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PERMANGANATE OXIDATION OF (−)-CITRONELLONITRILE

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The oxidation of (−)-citronellonitrile (I), obtained by dehydration of citronellal oxime, should afford optically active 4-methyl-5-cyanopentanoic acid (II). The use of II as a precursor in electrosyntheses would constitute a method of extending the carbon chain of fatty acids by an isoprene unit in a manner analogous to that envisaged by Linstead and co-workers (1) in their use of (±)-ethyl hydrogen β-methyladipate. It is known that the half nitriles of dicarboxylic acids are amenable to Kolbe coupling (2). Furthermore, the products obtained would be of known stereochemical configuration.

Ozonolysis of I (*via* decomposition of the ozonide in hydrogen peroxide-acetic acid) was unsuccessful in our hands; the product resinified in an attempt at distillation. We therefore resorted to the use of potassium permanganate in acetone solution, an oxidizing medium which has been employed successfully in the cleavage of oleonitrile to 8-cyanoöctanoic acid (3). After numerous experiments in which conditions of temperature, rate, and order of addition of reactants were varied, a procedure was adopted which seemed to give consistent results with regard to yield and appearance of product material. Fractional distillation of this material afforded a variety of identifiable compounds in addition to other products the identity of which was not established.

DISCUSSION

The number and variety of products obtained in the permanganate oxidation of I are the result, no doubt, of the particular reaction conditions employed, which of necessity were somewhat drastic. Although the desired product, (+)-II, was in fact isolated, the yield (less than one per cent) militates against use of this method as a substitute procedure for the synthesis of naturally occurring optically active compounds (*vide supra*). There is strong evidence that oxidative degradation took place along the side chain bearing the carboxyl group, one carbon at a time. The major product of the oxidation was β-methylglutarimide. This substance, which was formed *only during distillation*, may be regarded as the product of a thermal rearrangement of precursor 3-methyl-4-cyanobutanoic acid, which itself is not isolable. Established precedents exist for such a transformation (4–6).

Isolation of a small quantity of feebly levorotatory methylsuccinic acid gives credence to the supposition that this acid was derived by hydrolysis from 2-methyl-3-cyanopropanoic acid, which was not itself identified in the product mixture. Oxidation of 3-methyl-4-cyanobutanoic acid along the side chain bearing the cyano group would have yielded (+)-methylsuccinic acid.

The production of (+)-4-methyl-5-carbamidopentanoic acid, independently

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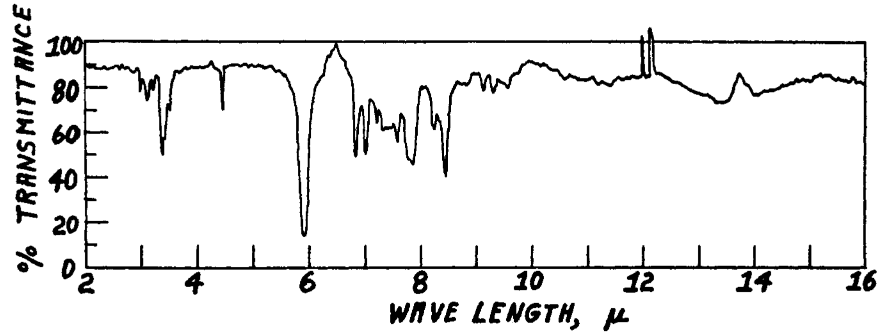

FIG. 1. INFRARED SPECTRUM (5% solution in CCl_4) OF $C_{12}H_{17}N_3O$ (Compound III).

prepared by permanganate oxidation of (+)-citronellamide, is explicable as the result of a partial and perhaps oxidative (7, 8) hydrolysis of (+)-II. The formation of (+)-3-methylcyclopentanone may be rationalized as proceeding *via* a classical cyclization-hydrolysis-decarboxylation of II (9) under the conditions of the reaction and isolation.

