[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

Solubility Relationships among Optically Isomeric Salts. IV. Salts of 6,6′-Dinitrodiphenic Acid, a New Type of Resolving Agent

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The work described in this paper was undertaken principally to test the possible usefulness of optically active acids of the ortho substituted diaryl type as agents for the resolution of racemic bases. The work also continues the earlier studies on optically isomeric salts.[1] In particular, there is described the preparation of *d*- and *l*-6,6′-dinitrodiphenic acids by an improved method, and their application to the resolution of *dl*-α-phenylethylamine. It appears that acids of this type have not previously been suggested as resolving agents; their selection for study was based on the following considerations.

It is well known that optically active acids suitable as resolving agents are practically limited to *d*-tartaric, *d*-camphor-10-sulfonic and *d*-α-bromocamphor-π-sulfonic acids. Occasional use has also been made of *l*-malic, *d*-camphoric, *l*-quinic, *l*-mandelic, *d*-α-bromocamphor-10-sulfonic and a few other acids. However, these acids do not afford a sufficient variety of properties to deal with the variety of bases whose resolution may be desired, and all of the acids named are defective in some respects. Thus a satisfactory resolving agent should be reasonably easy to prepare and recover, it should form stable, easily crystallized salts having convenient solubilities in the common solvents, and it should preferably be available in both active forms. Few of the acids named can qualify in all of these respects.

A serious disadvantage, to which all resolving agents are subject, is that the optically active agent often unites with the racemic substance to form a stable, partially racemic double salt rather than two separable diastereoisomeric salts. This difficulty may sometimes be overcome by recourse to other solvents or to other resolving agents. Nevertheless, a considerable number of racemic bases examined in this Laboratory were not resolved for this reason, even when as many as seven of the acids named above were tried in all suitable solvents. In other instances the resolution was unsatisfactory because of insufficient differences in solubility or lack of crystallizing power of the two salts.

(1) For Part III, see Ingersoll, Babcock and Burns, THIS JOURNAL, **55**, 411 (1933).

It has been noted that in nearly every instance in which the resolution of an acid derived from the ortho substituted diphenyls is theoretically probable because of large interferences of the ortho substituents,[2] such resolution has actually been accomplished. Moreover, in many instances the separation of the diastereoisomeric salts was remarkably easy because of a large difference in their solubilities. These observations suggest that were an active diphenyl acid combined with a racemic base, the resulting diastereoisomeric salts might have less than usual tendency to form a stable double salt and more than usual difference in solubility. While it has been found that solubility and stability relationships among optically isomeric salts cannot be predicted with much assurance, yet the possibilities referred to above seemed to warrant an experimental trial.

Resolution of dl-6,6′-Dinitrodiphenic Acid.—It appeared that the preparation[3] of the *dl*-acid and the classical resolution with brucine by Christie and Kenner[4] were unsuitable for the large quantities needed. A satisfactory method of preparation was developed and it was found that by using *d*-α-phenylethylamine, with acetone as solvent, the acid was resolved with remarkable ease. The less soluble *d*B*d*A salt separated nearly quantitatively and was pure after washing; the pure *d*B*l*A salt was obtained in smaller yield from the filtrate. The active acids were readily obtained by treating the salts with hydrochloric acid. Various modifications, which yielded both forms of the acid in large quantities, are also described in the experimental part. It is of interest to note that resolution did not occur with the closely related *d*-α-*p*-tolylethylamine.

Resolution of *dl*-α-Phenylethylamine.—When equimolecular amounts of the *dl*-amine and *d*-6,6′-dinitrodiphenic acid were combined in aqueous or alcoholic solutions, only the stable *dl*B*d*A salt was obtained. However, when the reagents were combined in acetone nearly the calculated amount of somewhat impure *d*B*d*A salt crystallized. The salt was purified by repeated digestion with boil-

(2) Yuan and Adams, *Chem. Rev.*, **12**, 262 (1933).
(3) Kenner and Stubbings, *J. Chem. Soc.*, **119**, 593 (1921).
(4) Christie and Kenner, *ibid.*, **121**, 614 (1922).

ing acetone. The practically pure *d*-amine, $[\alpha]_D$ +38.3°, was obtained from the salt by decomposition with hydrochloric acid and recovery in the usual way; the pure active acid was also recovered. Active acid which had been used and recovered repeatedly showed no racemization. Impure *l*-amine of $[\alpha]_D$ −32.6° was recovered from the acetone mother liquors.

