

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]  
**THE DEVELOPMENT OF A METHOD FOR THE RESOLUTION  
OF RACEMIC AMINES AT LOW TEMPERATURES**

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We may suppose<sup>1</sup> that optical activity has not definitely been found for trisubstituted amino or quaternary nitrogen  $(R_1)(R_2)(R_3)N$ ,  $[(H)(R_1)(R_2)(R_3)N]^+$ , either because the groupings are intrinsically not optically asymmetric, or because attempts to resolve racemic mixtures have failed.

By analogy with the behavior of active completely substituted quaternary nitrogen, which very commonly tends to racemize with great ease, and with the extreme mobility of hydrogen in comparison with other radicals, we should expect tri-substituted ammonium compounds—if capable of assuming enantiomorphous forms due to the central nitrogen—to racemize with great rapidity at ordinary temperatures. The velocity of racemization is, however, in general considerably decreased by decreasing temperature.<sup>2</sup>

The question arises, therefore, as to whether tri-substituted quaternary or amino nitrogen<sup>3</sup> could be found asymmetric by a resolution process and examination of products conducted entirely at a low temperature.

The present investigation consists of the development of a means of effecting and detecting resolution at low temperature applicable to the resolution of amino compounds, together with a testing of the method employing a known resolvable amino compound containing asymmetric carbon.

Brief mention only can be made of previous work. In 1927 E. Wedekind and Klatte<sup>4</sup> gave a clear and complete statement of the status of the problem of the stereochemistry of saturated trivalent nitrogen and reported some evidence for the existence of a tri-substituted ammonium ion which

<sup>1</sup> For excellent presentations of the theory of natural rotation from a stereochemical standpoint, see (a) F. M. Jaeger, "Lectures on the Principle of Symmetry," Elsevier Pub. Co., Amsterdam, 1920, pp. 204 *et seq.*; (b) J. B. Cohen, "Organic Chemistry," 5th Ed., Part II, Structure, Longmans, Green and Co., London, 1928, pp. 173 *et seq.*; (c) Eucken and Meyer, *Physik. Z.*, **30**, 397 (1929); (d) Born, *ibid.*, **16**, 251 (1915); *Ann. Physik*, [4] **55**, 177 (1918); Oseen, *ibid.*, [4] **48**, 1 (1915). See also Gans, *Z. Physik*, **27**, 164 (1924); *Ann. Physik*, [4] **79**, 547 (1926). Compare Bursian and Timorev, *Z. Physik*, **38**, 473 (1926). Note that the corrections to Born's theory made by Gans do not affect Born's stereochemical conclusions.

<sup>2</sup> Ref. 1 (b), p. 200.

<sup>3</sup> The structural similarity between tri-substituted amino and quaternary nitrogen should be noted. If  $H^+$  could be added to the grouping  $(R_1)(R_2)(R_3)N$ , or removed from the grouping  $[(H)(R_1)(R_2)(R_3)N]^+$  by a process during which racemization did not take place, or did not take place completely, we might expect to obtain one active form from the corresponding one.

<sup>4</sup> Wedekind and Klatte, *Ber.*, **60**, 2325 (1927).

cannot be considered as conclusive. They agreed with Meisenheimer<sup>6</sup> that "a stabilization results only if the fourth coördination position of nitrogen is occupied either by a positively charged hydrogen atom or alkyl group, or by an oxygen atom, or by a complex metal group."

That a molecular structure of the tertiary amine type could conceivably be asymmetric is seen in the case of several sulfoxides,  $\text{O}=\text{S}\begin{matrix} \text{OR} \\ \text{R}' \end{matrix}$  or  $\text{O}=\text{S}\begin{matrix} \text{R}' \\ \text{R} \end{matrix}$ , and what appears to be an analogous case of carbon attached to three radicals—the ion of 2-nitro-octane,  $\left[ \text{R}-\overset{\text{R}'}{\underset{|}{\text{C}}}-\overset{\text{O}}{\underset{\text{O}}{\text{N}^+}} \right]^-$ , which has been reported.<sup>7</sup> It should be noted, however, as the investigators of the sulfoxides have mentioned, that it seems characteristic of the above cases that there is present in the molecule a permanent dipole moment<sup>6,7,8</sup> involving the central atom.

Moreover, in addition to the fact that completely substituted quaternary nitrogen has been shown, by investigations of optical activity, to be tetrahedral, we have also the fact that tertiary nitrogen has been shown, by other evidence,<sup>9</sup> to be at any rate non-planar in structure. There is still reason, therefore, to expect tri-substituted amino and quaternary nitrogen to have a tetrahedral structure<sup>10</sup> and exhibit optical activity.

In our investigation the original intention was to agitate a solution of a suitable amine in contact, at a low temperature, with a finely powdered appropriate optically active acid, employing a solvent in which the amine, but not the acid or salt, would be soluble. Any activity then appearing in the solution would be due to the enantiomorph which was slower to react with the acid. It was intended, moreover, to keep the reaction mixture under observation in a polarimeter so that any transient activity could be detected. This process was found to be impractical however; salt formation appeared to occur extremely slowly if at all under such conditions.

The final method of salt formation consisted in dissolving the acid and base at room temperature in a solvent in which the salt would not be very

<sup>6</sup> Meisenheimer and co-workers, *Ber.*, **57**, 1744 (1924).