Of some interest was a neutral, water-insoluble, optically active oil, $C_{12}H_{17}N_3O$ (III), which was isolated in small yield from the product mixture. The infrared spectrum (Fig. 1) features distinct bands at 5.95 μ (amide carbonyl), 4.43 μ (nitrile), and 3.10 μ (associated —NH); the ultraviolet spectrum shows strong absorption below 225 mμ but virtually complete and undifferentiated transmission above 230 mμ. A Kuhn-Roth determination indicated the presence of two terminal methyl groups and a Van Slyke determination showed the absence of $—NH_2$. The oil gave a positive Baeyer test and failed to form a semicarbazone. Hydrolysis in concentrated hydrochloric acid yielded an oily solid which, after recrystallization, afforded (+)-β-methyladipic acid.

From the information thus gathered, a *tentative* structure may be assigned which has the virtue, at least, of accommodating the accumulated data. The molecular refraction found for the compound,

$$NCCH_2\overset{\overset{CH_3}{|}}{C}HCH_2CH_2CONHCH{=}\overset{\overset{CH_3}{|}}{C}CH_2CN$$

59.92, agrees satisfactorily with that calculated, 60.41, for the tentative proposed structure.

EXPERIMENTAL

Microanalyses by W. Manser (Zürich) and F. Schwarzkopf Labs. (Woodside, N. Y.). A Baird Model B spectrophotometer was employed in the determination of the infrared spectra. In connection with the I.R. and U.V. spectra, the helpful correspondence with Drs. A. Bader, D. R. Howton, and A. Kosak is gratefully acknowledged.

(−)-Citronellonitrile (I). The starting material (Givaudan-Delawanna Inc., N. Y.) was purportedly 85% pure (+)-citronellal with isopulegol the only contaminant. Oximation (10) of this mixture afforded a separation as well, inasmuch as the boiling point of the oxime is well above that of isopulegol. Yields of citronnellal oxime varied from 66 to 88 percent based on an 85% citronellal content in the starting mixture; the product distilled at 129–130° (10 mm.) and had n_D^{25} 1.4707 α_D^{30} −3.98° (*l*, 0.5, homogeneous) [lit. (11) b.p. 135–136° (14 mm.); lit. (12) n_D^{20} 1.4722, d_4^{20} 0.8920, $[\alpha]_D^{20}$ − 9.31°].

The oxime was dehydrated by a modification of the method described by Semmler (12a). To 160 g. (1.57 moles) of acetic anhydride at 100°, contained in a one-liter three-neck flask fitted with three efficient reflux condensers, was added 252 g. (1.49 moles) of citronellal oxime at a rate which permitted maintenance of gentle reflux. After addition was completed, refluxing was continued for ten minutes by means of external heating. The resulting mixture on distillation gave 72 to 86 percent yields of citronellonitrile, b.p. 105–107° (13 mm.), n_D^{25} 1.4468, α_D^{20} −3.85° (*l*, 0.5, homogeneous) [lit. (13) b.p. 104–106° (14 mm.); lit. (11) n_D 1.4545].

Oxidation of (−)-*citronellonitrile.* Preliminary experiments showed that use of the procedure described by Fitzpatrick and Meyers (3) gave 25–35 percent yields of an acidic oil, b.p. 123–125° (1.5 mm.), n_D^{25} 1.4544, α_D^{28} −2.93° (*l*, 0.5, homogeneous) the analytical values of which differed very considerably from those calculated for II: *Neut. Eq.* Calc'd: 141.2; Found: 137.3.

Anal. Calc'd for $C_7H_{11}NO_2$: C, 59.6; H, 7.85; N, 9.95.
Found: C, 55.9; H, 7.09; N, 8.70.

It should also be remarked that later work showed II to be dextrorotatory.