Solubility Relationships.—In an experiment in which the impure *l*-amine was combined with the *dl*-acid, it was found that the salt solubilities in acetone fall in Case 3,[5] (*d*B*d*A or *l*B*l*A) < *dl*B*dl*A < (*d*B*l*A or *l*B*d*A), which permits the purification of the active forms of both the base and the acid from mixtures containing one or both of these in partially resolved form. An instance of Case 3 has not previously been observed. On the other hand, if the same substances were combined in 95% ethanol, the system would illustrate the hitherto unobserved Case 5. With *dl*-amine and partially active acid, Case 8 would result. Incidentally, this instance afforded an opportunity to prepare, for the first time, a representative of each of the five possible types of isomeric salts, since both of the partially racemic types are stable in ethanol. The solubilities at 25° in this solvent are *dl*B*dl*A (1.78) < *d*B*dl*A (2.12) < *d*B*d*A (3.95) < *d*B*l*A (4.74) < *dl*B*d*A (5.63).

Attempted Resolution of Other Bases.—Preliminary experiments on the resolution of *dl*-fenchylamine with *d*-6,6′-dinitrodiphenic acid in acetone gave salts that were too soluble for satisfactory fractionation. The amine recovered from the more soluble fraction, however, was dextrorotatory. With *dl*-α-*p*-tolylethylamine the *d*-acid forms a stable, partially racemic double salt in acetone. With *dl*-α-*p*-methoxyphenylethylamine the *d*-acid forms salts too soluble to be crystallized from acetone. Although the active dinitrodiphenic acids thus appear not to be free in all cases from the tendency to form stable, partially racemic double salts, the remarkably easy resolution of *dl*-α-phenylethylamine and other favorable factors are distinctly encouraging. The work is being continued with a variety of bases and solvents.

Experimental Part

Methyl 2-Bromo-3-nitrobenzoate.—The acid was prepared by the method of Culhane.[6] Its conversion to the methyl ester by the method of Stoughton and Adams[7] was modified slightly. A solution of 180 g. of the acid in 1.5 liters of methanol was saturated with hydrogen chloride and refluxed for eight hours. Upon cooling and seeding about 55% of the expected ester crystallized. After filtering and washing with a little ice-cold methanol this was pure, m. p. 81°. Another 180 g. of the acid and 250 cc. of methanol were added to the filtrate and the process was repeated. After a third 180-g. portion of the acid had been treated in this way the remainder of the ester was recovered from the final filtrate as described by Stoughton and Adams. The yield was 94%.

***dl*-Methyl 6,6′-Dinitrodiphenate.**—The ester described above (104 g.) was melted in a 250-cc. Erlenmeyer flask clamped in a clear oil-bath held at 165–175°. Copper powder (50 g.) was added in 3-g. portions at two-minute intervals with constant hand stirring. In one experiment in which the copper was added rapidly the entire run was destroyed by a violent exothermic reaction. The addition of the copper required about forty-five minutes; the mixture was then maintained at 170–175° and stirred for thirty minutes longer. When cold, the reaction mass was broken up and extracted by digestion with benzene or in a Soxhlet extractor. The solution was treated with decolorizing carbon and the ester crystallized from benzene, or preferably 95% ethanol; m. p. 129° (uncorr.), yield 83%.

***dl*-6,6′-Dinitrodiphenic Acid.**—The ester (36 g.) was refluxed for three hours with 16 g. of sodium hydroxide in 400 cc. of 50% ethanol, most of the alcohol was distilled and the acid was precipitated with excess hydrochloric acid. Recrystallization from glacial acetic acid gave a product melting at 259° (uncorr.); yield 92%. Hydrolysis with more concentrated alcoholic alkali produced considerable decomposition. A portion of the *dl*-acid used was kindly supplied by Professor Roger Adams.

Resolution of *dl*-6,6′-Dinitrodiphenic Acid.—The acid (8.25 g., 0.025 mole) and *d*-α-phenylethylamine (6.1 g., 0.05 mole) were combined in 150 cc. of water. On concentrating and cooling, what appeared to be the normal salt separated as an oil and could not be fractionated. Hence a further 8.25 g. of the acid was added. The resulting acid salt was dissolved in 300 cc. of hot water and 19 g. separated on cooling. Repeated recrystallization from water showed no evidence of resolution and the salt became partially hydrolyzed. The salt was readily crystallized from methanol or ethanol, but without resolution.

***d*-α-Phenylethylamine - *dl*-6,6′ - dinitrodiphenate** forms massive, pale yellow crystals from ethanol, m. p. 199° (corr.), $[\alpha]_D^{25}$ about +1.0° (methanol). The solubility (expressed throughout this paper as grams per 100 g. of solvent) at 25° is 0.90 in water, 2.12 in 95% ethanol and 8.17 in absolute methanol.

