tions. Several runs carried out with only 2 moles of acetic anhydride and 5 moles of alkali gave considerably lower yields.

Purification and Criteria of Purity.—The material described above is pure enough after one recrystallization for use as a resolving agent.[8] For use in the preparation of L-leucine it was recrystallized three times more from water (15 cc./g.), or preferably by dissolving in 2.5 cc./g. of methanol and adding 5 cc./g. of hot water. If the solution became faintly cloudy on cooling the treatment with carbon was repeated. The product then had m.p. 185–185.5°; $[\alpha]^{25}D$ −24.0 ± 0.2° (*c* 4, methanol); $[\alpha]^{25}D$ −23.0° (*c* 4, abs. ethanol). Martin and Synge[6] report m.p. 183–184°; $[\alpha]^{24}D$ −22.6° (*c* 3.3, ethanol). A sample crystallized from acetone and then from water had m.p. 185–185.5°; $[\alpha]^{25}D$ −24.1° (*c* 4, methanol). It forms distinctive square tablets from dilute acetone solutions. A sample recovered from use in a resolution in which a sparingly soluble salt had been recrystallized and a sample obtained by resolution of the synthetic racemic form[9] both had m.p. 185–186°; $[\alpha]^{25}D$ −24.2°.

(8) A. W. Ingersoll and H. D. DeWitt, THIS JOURNAL, **73**, 3360 (1951).

(9) Unpublished results of Mr. W. A. H. Huffman.

Anal. Calcd. for $C_7H_{14}ON{\cdot}CO_2H$: N, 8.09; neut. equiv., 173. Found: N, 8.1; neut. equiv., 172.5.

Preparation of L-Leucine.—Thrice crystallized acetylleucine, $[\alpha]^{25}D$ −24.0° (17.3 g., 0.1 mole) was boiled under reflux with 35 cc. (0.12 mole) of 3 *N* hydrobromic acid. Solution was complete in 45 minutes but heating was continued for two hours. The colorless solution was diluted with 100 cc. of hot methanol and brought to *p*H 6 with aqueous ammonia. After cooling, the precipitate was collected on a filter and washed freely with warm methanol. The product (10.8 g.) had $[\alpha]^{25}D$ +15.3° (0.9905 g. made up to 25 cc. in 5.99 *N* hydrochloric acid). The filtrate was taken to dryness *in vacuo* and the residue digested with 100 cc. of hot methanol. Undissolved material (1.7 g.) resembled the first crop.

Several preparations made in this manner were combined, dissolved in 20 parts of water and crystallized after adding 30 parts of methanol. The product had $[\alpha]^{25}D$ +15.1° (*c* 4, 5.99 *N* HCl). A sample prepared by resolution had +15.2° under the same conditions. Stoddard and Dunn[2] give +15.2° and Thomas and Niemann[4] give +14.84° at 25° in approximately 6 *N* hydrochloric acid. Tests for ammonia, halogens, methionine and tyrosine were negative.

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[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

The Preparation and Resolution of DL-α-Fenchylamine

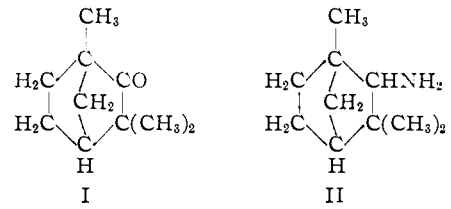
BY A. W. INGERSOLL AND H. D. DEWITT

Convenient procedures are described for preparing *dl*-α-fenchylamine and for its resolution into both active forms by means of N-acetyl-L-leucine, a new resolving agent. A resolution with active mandelic acid and other procedures for obtaining the active amines also are described. The active amines are useful resolving agents.

Resolutions of *dl*-mandelic acid and *dl*-malic acid by active fenchylamines have been noted previously.[1] Further studies have shown that these amines (now designated as the α-fenchylamines) form salts of exceptional crystallizing power with a wide variety of racemic acids, many of which are resolved into their antipodes. In some ten resolutions completed thus far[2] the active α-fenchylamines have shown considerable advantages over the commonly used alkaloids, especially with respect to resolving power, chemical stability, ease of recovery, moderate molecular weight and availability of both forms.