<sup>6</sup> Phillips, *Trans. Chem. Soc.*, **77**, 1072 (1900); Harrison, Kenyon and Phillips, *ibid.*, **129**, 2079 (1926); see also Clarke, Kenyon and Phillips, *ibid.*, **131**, 188 (1927).

<sup>7</sup> Kuhn and Albrecht, *Ber.*, **60**, 1297 (1927). Shriner and Young, *THIS JOURNAL*, **52**, 3332 (1930); see also Heubaum and Noyes, *ibid.*, **52**, 5070 (1930).

<sup>8</sup> For a recent discussion, see Fuson, *Chem. Rev.*, **7**, 359 (1930).

<sup>9</sup> For example, triethylamine has a permanent dipole moment. The space isomerism of multiply bonded N<sup>III</sup> (as in oximes, etc.) indicates also a non-planar structure of the nitrogen.

<sup>10</sup> Other cases reported by Harries, *Ann.*, **417**, 107 (1918), and by Hess, *Ber.*, **52**, 964, 1622 (1919); **53**, 129 (1920); and Hess and Gran, *Ann.*, **441**, 101 (1925), have been disposed of by Orthner, *ibid.*, **456**, 225 (1927), and by Meisenheimer and Mahler, *ibid.*, **462**, 301 (1928).

soluble, at concentrations such that considerable salt would precipitate as crystals upon cooling; then, after seeding if possible, cooling the solution and keeping it cold until cessation of crystallization. By this means we could utilize differences in solubility of the non-enantiomorphic salts, as well as differences in rates of formation. Activity in the solution could now be due not only to partial resolution but also to unprecipitated acid or salt. For amines racemizing rapidly at room temperatures, solutions showing activity after separation of the salt could be heated to room temperature, then cooled to the original low temperature and again examined. A difference in the original and final activity would then be evidence of racemization and hence of some resolution. Methods were developed to examine the crystalline phase also, at the low temperature.

A rather delicate solvent-concentration balance<sup>11</sup> was necessary in order to obtain solutions which when cooled would deposit crystals and leave optically clear supernatant solutions.

### Discussion of the Experiments

We have given our early experiments in considerable detail, because they form a study of salt formation in non-aqueous and slightly aqueous media. Employing a racemic amine (Expt. I), the antipodes of which are quite stable, and which is readily resolvable under a variety of conditions by the optically active acid employed, the amine was dissolved in a solvent in which the optically active acid is insoluble and the solution kept in contact with the solid acid for a long time. No resolution was attained by this procedure. What we found in this initial set of experiments could not have been predicted. We do not know whether or not the forces active at the surfaces of asymmetric crystals could themselves have any property of asymmetry. We know nothing regarding the symmetry or asymmetry of any forces associated with the boundary between a strongly optically active strong acid in the solid state and a readily resolvable strong base in solution.

Our second and third sets of experiments (see Expts. II and III) indicate the following: (1) Our optically active acid was somewhat soluble in the solvent media employed and some partial resolution was attained. (2) The formation of crystals rather than sirups seems necessary for resolution. (3) The initial formation of sirups which later turn into crystals may hinder the resolution process in two ways. The amount of time required is lengthened by the time necessary for the crystals to be formed from the sirup. The extent of resolution may be reduced by the sirup itself acting

<sup>11</sup> The effect of the presence of water in our solvents is interesting. A little water present before precipitation appeared to facilitate crystal formation (if moisture entered the solution, however, after precipitation was well under way, the solution became fogged).

as a solvent medium for the process and being a less favorable solvent than the main solution.<sup>12</sup>

The second point noted above is of particular interest. Several examinations of the sirups (and congealed sirups formed at low temperature) and of the supernatant solutions were made during this investigation. In all cases it was found that no detectable resolution had been brought about by the precipitation of the sirups. In the crystals formed from the sirups, however, except when pure ether was employed as solvent, partial resolution had been attained. This indicates that the actual *crystalline* salt must be obtained in order to bring about resolution by a salt formation process.

The next set of experiments (see Expt. IV) shows that upon employing a solvent more polar than the previous media we were able to obtain a much higher percentage resolution. Also, the time required for the crystal formation was materially reduced.

In the next set of experiments (see Expt. V) we find that: (1) neither the salt of the dextro antipode nor of the levo antipode of the amine we were using with the optically active acid employed was detectably soluble in dry ether.

(2) A mixture consisting of equal amounts of the salts of the amine isomers in contact with an excess of the dissolved racemic amine finally reaches a state in which an excess of the dextro amine is present in the solution and a corresponding excess of the salt of the levo amine is present in the solid phases. The data indicating this interesting result were not verified. Only a single experiment (of the type Vb) was carried out. We are not certain that we reached equilibrium in this experiment. We believe that the success of our resolution process depended upon a difference between the amine isomers in their *rate* of forming salt *crystals* with the optically active acid. The non-enantiomorphic salts of the base and optically active acid we were using should differ in solubility in any solvent. Although this relative difference in solubility might be appreciable in the solvent media we employed, so that with the racemic base and active acid initially in solution, one salt would be precipitated in greater amount to attain equilibrium, we do not regard such equilibrium considerations as particularly pertinent under the conditions of our resolution procedure. In a number of cases we found we were working with supersaturated solutions. Clear solutions decanted from good crops of crystals, after crystallization had been occurring for twelve hours or so, would slowly deposit more crystals over a period of several days or even weeks.<sup>13</sup>

<sup>12</sup> On numerous occasions sirup was thrown against the walls of containers (by shaking) above the reaction mixture and stuck there. This sirup, out of contact with the main solution, would give crystals directly, simultaneously with the appearance of crystals from the sirup in contact with the solution. This indicates that crystal formation took place in the sirup as solvent.

