[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Passerini Reaction. II. Optically Active Anilides[1,2]

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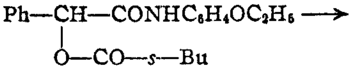
Passerini, in order to support his thesis that the reaction proceeded by way of reaction of isocyanide with a previously formed addition compound of the acid and ketone or aldehyde, cited the facts that the molecular rotations of certain optically active acids in acetone, methyl ethyl ketone, etc., were abnormally low, and certain of the systems showed mutarotation.[4] Since the acids he used contained hydroxyl groups which might have accounted just as well for the abnormalities, we have not considered his picture of the reaction mechanism as necessarily correct.[5] These speculations suggested, however, the use of the Passerini reaction in the synthesis of optically active products which has been realized.

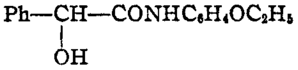
$$R_2CO + R'COOH + R''NC \longrightarrow R_2C(OCOR')CONHR''$$

Benzaldehyde reacted with *p*-ethoxyphenyl isocyanide and (+)α-methylbutyric acid to produce I, an apparently pure diastereomer, in 72% yield. The mandelo-*p*-phenetidide, II, obtained by saponification of I was racemic, a not surprising result since mandelic acid derivatives are easily racemized by bases and six hours of refluxing with sodium hydroxide was required to cleave the hindered ester. When the reaction was repeated with phenyl isocyanide and (−)menthoxyacetic acid the yield of crude III was 80%. This was crystallized to produce four fractions, 56%, of such nearly identical properties as would indicate that only one of the diastereomers was isolated. Although III could be hydrolyzed by only twenty minutes of boiling with alkali, the mandelanilide, IV, was, like the phenetidide, racemic.



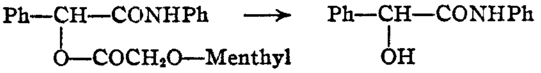
$$\underset{\text{O—CO—}s\text{—Bu}}{\text{Ph—CH}}\text{—CONHC}_6\text{H}_4\text{OC}_2\text{H}_5 \longrightarrow$$

I



$$\underset{\text{OH}}{\text{Ph—CH}}\text{—CONHC}_6\text{H}_4\text{OC}_2\text{H}_5$$

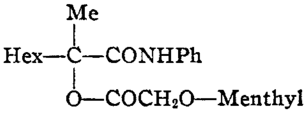
II



$$\underset{\text{O—COCH}_2\text{O—Menthyl}}{\text{Ph—CH}}\text{—CONHPh} \longrightarrow \underset{\text{OH}}{\text{Ph—CH}}\text{—CONHPh}$$

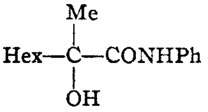
III IV

In contrast to the high yields obtained with benzaldehyde, 2-octanone gave only 17–19% of V. Again only one diastereomer was obtained in crystalline form and in this case the compound was stable enough to permit saponification to the active anilide of the hydroxyacid, VI, and quantitative recovery of menthoxyacetic acid. Prolonged hydrolysis of the anilide produced the active hydroxyacid, VII.



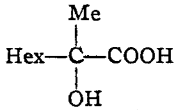
$$\text{Hex—}\overset{\text{Me}}{\underset{\text{O—COCH}_2\text{O—Menthyl}}{\text{C}}}\text{—CONHPh}$$

V, [α] −59.1°



$$\text{Hex—}\overset{\text{Me}}{\underset{\text{OH}}{\text{C}}}\text{—CONHPh}$$

VI, [α] −39.2°



$$\text{Hex—}\overset{\text{Me}}{\underset{\text{OH}}{\text{C}}}\text{—COOH}$$

VII, [α] +4.6°, 6.9°

The reaction mixture which had produced V, m. p. 135°, was extensively worked over in an effort to isolate the other diastereomer. In addition to the six fractions of V there was obtained (−)diphenylformamidine menthoxyacetate, VIII, m. p. 148°.

$$\text{Ph—NH—CH=N—Ph}\cdot 2\text{HOCOCH}_2\text{O—Menthyl}$$

VIII

When no more crystals could be produced the liquid residues were hydrolyzed. Two unidentified substances were isolated, m. p. 87.8–89.2° and 169.3–170°. The latter compound was optically active, [α] −32°. Finally the enantiomorph of VI was found, m. p. 66.5–67.5°; [α] +32°, in 4.9% yield. The high positive rotation of this compound indicated an almost complete removal of V had been effected before hydrolysis. The low yield of the (+) enantiomorph compared to the (−) one indicates than an asymmetric synthesis in the Marckwald sense[6] has been experienced.

