

1935

# The resolution of alpha-substituted pyrrolidines

Helen J. Bulbrook  
*Iowa State College*

Follow this and additional works at: <https://lib.dr.iastate.edu/rtd>

 Part of the [Biochemistry Commons](#), and the [Plant Sciences Commons](#)

## Recommended Citation

Bulbrook, Helen J., "The resolution of alpha-substituted pyrrolidines " (1935). *Retrospective Theses and Dissertations*. 13358.  
<https://lib.dr.iastate.edu/rtd/13358>

This Dissertation is brought to you for free and open access by the Iowa State University Capstones, Theses and Dissertations at Iowa State University Digital Repository. It has been accepted for inclusion in Retrospective Theses and Dissertations by an authorized administrator of Iowa State University Digital Repository. For more information, please contact [digirep@iastate.edu](mailto:digirep@iastate.edu).

# NOTE TO USERS

This reproduction is the best copy available.

**UMI**<sup>®</sup>



THE RESOLUTION OF ALPHA-SUBSTITUTED PYRROLIDINES

By

Helen J. Bulbrook

12/1/35

A Thesis submitted to the Graduate Faculty  
for the Degree of

DOCTOR OF PHILOSOPHY - 20

Major Subject: Plant Chemistry 31



Approved:

Signature was redacted for privacy.

In charge of Major work

Signature was redacted for privacy.

Head of Major Department

Signature was redacted for privacy.

Dean of Graduate College

Iowa State College - 18

1935

UMI Number: DP12609

### INFORMATION TO USERS

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleed-through, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

**UMI**<sup>®</sup>

---

UMI Microform DP12609

Copyright 2005 by ProQuest Information and Learning Company.

All rights reserved. This microform edition is protected against unauthorized copying under Title 17, United States Code.

ProQuest Information and Learning Company  
300 North Zeeb Road  
P.O. Box 1346  
Ann Arbor, MI 48106-1346

QD401  
B87r

- 2 -

1126-12

ACKNOWLEDGMENT

The writer expresses her appreciation to Dr. R. M. Hixon, Dr. I. B. Johns and Dr. D. F. Starr for suggesting the thesis problem and for guidance and help in carrying out the work. *RF*

T 5216

TABLE OF CONTENTS

	Page
INTRODUCTION . . . . .	4
STATEMENT OF THE PROBLEM . . . . .	11
EXPERIMENTAL . . . . .	12
Preparation and Resolution of Compounds . . . . .	12
Measurement of Optical Rotation . . . . .	29
Proof of the Configuration of d, $\alpha$ -Phenylpyrrolidine	33
DISCUSSION OF RESULTS . . . . .	35
Factors Affecting Resolution . . . . .	35
Rotations and Dissociation Constants . . . . .	38
Comparison with $\alpha$ -Substituted Ethylamines . . . . .	39
CONCLUSION . . . . .	43
SUMMARY . . . . .	44
REFERENCES . . . . .	45

### INTRODUCTION

Attempts to discover a quantitative connection between rotatory power and chemical constitution of an active molecule have been numerous since Crum Brown (1) and Guye (2) independently in 1890 published the theory connecting certain constants representing the radicals with molecular rotatory power. According to Guye (3) the product of asymmetry, P, which is a measure of the amount of rotation and its sign, depends only on the masses of the four groups attached to the asymmetric carbon atom. The value is represented thus:

$$P = \frac{(a-b)(a-c)(a-d)(b-c)(b-d)(c-d)}{(a+b+c+d)^3} K$$

where a, b, c, and d are the formula weights of the groups and K is a characteristic constant. It can be seen that if any two of the groups are alike, the product becomes zero and no rotation of the compound is expected. If any two of the formula weights are interchanged, a reversal of sign for P is produced.

In certain homologous series, Guye's hypothesis appeared at first to be confirmed (4) but later work brought out many discrepancies. With the homologous esters (5) the values of  $\frac{[\alpha]}{M}$  sometimes showed an increase and sometimes a decrease with increasing molecular weight of the alcohol radical; the actual effect of gradually increasing the size of the alcohol radical became less for higher members of the series. The changes in rotation due to the presence of unsaturated groups



and of several asymmetric carbon atoms in the same molecule were facts which could not be reconciled to the requirements of the hypothesis. Walden (6) gave many cases in which the theory failed to hold. Pickard and Kenyon (7) investigated a large number of optically active esters, alcohols and ethers and exposed wide departures from what may be termed the "normal alteration of rotatory power" with increase in molecular weight. It was finally concluded that in the majority of homologous series the changes in rotatory power and the product of asymmetry are not parallel.

Following the work of Crum Brown and Guye there were many investigations of the effect of changes in molecular structure on optical activity. Rupe (8) was led to conclude that generally the optical influence of saturated alkyl groups is a small one; Frankland (9) found that "the presence of unsaturated groups leads to an irregularity in rotatory effect and not necessarily to an increased rotation"; Haller (10) in studying the camphor series discovered that benzylidene camphor, having a conjugation of the phenyl group with a double linkage, showed an enormous elevation of the rotation, and that the rotatory power diminished greatly when the phenyl group was exchanged for the cyclohexyl radical or for the benzyl group where no conjugation exists.

Parallel to the collection of experimental data on the effects of various changes in constitution, fundamental theories of the real cause of optical rotation were developing.

Drude (11) in 1893 proposed the idea that optical rotation is due to a peculiar form of electronic motion. He assumed that the electrons which may be set in vibration by impacts of light waves, are found in active molecules to move to and fro in a spiral path instead of along straight lines, the direction of the motion corresponding with the sign of rotation.

On the basis of Drude's theory, Tschugaeff (12) in 1914 postulated that the most active electrons are attached to the asymmetric carbon atom itself or are situated in the immediate neighborhood of the center of asymmetry. These electrons will produce the chief part of the optical rotation, which depends on the deviation of the spiral path of these electrons from straight lines. The deviation should be proportional to the asymmetry of the molecule, which should, in turn, be determined by the four groups attached to the asymmetric carbon atoms. Thus it can be seen that the rotation may be influenced by the vibrations of the electrons attached to the four radicals of the asymmetric carbon atom. Consequently "each radical must contribute by means of its electrons to the value of the optical rotation produced by the molecule as a whole".

Later Born (13) and Oseen (14) in 1915 introduced the theory that optical rotatory power is due to coupling between various resonators inside a molecule. Following their idea Kuhn (15) in 1929 gave a mathematical treatment of optical activity which shows that vibrating electric oscillators,

resonators, within a molecule may cause circular dichroism which in turn is responsible for the rotation of plane polarized light. He suggested that the results of his calculations point to a definite way of studying the connection between rotatory power and chemical constitution and concluded that "the optical rotation of a compound is the sum of contributions of the various substituents, or, more accurately, of their absorption bands". A substituent brings into the molecule a certain absorption band which does not produce optical rotation by itself but becomes active by coupling with other bands present in the molecule. It can be seen that the coupling of the vibrating electric oscillators is fundamental in producing optical activity.

These investigations are clearly related to the work on the influence of polar substituents on the rotatory power and other physical and chemical properties of the molecule, e.g., dipole moment and dissociation constant. Rule (16) in 1924 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 on the polarity of the substituent". Betti (17) and Rule (18) have pointed out that a far-reaching parallel between the rotation and other molecular constants is shown in series of closely related compounds. Rule (19) has shown the relation between the rotations of homogeneous

l-menthyl esters of different monosubstituted acetic acids,  $\text{CH}_2\text{X-COOH}$ , and their dissociation constants and dipole moments. Since in these compounds substitution occurs at a relatively great distance from the menthyl radical, the rotatory power is varied only slightly. A significant parallelism is shown between the dipole moments of the substituents and, with the exception of malonic acid, the dissociation constants of the related acids. The same relations hold for the l-menthyl ethers of the form  $\text{C}_{10}\text{H}_{19}\text{-O-CH}_2\text{X}$  in which the rotatory power runs parallel to the dissociation constant of the acid,  $\text{CH}_2\text{X-COOH}$ , corresponding to the ether radical.

