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The Synthesis of Optically Active C-Methyl-2-oxoheptamethylenimines and C-Methyl-7-aminoheptanoic Acids

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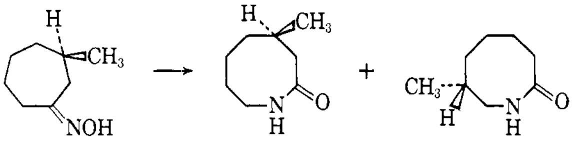
ABSTRACT: Three new optically active C-methyl-2-oxoheptamethylenimines were prepared by Beckmann rearrangement of (+)-3-methylcycloheptanone oxime and (−)-4-methylcycloheptanone oxime. Four new optically active C-methyl-7-aminoheptanoic acids were also prepared by hydrolyses of the corresponding 2-oxoheptamethylenimines and by independent synthesis from (+)-citronellic acid.

The previously unknown optically active 4-methyl- and 7-methyl-2-oxoheptamethylenimines (II and III) were obtained by Beckmann rearrangement of (+)-3-methylcycloheptanone oxime (I). Optically active 5-methyl-2-oxoheptamethylenimine (V) was also obtained in the same manner from (−)-4-methylcycloheptanone oxime (IV), but in somewhat less isomeric purity. Optically active 3-methyl- and 6-methyl-7-aminoheptanoic acids were prepared by the hydrolyses of the corresponding lactams (II and III).

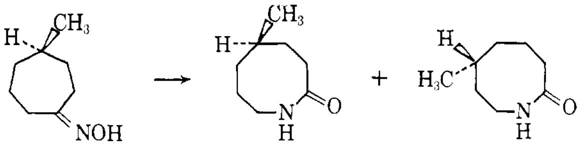


I II III

(−)-7-Amino-4-methylheptanoic acid and (+)-7-amino-5-methylheptanoic acid were also prepared from (+)-citronellic acid (3,7-dimethyl-6-octenoic acid).

(+)-3-Methylcycloheptanone and (−)-4-methylcycloheptanone were obtained by diazomethane ring enlargement of (+)-3-methylcyclohexanone as reported by us previously.[2] (+)-3-Methylcycloheptanone [$[\alpha]^{25}_{D}$ +62.6° in methanol) was converted into the oxime (I, $[\alpha]^{25}_{D}$ +39.9°) and the latter was subjected to Beckmann rearrangement in a 1:1 mixture of sulfuric and acetic acids. The crystalline product ($[\alpha]^{25}_{D}$ −15.9°) had a broad melting temperature range, which indicated that the material was an isomeric mixture. The fractional recrystallization of the isomeric lactam mixture (II and III) from heptane–benzene yielded hexagonal crystals which had a melting point of 105.5–106° and $[\alpha]^{25}_{D}$ +27.09° (methanol). The compound was identified as 7-methyl-2-oxoheptamethylenimine (III) from the nmr spectrum of the N-deuterated compound. The methylene protons of the $-CH_2N<$ group exhibited a pair of quadruplets typical for an ABX system at τ 6.68 and 7.08: $|\delta_A - \delta_B| = 24.0$ cps, $J_{AB} = 15.6$ cps, $J_{AX} = 3.8$ cps, $J_{BX} = 5.8$ cps. The results indicate that the asymmetric tertiary carbon which bears a single hydrogen is in the 7 position. This structural assignment was also confirmed, as described later, by the nmr spectrum of the corresponding amino acid obtained by hydrolysis of III.

From the filtrate was isolated the lower melting isomer, 4-methyl-2-oxoheptamethylenimine (II). However, the isomeric purity could not be improved by recrystallization. The compound was subjected to fractional sublimation followed by zone refining. The pure material (II) had a melting point of 70–71° and $[\alpha]^{25}_{D}$ −29.7° (methanol). The nmr spectrum of II appeared to be more complex than that of III and could not be resolved.



IV V VI

(−)-4-Methylcycloheptanone was converted into its oxime (IV, $[\alpha]^{25}_{D}$ −90.9°) and the latter was subjected to Beckmann rearrangement. The lactam mix-

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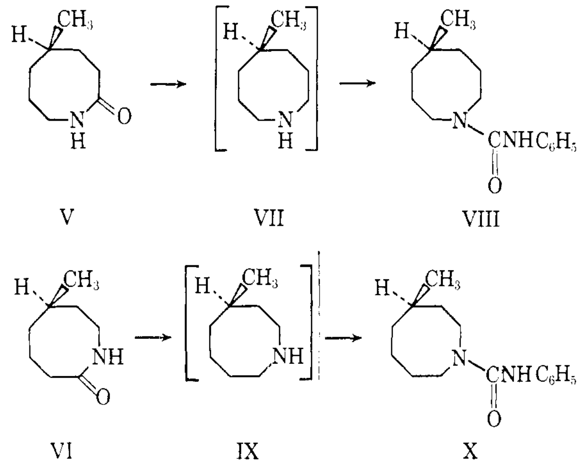
(1) Taken from part of the Ph.D. thesis of T. T., 1966.

(2) C. Djerassi, B. F. Burrows, C. G. Overberger, T. Takekoshi, C. D. Gutsche, and C. T. Chang, *J. Am. Chem. Soc.*, **85**, 949 (1963).

ture obtained was a viscous oil with $[\alpha]^{25}_{D}$ +83.2° (methanol). The material was repeatedly recrystallized from ether–hexane at low temperature to give in 13% yield crystals which had a melting point of 38–40° and $[\alpha]^{25}_{D}$ +81.66°. The isolation of the other isomer was unsuccessful. Since the structural assignment of the crystalline isomer could not be obtained by nmr spectroscopy, the experiment given in Scheme I was carried out.

