[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

A SECOND NEW METHOD FOR THE COMPLETE RESOLUTION OF EXTERNALLY COMPENSATED ACIDS AND BASES

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In a previous paper[1] the author has described a new method for the resolution of externally compensated acids and bases by which both active forms are obtained completely pure.[2] In its simplest form the method requires two main steps. First, for example, an inactive base (*dl*-B) is combined with an active acid, for example, *d*-A, and the resulting salts *d*-B-*d*-A and *l*-B-*d*-A are fractionally crystallized until the less soluble one, for example, *l*-B-*d*-A, is pure. From this salt pure *l*-B is obtained by hydrolysis. From the mother liquors there will be obtained on hydrolysis a mixture of the two active bases with *d*-B in excess. For convenience this mixture may be regarded as *dl*-B + *d*-B.

In the second step this mixture is dissolved with an equivalent amount of the inactive form of the acid originally used (*dl*-A), or with any suitable externally compensated acid. Upon crystallization the ions now in solution may combine in one of two ways, depending on whether the inactive acid is resolved by the active base present in excess (Equation 1) or forms a half racemic salt with it (Equation 2).

$$(dl\text{-B} + d\text{-B}) + dl\text{-A} \longrightarrow dl\text{-B-}dl\text{-A} + d\text{-B-}d\text{-A} + d\text{-B-}l\text{-A} \quad (1)$$

$$(dl\text{-B} + d\text{-B}) + dl\text{-A} \longrightarrow dl\text{-B-}dl\text{-A} + d\text{-B-}dl\text{-A} \quad (2)$$

When the situation is represented by Equation 1 and when the *d*-B-*l*-A salt is the least soluble, the latter can be obtained pure by fractional crystallization. From the pure *l*-B-*d*-A and *d*-B-*l*-A salts thus obtained in the two steps, both active forms of the base, and of the acid as well, may be obtained by hydrolysis. Two cases in which a complete resolution was effected in this way were described in the previous paper.

It is apparent, furthermore, that a complete resolution of the base (though not of the acid) is also possible when Equation 2 represents the second step of the process. Thus whenever the half racemic salt *d*-B-*dl*-A is less soluble than the inactive salt, the former, and its component base, can be obtained pure. The present paper contains a description of a complete resolution based upon this behavior. Thus inactive *iso*-diphenylhydroxy-ethylamine was partially resolved in the usual way with *d*-camphor-10-sulfonic acid,[3] the less soluble *d*-B-*d*-A salt being obtained

[1] Ingersoll, THIS JOURNAL, **47**, 1168 (1925).

[2] Some interesting modifications of the older methods have recently been described by Read and Reid, *J. Soc. Chem. Ind.*, **47**, 8T (1928).

[3] The resolution of *iso*-diphenylhydroxy-ethylamine was first carried out by Erlenmeyer, *Ber.*, **32**, 2377 (1899); **36**, 978 (1903); *Ann.*, **337**, 307 (1904), using helicin or tartaric acid. The resolution with tartaric acid has recently been improved by Read

pure in the first step. The base recovered from the mother liquors (*dl*-B + *l*-B) was combined with inactive camphorsulfonic acid and the salts fractionally crystallized. The half racemic salt *l*-B-*dl*-A was the first to separate and was readily purified. Alkaline hydrolysis of the pure *d*-B-*d*-A and *l*-B-*dl*-A salts thus obtained gave the pure isomeric bases in excellent yields. The pure *l*-B-*d*-A and *dl*-B-*dl*-A salts were also synthesized for comparison. All the salts of this series have one molecule of water of crystallization. The solubilities in water at 25° were in the order *d*-B-*d*-A < *l*-B-*dl*-A < *l*-B-*d*-A < *dl*-B-*dl*-A.

Generality of the Combined Methods

So far as the second step is concerned, both of the methods (depending on Equation 1 and Equation 2, respectively) appear to be new in principle and of rather general utility. Since the same reagents and procedure are used in both methods, these are mutually complementary and afford a double chance for successfully completing a resolution. They may be applied equally well to the resolution of an acid or a base. They should hold also for ester, amide, hydrazone, imine and similar combinations as well as for salts.

