer, q.v.). The dissimilarity in the two hypotheses is most striking, and Nickerson was prompted to suggest that the chemical basis established for the adrenergic-blocking agents should "serve to focus attention upon the importance of the chemical properties of pharmacologically active agents, which in the past have been almost completely neglected in favor of physical (steric) properties" (6).

The possibility that a chemical basis for activity and a physical basis for activity might be coexistent, cannot be denied. On the other hand, a common basis, be it chemical or physical, in keeping with the common necessity for adjacent orientations of groups in molecular structures, might resolve a number of incongruities now apparent in structure-activity relationships of the pharmacodynamically-active substances here under consideration. As an example of such incongruities, the anomalous effect of orientation of phenolic hydroxyls on pressor activity of phenylalkanolamines, might be mentioned.

In a working hypothesis, which serves as a guide in the present investigation, the basic assumption has been made, that the adjacent orientation of substituents on an ethylene group makes possible an interaction between the amino group and the group X (Formula II), that may vary from field effect through chelation to covalency. It is further assumed that such

interaction is prerequisite for a pharmacodynamic effect. The formation of an electrophilic ethylenium ion, a reaction dependent on the adjacent orientation of groups, is essential for adrenergic-blocking activity (q.v.). A similar interaction is involved in formation of adrenochrome (XIV) from epinephrine, and the reaction might be pictured as follows:



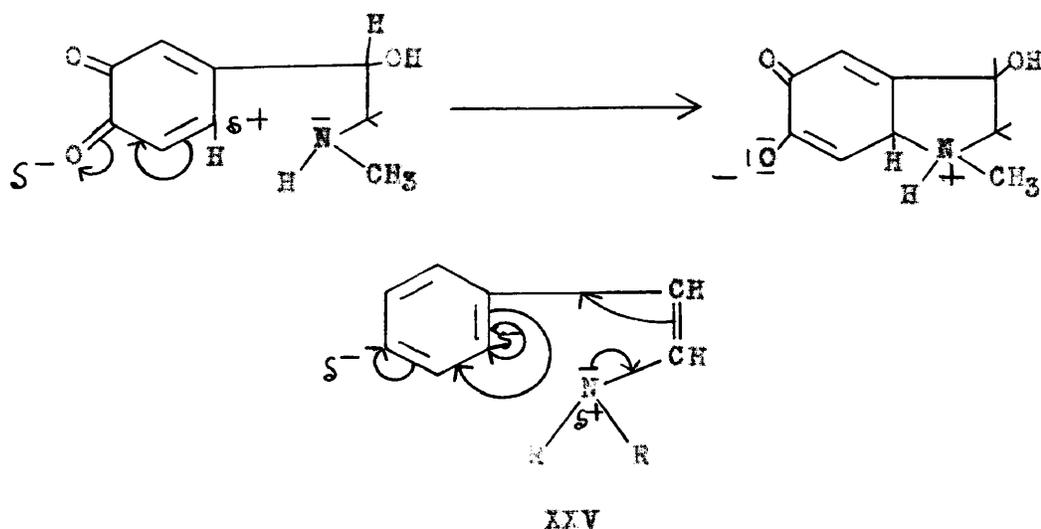
XIV

An obvious extension of the general idea of intramolecular interaction of the amine function with a group X on the adjacent carbon or with the adjacent carbon by a reaction which involves the group X , can be made in series of compounds with the other types of pharmacodynamic activity.

¹A dienone-phenol rearrangement.

The electrostatic interaction between the amine function and the group X in all the series of pharmacodynamically-active substances considered above, is in no instance propagated through the intervening alkylene group because conjugation is broken by a sequence of three single bonds. The alkylene group acts only in a passive way by providing a proper orientation for interaction between the two groups.

If the above assumptions concerning a chemical basis for pharmacodynamic activity are based on a reality, then it would be expected that an interaction of the amine group and the group X which is propagated through an unsaturated alkylene group, would result in pharmacodynamic activity in the compound. The analogy between the intramolecular interaction of groups in an intermediate in the above reaction for formation of adrenochrome and of the groups in the "unsaturated" analog (XXV), is an interesting speculation.



In each case, the nitrogen of the amine becomes electrophilic as a result of the interaction.

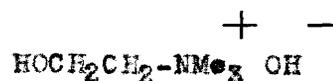
The objective in this investigation is the preparation of substituted vinylamines of the type indicated above (XXV).

VINYLAMINES-A LITERATURE SURVEY

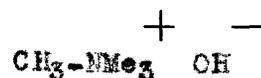
Pharmacologic studies of vinylamines have not been reported very extensively, probably because the number of vinylamines available has been rather limited. The muscarinic effects of neurine (XXVI), N,N,N-trimethylvinylammonium hydroxide, on the frog heart, resulted in retardation of cardiac rhythm (16) or diastolic arrest (17). Its parasympathomimetic effects on blood pressure of cats and dogs, has also been studied (18, 19, 20, 21). It is definitely more active than choline (XXVII), the corresponding alcohol (17, 21), and about as active as tetramethylammonium hydroxide (XXVIII) (22, 23, 24).



XXVI

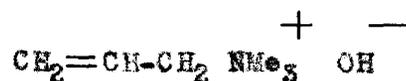


XXVII

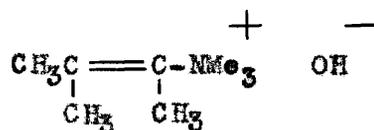


XXVIII

Related compounds possessing the general properties of quaternary ammonium compounds, differing little from those of the corresponding saturated compounds include allyl-trimethylammonium hydroxide (XXIX) or homoneurine (25, 26), valcarine (XXX) (27) and acetylenetrimethyl ammonium hydroxide (XXXI) (28, 29, 30).



XXIX

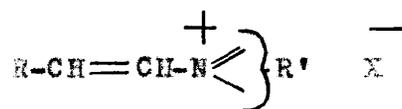


XXX



XXXI

King has reported the preparation of a series of 2-substituted-vinyl quaternary salts (XXXII) for testing as tumor damaging agents (31).



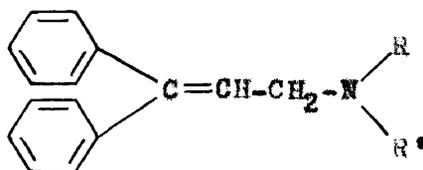
XXXII

where R = phenyl, 2-thienyl, 3,4-dimethoxyphenyl

R' = pyridine, 3-picoline, 4-n-amyropyridine,

isoquinoline

A series of substituted allylamines (XXXIII) was prepared by Adamson (32) and found to possess local anesthetic, spasmolytic, mydriatic and histaminolytic activity.