Scheme I



The reduction of lactams by lithium aluminum hydride generally yields azacycloalkanes in high yield.[3] Optically active 6-methyl-2-oxoheptamethylenimine (VI) was expected to yield optically active 4-methylheptamethylenimine (IX) by this same reaction, whereas optically active 5-methyl-2-oxoheptamethylenimine (V) should yield optically inactive 5-methylheptamethylenimine (VII). In the present work, the imines VII and IX were converted into the corresponding N-carbanilides (VIII and X) to facilitate the handling of the products and to increase the optical rotatory power by the introduction of a carbonyl chromophore.

The crystalline lactam isomer obtined by low-temperature recrystallization from ether–hexane was allowed to react with lithium aluminum hydride. The product, methylheptamethylenimine, was isolated as a solid hydrochloride: mp 145–146.5°; $[\alpha]^{25}_{D}$ -0.2 ± 0.1° (water). The imine salt was converted into its N-carbanilido derivative: mp 126–128°; $[\alpha]^{25}_{D}$ -0.85 ± 0.2°.

The lactam recovered from the combined filtrates of the low-temperature recrystallization, expected to be a mixture of the 4-methyl and 5-methyl isomers (V and VI), was also reduced to the corresponding methylheptamethylenimine. The hydrochloric acid salt had a melting point of 101–105° and $[\alpha]^{25}_{D}$ +2.31° (water). The N-carbanilido derivative had a melting point of 120–122° and $[\alpha]^{25}_{D}$ −14.92°.

From the above results, the lactam (mp 38–40°) isolated by means of low-temperature recrystallization from ether–hexane was found to be (+)-5-methyl-2-oxoheptamethylenimine (V), although the isomeric purity of this material did not seem to be very high.

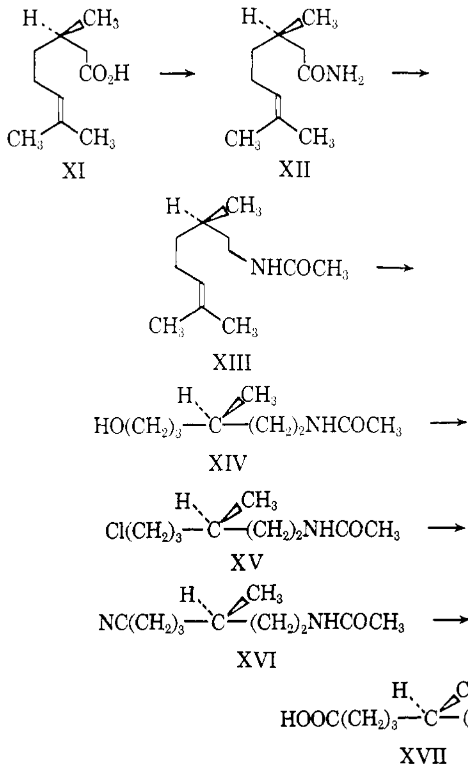
Optically active C-methyl-7-aminoheptanoic acids were prepared by the hydrolyses of the corresponding lactams or by independent synthesis from (+)-citronellic acid.

The hydrolysis of 7-methyl-2-oxoheptamethylenimine (III) with hydrochloric acid yielded (+)-7-amino-6-methylheptanoic acid hydrochloride: mp 168.5–169°; $[\alpha]^{25}_{D}$ +8.81° (water). The aqueous solution of the hydrochloride was treated with Amberlite IR45[4] to obtain (+)-7-amino-6-methylheptanoic acid: mp 156.5–157°; $[\alpha]^{25}_{D}$ +7.78° (water). The nmr spectrum of the amino acid was measured in deuterium oxide. The magnetic nonequivalence of the C-7 methylene protons was clearly seen as a quadruplet: δ_A 2.89 ppm, δ_B 2.85 ppm, $\delta_A - \delta_B = 2.6$ cps; $J_{AX} \simeq J_{BX} = 6.4$ cps. The result was consistent with the structure assignment of the parent lactam (III).

(−)-4-Methyl-2-oxoheptamethylenimine (II) was hydrolyzed to (+)-7-amino-3-methylheptanoic acid hydrochloride, $[\alpha]^{25}_{D}$ +8.22° (water), and the latter was converted into the free amino acid, $[\alpha]^{25}_{D}$ +10.31° (water). The triplet at τ 7.03 in the nmr spectrum of this acid taken in deuterium oxide was assigned to the C-7 methylene protons. The result was also consistent with the structure of the parent lactam (II).

Since (+)-5-methyl- and (−)-6-methyl-2-oxoheptamethylenimines (V and VI) could not be isolated in satisfactory isomeric purity for our purpose,[5] the corresponding methyl-7-aminoheptanoic acids were prepared from (+)-citronellic acid (XI) according to Scheme II.

Scheme II



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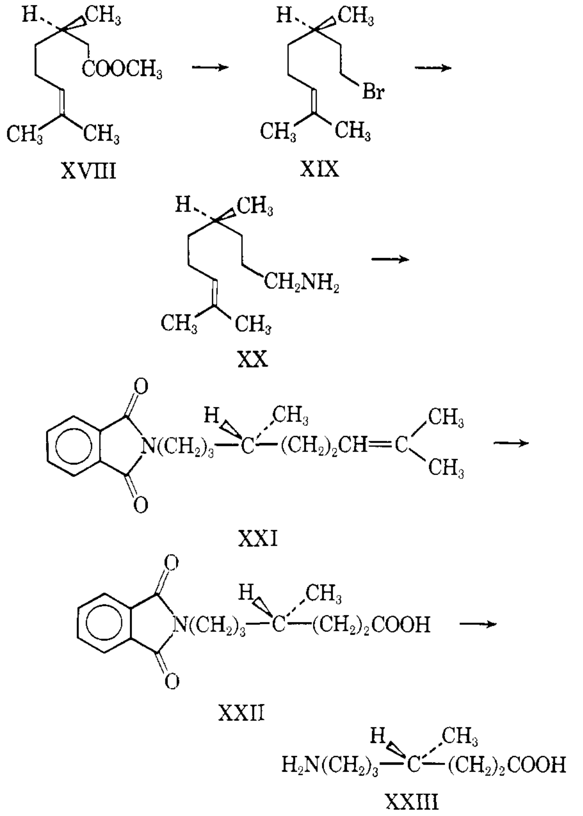
(3) L. Ruzicka, M. Kobelt, O. Hueflinger, and V. Prelog, *Helv. Chim. Acta*, 32, 545 (1949).

