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THE DISSOCIATION CONSTANTS AND ROTATIONS OF SOME ALPHA-SUBSTITUTED ETHYLAMINES

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By

J. Marvin Burch 12/1/54-6

A Thesis Submitted to the Graduate Faculty
for the Degree of

DOCTOR OF PHILOSOPHY

Major Subject: Plant Chemistry

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ACKNOWLEDGMENT

The writer wishes to express his appreciation to Dr. I. B. Johns and Dr. R. M. Hixon for suggesting the thesis problem and for the advice and encouragement needed for its proper development.

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INTRODUCTION

Optical activity, the property of rotating plane polarized light, has been investigated for one hundred and twenty-four years. Arago was the first to observe the phenomenon when he noticed the optical activity of quartz crystals in 1811. Since that date a vast amount of work has been done to add to our knowledge of this subject and to establish a physical and chemical explanation of this property possessed by many inorganic compounds and by thousands of organic compounds.

Biot laid the foundation for subsequent work on optical activity. In 1815, Biot and Seebeck (1) found that water solutions of sucrose and tartaric acid were optically active. This discovery inaugurated the many investigations on tartaric acid and hundreds of sugar derivatives. The discovery in 1817 by Biot (2) that turpentine vapor was capable of rotating plane polarized light proved the phenomenon was not dependent upon a specific orientation of molecules as is the case with crystals possessing this property. In 1835 Biot (3) observed that the rotation varied directly with the length of the column of active substance through which the polarized light passed and introduced the idea of specific rotation. For pure liquid and gaseous optically active compounds he defined the specific rotation by the following equation:

$$[\alpha] = \frac{\alpha}{d \cdot l}$$

where α is the observed rotation, d, the density of the liquid or gas, and l, the length of active substance through which the light passes. The specific rotation of a solution or gaseous mixture is given by the following expression:

$$[\alpha] = \frac{\alpha \cdot 100}{c \cdot l}$$

where α is the observed rotation, c is the concentration of active substance in grams per 100 cc. of solution, and l the distance through which the polarized light passes. The molecular rotation was defined by the following equation:

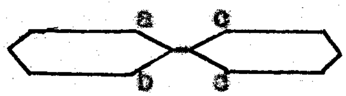
$$[M] = [\alpha]\frac{M}{100}$$

where $[\alpha]$ is the specific rotation and M the molecular weight of the optically active compound. These two concepts, that is, specific and molecular rotations have made it possible to systematize rotation data and to compare rotations on a rational basis.

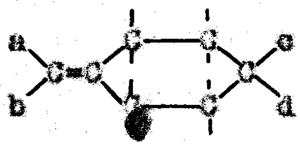
Biot (4) found in 1838 that, in the case of d-tartaric acid solutions, there was a monotonous increase in rotation in going from the long wave lengths to the short wave lengths of the visible spectrum. This phenomenon is known as rotatory dispersion and in the work of Biot is found the origin of the term "normal dispersion", by which a monotonous increase in rotation with a decrease in wave length of the light source is designated. Any other type of dispersion has been called "anomalous dispersion".

About 1848 Pasteur began his classic work on tartaric acid. He found that below 27° C the sodium ammonium salt of racemic tartaric acid was composed of crystals which differed in their crystalline structure, and he pointed out that the two types present were optical antipodes or mirror images of each other. Pasteur laboriously separated these crystals under the microscope and learned that one type was dextrorotatory and the other type laevo-rotatory. This great work led the way to a development of a method of resolving optically inactive racemic mixtures of basic or acidic compounds. Salts formed by the interaction of the dextro and laevo forms of racemic mixtures and the same optically active acid or base have different solubilities so that it is possible to separate the two salts by fractional crystallization. Pasteur discovered another method of resolving optically active compounds when he found that in some instances microörganisms act selectively in their dissimilation of racemic mixtures; that is to say, the living organisms attack one of the forms, dextro- or laevo-rotatory, more rapidly than they do the other form. This method is more restricted and more specific than the one based on fractional crystallization of salts, but it has the advantage of not being restricted to compounds having basic or acidic properties.

LeBel (5) in 1874 and Van't Hoff (6) in 1875 developed independently the concept of the asymmetric carbon atom and its relation to optically active compounds. While this theory has done much to direct investigation in the field of optical activity and to give a picture of dextro and laevo forms, it is neither a sufficient nor a necessary criterion for optical activity and has not explained the fundamental nature of the phenomenon. Since the work of LeBel and Van't Hoff, biphenyl compounds of the type,



and spirane compounds of the type,



have been shown to be optically active. Since compounds of these types do not contain asymmetric carbon atoms it is concluded that the latter are not necessary for optical activity.

Correlations between chemical constitution and optical activity can have very little meaning unless there is a clear understanding of the physical basis and significance of optical rotatory power. Such an understanding involves a thorough knowledge of atomic and molecular structure and the nature of and laws governing light. Although these two subjects are not fully understood it is only by applying what is known about them that real progress in the field of optical activity can be made.

As early as 1825 Fresnel (7) pointed out that optical rotation may be considered as circular double refraction. Plane polarized light may be considered to be composed of right-hand and left-hand circular polarized light, the resultant of whose vectors represents plane polarized light. These two components of plane polarized light may indeed be separated by virtue of the fact that their refractive indices, n_l and n_r, are different. Cotton (8) has observed that there is a difference in the intensity of absorption of right- and left-handed rays. This phenomenon is known as circular dichroism or the "Cotton effect".

In 1915 Born (9) and Oseen (10) suggested that resonators are the cause of optical activity. Following their work, Werner Kuhn (11) in 1929 gave a mathematical treatment of optical activity which shows that vibrating electric oscillators, resonators, in molecules may cause circular dichroism, which in turn is responsible for the rotation of plane polarized light.

As Fresnel (7) pointed out, optical rotatory power may be considered as circular double refraction. If n_l and n_r be the refractive indices for left-handed and right-handed circular light of wave length λ_{vac}, the rotation per centimeter will be:

$$\phi = \frac{\pi}{\lambda_{vac}} (n_l - n_r) \tag{1}$$

A rotation of 10° per centimeter corresponds to a double refraction $n_l - n_r = 3 \cdot 10^{-6}$ for yellow light, according to equation (1), and $\frac{n_l - n_r}{n}$ becomes of the order of one millionth. This calculation led Kuhn to state that (12) "the double refraction is extremely small and the optical activity is but a very small disturbance of ordinary refraction". He also concluded that "Optical activity is a phenomenon of light refraction and, we shall find, in analogy with the law of additivity in molecular refraction, that the optical rotation of a compound is the sum of contributions of the various substituents, or, more accurately, of their absorption bands" (12).

From the foregoing considerations it is clear that the asymmetry of vibrating electric oscillators in an optically active molecule is a more fundamental property than the asymmetry of masses or structural groups. It was pointed out by Kuhn (12) that a given substituent brings into the molecule a certain absorption frequency. This absorption band by itself produces no optical rotatory power but it becomes active by coupling with other bands present in the molecule. If there are two or more active absorption bands in a molecule the optical activity will be a summation of the contributions of the several coupled electric moments.

An attempt to determine the amount and direction of rotation from the molecular structure of the active molecule was made simultaneously by Ph. A. Guye (13) and Crum Brown (14) in 1890. The problem was handled in detail by Guye in a series of papers (15) published from 1891 to 1895. The hypothesis was summarized by Guye (16) in 1893. In his treatment, the so-called product of asymmetry depends only on the masses of the four groups attached to the asymmetric carbon atom. Thus if a, b, c, and d are the formula weights of the groups, then P, the product of asymmetry which is a measure of the amount of the rotation and its sign, is given by the following expression:

$$P = \frac{(a-b)(a-c)(a-d)(b-c)(b-d)(c-d)}{(a+b+c+d)^{*}} K$$

in which K is a characteristic constant. Thus if any two groups are the same, two of the formula weights will be the same and P becomes zero. Also if one interchanges any two of the formula weights a reversal of sign for P is produced. Such a change corresponds to the conversion of a right-rotating form of an active molecule to the left-rotating form.

Experimental results in some homologous series appeared at first to confirm Guye's hypothesis but later work has shown that there are many discrepancies. Isomeric groups having the same formula weights but differing in configuration produce different rotations. Examples are isomeric alkyl radicals and position isomers in aromatic radicals. It was also found that in the majority of homologous series the rotatory power and product of asymmetry are not parallel but subject to manifold deviations. These discrepancies led Guye (17) himself to admit "that it is not alone the masses of the four groups which exert the influence, but also their relative positions, the actions which they have on each other, their configurations, and finally the nature of the elements themselves which are important in determining the directions and extent of rotation".