XXXIII

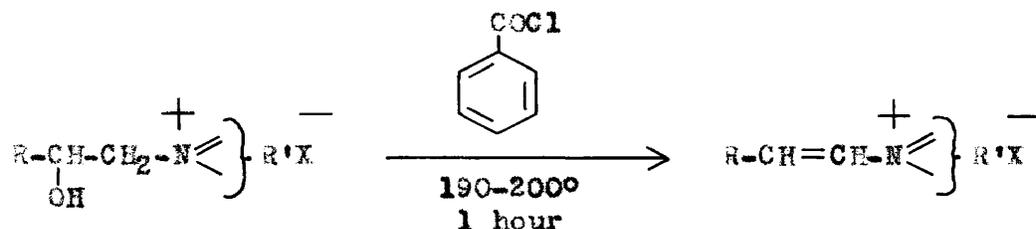
Review of Methods of Synthesis of Vinylamines. A search of the

literature failed to reveal a method for preparation of diphenyl-substituted vinylamines by dehydration of the corresponding tertiary amino alcohols.

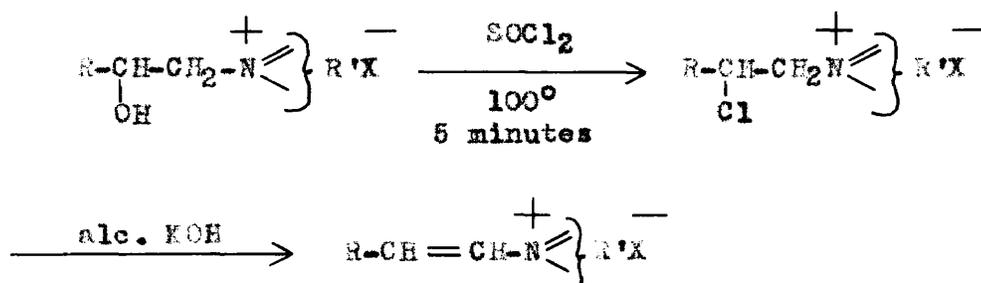
Dilute sulfuric acid, which is frequently used for the preparation of olefins

from tertiary alcohols (33, 34) was found to be unsatisfactory for the dehydration of the amino alcohols.

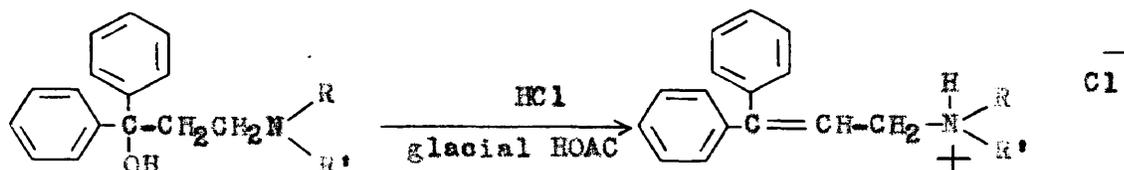
King (31) prepared a series of 2-substituted vinyl quaternary ammonium salts (XXXII) by dehydration of the corresponding secondary amino alcohols, using benzoyl chloride as the dehydrating agent.



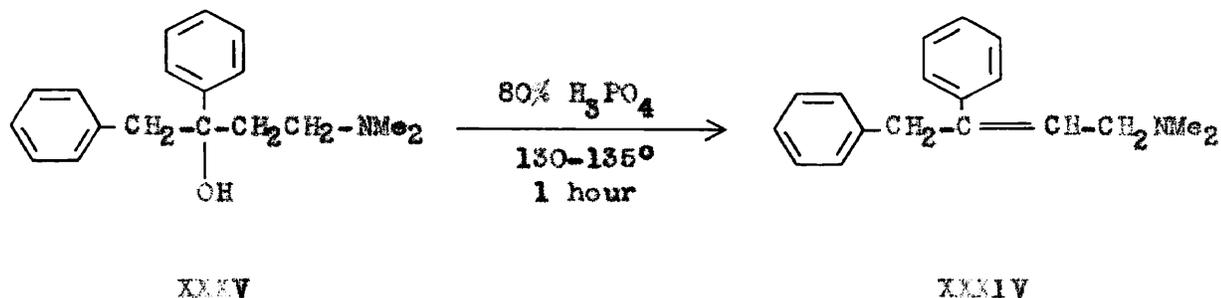
An alternate method used by King in the preparation of the vinyl quaternary ammonium salts was the reaction of the secondary amino alcohol with thionyl chloride followed by dehydrohalogenation with alcoholic potassium hydroxide.



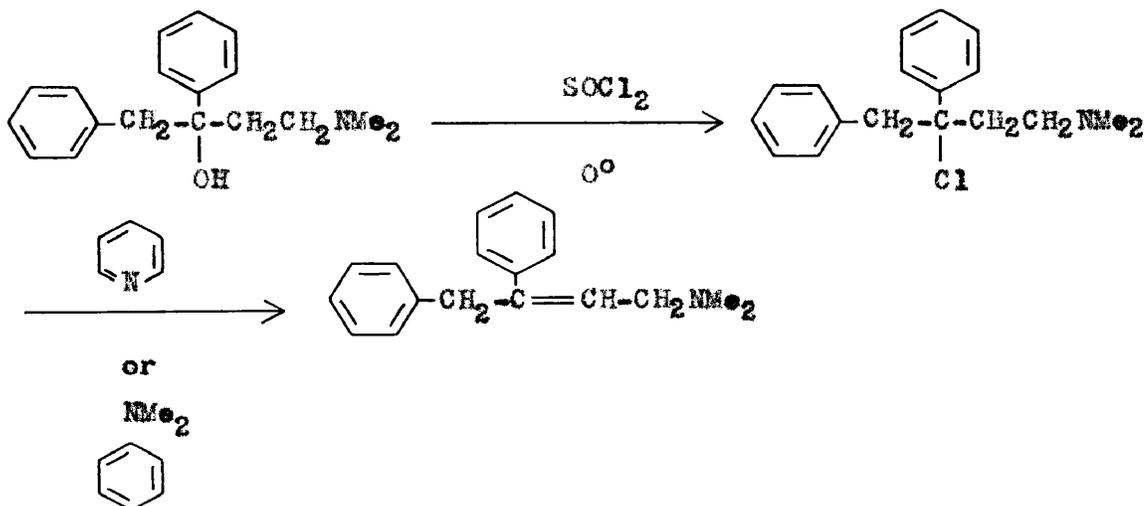
Adamson (32) prepared a series of 1,1-diphenyl-3-amino-1-propenes by the dehydration of the corresponding 1,1-diphenyl-3-amino-1-propanols, using concentrated hydrochloric acid and glacial acetic acid as the dehydrating agent.