In attempting to apply the reaction to other systems further limitations[2] have been discovered. The relatively hindered (+)α-methylbutyric acid produced no Passerini product with 2-octanone and phenyl isocyanide, and the aryl ketones do not react with either of the optically active acids used, in the presence of phenyl isocyanide. When the ketone fails to react the products of reaction of isocyanide with the acid are quite in evidence. The diarylformamidine salts have been noted previously by Passerini, but the formation of anilides (from phenyl isocyanide) of the acid apparently escaped his attention. (+)α-Methylbutyranilide has been identified as has also benzanilide. The latter resulted from an attempt to use styrene oxide as the carbonyl function, in a manner analogous to the behavior of epoxides in the cyanohydrin reaction.

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(1) This investigation was supported by a grant from the Abbott Fund of Northwestern University.

(2) For the preceding paper see Baker and Schlesinger, THIS JOURNAL, **67**, 1499 (1945).

(3) Abstracted from the Ph.D. Thesis of L. E. Linn, 1947.

(4) Passerini, *Gazz. chim. ital.*, **55**, 726 (1925).

(5) Even if the ketone–acid complex were known to exist it would not necessarily participate as such in the reaction.

(6) For reviews of this subject see Ritchie, "Asymmetric Synthesis and Asymmetric Induction," Oxford University Press, London, (1933); Ritchie in "Advances in Enzymology," Interscience Publishers, Inc., New York, N. Y., 1947, Vol. 7, p. 65 ff.

Experimental[7]

Reagents.—(+)α-Methylbutyric acid, (α^{24}D +35.56°, 2-dm. homogeneous; b. p. 66.5–68.5°, 9 mm.; n^{20}D 1.4058) was prepared by dichromate oxidation of (−)2-methyl-1-butanol (α^{21}D −4.78°, 1 dm., homogeneous; n^{20}D 1.4105).[8] The alcohol was produced by two fractionations of refined fusel oil in a Podbielniak Hyper-Cal column with a Heli-Grid-packed section, 2.2 × 91 cm. The optimum conditions for this column on the mixture were found to be distillation rate 2–2.5 ml./hr., reflux rate 4 drops/sec. and reflux ratio 120/1. From the recently published data,[9] the column was calculated to be operating at 60 plates.

(−)Menthoxyacetic acid, $[\alpha]^{27.8}$D −91.7° (*c*, 3.32 in ethanol), was supplied by Dr. L. T. Sherwood, Jr.

(+)α-Methylbutyrylmandelo-*p*-phenetidide, I.—A solution of 1.0 g. (0.007 mole) of *p*-ethoxyphenyl isocyanide, 6.3 g. (0.06 mole) of acid-free benzaldehyde and 0.9 g. (0.009 mole) of (+)α-methylbutyric acid was allowed to stand at 23° for forty-two hours. Dilution with Skellysolve A (petroleum ether, b. p. 40–50°) precipitated an oil which was washed by decantation with the Skellysolve. Upon evaporation of the residual wash liquid the oil solidified. This solid and a second crop obtained from the wash liquids, 1.8 g. (72%) was clarified by Norit A in ether solution and was crystallized from methanol, m. p. 98.7–99.2°; $[\alpha]^{22}$D +2.9° (*c*, 12.6 in benzene).

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.33; H, 7.02; N, 4.14.

***d,l*-Mandelo-*p*-phenetidide, II.**—A solution of 1.06 g. (0.003 mole) of the above, I, in 3 ml. of ethanol containing 0.0033 mole of sodium hydroxide was refluxed for six hours. The solvent was evaporated and the product was extracted with ether. Crystallization from ether–Skellysolve A gave white plates, m. p. 142.0–142.8°, which possessed no measurable optical activity, benzene.