In 1924 Rule (18) advanced the hypothesis "that the rotatory power of a molecule was a function of the moments of the four groups attached to the asymmetric atom, and that the influence of a substituent on the optical rotation would therefore depend in sign and magnitude upon the polarity of the substituent". While Rule admitted (19) that "no absolute method has yet been discovered for establishing the orientation of an electronegative or electropositive dipole with respect to the hydrocarbon chain to which the substituent is attached", he defined an electronegative group as one "having its dipole situated with the positive end towards the parent molecule and therefore in its electrical influence on the adjacent carbon chain resembling a positive charge. An electropositive group is assumed to be represented by a dipole of the opposite orientation".

Rule (19) discussed polar changes in terms of the electron shift hypothesis. Thus the dipole of the substituent in mono-substituted acetic acids brings about an electron shift which is measured by the degree of ionization of the acid. The effect is illustrated by the following:

$$\underleftarrow{\overset{-}{Cl}\cdot\overset{+}{C}H_2COO}\overset{\rightarrow}{\cdot}H$$

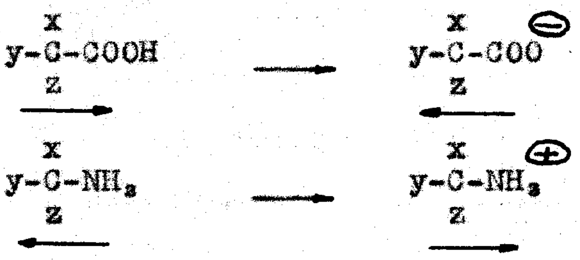
Electron shift facilitating ionization

$$\underrightarrow{H_3\overset{+}{C}\cdot\overset{-}{C}H_2COO}\overset{\leftarrow}{\cdot}H$$

Electron shift repressing ionization

Rule (19) pointed out that in a series of homogeneous l-menthyl esters of monosubstituted acetic acids, $XCH_2\cdot COOH$, the stronger the electronegative character of the substituent present in the acid the higher is the rotation of the ester. The same correlation was noticed in a series of l-menthyl ethers, $C_{10}H_{19}OCH_2X$ in the homogeneous state, where X is the substituent.

It is a general rule that the rotations of optically active acids and bases decrease in magnitude and sometimes even become reversed in sign when the compounds are changed to the ionized state. Where x, y, and z are comparatively non-polar hydrocarbon groups, the electron shift on ionization of acids and amines may be represented by the following:

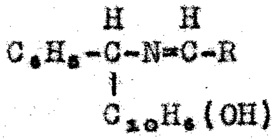


$$\underset{\xrightarrow{\qquad}}{y\text{-}\overset{x}{\underset{z}{C}}\text{-COOH}} \longrightarrow \underset{\xleftarrow{\qquad}}{y\text{-}\overset{x}{\underset{z}{C}}\text{-COO}^{\ominus}}$$

$$\underset{\xleftarrow{\qquad}}{y\text{-}\overset{x}{\underset{z}{C}}\text{-NH}_2} \longrightarrow \underset{\xrightarrow{\qquad}}{y\text{-}\overset{x}{\underset{z}{C}}\text{-NH}_3^{\oplus}}$$

Rule pointed out (19) that, according to his hypothesis that rotatory power is related to the polar properties of the substituent, "firstly, ionization tends to reverse the polar influences of the carbonyl and amino groups, leading to a lower rotatory power, or even to a reversal of sign (exceptions found especially with tartaric acid and its salts), and, secondly, the rotatory powers of the unionized carboxyl derivatives and of the ionized amine should tend to be of one sign and those of the ionized acid and unionized amine should tend to be of opposite sign, if the carboxyl be replaced by an amino group". This statement assumes that a Walden inversion does not occur.

In 1906 Betti began a series of researches (20) designed to show the influence of the chemical character of substituents on optical rotatory power. Working with a series of aldehydo-aminic derivatives of β-naphtholphenylamino methane,



$$C_6H_5-\overset{H}{\underset{C_{10}H_6(OH)}{C}}-N=\overset{H}{C}-R$$

Betti showed that there existed a "remarkable parallelism" between the variation of the rotatory power of the above derivatives and the variation of the dissociation constant of the carboxylic acid RCOOH. The aldehydes used were all substituted benzaldehydes. Betti concluded (20) on the basis of data obtained from over forty compounds of the above mentioned series that "it is easy to recognize that if atoms or groups which help to raise its 'electronegative' character are introduced into the phenylic group of the radical, $=HC-C_6H_5$, the rotation is displaced in a certain sense, whilst if the said substituents tend rather to diminish the negative character of the phenyl radical, the rotation is displaced in the opposite sense".

The rotations were observed in benzene at identical conditions of temperature and concentration, and the dissociation constants taken from Landolt (21) were values determined in water solution. Equations were formulated that expressed the molecular rotation $[M]_D$ in terms of only one variable, P_K for the acid RCOOH.

Betti pointed out (20) that a more fundamental comparison would be one between the permanent electric moment of the molecule and its rotatory power. The electric moments or dipole moments, as calculated from the temperature coefficients of the dielectric constant, were determined for some of these aldehydo-aminic derivatives. This comparison of molecular rotation and electric moments involves the same molecule in solution in the same solvent and at the same concentration, i.e., two different physical properties are determined under the same experimental conditions to obtain a relationship. In this manner Betti was able to show that as the whole electric moment of the compounds in the above mentioned series decreased the magnitude of the rotatory power diminished. He also pointed out "that for null electric moments the rotatory power of substances, even with asymmetric configurations, ought to become zero".

Considering the work of Rule and Betti, it is apparent that the electrical properties of organic radicals exert a marked influence on the rotatory power of optically active compounds. If the electron theory of valence holds, variations in the dissociation or ionization of organic compounds may be considered to be the result of variations in the electrical properties of the so-called non-polar radicals attached to the polar groups. Many investigations have been made in an attempt to find an index for the electrical properties of organic radicals; and Henrich, Johnson, and

Hahn (22) have given a summary of the earlier theories and work pertaining to classifying radicals on the basis of their electrical properties.

Hixon and Johns (23) established a functional relation between the logarithm of the dissociation constants of amines, RNH_2, and some property of the radical R which they termed "electron sharing ability". For each dissociation constant there corresponded a non-polar organic radical. When the logarithms of the dissociation constants of the amines were located on an arbitrarily drawn exponential curve as ordinates, abscissa values for the radicals were fixed. When the logarithms of the dissociation constants of a series of carboxylic acids, RCOOH, were plotted as ordinates against these fixed values for the radicals a smooth exponential curve was obtained. The curves for the amines and acids were expressed in mathematical form by expressions of the type:

$$\text{Log } K = Ke^{ax+b} + c$$

where log K represents the logarithm of the dissociation constant and x represents the abscissa value for the radical, termed "electron sharing ability".

Subsequent work by several investigators (24) which has further demonstrated the soundness of considering that the arbitrary abscissa values of the radicals are factors influencing the ionization of organic compounds and that this procedure is a dependable method for classifying organic radicals on a basis of their electrical properties, has been summarized by Carr (25). These investigations include ionizations of acids and bases in water, methanol, and ethanol, ionizations of organo mercuric nitrates in water, equilibrium constants of the reaction:

$$2RHgI \rightleftharpoons R_2Hg + HgI_2$$

in ethanol, and equilibrium constants for the reaction:

$$Cl_3CH(OH)SR \rightleftharpoons Cl_3CHO + RSH$$

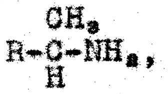
in benzene. Carr (26) added a true double decomposition reaction:

$$RHgCN + HCl \rightleftharpoons RHgCl + HCN$$

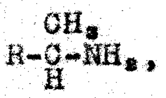
to the previous work. In all cases the logarithms of dissociation constants or equilibrium constants plotted against the abscissa value for the radicals gave smooth curves to which could be fitted mathematical equations of the form:

$$\text{Log } K = ke^{ax+b} + c$$

STATEMENT OF THE PROBLEM

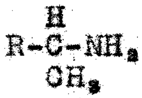
With a view further to clarify the effect of varying radicals in optically active organic compounds, the work presented in this thesis was undertaken. A series of α-substituted primary ethyl amines,  $R-\overset{CH_3}{\underset{H}{C}}-NH_2$, in which only the radical R varied, were prepared and resolved. In order to determine the influence of the substituent R on the rotatory power, rotations of the amines in the homogeneous state, in methanol, in ethanol, in hexane, and of the hydrochlorides in methanol were measured.

Studies were made to determine the effect of a change in pH on the rotatory power. This was accomplished by progressively adding gaseous HCl to the active base until complete neutralization had occurred and observing the rate of change of the rotation. It was expected that such an investigation would furnish evidence concerning the influence of ionization on rotatory power.

In the series,  $R-\overset{CH_3}{\underset{H}{C}}-NH_2$, it is conceivable that changing R from a comparatively "electronegative " radical to a comparatively "electropositive" radical may even reverse the sign of the rotation. To determine whether or not such is the case it is necessary to compare the rotations of compounds which have the same absolute configuration. In order to establish this fact one of the optically active compounds of the series must be converted into another member of the series and the influence on the direction of rotation observed.

