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A METHOD FOR THE COMPLETE, MUTUAL RESOLUTION OF INACTIVE ACIDS AND BASES

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The present methods for resolving an asymmetric compound, so that both forms are obtained in a condition of optical purity, are subject to limitations which often render their use tedious or uncertain. As both active forms are often required for the study of their differences in physiological action or dyeing properties,[1] and for other purposes, an improved method for their separation is desirable. This paper contains a description of two cases in which complete resolutions have been effected by what is believed to be a new and rather general method.

In the usual method in which, for example, an inactive base (*dl*B) is combined with an active acid, for instance *d*A, usually only the less soluble of the two salts formed, for instance, *l*B*d*A, can be obtained pure by crystallization. Hydrolysis of this salt yields one active form of the base pure (*l*B). In rare cases the other salt, *d*B*d*A, may be obtained pure by using another solvent.[2] Commonly the more soluble, impure salt, here impure *d*B*d*A, which remains in the mother liquor is also hydrolyzed and the partially resolved base, impure *d*B, is recovered and recombined with various active acids until a pair of salts is formed which possess the reverse order of solubility. As active acids which can form stable salts of high crystallizing power are not numerous, it often happens that such a pair of salts cannot be found. Another method, described by Marckwald,[3] is based upon the fact that the salts, *d*B*d*A and *l*B*l*A, as well as *d*B*l*A and *l*B*d*A, respectively, are enantiomorphic. Hence, if the partially resolved base obtained as above, impure *d*B, be recombined with the optical isomer of the original active acid (*l*A), the salt of opposite sign (*d*B*l*A) will now be the first to crystallize. As, unfortunately, few suitable acids are available in both active forms this method has been little used.

The new method, while related to Marckwald's, requires only one active form and the inactive (*dl*) form of a suitable acid—materials which are usually readily available. The procedure used may best be made clear by the description of one of the resolutions actually carried out. When Reychler's *d*-camphor-sulfonic acid (*d*A) was combined with inactive phenylamino-acetic acid (*dl*B) in water solution, the *l*B*d*A salt separated first and was recrystallized until pure. From this salt, ammonium hydroxide

[1] Ingersoll with Adams, THIS JOURNAL, **44**, 2930 (1922).

[2] Dakin, *J. Biol. Chem.*, **59**, 7 (1924).

[3] Marckwald, *Ber.*, **29**, 43 (1896).

precipitated the pure *l*-base.[4] The mother liquors from the original crystallization gave with ammonium hydroxide the partially resolved base (*d*B + *dl*B). From this point two closely related procedures were used to obtain the pure *d*-base.

Procedure A.—The partially resolved base was dissolved with an equivalent quantity of *inactive* camphor-sulfonic acid (*dl*A). From the ions then present in the solution the three salts, *d*B*l*A, *dl*B*dl*A and *d*B*d*A, could be formed. Of these *d*B*l*A is enantiomorphic with the *l*B*d*A salt obtained as described above and should be expected to separate first. This in fact happened, and by careful fractional crystallization the salt was obtained in an amount nearly equivalent to half the excess of *d*-base in the mixture. Hydrolysis of the pure salt gave the pure *d*-base in good yield.

Procedure B.—One molecular equivalent of the pure *l*-base obtained in the original resolution was dissolved with two molecular equivalents of the *dl*-acid. Upon concentration of the solution nearly one molecular equivalent of the *l*B*d*A salt crystallized. The mother liquor then contained one molecular equivalent of the *l*-acid together with the remainder of the *l*B*d*A salt. This liquor was then combined with one molecular equivalent of the partially resolved base (*d*B + *dl*B). The salts *d*B*l*A, *dl*B*dl*A and *d*B*d*A were again formed. From this point the procedure was the same as in Procedure A, above. The *d*B*l*A salt was obtained in a yield somewhat greater than is possible by Procedure A.

By concentrating the mother liquors from either procedure, first the *dl*B*dl*A and then the *d*B*d*A salt were obtained, the former completely pure.

Hydrolysis of each of the salts *l*B*d*A, *d*B*l*A and *dl*B*dl*A with ammonium hydroxide gave the respective bases and also the ammonium salts of the acids. The salts were subsequently converted to the corresponding acids. The method, therefore, constitutes a *complete resolution of both base and acid.* Inactive or partially resolved fractions may be put through the process again or, since all of the active forms are now available, the method of Marckwald may be applied.