It is clear, however, that each method depends for its success on a favorable order of solubility of the isomeric compounds involved. This point has been discussed in the previous paper, for resolutions depending on Equation 1. While there seems to be no rule known at present from which it can be predicted that the order of solubility will always be favorable, it is remarkable that of the three cases thus far studied all have resulted in complete resolutions. A fourth case now being studied, that of the acid tartrates of *iso*-diphenylhydroxy-ethylamine, has also given preliminary results indicating a similar behavior. The uniformity of these results points to the probable existence of an underlying rule and the study is being continued in the hope of disclosing such a rule.

Experimental Part

Partial Resolution of the Base.—In one experiment a solution containing 42.6 g. of inactive *iso*-diphenylhydroxy-ethylamine, m. p. 130°, and 48.0 g. of *d*-camphor-10-sulfonic acid in 1 liter of water was decolorized and the solute fractionally crystallized. While the first crop of crystals showed a strongly positive rotation the following crops showed an alternation of low and high rotations. The further separation of these was therefore best carried out by combining similar fractions in fresh solvent and seeding with samples of the extreme fractions. Working in this way there was obtained 35.2 g. of the pure *d*-B-*d*-A salt in the less soluble

and Steele, *J. Chem. Soc.*, **131**, 910 (1927), who mentioned also the use of camphorsulfonic acid but gave no details.

fraction. In later experiments it was found that the separation could also be effected readily by using moist ethyl acetate (3% water) as solvent.

d-iso-**Diphenylhydroxy-ethylamine** *d*-**Camphorsulfonate** forms masses of small prisms from water or distinct crystals from moist ethyl acetate, both being hydrated. It is soluble in about 59 parts of water at 25°. The anhydrous salt melts indistinctly at 207–208° (corr.) but the melting points of this series of salts are not good indications of purity.

Anal. Subs., 1.8429: lost 0.0704 g. at 105°. Calcd. for $C_{24}H_{31}O_5NS \cdot H_2O$: H_2O, 3.88. Found: H_2O, 3.82.

Rotation (Hydrated salt). Subs., 0.8005: made up to 50 cc. in water gave $\alpha_D^{22} = +1.88°$ in a 2-dm. tube. Hence $[\alpha]_D^{22} = +58.7°$. (Anhydrous salt). Subs., 0.9442: made up to 50 cc. in water gave $\alpha_D^{22} = +2.31°$ in a 2-dm. tube. Hence $[\alpha]_D^{22} = +61.2°$; $[M]_D = +272°$. Assuming +52° as the molecular rotation of the *d*-camphorsulfonate ion, $[M]_D$ for the base ion is +220°.

d-iso-**Diphenylhydroxy-ethylamine.**—A warm solution of the *d*-B-*d*-A salt was treated with excess ammonium hydroxide. The precipitated base after one crystallization from alcohol melted at 115.2° (corr.) and had $[\alpha]_D^{22} = +125.1°$ in absolute alcohol, values that confirm those of Read and Steele.[3]

l-iso-**Diphenylhydroxy-ethylamine** *d*-**Camphorsulfonate.**—The more soluble fractions obtained in the resolution were combined and recrystallized several times from water. The extreme specific rotation observed was −33.5°. In a later experiment the pure *l*-B-*d*-A salt was obtained by combining the pure *l*-base (obtained as described in the next section) with *d*-camphorsulfonic acid. As its specific rotation was −36.1° the salt obtained in the resolution was still somewhat impure. The pure salt crystallizes from water in long, tetragonal prisms. It is soluble in about 32 parts of water at 25° and is hydrated. It is much more soluble in ethyl acetate than the *d*-B-*d*-A salt. The anhydrous salt melts at 205–206° (corr.).

Anal. Subs., 1.1226: lost 0.0434 g. at 105°. Calcd. for $C_{24}H_{31}O_5NS \cdot H_2O$: H_2O, 3.88. Found: H_2O, 3.87.

Rotation. (Hydrated salt). Subs., 0.8113: made up to 50 cc. in water gave $\alpha_D^{22} = -1.17°$ in a 2-dm. tube. Hence $[\alpha]_D^{22} = -36.1°$. (Anhydrous salt). Subs., 1.0792: made up to 50 cc. in water gave $\alpha_D^{22} = -1.62°$ in a 2-dm. tube. Hence $[\alpha]_D^{22} = -37.5°$: $[M]_D = -167°$; $[M]_D$ for the base ion −219°.