Configurational studies of this type were carried out in such a manner that the probability of a Walden inversion occurring was remote.

The dissociation constants of six of the series of α-substituted ethyl amines were determined in methanol by the half-neutralization method in order to contribute further data in support of the work of Hixon and Johns (23) and to establish a relationship between electrical properties of the radicals R and $[M]_D$ for the amines, $R-\overset{H}{\underset{CH_3}{C}}-NH_2$



EXPERIMENTAL PART

Preparation and Resolution of Compounds.

Secondary butylamine was prepared by the reduction of ethyl methyl ketoxime (27) with sodium and absolute alcohol. The oxime was prepared by mixing 265 grams (3.7 moles) methyl ethyl ketone with a solution of 260 grams (3.7 moles) hydroxylamine hydrochloride and 150 grams (3.7 moles) sodium hydroxide in 500 cc. water. The mixture was allowed to stand at room temperature for 40 hours whereupon an oily layer separated. The oxime distilled at 149-151° C. The yield was 86 per cent of the theoretical amount. Ninety grams of the oxime reduced with 250 grams of sodium in 2 liters of absolute alcohol gave 60 grams of the amine hydrochloride (55 per cent of the theoretical amount). The base was liberated with KOH and dried over solid KOH. The amine was then distilled at atmospheric pressure, b.p. 65-66° C.

Resolution of secondary butylamine was carried out according to the method of Leithe (28). Enough d-tartaric acid was added to a water solution of the amine to form the acid tartrate. The d-base-d-hydrogen tartrate, which crystallizes first, was recrystallized three times to a constant melting point of 98-99° C. When dried in a vacuum desiccator at 80° C the melting point of the salt was raised to 150° C. The free amine was liberated with KOH, dried over solid KOH and distilled at atmospheric pressure. B.P. 65° C, $d_4^{20} = 0.726$,

α_D (no solvent) = +5.15, 20°, 1 dm. tube, $[\alpha]_D^{20}$ = +7.10°, Leithe's value $[\alpha]_D^{15}$ = +7.80 (28).

$[\alpha]_D^{20}$ (methyl alcohol, c = 9.54) = +2.93°
$[\alpha]_D^{25}$ (ethyl alcohol, c = 2.49) = +4.01°
$[\alpha]_D^{25}$ (hexane, c = 13.4) = +6.91°

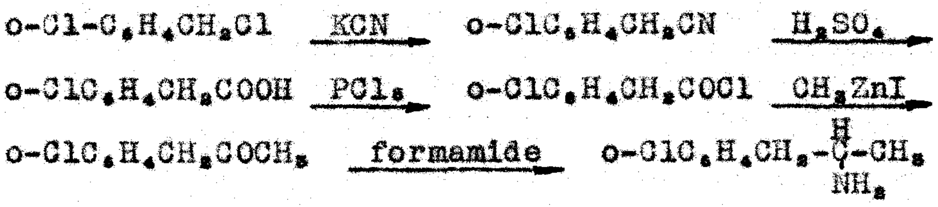
α-Benzylethylamine was prepared from benzylmethyl ketone by a modification of the Wallach (29) reaction. Benzylcyanide was prepared by refluxing for six hours an alcoholic solution of benzyl chloride and potassium cyanide. B.P. 95°/10 mm. Phenylacetic acid was prepared by hydrolyzing benzyl cyanide with conc. H_2SO_4 (1:1). Benzylmethyl ketone was prepared by the method of Sabatier (30). This method involves passing a mixture of glacial acetic acid and phenylacetic acid over a manganese oxide catalyst at 400° C. The ketone, boiling at 215-230° C, was prepared in 46 per cent yield by this method.

The method of Wallach for preparing primary amines from ketones was modified by using formamide instead of ammonium formate. Fifty-seven grams of benzylmethyl ketone and 70 grams formamide were refluxed gently without stirring for 20 hours. The contents of the flask was homogeneous at the end of this time. Concentrated sodium hydroxide was added and the mixture refluxed for 12 hours. The reaction mixture was extracted with ether. The ether extract was then extracted with an aqueous HCl solution. The base was regenerated from the HCl solution with sodium hydroxide and extracted again with ether. After drying the ether extract over solid KOH the benzylamine hydrochloride was prepared by passing dry HCl gas into the ether solution. Yield, 30 grams hydrochloride (46 per cent of the theoretical amount). The base was freed by adding KOH and was then dried over solid KOH for two days. The amine was distilled under reduced pressure, b.p. 70-80°/8 mm. A benzoyl derivative which melted at 130° C was prepared.

Analysis of benzoyl derivative:

Wt. sample	cc. N_2	Temp.	Pressure	Per cent nitrogen Found	Per cent nitrogen Calcd. for $C_{16}H_{17}ON$
0.00267 g.	0.139	22° C	725	5.62	5.86

α-o-Chlorobenzylethylamine was prepared for the first time by the following series of reactions:



$$\text{o-Cl-}C_6H_4CH_2Cl \xrightarrow{KCN} \text{o-}ClC_6H_4CH_2CN \xrightarrow{H_2SO_4}$$

$$\text{o-}ClC_6H_4CH_2COOH \xrightarrow{PCl_5} \text{o-}ClC_6H_4CH_2COCl \xrightarrow{CH_3ZnI}$$

$$\text{o-}ClC_6H_4CH_2COCH_3 \xrightarrow{\text{formamide}} \text{o-}ClC_6H_4CH_2\text{-}\underset{NH_2}{\overset{H}{C}}\text{-}CH_3$$

o-Chlorobenzylcyanide, b.p. 120° C/9 mm., was prepared in 90 per cent yield from o-chlorobenzyl chloride. o-Chlorophenylacetic acid was prepared in 95 per cent yield by hydrolyzing o-chlorobenzyl cyanide with H_2SO_4. o-Chlorophenylacetyl chloride was prepared by the method of Metzner (31). A product boiling at 130-135° C/20-30 mm. was prepared in 83 per cent yield. o-Chlorobenzylmethyl ketone was prepared by reacting zinc methyl iodide with the acid chloride. One hundred and sixty-five grams of the acid chloride gave 105 grams of the ketone, b.p. 125-130° C/ 15 mm. This was a yield of 70 per cent of the theoretical amount.

The o-chlorobenzylmethyl ketone was characterized by preparing the oxime which melted at 120°C. The white crystalline body was recrystallized from petroleum ether and dried in a vacuum desiccator.

Analysis of the oxime:

				Per cent nitrogen	
Wt. Oxime	cc. N_2	Temp.	Bar. Pres.	Found	Calcd. for $C_9H_{10}NOCl$
0.007200	0.550	23°C	737	7.43	7.63

α-o-Chlorobenzylethylamine was prepared by the method of Wallach (29) modified as in the preparation of α-benzylethylamine. Twenty-four grams of ketone and 50 grams of formamide gave 15 grams of the hydrochloride, a yield 52 per cent of the theoretical amount. The free amine was regenerated with KOH and dried over solid KOH. B.P. 75-80°C/8 mm., $d_4^{25} = 1.0789$, $n_D^{25} = 1.5418$.

Analysis of amine:

				Per cent nitrogen	
Wt. Amine	cc. N_2	Temp.	Bar. Pres.	Found	Calcd. for $C_9H_{12}NCl$
0.028584	2.120	20°C	737	8.22	8.27
0.016090	1.182	20°C	745	8.16	

The benzoyl derivative was prepared by shaking the amine with benzoyl chloride in a weak KOH solution and recrystallizing from alcohol. M.P. of benzoyl derivative, 135-136°C.

Analysis of benzoyl derivative:

				Per cent nitrogen	
Wt. Compound	cc. N_2	Temp.	Bar. Pres.	Found	Calcd. for $C_{16}H_{16}ONCl$
0.010840	0.538	28°C	729	5.27	5.12
0.008274	0.406	28°C	728	5.23	

α-o-Chlorobenzylethylamine was resolved by using d-tartaric acid. Twelve grams of the pure amine and 10 grams tartaric acid were dissolved in a boiling solution of 100 cc. water and 100 cc. ethyl alcohol. The solution was allowed to cool to room temperature. At the end of three days 16 grams of solid material had crystallized. The mother liquor was filtered off and the first fraction of crystals recrystallized twice from an alcohol water solution made up of equal parts alcohol and water. Seven and five-tenths grams of the d-base d-acid, which melted at 175°C, was obtained. $[\alpha]_D^{24}$ (in water conc. = 2.74) = +21.1°.