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.31; N, 5.16. Found: C, 71.46; H, 6.24; N, 5.18.

(−)Menthoxyacetylmandelanilide, III.—A solution of 0.01 mole each of benzaldehyde and phenyl isocyanide with 0.0047 mole of (−)menthoxyacetic acid was allowed to stand four days at −5° and an additional two days after dilution with ether. Skellysolve A precipitated 80% of crude product which was divided into two fractions by crystallization from methanol. The Skellysolve solution was concentrated, treated with 0.5 g. of benzaldehyde and when allowed to stand furnished two more fractions. There was no significant difference in either the m. p. or $[\alpha]$D of the four fractions; yield 56%, m. p. 122–122.6°; $[\alpha]^{25}$D −55.1° (*c*, 7.3 in acetone).

Anal. Calcd. for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.88; H, 8.02; N, 3.48.

***d,l*-Mandelanilide, IV.**—A solution of 0.20 g. of III and 0.04 g. of sodium hydroxide in 3 ml. of methanol was refluxed for twenty minutes. The product, obtained by adding water to the methanolic solution, was white plates, m. p. 148–150°, yield 88%. Crystallization from acetone–ether gave m. p. 149.7–150.5°; lit.[10] 151–152°. Acetone solutions of the anilide had no observable rotation. The methanolic filtrate and washings, 15.4 g., had α^{25}D −0.52°, *l*, 1 dm.

(−)2-Menthoxyacetoxy-2-methyloctananilide, V.—A solution of 0.013 mole each of the isocyanide, acid and 2-octanone was allowed to stand two days, diluted with ether, and after twelve more days yielded 0.7 g. of crystals. The mother liquor in another twenty days gave an additional 0.4 g., 19% yield. Fractionation of these two crops from either acetone or Skellysolve A gave five fractions $[\alpha]^{26}$D −55.6–59.1° (*c*, 2.04 in acetone). The top fraction had m. p. 134.6–135.1°.

Anal. Calcd. for $C_{27}H_{43}NO_4$: C, 72.77; H, 9.73; N, 3.14. Found: C, 72.59; H, 9.55; N, 3.20.

An experiment with three times the above quantities was carried out in a careful search for the other diastereoisomer. Six fractions of anilide, m. p. 131–134.8°, $[\alpha]^{26}$D −56.4 to −58.1°, in 17% yield were obtained. Additional isocyanide and ketone were added from time to time and after fourteen days the mother liquors gave 1.08 g., crystallized from Skellysolve B (petroleum ether, b. p. 60–70°), and then methanol, of (−)**diphenylformamidine *l*-menthoxyacetate**, m. p. 148.2–148.6°, $[\alpha]^{30}$D −74.8° (*c* 1.60 in acetone).

Anal. Calcd. for $C_{37}H_{56}O_6N_2$: C, 71.12; H, 9.03; N, 4.49. Found: C, 71.12, 71.69; H, 8.55, 8.53; N, 4.28.

When the reaction mixture could no longer be induced to produce crystals it was subjected to distillation at 0.7 mm. and there distilled the excess phenyl isocyanide and 2-octanone, the distillation being stopped at 140°. The work up of the remaining red oil, *ca.* 8 g., to prove the presence of a small amount of the diastereomeric Passerini product is described later.

(−)2-Hydroxy-2-methyloctananilide, VI.—A solution of 2.037 g. (0.0046 mole) of V, and two equivalents of sodium hydroxide in 25 ml. of methanol was boiled for thirty-five minutes and evaporated *in vacuo*. Water was added and the alkaline solution was separated from the solid residue by filtration. The residue was decolorized in ether solution by Norit and crystallized from Skellysolve B then washed with Skellysolve A to give 0.788 g. of white needles, m. p. 67–68.1°; $[\alpha]^{29.2}$D −39.2° (*c*, 1.17 in acetone). Two additional crops of 0.209 and 0.064 g., m. p. 65–66°, were recovered from the mother liquors, total yield 1.061 g., 93%.

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30. Found: C, 72.13; H, 9.36.