<sup>13</sup> The containers were stoppered; moreover the mother liquors, after long standing

Moreover, during our work at low temperature we frequently observed the unusual phenomena of crystals being deposited while solutions<sup>14</sup> were warming up. Clear solutions decanted from crystals at  $-70^{\circ}$  would give small additional crops during one or two hours' warming to room temperature.

We suppose, but we did not prove, that salt formation took place much faster than crystal formation in our ethereal solutions. In more concentrated solution—in solvent media high in alcohol or ethyl acetate or acetone content—the addition of amine to acid was accompanied by a very obvious heat effect. In the more dilute solutions, no heat of neutralization was noticed, but we did not try experiments in a calorimeter.

The next series of experiments (see Expt. VI) and the last three series (see Expts. VIII, IX and X) describe the low temperature resolution of 1-amino-1-phenylethane and summarize the unsuccessful attempts to resolve benzylethylaniline.

We wish to comment on our method of freeing amines at low temperature (see Expt. VII). By the use of a relatively strong (optically inactive) amine we were able to liberate our resolved amine at low temperatures from a salt into a solvent permitting of polarimetric examination. The process would appear to be serviceable in many cases. However, a comprehensive investigation with a large number of resolved amines would be necessary to demonstrate the general applicability of the method. The solvent media might have to be changed somewhat depending upon the amine investigated. The method given is considered an improvement over the older method of liberating rapidly racemizing amines by ether extraction from a basic aqueous solution of a salt.

### Experimental Part

**Polarimeter.**—A Laurent polarimeter was equipped with quarter-wave plate for sodium light. The trough for supporting ordinary polarimeter tubes was removed and the polarizing and analyzing mechanisms mounted firmly on a steel base with guides and screws for adjustment. Space and rests were provided between the polarizer and analyzer so that either the trough and ordinary tubes or the heat-insulated low temperature tubes could be accommodated at will.

The polarimeter tube consisted of a copper tube gold-plated inside, 17.43 cm. in length between end disks and 1.8 cm. inside diameter. Vertical side tubes—offset from the center line—were attached for the thermometer and for introducing and removing solutions. A glass tube ran down one side tube to the bottom of the polarimeter tube and extended some distance in the upward direction; from this a horizontal branch connected with a reaction vessel containing the solution whose activity was to be measured. The other side tube, in addition to accommodating a thermometer, had a vertical glass tube attached. The two vertical glass tubes were connected to drying towers.

and further crystallization, would frequently have lower rotations. If accidental evaporation had occurred and the crystallization took place in response to this, the final solutions should have the same or higher rotations.

<sup>14</sup> Protected against appreciable evaporation or the entrance of moisture by long tubes filled with drying agent.

The windows were simply ordinary polarimeter tube disks 2.4 cm. in diameter, held tightly—protected by washers<sup>16</sup>—by means of threaded brass rings, into threaded depressions at the ends of the tube. Hard rubber tubes were attached to each end of the tube to prevent currents of moist air from striking the windows. The polarimeter tube was set into a heat-insulated box.

The reaction vessels were simply glass containers in the shape of large test-tubes closed by stoppers bearing siphons and short connections to drying tubes. These vessels were placed in larger test-tubes containing some light liquid for thermal contact and the larger test-tubes surrounded by freezing mixture in gallon Dewar jars. A reaction vessel could be removed momentarily from the cold bath for examination without any freezing mixture adhering.

By applying gentle air pressure through the drying tube attached to the reaction vessel, solution could be forced over into the polarimeter tube. Applying dry air over the solution in the polarimeter tube, the tube could be emptied. The contents of the polarimeter tube could be stirred by sending portions of the solution up and down the vertical glass tubes attached. The polarimeter tube windows were freed from condensed moisture by spraying them with alcohol; a time interval of from five to ten minutes—ample for making an observation—would elapse during which the window would be absolutely clear. When solutions were removed from the polarimeter tube for boiling and re-cooling, flasks with long reflux condensers, capped by drying tubes, were used.

Dewar and Jones, and Molby<sup>16</sup> have used low temperatures in measuring optical activity. Molby found successful a glass polarimeter tube equipped with double windows. The windows were sealed by water-glass joints to rings, forming window chambers which were evacuated, or dried by phosphorus pentoxide. We found a glass polarimeter tube equipped with two side tubes, all carefully annealed, to be subject to some distortion upon cooling, unless the freezing mixture were carefully applied. Molby needed only one side connection and encased the glass tube in close fitting copper tubing to obtain uniform conduction, so very likely did not experience any distortion. By using washered, rather than sealed-in or cemented-in windows, we could be sure that we would never have any distortion giving rise to rotations which we might attribute to mutarotation.

The temperature was measured by ligroin or pentane thermometers checked against one calibrated by the Bureau of Standards. We used acetone and carbon dioxide snow for keeping the reaction vessels cold. Instead of acetone we employed a mixture of acetone (60%) with carbon tetrachloride (20%) and chloroform (20%) by volume for cooling the polarimeter tube. The latter mixture (with solid carbon dioxide) would give temperatures around  $-78^{\circ}$  and was not flammable.