Wallach,[3] by reduction of the oximes or by the Leuckart reaction, prepared a levorotatory fenchylamine from (+)-fenchone of fennel oil and the corresponding dextrorotatory amine from (−)-fenchone of thuja oil. These oils contain only 15–20% of the respective active fenchones and these and other sources are expensive and not sufficiently available to provide an adequate supply of the desired amines. On the other hand, a commercial *dl*-fenchone is abundantly available from the fenchyl alcohols of pine stump oil and related sources. We have readily converted this into crude *dl*-fenchylamine by a modified Leuckart synthesis.[4] The separation and resolution of this crude amine afford both active α-fenchylamines in large amounts.

Fenchone (I) may be expected to give rise to two diastereoisomeric (α- and β-) fenchylamines (II) having inverse configurations of the $CHNH_2$ group. It is apparent from our results and other



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recent work[5] that the active amines characterized by Wallach were the predominant α-isomers. The crude amine from commercial *dl*-fenchone was found to contain 10 to 25% of the β-isomer, depending on reaction conditions. The isolation of pure amines from the mixture was further complicated by the presence in the commercial fenchone of 10–12% of (+)-fenchone, some camphor and other unidentified ketones. Accordingly, the crude amine contains the corresponding active and racemic α- and β-fenchylamines together with small amounts of bornylamines, neobornylamines and other minor amines.

The key to the separation of pure active and racemic forms of the α-amine from this mixture and from partially active fractions obtained in subsequent resolution procedures was found in the

(1) H. L. Dickison and A. W. Ingersoll, THIS JOURNAL, **61**, 2477 (1939).

(2) For examples see L. R. Overby and A. W. Ingersoll, *ibid.*, **73**, 3363 (1951).

(3) O. Wallach, *et al.*, *Ann.*, **259**, 324 (1890); **263**, 140 (1891); **269**, 358 (1892); **276**, 317 (1893).

(4) A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beauchamp and G. Jennings, THIS JOURNAL, **58**, 1808 (1936).

(5) W. Hückel, H. Kindler and H. Wolowski, *Ber.*, **77B**, 220 (1944); *C. A.*, **39**, 3273 (1945).

behavior of the salicylidene derivatives. The mixture of derivatives from the crude amine on fractional crystallization rapidly gave the sparingly soluble derivative of (−)-α-fenchylamine and then the moderately soluble *dl*-α-fenchylamine derivative; the very soluble derivatives of the β-amines and other minor amines remained in the liquors. Fractionation of the hydrochlorides, mandelates and N-formyl derivatives also afforded useful separations of the crude amine.

Resolution of purified *dl*-α-fenchylamine, preferably taken as hydrochloride, through the salts of N-acetyl-L-leucine[6] gave the (+)-amine in 80–85% yields. The corresponding (−)-amine was isolated in 65–70% yield by fractionation of the salicylidene derivatives of the residual amine recovered from the soluble fractions of the salts. Mixtures containing *dl*-α-fenchylamine and *dl*-β-fenchylamine were resolved similarly, since the N-acetyl-L-leucine salts of the β-amines were quite soluble and did not interfere. The crude amine mixture obtained directly from the Leuckart synthesis was likewise resolved. Minor amines present in this, however, formed small amounts of a difficultly separable, sparingly soluble salt which contaminated the salt of the (+)-α-fenchylamine. Hence it was desirable in this instance to purify both forms of the active amine through the salicylidene derivatives. Various modifications of these processes, together with a resolution of *dl*-α-fenchylamine with (+)-mandelic acid, are described in the Experimental part.

β-Fenchylamine and other minor amines in various fractions from separations of the α-amines have been separated and the β-amine resolved with active mandelic acids. Description of this work is reserved for a later paper.

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Experimental

Preparation of Crude *dl*-α-Fenchylamine.—The method is an adaptation of the general Leuckart procedure described earlier,[4] modified by the use of formic acid and other variations. Technical *dl*-fenchone[7] (304 g., 2 moles), 99% formamide (540 g., 12 moles) and technical 90% formic acid (50 cc.) are placed in a 2-l. round flask having a thermometer inlet and ground neck. The latter is fitted with a 1-m. or longer air cooled indented column surmounted by a condenser with controllable take-off head, such as that of Hershberg.[8] Heat is applied directly with a soft flame. Evolution of carbon dioxide and refluxing occur freely at 160°; the temperature is held in the range 160–185° throughout the reaction. More formic acid is admitted through the condenser in 30–40-cc. portions whenever much ammonia and ammonium carbonate appear in the condenser. Formic acid prevents clogging by ammonium carbonate, reduces discoloration and permits more complete reaction; usually 200–300 cc. is needed. The pale brown mixture becomes homogeneous in about three hours. The temperature of the actively boiling mixture depends on the amount of water and formic acid present and is raised when necessary by brief distillation so conducted that chiefly water distils. The proportion of α-amine is somewhat greater when the reaction is conducted at the higher temperature. The reaction requires 12 to 16 hours (in several periods, if desired), the time being inversely related to the average temperature maintained. The total aqueous distillate is usually 150–200 cc. Distilled fenchone is separated periodically and returned. Completion of the reaction is indicated by reduced distillation of fenchone and slower consumption of formic acid.