Completion of the Resolution

A sample of the base (16.0 g.) recovered from the intermediate fractions of the original resolution ($[\alpha]_D = -58°$; 46% excess *l*-base) was combined with inactive camphorsulfonic acid (18.0 g.) in sufficient water (450 cc.) so that about half of the total salt separated on cooling. The first crop (15.3 g.) had $[\alpha]_D = -43°$. By systematic crystallization there was finally obtained 12.7 g. of pure, hydrated *l*-B-*dl*-A salt in the less soluble fraction. In a further experiment 12.3 g. of base having $[\alpha]_D = -108°$ (87% excess *l*-base) was combined with 14.0 g. of inactive camphorsulfonic acid. There was easily obtained 20.3 g. of pure *l*-B-*dl*-A salt.

l-iso-**Diphenylhydroxy-ethylamine** *dl*-**Camphorsulfonate** crystallizes from water in small prisms or feathery clusters. It is soluble in about 42 parts of water at 25° and is hydrated. The anhydrous salt melts at 206–207° (corr.).

Anal. Subs., 3.3332: lost 0.1306 g. at 105°. Calcd. for $C_{24}H_{31}O_5NS \cdot H_2O$: H_2O, 3.88. Found: H_2O, 3.92.

Rotation (Hydrated salt). Subs., 0.8397: made up to 50 cc. in water gave $\alpha_D^{22} = -1.62°$ in a 2-dm. tube. Hence $[\alpha]_D^{22} = -48.4°$. (Anhydrous salt). Subs., 0.8443:

made up to 50 cc. in water gave $\alpha_D^{22} = -1.72°$ in a 2-dm. tube. Hence $[\alpha]_D^{22} = -50.3°$; $[M]_D = -223°$.

l-iso-**Diphenylhydroxy-ethylamine** was obtained from the pure *l*-B-*dl*-A salt and purified as described for the *d*-base. It melted at 115.2° (corr.) and had $[\alpha]_D^{22} = -125.6°$ in absolute alcohol; values in agreement with those of the *d*-base.

d-iso-**Diphenylhydroxy-ethylamine** *dl*-**Camphorsulfonate.**—For comparison this salt was made from the pure components. It is similar in all respects to the enantiomorphous *l*-B-*dl*-A salt.

Rotation (Hydrated salt). Subs., 1.0242: made up to 50 cc. in water gave $\alpha_D^{22} = +1.98°$ in a 2-dm. tube. Hence $[\alpha]_D^{22} = +48.2°$.

dl-iso-**Diphenylhydroxy-ethylamine** *dl*-**Camphorsulfonate.**—From the mother liquors from the separation of the *l*-B-*dl*-A salt there was obtained a much more soluble salt in masses of poorly formed prisms. It still showed a faint negative rotation. For comparison the pure salt was made from the pure components. It is soluble in about 26 parts of water at 25° and is hydrated. The anhydrous salt melts at 198–199° (corr.).

Anal. Subs., 3.6527: lost 0.1392 g. at 105°. Calcd. for $C_{24}H_{31}O_5NS \cdot H_2O$: H_2O, 3.88. Found: H_2O, 3.81.

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Summary

A second new method for the complete resolution of externally compensated compounds has been described in connection with a related method previously described. The method was applied to the resolution of inactive *iso*-diphenylhydroxy-ethylamine with *d*- and *dl*-camphorsulfonic acids.

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THE MECHANISM OF CARBOHYDRATE OXIDATION. IX. THE ACTION OF COPPER ACETATE SOLUTIONS ON GLUCOSE, FRUCTOSE AND GALACTOSE[1]

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The mechanisms proposed in some of the more recent literature dealing with the oxidation of carbohydrates in alkaline solutions rest on one or more of the following ideas: (*a*) that carbohydrates in alkaline solutions are converted into equilibrated systems consisting of a number of isomeric carbohydrates;[3] (*b*) that these carbohydrates give rise to a series of three

[1] Presented to the Second National Symposium on Organic Chemistry, Columbus, Ohio, December 29, 1927. References have been made in this communication to papers which have appeared subsequently.

[2] E. I. DuPont de Nemours Fellow, 1927.

[3] (a) De Bruyn and van Ekenstein, *Rec. trav. chim.*, **14**, 156, 203 (1895); (b) **15**, 92 (1896); (c) **16**, 257, 262, 274 (1897); (d) **19**, 1 (1900); (e) **27**, 1 (1908); (f) Wolfrom with Lewis, THIS JOURNAL, **50**, 842 (1928).