Betti (20) prepared a number of condensation products of d, $\beta$ -naphthol benzylamine,  $\text{C}_6\text{H}_5\text{-}\overset{\text{H}}{\underset{\text{C}_{10}\text{H}_9\text{OH}}{\text{C}}}\text{-NH}_2$ , and a series of substituted benzaldehydes. He compared their rotatory powers with the dissociation constants of the acids corresponding to the aldehydes, and found in general the same parallelism. It was especially good in the para series. If atoms or groups were introduced which raised the electronegative character of the phenylic group of the radical,  $\text{-HC-C}_6\text{H}_5$ , the rotation was displaced in one direction, while if the substituents tended to diminish the negative character, the rotation was displaced in the opposite direction. The compounds which exhibited greater dextro rotation than that of the benzaldehyde derivative contained the radical of the aldehydes corresponding to acids with dissociation constants less than benzoic acid. Those less dextro rotatory or laevo rotatory

corresponded to acids with dissociation constants greater than benzoic acid.

Similar examples are found in Levene's (21) researches of 1929 on the derivatives of disubstituted acetic acids,  $R_1-\overset{\text{H}}{\underset{\text{R}_2}{\text{C}}}-\text{COOH}$ . He concluded: "In the series of aliphatic substances which may be regarded as derivatives of disubstituted acetic acid formed by the substitution of the carboxyl, or of the corresponding carbinol by the substitution of the alcohol group, by other groups, the direction of the rotation and the respective numerical values of the latter may be regarded as functions of the polarity of the substituting group."

From the preceding discussion it is apparent that the electrical properties of substituents exert a marked influence on the rotatory power of optically active compounds. Many attempts have been made to determine the relative order of the electrical influence of organic radicals. The earlier theories pertaining to the classification of radicals on the basis of their electrical properties have been summarized by Henrich, Johnson and Hahn (22).

One method which has been employed for rating respective polarities is the determination of the influence of the group on the dissociation constant of the substituted acid. It may be considered that the variations in the dissociation of organic compounds is a measure of the result of variations in the electrical properties of the so-called non-polar radicals attached to the polar groups. Hixon (23) and his


associates (24) have investigated the relation between the logarithms of the dissociation constants of various series of compounds and some property of the radical, R, which they termed "electron sharing ability". They found that the relationships could be expressed by mathematical expressions of the type:

$$\text{Log } K = K e^{ax+b} + C$$

Where Log K represents the logarithm of the dissociation constant and X represents the abscissa value for the radical or its "electron sharing ability". In all the reversible reactions studied, they found that when the logarithms of the dissociation constants or equilibrium constants of each series were plotted against the abscissa values for the radicals, smooth curves were obtained to which mathematical equations of the form above could be fitted. These results indicate the validity of considering that the arbitrary values for "electron sharing ability" are a measure of the electrical properties of the radicals which determine the dissociation constants of the compounds.

In the study of the rotatory power of a series of  $\alpha$ -substituted ethylamines, Burch (25) found that there is a qualitative relation between the "electron sharing ability" or the electrical properties, as measured by the dissociation constants and dipole moments, of the radical, R, and the molecular rotation.

STATEMENT OF THE PROBLEM

In order to initiate a study of the effect on the rotatory power due to varying the radical, R, attached to the asymmetric carbon atom in a series of  $\alpha$ -substituted pyrrolidines, , the work presented in this thesis was undertaken. These compounds were prepared and resolved. The rotatory powers of the pyrrolidines were measured in the liquid state and in absolute alcohol.

Since it is possible that in such a series, substituting a relatively "electropositive" group for a relatively "electronegative" group may reverse the sign of rotation, it was necessary to establish the configuration of the compounds. Configurational studies were carried out by converting one optically active member of the series into another and observing the direction of the rotation.

This problem also constitutes a part of the program of study on the insecticidal properties of nitrogen heterocyclics which are related to nicotine. Since it is known that the laevo form of nicotine is more toxic to insects than the racemic form, it is possible that the active pyrrolidines may show a similar difference in toxicity.

EXPERIMENTAL

Preparation and Resolution of Compounds.

$\alpha$ -cyclohexylpyrrolidine was prepared by the catalytic reduction of  $\alpha$ -cyclohexylpyrroline. The pyrroline was prepared by a general method developed by Craig, Bulbrook and Hixon (26) for preparing  $\alpha$ -substituted pyrrolines and applied to the synthesis of the  $\alpha$ -cyclohexylpyrroline by Starr (240). A solution of cyclohexyl magnesium chloride was prepared using 150 cc. of anhydrous ether, 9 grams of magnesium, and 46 grams of freshly distilled chlorocyclohexane, b.p. 140-142° C. To this 34 grams of  $\gamma$ -chlorobutyronitrile in an equal volume of ether was added. The Grignard addition product precipitated as the nitrile was added. The mixture was refluxed two hours; the reflux condenser was then reversed and the ether was distilled off, keeping the volume constant by the addition of xylene. When the ether had almost completely distilled, the mixture suddenly reacted to give a solid mass. It was then treated with a solution of ammonium chloride, and the xylene layer removed. The aqueous layer was extracted once with ether, and the ether extract was added to the xylene layer. The  $\alpha$ -cyclohexylpyrroline was extracted from the organic solvents with 50 cc. of hydrochloric acid; the hydrochloric acid layer was washed once with ether to remove the xylene and was then heated to remove the ether. It was treated with excess strong caustic solution, the oily layer dried over



solid potassium hydroxide and distilled. Eighteen grams boiling at 90-92° C/4-7 mm. were obtained. This  $\alpha$ -cyclohexylpyrrolidine was reduced, giving 16 grams of the pyrrolidine boiling at 80-85° C/5 mm. and 3 grams distilling at less than 80° C. This last portion was estimated to contain 1 gram of the base.

Resolution of  $\alpha$ -cyclohexylpyrrolidine was attempted with d-tartaric acid, but with all solvents and temperatures used the  $\alpha$ -cyclohexylpyrrolidine d-tartrate formed syrup on standing and no resolution occurred. Its resolution was accomplished with d-camphoric acid. Eighteen grams of  $\alpha$ -cyclohexylpyrrolidine and 24 grams of d-camphoric acid were dissolved in 125 cc. of 95 per cent ethyl alcohol. Two hundred fifty cubic centimeters of water were added to the clear alcohol solution. There appeared a milky precipitate which became curdy on stirring. The mixture was heated until a clear solution was obtained. Crystallization was started by sprinkling small crystals formed on the stirring rod into the crystallizing dish. The d-base-d-camphorate, which crystallizes first, was recrystallized three times to a constant melting point of 156° C. Ten grams were obtained.

$$[\alpha]_D^{28} (\text{abs. alc., } c = 8.62) = +25.60^\circ$$

Analysis of salt:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for C <sub>10</sub> H <sub>19</sub> N·C <sub>10</sub> H <sub>14</sub> O <sub>4</sub>
21.844	0.595	35°	733	2.86	3.97
9.510	0.258	35°	738	2.85	
11.162	0.305	32°	735	2.90	Calcd. for C <sub>10</sub> H <sub>19</sub> N·(C <sub>10</sub> H <sub>14</sub> O <sub>4</sub> ) <sub>2</sub> 2.54

Neutralization equivalent. N of acid = 0.01522

Wt. sample mg.	cc. HCl = base	cc. HCl = excess base	cc. HCl = comp.	N. E. found
6.835	3.58	1.00	2.58	174.5

Calcd. for C<sub>10</sub>H<sub>19</sub>N·C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>, 353; for C<sub>10</sub>H<sub>19</sub>N·(C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>)<sub>2</sub>, 184.