The procedure finally adopted, after a number of other modifications had been explored was the following. (−)-Citronellonitrile (100 g., 0.66 mole) was added dropwise to a vigorously stirred mixture of 500 g. (3.17 moles) of potassium permanganate in 750 ml. of U.S.P. acetone. The time of addition of the nitrile averaged about two hours, and the temperature of the mixture during addition was maintained at 40° to 50° by external cooling. Stirring was continued until the violet color had been discharged (about 18 hours) and 75 ml. of water was added. Filtration and decomposition of the manganese dioxide (454 g. of sodium sulfite, 750 ml. of water, and 125 g. of concentrated sulfuric acid) yielded an oily layer. The aqueous layer was extracted with ether (6 × 100 ml.) and the combined organic layers were stripped of solvent and taken up in sodium carbonate solution. The alkaline layer was extracted with ether and then acidified with dilute sulfuric acid. A pale yellow oil (51 g.) separated. In a series of nine runs the total crude yield from 912 g. of (−)-citronellonitrile was 527g. It was soon discovered that the product was a complex mixture, for on four successive distillations from a simple Claisen distilling flask, each successive distillation being performed on the main fraction of the preceding one, a solid, m.p. 144–145°, persistently separated (Table I).

Main fraction 4 (Table I) then was subjected to fractional distillation under nitrogen through a 42 x 1.3 cm. helix-packed, externally heated (190° at the top) column. The tem-

TABLE I

RESULTS OF PRELIMINARY SUCCESSIVE DISTILLATIONS OF OXIDATION PRODUCT OF CITRONELLONITRILE

Successive Distillation No.	Forerun			Main Fraction			Solid[b] wt., g.	Residue	
	B.p., °C.	Mm.	Wt., g.	Bp., °C.	Mm.	Wt., g.		Description	Wt., g.
1[a]	115	1.4	32.2	105–147	1.6–2.0	341.0	15.0	Tar; rejected	—
2	100–134	1.9–2.2	29.5	123–157	1.3–2.0	264.2	7.8	Oil; crystals on standing	23.0
3	—	—		119–148	1.6–1.9	242.0	0.3	Dark oil	17.5
4	—	—		115–156	1.9–2.8	222.0	7.1	Oil; crystals on standing	12.0

[a] The ice trap contained 50.0 g. of low-boiling fractions not further investigated. [b] M.p. 144–145°; sublimed.

TABLE II

RESULTS OF DISTILLATION OF FRACTION 4, TABLE I

Fraction No.	Boiling Range, °C.	Mm.	Description	Weight, g.
1	81–89	1.3	Colorless liquid	3.0
2	96–109	1.5	Colorless liquid	8.0
3–4	110–130	1.5–2.6	Solid, m.p. 144°	66.0
5–7	106–138	0.75–2.5	Solid-liquid	20.1
8–11	122–146	1.3–1.8	Colorless liquid	37.8
12	139–159	1.3–1.6	Colorless liquid	6.3
Residue			Intractable tar	37.5
Trap distillate			Ketonic-smelling oil	5.0
			Water	3.0

perature of the heating bath never exceeded 260°. The distillation took a total of 35 hours, fractions being taken rather arbitrarily, with regard being taken to width of boiling range and appearance of distillate (Table II).

(+)-*4-Methyl-5-cyanopentanoic acid* (II). Fraction 12 (Table II), which was acidic, was made basic with sodium carbonate (8 g. in 50 ml. of water) and extracted with ether. The ether extracts yielded 1 g. of an oil which was not examined further. Acidification of the aqueous solution effected the separation of a colorless liquid (5.56 g.) distillation of which through a 10 x 0.5 cm. Vigreux column afforded two fractions: (a) 0.32 g., b.p. 116–120° (0.23–25 mm.), n_D^{25} 1.4622, and (b), the desired acid, 2.16 g., b.p. 120–124° (0.23–0.25 mm.), n_D^{25} 1.4559, d_4^{25} 1.068, α_D^{26} +1.51° (*l*, 0.5, homogeneous). *Neut. Eq.* Calc'd: 141.2; Found; 141.5. M_D Calc'd:[2] 35.88; Found: 35.86. The infrared spectrum (chloroform solution) featured the expected carboxyl (2.9 and 5.90 μ) and nitrile (4.45 μ) bands.

Anal. Calc'd for $C_7H_{11}NO_2$: C, 59.6; H, 7.85; N, 9.95.