Generality of the Method

Two conditions, both of which, however, can be tested in advance, are essential to the success of either of the procedures outlined above. First, it is obvious that the acid and base must be mutually resolvable. In the second place, the desired active salt must be less soluble than the racemic salt, *dl*B*dl*A. This is evidently true in the case just discussed, in which the salts *d*B*l*A(*l*B*d*A), *dl*B*dl*A and *l*B*l*A(*d*B*d*A) are here arranged in the order of increasing solubility. As it did not seem possible to predict that this order of solubility would hold for all cases, a search was made

[4] Betti and Mayer, *Ber.*, **41**, 2071 (1908).

through the literature for instances in which the solubilities of similarly related salts have been compared. Only four instances were found in which the necessary salts have been prepared, and in only three of these were the solubilities reported. In the bromocamphor-sulfonates of pavine[5] the order is *l*B*d*A < *d*B*d*A < *dl*B*dl*A. In the bromocamphor-sulfonates of hydroxy-hydrindamine[6] the order is *l*B*d*A < *dl*B*dl*A < *d*B*d*A. Of the bromocamphor-sulfonates of narcotine, however, Perkin and Robinson[7] state that the *dl*B*dl*A salt is more sparingly soluble in ethyl acetate than any of the other salts prepared. As these were *l*B*d*A.EtAc[8] and *d*B*d*A, the relative solubility of the non-solvated *l*B*d*A is uncertain. From these cases it seems likely that the method described above should succeed in most cases, although the possibility of unequal solvation of the various salts may require some discretion in the choice of a solvent.

In order to test further the above rule of solubility and to confirm the generality of the method, the resolution of α-phenylethylamine by means of *l*- and *dl*-malic acids (Procedure B) was carried out. No difficulty was experienced in obtaining the *d*B*l*A and *l*B*d*A salts and their component bases. The order of solubility was *l*B*d*A < *dl*B*dl*A < *l*B*l*A. The active malic acids were obtained as their sodium salts, which Dakin[2] has shown can readily be converted to the free acids.

Experimental Part

Materials.—Reychler's *d*- and *dl*-camphor-sulfonic acids and phenyl-amino-acetic acid were prepared by the Organic Manufactures Department of the University of Illinois. The α-phenylethylamine was prepared in 72% yield by the reduction of acetophenone oxime by an electrolytic amalgam method to be described elsewhere.

Partial Resolution of *dl*-Phenyl-amino-acetic Acid.—In one experiment 151 g. (1 mole) of the amino acid and 240 g. (1.03 moles) of *d*-camphor-sulfonic acid were dissolved in 900 cc. of boiling water and the solution was treated with Norit. By fractional crystallization in the usual way, there was obtained a total of 119 g. of pure *l*B*d*A salt. This was dissolved in hot water, hydrolyzed with the calculated quantity of aqueous ammonia, and the pure *l*-base filtered off.

The mother liquor from the original crystallization was likewise treated with aqueous ammonia for the recovery of the partially resolved base.

Rotation. Subs., 2.2314 g. in 20.1 cc. of *N* hydrochloric acid and 9.0 cc. of water at 20°: $\alpha_D = +14.65°$ in a 2-dm. tube. The same concentration of pure *d*-base should give[9] $\alpha_D = +23.35°$.

The proportion of *d*-base in excess was therefore 62.7%.

[5] Pope and Gibson, *J. Chem. Soc.*, **97**, 2207 (1910).

[6] Pope and Read, *ibid.*, **101**, 758 (1912).

[7] Perkin and Robinson, *ibid.*, **99**, 788 (1911).

[8] Ethyl acetate.

[9] Fischer and Weichhold, *Ber.*, **41**, 1286 (1908).

l-**Camphor-sulfonate of** *d*-**Phenyl-amino-acetic Acid.** *Procedure A.*—Sixty-six g. of the partially resolved base was dissolved with 106 g. (1.03 molecular equivalents) of inactive camphor-sulfonic acid in 450 cc. of water and the solution was decolorized and allowed to cool slowly. The liquid was decanted from the crystalline deposit, concentrated to half its volume and again allowed to crystallize. When the decanted liquid was again concentrated to half its volume, the material that separated on cooling was different in crystalline form from the first two crops. The latter were combined and recrystallized with slow cooling from water containing a few grams of the inactive acid to prevent hydrolysis of the salt. The final yield of completely pure *d*B*l*A salt was 51.0 g. (calcd., 53.5 g., based on half the excess of *d*-base in the mixture).