**The Light Source.**—It appeared early in our work that we would need a light source of very high intensity. We found entirely satisfactory a simple modification of a light originally used by Perkin.<sup>17</sup> Perkins vaporized sodium in a current of hydrogen and burned the sodium-laden hydrogen in air. Our modification consisted of burning the sodium-laden hydrogen in a current of oxygen, thus increasing the intensity many fold. The light consists of a horizontal piece of 5-cm. pipe about 30 cm. long with, at one end, a capped vertical elbow (for introducing sodium every few days) pierced horizontally by a small pipe carrying hydrogen; the other end terminated also in a vertical elbow, pierced vertically by a small pipe carrying oxygen, the oxygen pipe ending flush with the elbow

<sup>16</sup> Fiber-like washers were found best: rubber washers would often crack when cold, leather or asbestos-like washers would leak solvents when cold.

<sup>16</sup> Dewar and Jones, *Proc. Roy. Soc. (London)*, [A] **80**, 236 (1908); Molby, *Phys. Rev.*, **28**, 57 (1909); **30**, 84 (1910); **31**, 291 (1910).

<sup>17</sup> Perkin, *Trans. Chem. Soc.*, **45**, 421 (1884); **69**, 1027 (1896).

around it to form the burner. The sodium is vaporized by an electric furnace element surrounding the horizontal pipe.

The light given by the modified Perkins lamp is of approximate spectral purity, no monochromator or filter was necessary.

**Preparation of Materials.** 1-Bromo-*d*-camphor-10-sulfonic Acid.—Bromocamphor, white crystals, m. p. 76–77°, was sulfonated by the method of Pope and Read<sup>18</sup> except that a better yield was obtained through the use of a less concentrated sulfonating mixture. For 150 g. of bromocamphor, 110 cc. of 95% sulfuric and 165 cc. of 30% fuming sulfuric acid were used. This yielded 35% of the theoretical amount of ammonium salt of the acid, against 25% using Pope and Read's reaction mixture. The ammonium salt was recrystallized from water until its rotation rose to the required value; colorless crystals, dec. 270°; 3.8875 g. in 50 cc. of aqueous solution,  $[\alpha]_D^{25}$  86.4°. Washing the moist ammonium salt with cold acetone facilitated the purification. An aqueous solution of the acid was made by Pope and Read's method, and evaporated on a steam-bath to a thick sirup and finally to dryness over phosphorus pentoxide *in vacuo*. The resinous mass was finally obtained as a white powder, m. p. 196°, forming a clear solution in water, only slight trace of barium: 1.050 g. in 50 cc. of aqueous solution,  $[\alpha]_D^{25}$  85.3°. To phenolphthalein, 1.050 g. of the acid used 0.003272 equivalent of sodium hydroxide; equivalent weight found, 321; calculated, 311.

*d*-Camphor-1'-sulfonic acid, from Eastman, was recrystallized twice from moist ethyl acetate and dried over phosphorus pentoxide *in vacuo*; colorless crystals, dec. 195°. To phenolphthalein, 1.000 g. used 0.00409 equivalent of sodium hydroxide, whereas one gram of pure acid should use 0.00431 equivalent, hence it was 94.8% pure. 2.000 g. in 100 cc. of aqueous solution,  $[\alpha]_D^{25}$  20.9°.

1-Amino-1-phenylethane was prepared by the reduction of acetophenone oxime,<sup>19</sup> using five times the amounts specified; yield, 70%, b. p. 186°.

Benzylethylaniline from Schering-Kahlbaum, A. G., was twice distilled *in vacuo* over a one-degree range. The light yellow oil distilled at 312–313° at 750 mm. with some decomposition; picrate, m. p. 117°.

**Solvents.**—The methyl alcohol, ethyl alcohol, ethyl acetate and acetone were of "U. S. P." grade, dried with anhydrous copper sulfate. The ether, denoted in the experiments as "comm. ether" was moist, alcoholic, "U. S. P.," 99% pure. Ether specified as "dry ether" was dried and stored over sodium wire. The petroleum ether was the "U. S. P." grade "Oronite."

TABLE I  
DATA USED IN CALCULATIONS

Compound	Mol. wt.	Molecular rotation (dilute aqueous soln.)	Abbreviation
1-Bromo- <i>d</i> -camphor-10-sulfonic acid	311	271°	HK
Salt (anion)	...	271°	K <sup>-</sup>
<i>d</i> -Camphor-1'-sulfonic acid	232	50°	HR
Salt (anion)	...	50°	R <sup>-</sup>
1-Amino-1-phenylethane	121	30.2° 50° (in dry ether)	A
Salt (cation)	...	0°	AH <sup>+</sup>
Benzylethylaniline	211	.....	B

**Definition of "Per Cent. of Resolution."**—Let  $[M]$ , be the molecular rotation of the

<sup>18</sup> Pope and Read, *J. Chem. Soc.*, 97, 2200 (1910).