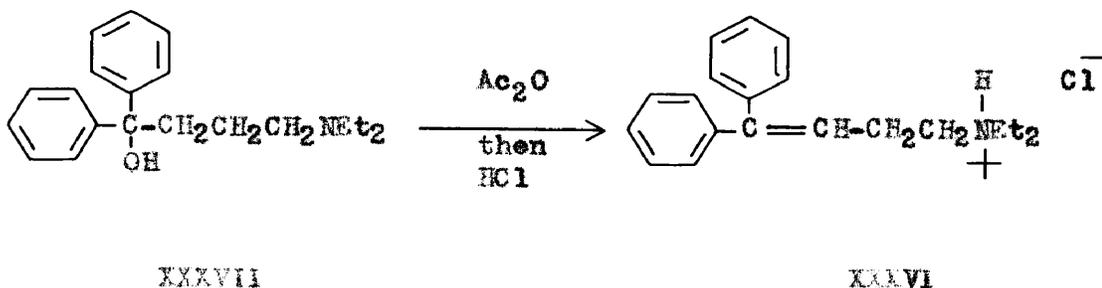
Stoll (35) has described the preparation of 1,2-disubstituted-4-amino-2-butenes by dehydration of the corresponding tertiary amino alcohols. 1,2-Diphenyl-4-dimethylamino-2-butene (XXXIV) was prepared from 1,2-diphenyl-4-dimethylamino-2-butanol (XXXV) by two methods, viz., heating the alcohol with 80% phosphoric acid at 130-135° for one hour,



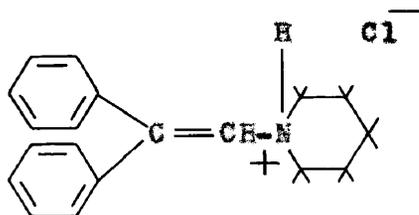
or treating the alcohol with thionyl chloride at 0°, and then heating with pyridine or dimethylaniline.



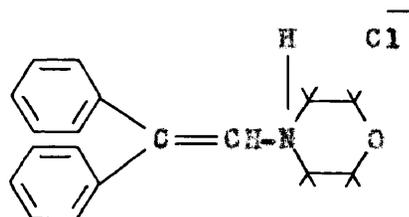
Marxer (36) prepared 1,1-diphenyl-4-diethylamino-1-butene hydrochloride (XXXVI) by heating 1,1-diphenyl-4-diethylamino-1-butanol (XXXVII) with acetic anhydride for four hours.



In the present investigation, two substituted vinylamine hydrochlorides were prepared, viz., 1,1-diphenyl-2-(1-piperidino)-ethylene hydrochloride (XXXVIII) and 1,1-diphenyl-2-(4-morpholino)-ethylene hydrochloride (XXXIX).

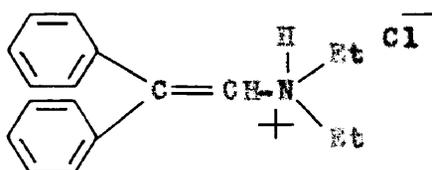


XXXVIII

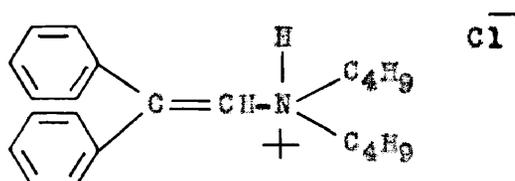


XXXIX

In attempts to prepare 1,1-diphenyl-2-diethylamino-ethylene hydrochloride (XL) and 1,1-diphenyl-2-di-n-butylamino-ethylene hydrochloride (XLI) by a number of methods, deamination with formation of diethylamine and di-n-butylamine occurred.



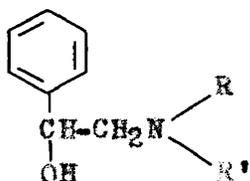
XL



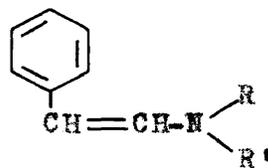
XLI

However, it appears that these compounds can be prepared by the reaction which was used for the preparation of 1,1-diphenyl-2-(1-piperidino)-ethylene hydrochloride and 1,1-diphenyl-2-(4-morpholino)-ethylene hydrochloride, provided proper conditions are employed. An extension of the present work will include the preparation of these compounds.

It was hoped that the preparation of 1-phenyl-2-substituted-amino-ethylenes (XLII) from the corresponding 1-phenyl-2-substituted-amino-ethanols (XLIII) might be included in this investigation.



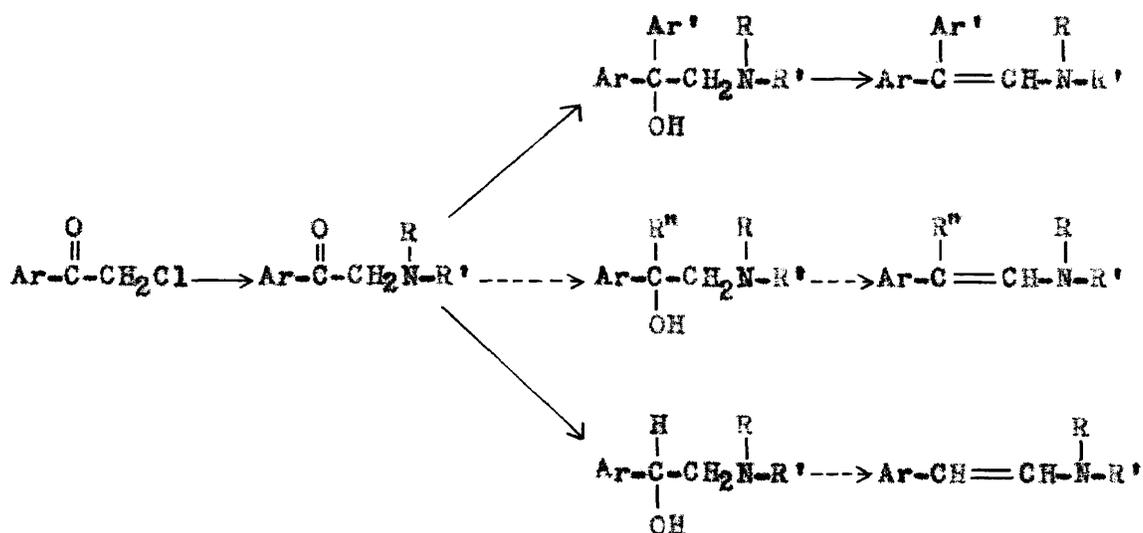
XLIII



XLII

Because of difficulties encountered in the dehydration of the tertiary alcohols, the dehydration of the secondary alcohols has not yet been attempted. An extension of the work herewith reported will include the dehydration of secondary amino alcohols.

