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SOLUBILITY RELATIONSHIPS AMONG OPTICALLY ISOMERIC SALTS. II. THE CAMPHORATES OF ALPHA-PARA-TOLYLETHYLAMINE

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An analysis of the equilibria and solubility relationships among the isomeric salts of optically active and racemic bases and acids has been presented in Part I.[1] A maximum of five types of salts (including stable double salts) may be formed when the isomeric base and acid ions are combined in all possible ways. These are (*d*B*d*A or *l*B*l*A); (*d*B*l*A or *l*B*d*A); *dl*B*dl*A; (*d*B*dl*A or *l*B*dl*A); (*dl*B*d*A or *dl*B*l*A). One or both of the partially racemic types may be unstable; also it can be shown that not more than three of the nine varieties of salts can coexist in a solution, no matter what proportions of active base and acid ions are originally introduced. Thus in Part I it was shown that when a partially active base (or acid) is combined in solution with a racemic acid (or base), the resulting mixture must constitute one of eight possible *cases* (Nos. 1–8)[2] characterized by differences in the stability and order of solubility of the salts. When both the base and the acid are partially active, twelve additional cases (9–20)[2] are possible. These cases have been discussed as to their bearing on the problem of separating the active and inactive components of partially active substances, with particular reference to the problem of complete optical resolution.[3]

As yet only a few of these cases have been illustrated by actual instances. Many more groups of salts must be examined before it can be learned whether, and how frequently, each case will be encountered. Also little is known of the relative solubilities of isomeric salts when four, or even five, of the types are stable and can be compared. Hence, in continuation of the work, various groups of isomeric salts are being prepared from such asymmetric bases and acids as can be obtained in at least one active form and the inactive form. For the purposes in mind the group studied must consist of at least one variety of all of the stable types, that is, the first three types shown above and one or both of the other types when these are stable. Whenever possible the salts are completely purified, so that their common physical properties as well as their solubilities can be compared. It is expected that when the properties of a considerable number of such groups of salts are known, many interesting regularities will appear.

[1] Ingersoll and White, THIS JOURNAL, **54**, 274 (1932).

[2] The cases were described in Part I. To avoid repetition in future papers they were assigned permanent reference numbers.

[3] Ingersoll, THIS JOURNAL, (a) **47**, 1168 (1925); (b) **50**, 2264 (1928).

In the previous papers there were described two instances of Case 4,[3a] one of Case 8 (or 12),[1] and one of Case 7 (or 9).[3b] The double salts present in Cases 7 and 8, namely, *dl*B*dl*A and either (*d*B*dl*A or *l*B*dl*A) or (*dl*B*d*A or *dl*B*l*A), may be accompanied in solutions by one of the varieties of simple salts (*d*B*d*A or *l*B*l*A) or (*d*B*l*A or *l*B*d*A). Thus these cases always overlap one of the cases 9–20. Also four of the five types of salts can then be prepared. In the instance of Case 7 just referred to the order of solubility was

(*d*B*d*A or *l*B*l*A) < (*d*B*dl*A or *l*B*dl*A) < (*d*B*l*A or *l*B*d*A) < *dl*B*dl*A (a)

In the present paper there is described another instance of Case 7 but this overlaps Case 10 and the order of solubility of the four stable salts is

(*d*B*l*A or *l*B*d*A) < (*d*B*dl*A or *l*B*dl*A) < *dl*B*dl*A < (*d*B*d*A or *l*B*l*A) (b)

The instance in question is the group of salts formed from the active and inactive forms of camphoric acid and α-*p*-tolylethylamine. The resolution of this base was briefly described by Stenberg,[4] who obtained the *d*-base as *l*-malate and the *l*-base from the residue as *d*-camphorate. The salts were not described. Although Stenberg's work was confirmed, it was found that both active forms of the base could be obtained much more easily by the use of *d*-camphoric acid alone. Thus an aqueous alcoholic solution of equivalent amounts of *d*-acid and *dl*-base could be made to deposit both the *l*B*d*A and *d*B*d*A hydrogen camphorates in greatly unequal proportions; both salts were purified with high yields. This is one of the uncommon instances in which complete resolution can be effected by the use of a single agent. In order, however, to classify the instance and test the method of complete resolution, partially active base (*l*B + *dl*B) was combined with *dl*-camphoric acid and the salts crystallized. With some difficulty there was finally obtained a less soluble fraction of pure *l*B*dl*A salt and a residue of impure *dl*B*dl*A salt. The latter was also prepared pure from its pure components. The four salts were found to have the solubility order shown in (b) above. This order differs from any previously observed.