<sup>19</sup> Cummings, Hopper and Wheeler, "Systematic Organic Chemistry," D. Van Nostrand Co., New York, 1923, p. 361.

completely resolved salt,  $A \cdot HK$ ,  $[M]_u$  that of the unresolved salt and  $[M]$  that of the sample in question, each in distinctly alkaline solution, then

$$\text{Per cent. of resolution} = 100\{[M]_u - [M]\} / \{[M]_u - [M]_r\}$$

For a dry ethereal extract of the base A

$$\text{Per cent. of resolution} = 100 (\text{moles of excess } d \text{ or } l \text{ base}) / \text{total base}$$

The total base may be determined by titration and the amount of active base in excess of racemic base from the optical activity. The two methods of determination agree. In water, the rotations of the active acid and base and their ions may be superimposed.

**Record of Experiments.**—Since all measurements were made with sodium light, the subscript D will be omitted in giving the rotations. A subscript to denote the length of the observation tube in decimeters will be used.

**Preparation of (1)  $A \cdot HK$  and Tests of the Method of Analysis.**—15.5 g. (0.05 mole) (HK) and 12.1 g. (0.1 mole) (A) were added to 50 cc. of 1 *N* (0.05 mole) HCl (aq.) and dissolved by warming. In order to obtain crystals, the solution had to be evaporated to a sirup. After four days' standing, a crop of crystals was formed. The crystals were filtered off, washed with a little cold ethyl acetate and recrystallized twice from ethyl acetate; yield, 6 g. of colorless crystals, m. p. 207–208°.

The ethyl acetate from the crystallizations and washing was added to the sirup, the solution evaporated to a sirupy consistency and let stand. After seven days a large crop of crystals was obtained which was filtered off, washed and recrystallized three times from ethyl acetate; yield, 11 g. of colorless crystals, m. p. 207–208°. The two crops were mixed and recrystallized from water; m. p. 207–208°.

For 0.8652 g. of the crystals made up to 50 cc. aqueous soln.,  $\alpha_{4dm}^{22^\circ}$ , 4° 24', therefore  $[M]^{22^\circ}$  268. According to the literature, for (*l*)  $A \cdot HK$ , m. p. 206–207°,  $[M]^{20.5^\circ}$  271°. Hence the crystals were practically pure (*l*) $A \cdot HK$ .

**The Quantitative Separation of A from its Salt.**—2.000 grams of (*l*) $A \cdot HK$ , 20 cc. of water, 3 cc. of 12 *N* sodium hydroxide and 30 cc. of ether (comml.) were shaken thoroughly. The ethereal layer was separated (one extraction proved sufficient) and dried with solid potassium hydroxide, by decanting from any aqueous layer to fresh drier and allowing it to stand on the drier in a stoppered vessel for twelve hours. The ether layer was finally decanted from the drier, the latter washed with dry ether and the combined solution and washings measured for volume. The original aqueous layer was analyzed for  $K^-$  polarimetrically.

$$\text{Equivalents of salt by weight } 2/432 = 4.63 \times 10^{-3} \text{ eq.}$$

$$\text{Equivalents of salt by rotation} = 4.63 \times 10^{-3} \text{ eq.}$$

The rotation of the ether solution containing the base gave values of  $[M]^{22.5^\circ}$  (for three dilutions) of  $-49.5^\circ$ ,  $-49.0^\circ$ ,  $-50.3^\circ$ , respectively. Blank experiments with a known amount of unresolved base showed that the base could be dissolved in ether, the solution shaken with 4 *N* sodium hydroxide solution, separated and dried as above, the base then extracted from it with a known excess of standard acid and the acid back-titrated to show within 2% the original amount of base. It was shown further that within 1% the molecular rotations of (*l*) A and  $K^-$  are additive and independent of wide variations in the alkalinity of the solution and of the presence or absence of alcohol in the solution. The average value of  $[M]$  for the base A in dry ether was taken as 50.0° as a result of these experiments.

**Experiments in Detail. I. Room Temperature Experiments with (*dl*)A Dissolved and HK Insoluble.**—(a) 2.3035 g. of HK was added to 250 cc. of petroleum ether and the mixture left to stand with occasional shaking. (b) 2.1845 g. of HK (0.0073 mole) was added to a solution of 2 cc. of (A) (0.0154 mole) in 250 cc. of petroleum ether and the mixture left to stand with occasional shaking. The two mixtures were examined for ro-



tation (in 2-dm. tube) after standing for one week, two weeks and then after being shaken continuously for an additional week. All rotations were zero. The only change noted was that the HK which remained a loose powder throughout in (a) and was originally a loose powder in (b), became, after ten days' standing in (b), too gummy to move around freely. Similar experiments for shorter periods of time also showed no indication of partial resolution.

II. With HK Originally Undissolved but Soluble; Sirup Formed.—(a) A solution of 1 cc. of A (0.0078 mole) in 50 cc. of ether was kept, with occasional moderate shaking, in contact with 1.21 g. of HK (0.0039 mole). A sirupy coating rapidly formed about the HK. The ethereal solution was examined from time to time for rotation; twenty-four, thirty-six and forty-eight hours after mixing,  $\alpha_{2\text{ dm.}}^{\text{room temp.}}$  8'. After forty-eight hours' standing the solid acid and sirupy coating were mixed together and shaken with the ether solution thoroughly for six hours, then  $\alpha_{2\text{ dm.}}^{\text{room temp.}}$  16'. Examination of the ethereal solution at this point showed it to contain a small amount of K<sup>-</sup> and 0.0031 equiv. of A with 0.0009 equiv. excess (*d*)A. Hence the resolution was 29% complete. The solid and semi-solid material contained considerable unused HK. (b) A solution of 2.58 cc. of A (0.02 mole) in 200 cc. of ether was kept, with occasional moderate shaking, in contact with 3.11 g. of HK (0.01 mole). A sirupy coating gathered about the powdered solid acid upon mixing. The mixture did not change in appearance over a period of twenty-four hours. The sirupy substance then, however, began forming powdery crystals. This change appeared to be complete after forty-eight hours (seventy-two hours after mixing) and the mixture was filtered. The solid matter, washed with a little ether, consisted of 3.72 g. of white powdery crystals, melting from about 150° to 185°. Examination of the solid showed it to be practically pure A·HK, about 20% resolved.