The resolution of this salt was accomplished with acetone. The pure salt (52.8 g.) was digested seven times with 150-cc. portions of boiling acetone and the cold extracts decanted. At this point 25.0 g. (47.3%) of a microcrystalline salt remained. The specific rotation of the air-dried material was +139 to +141° in methanol. The salt contains one molecule of acetone of crystallization which it loses slowly on standing, rapidly at 80°, or upon crystallization from ethanol. The rotation is then about +157°. Salt thus dried regains the acetone (rotation about +140°) on digestion or long contact with the solvent.

(5) Ingersoll and White, THIS JOURNAL, **54**, 274 (1932).
(6) Culhane, "Organic Syntheses," 1932, Coll. Vol. I, p. 120.
(7) Stoughton and Adams, THIS JOURNAL, **54**, 4426 (1932).

Anal. Subs. 0.7818 g. lost 0.0880 g. at 80°. Calcd. for $C_{14}H_8O_8N_2 \cdot C_8H_{11}N \cdot C_3H_6O$: acetone, 11.35%. Found: 11.25%.

***d*-α-Phenylethylamine-*d*-6,6′-dinitrodiphenate** crystallizes from ethanol in pale yellow hexagons, m. p. 217–219° (corr.). The solubility at 25° is 0.79 in water, 3.95 in 95% ethanol and 0.61 in acetone.

Rotation. Subs., 0.7590 g. made up to 25 cc. in absolute methanol at 20° gave α_D^{28} +9.54° in a 2-dm. tube; $[\alpha]_D^{28}$ +157.1°; $[M]_D$ +712°.

***d*-6,6′-Dinitrodiphenic Acid.**—The pure *d*B*d*A salt (18.5 g.) was dissolved in 250 cc. of hot water and 7 cc. of concd. hydrochloric acid added. Eleven grams of the pure *d*-acid crystallized as yellow needles on cooling; 1 g. more was obtained by evaporation of the solution; yield 98%. The first crop melted at 231–231.5° (corr.) and its properties were not changed by recrystallization from water or other solvents. Christie and Kenner[4] found m. p. 230–231°.

Rotation. Subs., 0.4493 g. neutralized with 20.55 cc. of 0.1317 *N* sodium hydroxide and made up to 25 cc. at 20° gave α_D^{27} +9.50° for 2 dm. Calcd. for 0.5087 g. of sodium salt, $[\alpha]_D^{27}$ +233.3°. For a similar determination Christie and Kenner[4] give $[\alpha]_D$ +225.3°.

Subs., 0.5006 g. made up to 25 cc. in abs. methanol at 20° gave α_D^{25} +5.09 for 2 dm.; $[\alpha]_D^{25}$ +127.0°. Similar determinations gave $[\alpha]_D^{27}$ +133.7° in 95% ethanol and $[\alpha]_D^{25}$ +132.2° in acetone.

***d*-α-Phenylethylamine-*l*-6,6′-dinitrodiphenate.**—The acetone extracts from the original resolution were combined and evaporated to 150 cc. Massive crystals slowly separated. Upon systematic recrystallization from acetone there was obtained 1.0 g. of nearly insoluble dextrorotatory material, a sirupy dark brown mother liquor, and about 12 g. of what proved to be nearly pure *d*B*l*A salt, $[\alpha]_D^{25}$ −150.1° in methanol. A sample of this salt recrystallized from acetone and then from ethanol melted at 204–205° (corr.). The solubility at 25° is 0.74 in water, 4.74 in 95% ethanol and 13.0 in acetone.

Rotation. Subs., 1.0399 g. made up to 25 cc. in methanol at 20° gave α_D^{26} −12.88° for 2 dm.; $[\alpha]_D^{26}$ −154.8°; $[M]_D$ −702°.

The purest sample of this salt when hydrolyzed with hydrochloric acid gave *l*-6,6′-dinitrodiphenic acid, m. p. 228–229°. The rotation of the sodium salt, determined as described for the *d*-form, was $[\alpha]_D^{27}$ −231.4°. The acid is thus substantially pure. The complete purification of the remaining *d*B*l*A salt (and the *l*-acid) from the original resolution appeared impracticable because of the sluggish crystallization from acetone. The various levorotatory fractions were accordingly united, evaporated to dryness and hydrolyzed with hydrochloric acid as described for the *d*B*d*A salt. The recovered acid (25 g.) had $[\alpha]_D^{25}$ −111° in methanol.