The crude N-fenchylformamide separates as an upper layer on cooling; if the reaction is complete, the product solidifies. When it is to be hydrolyzed it is extracted before solidification with benzene. The residual formamide is somewhat colored but satisfactory for use in later runs. The extract is washed with water and transferred to a 3-l. flask. Concentrated hydrochloric (380 cc.) and water (300 cc.) are added and the mixture is heated cautiously while the benzene distils and then more briskly for an hour to complete the hydrolysis. A little fenchone may distil during this stage.

When the free amine is desired it is liberated with sodium hydroxide and distillation is continued until little more volatile amine distils and only a small oily layer, largely difenchylamine, remains in the distilling flask. The slightly soluble amine is extracted from the distillate with at least four portions of sulfur-free benzene totalling 300–400 cc. The extract is dried and the amine recovered as usual. It rapidly absorbs carbon dioxide and should be protected during handling and storage. The fraction, b.p. 184–192°, $[\alpha]^{25}D$ −3.0 ± 0.3° (*c* 5, ethanol), amounts to 245–260 g. (80–85%). Six-mole runs were carried out similarly in a 5-l. reaction flask.

Separation of the Crude Amine.—Four principal methods for obtaining pure amines or useful fractions were studied. These methods or suitable combinations are variously useful depending on the composition of the mixture and the components desired.

(**a**) **Fractionation of the Hydrochlorides.**—The steam distillate from the Leuckart synthesis was acidified with hydrochloric acid and the very soluble salts were systematically crystallized from water. Alternatively, a considerable part of the hydrochloride was crystallized in successive crops directly from the hydrolysis mixture; the remainder of the amine was then liberated, distilled with water and reconverted to the hydrochloride. The order of solubility (as hydrochlorides) was found to be β-fenchylamines < α-fenchylamines < minor amines (including difenchylamines, if present). The active forms of the β- and α-amines are slightly less soluble than the corresponding *dl*-forms. The β-amine salts (10–25%) were not obtained completely pure by this procedure but rapidly concentrated in the head fractions. The intermediate fractions (65–80%) were correspondingly enriched in the α-amine salts. The β-salts crystallize as fine needles. The α-salts usually crystallize initially in this form but change slowly on standing in the mother liquor to characteristic massive forms which may be separated mechanically. The active forms appear as long prisms, the *dl*-form as rhomboids. The salts of the small amounts of minor amines (5–10%) pass to the foot of the series as sirupy solutions which do not readily yield crystals. For practical purposes the fractionation is continued only long enough to remove the minor amines and most of the β-amine. The fractions rich in α-amine are satisfactory for use in resolution or for conversion to other derivatives.

(**b**) **Fractionation of Mandelates.**—The steam distillate from the Leuckart synthesis is neutralized with *dl*-mandelic acid and the salts crystallized from water. Salts of the α-amine are considerably less soluble than those of the β-amine and minor amines and rapidly accumulate in the head fractions. The system is somewhat complicated by the presence of 10–12% of the (−)-α-amine. This amine resolves a portion of the mandelic acid forming, as least soluble fraction, the (−)-α-amine-(−)-mandelate and the much more soluble (−)-α-amine-(+)-mandelate. Fractionation yields, in order, the (−)-α-amine-(−)-mandelate (*ca.* 5%) as large prisms, m.p. 190–190.5°; $[\alpha]^{25}D$ + 60.6° (*c* 4, water) and the *dl*-α-amine-*dl*-mandelate (65–80%) as a crust of glistening plates, m.p. 180°. The respective solubilities in 100 cc. of water solution at 25° are 2.66 g. and 4.11 g. The remaining more soluble salts (15–30%) usually were not further fractionated.