Rotation. Subs., 0.5077 g. made up to 25 cc. in water at 20°: $\alpha_D = +1.79°$ in a 2-dm. tube. Hence, $[\alpha]_D^{20} = +44.1°$.

The salt obtained by slow cooling consists of large triclinic crystals, enantiomorphic with respect to the *l*B*d*A variety. The asymmetry is easily visible to the unaided eye.

d-**Phenyl-amino-acetic Acid.**—The salt described above, when hydrolyzed with ammonium hydroxide in the usual way, gave the pure amino acid.

Rotation. Subs., 1.6160 g. dissolved in 14.60 cc. of *N* HCl and 6.50 cc. of water at 20° $\alpha_D = +22.70°$. For the same concentration Fischer and Weichhold found $\alpha_D = +22.80°$.

Procedure B.—Fifty g. of pure *l*-base obtained in the first step described above was combined with 158 g. (two molecular equivalents) of inactive camphorsulfonic acid in 300 cc. of water. The decolorized solution was concentrated in stages until a total of 109 g. (86%) of the *l*B*d*A salt had separated. The mother liquor was diluted to the original volume and there was added 45 g. of some partially resolved base which, from its rotation, contained 14% excess of the *d*-base. From this point Procedure A was followed and there was finally obtained 31 g. of the pure *d*B*l*A salt. The yield calculated from 86% of the total *d*-base in the mixture would be 34.2 g.

dl-**Camphor-sulfonate of** *dl*-**Phenyl-amino-acetic Acid.**—The mother liquors remaining after either of the above procedures, upon further concentration and cooling, deposited crusts of crystals of indefinite form. A sample after three recrystallizations was completely inactive and identical with other samples prepared by crystallizing equal quantities of either *dl*B and *dl*A, or *l*B*d*A and *d*B*l*A. Crystals obtained by slow cooling were anhydrous twinned hexagonal plates. Ammonia hydrolysis gave the pure *dl*-amino-acid.

The final mother liquors were concentrated on a water-bath to a thick sirup which set to a mass of small crystals that were not obtained pure. The amino acid precipitated by ammonium hydroxide contained a con-

siderable excess of the *l*-form. This was subsequently used in the first step of another run.

The Ammonium Camphor-sulfonates.—The filtrates from the hydrolysis of the *l*B*d*A, *d*B*l*A and *dl*B*dl*A salts with aqueous ammonia were evaporated to dryness, redissolved in a little cold water and filtered to remove small amounts of the slightly soluble amino acids. The solutions were then concentrated and allowed to crystallize. The *l*-form was similar to the *d*-form, which has been previously described.[5] The *dl*-form gave feathery, anhydrous crystals, somewhat more soluble than the active forms.

***l*-Camphor Sulfonic Acid.**[10]—A solution of pure *l*-ammonium-camphor-sulfonate was boiled with an excess of barium hydroxide to expel the ammonia. The barium was quantitatively removed with sulfuric acid and the solution evaporated to a sirup, which solidified. The acid was crystallized from ethyl acetate in hygroscopic needles; m. p., 194° (corr.).

The *d*- and *dl*-acids were recovered only as aqueous solutions.[7]

Partial Resolution of α-Phenylethylamine.—A solution containing 60 g. of *dl*-phenylethylamine and 66.5 g. of *l*-malic acid in 250 cc. of water was treated with bone black, filtered and the solute fractionally crystallized in the usual way.[11] There was obtained 39.4 g. of the pure *d*B*l*A salt; m. p., 184° (corr.). A 4% solution of this salt in water gave too small a rotation (about —0.15°) to be accurately measured. Accordingly, the enhanced value due to a definite amount of ammonium molybdate was determined.

Rotation. Subs., 2.0004 g. and ammonium molybdate (Merck) 0.2000 g. made up to 50 cc. in water at 20°: α_D = —1.52° in a 2-dm. tube: $[\alpha]_D^{20}$ = —18.9°.

A portion of this salt was treated with the calculated amount of dil. sodium hydroxide solution, the liberated base dissolved in ether, dried and distilled; b. p., 185° (uncorr.). The rotation was observed without a solvent.