The alkaline solution was acidified with sulfuric acid and extracted with toluene. The toluene solution was dried by distillation, decolorized with Norit, filtered and evaporated *in vacuo*. The final traces of toluene were removed by evaporations with methanol and Skellysolve A to yield 0.897 g. (92%) of (−)**menthoxyacetic acid**, $[\alpha]^{30.4}$D −92.2° (*c*, 2.83 in ethanol).

(+)2-Hydroxy-2-methyloctananilide.—The red oil, 7 g., remaining from the preparation of V above was refluxed for thirty-five minutes in methanol solution containing 3 g. of sodium hydroxide. Evaporation and dilution with water produced a suspension of brown oil which was extracted with ether. The alkaline solution when worked as previously described gave 2.16 g. of (−)menthoxyacetic acid, $[\alpha]^{24}$D −88°. A small amount of aniline was extracted from the ether solution with hydrochloric acid. The neutral ether solution on evaporation left an oil from which, by crystallizing from ether–Skellysolve A, there was obtained 0.23 g. of unidentified crystals, m. p. 163–165°. The filtrate and washings were evaporated and crystallized from acetone–water to produce 0.476 g. more of the unknown compound which after crystallizing from benzene, m. p. 169.5–170°; $[\alpha]^{23}$D −32° (*c*, 0.43 in acetone). The m. p. of the compound was unaltered by refluxing for one hour with methanolic sodium hydroxide.

The remaining oil obtained from the filtrates could not be induced to crystallize and was subjected to another hour of alkaline hydrolysis. The product was extracted with a mixture of Skellysolves A and B (50 ml. of each) to yield 0.170 g. of a tan powder, m. p. 87.8–89.2°, unidentified. The soluble fraction was concentrated and cooled to yield 0.752 g., recrystallized from Skellysolve, 0.585 g. (4.9%) of (+)**2-hydroxy-2-methyloctananilide**, m. p. 66.5–67.5°; $[\alpha]^{24.5}$D +32.3° (*c*, 2.75 in acetone).

Anal. Calcd. for $C_{15}H_{23}NO_2$: N, 5.62. Found: N, 5.75.

(+)2-Hydroxy-2-methyloctanoic Acid, VII.—A solution of 0.565 g. (0.0023 mole) of the (−)anilide, VI, and 1.12 g. (0.020 mole) of potassium hydroxide in 10 ml. of ethanol

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[7] All melting points are uncorrected. Microanalyses were performed by Misses Patricia Craig, June Anderson, Margaret Hines and Mrs. Nelda Mold.

[8] Marckwald, *Ber.*, **37**, 1045 (1904).

[9] Hafslund and Lowell, *Ind. Eng. Chem.*, **38**, 556 (1946).

[10] Fischer and Fischer, *Ber.*, **47**, 779 (1914); Passerini, *Gazz. chim. ital.*, **51**, II, 181 (1921).

was refluxed for eighteen hours. An ether extraction of the alkaline solution yielded, by acid extraction, aniline. The neutral fraction from the ether extract was unchanged anilide, 0.35 g., m. p. 65.6–66.2°; $[\alpha]^{35}D$ −39.4°. The alkaline solution was acidified with hydrochloric acid and was extracted with ether. Evaporation *in vacuo* produced 0.0872 g. of the liquid acid (yield based on unrecovered anilide 62%); $[\alpha]^{33}D$ +4.6° (*c*, 4.36 in acetone).

Acid hydrolysis was also successful. A solution of 0.350 g. of the anilide in 8 ml. of 75% aqueous dioxane containing 0.2 ml. of sulfuric acid was refluxed for eighteen hours to yield a red solution which was concentrated, made basic and worked up as above. There was recovered 0.17 g. of the anilide, m. p. 67.0–68.2°; $[\alpha]^{31}D$ −41° (*c*, 1.06 in acetone).(11)

The hydroxy acid, 0.082 g., was obtained in 67% yield with $[\alpha]^{32}D$ +8.2° (*c*, 8.2 in acetone).(12) The **ammonium salt** was prepared, m. p. 100–109°; $[\alpha]^{31}D$ +6.9° (*c*, 1.58 in aqueous ammonia).