III. With HK Originally Dissolved; Sirup Formed.—(a) 1 cc. of A added to 128 cc. of a solution of HK in ether, 0.061 mole/liter (equivalent amounts) gave immediately a great deal of suspension which rapidly gathered into clear sirupy droplets. The clear supernatant solution was decanted twenty minutes after the mixture was made up. Examination of the supernatant solution showed it to be appreciably acidic and that no partial resolution had been effected by precipitating the sirupy phase. (b) 1 cc. of A was dissolved in 19 cc. of ether and the solution added to 128 cc. of a solution of HK in ether, 0.061 mole/liter (equivalent amounts). A great deal of suspension was immediately produced (just as in the previous case) and soon gathered into sirupy droplets. Twenty-four hours later the sirupy phase had partially solidified and changed into powdery crystals. The powdery substance was loosened from the containing vessel, filtered off and washed with a little ether; 0.82 g. of a white powder, melting from about 103° to about 175°, was thus obtained. Examination showed the powder to be fairly pure A·HK not resolved to more than 2%. A duplicate experiment which stood for seventeen days produced no detectable resolution. (c) 1 cc. of A dissolved in 36 cc. of ether was added to 64 cc. of a solution of HK in ether, 0.061 mole/liter (ratio A/HK = 2). The addition of the amine solution produced a copious suspension which rapidly gathered into sirupy droplets. During three days' standing the sirup changed over into white powdery crystals. The powder, filtered off and washed with a little ether, weighed 0.87 g. and melted at about 105–180°. Examination showed the powder to be practically pure (*dl*) A·HK. (d) Added 1.29 cc. of A, 2.5 cc. of acetone and 2.5 cc. of alcohol to 140 cc. of a solution of HK in ether (comm.), 0.0715 mole/liter (equivalent amounts). A suspension formed upon adding the amine soon disappeared, leaving a clear solution. Upon slight shaking, however, the suspension reappeared. It was found that a separate liquid phase was present, spread out thinly and uniformly along the container in contact with the solution. Within an hour crystals began to form. After twenty-four hours the crystals were filtered off and washed with a little ether: 2.01 g. of colorless crystals, melting 165–178°. Examination showed the solid matter to be prac-

tically pure A·HK, about 27% resolved. (e) 1 cc. of A added to 64 cc. of a solution of HK in ether, 0.061 mole/liter (ratio A/HK = 2), produced a suspension which collected into a sirupy phase. Within an hour the sirupy phase began changing over into a white powder; this change was completed after about eighteen hours. During two weeks' further standing the powdery substance steadily disappeared and a new type of crystals—feathery needle clusters—formed. The feathery needle clusters were filtered off and washed with a little ether: 1.510 g. of colorless crystals, melting at 175–192°. Examination showed the crystals to be practically pure A·HK, 38% resolved.

IV. With (HK) Originally Dissolved; No Sirup Formed.—(a) In 150 cc. of a solution of 2800 cc. of ether (comm.), 100 cc. of acetone and 100 cc. of alcohol, there was dissolved 3.11 g. of HK, then 1.3 cc. of A was added (equivalent amounts). Only a faint turbidity appeared on mixing. Three hours later colorless crystals began to appear and grew rapidly. After forty-eight hours the crystals were filtered off and washed with a little petroleum ether: 0.81 g. of crystals, melting at about 186–207°. Examination showed the crystals to be practically pure A·HK, about 80% resolved. (b) In 150 cc. of a solution of 2800 cc. of ether (comm.), 100 cc. of acetone, 100 cc. of alcohol was dissolved 3.11 g. of HK, then 2.6 cc. of A (ratio A/HK = 2) added. Only a faint turbidity appeared on mixing. Two hours after mixing colorless crystals began forming; forty-eight hours later they were filtered off and washed with a little petroleum ether: 0.75 g. of crystals, melting at about 186–207°. Examination showed the crystals to be practically pure A·HK, about 80% resolved. (c) 2.58 cc. of A, 5 cc. of acetone and 5 cc. of alcohol added to 140 cc. of a solution of HK in ether (comm.), 0.0715 mole/liter (Ratio A/HK = 2), produced only a slight suspension. The mixture seeded with (*l*)A·HK, began depositing crystals within forty-five minutes. Twelve hours later the crystals were filtered off and washed with a little ether: 2.09 g. of white powdery crystals, melting at 175–187°. Examination showed the crystals to be practically pure A·HK, about 75% resolved.