Rotation. α_D = +37.59°, d = 0.950, l = 1. Hence, $[\alpha]_D^{20}$ = +39.5°. Marckwald and Meth[12] give $[\alpha]_D$ = +39.7°.

The sirupy mother liquors from the original crystallization were treated with sodium hydroxide and the partially resolved base was recovered as described above for the *d*-base; b. p., 186–197° (uncorr.).

Rotation. α_D = —22.5°, which corresponds to a 59.8% excess of *l*-base.

Partial Resolution of Malic Acid.—Seventeen g. of the pure *d*-phenylethylamine described above was dissolved with 37.7 g. (two molecular equivalents) of synthetic malic acid (Eastman) in 150 cc. of water. From this solution there was finally obtained 22.3 g. (62.3%) of practically pure *d*B*l*A salt; m. p., 182–183°. The mother liquor was used in the next step.

***l*-Phenylethylamine-*d*-malate.**—The mother liquor from the material obtained in the preceding step was diluted to 150 cc. and 17 g. of the partially resolved base described above was added. Cooling and stirring gave a finely divided solid which was later found to be chiefly the *l*B*d*A salt. The filtrate, when concentrated to two-thirds its volume, seeded and cooled without agitation, gave a further small crop of crystals. The filtrate when again concentrated to half its volume gave an abundant crop of pow-

[10] Pope and Harvey, *J. Chem. Soc.*, **79**, 74 (1901).

[11] Lovén, *J. prakt. Chem.*, **72** (ii), 307 (1905).

[12] Marckwald and Meth, *Ber.*, **38**, 801 (1905).

dery crystals, later found to be chiefly the *dl*B*dl*A salt. The first two crops after two recrystallizations obtained by slowly cooling the liquid gave 10.7 g. of completely pure *l*B*d*A salt; m. p., 184° (corr.).

Rotation. Subs., 2.0017 g. and ammonium molybdate 0.2000 g., made up to 50 cc. in water at 20°: $\alpha_D = +1.50°$ in a 2-dm. tube; $[\alpha]_D^{20} = +18.5°$.

***l*-Phenylethylamine.**—The base was obtained from the *l*B*d*A salt in the usual way but was not distilled. The rotation was observed in aqueous solution.

Rotation. Subs., 1.5505 g. made up to 50 cc. in water and a few drops of alcohol: $\alpha_D = -1.43°$ in a 2-dm. tube: $[\alpha]_D = -23.1°$. Kipping and Hunter[13] found $[\alpha]_D = -25°$.

***dl*-Phenylethylamine-*dl*-malate.**—From the mother liquors of the *l*B*d*A salt, the *dl*B*dl*A salt was obtained. After two recrystallizations it still gave a slight dextro-rotation. On slow cooling it formed coarse prisms; m. p., 161–161.5° (corr.). The salt prepared from the *dl*-base and *dl*-acid was similar in appearance and melted at 162° (corr.). The sirupy mother liquor was not further examined.

The solutions remaining from the hydrolysis of the *d*B*l*A and *l*B*d*A salts with sodium hydroxide were evaporated to dryness on the water-bath for the recovery of the active sodium malates. The isolation of the free acids was not attempted.

Summary

1. A new general method for obtaining both pure active forms of an optically inactive base is described. Only one active form and the inactive form of the acid used for the resolution are required. The other active form of the acid is also obtained in the process.

2. The method has been used for the complete resolution of phenylamino-acetic acid and camphor-sulfonic acid, and α-phenylethylamine and malic acid, respectively. Several new salts are described.

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FURTHER SYNTHESES WITH β,β′-DICHLORO-DIETHYL ETHER

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In a recent paper from this Laboratory[1] it was shown that the chlorine in β,β′-dichloro-diethyl ether can be removed by reaction with sodium alcoholates, aromatic primary amines and the sodium salts of organic acids, with the formation of the expected ethers, substituted morpholines and esters. This work has been continued to include a study of the action of the sodium salts of phenol, thiophenol and naphthols, potassium phthalimide and sodium hydroxide. Further experiments leading to an improvement in the previously described method for preparing substituted morpholines have also been made.

[13] Kipping and Hunter, *J. Chem. Soc.*, **83**, 1147 (1903).

[1] Cretcher and Pittenger, THIS JOURNAL, **47**, 163 (1925).