Analysis of d-base d-acid tartrate:

Wt. Sample	cc. N_2	Temp.	Bar. Pres.	Per cent nitrogen Found	Per cent nitrogen Calcd. for $C_{13}H_{18}NO_6Cl$
0.003470	0.138	27°C	745	4.34	4.38
0.003704	0.152	27°C	745	4.48	

The free base dried over solid KOH gave the following constants: b.p. 75-77°/6 mm., d_4^{25} = 1.078, α_D = +14.9 at 25°C 1 dm. tube, $[\alpha]_D^{25}$ = +13.7°, $[\alpha]_D^{25}$ (methanol, conc. = 10.3) = +11.4°, (hexane, conc. = 13.0) = +12.7°.

The hydrochloride of the dextro base gave the following constants: m.p. 175-176°C, $[\alpha]_D^{27}$ (in water, c = 3.78) = +9.0°, $[\alpha]_D^{27}$ (in methyl alcohol, c = 8.66) = +4.1°.

The benzoyl derivative of the d-base gave the following constants: m.p. 166°C, $[\alpha]_D^{28}$ (in ethyl alcohol, c = 0.97) = +97°.

Analysis of benzoyl derivative:

Wt. Sample	cc. N_2	Temp.	Bar. Pres.	Per cent nitrogen Found	Per cent nitrogen Calcd. for $C_{16}H_{16}ONCl$
0.001926	0.093	26°C	725	5.15	5.12

α p-Tolylethylamine was prepared by a modification of Wallach's method (29). One hundred grams p-tolylmethyl ketone and 200 grams ammonium formate were refluxed at 135-145°C for 65 hours. Concentrated sodium hydroxide was added and the mixture refluxed for 40 hours. Water was added and the basic material distilled into a 1:1 solution of HCl and water. The excess water and HCl were distilled off under reduced pressure until the hydrochloride crystallized in the distilling flask. The amine was regenerated with KOH and extracted with ether. After drying the ether over solid KOH the hydrochloride was precipitated by passing in dry HCl gas. Yield, 60 grams (50 per cent of the theoretical amount).

The hydrochloride was treated with KOH and the liberated amine dried over solid KOH and distilled at atmospheric pressure. B.P. 204°C, d_4^{20} = 0.917.

The resolution of α-p-tolylethylamine was carried out according to the method of Ingersoll (32). Nineteen grams of d-camphoric acid and 13 grams of the pure amine were dissolved in 100 cc. ethyl alcohol and 200 cc. water. The solution was boiled until clear and allowed to stand at room temperature for several days. The octahedral crystals of the salt formed by the l-base with the d-acid separating first were recrystallized twice from a water-alcohol mixture. Fifteen grams of the pure salt, melting at 172° C, was obtained. By evaporating the mother liquor and recrystallizing several times, 13 grams of the d-base d-acid salt, m.p. 188° C, was obtained. One and seven hundred and two thousandths grams of the l-base d-acid salt made up to 25 cc. with 95 per cent ethyl alcohol gave the following rotation in a 2 dm. tube: $\alpha_D^{25} = 1.23°$, $[\alpha]_D^{25} = +9.05°$. Ingersoll's value, $[\alpha]_D^{25} = 8.75°$ (32).

One and six hundred and five thousandths grams of d-base d-acid salt made up to 25 cc. with 95 per cent ethyl alcohol gave the following rotation in a 2 dm. tube: $\alpha_D^{25} = +2.60$, $[\alpha]_D^{25} = +20.2°$. Ingersoll's value, $[\alpha]_D^{25} = +23.1°$ (32).

The camphorates were treated with KOH and dried over solid KOH before distilling.

l-α-p-Tolylethylamine, b.p. 205° C. Rotation without solvent, 1 dm. tube $\alpha_D^{25} = -24.9°$, $[\alpha]_D^{25} = -27.1°$.

d-α-p-tolylethylamine, b.p. 204° C. Rotation without solvent 1 dm. tube $\alpha_D^{25} = +30.3°$, $[\alpha]_D^{25} = +32.4°$. This value is slightly less than Ingersoll's value, $[\alpha]_D^{25} = +34.6°$ (32), $[\alpha]_D^{20}$ (in hexane, c = 13.5) = +31.5°, (in methyl alcohol, c - 9.91) = +22.7°, (in ethyl alcohol, c = 20.6) = +22.1°, $[\alpha]_D^{20}$ (hydrochloride in methyl alcohol, c = 19.0) = 6.3°.

α-Phenylethylamine was prepared by a modification of the Wallach method (29). One hundred grams acetophenone and 100 grams formamide, heated at 160-170° for 40 hours and then refluxed with concentrated sodium hydroxide, yielded 75 grams of the amine hydrochloride, 58 per cent of the theoretical amount. The extraction and purification were carried out as in the preparation of α-benzylethylamine. The free base dried over solid KOH boiled at 185-187°C.

The resolution of α-phenylethylamine was carried out according to the method of Ingersoll (33). Fifty grams of amine, b.p. 185-187°C, and 30 grams l-malic acid were dissolved in 90 cc. water. Enough acetic acid to neutralize the excess base was added and then enough water to make the total volume 200 cc. The solution was boiled until clear and then allowed to evaporate at room temperature for several days. The salt, which crystallized slowly, was filtered off and recrystallized twice from water. Twenty-six grams of the d-α-phenylethylamine l-malate, with a melting point of 182°C, was obtained. The free base dried over solid KOH boiled at 184-185°C. d_4^{20} = 0.950 (33).

Rotation without solvent: 1 dm. tube, α_D^{25} = +37.0°, $[\alpha]_D^{25}$ = 38.9°.

Ingersoll's value $[\alpha]_D^{20}$ = +39.5° (33).

$[\alpha]_D^{25}$ (in hexane, c = 9.75) = +38.4

$[\alpha]_D^{25}$ (in methyl alcohol, c = 7.36) = +28.0°

$[\alpha]_D^{20}$ (in ethyl alcohol, c = 14.31) = +25.8°

$[\alpha]_D^{20}$ (hydrochloride in methyl alcohol, c = 13.1) = +7.25°

α-p-Xenylethylamine (α-p-diphenylethylamine).

p-Phenylacetophenone was prepared by the method of Drake and Bronitsky (34). A product melting at 119-120° was used for preparing p-phenylacetophenone oxime by the method of Ingersoll and White (35). One hundred and fifty grams of the ketone yielded 150 grams of the oxime melting at 180° C. α-p-Diphenylethylamine was made by the method of Ingersoll and White (35). Forty grams of oxime, m.p. 180° C, was reduced with 3 per cent sodium amalgam in ethyl alcohol. Twenty-five grams of the hydrochloride melting at 220° C represented a 58 per cent yield.

The amine was freed with NaOH, extracted with benzene, and dried over solid KOH. After removing the benzene under reduced pressure the amine remained as an oil which solidified on cooling. The amine forms a carbonate readily in air and is extremely difficult to purify. Some of the amine was sealed in ampules for dissociation constant measurements. The benzoyl derivative obtained melted at 184° C. Ingersoll gives 179° C (corrected) (35).

Resolution of α-p-diphenylethylamine was accomplished by the method of Ingersoll and White (35). Twenty grams of the amine hydrochloride was treated with NaOH solution to liberate the free base. Twelve grams of l-malic acid was added to the free base in 300 cc. of hot water. The d-base l-acid crystallized from the water solution on cooling and was recrystallized from alcohol. Ten grams of the d-base l-acid, melting at 178-179° C, was obtained.

Rotation of the hydrochloride of d-α-p-diphenylethylamine: $[\alpha]_D^{20}$ (in water, c = 2.24) = +10°. Ingersoll's value (35) (c = 2.0) $[\alpha]_D^{28}$ = 12.8°.

Ingersoll's value for the free base in ethyl alcohol (35): $[\alpha]_D^{25}$ (in ethyl alcohol, c = 8.92) = +24.8°.

Absolute methyl alcohol used in the measurement of dissociation constants was prepared by the method of Hartley and Raikes (36). Synthetic methanol was refluxed over aluminum amalgam and distilled through a fractionating column. The methanol was then distilled from freshly prepared anhydrous copper sulfate to remove volatile impurities, and kept in stoppered Erlenmeyer flasks.

Measurement of Dissociation Constants in Methyl Alcohol.

The apparatus used in this work was modeled after that of Goodhue and Hixon (37). The vacuum tube potentiometer of Goodhue, Schwarte and Fulmer (38) was used to eliminate difficulties arising from the high resistances of the methyl alcohol solutions. A calomel half-cell made up in a 0.1 normal methyl alcohol solution of sodium chloride was used as reference cell. Since the cell can not conveniently be prepared to give a definite potential, the e.m.f. of the calomel half-cell was checked against silver-silver chloride electrodes, freshly prepared by the method of Harned (39). The cell used had an e.m.f. of 0.0453 volt referred to the silver-silver chloride electrode. After three months time this value had changed to 0.0462 volt.