(4) C. Y. Meyers and L. E. Miller, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N.Y., 1963, p 39.

(5) C. G. Overberger and T. Takekoshi, *Macromolecules*, 1, 7 (1968).

Optically pure (+)-citronellic acid (XI, $[\alpha]^{25}_{\mathrm{D}}$ +10.79°) was prepared from (+)-pulegone by the procedure of Lukes.[6] Citronellic acid was converted into (+)-citronellamide (XII, 3,7-dimethyl-6-octenamide, $[\alpha]^{25}_{\mathrm{D}}$ +8.86°) according to the procedure of Guthrie and Rabjohn.[7] (−)-N-Citronellylacetamide (XIII, $[\alpha]^{25}_{\mathrm{D}}$ −7.80°) was obtained from citronellamide (XII) by lithium aluminum hydride reduction and subsequent acetylation. Amide XIII was subjected to reductive ozonolysis to give (+)-6-acetamido-4-methylhexanol (XIV, $[\alpha]^{25}_{\mathrm{D}}$ +0.40°). The latter was converted into (+)-7-acetamido-5-methylheptanonitrile (XVI, $[\alpha]^{25}_{\mathrm{D}}$ +3.91°) *via* (+)-6-acetamido-4-methylhexyl chloride (XV, $[\alpha]^{25}_{\mathrm{D}}$ +2.44°). Finally, (+)-7-amino-5-methylheptanoic acid (XVII, $[\alpha]^{25}_{\mathrm{D}}$ +1.89°) was obtained by the hydrolysis of the nitrile (XVI) according to Scheme III.

SCHEME III



Optically active (+)-methyl citronellate (XVIII, $[\alpha]^{25}_{\mathrm{D}}$ +7.39°) was converted into (−)-citronellyl bromide (XIX, $[\alpha]^{25}_{\mathrm{D}}$ −4.85°) according to Lukes.[6] (−)-4,8-Dimethyl-7-nonenylamine (XX, $[\alpha]^{25}_{\mathrm{D}}$ −5.04°) was prepared by the reaction of bromide XIX with sodium cyanide followed by lithium aluminum hydride reduction. Amine XX was converted into the phthalimido derivative (XXI, $[\alpha]^{25}_{\mathrm{D}}$ −7.94°) and the latter was subjected to oxidative ozonolysis to yield (−)-7-phthalimido-4-methylheptanoic acid (XXII, $[\alpha]^{25}_{\mathrm{D}}$ −3.51°). The phthalimido acid (XXII) was hydrolyzed to form (−)-7-amino-4-methylheptanoic acid (XXIII, $[\alpha]^{25}_{\mathrm{D}}$ −2.99°).

Experimental Section

(*R*)-(+)-3-Methylcycloheptanone Oxime (I). A mixture of (+)-3-methylcycloheptanone[2] (7.98 g, 0.0632 mole; n^{25}_{D} 1.4547; $[\alpha]^{25}_{\mathrm{D}}$ +62.6° (*c* 3.22, methanol)), hydroxylamine hydrochloride (4.39 g, 0.0632 mole), and water (20 ml) was magnetically stirred to form a fine dispersion. To this dispersion was added sodium carbonate (3.35 g) and the mixture was stirred overnight at room temperature. The product was extracted with ether; the ether extract was dried and distilled to give 7.95 g (89.1%) of the oxime (I): bp 80–81° (0.5 mm); $[\alpha]^{25}_{700}$ +31.1°, $[\alpha]^{25}_{589}$ +39.9°, $[\alpha]^{25}_{500}$ +59.7°, and $[\alpha]^{25}_{400}$ +108.8° (*c* 2.80, methanol).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.89; H, 10.71; N, 9.77.

(*R*)-(−)-4-Methylcycloheptanone Oxime (IV). (−)-4-Methylcycloheptanone[2] (9.5 g, 0.0754 mole; n^{25}_{D} 1.4555; $[\alpha]^{25}_{\mathrm{D}}$ −136.5° (*c*, 2.23 methanol)) was converted into (−)-4-methylcycloheptanone oxime (IV) in the same manner as described for the 3-methyl isomer: yield, 9.30 g (87.4%); bp 85–86° (0.7 mm); $[\alpha]^{25}_{700}$ −78.7°, $[\alpha]^{25}_{589}$ −90.9°, $[\alpha]^{25}_{500}$ −132.3°, and $[\alpha]^{25}_{400}$ −233° (*c* 0.90, methanol).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.89; H, 10.52; N, 9.85.

Beckmann Rearrangement of (+)-3-Methylcycloheptanone Oxime (I). The procedure of Wallach[8] was used. A mixture of (+)-3-methylcycloheptanone oxime (I, 7.54 g, 0.0534 mole) and glacial acetic acid (8 ml) was stirred with cooling in an ice bath. To this solution 8 ml of concentrated sulfuric acid was added dropwise at a rate such that the temperature of the solution was maintained below 30°. The ice bath was removed and the reaction flask was carefully heated with a bunsen burner. A vigorous exothermic reaction started when the temperature of the reaction mixture reached 120°. The reaction temperature rose spontaneously without external heating and the acetic acid refluxed. The maximum temperature reached was 160°. After the exotherm had subsided, the flask was further heated at 130° for 10 min. The reaction mixture was cooled in an ice bath and neutralized with a 30% aqueous solution of sodium hydroxide below 25°. The resulting solution was extracted several times with chloroform. The combined chloroform extracts were dried over anhydrous magnesium sulfate and evaporated. The residue was distilled to yield 7.36 g (97.6%) of the lactam mixture (II and III): bp 110–111° (0.4 mm). The lactam solidified on standing at room temperature: mp 65–90°; $[\alpha]^{25}_{700}$ −11.3°, $[\alpha]^{25}_{589}$ −15.9°, $[\alpha]^{25}_{500}$ −22.3°, $[\alpha]^{25}_{400}$ −31.9°, and $[\alpha]^{25}_{380}$ −34.0° (*c* 1.29, methanol).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.09; H, 10.66; N, 9.98.