Found: C, 59.1; H, 7.88; N, 9.85.

Hydrolysis of this compound in hot concentrated hydrochloric acid, followed by extraction with chloroform and evaporation of the solvent, gave a white solid. Recrystallization from carbon tetrachloride afforded needles, m.p. 84.6–85.6°, undepressed by admixture of an authentic sample of (+)-β-methyladipic acid.

(+)-*4-Methyl-5-carbamidopentanoic acid.* The oily residues from distillations 2 and 4 (Table I) had deposited crystalline solids on standing for several weeks. Filtration and recrystallization from diethyl carbonate, gave 1.30 g. of glistening flat needles, m.p. 131–132°, $[\alpha]_D^{27}$ +7.1° (*c*, 3.80, abs. ethanol), $[\alpha]_D^{30}$ +6.9° (*c*, 1.30, abs. ethanol) [lit. (15) m.p. 132–133°, $[\alpha]_D^{22}$ +13.5° (*c*, 1.18, abs. ethanol)]. *Neut. Eq.* Calc'd: 159.2; Found: 160.2.

Anal. Calc'd for $C_7H_{13}NO_3$: C, 52.8; H, 8.29; N, 8.80.

Found: C, 52.9; H, 8.56; N, 8.89.

Hydrolysis of 278 mg. of this compound in 0.5 ml. of hot concentrated hydrochloric acid, followed by extraction with chloroform and evaporation of the solvent, gave a white solid. Recrystallization from carbon tetrachloride, followed by recrystallization from 3:1 pet. ether-ethyl acetate, yielded 100 mg. of β-methyladipic acid as waxy needles; m.p. 85–87°; $[\alpha]_D^{26}$ +7.5 ± 0.5° (*c*, 10.9, water) [lit. (16) m.p. 85°, $[\alpha]_D^{22}$ +8.43°].

A solution of (+)-citronellamide (17) (4.15 g.) in 250 ml. of acetone was stirred vigorously while 20 g. of potassium permanganate was added in small proportions over a period of two hours. After addition of sodium thiosulfate (5.0 g. in 50 ml. of water) and isopropyl alcohol (30 ml.) the mixture was filtered, concentrated, made basic (sodium carbonate) and extracted with ether. The aqueous layer was acidified and saturated with ammonium sulfate; the oil which separated solidified readily. Recrystallization from 10:1 benzene-ethanol followed by several recrystallizations from ethyl acetate gave 30 mg. of platelets,

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[2] The refractive equivalent for —C≡N, 5.54, was calculated from data given in (14).

m.p. 130–133°. Recrystallization from diethyl carbonate produced glistening flat needles, m.p. 131–133° alone or admixed with a sample obtained by oxidation of I (*vide supra*).

(+)-*3-Methylcyclopentanone*. The trap distillate (Table II) was fractionated at atmospheric pressure. A broad forerun (b.p. 80–143°) was followed by 1.2 g. of a mobile liquid, b.p. 143–144°, n_D^{19} 1.4337; α_D^{23} +57.21° (l, 0.5, homogeneous), $[\alpha]_D^{16.5}$ +121.1° (c, 10.1, ethanol) [lit. (18) b.p. 143°; lit. (19) n_D^{19} 1.4434; lit. (20) α_D^{12} +122.44° (l, 1.0, homogeneous), $[\alpha]_D^{15.5}$ +124.2° (c, 9.99, ethanol)]. Semicarbazone, m.p. 179–181°.

Anal. Calc'd for $C_7H_{13}N_3O$: C, 54.2; H, 8.44; N, 27.1.

Found: C, 53.9; H, 8.47; N, 26.8.

β-Methylglutarimide. The solid sublimate (Table I; fractions 3–4, Table II) was recrystallized from benzene; hexagonal prisms m.p. 144–145°, $[\alpha]_D$ 0.0° (ethanol); the infrared spectrum (Nujol mull) exhibited distinct bands at 3.18 μ and 5.85–6.02 μ (amide). The material was non-acidic.

Anal. Calc'd for $C_6H_9NO_2$: C, 56.7; H, 7.14; N, 11.02.