The work carried out to date and part of the work contemplated as a continuation of this study, is summarized in the following equations.



in which Ar and Ar' = aryl groups or substituted aryl groups.

and R, R' and R'' = alkyl groups

Pharmacological tests of the vinylamines reported in this investigation have not yet been carried out.

EXPERIMENTAL

All melting points are uncorrected. In most cases, the phenacyl chloride used was not recrystallized. The secondary amines used, with the exception of morpholine, were Eastman "white label" grade, freshly distilled before use. The morpholine was obtained from Carbide and Carbon Chemicals Corporation, and it was also freshly distilled before use.

ω -Aminoacetophenones. The following amino ketones were prepared by the condensation of phenacyl chloride with the appropriate secondary amine. Details of the procedure are given in the description of each compound.

ω -Diethylaminoacetophenone. The method of Marvel and Du Vigneaud (37) was employed for the preparation of this compound. A solution of 154 g. (1 mole) of phenacyl chloride in 500 ml. of benzene was added to a solution of 150 g. (2 moles) of diethylamine in 150 ml. of benzene. The mixture was allowed to stand for about two days. The diethylammonium chloride which separated was filtered off. The benzene was removed by distillation under reduced pressure. The residue was distilled under reduced pressure, and a light yellow oil, b.p. 103-105° (3 mm.), 150 g. (79% of theoretical), was collected.

Marvel and Du Vigneaud (37) have reported the boiling point of this compound to be 148-152° (30 mm.).

ω -Diethylaminoacetophenone Methiodide. ω -Diethylaminoacetophenone (5.7 g., 0.03 mole) was dissolved in 30 ml. of dry ether, and 8.5 g. (0.06 mole) of methyl iodide was added. The solution was allowed to stand for two days, and the crude methiodide separated as yellowish-white crystals. Recrystallization from absolute alcohol and dry ether produced white crystals, m.p. 153-154° dec. Yield, 8.0 g. (60% of theoretical).

ω -Di-n-butylaminoacetophenone. A solution of 77.0 g. (0.5 mole) of phenacyl chloride in 300 ml. of benzene was added to a solution of 129 g. (1 mole) of di-n-butylamine in 150 ml. of benzene. After two days, the di-n-butylammonium chloride which separated was filtered off. The benzene was removed by distillation under reduced pressure, and the residue was distilled under reduced pressure. A light yellow oil was obtained, b.p. 163-170° (5 mm.). Yield, 80.0 g. (64.8% of theoretical).

Golding and McNoely (38) have reported the boiling point of this compound to be 122-123° (1 mm.).

ω -(1-Piperidino)-acetophenone. The method of Henley and Turner (39) was employed for the preparation of this compound. A solution of 154 g. (1 mole) of phenacyl chloride in 200 ml. of benzene was added to a well-shaken, cold mixture of 130 g. (1.5 moles) of piperidine, 130 g. of anhydrous potassium carbonate and 200 ml. of benzene. Water was added, and the benzene layer was separated. The benzene layer was extracted three times with water and twice with 20% hydrochloric acid. The combined acid solutions were rendered alkaline with ammonia and extracted with ether. The ethereal layer was washed with a little water and dried over anhydrous sodium sulfate. The ether was removed by distillation under reduced pressure, and the residue was distilled under reduced pressure. The product was obtained as a light yellow oil, b.p. 130-140° (3 mm.). Yield, 119.3 g. (59% of theoretical).

Henley and Turner (39) have reported the boiling point of this compound to be 168° (26 mm.).

ω -(1-Piperidino)-acetophenone Methiodide. Methyl iodide (2.8 g., 0.02 mole) was added to a solution of 2.0 g. (0.01 mole) of ω -(1-piperidino)-acetophenone in 30 ml. of dry ether. After three days, white crystals of

the methiodide separated. They were recrystallized from absolute alcohol and dry ether. M.p. 170-171° dec. Yield, 2.3 g. (67% of theoretical).

ω -(4-Morpholino)-acetophenone Hydrochloride. The method of Rubin and Day (40) was employed for the preparation of this compound. To 77.3 g. (0.8 mole) of phenacyl chloride mixed with 350 ml. of alcohol and cooled to 0°, 73.0 g. (1 mole) of morpholine was slowly added with stirring, the addition being made at such a rate as to maintain the temperature below 15°. The mixture was then allowed to warm up to room temperature and allowed to stand for two hours, at the end of which time 500 ml. of ether was added. After standing for several days, the crystalline morpholine hydrochloride was filtered off and washed with ether, which was added to the filtrate. The amino ketone hydrochloride was precipitated by passage of dry hydrogen chloride over the ether solution. The white crystalline material was collected on a filter and washed with ether. Recrystallization from absolute alcohol and dry ether produced white crystals, m.p. 215-216° dec. Yield, 74.5 g. (61.5% of theoretical).

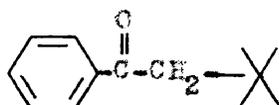
Rubin and Day (40) have reported the melting point of this compound to be 223-224°. It has been reported in a patent (41) as melting at 213-214°.

ω -(4-Morpholino)-acetophenone Methiodide. ω -(4-Morpholino)-acetophenone hydrochloride (8.0 g., 0.025 mole) was dissolved in 25 ml. of water, and the solution was rendered alkaline with 10% sodium hydroxide and extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. After addition of 7.1 g. (0.05 mole) of methyl iodide, the solution was allowed to stand for several days. Crystals of the methiodide separated. Recrystallization from absolute alcohol and

dry ether produced white crystals, m.p. 155-156° dec. Yield, 6.1 g. (70% of theoretical).

The ω -aminoacetophenones and derivatives which are described above are summarized in Table II.