From this data it appears that the salt formed is more complex than the simple d-base-d-hydrogen camphorate.

The free  $\alpha$ -cyclohexylpyrrolidine was liberated with KOH, dried over solid KOH with slight warming, and centrifuged to remove suspended particles.  $d_4^{20}$  = 0.915;  $n_D^{20}$  = 1.4800;  
 $\alpha_D$ (no solvent) = +8.60°, 20° C, 1 dm. tube,  $[\alpha]_D^{20}$  = +9.41°.  
 $[\alpha]_D^{20}$  (ethyl alcohol, c = 11.70) = +25.12°  
 $[\alpha]_D^{20}$  (ethyl alcohol, c = 8.37) = +27.20°

The remaining portion of the free base was distilled by a micro method and the rotation of the distillate determined in alcohol solution.

$[\alpha]_D^{29}$  (ethyl alcohol, c = 8.18) = +15.28°  
 $[\alpha]_D^{29}$  (ethyl alcohol, c = 5.45) = +15.40°

These rotations indicate that some racemization may have occurred during distillation.

A second fraction, 8 grams, of crystals, melting at 98°C, came from the solution. The residue became syrupy, indicating that the normal salt might have formed, since the first fraction of d-base-d-camphorate had removed more than enough camphoric acid to make the simple acid salt. More camphoric acid was added, and 8 grams of salt crystallized out. After five recrystallizations a salt melting at 102°C was obtained.

$$[\alpha]_D^{25} \text{ (ethyl alcohol, } c = 13.35) = +26.85^\circ$$

Analysis of salt:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for
14.228	0.365	32°	733	2.72	3.97
8.195	0.215	36°	735	2.76	2.54

C<sub>10</sub>H<sub>19</sub>N·C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>  
C<sub>10</sub>H<sub>19</sub>N·(C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>)<sub>2</sub>

Neutralization equivalent. Ratio  $\frac{\text{acid}}{\text{base}} = 1.03$ , N of acid = 0.01522

Wt. sample mg.	cc. base	cc. acid	N. E. found	N. E. calcd. for	
				C <sub>10</sub> H <sub>19</sub> N·C <sub>10</sub> H <sub>14</sub> O <sub>4</sub>	
7.386	3.00	0.37	176	353	
9.168	3.34	0.00	176		
8.904	3.25	0.00	176.1	184	

C<sub>10</sub>H<sub>19</sub>N·(C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>)<sub>2</sub>

Laevo-α-cyclohexylpyrrolidine was liberated from the camphorate with KOH, dried over solid KOH, and the solid suspended material centrifuged out. The base was of a dark

color, and the rotation difficult to read,  $d_4^{20} = 0.915$ ;  
 $n_D^{21} = 1.4801$ ;  $\alpha_D$  (no solvent) =  $-7.30^\circ$ ,  $27^\circ\text{C}$ , 1 dm. tube,  
 $[\alpha]_D^{27} = -7.99^\circ$ .

$[\alpha]_D^{28}$  (ethyl alcohol,  $c = 30.80$ ) =  $-10.71^\circ$

$[\alpha]_D^{28}$  (ethyl alcohol,  $c = 15.61$ ) =  $-10.35^\circ$

$\alpha$ -Phenylpyrrolidine was prepared by chemical reduction of  $\alpha$ -phenylpyrroline with tin and hydrochloric acid, according to the method of Gabriel and Colman (27).  $\alpha$ -Phenylpyrroline was made by the general method for  $\alpha$ -substituted pyrrolines previously described (26).

Resolution of  $\alpha$ -phenylpyrrolidine was carried out with d-tartaric acid. Eleven and ninety-four hundredths grams of base and 12.4 grams of tartaric acid were dissolved in 175 cc. of 95 per cent ethyl alcohol. The resulting solution was somewhat turbid and was filtered. It was seeded with some powdered d-base-d-hydrogen tartrate and allowed to evaporate. No crystallization took place, possibly due to the water in the alcohol. The residue was evaporated to dryness over sulfuric acid, seeded with d-base-d-hydrogen tartrate and allowed to crystallize slowly. Platelike crystals formed in the syrupy mass. The mixture was warmed with absolute alcohol until nearly all the crystals had dissolved, and allowed to cool in vacuo over sulfuric acid. Seven and two-tenths grams of the d-base-d-hydrogen tartrate were obtained. The salt was recrystallized from absolute alcohol to a melting point of  $132^\circ\text{C}$ .

$$[\alpha]_D^{28} (\text{ethyl alcohol, } c = 9.88) = +12.45^\circ$$

$$[\alpha]_D^{29} (\text{water, } c = 12.55) = +2.07^\circ$$

Analysis of d,  $\alpha$ -phenylpyrrolidine-d-hydrogen tartrate:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for C <sub>10</sub> H <sub>13</sub> N·C <sub>4</sub> H <sub>4</sub> O <sub>6</sub>
5.095	0.219	27°	738.0	4.66	4.72
5.352	0.234	27°	745.3	4.79	4.72

Neutralization equivalent, calcd. for C<sub>14</sub>H<sub>19</sub>O<sub>6</sub>N = 297.16.

Found 295.00.

On the addition of KOH to 1.5 grams of the d-base-d-hydrogen tartrate, d,  $\alpha$ -phenylpyrrolidine was liberated. It was dried over solid KOH.  $d_4^{20} = 0.991$ ;  $n_D^{25} = 1.5458$ ;  $\alpha_D = +69.00^\circ$ , 25° C, 1 dm. tube,  $[\alpha]_D^{25} = +69.60^\circ$ . Neutralization equivalent, calcd. for C<sub>10</sub>H<sub>13</sub>N·C<sub>4</sub>H<sub>4</sub>O<sub>6</sub> = 148.5. Found 146.9.

$$[\alpha]_D^{24} (\text{abs. alc., } c = 6.65) = +45.6^\circ$$

$$[\alpha]_D^{24} (\text{abs. alc., } c = 3.76) = +46.7^\circ$$

$$[\alpha]_D^{25} (\text{benzene, } c = 6.70) = +67.0^\circ$$

The mother liquor from the d-base-d-hydrogen tartrate was evaporated to dryness, treated with KOH, and the amine recovered and distilled at 113° C/10 mm. Six grams of the amine ( $\alpha_D^{25} = -24^\circ$ ) and 6.12 grams of l-tartaric acid were dissolved in 75 cc. of absolute alcohol. The solution was evaporated over sulfuric acid to a thick syrup, which crystallized in rosette patterns. When mixed with 50 cc. of absolute alcohol,

a white crystalline salt resulted. Six and four-tenths grams were obtained. After recrystallizing twice from absolute alcohol the melting point was 132.5° C.

$$[\alpha]_D^{29} \text{ (water, } c = 12.58) = -2.14^\circ$$

Analysis of salt:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for C <sub>10</sub> H <sub>12</sub> N·C <sub>4</sub> H <sub>8</sub> O <sub>4</sub>
5.274	0.241	29°	735.6	4.90	4.72
6.734	0.307	22°	737.8	5.01	4.72

Neutralization equivalent, calcd. for C<sub>10</sub>H<sub>12</sub>N·C<sub>4</sub>H<sub>8</sub>O<sub>4</sub> = 147.

Found 147.1.

The method of Marckwald (28) was used for the preparation of l-tartaric acid. Racemic acid was resolved by means of cinchonine which gave the cinchonine salt of l-tartaric acid. By conversion of this salt into ammonium l-tartrate, then into lead l-tartrate and by precipitation of the lead with hydrogen sulfide, a solution of l-tartaric acid was obtained. Upon evaporation crystalline l-tartaric acid resulted.