Diphenylformamidine Salts.—Solutions of 0.05 mole of (+)α-methylbutyric acid and an equal number of moles of phenyl isocyanide and either 2-octanone or *p*-methylacetophenone were allowed to stand two months. The excess reagents were removed either by steam distillation or by washing with Skellysolve A. Crystallization from Skellysolve B or methanol gave 0.25–0.31 g. of **(−)diphenylformamidine α-methylbutyrate,** needles, m. p. 127–127.8°, $[\alpha]^{30}D$ −20.4° (*c*, 3.62 in acetone).

Anal. Calcd. for $C_{23}H_{32}N_2O_4$: N, 7.00. Found: N, 7.15.

In an analogous manner the isocyanide, (−)menthoxyacetic acid, and either propiophenone or *p*-methylacetophenone were allowed to stand two months and the excess reagents removed at 0.3 mm. followed by washing with alkali. The products, crystallized from methanol, were **(−)diphenylformamidine menthoxyacetate,** m. p. 146–147°, previously characterized.

A solution of 0.01 mole each of benzoic acid, styrene oxide and phenyl isocyanide gave crystals after one month and the odor of isocyanide had disappeared. Upon adding progressively more ether to the solution four fractions of crystals were obtained. Two additional fractions were obtained from the mother liquor by evaporation and crystallizing from Skellysolve A. The first two fractions, m. p. 169–173°, 0.54 g. were recrystallized from benzene to yield **diphenylformamidine benzoate,** m. p. 172.5–174.0°, lit.,(13) 175–176°.

Anal. Calcd. for $C_{27}H_{24}N_2O_4$: C, 73.61; H, 5.49. Found: C, 74.24; H, 5.55.

Benzanilide.—The last two fractions mentioned in the previous experiment, 0.23 g., were crystallized from ether, m. p. 161.8–162.8°. Benzanilide melts at 163°.

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62. Found: C, 79.32; H, 5.75.

The unidentified compound, m. p. 161°, reported by Passerini(14) to be a by-product of the reaction of benzaldehyde, benzoic acid, and phenyl isocyanide may well have been this.

(+)α-Methylbutyranilide.—A mixture of 0.05 mole each of acetophenone, m. p. 19.8°, and phenyl isocyanide and 0.06 mole of (+)α-methylbutyric acid was diluted with 15 ml. of ether and allowed to stand fifteen days. The ether was evaporated and after another twenty days the mixture was steam distilled. The viscous residue crystallized in a month. The whole mass was crystallized fractionally from methanol yielding 40 mg. of **(−)diphenylformamidine α-methylbutyrate,** m. p. 127–127.8°.

The filtrates gave large needles after a week. These were recrystallized from Skellysolve A to yield 42 mg. of α-methylbutyranilide, m. p. 95.0–95.5°; $[\alpha]^{30}D$ +38.3° (*c*, 1.28 in acetone).(15)

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.58; H, 8.47. Found: C, 74.45; H, 8.81.

Acknowledgment.—We wish to thank Mr. David Stanonis for completing the purification and characterization of most of the diphenylformamidine salts.

Summary

1. The Passerini reaction has been used to introduce the resolving agent, an optically active acid, into the α-hydroxyanilide molecule.

2. The reaction is subject to asymmetric induction and an excess of one diastereomeric form of the anilide ester is produced.

3. The subsequent hydrolysis of the anilide ester completes a sequence which, in the Marckwald sense, may be considered as an asymmetric synthesis to produce an active α-hydroxy acid or its anilide.

4. Further limitations to the Passerini reaction have been discovered.

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(11) This rotation is cited to show that the anilide is not racemized by the reagents. It is to be noted that no significance should be attached to the fact that the value is higher than those previously encountered because of the lower concentration used.

(12) From the data of Maehlmann, *Arb. Pharm. Inst. Univ. Berlin*, **11**, 107 (1914); *Chem. Zentr.*, **86**, II, 1178 (1915), on the (−) acid obtained by strychnine resolution α −9.4 may be calculated, alcohol solution.

(13) Passerini, *Gazz. chim. ital.*, **52**, II, 250 (1922).

(14) Passerini, *Gazz. chim. ital.*, **51**, II, 181 (1921).

(15) The optically impure compound is reported, m. p. 95–96°; α +10.5°, by Guye and Babel, *Chem. Zentr.*, **70**, I, 467 (1899).