Separation of (*R*)-(+)-7-Methyl-2-oxoheptamethylenimine (III). The mixture of 4-methyl- and 7-methyl-2-oxoheptamethylenimines (II and III, 6.715 g) was recrystallized from a 2:5 mixture of benzene and heptane. After five consecutive recrystallizations from the same solvent, lactam III was isolated as large hexagonal plates. Further recrystallization of the material did not increase its optical rotatory power. Lactam III weighed 1.039 g (15.5%) and possessed the following properties: mp 105.5–106°; $[\alpha]^{25}_{589}$ +27.09°, $[\alpha]^{25}_{500}$ +42.1°, $[\alpha]^{25}_{450}$ +53.6°, $[\alpha]^{25}_{400}$ +77.1°, and $[\alpha]^{25}_{350}$ +117.1° (*c* 1.97, methanol).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.22; H, 10.73; N, 10.00.

Separation of (*R*)-(−)-4-Methyl-2-oxoheptamethylenimine (II). The filtrate from the first recrystallization of the above lactam mixture was evaporated to dryness. The residue (3.56 g) was sublimed at 58–60° and 10^{-4} to 10^{-5} mm. The first fraction (3.34 g) melted at 63–66° and the

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(6) R. Lukes, A. Zabacova, and J. Plesek, *Croat. Chem. Acta*, **29**, 201 (1957).

(7) J. L. Guthrie and N. Rabjohn, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 513.

(8) O. Wallach, *Ann. Chem.*, **309**, 1 (1899).

second fraction (0.19 g) melted at 85–96°. The first fraction was resublimed, leaving behind a small fraction of a higher melting point material. Upon standing at room temperature for a few weeks, the melting point of the sublimate rose from 61.5–63.5° to 69–70°, $[\alpha]^{25}_{D}$ −28.9° (methanol). The compound was further purified by repeated fractional sublimation and zone-melting refining. The final product had a melting point of 70–71° and $[\alpha]^{25}_{D}$ −29.7° (methanol).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.08; H, 10.51; N, 10.19.

Beckmann Rearrangement of (*R*)-(−)-4-Methylcycloheptanone Oxime (IV). (−)-4-Methylcycloheptanone oxime (IV, 8.21 g, 0.0581 mole) was converted into a mixture of 5-methyl- and 6-methyl-2-oxoheptamethylenimines (V and VI) by the same procedure as that employed for (+)-3-methylcycloheptanone oxime (I). The lactam mixture (V and VI) weighed 7.67 g (93.4%): bp 111–112° (0.4 mm); $[\alpha]^{25}_{700}$ +63.8°, $[\alpha]^{25}_{589}$ +83.2°, $[\alpha]^{25}_{500}$ +120.6°, $[\alpha]^{25}_{400}$ +205.7°, and $[\alpha]^{25}_{380}$ +231.7° (*c* 1.75, methanol).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.11; H, 10.60; N, 10.01.

Separation of (*R*)-(+)-5-Methyl-2-oxopheptamethylenimine (V). The mixture of 5-methyl- and 6-methyl-2-oxoheptamethylenimines (V and VI, 7.60 g) was dissolved in a mixture of 5 ml of dry ether and 20 ml of hexane. The solution was cooled in a Dry Ice bath overnight. The crystals were separated from the mother liquor by decantation. The same recrystallization procedure was repeated three additional times to obtain 0.98 g (13.0%) of the lactam (V): mp 38–40°; $[\alpha]^{25}_{600}$ +79.81°, $[\alpha]^{25}_{589}$ +119.6°, $[\alpha]^{25}_{400}$ +200.5°, $[\alpha]^{25}_{350}$ +276° (*c* 1.33, methanol).

5-Methylheptamethylenimine Hydrochloride. (+)-5-Methyl-2-oxoheptamethylenimine (V, 92.3 mg, 0.654 mmole) was dissolved in ether (7 ml) and the solution was added dropwise to a suspension of lithium aluminum hydride (70 mg, 1.84 mmoles) in ether (5 ml). The resulting mixture was stirred at room temperature overnight. Aqueous sodium hydroxide solution (30%) was carefully added to the reaction mixture with strong stirring. The addition was discontinued when a heavy inorganic precipitate had formed. The precipitate was removed by filtration. A dry ethereal hydrogen chloride solution was added dropwise to the filtrate until the precipitation of the amine salt was complete. The amine salt was collected by filtration and washed with ether: yield, 75.1 mg (70.6%). The product was recrystallized from tetrahydrofuran–ether mixture: mp 145–146.5°; $[\alpha]^{25}_{D}$ −0.2 ± 0.1° (*c* 1.50, water).

Anal. Calcd for $C_8H_{18}NCl$: C, 58.70; H, 11.08; N, 8.56. Found: C, 59.16; H, 10.74; N, 8.82.

1-Carbanilido-5-methylheptamethylenimine (VIII). 5-Methylheptamethylenimine hydrochloride (30 mg), sodium carbonate (10 mg), and water (1 ml) were placed in a 10-ml flask and an ethereal solution (3 ml) of phenyl isocyanate (*ca.* 20 mg) was added. The mixture was shaken for 10 min and the ether was evaporated to form a colorless precipitate in the aqueous layer. The precipitate was filtered and washed with water to give 45.0 mg (99%) of the crude carbanilide (VIII). The compound was recrystallized from ethanol–water: mp 126–128°; $[\alpha]^{25}_{D}$ −0.85 ± 0.2° (*c* 1.0, methanol).

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.04; H, 8.84; N, 11.54.