Experimental

Resolution of *dl*-α-*p*-Tolylethylamine.—The base, b. p. 204–205°, was prepared by the reduction of *p*-methylacetophenone oxime with sodium amalgam or, better, with sodium and absolute alcohol.[5] Its resolution with *l*-malic acid by Stenberg's method was confirmed, but seven recrystallizations of the head fraction were necessary to obtain the pure *d*-base and the yield was small. *d*-Camphoric acid was then used. In a typical experiment 40 g. of the acid was dissolved in 200 cc. of 95% ethanol and 27.5 g. of the base added. Water (400 cc.) was added and the mixture boiled until clear. On cooling, the first crop was 21.8 g. of coarse octahedra (*l*B*d*A, acid salt). After evaporation to 400 cc., the cooled solution deposited a mass of slender prisms (chiefly *d*B*d*A

[4] Stenberg, *Z. physik. Chem.*, **70**, 534 (1910).

[5] "Organic Syntheses," John Wiley and Sons, Inc., New York, 1931, Vol. XI, p. 58.

salt) mixed with more of the tetrahedra. Further crops containing more of the prisms and some oily material were obtained by concentrating the mother liquor in stages. The main fractions were then separately recrystallized from about 15 parts of water with decolorizing carbon and the mother liquors used to recrystallize the smaller fractions. By combining similar fractions and inoculating the solutions with whichever salt was present in excess, a nearly quantitative separation of the pure salts was made. The combined yield from four similar runs was 136 g. of the *l*B*d*A salt (monohydrate), 118 g. of the *d*D*d*A salt, and 17 g. of partially oily intermediate fractions.

***l*-α-*p*-Tolylethylamine *d*-camphorate** crystallizes as the monohydrate from water or dilute ethanol in well-developed or truncated octahedra. A water solution (19.637 g.) saturated at 25° contained 0.1948 g. of anhydrous salt; hence the solubility is 1.00 g. of anhydrous salt or 1.05 g. of hydrated salt per 100 g. of water. The anhydrous salt melts at 173° (corr.).

Anal. Hydrated salt: 1.1835 g. lost 0.0635 g. at 95°. Calcd. for $C_{19}H_{29}O_4N \cdot H_2O$: H_2O, 5.10. Found: H_2O, 5.27.

Rotation. Anhydrous salt: 1.6435 g. made up to 25 cc. in 95% ethanol gave α_D^{25} +1.15° in 2 dm.; $[\alpha]_D^{25}$ +8.75°; M_D +29.3°(10²).

***d*-α-*p*-Tolylethylamine *d*-camphorate** forms anhydrous, slender prisms, m. p. 187° (corr.). The solubility in water at 25° is 2.49 g. per 100 g. water.

Rotation. Subs., 1.7240 g. made up to 25 cc. in 95% ethanol gave α_D^{25} +3.19 in 2 dm.; $[\alpha]_D^{25}$ +23.1°; M_D +77.5(10²).

***l*-α-*p*-Tolylethylamine.**—Pure *l*B*d*A salt was treated with excess dilute sodium hydroxide and the base distilled with steam, extracted with benzene, and distilled; b. p. 205°; d_4^{25} 0.9190.

Rotation. Without solvent α_D^{25} −31.5°, $[\alpha]_D^{25}$ +34.3°.

***d*-α-*p*-Tolylethylamine.**—This base was obtained from the pure *d*B*d*A salt as described for the *l*-base; b. p. 205°; d_4^{25} 0.9185; α_D^{25} +31.8°; $[\alpha]_D^{25}$ +34.6°. The rotation values for both forms are slightly smaller than Stenberg's values, −36.4° and +36.9° at 20°. Samples of the salts described above were therefore recrystallized, but their properties and the rotations of the active bases were not appreciably changed.