V. Solubility of A·HK in Ethereal Solutions.—(a) 1.802 g. of (*dl*)A·HK was added to 200 cc. of ether and the mixture shaken for ten hours daily on an efficient shaker for four weeks. The ether was examined (in a 2-dm. tube) each week; rotations all zero. No measurable amount of HK or K<sup>-</sup> was dissolved. (b) 3.105 g. of (*dl*)A·HK was added to a solution of 1 cc. of A (racemic) in 200 cc. of ether and the mixture shaken for ten hours daily on an efficient shaker for four weeks. The ethereal solution was examined each week for rotation:  $\alpha_D^{room\ temp.}$  0.06'. Examination of the solution and of the salt recovered indicated that the amine had been partially resolved. (c) 6.14 g. of powdered (*l*)A·HK was added to 300 cc. of a solvent mixture consisting of 280 cc. of ether (comm.), 10 cc. of acetone and 10 cc. of alcohol. The mixture was shaken violently for twelve hours, allowed to stand for twelve hours and then filtered. Examination of the filtrate indicated that the salt had dissolved to the extent of roughly 0.005 mole/liter.

VI. Partial Resolution of A at a Low Temperature.—The investigation of the resolution of A by HK at a low temperature paralleled that at room temperature. The behavior of the reaction mixtures was analogous. The course of the development of the resolution process is clear from the results at room temperature. We shall summarize only the salient findings of the preliminary low temperature investigation.

Solutions of (*dl*)A and HK, 1/1 or 2/1 by mols, saturated at room temperature with respect to (*l*)A·HK in acetone, alcohol, ethyl acetate, or in 25% by volume or 50% by volume alcoholic ether as solvents, could be cooled in contact with and kept in contact with (*l*)A·HK at about -70° for twenty-four hours with thorough shaking from time to time without any noticeable precipitation or crystal growth occurring. These same solutions warmed to room temperature deposited large crops of crystals rapidly—obvious crystal growth getting well under way in each case within thirty minutes after warming to 20°.

The addition of considerable ether to the solvent media reduces the viscosity of the solutions, permitting rapid precipitation and optically clear supernatant solutions.

Pure ether or ether containing only very small amounts of water, alcohol, acetone or ethyl acetate causes precipitation of sirups, separation of sirups not being accompanied by any resolution. The sirups, or congealed sirups, at low temperature change extremely slowly into crystals.

By proper choice of solvents there can be brought about at  $-70^{\circ}$  rapid crystal formation resulting in high resolution and clear mother liquor. The following is an example of a satisfactory low temperature resolution test: 5.16 cc. of A (0.04 mole), 10 cc. of acetone, and 10 cc. of alcohol were added to 280 cc. of a solution of HK in ether (comml.), 0.0715 mole/liter (0.02 mole). The clear solution was seeded with (*l*)A·HK and two hours later when crystal growth was barely visible the mixture was immediately cooled to about  $-70^{\circ}$ . Rapid crystal growth ensued; eleven hours later the mixture consisted of clear solution above a good crop of crystals. A sample of solution was then introduced into the low temperature polarimeter tube

Time	Temp., °C.	
8:25	-72	2°36' ± 3'
8:35	-73	

The sample was removed, boiled, cooled, re-introduced into the tube

8:55	-72	2°37' ± 3'
9:05	-71	

The rest of the solution was decanted from the crystals and the latter washed with a little ether. There was obtained 2.53 g. of colorless crystals, melting at  $193-207^{\circ}$ . Examination showed the crystals to be practically pure A·HK, about 90% resolved.

**VII. A Method of Freeing Amines at Low Temperature.**—By the use of a relatively strong amine, amines can be liberated from salts at low temperatures into solvents permitting of polarimetric observation. A comparison of the process at room temperature and at  $-70^{\circ}$  follows. (The polarimeter observations in the test below were made at room temperature. For a rapidly racemizing amine, the observations would be made at low temperature.) (a) Two grams of (*l*)A·HK was added to 250 cc. of a solvent consisting of 28 parts ether (comml.), 1 part acetone, 1 part alcohol by volume and the mixture kept, with moderate shaking from time to time, for twelve hours. A sample of solution then showed  $\alpha_{4\text{ dm.}}^{22.5^{\circ}}$  26'.

One cc. of diethylamine was then added and the mixture shaken; the solid entirely dissolved, giving a clear solution,  $\alpha_{2\text{ dm.}}^{23^{\circ}}$  1° 9'. Another 1 cc. of diethylamine and shaking, and still another 1 cc. and more shaking, gave in both cases  $\alpha_{2\text{ dm.}}^{23^{\circ}}$  1° 10'. (b) Two grams of (*l*)A·HK was added to 250 cc. of the solvent described in (a) and the mixture cooled to about  $-70^{\circ}$  and kept, with occasional moderate shaking, for twelve hours. A sample of solution (warmed) gave  $\alpha_{2\text{ dm.}}^{22.5^{\circ}}$  21'.

One cc. of diethylamine was then added at  $-70^{\circ}$  and the mixture shaken (still at about  $70^{\circ}$ ) moderately for an hour; all the solid did not dissolve. A clear sample of solution was withdrawn through cloth (to remove crystals in suspension) and warmed.  $\alpha_{2\text{ dm.}}^{23^{\circ}}$  52'.

**VIII. Experiments with B and HK.**—We did not succeed in obtaining crystalline B·HK formed at low temperature. We tried various mixtures of B and HK, 1/1 or 2/1 by mols, in ether, ether (comml.), with and without alcohol, acetone, ethyl acetate or *n*-butanol. The addition of the base to the acid was varied by having the B concentrated or in solution, the HK undissolved or dissolved, the mixtures originally at room temperature then cooled, or originally cold. In all cases in which the solutions were such as to give a precipitate at low temperature, the precipitate was a sirup (or con-

gealed sirup) which would not change into crystals at a measurable rate at the low temperature.