(**c**) **Fractionation of the Salicylidene Derivatives.**—The crude steam distilled amine or any suitable fraction may be used. It must be free of benzene, small amounts of which inhibit crystallization. The derivatives are formed from equivalents of amine and aldehyde in warm methanol and

(6) H. D. DeWitt and A. W. Ingersoll, THIS JOURNAL, **73**, 3359 (1951).

(7) Eastman Kodak Co., $[\alpha]^{25}D$ +7.3–7.6°; pure (+)-fenchone has $[\alpha]^{18}D$ +62.8° (ref. 5).

(8) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 323.

crystallized in successive fractions by cooling and concentration. The main crystalline fractions are derived from α-fenchylamines, the more soluble oily residual fractions from β-fenchylamines and minor amines. Systematic recrystallization from methanol (3–4 cc./g.) rapidly concentrates the pure active form in the head fractions as large lemon-yellow needles, m.p. 95.5°[3]; $[\alpha]^{25}D$ ±73.5° (*c* 4, methanol), ±67.4° (*c* 5, chloroform)[3]; solubility, 5.8 g./100 cc. of methanol solution at 25°. The (+)-form of the derivative corresponds to (−)-α-fenchylamine and (+)-fenchone. The *dl*-form from intermediate fractions forms smaller needles, m.p. 66°[3]; solubility 11.3 g./100 cc.

In a typical experiment the crude, steam distilled amine from a six-mole run with technical *dl*-fenchone[7] gave 196 g. (11.8%) of salicylidene derivative $[\alpha]^{25}D$ +73.0–73.5° (*c* 4, methanol) and 693 g. (42%) of the nearly pure *dl*-form. Mixed amines recovered from the mother liquors amounted to 206 g. (22.4%) and brought the total yield, based on technical *dl*-fenchone, to 76.2%. In most experiments the fractionation was pursued only sufficiently to obtain the crystalline salicylidene derivatives; the partially active α-amine recovered from this was taken for resolution. For hydrolysis the salicylidene derivatives were warmed briefly with 1.2 equivalents of 15% sulfuric acid and the aldehyde was extracted with benzene. The aldehyde and amines were recovered by usual methods.

(d) **Fractionation of the Formyl Derivatives.**—For this purpose the crude solid N-fenchylformamide from the Leuckart reaction is filtered from excess formamide, washed with water and dried. It is then dissolved in about an equal weight of acetone and allowed to crystallize in open erlenmeyer flasks by spontaneous evaporation of solvent. Successive crops are collected by decantation and recrystallized systematically. The *dl*-α-derivative then forms the head fraction (55–65% of the total) and when pure crystallizes in massive rectangular blocks, m.p. 91–92°. The next fractions (6–8%) contain mainly the *dl*-β-derivative, which forms a dense crust, m.p. 80–82°. The further separation of crystalline fractions from the sirupy liquors is impractical; the material is best hydrolyzed and processed through the salicylidene derivatives to obtain residual active and racemic α-amines.

Resolution of *dl*-α-Fenchylamine (a).—Pure *dl*-α-fenchylamine hydrochloride (189.5 g., 1.0 mole) obtained from the formyl derivative was dissolved in 900 cc. of hot water and mixed with a solution of 173.1 g. (1.0 mole) of N-acetyl-L-leucine exactly neutralized (phenolphthalein) with about 400 cc. of 10% sodium hydroxide. The solution was heated to dissolve solids and left overnight. The crystalline deposit (*ca.* 150 g.) was collected and additional small crops were obtained by stepwise evaporation of the liquors and seeding. The liquors eventually set to a soft gel on cooling and gave no further crystals. The crystalline crops were systematically recrystallized from water (7 cc./g.) and eventually gave 142 g. (87%) of the (+)-amine salt. Prolonged boiling or evaporation in open vessels is accompanied by slight loss of amine. In later experiments this was avoided by distillation of the solutions under reduced pressure.

Pure (+)-α-fenchylamine-N-acetyl-L-leucine salt crystallizes in coarse prisms, m.p. 185–192°; $[\alpha]^{25}D$ −7.8° (*c* 4, methanol), −11.1° (*c* 4, water); solubility in water at 25°, 5.4 g./100 cc. of solution.

Several similar resolutions were carried out with fenchylamine hydrochloride preparations containing various proportions, up to 40%, of the *dl*-β-amine. Except for the correspondingly lower yields the results were similar; the soluble salts of the β-amine remained in the liquors.