Mixture of 4- and 5-Methylheptamethylenimine Hydrochlorides. The mixture of optically active 5-methyl- and 6-methyl-2-oxoheptamethylenimines (V and VI, 200 mg) was converted into a mixture of 4- and 5-methylheptamethylenimine hydrochlorides by the same procedure as that used for the preparation of 5-methylheptamethylenimine hydrochloride. The hygroscopic product weighed 242 mg (70.2%): mp 101–105°; $[\alpha]^{25}_{D}$ +2.31° (*c* 1.5, water).

Anal. Calcd for $C_8H_{18}NCl$: C, 58.70; H, 11.08; N, 8.56; Cl, 21.66. Found: C, 58.94; H, 10.70; N, 8.53; Cl, 21.71.

Mixture of 4- and 5-Methyl-1-carbanilidoheptamethylenimines (VIII and X). The mixture of 4- and 5-methylheptamethylenimine hydrochlorides (125.7 mg) was treated with phenyl isocyanate in the manner described above to obtain the mixture of VIII and X: yield, 184.4 mg (96.8%). The product was recrystallized from 30% ethanol: mp 120–122°; $[\alpha]^{25}_{589}$ −14.9°, $[\alpha]^{25}_{480}$ −26.62°, $[\alpha]^{25}_{400}$ −46.52°, $[\alpha]^{25}_{380}$ −63.1° (*c* 1.59, methanol).

Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.96; H, 8.86; N, 11.61.

(+)-7-Amino-6-methylheptanoic Acid. (+)-7-Methyl-2-oxoheptamethylenimine (0.173 g, 1.22 mmoles) was dissolved in 2 ml of concentrated hydrochloric acid and the solution was heated to reflux for 24 hr. The mixture was evaporated under vacuum leaving behind colorless crystals of 7-amino-6-methylheptanoic acid hydrochloride: mp 168.5–169°; $[\alpha]^{25}_{D}$ +8.81° (*c* 1.07, water).

Anal. Calcd for $C_8H_{18}NO_2Cl$: C, 49.10; H, 9.27; N, 7.16; Cl, 18.12. Found: C, 49.04; H, 9.38; N, 7.19.

The amino acid hydrochloride was dissolved in 2 ml of water and the solution was passed through a column packed with Amberlite IR45 resin.[4] The material was eluted with 50 ml of water and the eluate was evaporated under vacuum. (+)-7-Amino-6-methylheptanoic acid, obtained as a crystalline residue, was recrystallized from ethanol: yield, 0.1411 g (82%); mp 156.5–157°; $[\alpha]^{25}_{D}$ +7.78° (*c* 1.45, water).

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.47; H, 10.78; N, 9.04.

(+)-7-Amino-3-methylheptanoic Acid. (−)-4-Methyl-2-oxoheptamethylenimine (0.2002 g, 1.417 mmoles) was hydrolyzed as in the case of the 7-methyl isomer. The colorless hydrochloride salt weighed 0.2475 g (89.3%): mp 141–143°; $[\alpha]^{25}_{D}$ +8.22° (*c* 2.11, water).

Anal. Calcd for $C_8H_{18}NO_2Cl$: C, 49.10; H, 9.27; N, 7.16; Cl, 18.12. Found: C, 48.92; H, 9.26; N, 7.12; Cl, 18.18.

The amino acid hydrochloride (0.1814 g, 0.927 mmole) was treated in the same manner as for the previous case to yield 0.1126 g (76.1%) of 7-amino-3-methylheptanoic acid: mp 141–143°; $[\alpha]^{25}_{620}$ +9.52°, $[\alpha]^{25}_{589}$ +10.31°, $[\alpha]^{25}_{550}$ +12.2°, and $[\alpha]^{25}_{450}$ +18.8° (*c* 0.45, water).

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.25; H, 10.82; N, 8.65.

(*R*)-(+)-Citronellic Acid (XI). (+)-Pulegone (546 g, $[\alpha]^{25}_{D}$ +26.45° in carbon tetrachloride) was converted by the modified method of Lukes[6] into (+)-citronellic acid: yield, 318 g (52%); bp 108° (1.0 mm); n^{25}_{D} 1.4540; $[\alpha]^{25}_{D}$ +10.79° (carbon tetrachloride) (lit.[6] bp 112–113° (0.6 mm), n^{20}_{D} +1.4540, $[\alpha]^{20}_{D}$ +8.40° (neat)).

Esterification of (*R*)-(+)-Citronellic Acid. A mixture of citronellic acid (316 g, 1.86 moles), absolute methanol (1500 ml), and concentrated sulfuric acid (1 ml) was heated at 55° for 20 hr. The reaction mixture was cooled and the catalyst was neutralized with a methanol solution of potassium hydroxide. The methanol was removed under vacuum. The residual oil was washed with water, dried with sodium sulfate, and distilled through a 40-cm Podbielniak column. Two fractions were obtained as the products; each was homogeneous by vapor phase chromatography (polyethylene glycol). The first fraction was (+)-methyl citronellate (XVIII): yield, 308 g (90.1%); bp 77° (3.6 mm); n^{25}_{D} 1.4402; $[\alpha]^{25}_{D}$ +7.39° (*c* 5.95, methanol) (lit. bp 78° (3.0 mm), n^{20}_{D} 1.4415, $[\alpha]^{20}_{D}$ +5.45° (neat);[6] bp 145° (70 mm), n^{28}_{D} 1.4386, $[\alpha]^{25}_{D}$ +4.1° (neat)[9]). Based upon the elemental analysis, the infrared spectrum, and the absence of unsaturation, the second fraction was identified as (+)-methyl 3,4-dimethyl-7-methoxyoctanoate, the methanol

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(9) C. Djerassi and G. W. Krakower, *J. Am. Chem. Soc.*, **81**, 237 (1959).

adduct of the unsaturated ester:[10] yield, 18.0 g (4.5%); bp 84° (1.4 mm); $n^{25}{}_{D}$ 1.4327; $[\alpha]^{25}{}_{D}$ 7.69° (*c* 2.60, methanol).

Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18; OCH_3, 28.70. Found: C, 66.52; H, 11.56; OCH_3, 28.74.