Subsequently it was found that the resolution of the *dl*-acid is more easily carried out by dissolving it in about five times its weight of acetone and adding an equimolecular amount of the active amine in a little acetone. The mixture is then heated to boiling and the hot solution decanted from the crude *d*B*d*A salt. This is digested three or four times with about 3 parts of fresh acetone, filtered, washed with acetone and heated for two to three hours at 80° to drive off acetone of crystallization. The yield of pure *d*B*d*A salt is then 90–92%. The acetone filtrates are evaporated to small volume and hydrolyzed to recover the impure *l*-acid as previously described. The amine is recovered from the aqueous hydrochloric acid filtrates in the usual way. A similar resolution in which only one-half of the equimolecular amount of active amine was used was carried out with 95.6 g. of the *dl*-acid and 17.5 g. of the *d*-amine. The pure salt obtained was 51.2 g. instead of the 56.4 g. calculated. The impure *l*-acid was recovered as previously described.

***l*-α-Phenylethylamine-*l*-6,6′-dinitrodiphenate.**—A sample (25 g.) of impure *l*-acid, $[\alpha]_D^{25}$ −111°, was combined with 8.2 g. of *l*-α-phenylethylamine in 200 cc. of acetone. The precipitated *l*B*l*A salt was purified as described for the *d*B*d*A salt, to which it corresponds in all ordinary properties. The yield was 27.4 g.

Rotation. Subs., 0.7369 g. made up to 25 cc. in methanol at 20° gave α_D^{25} −9.40° for 2 dm.; $[\alpha]_D^{25}$ −156.4°.

***l*-6,6′-Dinitrodiphenic acid** was obtained from the pure *l*B*l*A salt exactly as described for the *d*-acid, which it closely resembles; m. p. 229° (corr.).

Rotation. Subs., 0.5095 g. made up to 25 cc. in methanol at 20° gave α_D^{27} −5.14° for 2 dm.; $[\alpha]_D^{27}$ −126.0°.

***dl*-α-Phenylethylamine-*dl*-6,6′-dinitrodiphenate.**—The salt was formed from the pure components and crystallized from water in feathery clusters. It crystallizes from acetone as prisms containing one molecule of solvent. A sample recrystallized from 95% ethanol melted at 206–208° (corr.). The solubility at 25° is 0.76 in water, 1.78 in 95% ethanol and 1.27 in acetone.

Resolution of *dl*-α-Phenylethylamine.—Equimolecular amounts of the *dl*-amine (2.45 g.) and the *d*-acid (6.65 g.) were combined in water. The salt, which is undoubtedly ***dl*-α-phenylethylamine-*d*-6,6′-dinitrodiphenate,** was not resolved by recrystallization from water, ethanol or methanol. It forms flat needles from water, m. p. 207–208°. The solubility at 25° is 0.96 in water and 5.63 in 95% ethanol.

Rotation. Subs., 0.7691 g. made up to 25 cc. in methanol at 20° gave α_D^{25} +6.49° for 2 dm.; $[\alpha]_D^{25}$ +155.1°.

When the salt was heated with acetone, the characteristic needles fell to a fine powder and the salt was readily resolved into two approximately equal fractions melting at 216–217° and 206–207°, respectively, and otherwise resembling the *d*B*d*A and *l*B*d*A salts. To confirm the resolution it was necessary to obtain enough of the active amine for a determination of its rotation since there is but little difference in the rotations of the expected *d*B*d*A and *l*B*d*A salts and the *dl*B*d*A salt. Accordingly 16 g. of the *dl*-amine was combined with 39 g. of *d*-acid in 350 cc. of warm acetone. The liquor was decanted from the microcrystalline deposit and the latter digested four or five times on a water-bath with 150-cc. portions of fresh acetone. The residual solid (25 g.) was hydrolyzed with hydrochloric acid as previously described and the acid recovered. The acetone extracts were evaporated and similarly hydrolyzed. The amines were liberated from the hydrochloric acid filtrates with alkali and distilled with steam. The recovered *d*-acid was then combined with more *dl*-amine and the entire process repeated several times. The amine (presumably *d*-amine) recovered from the sparingly soluble

salt was extracted with benzene, dried and distilled. Its specific rotation, however, was only +32.5° instead of the accepted value +38 to +39°. It appeared probable that some *dl*B*d*A salt had been formed and incompletely resolved by digestion with acetone. The amine was accordingly recombined with *d*-acid in acetone and the crystalline deposit was digested four more times with boiling acetone. The amine recovered from this salt was then about 80% of the amount calculated from the total *dl*-amine taken and the rotation was +38.3°. The amine recovered from the acetone extracts had a rotation of −32.6°.