Table II
 ω -Aminoacetophenones



X	b.p.		m.p. of Hydrochloride		m.p. of Methiodide
	Found	Reported	Found	Reported	
$-\text{N}(\text{C}_2\text{H}_5)_2$	103-105° (3 mm.)	148-152° (30 mm.)			153-154° dec.
$-\text{N}(\text{C}_4\text{H}_9)_2$	163-170° (5 mm.)	122-123° (1 mm.)			
	130-140° (3 mm.)	168° (26 mm.)			170-171° dec.
			215-216°	213-214° or 223-224°	155-156° dec.

1-Phenyl-2-amino-1-ethanols. The following amino alcohols were prepared by catalytic hydrogenation of the appropriate amino ketone. Details of the procedure are given in the description of each compound.

1-Phenyl-2-diethylamino-1-ethanol. The method of Marvel and Du Vigneaud (37) was employed for the preparation of this compound. ω -Diethylaminoacetophenone (19.1 g., 0.1 mole) was dissolved in 50 ml. of alcohol, and

0.5 g. of platinum oxide catalyst was added. The mixture was shaken at an initial pressure of 50#, and the reduction was complete in one-half hour. The catalyst was filtered off, and the alcohol was removed by distillation under reduced pressure. The residue was distilled under reduced pressure and the product was obtained as a light yellow oil, b.p. 100-104° (3 mm.). Yield, 13.7 g. (71% of theoretical).

Marvel and Du Vigneaud (37) have reported the boiling point of this compound to be 134-135° (15 mm.).

1-Phenyl-2-diethylamino-1-ethanol Hydrochloride. 1-Phenyl-2-diethylamino-1-ethanol (6.0 g., 0.03 mole) was dissolved in 30 ml. of absolute ether, and dry hydrogen chloride was passed into the solution. The solution turned red, and the hydrochloride separated as an oily wax. Recrystallization from absolute alcohol and dry ether produced white crystals, m.p. 81-82°. Yield, 5.5 g. (77% of theoretical). (Note: these crystals were extremely hygroscopic).

1-Phenyl-2-diethylamino-1-ethanol Methiodide. 1-Phenyl-2-diethylamino-1-ethanol (6.0 g., 0.03 mole) was dissolved in 25 ml. of dry ether, and 8.0 g. (0.06 mole) of methyl iodide was added. After three days, white crystals of the methiodide separated. They were recrystallized from absolute alcohol and dry ether. M.p. 157-158°. Yield, 8.8 g. (85% of theoretical).

1-Phenyl-2-di-n-butylamino-1-ethanol. ω -Di-n-butylaminoacetophenone (21.0 g., 0.085 mole) was dissolved in 50 ml. of alcohol, and 0.1 g. of platinum oxide catalyst was added. The mixture was shaken at an initial pressure of 50#. The reduction was complete in several hours. The catalyst was filtered off, and the alcohol was removed by distillation under reduced pressure. The residue was distilled under reduced pressure, and the product

was collected at 120-130° (3 mm.). Yield, 14.0 g. (66% of theoretical).

Golding and McNeely (38) have reported the boiling point of this compound to be 119-121° (1 mm.).

1-Phenyl-2-(1-piperidino)-1-ethanol. ω -(1-Piperidino)-acetophenone (20.0 g., 0.1 mole) was dissolved in 100 ml. of alcohol, and 0.5 g. of platinum oxide catalyst was added. The mixture was shaken at an initial pressure of 60#. Reduction was complete in forty minutes. The catalyst was filtered off, and the solution was concentrated to a small volume by distillation under reduced pressure. Upon cooling, impure crystals of the alcohol separated. Recrystallization from alcohol and water produced white crystals, m.p. 70-71°. Yield, 18.5 g. (90% of theoretical).

Blicke and Blake (42) have reported the melting point of this compound to be 69-70°.

1-Phenyl-2-(1-piperidino)-1-ethanol Hydrochloride. 1-Phenyl-2-(1-piperidino)-1-ethanol (5.0 g., 0.024 mole) was dissolved in dry ether, and dry hydrogen chloride was passed into the solution. Crystals of the hydrochloride separated. Recrystallization from absolute alcohol and dry ether produced white crystals, m.p. 199-200°. Yield, 5.8 g. (100% of theoretical).

Menley and Turner (39) and Blicke and Blake (42) have reported the melting point of this compound to be 193-194°.

1-Phenyl-2-(1-piperidino)-1-ethanol Methiodide. 1-Phenyl-2-(1-piperidino)-1-ethanol (8.0 g., 0.039 mole) was dissolved in 50 ml. of dry ether, and 11.0 g. (0.078 mole) of methyl iodide was added to the solution. After five days, the crude methiodide separated as yellowish-white crystals. Recrystallization from absolute alcohol and dry ether produced white crystals, m.p. 145-146°. Yield, 12.3 g. (91% of theoretical).

1-Phenyl-2-(4-morpholino)-1-ethanol Hydrochloride. ω -(4-Morpholino)-acetophenone hydrochloride (8.0 g., 0.033 mole) was added to 100 ml. of alcohol containing 4.7 g. of dry hydrogen chloride and 3.3 g. of palladium on charcoal catalyst. The mixture was shaken at an initial pressure of 50#. The reduction was complete in forty-five minutes. The catalyst was filtered off, and the solution was concentrated to a small volume by distillation under reduced pressure. After cooling, twice the volume of ether was added, and the mixture was allowed to stand in the cold for complete precipitation. White crystals separated, which were recrystallized from absolute alcohol and dry ether. M.p. 190-191°. Yield, 6.5 g. (81% of theoretical).

Rubin and Day (40) have reported the melting point of this compound to be 188-188.7°.

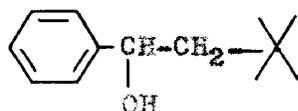
The 1-phenyl-2-amino-1-ethanols and derivatives which are described above are summarized in Table III.

1,1-Diphenyl-2-amino-1-ethanols. The following 1,1-diphenyl-2-amino-1-ethanols were prepared by a Grignard reaction between an excess of phenyl magnesium bromide and the appropriate ω -aminoacetophenone. In all cases, the ratio of molar quantities of reagents used was as follows: 4 gram-atoms of magnesium, 2 moles of bromobenzene and 1 mole of the amino ketone.