The l,α-phenylpyrrolidine was liberated with KOH and dried over solid KOH.  $d_4^{20} = 0.991$ ;  $n_D^{25} = 1.5451$ ;  $\alpha_D$  (no solvent) = -70.03° at 26° C,  $\alpha_D$  (no solvent) = -70.69° at 22° C in 1 dm. tube,  $[\alpha]_D^{25} = -70.09$ .

$$[\alpha]_D^{28} \text{ (ethyl alcohol, } c = 62.86) = -44.30^\circ$$

α-Ethylpyrrolidine was prepared by catalytic reduction of α-ethylpyrroline with Adams and Shriner platinum oxide platinum

black catalyst. The pyrrolidine was synthesized by the method previously described (26).

Resolution of  $\alpha$ -ethylpyrrolidine was accomplished by means of d-tartaric acid. In 110 cc. of boiling absolute alcohol 13.3 grams of the amine and 20.15 grams of d-tartaric acid were dissolved and cooled in a vacuum desiccator over sulfuric acid. The solution evaporated to a syrup. It was dissolved in a little alcohol, and petroleum ether was added until the solution was just turbid. On standing the d-base-d-hydrogen tartrate crystallized in needlelike crystals. It was recrystallized three times from absolute alcohol to a melting point of 89° C.

$$\begin{aligned} [\alpha]_D^{21} (\text{water, } c = 11.43) &= +22.74^\circ \\ [\alpha]_D^{21} (\text{water, } c = 4.57) &= +23.83^\circ \\ [\alpha]_D^{22} (\text{ethyl alcohol, } c = 5.94) &= +17.66^\circ \\ [\alpha]_D^{22} (\text{ethyl alcohol, } c = 2.37) &= +18.91^\circ \end{aligned}$$

Analysis of salt:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for C <sub>6</sub> H <sub>11</sub> N·C <sub>4</sub> H <sub>4</sub> O <sub>6</sub>
4.046	0.252	30°	737.4	5.46	5.62
6.614	0.358	35°	733.0	5.67	5.62

The d, $\alpha$ -ethylpyrrolidine was liberated by adding KOH and was dried over solid KOH for twenty-four hours.  $d_4^{25} = 0.831$ ;  $n_D^{25} = 1.4351$ ;  $\alpha_D = +1.46^\circ$ , 25° C, 1 dm. tube,  $[\alpha]_D^{25} = +1.76$ .  
 $[\alpha]_D^{28} (\text{ethyl alcohol, } c = 42.4) = +1.58$

In a second resolution of  $\alpha$ -ethylpyrrolidine 8.13 grams of base (b.p.  $126-7^{\circ}\text{C}$ ) and 12.59 grams of d-tartaric acid were dissolved in 50 cc. of absolute alcohol. It proved to be extremely difficult to start crystallization. The addition of petroleum ether to turbidity did not cause crystals to form. Seeding with crystals from the previous resolution was unsuccessful. Finally upon evaporating off all solvents under a vacuum, and stirring the resulting thick syrup, crystallization began. The salt was recrystallized from absolute alcohol three times and melted at  $75^{\circ}\text{C}$ . Further recrystallization did not change the melting point. The  $\alpha$ -ethylpyrrolidine, liberated from this salt and dried over solid KOH gave a rotation of  $+1.30^{\circ}$  at  $27^{\circ}\text{C}$  in a decimeter tube. The rotation was lower than that of the pyrrolidine liberated from the salt melting at  $89^{\circ}\text{C}$ . A third resolution of freshly prepared  $\alpha$ -ethylpyrrolidine gave the same results as the second.

l, $\alpha$ -Ethylpyrrolidine was obtained from the mother liquor after the d-base-d-hydrogen tartrate had crystallized out. The alcohol was evaporated. Potassium hydroxide was added to liberate the base. After drying over solid KOH, the amine was added to enough l-tartaric acid in absolute alcohol to make the l-hydrogen tartrate. The solution formed a syrup on standing over sulfuric acid. It was dissolved in a small volume of absolute alcohol, and petroleum ether was added until turbidity appeared. Crystals of l-base-l-hydrogen tartrate formed from this solution. After recrystallizing three times from



absolute alcohol and petroleum ether the melting point was 75° C. Further recrystallization did not change the melting point.

$$\begin{aligned} [\alpha]_D^{25} (\text{water, } c = 11.05) &= -15.15^\circ \\ [\alpha]_D^{27} (\text{water, } c = 14.20) &= -15.00^\circ \\ [\alpha]_D^{27} (\text{water, } c = 6.74) &= -19.32^\circ \end{aligned}$$

Analysis of salt:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for C <sub>8</sub> H <sub>11</sub> N·C <sub>4</sub> H <sub>8</sub> O <sub>2</sub>
12.972	0.680	34°	733	5.51	5.62

The pyrrolidine was liberated with KOH and dried over solid KOH. The readings of the rotation were not sharp, due to the color of the base.  $d_4^{25} = 0.831$ ;  $n_D^{25} = 1.3362$ ;  $\alpha_D$  (no solvent) = -2.84°, 27° C, 1 dm. tube,  $[\alpha]_D^{27} = -3.42^\circ$ .

$$\begin{aligned} [\alpha]_D^{27} (\text{ethyl alcohol, } c = 22.12) &= -5.68^\circ \\ [\alpha]_D^{27} (\text{ethyl alcohol, } c = 14.99) &= -3.34^\circ \end{aligned}$$

$\alpha$ -(p-Tolyl)pyrrolidine was prepared according to the method reported by Starr, Bulbrook and Hixon (24c) from  $\alpha$ -(p-tolyl)pyrroline by catalytic reduction. Fourteen grams of the base, boiling at 145-146°/32-33 mm. were obtained.

Resolution of  $\alpha$ -(p-tolyl)pyrrolidine was accomplished by adding 14 grams of the base to 13.1 grams of d-tartaric acid dissolved in 500 cc. of absolute alcohol. The solution was warmed, filtered, and allowed to evaporate in a vacuum

desiccator over sulfuric acid to volume of 400 cc. It was chilled, and the crystals formed were filtered off. Nine and eight-tenths grams of d-base-d-hydrogen tartrate, m.p. 155.5° C, were obtained after recrystallizing twice from absolute alcohol. From this salt the base was liberated and dried. The rotation was found to be lower than that from a previous resolution. Three and nine-tenths grams of it were converted to the d-hydrogen tartrate by the addition of 3.7 grams of d-tartaric acid. Six grams of salt, m.p. 156° C, were obtained upon recrystallizing three times from absolute alcohol.

$$[\alpha]_D^{29}(\text{water, } c = 11.10) = +2.30$$

Rotations in ethyl alcohol; 2 dm. tube:

Conc.	$\alpha_D^{29}$	$[\alpha]_D^{29}$
3.43	+0.44	+11.7
1.06	+0.29	+13.7
0.53	+0.17	+16.0
0.27	+0.09	+16.7

Nitrogen analysis, calcd. for  $C_{11}H_{15}N \cdot C_4H_6O_4 = 4.50$ . Found 4.37, 4.50.

The pyrrolidine was liberated with KOH and dried over solid KOH.  $d_4^{25} = 0.985$ ;  $n_D^{27} = 1.5376$ ; 1 dm. tube,

$$[\alpha]_D^{25} = +63.50^\circ.$$

Rotation (no solvent):

Temp. C.	$\alpha_D$
23°	+62.50°
21°	+62.75°
18°	+63.16°
17°	+63.29°
16°	+63.41°

The mother liquors from the preparation of the d-base-d-hydrogen tartrate were evaporated; the impure 1, $\alpha$ -(p-tolyl)-pyrrolidine was liberated with KOH, dried over solid KOH, and distilled. Six and four-tenths grams, boiling at 75-77°/1-2 mm., were obtained. To a solution of the base in 200 cc. of absolute alcohol 6.16 grams of l-tartaric acid were added. The l-base-l-hydrogen tartrate, which crystallized out, was recrystallized several times to a melting point of 156.5° C. Using a 2 dm. tube, the following rotations of the salt were obtained:

$\angle \alpha T_D^{25}$ (water, c = 12.23)	= -2.72°
$\angle \alpha T_D^{25}$ (water, c = 6.12)	= -1.77°
$\angle \alpha T_D^{25}$ (ethyl alcohol, c = 0.568)	= -8.40°
$\angle \alpha T_D^{25}$ (ethyl alcohol, c = 0.342)	= -7.01°

Nitrogen analysis, calcd. for  $C_{11}H_{15}N \cdot C_4H_6O_6$  = 4.50. Found 4.47, 4.49.