(*R*)-(+)-Citronellamide (XII). A mixture of optically pure (*R*)-(+)-citronellic acid (120 g, 0.705 mole; obtained by hydrolysis of the methyl ester (XVIII)) and urea (90 g, 1.50 moles) was heated at 170 ± 5° for 4 hr. After the reaction mixture had cooled to 120°, 600 ml of 5% aqueous sodium carbonate solution was added. The reaction mixture was cooled to room temperature and extracted with ether. The ether extract was washed with water, dried, and evaporated. The resulting oily residue was dissolved in 200 ml of warm heptane and the solution allowed to stand to precipitate the crystalline amide (XII): yield, 63.0 g (52.7%); mp 77–81°. The crude material was recrystallized from heptane: mp 76–78°; $[\alpha]^{25}{}_{D}$ +8.86° (*c* 2.27, methanol).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 70.87; H, 11.28; N, 8.44.

(*R*)-(−)-3,7-Dimethyl-6-octenylamine (Citronellylamine). A solution of the amide (XII; 66.5 g, 0.393 mole) in ether (400 ml) was added dropwise to a stirred dispersion of lithium aluminum hydride (38 g, 1.0 mole) in ether (500 ml). After the addition, the reaction mixture was stirred for 4 hr at room temperature. The excess hydride was decomposed by careful addition of 39 ml of water and 44% aqueous sodium hydroxide solution was added dropwise with vigorous stirring until a heavy inorganic precipitate formed. The reaction mixture was filtered and the precipitate was washed with ether. The combined filtrate and wash were distilled through a 20-cm Podbielniak column, yielding 51.44 g (84.3%) of citronellylamine: bp 67–68° (3.2 mm); $n^{25}{}_{D}$ 1.4531; $[\alpha]^{25}{}_{D}$ −0.62° (*c* 4.19, methanol).

Anal. Calcd for $C_{10}H_{21}N$: C, 77.34; H, 13.63; N, 9.02. Found: C, 77.26; H, 13.78; N, 9.27

(*R*)-(−)-8-Acetamido-2,6-dimethyloctene-2 (XIII, N-Citronellylacetamide). A mixture of (−)-3,7-dimethyl-6-octenylamine (38.14 g, 0.246 mole), sodium hyrdoxide (11.0 g), ether (100 ml), and water (50 ml) was vigorously stirred and cooled in an ice bath. To this solution acetic anhydride (27.6 g, 0.27 mole) was added dropwise. After the addition, the solution was stirred for 1 hr at room temperature. The organic and aqueous layers were separated and the latter was extracted with ether. The organic layer and ether extracts were combined, dried, and distilled through a 20-cm Podbielniak column, yielding 47.83 g (98.7%) of the amide (XIII): bp 107° (0.1 mm); $n^{25}{}_{D}$ 1.4681; $[\alpha]^{25}{}_{D}$ −7.84° (*c* 4.07, methanol), homogeneous by vpc (silicone grease).

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 73.10; H, 11.95; N, 7.34.

(*R*)-(+)-6-Acetamido-4-methylhexanol (XIV). A mixture of the amide (XIII, 14.29 g, 0.0724 mole) and 40 ml of methanol was saturated with ozone at Dry Ice–acetone temperature. Sodium borohydride (8.5 g, 0.55 mole) was carefully added in portions with stirring to the above ozonide solution at −40 ± 10°. After the addition, the reaction mixture was stirred and slowly warmed up. A vigorous decomposition of the excess hydride occurred at around −20 to 0° and cooling was necessary to control the reaction. The reaction mixture was allowed to stand at room temperature for 2 hr and the methanol was removed under vacuum. The viscous residue was added dropwise with stirring to a solution of 35 g of sulfuric acid in 100 ml of water at −15 to −20°. The reaction mixture was filtered and the precipitate was washed with ether. The combined filtrate and the washes were made slightly basic by the addition of 10 *N* sodium hydroxide solution and the resulting solution was continuously extracted with ether for 2 days. The extract was distilled through a 15-cm Podbielniak column to yield 9.35 g (74.5%) of the alcohol (XIV): bp 148° (0.2 mm); $n^{25}{}_{D}$ 1.4725; $[\alpha]^{25}{}_{D}$ +0.40° (*c* 3.83, methanol).

Anal. Calcd for $C_9H_{19}NO_2$: C, 62.38; H, 11.06; N, 8.08. Found: C, 62.59; H, 11.01; N, 8.16.

(*R*)-(+)-6-Acetamido-4-methylhexyl Chloride (XV). A mixture of the alcohol (XIV, 11.8 g, 0.0681 mole) and concentrated hydrochloric acid (20 ml) was heated to reflux for 2 hr. The solution was evaporated under vacuum to leave a viscous residue. The residue was dissolved in 10 ml of concentrated hydrochloric acid and the solution was heated at 100° for 1 hr. The reaction mixture was evaporated under vacuum to yield a viscous oil, which was redissolved in 15 ml of water. A mixture of the above solution, 20 ml of chloroform, and 20 ml of acetic anhydride was stirred at −5 to −10° and a 40% aqueous sodium hydroxide solution was added dropwise until the reaction mixture turned basic to litmus. The organic layer was separated and the aqueous layer wax extracted with three portions of 20 ml of chloroform. The organic layer and chloroform extracts were combined, dried over magnesium sulfate, and distilled, yielding 6.39 g (49.0%) of the chloride (XV): bp 122–123° (0.15 mm); $n^{25}{}_{D}$ 1.4727; $[\alpha]^{25}{}_{D}$ +2.44° (*c* 2.29, methanol).

Anal. Calcd for $C_9H_{18}NOCl$: C, 56.38; H, 9.46; N, 7.31; Cl, 18.49. Found: C, 56.24; H, 9.53; N, 7.49; Cl, 18.25.