According to Buckley and Hartley (40) the e.m.f. of the silver-silver chloride electrode referred to the normal hydrogen electrode in methyl alcohol is 0.0711 volt. This value must be added to the voltage of the calomel half-cell to refer it to the normal hydrogen electrode.

The hydrogen electrodes used were made of flags about 5 mm. square and were always used in duplicate. The electrodes were platinized in a 3 to 5 per cent solution of platinic chloride with a current density of 0.4 amperes for four minutes. After being washed with distilled water the platinized electrodes were electrolyzed in dilute sulfuric acid for about five minutes. They were then washed with distilled water and finally with absolute methyl alcohol. Freshly prepared electrodes which checked within ±0.0002 volt were used for each e.m.f. determination. Palladium electrodes were prepared in a similar manner using 3 to 5 per cent palladium chloride in HCl solution instead of platinic chloride.

The procedure used for the actual measurement of the e.m.f.'s was the same as that used by Goodhue and Hixon (37). The pure amines, weighed samples sealed in ampules, were half-neutralized with methyl alcohol solutions of hydrochloric acid. The HCl solutions were prepared by passing dry HCl gas into absolute methyl alcohol which was then standardized by titrating with a standard aqueous solution of sodium hydroxide. All concentrations were expressed as molal concentrations of the total amine content. Care was taken to exclude moisture from the solutions. The half-neutralized solutions were placed in the U-tube of Figure 1. The hydrogen electrodes

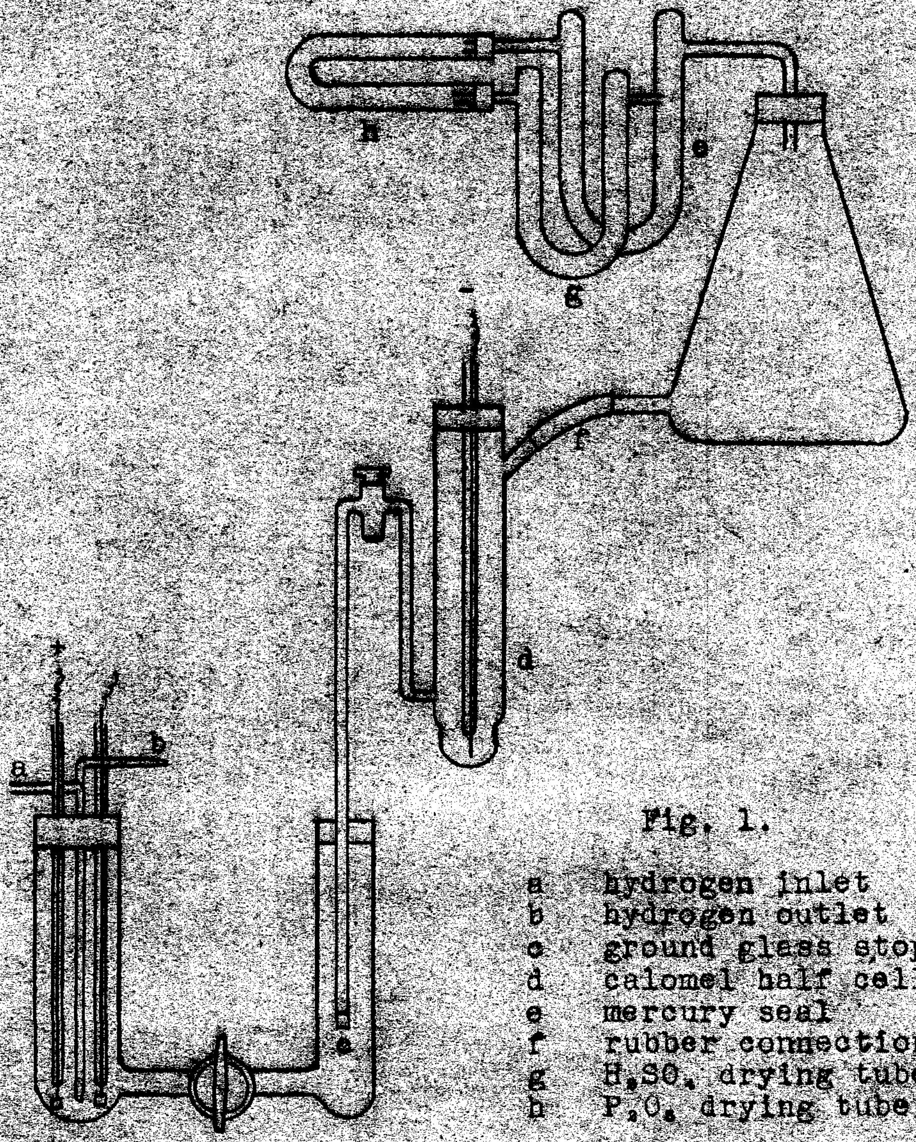


Fig. 1.

a	hydrogen inlet
b	hydrogen outlet
c	ground glass stopper
d	calomel half cell
e	mercury seal
f	rubber connection
g	H_2SO_4 drying tube
h	P_2O_5 drying tube

This drawing is used through the courtesy of C. Mehltretter.

were placed in the left arm of the U-tube which was connected with the right arm by means of a ground glass stop-cock. The calomel half-cell, d, was introduced into the right arm by means of a ground glass joint, c, which prevented the mixing of the two solutions and subsequent poisoning of the hydrogen electrodes. Dry hydrogen, bubbled through absolute methyl alcohol, entered the cell through the tube, b, and left through tube a. Voltage readings were taken on the vacuum tube potentiometer set mentioned above for a period of at least two hours. Measurements were made in an air thermostat at 25° C, ±0.1° C. All hydrogen chloride solutions and half-neutralized amine solutions were used immediately to avoid errors due to esterification (41).

The calculation of the dissociation constants in methyl alcohol at 25° C was the same as the calculation in water except that the dissociation constant for methyl alcohol (1.95×10^{-17}) (40) was substituted for that of water. The equations used in the calculations were:

$$-\log a_H = \frac{E + E_{bar} - E_{cal}}{0.0591}$$

$$pK_{B_{CH_3OH}} = -\log K_{CH_3OH} - (-\log a_H)$$

$$pK_{B_{CH_3OH}} = 16.6990 - (\log a_H)$$

$$K_{B_{CH_3OH}} = \text{antilog}\left[-\,(pK_{B_{CH_3OH}})\right]$$

Where:

a_H = activity of hydrogen ion

E = observed e.m.f.

E_{bar} = e.m.f. correction for barometric pressure

E_{cal} = e.m.f. of calomel half-cell referred to normal hydrogen electrode.

K_{CH_3OH} = dissociation constant of methyl alcohol at 25°C

$K_{B_{CH_3OH}}$ = dissociation constant of amine in methyl alcohol

The data for the dissociation constants are given in Table I.

TABLE OF RESULTS I.

Compound	Molal conc.	e.m.f. corr. to 760 mm.	$-\log a_H$	$pK_{B_{CH_3OH}}$	$K_{B_{CH_3OH}}$ (avg.)
sec-Butylamine	0.0539 0.0554	0.8090 0.8104	11.72 11.74	4.98 4.96	1.08×10^{-5}
α-benzylethylamine	0.0776	0.7796(a)	11.23	5.47	3.38×10^{-6}
α-o-chlorobenzyl ethylamine	0.0384	0.7696(a)	11.04	5.66	2.19×10^{-6}
α-p-tolylethylamine	0.0472 0.0391	0.7686 0.7679	11.03 11.02	5.67 5.68	2.11×10^{-6}
α-phenylethylamine	0.0625 0.0571	0.7604 0.7603	10.90 10.90	5.80 5.80	1.58×10^{-6}
α-p-diphenylethylamine	0.0519 0.0549	0.7545 0.7543	10.80 10.79	5.90 5.91	1.24×10^{-6}

(a) e.m.f. calomel half-cell = 0.1173 volt.
e.m.f. calomel half-cell for other measurements = 0.1164 volt.

Measurement of Rotations.

Apparatus Used.

The polariscope used was a Franz Schmidt and Haensch instrument. The light source used throughout the work was a sodium arc light of wave length 5896 Å. Most of the measurements were made with a micro tube 10 cm. in length. A few measurements were made with a 20 cm. tube.

The polariscope and sodium arc lamp were enclosed in a composition board air bath. Although no effort was made to maintain a constant temperature, nearly all of the measurements were made between 20 and 25° C. The tube was placed in the polariscope and the rotation read after the temperature of the tube and its contents had acquired that of the surrounding air. The temperature, at which each observation was made, was recorded. Observed readings could be checked by different observers to ±0.05°.

Measurement of Rotation of Solutions.

Solvents used in the rotation studies were 95 per cent ethyl alcohol, purified methyl alcohol, and hexane (Skelly solvent B, fraction boiling at 62-68° C). Solutions of the amines were made up from weighed ampules. The amine hydrochloride solutions were made up by neutralizing the amines with the calculated amount of a methyl alcohol HCl solution. All concentrations were expressed in grams per hundred cc. of solvent.