The l-base-l-hydrogen tartrate was treated with KOH. The liberated base was dried over solid KOH.  $d_4^{25} = 0.9864$ ,  $n_D^{25} = 1.5390$ ,  $\alpha_D$ (no solvent) = -61.94°, 25° C, 1 dm. tube,

$$[\alpha]_D^{25} = -62.50^\circ$$

Analysis of l-base:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for C <sub>11</sub> H <sub>16</sub> N
13.310	1.067	24°	741	8.79	8.69

$\alpha$ ,p-Chlorophenylpyrrolidine was prepared for the first time from  $\alpha$ ,p-chlorophenylpyrroline. The same general method (26) was used for the preparation of the pyrroline. A Grignard reagent was prepared from 65 grams of bromochlorobenzene, 8.6 grams of magnesium and 200 cc. of anhydrous ether. Upon the addition of  $\gamma$ -chlorobutyronitrile a solid addition product separated immediately. A large quantity formed when 34 grams of nitrile were added. The mixture was refluxed two hours. The ether was distilled off as xylene was added. When the temperature increased, the whole mass solidified in the flask. Hydrolysis of the addition product and extraction of the pyrroline hydrochloride was carried out in the manner described previously (25). On the addition of KOH to the solid hydrochloride a large quantity of oil separated, which could be drawn off with a pipette while hot. On slight cooling the compound solidified and could be lifted from the KOH layer. Forty-five grams of the crude compound were obtained, corresponding to a 75 per cent yield. A very small quantity of white crystalline material was obtained by distilling at 132-136° C with prolonged heating at 5 mm. Small quantities

of it were purified by sublimation at 87° C/5 mm. The sublimate was a white, crystalline compound, m.p. 74° C, which decomposed readily on standing.

Analysis of pyrroline:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for C <sub>10</sub> H <sub>10</sub> NCl
4.454	0.322	29°	736.7	7.77	7.80
3.372	0.246	30°	737.4	7.80	7.80

A picrate was prepared in absolute alcohol. After recrystallization from alcohol it began to melt at 203° C and decomposed at 208° C.

$\alpha$ ,p-Chlorophenylpyrrolidine was made by reducing the crude pyrroline with tin and hydrochloric acid (27). Twenty-four grams of the pyrroline were added to 80 cc. of concentrated hydrochloric acid and 10 grams of granulated tin. The mixture was heated on a steam bath for four hours. A dark brown tar separated which would not dissolve in hydrochloric acid. The solution was decanted. The residual tin and tar were washed with water which was added to the acid solution. Strong caustic was added to alkalinity. The mixture was steam distilled. A white solid separated immediately from the distillate as it cooled. The yield was 15 grams of the pyrrolidine, m.p. 68-70° C. A portion of it was purified by sublimation, m.p. 70° C.

Analysis of pyrrolidine:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for C <sub>10</sub> H <sub>13</sub> NCl
3.106	0.228	33°	734.5	7.74	7.73
3.542	0.265	29°	734.3	7.79	

Neutralization equivalent, calcd. for C<sub>10</sub>H<sub>13</sub>NCl = 181.5.

Found 181.4, 182.1.

A picrate was prepared and recrystallized from absolute alcohol. It melted with decomposition at 210° C.

Resolution of  $\alpha$ ,p-chlorophenylpyrrolidine proved unsuccessful under all the conditions tried. With d-tartaric acid in absolute alcohol and in alcohol-water mixtures a white crystalline salt was obtained. The salt melted at 139-140° C.

$$[\alpha]_D^{25} \text{ (water, } c = 1.101) = +18.16^\circ$$

$$[\alpha]_D^{25} \text{ (water, } c = 3.65) = +13.70^\circ$$


Analysis of salt:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for C <sub>10</sub> H <sub>13</sub> NCl · C <sub>4</sub> H <sub>4</sub> O <sub>6</sub>
10.580	0.417	33°	733	4.17	4.23
13.728	0.547	33°	733	4.20	

The base liberated from the d-hydrogen tartrate showed no rotation.

With l-malic acid and  $\alpha$ ,p-chlorophenylpyrrolidine in 50 per cent alcohol the solution evaporated to a brown syrup from which rosette-like crystals separated. These were not

purified by repeated crystallization from alcohol. The free base from these crystals showed slight rotation in alcohol solution.  $[\alpha]_D^{25}$  (alcohol, c = 10.41) = +1.64°. With d-camphoric acid in absolute alcohol and in water-alcohol mixtures, syrups were obtained.

$\alpha$ ,n-Butylpyrrolidine was reported by Hess (29) to have been made from 1, $\alpha$ -pyrrolidyl-1-butanol by heating with HI and phosphorus. The compound boiled at 154-156°C, gave a chloroplatinate melting at 178°C and a chloraurate melting at 145°C. Hess (30) also reported a synthesis from the hydrazone of -CH<sub>2</sub>CO-Et by reduction with sodium in alcohol. Blaise and Cornillot (31) prepared  $\alpha$ -butylpyrroline by condensing iodoethylphthalimide with the potassium salt of ethylvalerylacetate and hydrolyzing the product with HBr. By hydrogenation of the pyrroline, using Sitka's method, they obtained  $\alpha$ -butylpyrrolidine.

In this laboratory  $\alpha$ ,n-butylpyrrolidine was prepared by catalytic hydrogenation of  $\alpha$ ,n-butylpyrroline using Adams and Shriner platinum oxide platinum black catalyst. The pyrroline was made by the general method mentioned (26), except that ice water was used for hydrolyzing the Grignard addition product and the water layer was steam distilled after separation from the xylene layer, which contained the major portion of the pyrroline. The first 100 cc. of distillate was acidified with 30 cc. of concentrated hydrochloric acid and used to extract

the pyrroline from the xylene layer. The acid solution was concentrated in vacuo until solid pyrroline hydrochloride separated out. The base was liberated with KOH, dried over solid KOH and distilled, b.p.  $62^{\circ}\text{C}/7\text{ mm}$ . Nine grams were obtained corresponding to a 21 per cent yield.

A chloroplatinate derivative began to decompose at  $168^{\circ}\text{C}$  and melted to a dark mass at  $182^{\circ}\text{C}$ . A urea derivative, prepared by a method of Werthien (32), melted at  $104-105^{\circ}\text{C}$ . These values are in agreement with those obtained by Blaise and Cornillot (31).

$\alpha$ ,n-Butylpyrroline was hydrogenated to the pyrrolidine according to the method described (26). Eleven grams of the pyrroline, 125 cc. of alcohol, 8 cc. of concentrated hydrochloric acid and 0.2 gram of platinum oxide platinum black catalyst were shaken in an atmosphere of hydrogen under pressure. When reduction was complete, the alcohol was distilled off. The base was liberated from the hydrochloride with KOH, dried over solid KOH, and distilled. A colorless oil with a foul odor was obtained, b.p.  $55-60^{\circ}\text{C}/5-7\text{ mm}$ . A yield of 10.2 grams was obtained. A chloroplatinate was prepared which melted at  $122-123^{\circ}\text{C}$ . This value checks the melting point obtained by Blaise and Cornillot (31), but not the value ( $178^{\circ}$ ) obtained by Hess (29).