(*R*)-(+)-7-Acetamido-5-methylheptanonitrile (XVI). A mixture of the chloride (XV, 6.39 g, 0.0334 mole), sodium cyanide (4.0 g, 0.0816 mole), and dimethylformamide (15 ml) was heated to 90° and stirred overnight. The solvent was removed under vacuum and 20 ml of chloroform was added to the residue. The solution was filtered and the precipitate was washed with chloroform. The combined chloroform solutions were washed with water, dried with sodium sulfate, and distilled to yield 5.62 g (92.5%) of the nitrile (XVI): $n^{25}{}_{D}$ 1.4682; $[\alpha]^{25}{}_{D}$ +3.91° (*c* 3.11, methanol), homogeneous by vpc (polypropylene glycol).

Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.89; H, 9.96; N, 15.37. Found: C, 65.85; H, 10.12; N, 15.54.

(*R*)-(+)-7-Amino-5-methylheptanoic Acid (XVII). A mixture of the nitrile (XVI, 9.31 g, 0.0511 mole) and concentrated hydrochloric acid (25 ml) was heated on a steam bath for 0.5 hr and then refluxed for 6 hr. The reaction mixture was evaporated under vacuum to dryness, the residue was dissolved in 20 ml of isopropyl alcohol, and the solution was filtered to remove ammonium chloride. The filtrate was evaporated to dryness to yield solid 7-amino-5-methylheptanoic acid hydrochloride. Since the material was hygroscopic it was converted into the hydrobromide salt to facilitate handling. The crude hydrochloride was dissolved in 20 ml of water and the solution was treated with an Amberlite IR45 column. The eluate was evaporated and the residue was dissolved in 20 ml of concentrated hydrobromic acid. 7-Amino-5-methylheptanoic acid hydrobromide was obtained by evaporation of the acid solution as a brownish solid; yield, 10.40 g (84.8%); mp 100–103°. The material was recrystallized three times from tetrahydrofuran: yield, 6.10 g (49.7%); mp 107–108°; $[\alpha]^{25}{}_{D}$ +1.34°; $[\alpha]^{25}{}_{460}$ +2.60°, $[\alpha]^{25}{}_{400}$ +3.49°.

Anal. Calcd for $C_8H_{18}NO_2$: C, 40.01; H, 7.56; N, 5.83; Br, 33.28. Found: C, 39.82; H, 7.68; N, 5.97; Br, 33.49.

An aqueous solution of (+)-7-amino-5-methylheptanoic acid hydrobromide (2.209 g, 0.092 mole) was treated with an Amberlite IR45 column. The material was eluted with 200 ml of water and the eluate was evaporated under vacuum to obtain colorless crystals of the amino acid (XVII): yield, 1.473 g (97.9%); mp 154–155°; $[\alpha]^{25}{}_{D}$ +1.89°; $[\alpha]^{25}{}_{450}$ +3.50° (*c* 3.66, water).

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(10) The increased catalyst concentration and the prolonged reaction time increased the yield of methyl 3,7-dimethyl-7-methoxyoctanoate. The compound eliminated 1 equiv mole of methanol to form methyl citronellate by heating with a catalytic amount of *p*-toluenesulfonic acid.

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.25; H, 10.94; N, 8.94.

(*R*)-(+)-Citronellol. (*R*)-(+)-Citronellol was prepared according to the method of Lukes.[6] From 128 g (0.696 mole) of methyl citronellate, 105 g (96.8%) of (+)-citronellol was obtained: bp 90° (2.5 mm); $[\alpha]^{25}_{D}$ +4.76° (*c* 4.83, methanol), homogeneous by vpc (polypropylene glycol) (lit.[6] bp 110° (10 mm), $[\alpha]^{25}_{D}$ +5.37° (neat)).

(*R*)-(−)-Citronellyl bromide (XIX) was prepared from (+)-citronellol (59.4 g, 0.494 mole) according to the procedure of Lukes:[6] yield, 39.4 g (47.3%); n^{25}_{D} 1.4714; $[\alpha]^{25}_{D}$ −4.85° (*c* 1.67, methanol), homogeneous by vpc (polypropylene glycol) (lit.[6] $[\alpha]^{20}_{D}$ −6.93° (neat)).

(*R*)-(+)-4,8-Dimethyl-7-nonenonitrile. A mixture of the bromide (XIX, 37.85 g, 0.173 mole), pulverized sodium cyanide (20 g, 0.408 mole), and dimethylformamide (50 ml) was heated with stirring at 90° for 20 hr. After cooling, the precipitate was removed by filtration and the filtrate was condensed by vacuum distillation. The residual oil was dissolved in 50 ml of ether. The solution was washed with water, dried with sodium sulfate, and distilled, yielding 23.5 g (82.9%) of (*R*)-(+)-4,8-dimethyl-7-nonenonitrile: bp 82° (1.7 mm); n^{25}_{D} 1.4498; $[\alpha]^{25}_{D}$ +6.58° (*c* 3.15, methanol), homogeneous by vpc (polypropylene glycol).

Anal. Calcd for $C_{11}H_{19}N$: C, 79.93; H, 11.59; N, 8.48. Found: C, 79.75; H, 11.50; N, 8.55.

(*R*)-(−)-4,8-Dimethyl-7-nonenylamine (XX). (*R*)-(+)-4,8-Dimethyl-7-nonenonitrile (20.6 g, 0.125 mole) was dissolved in ether (50 ml) and the solution was added dropwise with stirring to a suspension of lithium aluminum hydride (10 g, 0.264 mole) in ether (200 ml). The reaction mixture was stirred at 30–35° for 20 hr. The excess hydride was decomposed by the careful addition of 10 ml of water and 20 *N* aqueous sodium hydroxide solution was added dropwise until a heavy inorganic precipitate was formed. The solution was filtered and the precipitate was washed with ether. The filtrate and wash were combined, dried with potassium hydroxide pellets, and distilled to yield 19.28 g (91.4%) of the amine (XX): bp 77° (2.7 mm); n^{25}_{D} 1.4541; $[\alpha]^{25}_{D}$ −5.04° (methanol). The product was homogeneous by vpc (polypropylene oxide).