Optical examinations were made shortly after mixing and at intervals during long standing. The solutions above the sirups, and the sirups themselves dissolved in alcoholic ether, were examined for rotation, heated to boiling, cooled, and re-examined. No changes in rotation (greater than 2 or 3', within our experimental error) were found.

Samples of the crystalline salt, B·HK, were obtained at room temperature from the slow evaporation of an ethyl acetate solution of the base and acid (ratio 2:1). It melted at 103–106°. Examination showed that its optical activity was entirely due to the anion, K<sup>-</sup>.

**IX. Experiments with B and HR at Room Temperature.**—The behavior of solutions of B and HR was entirely analogous to the behavior of similar solutions of A and HK. The same mixed solvent (29 parts ether (comml.), 1 part alcohol, 1 part acetone by volume) which rapidly precipitated crystalline A·HK also rapidly precipitated crystalline B·HR from concentrations of 0.02 mole of B, 0.01 mole of HR in 150 cc. of solvent. A number of crops of B·HR obtained consisted of colorless crystals, each crop melting in a range of approximately 2° from 120 to 127°.

Twenty-one grams of crude salt was crystallized twice, yielding 20 g. of colorless crystals. Two grams of this was retained for examination and the remaining 18 g. again crystallized, the crystallization not being allowed to go to completion. In this way 15 g. was obtained, of which 2 g. was kept and the 13 g. again crystallized, yielding 10 g.

The three crops, after drying, melted, respectively, at 120–122°, 121–124°, 122–124°; 1.000-g. samples were made up to 50 cc. in aqueous solution containing 10 cc. of N/10 hydrochloric acid. These solutions gave the following

	Rotation	Vol. N/10 NaOH to titrate to phenolphthalein, cc.
i	$\alpha_D^{22}$ dm. 26'	32.65
ii	$\alpha_D^{22}$ dm. 27'	32.65
iii	$\alpha_D^{22}$ dm. 27'	32.63

These results show that the crystals were practically pure salt (containing no solvent of crystallization), not detectably resolved.

**X. Experiments with B and HR at Low Temperature.**—Experiments entirely similar to those carried out with A and HK were carried out with B and HR. No evidence was obtained of resolution. The crystalline salt, practically pure, was formed (at about -70°) in a number of tests. In no case was any racemization by heat, or any resolution, detected.

### Summary

A method has been developed for the resolution of racemic amines at low temperatures, -70°. The resolution process employed was that of salt formation between amine antipodes and optically active acids. The method was tested and proved using 1-amino-1-phenylethane, an amine known to be resolvable and 1-bromo-*d*-camphor-10-sulfonic acid, a suitable acid. In the course of testing the method, it was found that formation of *crystalline* salt was necessary for resolution. Under the conditions most favorable for resolution at low temperatures, success in the resolution process appeared to depend upon a difference between the amine enantiomorphs in their *rate* of forming salt crystals from supersaturated

solutions, rather than upon a difference in the solubility of the non-enantiomorphic salts.

The resolution of an asymmetrically substituted amine, benzylethylaniline, possessing no carbon asymmetry, was finally attempted employing, in turn, 1-bromo-*d*-camphor-10-sulfonic acid, and *d*-camphor-1'-sulfonic acid. No evidence of resolution was found.

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

## THE FREE ENERGY OF ENOLIZATION IN THE GASEOUS PHASE OF SUBSTITUTED ACETOACETIC ESTERS

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Previous measurements of the equilibrium constants of the change keto  $\rightarrow$  enol have all been carried out with solutions of the two components or with the equilibrium liquid mixture. K. H. Meyer,<sup>1</sup> the first investigator to obtain satisfactory quantitative results, found that the nature of the solvent affected enormously the equilibrium constant. It was thus difficult to obtain a satisfactory comparison of a series of substituted ketonic esters or diketones; his proposal to compare them all in the same solvent was only partially successful as the comparisons in many cases varied with the nature of the solvent. The use of the pure liquid equilibrium mixtures as a basis of comparison is clearly open to the same sort of error and a serious and unknown solvent effect is introduced into the measurements. It seemed probable that the greatest regularity between structure and free energy of enolization would be found by taking the gaseous phase (preferably at low pressure) as the standard state. Such a choice of the standard state in the reduction of a series of chloroquinones brings out regularities which are obscured by physical forces when the solid state or a solution is used as the standard state.<sup>2</sup> We have therefore undertaken to measure the equilibrium constant of enolization in the gaseous state for acetoacetic ester, eight substituted acetoacetic esters, four  $\beta$ -diketones and a few other related compounds. The results show clearly that there is a regularity between the structure of the compound and the free energy of enolization in the gaseous state.

Since the interconversion of the two tautomeric isomers does not proceed at all readily in the gaseous state at room temperature, it was necessary to use the liquid phase as an intermediary. It is clear that if chemical

<sup>1</sup> Meyer, *Ber.*, **45**, 2846 (1912).

<sup>2</sup> Conant, *THIS JOURNAL*, **49**, 293 (1927); a further discussion of this point and a preliminary statement of the results of the present investigation are given in *Ind. Eng. Chem.*, **24**, 466 (1932).