Resolution of  $\alpha$ ,n-butylpyrrolidine was attempted with d-tartaric acid in various solvents. Syrup which would not



crystallize was obtained.

$\alpha$ -Benzylpyrrolidine was prepared according to the method reported by Starr, Bulbrook and Hixon (24c).

Resolution of  $\alpha$ -benzylpyrrolidine proved to be unsuccessful. Using d-tartaric acid as the resolving agent a white crystalline compound was obtained from an absolute alcohol solution, m.p.  $137^{\circ}\text{C}$ .  $[\alpha]_{\text{D}}^{25}$  (water,  $c = 9.77$ ) =  $+14.73^{\circ}$ . The pyrrolidine liberated from this salt with KOH and dried over solid KOH failed to give any rotation. Alcohol-water mixtures, alcohol-ether mixtures, and acetone failed to assist resolution. Syrups resulted when l-malic acid in various solvents was used. A few crystals were formed in the syrup which resulted from the evaporation of an acetone-benzene solution, but they could not be purified before decomposition had taken place.

#### Measurement of Optical Rotation.

##### Apparatus Used.

A Franz Schmidt and Haensch polariscope with a sodium arc light of wave length 5890 and 5896  $\text{\AA}$  was used for measuring rotations. A micro tube 10 cm. in length was used for most substances. A few measurements were made with a 20 cm. tube.

No effort was made to maintain a constant temperature for all readings. Most of the measurements were made between  $20^{\circ}\text{C}$  and  $30^{\circ}\text{C}$ . The tube was placed in the polariscope and allowed

to acquire the temperature of the surrounding air. The rotation was read, and the temperature at which the observation was made was recorded. It was possible for different observers to check the values to  $\pm 0.05^\circ$  in most cases.

Measurement of Rotation of Pyrrolidines.

The measurements of rotations on the pyrrolidines were made without distillation. It was found by Starr (unpublished data) that the rotation of l-nicotine liberated from the tartrate by the method described for the pyrrolidines and measured without being distilled, compared very favorably with the highest value reported in the literature. The rotatory power of l, $\alpha$ -(p-tolyl)pyrrolidine was lower after distillation.

Rotation of l, $\alpha$ -(p-tolyl)pyrrolidine:

Dried over KOH

$$\alpha_D^{27^\circ} = -58.3$$

First distillation

$$\alpha_D^{22^\circ} = -52.5$$

Second distillation

$$\alpha_D^{22^\circ} = -45.2$$

Second distillation  
in contact with KOH

$$\alpha_D^{22^\circ} = -44.8$$

It appeared that d, $\alpha$ -cyclohexylpyrrolidine gave a similar decrease, although the rotation on the distilled material had to be measured in alcohol solution (page 14).

Measurement of Rotation of Solutions.

Water and absolute ethyl alcohol were the solvents used in the rotation studies. Solutions were made by weighing the

compound in a small bulb, adding nearly all the solvent and mixing well, and finally adding solvent to make the volume. The solution was mixed again before filling the polariscope tube. All concentrations were expressed in grams per 100 cc. of solvent.

Table of Rotation Data.

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

for pyrrolidines:

$$\angle \alpha_D^t = \frac{\alpha}{d \cdot l}$$

for the solutions:

$$\angle \alpha_D^t = \frac{\alpha \cdot 100}{C \cdot l}$$

where  $\angle \alpha_D^t$  = specific rotation of D line at temperature t

$\alpha$  = observed rotation

d = density of pure amine

C = concentration in grams/100 cc. solvent

l = length of the tube in decimeters

and

$$\angle M_D^t = \frac{\angle \alpha_D^t \cdot \text{M.W.}}{100}$$

where  $\angle M_D^t$  = molecular rotation of D line at temperature t

$\angle \alpha_D^t$  = specific rotation of D line at temperature t

M.W. = molecular weight of amine

TABLE I.

Summary of Rotation Data for a Series of  
 $\alpha$ -Substituted Pyrrolidines

Radical		d-form (no solvent)	d-form ethyl alcohol	l-form (no solvent)	l-form ethyl alcohol
Cyclohexyl	$\Delta M_D$	+14.38	+38.43	-12.20	-15.81
	Temp.	20°	30°	27°	26°
	Conc.		11.70		15.61
Ethyl	$\Delta M_D$	+1.71	+1.53	-3.31	-5.31
	Temp.	25°	28°	27°	27°
	Conc.		42.4		22.12
p-Tolyl	$\Delta M_D$	+102.28		-101.90	
	Temp.	25°		25°	
	Conc.				
Phenyl	$\Delta M_D$	+102.30	+62.0	-103.0	
	Temp.	25°	24°	26°	
	Conc.		+6.65		

Proof of the Configuration of d, $\alpha$ -Phenylpyrrolidine.

d, $\alpha$ -Phenylpyrrolidine was changed to d, $\alpha$ -cyclohexylpyrrolidine by catalytic hydrogenation. The d, $\alpha$ -phenylpyrrolidine was liberated from 2 grams of the d-hydrogen tartrate with KOH and dried over solid KOH.  $n_D^{20} = 1.5416$ ,  $\alpha_D(\text{no solvent}) = +69.15^\circ$ . A quantity weighing 0.6286 grams was dissolved in absolute alcohol and made up to 10 cc.  $[\alpha]_D^{20}$  (absolute alcohol, c = 6.286) = +44.30. Dry gaseous HCl was passed into the solution, the mixture being shaken after each addition of 10 or 20 bubbles until the solution was just acid to litmus.  $[\alpha]_D^{20}$  (alcohol, c = 6.90) = -5.04°. The hydrochloride was catalytically reduced using 0.2 grams of platinum oxide catalyst. The catalyst was prepared by the method of Shriner and Adams (37). The hydrogenation was carried out at room temperature and 98 lb. pressure for 16 hours. The solution was filtered.  $[\alpha]_D^{20}$  (alcohol, c = 7.20) = -1.25°. The alcohol was distilled off in vacuo, the hydrochloride dissolved in a small volume of water, and KOH added to liberate the base. After drying over solid KOH and centrifuging, the base was too cloudy and dark colored to measure its rotation. Alcohol solutions were prepared.  $[\alpha]_D^{20}$  (alcohol, c = 10.98) = +11.72°  
 $[\alpha]_D^{20}$  (alcohol, c = 20.90) = +10.19°

The chloraurate and d-camphorate derivatives which were prepared from the product of this reduction are shown by the following data to be identical with those obtained from

d,α-cyclohexylpyrrolidine.

Pyrrolidine	Chloraurate	d-Camphorate
d,α-Cyclohexylpyrrolidine from resolution with d-camphoric acid	m.p. 108-9° C	m.p. 156° C
d,α-Cyclohexylpyrrolidine by reduction of d,α-phenylpyrrolidine	m.p. 108-9° C	m.p. 156° C

The remaining portion of the d,α-cyclohexylpyrrolidine was distilled at 78° C/3-5 mm. Samples for analysis were sealed in glass tubes.

Analysis of pyrrolidine:

Wt. sample mg.	cc. N <sub>2</sub>	Temp. C	Bar. Press.	Per cent nitrogen	
				Found	Calcd. for C <sub>10</sub> H <sub>19</sub> N
7.952	0.704	35°	739	9.34	9.15
2.499	0.218	36°	739	9.20	

Neutralization equivalent, calcd. for C<sub>10</sub>H<sub>19</sub>N = 153.0. Found 153.5, 153.5.