The phenyl magnesium bromide was prepared in the usual manner (43). The calculated quantity of dry magnesium turnings was placed in a 3-necked flask of appropriate size, fitted with a mercury-sealed mechanical stirrer, an efficient reflux condenser and dropping funnel. (The magnesium was previously dried at 115° in an oven and cooled in a desiccator). Enough dry ether was placed in the flask to cover the magnesium. Bromobenzene (0.5 g.) in about 20 ml. of dry ether and a crystal of iodine were added. After a short time, the reaction started as evidenced by continued boiling

Table III

1-Phenyl-2-amino-1-ethanols



X	b.p. or m.p.*		m.p. of Hydrochloride		m.p. of Methiodide
	Found	Reported	Found	Reported	
$-\text{N}(\text{C}_2\text{H}_5)_2$	100-104° (3 mm.)	134-135° (15 mm.)	81-82°		157-158°
$-\text{N}(\text{C}_4\text{H}_9)_2$	120-130° (3 mm.)	119-121° (1 mm.)			
	70-71°*	69-70°*	199-200°	193-194°	145-146°
			190-191°	188-188.7°	

without the application of external heat and the appearance of a milky color. Stirring was started, and the remaining bromobenzene in dry ether was added from the dropping funnel at such a rate as to keep the ether boiling without the application of external heat. The mixture was refluxed gently for one hour longer in order to complete the reaction, at the end of which time it acquired a dark color. The Grignard reagent was decanted from excess magnesium into a second 3-necked flask which was fitted with a mercury-sealed mechanical stirrer, efficient reflux condenser and dropping funnel.

The amino ketone was added and the tertiary alcohol was obtained according to the method of Henley and Turner (39).

1,1-Diphenyl-2-diethylamino-1-ethanol. A solution of 38.2 g. (0.2 mole) of ω -diethylaminoacetophenone in 100 ml. of dry ether was added dropwise with stirring to the Grignard reagent at such a rate as to keep the reaction mixture boiling without the application of external heat. After the addition was complete, the mixture was refluxed gently for one hour, cooled and decomposed with cracked ice and a solution of 100 g. of ammonium chloride in 300 ml. of water. The mixture was acidified with 10% acetic acid, and the ethereal layer was extracted with dilute hydrochloric acid. The combined acid extracts, after being washed with a little ether, were rendered alkaline with ammonia and cooled. Crystals of the impure alcohol separated. Recrystallization from alcohol and water produced white crystals, m.p. 48-49°. Yield, 32.0 g. (59.3% of theoretical).

1,1-Diphenyl-2-diethylamino-1-ethanol Hydrochloride. 1,1-Diphenyl-2-diethylamino-1-ethanol (7.0 g., 0.026 mole) was dissolved in dry ether, and the ether solution was dried over anhydrous sodium sulfate. A sufficient amount of alcoholic HCl was added to precipitate the hydrochloride. Recrystallization from absolute alcohol and dry ether produced white crystals, m.p. 176-177°. Yield, 7.5 g. (94% of theoretical).

1,1-Diphenyl-2-diethylamino-1-ethanol Methiodide. 1,1-Diphenyl-2-diethylamino-1-ethanol (5.0 g., 0.019 mole) was dissolved in 25 ml. of absolute alcohol, and 5.7 g. (0.04 mole) of methyl iodide was added. The mixture was refluxed for two hours, cooled, and dry ether was added until incipient cloudiness was apparent. The methiodide separated upon cooling. Recrystallization from absolute alcohol and dry ether produced white crystals, m.p. 204-205°. Yield, 5.3 g. (68% of theoretical).

1,1-Diphenyl-2-di-n-butylamino-1-ethanol. A solution of 61.8 g. (0.25 mole) of ω -di-n-butylaminoacetophenone in 200 ml. of dry ether was added to the Grignard reagent dropwise with stirring at such a rate as to keep the reaction mixture boiling without the application of external heat. After the addition was complete, the reaction mixture was refluxed gently for one hour, cooled and decomposed with cracked ice and a solution of 500 g. of ammonium chloride in 1500 ml. of water. The ethereal layer was extracted with dilute hydrochloric acid, and the combined acid extracts, after being washed with a little ether, were rendered alkaline with 10% sodium hydroxide. A yellow layer separated, which did not crystallize upon cooling. The mixture was extracted with ether, and the combined ether extracts, after being washed with a little water, were dried over anhydrous sodium sulfate. The ether was removed by distillation under reduced pressure, and the residue was dissolved in hot absolute alcohol. Upon addition of a little water, and cooling, crystals separated which tended to turn to an oil upon filtering. These impure crystals were dissolved in ether, and the ether was removed by distillation under reduced pressure. (In an attempt to obtain the hydrochloride, a small amount of the ether solution was dried over anhydrous sodium sulfate, and dry hydrogen chloride was passed in. The hydrochloride separated out as an oil which could not be crystallized.) The residue was dissolved in hot absolute alcohol, and water was added to the hot solution until incipient cloudiness was apparent. The impure amino alcohol separated out upon cooling. Recrystallization from alcohol and water produced white crystals, m.p. 36-37°. Yield, 20.0 g. (24.6% of theoretical).

1,1-Diphenyl-2-(1-piperidino)-1-ethanol Hydrochloride. A solution of 80.0 g. (0.39 mole) of ω -(1-piperidino)-acetophenone in 250 ml. of dry

ether was added dropwise with stirring to the Grignard reagent at such a rate as to keep the ether boiling without the application of external heat. After the addition was complete, the mixture was refluxed gently for one hour, cooled and decomposed with cracked ice and a solution of 500 g. of ammonium chloride in 1000 ml. of water. The ether layer was extracted with dilute hydrochloric acid. The combined acid extracts, after being washed with a little ether, were rendered alkaline with ammonia, and extracted with ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. When dry hydrogen chloride was passed into the dried ether solution, the crude hydrochloride separated as a reddish semi-solid. Recrystallization from absolute alcohol and dry ether produced white crystals, m.p. 223-224° dec. Yield, 55.0 g. (51% of theoretical).

Henley and Turner (39) have reported the melting point of this compound to be 214-219°.

1,1-Diphenyl-2-(1-piperidino)-1-ethanol. The free amino alcohol was obtained as follows: the hydrochloride (20.0 g., 0.063 mole) was dissolved in water, the mixture rendered alkaline with 10% sodium hydroxide and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, and the ether was removed by distillation under reduced pressure. The residue, after recrystallization from absolute alcohol and water, produced white crystals, m.p. 67-68°. Yield, 17.5 g. (97% of theoretical).