Table of Rotation Data.

The rotation data are tabulated in Table II. The equations used in the calculations are the following:

For pure amines,

$$[\alpha]_D^t = \frac{\alpha}{d \cdot l}$$

For the solutions,

$$[\alpha]_D^t = \frac{\alpha 100}{c \cdot l}$$

Where,

$[\alpha]_D^t$ = specific rotation of D line at temperature t

α = observed rotation

d = density of pure amine

c = concentration in grams per 100 cc. solvent

l = length of tube in decimeters

And,

$$[M]_D^t = \frac{[\alpha]_D^t \, 100}{M.W.}$$

Where,

$[M]_D^t$ = molecular rotation of D line at temp. t

$[\alpha]_D^t$ = specific rotation of D line at temp. t

M.W. = molecular weight of amine

Effect of pH on Rotation of d-α-Phenylethylamine.

One and two hundred and seventeen thousandths grams of d-α-phenylethylamine was dissolved in 26.5 cc. of methyl alcohol. The e.m.f. of the hydrogen electrode against the calomel half-cell in methyl alcohol was determined by means of the vacuum tube potentiometer described previously. Dry gaseous HCl was passed into the solution in steps and the e.m.f. and rotation measured after each addition until the

SUMMARY OF ROTATION DATA FOR A SERIES OF α-SUBSTITUTED ETHYLAMINES

TABLE II.

Radical		No solvent	Hexane	Methyl alcohol	Ethyl alcohol	Hydrochloride in CH_3OH	Hydrochloride in H_2O
Ethyl-	$[M]_D$	5.20	5.05	2.14	2.92	-0.99	
	Temp.	20	22	20	23	20	
	Conc.		13.40	9.54	2.49	7.56	
Cyclohexyl- (a)	$[M]_D$	-4.06					-6.35
	Temp.	15					15
	Conc.						10.22
Hexahydrobenzyl- (a)	$[M]_D$	11.80					-2.54
	Temp.	15					15
	Conc.						5.65
o-Chlorobenzyl-	$[M]_D$	23.2	21.5	19.0		6.93	15.4
	Temp.	25	25	25		27	27
	Conc.		13.0	10.3		8.66	3.78
Benzyl- (a)	$[M]_D$	48.1	48.3	39.7	46.6		33.5
	Temp.	15	15(b)	15	15		15
	Conc.		9.23	8.62	10.62		9.0
p-Tolyl-	$[M]_D$	44.5	42.5	30.7	29.9	10.8	
	Temp.	20	20	20	22	16	
	Conc.		13.5	9.9	20.6	19.	
Phenyl-	$[M]_D$	47.0	46.5	33.2	31.7	11.4	
	Temp.	25	26	25	20	15	
	Conc.		9.75	7.36	14.1	13.1	
p-Xenyl- (c)	$[M]_D$	solid			48.9		30.
	Temp.				25		25
	Conc.				8.92		2.02

(a) Leithe, *Ber.*, *65*, 663-666.
(b) Measured *in* cyclohexane.
(c) Ingersoll, *J. Am. Chem. Soc.*, *54*, 279 (1933).

amine was completely neutralized. Table III gives the data obtained in this experiment. Similar runs were made with α-p-xenylethylamine and α-p-tolylethylamine.

TABLE III.

Concentration = 4.59 grams per 100 (based on amine at start)

0.1156 v. = e.m.f. of calomel half-cell

Temp. = 25° C

e.m.f.	+α	pH	$[\alpha]_D^{25}$	$[M]_D^{25}$
0.895	1.28	13.3	28.05	34.0
0.801	1.10	11.7	24.10	29.2
0.795	1.06	11.6	23.21	28.1
0.774	0.90	11.2	19.70	23.8
0.729	0.52	10.5	11.38	13.8
0.200	0.37	1.5	8.11	9.8

pH for 1/2 neutralization of α-phenylethylamine = 10.9

Proof of Configuration of d-o-Chlorobenzylethylamine.

d-α-o-Chlorobenzylethylamine was changed to d-α-benzylethylamine by catalytic hydrogenation. Sixty-three hundredths gram of the pure dextro amine dissolved in 25 cc. ethyl alcohol and 5 cc. glacial acetic acid was catalytically reduced using 0.1 gram palladium oxide catalyst. The catalyst was prepared by the method of Shriner and Adams (42). The hydrogenation was carried out at room temperature and about six atmospheres pressure for five hours. A test with silver nitrate showed the presence of the chloride ion at the end of this time.

After evaporating nearly to dryness on the steam plate, the base was liberated with solid KOH and extracted with ether. After evaporating off the ether the benzoyl derivative was prepared by shaking the base with benzoyl chloride and dilute KOH.

The benzoyl derivative after recrystallization from alcohol gave the following constants: m.p. 160° C, $[\alpha]_D^{22}$ (in ethyl alcohol c = 1.66) = +69°, $[\alpha]_D^{22}$ (in chloroform c = 3.00) = -13.7°.

Analysis of benzoyl derivative:

Wt. sample	cc. N_2	Temp.	Pres.	Per cent nitrogen
0.006996	0.378	23°	731	5.80

Calcd. for $C_{16}H_{17}ON$, per cent N = 5.86

Qualitative analysis of the benzoyl derivative showed the absence of chlorine.

DISCUSSION OF RESULTS

Inspection of the data on the dissociation constants of the α-substituted ethylamines, Table I, shows that the compounds have been arranged in the decreasing order of their dissociation constants. This variation in dissociation constants may be considered to represent a variation in the properties of the radical, R, in $R-\overset{CH_3}{\underset{H}{C}}-NH_2$ which influences the degree of dissociation. While there may be more than one property which influences dissociation, the predominating property is surely an electrical characteristic of the radical which tends to repel or attract the hydroxyl ion if the electronic theory of valence is valid.

According to the work of Hixon and Johns (23) and others (24), it is to be expected that plotting the dissociation constants of the amines, $R-\overset{CH_3}{\underset{H}{C}}-NH_2$, as ordinates against the arbitrary abscissa values for the radical R will result in a smooth curve of the exponential type:

$$\log K = ke^{ax+b} + c$$

The curve shown in Figure 2 is obtained by plotting the logarithms of the dissociation constants of the α-substituted ethylamines in methanol as ordinates and the abscissa values for the radicals as abscissa. The curve obtained by Goodhue and Hixon (24d) for primary amines in methanol is put on the same graph for the sake of comparison. The slope of the curve for the α-substituted ethylamines is less than that of the