In a further experiment impure *l*-α-phenylethylamine (3 g.) containing about 85% of the *l*-form was combined with *dl*-acid (8.1 g.) in acetone. By repeated digestion of the precipitate and concentration of the extracts there were obtained, in order, 3.6 g. $[\alpha]_D$ −148°, 1.6 g. $[\alpha]_D$ +12°, and a mother liquor having a high dextro rotation. The fractionation was not continued, but it is evident that the fractions are principally the *l*B*l*A, *dl*B*dl*A and *l*B*d*A salts, respectively, as would be predicted from the solubilities previously recorded.

***d*-α-*p*-Tolylethylamine-*dl*-6,6′-dinitrodiphenate.**—Equimolecular amounts of the *d*-amine and *dl*-acid were combined in water and the resulting salt fractionated from water and also from ethanol and acetone. No resolution occurred. The salt forms large diamond-shaped crystals from acetone, m. p. 211.5–213° (corr.).

***dl*-α-*p*-Tolylethylamine-*d*-6,6′-dinitrodiphenate.**—The salt was formed in acetone but was not resolved by repeated crystallization from this solvent. It melts at 197.5–198° (corr.) and is more soluble in acetone than the corresponding *d*B*dl*A salt.

***dl*-α-*p*-Methoxyphenylethylamine-*d*-6,6′-dinitrodiphenate.**—The salt was formed in water, from which it separated partly as an oil, partly as powdery crystals. The salt is extremely soluble in ethanol and acetone, from which it could not be crystallized.

Partial Resolution of *dl*-Fenchylamine.—Equimolecular amounts of the *dl*-amine and *d*-acid were combined in acetone. A large amount of a powdery solid separated. When this was heated with a large volume of fresh acetone it dissolved very slowly, but only about 25% of the total salt crystallized even when the solvent was evaporated to small volume. A satisfactory method of fractionation could not be devised. The acetone mother liquor was evaporated, the sirupy residue hydrolyzed with hydrochloric acid and the amine recovered as previously described for α-phenylethylamine. The rotation of this part of the amine was +4.2° instead of +24.9° reported for the pure *d*-amine.[8]

Summary

1. *dl*-6,6′-Dinitrodiphenic acid was prepared and resolved into both active forms by means of *d*- and *l*-α-phenylethylamine in acetone solution.

2. *dl*-α-Phenylethylamine was similarly resolved with *d*-6,6′-dinitrodiphenic acid, the *d*-amine being obtained pure. All five types of the isomeric salts are described.

3. Unsuccessful attempts were made to resolve *dl*-6,6′-dinitrodiphenic acid with *d*-α-*p*-tolylethylamine and to resolve *dl*-α-*p*-tolylethylamine and *dl*-α-*p*-methoxyphenylethylamine with the corresponding *d*-acid. *dl*-Fenchylamine was partially resolved.

(8) Wallach and Binz, *Ann.*, **276**, 317 (1893).

NASHVILLE, TENNESSEE RECEIVED JULY 2, 1934

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF HAWAII]

The Preparation of Chaulmoogra Derivatives. I. Substituted Amines and Amides

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Derivatives of chaulmoogric acid and hydnocarpic acid have been used for some years in the treatment of leprosy, the sodium salts and the ethyl esters having found most extensive application.[2] The irritating action of these compounds when injected has been recorded frequently as an objection to their use. Sodium salts are subject to marked hydrolysis with deposition of the insoluble acids and liberation of sodium hydroxide. Both the fatty acids and the ethyl esters are relatively slowly absorbed. It would appear reasonable to expect that compounds soluble in water and not readily undergoing hydrolysis would prove more satisfactory. In order to develop such properties several derivatives have been prepared by various investigators.[3]

From a theoretical standpoint the introduction of amino, substituted amino, hydroxyl, carboxyl, sulfonic or phosphoric acid groups into compounds of chaulmoogric acid should render them more soluble in most instances. Furthermore, the incorporation of structures of known and

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(2) These papers, too numerous to cite here, have been recorded at various times in the literature, *e. g.*, see Hasseltine, U. S. Pub. Health Bull. No. 141, 1924; Report of Leonard Wood Memorial Conference on Leprosy, *Philippine J. Sci.*, **44**, 449–80 (1931); Tomb, *J. Trop. Med. Hyg.*, **36**, 170–178, 186–189, 201–207 (1933).

(3) These papers are again too numerous to cite here, *e. g.*, see Perkins, *Philippine J. Sci.*, **21**, 1 (1922); Dean, Wrenshall and Fujimoto, THIS JOURNAL, **47**, 403 (1925); Santiago and West, *Philippine J. Sci.*, **33**, 265 (1927); DeSantos and West, *ibid.*, **38**, 293, 445 (1929).