1,1-Diphenyl-2-(4-morpholino)-1-ethanol. ω -(4-Morpholino)-acetophenone hydrochloride (40.0 g., 0.165 mole) was dissolved in 100 ml. of water, the solution was rendered alkaline with 10% sodium hydroxide and extracted with ether. The combined ether extracts were washed with a little water and dried over anhydrous sodium sulfate. The ether was removed by distillation under reduced pressure, and the residue was dissolved in 100 ml. of dry ether. This solution of the morpholino ketone in dry ether

was added dropwise with stirring to the Grignard reagent at such a rate as to keep the ether boiling without the application of external heat. After the addition was complete, the mixture was refluxed gently for one hour, cooled and decomposed with cracked ice and a solution of ammonium chloride. The ether layer was extracted with dilute hydrochloric acid. The combined acid extracts were washed with a little ether, and rendered alkaline with 10% sodium hydroxide. After cooling, the crude morpholino alcohol separated. Recrystallization from 70% alcohol produced white crystals, m.p. 77-78°. Yield, 17.5 g. (33% of theoretical).

1,1-Diphenyl-2-(4-morpholino)-1-ethanol Hydrochloride. 1,1-Diphenyl-2-(4-morpholino)-1-ethanol (1.0 g., 0.0035 mole) was dissolved in dry ether, and dry hydrogen chloride was passed into the solution. The crude hydrochloride separated, and recrystallization from absolute alcohol and dry ether produced white crystals, m.p. 204-205°. Yield, 1.1 g., (98% of theoretical).

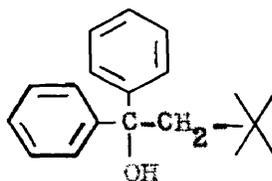
The 1,1-diphenyl-2-amino-1-ethanols which are described above are summarized in Table IV.

1,1-Diphenyl-2-amino-ethylenes. The method of Marxer (36) was employed for the preparation of the following substituted vinylamines. The appropriate tertiary amino alcohols were dehydrated, using acetic anhydride as the dehydrating agent.

Attempted Preparation of 1,1-diphenyl-2-diethylaminoethylene Hydrochloride. The method of King (31) was used for the attempted preparation of this compound. Benzoyl chloride (8.0 ml.) was added to 4.0 g. (0.013 mole) of 1,1-diphenyl-2-diethylamino-1-ethanol hydrochloride, and the mixture was heated for one hour in an oil bath at a temperature of 190-200°. The mixture was cooled to 0°, and dry hydrogen chloride was passed in. After

Table IV

1,1-Diphenyl-2-amino-1-ethanols



X	m.p.	m.p. of Hydrochloride		m.p. of Methiodide
		Found	Reported	
$-\text{N}(\text{C}_2\text{H}_5)_2$	48-49°	176-177°		204-205°
$-\text{N}(\text{C}_4\text{H}_9)_2$	36-37°			
	67-68°	223-224° dec.	214-218°	
	77-78°	204-205°		

standing for some time, white crystals separated, which were recrystallized from alcohol. These crystals, m.p. 98-99°, were not the desired product, since they contained neither nitrogen nor halogen.

The mother liquor was shaken with 10% sodium hydroxide to remove benzoyl chloride. An oil separated which was extracted with ether, and the ether solution was extracted with dilute hydrochloric acid. The acid solution was rendered alkaline with 10% sodium hydroxide, extracted with

ether and the ether solution was dried over anhydrous sodium sulfate. After dry hydrogen chloride was passed in, an oil separated which could not be crystallized. The oil was dissolved in absolute alcohol, and dry ether was added. No product could be obtained.

The method of King was again employed for the attempted preparation of this compound, using the methiodide of 1,1-diphenyl-2-diethylamino-1-ethanol instead of the hydrochloride. Benzoyl chloride (8.0 ml.) was added to 3.5 g. (0.0085 mole) of the methiodide, and the mixture was heated for one hour in an oil bath at 190-200°. The mixture was cooled to 0°, and the product was not obtained. Alcohol was added to destroy the benzoyl chloride, and after dry ether was added, the product could not be obtained. It appeared as though decomposition had occurred, because the reaction mixture was very dark in color, and there was evidence of the liberation of iodine.

The alternate method of King (31) was employed for the attempted preparation of 1,1-diphenyl-2-diethylamino-ethylene. 1,1-Diphenyl-2-diethylamino-1-ethanol hydrochloride (5.0 g., 0.016 mole) was heated with 5 ml. of thionyl chloride at 100° for five minutes. The excess thionyl chloride was removed by heating under reduced pressure, and the residual oil was dissolved in hot acetone. Dry ether was added, and an oily gum separated. The acetone-ether mixture was decanted off, and the residual gum was dissolved in absolute alcohol. After the addition of dry ether, the expected product could not be obtained.

The above procedure was repeated, using the methiodide of 1,1-diphenyl-2-diethylamino-1-ethanol instead of the hydrochloride. This also resulted in failure to obtain the desired compound.

Preparation of 1,1-diphenyl-2-diethylamino-ethylene Hydrochloride.

The method of Marxer (36) was employed for the preparation of this compound.

1,1-Diphenyl-2-diethylamino-1-ethanol (1.5 g., 0.0056 mole) was refluxed with 20 ml. of acetic anhydride for fifteen minutes. The acetic anhydride was removed by heating on a steam bath under reduced pressure. The residue was dissolved in ether, and the ether solution was allowed to stand over anhydrous potassium carbonate for thirty minutes and filtered through cotton. Dry hydrogen chloride was passed into the ether solution, and the crude hydrochloride separated after cooling. Recrystallization from absolute alcohol and dry ether produced white crystals, m.p. 178-179°. Yield, 0.8 g. (57% of theoretical).

The melting point of 1,1-diphenyl-2-diethylamino-1-ethanol hydrochloride, the starting product, is 176-177°. Mixed m.p. of this compound and the product, 157-158° (a depression of 20°).

The nitrogen analysis was a little low, probably because the compound required further purification.

Anal. calc. for $C_{18}H_{22}ClN$: N, 4.87. Found: N, 3.86, 3.79.

(Note: longer periods of reflux time resulted in deamination with the formation of diethylammonium chloride).

Attempted Preparation of 1,1-diphenyl-2-di-n-butylamino-ethylene Hydrochloride. The method of Adamson (32) was employed for the attempted preparation of this compound. 1,1-Diphenyl-2-di-n-butylamino-1-ethanol (5.0 g., 0.015 mole) was dissolved in a mixture of 15 ml. of concentrated hydrochloric acid and 50 ml. of glacial acetic acid, and the mixture was refluxed for three hours. The acids were removed by distillation under reduced pressure, and the residue was dissolved in hot absolute alcohol. Upon the addition of a great excess of dry ether, a small amount of white crystals separated, and were recrystallized from absolute alcohol and dry ether. Melting point determinations indicated that the product was di-n-butylammonium chloride, and that deamination had occurred.