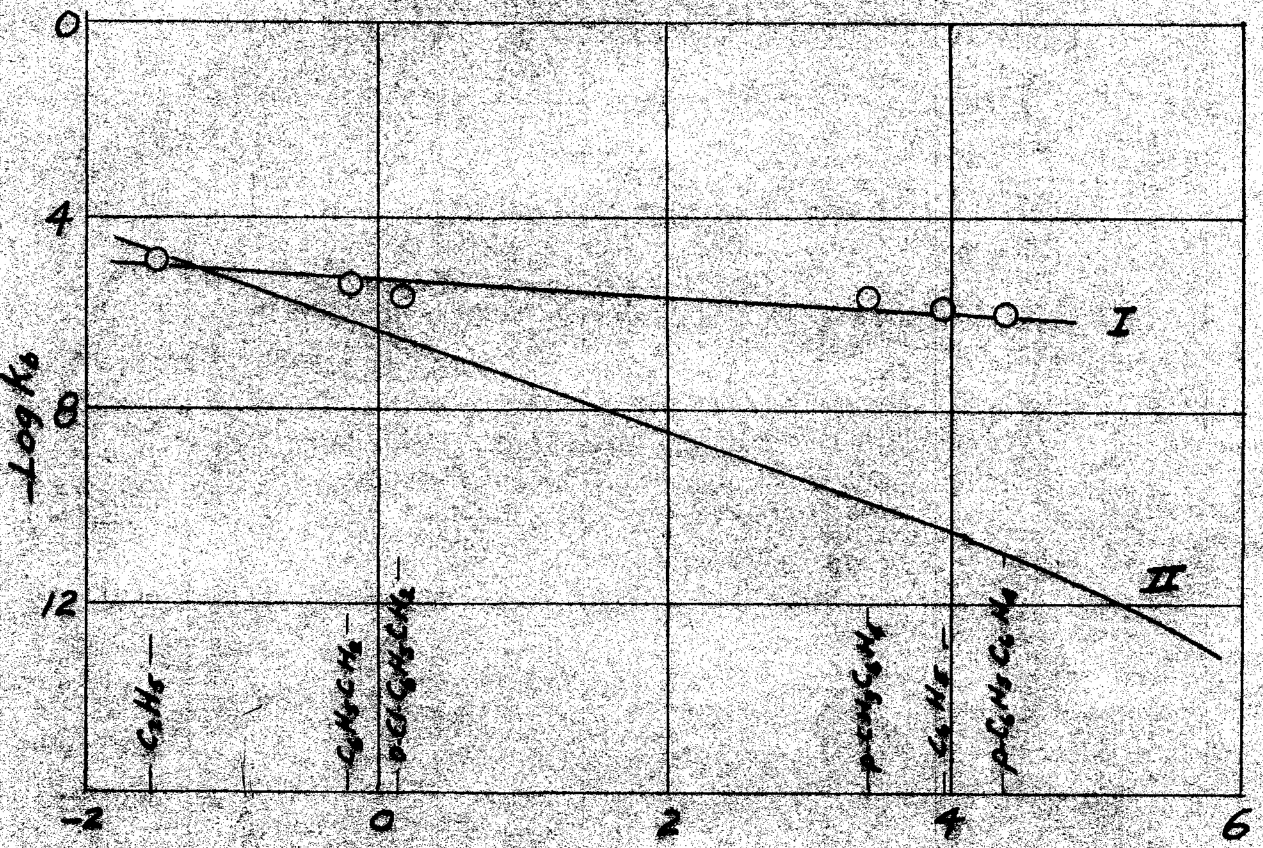


Fig. 2. Logarithms of dissociation constants plotted against abscissa values for the radicals.

I. alpha-Substituted ethylamines in methanol.

II. Primary amines in methanol.

primary amine curve. This relationship is to be expected from the work of Hixon and Johns (23) who pointed out that the effect of removing the substituting group one or more carbons from the polar group is to diminish its influence on the dissociation.

Comparison of rotation data must be attempted with reservations. It must first be ascertained that the data are comparable, that measurements are made under as nearly identical experimental conditions as possible. The specific rotation is that angle of rotation which a liquid would produce if it contained one gram of active substance per cubic centimeter and if a column ten centimeters in length opposed the passage of the plane polarized ray. The molecular rotation is that angle of rotation which a liquid would produce if it contained one gram molecule of the active substance per hundred cubic centimeters and if a column ten centimeters in length opposed the light passage. Since the molecular rotation is that obtained when the light passes through equal numbers of molecules, it should be used in comparing the optical activity of a series of compounds.

A second consideration is the state of the substance the optical activity of which is being determined. For comparative purposes the gaseous state would perhaps be the best since intermolecular forces are at a minimum, but the experimental difficulties involved make it extremely difficult if not impossible to measure the rotations of a series of compounds by this method. The influence of solvents on the rotation is different for various compounds since some active substances in solution will show a maximum or minimum in rotation as the concentration varies and these maxima or minima will not be at identical concentrations for different compounds. These considerations make it unwise to attribute much significance to comparisons of the rotations of solutions, unless the variation of rotation with concentration is known for each member of a series. Measurements of the rotation of optically active liquids may be considered comparable, because the substances are at similar states. Comparison on this basis will be made in this study.

A third consideration is the wave length of the polarized light used in making rotation measurements. As has been pointed out the optical activity of substances varies with the wave length of the light source and this variation may be abnormal or anomalous in some instances. The ideal study would include dispersion data for each compound studied and the comparison of rotations would be made on the basis of absolute molecular rotation which eliminates errors due to differences in dispersion among various members of a series. Lowry (43) defines absolute molecular rotation and stresses the advisability of using it in comparisons whenever possible. The equation for simple dispersion, neglecting terms after the first one, is:

$$\alpha = \frac{K}{\lambda^2 - \lambda_0^2}$$

Where α = observed rotation
λ = wave length of light
λ_0 = characteristic wave length for compound determined from the dispersion data

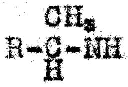
Now K is defined as the absolute rotation and may be determined by measuring the rotation at a wave length, λ, such that $\lambda^2 - \lambda_0^2 = 1$. Under these conditions $\alpha = K$. Then the absolute molecular rotation, $[M]_{abs} = \frac{[\alpha]_{abs} \text{ M.W.}}{100}$, where $[\alpha]_{abs}$ = absolute specific rotation, and M.W. = molecular weight.

If it is reasonably sure, however, that the dispersion is normal, comparisons may be made using rotations measured at a definite wave length. Ott (44) determined dispersion data for α-phenylethylamine in the liquid state. Analysis of his data shows that the dispersion is simple and normal. While this fact may not be taken as conclusive evidence that the other members will have normal dispersion, it strongly suggests that they may be considered to possess the same type of dispersion curve. On the basis of these considerations the rotations of the D line of the sodium flame will be used in the comparisons.

A fourth consideration is the configuration of each member of the series. If magnitudes of molecular rotations for a given series are to be compared the values for compounds having the same configuration should be used. When a series of derivatives of optically active compounds, such as l-menthyl esters, and tartaric acid esters are studied, all members of the series have the same configuration since the same optically active substance is used to prepare the derivatives. When each member of the series is synthesized and resolved, as is the case with the series studied in this thesis, it becomes necessary to convert active members of the series to other members in order to prove the relative configurations.

Leithe (28) converted active α-phenylethylamine into α-cyclohexylethylamine by catalytic hydrogenation and showed that they had opposite signs of rotation for the same configuration. Therefore the dextro form of α-phenylethylamine must be compared with the laevo form of α-cyclohexylethylamine. By catalytic hydrogenation, Leithe (28) also converted α-benzylethylamine into α-hexahydrobenzylethylamine and showed that they had the same sign of rotation for the same configuration. Therefore the dextro forms of these two compounds should be compared. The work done in this thesis on the proof of configuration of α-o-chlorobenzylethylamine shows that the dextro form of this amine should be compared with the dextro form of α-benzylethylamine. By hydrogenation in the presence of palladium oxide the chlorine present in the dextro form of the former compound was replaced with hydrogen and the α-benzylethylamine obtained was shown to be the dextro compound.

Configurational studies have not been made on secondary butylamine or α-p-tolylethylamine. It will be necessary to assume that the dextro forms of these two members of the series have the same configuration as the dextro forms for α-phenylethylamine, α-o-chlorophenylethylamine, α-benzylethylamine, α-hexahydrobenzylethylamine, and the laevo form of α-cyclohexylethylamine. The validity of the comparisons made in this thesis will depend on this assumption.

When the radical R in the α-substituted ethylamines,  $R\text{-}\overset{CH_3}{\underset{H}{C}}\text{-}NH_2$, is varied, the molecular rotation of the pure active liquid varies. Changing R from phenyl to cyclohexyl changes the molecular rotation from +49.4° at 15° C to -4.06° at 15° C, that is, replacing the relatively "electro-negative" group, phenyl, by the relatively "electro-positive" group, cyclohexyl, produces a marked change in the optical activity even to the extent of changing the sign of rotation. Members of the series derived from radicals with intermediate electrical properties have molecular rotations between these two extreme values.

In the introduction it was pointed out that the electrical properties of the radicals attached to the asymmetric carbon atom are the fundamental properties which affect the rotation. The compounds,  $R\text{-}\overset{CH_3}{\underset{H}{C}}\text{-}NH_2$, studied in this thesis differ only in the radical R. The influence exerted by R on the molecular rotations is to be compared with the influence exerted on dissociation constants and dipole moments. The data tabulated in Table IV are arranged so that the molecular rotations of the pure liquids increase from the top to the bottom of the table. The other physical constants listed are: the dissociation constants of α-substituted ethylamines in methanol, the dissociation constants of primary amines in water, the dissociation constants of the carboxylic acids in water, and the dipole moments of the chlorides measured in benzene.

The molecular rotation listed for α-p-diphenylethylamine is the value for the amine in ethyl alcohol. The pure amine is a solid at room temperature. Comparison of the data given in Table II will show that the molecular rotations for the pure amines are higher in every case than the molecular rotations for the ethyl alcohol solutions. From these considerations it is apparent that the α-p-diphenylethylamine should be placed below α-phenylethylamine in Table IV.

With the exception of the constant for α-benzylethylamine, the dissociation constants of the α-substituted ethylamines decrease as the molecular rotations increase. With the exception of primary benzylamine, the dissociation constants for the primary amines in water decrease as the molecular rotations increase. With the exception of the constant for o-chlorophenylacetic acid, as the dissociation constants of the carboxylic acids, RCOOH, increase there is an increase in the molecular rotations of the α-substituted ethylamines. The dipole moments of the chlorides, RCl, decrease with a corresponding increase in rotation. Ortho-chlorobenzyl chloride is seen to be an exception in this comparison.

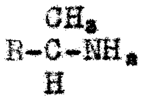
If we adopt Rule's conception of the charge of the

TABLE IV.