(+)-α-Fenchylamine.—A quantity of the finely powdered (+)-amine salt (260 g.) was decomposed with a slight excess of 10% sodium hydroxide by shaking in a separatory funnel in the presence of benzene. The amine was repeatedly extracted with benzene and distilled; yield 89.8%. The pure amine had b.p. 189–190°; d^{20}_{20} 0.897; $[\alpha]^{25}D$ +25.5° (*c* 5, 95% ethanol), in agreement with reported values.[1] N-Acetyl-L-leucine suitable for re-use was recovered nearly quantitatively from the aqueous layer.

(−)-α-Fenchylamine.—The mother liquors from the first resolution were treated with alkali and the crude (−)-amine recovered as described previously. In a typical experiment 64 g. of this amine, calculated to contain 86% of excess (−)-amine, was mixed with 44 g. of salicylaldehyde and fractionation was effected in methanol. Initial crops were already nearly pure (−)-amine derivative (m.p. 90° to 94°) and systematic recrystallization easily gave 74.8 g. of the pure compound, m.p. 95.5°; $[\alpha]D$ +73.5° (*c* 4, methanol), +70.8° (*c* 4, 95% ethanol). The amount of this derivative corresponds to 79% of the calculated excess of (−)-amine. The corresponding amine obtained by hydrolysis (91%) had $[\alpha]^{25}D$ −25.4° (*c* 4, 95% ethanol). Slightly impure *dl*-amine derivative (m.p. 60–63°) was obtained from foot fractions. Later large scale experiments gave average over-all recoveries of about 70% of the (−)-amine contained in the original *dl*-amine.

(b) Preliminary experiments showed that pure *dl*-α-fenchylamine was resolved directly by acetylleucine as readily as by use of the salts. In an attempt to avoid the necessity of previous purification of the amine this procedure was then applied to the mixture of crude steam distilled amines from technical *dl*-fenchone. The amine (153 g.) and acetylleucine (173.1 g.) were combined in 1200 cc. of water and the salts were systematically recrystallized as usual. The head fractions (143 g.) contained the characteristic (+)-α-amine salt admixed with about 5% of sparingly soluble needles; the (−)-α-amine and β-amine salts remained in the liquors. The sparingly soluble needles, presumably a salt of a minor amine, could not readily be separated completely by crystallization. Accordingly, the amine recovered from the combined crystalline salts, as well as that from the mother liquors, was purified through the salicylidene derivative as previously described. Both active α-amines were thus obtained pure in good yields. The procedure is regarded as the most expeditious route to these amines.

(c) *dl*-α-Fenchylamine (30.6 g., 0.2 mole) was combined in 250 cc. of water with 30.4 g. (0.2 mole) of (+)-mandelic acid, $[\alpha]^{25}D$ +156.6° (*c* 4, water) previously prepared by resolution of the *dl*-acid with (+)-α-fenchylamine. Undisturbed crystallization gave massive pyramids identified as the *dl*-amine-(+)-acid double salt, $[\alpha]^{25}D$ +55.5° (*c* 4, water). On redissolving and seeding the warm solution with (+)-amine-(+)-acid salt, the deposit was a mixture of this salt and the double salt. Systematic recrystallization aided by mechanical separation eventually gave 29.5 g. (96%) of pure (+)-α-fenchylamine-(+)-mandelate as characteristic large prisms. It crystallizes from methanol or ethanol in small prisms, m.p. 190–190.5°; $[\alpha]^{25}D$ +60.6° (*c* 4, water), +48.5° (*c* 4, 95% ethanol). The amine from this salt had $[\alpha]^{25}D$ +25,5° (*c* 5, ethanol). The much more soluble (−)-amine-(+)-acid salt formed a mass of small needles and was obtained in slightly impure form, $[\alpha]^{25}D$ +53.7° (*c* 4, water). The corresponding amine had $[\alpha]^{25}D$ −23.8° (*c* 5, ethanol).

The resolution with mandelic acid is regarded as satisfactory but more tedious than that with acetylleucine. The reciprocal resolvability of the acid and the amine, and an order of salt solubilities favorable for application of the three-salt method,[9] however, have enabled us to prepare large quantities of all of the corresponding active forms by the use of active and racemic mandelic acids.

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(9) A. W. Ingersoll and E. G. White, THIS JOURNAL, **54**, 274 (1932).