***l*-α-*p*-Tolylethylamine *dl*-camphorate** was first prepared by combining 20 g. of *dl*-camphoric acid with 13.5 g. of mixed bases having $[\alpha]_D^{25}$ −28.5° (about 82% excess *l*-base) and crystallizing the salts from water. These separated first as a mass of small needles and irregular particles. By prolonged fractionation there were obtained 18.2 g. of large, square tablets (*l*B*dl*A salt, monohydrate) and smaller fractions resembling the first deposit. The salt was identical with that prepared from pure *l*-base and *dl*-acid. After drying at 95° it melted at 169° (corr.). The solubility, calculated for the hydrated salt, was 1.53 g. per 100 g. of water at 25°.

Anal. Calcd. for monohydrate: H_2O, 5.10. Found: H_2O, 5.36.

Rotation. Anhydrous salt, 1.8190 g. made up to 25 cc. in 95% ethanol gave α_D^{25} −0.45 in 1 dm.; $[\alpha]_D^{25}$ −6.18°; M_D −20.7°(10²).

After many crystallizations of the smaller fractions mentioned above the extreme fraction still showed a faint levo rotation. Since it was similar to the salt prepared from pure *dl*-base, and *dl*-acid, it was probably the slightly impure *dl*B*dl*A salt.

***dl*-α-*p*-Tolylethylamine *dl*-camphorate** forms spherules of microscopic needles from water and is anhydrous, m. p. 180° (corr.). The solubility is 1.66 g. per 100 g. of water at 25°.

Summary

1. The complete resolution of *dl*-α-*p*-tolylethylamine with *d*-camphoric acid is described.

2. Four stable, isomeric α-*p*-tolylethylamine camphorates have been prepared and found to illustrate Case 7 (or 10) and the solubility order *l*B*d*A < *l*B*dl*A < *dl*B*dl*A < *d*B*d*A.

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REDUCTIONS IN THE MORPHINE SERIES. I. DIHYDROPSEUDOCODEINE[1,2]

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In respect to their behavior on catalytic hydrogenation, the alkaloids of the morphine series may be divided sharply into two classes. The one class includes all of those derivatives having an ethylenic double linkage in the 7,8-position of the hydroaromatic ring. Hydrogenation of such compounds in the presence of platinum or palladium under the ordinary conditions of temperature and pressure results in addition of one molecule of hydrogen at the hydroaromatic unsaturation, without disturbance of the 4,5-ether bridge.[3] This type of reduction, which we designate as normal (*i. e.*, in the sense, expected), is met in the cases of morphine,[4] codeine (I),[4a] isocodeine,[5] codeinone,[6] hydroxycodeinone[7] and α-[8] and γ-methylmorphimethines.[9,10]

The other class of morphine derivatives, in which the hydroaromatic unsaturation lies between carbon atoms 6 and 7, has heretofore been re-

[1] This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc.

[2] Presented in part at the New Orleans meeting of the American Chemical Society, March 30, 1932.

[3] The halogeno derivatives of morphine and codeine are exceptional in this respect, and the mechanism of their reduction is uncertain. Under some conditions, however, they also yield hydrogenation products in which the ether bridge is intact. See Mosettig, Cohen and Small, THIS JOURNAL, **54**, 793 (1932).

[4] (a) Oldenberg, *Ber.*, **44**, 1829 (1911); (b) German Patent 260,233 (1913); (c) Skita and Franck, *Ber.*, **44**, 2862 (1911).

[5] Speyer and Wieters, *ibid.*, **54**, 2647 (1921).

[6] Mannich and Löwenheim, *Arch. Pharm.*, **258**, 295 (1920).

[7] Freund and Speyer, *J. prakt. Chem.*, **94**, 135 (1916); Freund and Speyer, German Patent 296,916 (1916); *Friedländer*, **13**, 880; U. S. Patent 1,468,805 (Sept. 25, 1923); Freund, U. S. Patent 1,485,673 (March 4, 1924).

[8] Von Braun and Cahn, *Ann.*, **451**, 55 (1927).

[9] Speyer and Koulen, *ibid.*, **438**, 34 (1924).

[10] The dimolecular oxidation product of morphine, pseudomorphine, also reduces normally (unpublished results, L. F. Small and F. L. Cohen) and this fact may be taken as evidence that the unsaturation in the two morphine nuclei still occupies the original 7,8-position.