Radical R	$R-\overset{CH_3}{\underset{H}{C}}-NH_2$ [M]	$R-\overset{CH_3}{\underset{H}{C}}-NH_2$ $K_{B_{CH_3OH}} \times 10^5$	RNH_2 $K_{B_{H_2O}} \times 10^5$	R-COOH $K_{A_{H_2O}} \times 10^5$	RCl Dipole moment in benzene
Cyclohexyl	-4.06 (15°)		48.00	1.26	2.09
Ethyl	5.20 (20°)	1.080	50.00	1.40	2.06
Hexahydro-benzyl	11.80 (15°)			2.20	
o-Chloro-benzyl	23.30 (25°)	0.219	0.63	8.82(a)	2.39
p-Tolyl	44.50 (20°)	0.211	0.00017	5.20	1.92
Benzyl	48.10 (15°)	0.338	2.00	5.50	1.85
Phenyl	49.40 (15°)	0.158	0.00005	6.60	1.56
p-Diphenyl	48.90 in ethanol	0.124			1.44
Reference	Table II	Table I	(24d)	(24d)	(45)

(a) Dippy and Williams, *J. Chem. Soc.*, 1188-92 (1934).

dipole characteristic of a substituent (19), an electronegative substituent is one having its dipole oriented with the positive charge adjacent to the carbon chain. This orientation would bring about a repulsion of the hydrogen ion of the carboxylic acid and an increase in ionization. From this standpoint the dissociation constants of the acids may be taken as an index to the relative "electronegativity" of the substituent dipoles. Similarly the dissociation constants of the α-substituted ethylamines and the primary amines may be considered as an index to the electrical properties of the radical influencing the ionization. Hixon and Johns (23) have termed this property of radicals "electron sharing ability" and have arranged the non-polar organic radicals in the order of their capacity for exhibiting this property in influencing the equilibria of reversible processes.

From the foregoing considerations based on the data given in Table IV it can be concluded either that there is a relation between the molecular rotations of the amines,  $R-\overset{CH_3}{\underset{H}{C}}-NH_2$, and the electrical property of the radical, R, as measured by dissociation constants and the dipole moments of the chlorides, RCl, or that the parallelisms noted are coincidental. If a parallelism were observed for only one case it might be concluded that the relation is accidental; but since four cases have been shown to exhibit parallelisms with only four discrepancies in twenty-six comparisons, it is logical to conclude that there is a relation between the electrical property or "electron sharing ability" of the radical, R, and the optical activity of the α-substituted ethylamines.

It must be emphasized, however, that the relationship mentioned above is not a simple one. While there may be a mathematical relation between the molecular rotation and some electrical property of the radical, R, it does not fall within the scope of this thesis to point out or develop such a relationship. The evidence presented does show, however, that there exists a qualitative relationship.

In 1925 Liquier (46) showed the effect of pH on the rotation of asparagine and in 1926 Vellinger (47) published some work on the influence of pH on the rotation of glucosamine. Both of these workers plotted rotation against pH and pointed out that the rate of change of rotation with respect to pH was the greatest when $ph = pK_b$ and when $pH = pK_a$.

In the work reported in this thesis, a methanol solution of d-α-phenylethylamine was neutralized in steps with gaseous hydrogen chloride and the rotation and pH observed at intervals. The data obtained are plotted in Figure 3. The greatest slope in the rotation-pH curve occurs at pH - 10.9 which is the pH for half-neutralization of the base α-phenylethylamine or pK_b. As the pH of the solution decreases, that is, as the concentration of hydrogen ions increases the rotation decreases. Inspection of Table II shows that the molecular rotations of the hydrochlorides in methanol are lower

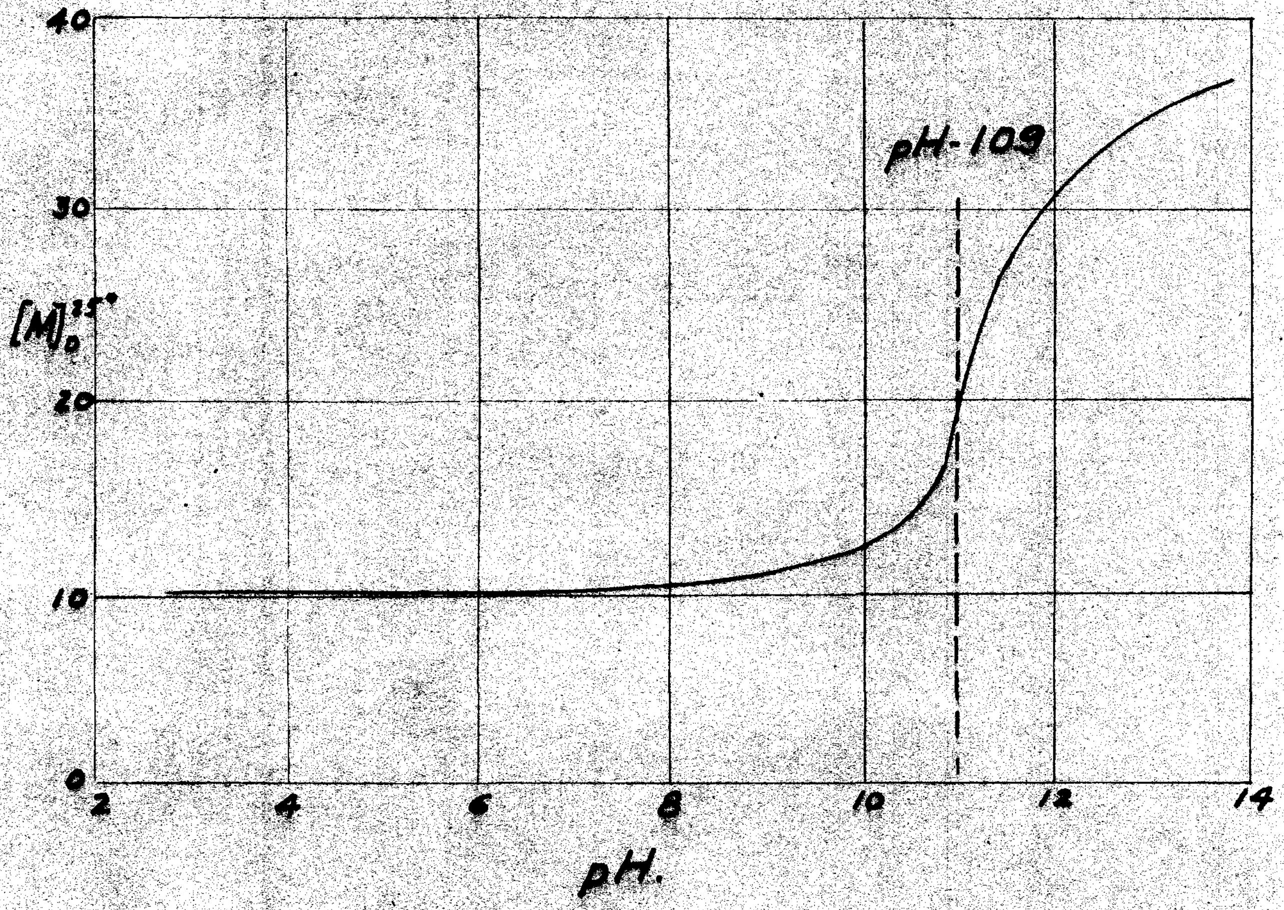


Fig. 3. Molecular rotations of d-α-phenylethylamine in methanol plotted against pH as the solution is neutralized with gaseous hydrogen chloride.

than the molecular rotations of the pure amines and that the order is unchanged if the members be placed according to the magnitude of the rotations. These observations are in support of Rule's generalization (see page 12) concerning the effect of salt formation on optical activity.

CONCLUSIONS

(1) The dissociation constants of a series of α-substituted ethylamines place the non-polar organic radicals in the same order as do the dissociation constants of the primary amines.

(2) There is a qualitative relation between the electrical properties, as measured by dissociation constants and dipole moments, of the radical, R, and the molecular rotations of a series of α-substituted ethylamines.

(3) The dextro forms of α-o-chlorobenzylethylamine and α-benzylethylamine have the same configuration.

(4) The effect of a change of pH on the rotation of α-phenylethylamine is greatest at half-neutralization of the amine.

(5) Converting the series of α-substituted ethylamines to the hydrochlorides lowers the rotation. The order of the members of the series placed by the magnitude of rotations is not changed in this conversion.

SUMMARY

(1) Secondary butylamine, α-benzylethylamine, α-p-tolylethylamine, α-phenylethylamine and α-p-diphenylethylamine have been prepared and resolved into optically active forms.

(2) α-o-Chlorobenzylamine has been prepared and resolved into its optically active forms for the first time.

(3) The dissociation constants of the α-substituted ethylamines mentioned in (1) and (2) have been measured in methanol by the half-neutralization method.

(4) A proof of the relative configurations of α-o-chlorobenzylethylamine and α-benzylethylamine has been given.

(5) The effect of pH on the rotation of d-α-phenylethylamine has been determined.

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