### DISCUSSION OF RESULTS

The attempts at resolving  $\alpha$ -substituted pyrrolidines have been successful in the cases of  $\alpha$ -phenylpyrrolidine,  $\alpha$ -(p-tolyl)pyrrolidine,  $\alpha$ -cyclohexylpyrrolidine and  $\alpha$ -ethylpyrrolidine; and unsuccessful in the cases of  $\alpha$ -(n-butyl)pyrrolidine,  $\alpha$ ,p-chlorophenylpyrrolidine and  $\alpha$ -benzylpyrrolidine. Resolution is complicated by many factors such as conditions of temperature, concentration, solvent, the kind of resolving agent, and the solubility of the salts formed. If any one of these conditions is unfavorable, no resolution occurs. Since none of them is known for these new compounds, success in resolution becomes a matter of chance in selecting favorable conditions. In this series the resolution is made more complex by the instability of the compounds. Decomposition occurred to some extent in all cases before the salts crystallized from the solutions.

The resolution of  $\alpha$ -phenyl-,  $\alpha$ -(p-tolyl)- and  $\alpha$ -cyclohexylpyrrolidines was complete enough so that the dextro and laevo forms show approximately the same magnitude of rotation. The  $\alpha$ -ethylpyrrolidine appeared to be somewhat less completely resolved, the dextro form showing a molecular rotation of +1.71 and the laevo form of -3.31.

Interpretation of rotational data which is made in this thesis is subject to a consideration of the following factors: the optical purity of the compound, the temperature at which

measurements were made, molecular rotation and the influence of solvents, rotatory dispersion, and configuration.

The active pyrrolidines were liberated from salts which had been repeatedly crystallized to a constant melting point, and were dried according to a consistent method. The melting point of the salts was thus used as the criterion of optical purity of the bases.

From an inspection of the data (p. 18 and 23) it can be seen that the rotatory powers of  $\alpha$ -(p-tolyl)pyrrolidine and of  $\alpha$ -phenylpyrrolidine vary approximately one-tenth of a degree for one degree change in temperature. The rotations of the other active pyrrolidines were not determined at various temperatures. The figures obtained, however, indicate that the changes would be small over the narrow range of temperature at which measurements were made.

The molecular rotation of the compounds was chosen as a basis for comparison. It gives a direct comparison of the rotation produced by equal numbers of active molecules per unit volume, and according to Tschugaeff (12) has more significance than the specific rotatory power from the standpoint of the molecular hypothesis and of stereochemistry. It is defined as that angle of rotation which is produced by a liquid containing one gram molecule of the active compound per hundred cubic centimeters, if a column ten centimeters in length opposes the passage of plane polarized light.

The influence of solvents on optical rotation is well



recognized. An interesting example of solvent action is furnished by the case of  $d,\beta$ -octyl acetate (33) whose molecular rotation with no solvent was +11.77. Of fourteen solvents used, ethylene dibromide raised this figure to +16.84 and the other thirteen exerted the reverse effect producing continuously varying values through zero to a molecular rotation of -15.42. It has also been found that when the same solvent is used, some active substances show a maximum and some a minimum as the concentration in solution varies, and these points will not come at identical concentrations for different compounds. The effect of solvents on the  $\alpha$ -substituted pyrrolidines has not been studied fully enough to make their optical rotatory powers in solution comparable. The only method at present available is to compare the rotations of these substances in the liquid state.

Unless it has been ascertained that the rotatory dispersion is normal for each of a series of compounds, comparison of their optical activity at a given wave length may introduce a serious error. Since no investigations have been made on the rotatory dispersion of  $\alpha$ -substituted pyrrolidines, in making the comparisons to follow it is assumed that their rotatory dispersions are normal. This is possibly the case since no noticeable absorption occurs in the visible region of the spectrum. The values for the rotations of the D line are used.

Finally, if magnitudes of molecular rotation are to be

compared properly the configurations of each member of the series should be known. When each compound is prepared as the racemic form and resolved, it becomes necessary to convert one active member into another in order to prove relative configuration. In the series of  $\alpha$ -substituted pyrrolidines, d, $\alpha$ -phenylpyrrolidine has been converted into d, $\alpha$ -cyclohexylpyrrolidine by catalytic hydrogenation, showing that these two compounds have the same configuration. It is assumed that the dextro forms of  $\alpha$ -ethyl and  $\alpha$ -(p-tolyl)pyrrolidines have the same configurations as the dextro forms of  $\alpha$ -phenyl and  $\alpha$ -cyclohexylpyrrolidines.

The validity of the comparisons which follow depends upon the limitations and assumptions mentioned in the foregoing paragraphs. When the radical, R, is varied, the molecular rotation of the active liquid varies. Changing R from a relatively "electropositive" group, cyclohexyl, to a relatively "electronegative" group, phenyl, changes the rotatory power from +14.58 at 25° to +103 at 25°. The other two members of the series show molecular rotations between these two values.

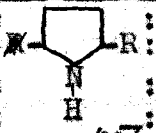
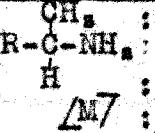
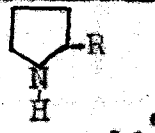
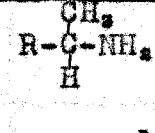
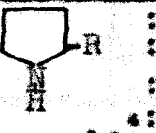
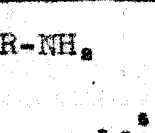
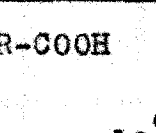
It has been pointed out (p. 6) that the electrical forces of the radicals attached to the asymmetric carbon atom are the fundamental properties which affect the rotation. The resolved  $\alpha$ -substituted pyrrolidines differ only in the radical R. The influence exerted by R on the molecular rotatory power will be compared with the effect on the

dissociation constants and with similar variations in a series of  $\alpha$ -substituted ethylamines. The data in Table II. are arranged to show an orderly decrease in the dissociation constants of these compounds in methanol, in the dissociation constants of the  $\alpha$ -substituted pyrrolidines in water, and in the dissociation constants of the corresponding primary amines and carboxylic acids. The rotatory powers of the  $\alpha$ -ethylamines and of the  $\alpha$ -substituted pyrrolidines with the exception of the ethyl derivative, are found to fall in increasing order of magnitude.

The variation in dissociation constants may be considered to represent a variation in the properties of the radical, R, which influence the degree of dissociation of these bases. Although there may be more than one property which influences dissociation, the predominating property is surely an electrical characteristic of the radical which tends to attract or repel the hydroxyl ion.

It has been shown by Burch (25) that when the logarithms of the dissociation constants of  $\alpha$ -ethylamines in methanol as ordinates are plotted against the values of the radicals as abscissas, a smooth curve is obtained which has a slope less than that of the primary amine curve obtained by Goodhue and Hixon (24d). In the case of the  $\alpha$ -substituted pyrrolidines, a similar decrease in slope was observed (24c). This relationship was to be expected from the fact that the effect of removing the substituting group one carbon atom from the

TABLE II.

Radical							
	$\Delta M$	$\Delta M$	$K_b \times 10^6$	$K_b \times 10^6$	$K_b \times 10^4$	$K_b \times 10^6$	$K_b \times 10^6$
			$CH_2OH$	$CH_2OH$	$H_2O$	$H_2O$	$H_2O$
Cyclohexyl	14.38 (26°)	-4.06 (15°)	1.26		60.30	48.00	1.26
Ethyl	1.71 (25°)	5.80 (20°)		1.08	2.70	50.00	1.40
p-Tolyl	102.28 (25°)	44.50 (20°)	0.219	0.211	1.00	0.00017	5.20
Phenyl	103.0 (26°)	49.40 (15°)	0.148	0.158	0.40	0.00005	6.60
Carboxyl*	94.18 (20°)						$1 \times 10^{-12}$
Reference	Table I.	(22)	(24d)	(22)	(24b) (24c)	(23)	(24a)

\* Proline (35, 36) is the only active  $\alpha$ -substituted pyrrolidine which was found in the literature. It does not rightly belong in this series because of the influence of the carboxyl radical which introduces a second polar group into the molecule.

polar group is to diminish its influence on dissociation. From Table II. it can be seen that the actual values obtained for dissociation constants of corresponding members of the two series are nearly equal.