Found: C, 57.1; H, 7.28; N, 10.99.

Hydrolysis of 1.0 g. of this material in 10 ml. of concentrated hydrochloric acid, followed by extraction with chloroform and evaporation of the solvent, gave a solid. Recrystallization from 10:1 chloroform-carbon tetrachloride gave 0.22 g. of needle rosettes, m.p. 85–85.8° alone or admixed with an authentic sample of β-methylglutaric acid. β-Methylglutarimide is reported (21) to melt at 142–143°.

(−, ±)-*Methylsuccinic acid*. Fraction 1 (Table II) deposited crystals on standing. The solid was separated from its liquid cogener and on recrystallization from benzene it melted at 85–100°. The liquid portion deposited a second crop of crystals on standing in the refrigerator. Several recrystallizations of the second crop from benzene yielded 0.58 g. of prisms, m.p. 110–113°, $[\alpha]_D^{24}$ −0.29° (c, 8.84, water).

Anal. Calc'd for $C_5H_8O_4$: C, 45.5; H, 6.10.

Found: C, 44.6; H, 6.24.

The substance was acidic, and the melting point of a mixture of $C_5H_8O_4$ and authentic (±)-methylsuccinic acid (22), m.p. 110°, was undepressed (110–113°). The reported (23) $[\alpha]_D^{17}$ +9.79° (c, 19.8, water) suggests that our sample was 3% optically pure.

Neutral compound (III). Fractions 8–11 (Table II) were combined and treated with a solution of 8.0 g. of sodium carbonate in 50 ml. of water. The oily layer which persisted over the alkaline solution was separated, washed once with a small volume of water, combined with ether extracts of the alkaline layer, dried, and distilled. After a brief forerun there was collected 9.5 g. of a colorless oil, b.p. 105–107° (0.6 mm.), n_D^{25} 1.4567, d_4^{25} 0.9981, $[\alpha]_D^{27}$ +3.49° (homogeneous), M_D Calc'd: 60.41; Found: 59.92.

Anal. Calc'd for $C_{12}H_{17}N_3O$: C, 65.7; H, 7.82; N, 19.2; O, 7.30.

Found: C, 65.7; H, 7.67; N, 19.2; O, 7.48.

Molecular weight: Calc'd, 219.2; Found, 202.0 (Signer's isopiestic method).

Free amino groups: Found, 0.0. Terminal methyl groups: Calc'd for 1 CH_3, 7.18; Calc'd for 2 CH_3, 14.36; Found, 10.54.

The infrared absorption spectrum (Fig. 1) and the ultraviolet spectrum are discussed in the Introduction. The compound is unfortunately insoluble in carbon disulfide, so that certain olefinic bands in the infrared spectrum are masked.

The substance is neutral, insoluble in water, decolorizes dilute aqueous permanganate at room temperature and does not yield a semicarbazone after several weeks standing in methanolic semicarbazide acetate.

Hydrolysis in concentrated hydrochloric acid gave an oil-ridden solid which was rubbed on a porous plate and recrystallization thrice from 1:1 benzene-carbon tetrachloride; m.p. 84.4–85.4°, $[\alpha]_D^{26}$ +7.5° ±0.5° (c, 10.9, water). *Neut Eq*. Calc'd: 80.5; Found: 78.2.

Anal. Calc'd for $C_7H_{12}O_4$: C, 52.5; H, 7.27.

Found: C, 52.2; H, 7.35.

Properties reported for (+)-β-methyladipic acid are: m.p. 84.5° (24) and $[\alpha]_D^{22}$ +8.43° (water) (16).

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SUMMARY

Oxidation of (−)-citronellonitrile with excess potassium permanganate in acetone has yielded β-methylglutarimide as the major product and, in lesser amounts, (+)-4-methyl-5-cyanopentanoic acid, (+)-4-methyl-carbamidopentanoic acid, (−, ±)-methylsuccinic acid, and an unusual compound, $C_{12}H_{17}N_3O$, to which a tentative structure has been assigned.

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