Attempted Preparation of 1,1-diphenyl-2-(1-piperidino)-ethylene

Hydrochloride. The method of Adamson (32), employing the same procedure which was used for the attempted preparation of 1,1-diphenyl-2-di-n-butylamino-ethylene hydrochloride (q.v.), resulted in desmination of 1,1-diphenyl-2-(1-piperidino)-1-ethanol. The product isolated was piperidine hydrochloride.

Preparation of 1,1-diphenyl-2-(1-piperidino)-ethylene Hydrochloride.

The method of Marxer (36) was employed for the preparation of this compound. The procedure was identical with that used for the preparation of 1,1-diphenyl-2-diethylamino-ethylene hydrochloride (q.v.). White crystals, m.p. 186-187° dec. Yield, 82.5% of theoretical.

Anal. calc. for $C_{19}H_{22}ClN$: N, 4.57. Found: N, 4.48, 4.55.

(Note: longer periods of reflux time resulted in desmination with the formation of piperidine hydrochloride.)

Attempted Preparation of 1,1-diphenyl-2-(4-morpholino)-ethylene

Hydrochloride. The method of Adamson (32), employing the same procedure which was used for the attempted preparation of 1,1-diphenyl-2-di-n-butylamino-ethylene hydrochloride (q.v.), resulted in desmination of the of the 1,1-diphenyl-2-(4-morpholino)-1-ethanol. The product isolated was morpholine hydrochloride.

Preparation of 1,1-diphenyl-2-(4-morpholino)-ethylene Hydrochloride.

The method of Marxer (36) was employed for the preparation of this compound. The procedure was identical with that used for the preparation of 1,1-diphenyl-2-diethylamino-ethylene hydrochloride (q.v.), with the exception that the mixture was refluxed for one and one-half hours. White crystals, m.p. 154-155°. Yield, 41.7% of theoretical.

Anal. calc. for $C_{18}H_{20}ClNO$: N, 4.64. Found: N, 4.64, 4.63.

LITERATURE CITED

- (1) Barger and Dale, *J. Physiol.*, 41, 19 (1910)
- (2) Graham and Cortland, *J. Pharmacol. Exp. Therap.*, 81, 360 (1944)
- (3) Bovet et Bovet-Nitti. Structure et Activite Pharmacodynamique des Medicaments du Systeme Nerveux Vegetatif. Bale, Switzerland: S. Karger, 1948. 849 pp.
- (4) Tainter, *Quart. J. Pharm. Pharmacol.*, 3, 584 (1930)
- (5) Tiffeneau. Titres et Travaux Scientifiques. Paris: Masson and Co., 1939. 103 pp.
- (6) Nickerson and Gump, *J. Pharmacol. Exp. Therap.*, 97, 25 (1949)
- (7) Nickerson, Nomaguchi and Goodman, *Federation Proc.*, 5, 195 (1946)
- (8) Columbic, Fruton and Bergmann, *J. Org. Chem.*, 11, 518 (1946)
- (9) Fruton and Bergmann, *J. Org. Chem.*, 11, 543 (1946)
- (10) Gibbs and Marvel, *J. Am. Chem. Soc.*, 56, 725 (1934)
- (11) Pfeiffer, *Science*, 107, 94 (1948)
- (12) Haley, *J. Am. Pharm. Assoc. Sci. Ed.*, 37, 383 (1948)
- (13) Loew, Kaiser and Moore, *J. Pharmacol. Exp. Therap.*, 83, 120 (1945)
- (14) Rohmann and Scheurle, *Arch. Pharm.*, 274, 110 (1936)
- (15) Eddy, *J. Am. Pharm. Assoc. Sci. Ed.*, 39, 245 (1950)
- (16) Cervello, *Arch. ital. Biol.*, 7, 172 (1886)
- (17) Heffter. Handbuch der Experimentellen Pharmakologie, Vol. I. Berlin: J. Springer, 1923. 632 pp.
- (18) Formanek, *Arch. intern. Pharmacodynamie*, 10, 273 (1902)
- (19) Mott and Halliburton, *Trans. Roy. Soc. (London)*, B191, 211 (1899)
- (20) Halliburton, *Ergebn. Physiol.*, 4, 67 (1905)
- (21) Pal, *Z. exp. Path. Therap.*, 9, 191 (1911)
- (22) Kulz, *Arch. exp. Path. Pharmacol.*, 102, 286 (1924)
- (23) Boehm, *Arch. exp. Path. Pharmacol.*, 63, 177 (1910)
- (24) Hunt, *J. Pharmacol. Exp. Therap.*, 28, 367 (1926)

- (25) Hunt and Taveau, Pub. Health and Marine Hosp. Service, Hyg. Lab. Bull., 73, 1 (1911)
- (26) Hunt, J. Pharmacol. Exp. Therap., 6, 477 (1915)
- (27) Schmiedberg and Harnack, Arch. exp. Path. Pharmacol., 6, 101 (1877)
- (28) Schmidt, Arch. Pharm., 242, 705 (1904)
- (29) Meyer, Arch. exp. Path. Pharmacol., 32, 101 (1893)
- (30) Westphal and Hecht, Mediz. u. Chem., 3, 393 (1936). Through Bovet et Bovet Nitti. Structure et Activite Pharmacodynamique des Medicaments du Systeme Nerveux Vegetatif, p. 679. Bale, Switzerland: S. Karger, 1948. 849 pp.
- (31) King and Brownell, J. Am. Chem. Soc., 72, 2507 (1950)
- (32) Adamson, J. Chem. Soc., Suppl. Issue, No. 1, (1949) S144
- (33) Gilman and Blatt. Organic Syntheses, Collective Vol. I. New York: John Wiley and Sons, Inc., 1941. 562 pp.
- (34) Blatt. Organic Syntheses, Collective Vol. II. New York: John Wiley and Sons, Inc., 1943. 632 pp.
- (35) Stoll, Morel and Frey, Helv. Chim. Acta, 33, 1194 (1950)
- (36) Marzer, Helv. Chim. Acta, 24, 209E (1941)
- (37) Marvel and Du Vigneaud, J. Am. Chem. Soc., 46, 2098 (1924)
- (38) Golding and McNeely, J. Am. Chem. Soc., 68, 1847 (1946)
- (39) Henley and Turner, J. Chem. Soc., (1931) 1182
- (40) Rubin and Day, J. Org. Chem., 5, 57 (1940)
- (41) German Patent, 667,356, November, 1938
- (42) Blicke and Blake, J. Am. Chem. Soc., 52, 240 (1930)
- (43) Fieser. Experiments in Organic Chemistry, Part I. New York: D. C. Heath & Co., 1941. 297 pp.