With the exception of the constant for  $\alpha$ -ethylpyrrolidine, the dissociation constants of this series decrease as the molecular rotations increase. The same exception is observed in comparing the rotations with the dissociation constants of the primary amines and of the carboxylic acids. The constants of the  $\alpha$ -ethylamines also show a decrease with increasing molecular rotation.

In comparing the rotatory powers of the two series, a large difference in the values for the molecular rotations of the members having like R substituents is observed. If the structure of the compounds is examined, it is evident that three of the bonds of the asymmetric carbon atom are held by a nitrogen, a hydrogen and R-group in both series and that the fourth bond in the  $\alpha$ -ethylamines is attached to a  $\text{CH}_2$  group, whereas, in the  $\alpha$ -substituted pyrrolidines, it is attached to a  $\text{CH}_2$  group which is part of a closed ring. So far as the dissociation constants are concerned it appears that the values are only slightly affected by the presence of the ring. The rotatory powers seem to be influenced to a greater extent.

It happens also that the configurations in the two series are dissimilar. In the  $\alpha$ -substituted ethylamine series Leithe (34) converted  $\alpha$ -phenylethylamine into  $\alpha$ -cyclohexylethylamine by catalytic hydrogenation and showed that they

had opposite signs of rotation for the same configuration. The dextro form of  $\alpha$ -phenylpyrrolidine was reduced to the dextro form of  $\alpha$ -cyclohexylpyrrolidine showing that the sign of rotation remains the same. As Betti (19) has pointed out, the presence of the asymmetric carbon atom in a cyclic configuration hinders the clear evaluation of the effects of substituents on the optical rotatory power.

From the above considerations it can be concluded that some relationship exists between the optical rotatory power of the  $\alpha$ -substituted pyrrolidines and the electrical property or "electron sharing ability" of the radical, R, as measured by dissociation constants and that the relation is even more complex than the one exhibited by the  $\alpha$ -ethylamines. If these results should find wider confirmation in numerous other compounds, it may be possible to establish a quantitative relationship between them. The evidence presented in this thesis supports qualitative comparisons.

CONCLUSION

1. There is a qualitative relation between the electrical properties, as measured by dissociation constants, of the radical, R, and the molecular rotations of a series of  $\alpha$ -substituted pyrrolidines.

2. The dextro forms of  $\alpha$ -phenylpyrrolidine and  $\alpha$ -cyclohexylpyrrolidine have the same configuration.

3. The presence of the asymmetric carbon atom in the pyrrolidine ring has considerable effect on *its* rotatory power.

SUMMARY

1.  $\alpha$ -Cyclohexylpyrrolidine,  $\alpha$ -ethylpyrrolidine,  $\alpha$ -phenylpyrrolidine and  $\alpha$ ,p-tolylpyrrolidine have been prepared and, for the first time, resolved into optically active forms.
2.  $\alpha$ ,p-Chlorophenylpyrrolidine and  $\alpha$ ,p-chlorophenylpyrrolidine have been prepared for the first time.
3.  $\alpha$ ,n-Butylpyrrolidine and  $\alpha$ ,n-butylpyrrolidine have been synthesized by a new method.
4. A proof of the relative configuration of  $\alpha$ -phenylpyrrolidine and  $\alpha$ -cyclohexylpyrrolidine has been given.
5. Attempts have been made to resolve  $\alpha$ ,p-chlorophenylpyrrolidine,  $\alpha$ ,n-butylpyrrolidine and  $\alpha$ -benzylpyrrolidine.



REFERENCES

1. Crum Brown, Proc. Roy. Soc. Edinburgh, 17, 181. 1890.
2. Guye, Compt. rend., 110, 714. 1890.
3. Guye, Compt. rend., 111, 745. 1891; ibid., 114, 473. 1892; ibid., 116, 1133, 1378, 1451, 1454. 1893.
4. Guye and Chavanne, Bull. soc. chim., /37 15, 275. 1896.
5. Landolt, "Optical Rotating Power of Organic Substances", p. 290-305. The Chemical Publishing Company, Easton, Pa. 1902.
6. Walden, Z. physik. Chem., 15, 638. 1894; ibid., 17, 245, 705. 1895.
7. Pickard and Kenyon, J. Chem. Soc., 99, 45. 1911; ibid., 101, 620. 1912; ibid., 101, 1427. 1912; ibid., 105, 830. 1914; ibid., 105, 2226, 2262, 2644. 1914; ibid., 123, 1. 1923.
8. Rupe, Trans. Faraday Soc., 10, 46. 1914.
9. Frankland, Trans. Chem. Soc., 101, 661. 1912.
10. Haller, Compt. rend., 136, 1222. 1903.
11. Drude-Mann and Millikan, "Theory of Optics", Chapter 6. Longman, Green and Company, New York. 1902.
12. Tschugaeff, Trans. Faraday Soc., 10, 74. 1914.
13. Born, Physik. Z., 16, 251. 1915.
14. Oseen, Ann. Physik., 48, 1. 1915.
15. Kuhn, Trans. Faraday Soc., 26, 293. 1930.
16. Rule, J. Chem. Soc., 125, 1121. 1924.
17. Betti, Gazz. chim. ital., 36, II, 392. 1906; ibid., 46, I, 200. 1916; ibid., 50, II, 276. 1920.
18. Rule, Trans. Faraday Soc., 26, 321. 1930.
19. Rule and Smith, J. Chem. Soc., 127, 2188. 1925.
20. Betti, Gazz. chim. ital., 53, 424. 1923.

21. Levene and Mikeska, J. Biol. Chem., 84, 571. 1929.
22. Henrich, Johnson and Hahn, "Theories of Organic Chemistry", p. 75-167. John Wiley and Sons, New York. 1922.
23. Hixon and Johns, J. Am. Chem. Soc., 49, 1786. 1927.
24. (a) Johns and Hixon, J. Phys. Chem., 34, 2118. 1930.  
(b) Craig and Hixon, J. Am. Chem. Soc., 53, 4367. 1931.  
(c) Starr, Bulbrook and Hixon, ibid., 54, 3971. 1931.  
(d) Goodhue and Hixon, ibid., 56, 1329. 1934.  
(e) Johns and Hixon, J. Phys. Chem., 34, 2226. 1930.  
(f) Johns and Hixon, J. Am. Chem. Soc., 56, 1333. 1934.  
(g) Carr, "The Reversible Splitting of Organomercuric Cyanides with Hydrogen Chloride". Unpublished thesis for Ph.D. Iowa State College Library. 1934.
25. Burch, "The Dissociation Constants and Rotations of Some Alpha-Substituted Ethylamines". Unpublished thesis for Ph.D. Iowa State College Library. 1934.
26. Craig, Bulbrook and Hixon, J. Am. Chem. Soc., 53, 1831. 1931.
27. Gabriel and Colman, Ber., 41, 517. 1908.
28. Marckwald, Ber., 29, 42. 1896.
29. Hess, Ber., 52B, 1636. 1919.
30. Hess, Ber., 52B, 1622. 1919.
31. Blaise and Cornillot, Compt. rend., 178, 1186. 1924;  
ibid., 178, 1617. 1924.
32. Werthien, J. Am. Chem. Soc., 56, 735. 1934.
33. Pickard and Kenyon, J. Chem. Soc., 105, 835. 1914.
34. Leithe, Ber., 63, 800. 1930.
35. Fischer and Zemplin, Ber., 42, 2989. 1909.
36. McCay and Schmidt, J. Gen. Physiol., 9, 333. 1926.
37. Adams, Voorhees and Shriner, "Organic Syntheses", Volume 8, p. 92. John Wiley and Sons, New York. 1928.