Anal. Calcd for $C_{11}H_{23}N$: C, 78.03; H, 13.69; N, 8.27. Found: C, 77.95; H, 13.61; N, 8.42.

(*R*)-(−)-9-Phthalimido-2,6-dimethyl-2-nonene (XXI). Phthalic anhydride (12.4 g, 0.0837 mole) was added in portions to a solution of the amine (XX, 14.17 g, 0.0837 mole). After the spontaneous exothermic reaction had subsided the solution was heated to reflux for 20 min and the water formed was continuously removed by distillation. The solvent was evaporated and the residue was distilled through a 20-cm Podbielniak column to yield 24.24 g (97%) of the phthalimide (XXI): bp 146° (0.1 mm); n^{25}_{D} 1.5294; $[\alpha]^{25}_{D}$ −7.94° (*c* 3.83, methanol).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.15; H, 8.37; N, 4.81.

Ozonolysis of (*R*)-(−)-9-Phthalimido-2,6-dimethyl-2-nonene (XXI). The solution of the phthalimide (XXI, 24.2 g, 0.0808 mole) in ethyl acetate (60 ml) was ozonized at Dry Ice–acetone temperature. The solvent was removed from the reaction mixture below 0° under vacuum and the viscous residue was dissolved in a mixture of glacial acetic acid (400 ml) and 30% hydrogen peroxide (20 ml). The solution was allowed to stand at room temperature for 3 days. The solvent was removed below room temperature under vacuum and the residual oil was dissolved in a mixture of benzene (150 ml) and ether (100 ml). The solution was shaken with a sodium sulfite solution to decompose the residual peroxides and the organic layer was extracted five times with 5% aqueous sodium carbonate solution. The combined aqueous extracts were acidified with dilute sulfuric acid and extracted with ether. Evaporation of the ether extract yielded 2.81 g (12.0%) of the crude product, 7-phthalimido-4-methylheptanoic acid (XXII).

The organic layer of the above carbonate extraction was evaporated under vacuum leaving a viscous oil (20.4 g). The infrared spectrum of this material indicated it was 7-phthalimido-4-methylheptanal. Part of the crude aldehyde was converted by the standard procedure into the 2,4-dinitrophenylhydrazone, mp 170–171°.

Anal. Calcd for $C_{22}H_{23}N_5O_6$: C, 58.27; H, 5.11; N, 15.45. Found: C, 58.37; H, 5.31; N, 15.49.

(*S*)-(−)-7-Phthalimido-4-methylheptanoic Acid (XXII). To a mixture of the crude 7-phthalimido-4-methylheptanal (20.0 g, 0.0732 mole), acetone (200 ml), and water (200 ml), potassium permanganate (7.7 g, 0.0487 mole) was added in portions with stirring. During the addition, the reaction temperature was maintained below room temperature and carbon dioxide was bubbled in the reaction mixture. After the permanganate color had disappeared, the solution was filtered and the precipitate was washed with 20 ml of acetone and then with 50 ml of 5% sodium carbonate solution. The acetone was evaporated from the combined filtrate and wash and the remaining aqueous solution was extracted with ether. The aqueous layer was acidified with dilute sulfuric acid and extracted a second time with ether. The second ether extract was dried and distilled to yield 15.0 g (70.8%) of the acid (XXII): bp 206° (0.2 mm); mp 49–51°; n^{25}_{D} 1.5438; $[\alpha]^{25}_{D}$ −3.51° (*c* 5.5, methanol).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.51; H, 6.50; N, 5.02.

(*S*)-(−)-7-Amino-4-methylheptanoic Acid (XXIII). Hydrazine hydrate (2.3 g, 0.046 mole) was added dropwise to a stirred solution of the acid (XXII, 12.72 g, 0.044 mole) in absolute ethanol (100 ml). After the exothermic reaction had subsided, the solution was heated to reflux for 5 hr and the reaction mixture was evaporated to dryness under vacuum. The residue was taken up in 50 ml of water and the solution was filtered. The filtrate was evaporated to leave an oily residue. The residue was dissolved in 10 ml of concentrated hydrochloric acid and the solution heated at 90 ± 10° overnight. The aqueous layer was then evaporated under vacuum to yield a viscous oil. The material was dissolved in 20 ml of water and the solution treated with an Amberlite IR45 column. The column was eluted with 200 ml of water and the eluate was evaporated under vacuum. The residual oil was redissolved in 3 ml of concentrated hydrochloric acid and the solution was evaporated under vacuum to dryness. The brown solid residue was recrystallized twice from a 5:1 mixture of tetrahydrofuran and isopropyl alcohol to obtain colorless crystals of (*S*)-(−)-7-amino-4-methylheptanoic acid hydrochloride: yield, 3.20 g (37.2%); mp 133°; $[\alpha]^{25}_{589}$ −0.02° ± 0.02°, $[\alpha]^{25}_{460}$ +0.52° (*c* 4.36, water).

Anal. Calcd for $C_8H_{18}NO_2Cl$: C, 49.10; H, 9.27; N, 7.16; Cl, 18.12. Found: C, 49.21; H, 9.24; N, 7.37; Cl, 18.02.

A solution of (−)-7-amino-4-methylheptanoic acid hydrochloride (1.638 g, 8.37 mmoles) in 10 ml of water was treated with an Amberlite IR45 column in the manner described previously. The aqueous eluate was evaporated to dryness and the solid residue was recrystallized from isopropyl alcohol to obtain colorless crystals of the amino acid (XXIII): yield, 0.940 g (70.5%); mp 137–137.5°; $[\alpha]^{25}_{620}$ −2.80°, $[\alpha]^{25}_{589}$ −2.99°, $[\alpha]^{25}_{550}$ −3.38°, $[\alpha]^{25}_{500}$ −4.10°, $[\alpha]^{25}_{450}$ −5.34°, and $[\alpha]^{25}_{400}$ −6.97° (*c* 3.266, water).

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.36; H, 10.73; N, 8.79.

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