

organolithium compound were unsuccessful as the chief products were neutral, halogen-free oils. Degradation of cycloheptadecanecetic acid according to the Barbier-Wieland procedure⁷ gave a low yield of the carboxylic acid. Although 1-hydroxycycloheptadecanecarboxamide was obtained in excellent yield from cycloheptadecanone cyanohydrin its conversion to the carboxylic acid did not appear promising. Further, since methyl α -civetonecarboxylate, an intermediate in the civetone synthesis, could not be readily purified, it was not used as a starting material for the synthesis of the carboxylic acid.

Civetol, characterized as its acid phthalate ester, was obtained in 95% yield by reduction of civetone with aluminum isopropoxide and was converted quantitatively into cycloheptadecanol by hydrogenation over platinum.

Civetone was converted smoothly into an hydantoin derivative by treatment with sodium cyanide and ammonium carbonate.

Experimental^{7a}

Preparation of Civetone

16-Bromo-9-hexadecenoic Acid.—A mixture of 190 g. (2.9 moles) of commercial zinc dust, 1800 cc. of methanol and 5 cc. of 14.5% hydrogen bromide solution in acetic acid was placed in a 5-liter, three-necked flask equipped with a stirrer, reflux condenser, and a thermometer which dipped below the surface of the liquid. The mixture was heated to gentle reflux and then was cooled to about 55°. A solution of 286 g. of crude 9,10,16-tribromopalmitic acid (prepared from 182 g. of aleuritic acid exactly as described by Hunsdiecker⁸) in 300 cc. of methanol was added slowly. The mixture was warmed and refluxed for 5.5 hours during which time additional 10-g. portions of zinc dust were added at one-hour intervals. The hot solution was decanted from unreacted zinc and cooled.

The zinc salt was collected, recrystallized from 6400 cc. of boiling methanol (heated on a steam-bath to avoid overheating the solid zinc salt) and dried in air: yield 136 g., 62% from aleuritic acid.

The acid was liberated by shaking the zinc salt with a mixture of 6 *N* hydrochloric acid and ether. The 16-bromo-9-hexadecenoic acid weighed 125 g., m. p. 38–41° (62% from aleuritic acid). It was recrystallized from 160 cc. of pure methanol: first crop 72 g., m. p. 40.5–42°, second crop 7 g., m. p. 40–42°. The second crop was recrystallized from 25 cc. of methanol by cooling the solution first in the refrigerator and then in Dry Ice: weight 6.6 g., m. p. 40.5–42°. The total yield was 39% from aleuritic acid.

Methyl 18-Bromo-3-oxo-11-octadecenoate.—The acylation of ethyl acetoacetate was carried out in a three-necked, 500-cc. flask equipped with a stirrer, reflux condenser and dropping funnel. The sodium enolate was prepared from 38 g. (0.29 mole) of freshly distilled ethyl acetoacetate by adding small pieces of sodium totalling 5.75 g. (0.25 mole) to a solution of ethyl acetoacetate in 40 cc. of absolute ether. About three-quarters of the sodium dissolved before the sodium enolate began to precipitate. The remainder of the sodium was added, the mixture diluted with 100 cc. of absolute ether, and stirring was continued for three hours.

While the above mixture was being stirred, 72 g. (0.22 mole) of 16-bromo-9-hexadecenoic acid was mixed with 18.5 cc. (30.3 g., 0.25 mole) of pure thionyl chloride and 30 cc. of absolute ether was added. The mixture was warmed

very slightly on a steam-bath until the rapid evolution of sulfur dioxide and hydrogen chloride had slowed. The remaining ether was distilled and the temperature raised to approximately 80° over an additional hour. The excess thionyl chloride was removed at water pump pressure, finally at 80°. The acid chloride, 76 g., was dissolved in 75 cc. of absolute ether.

The suspension of sodium enolate of ethyl acetoacetate was diluted to give a total volume of 200 cc. A few small pieces of unreacted sodium remained. The solution of acid chloride in ether was added to this suspension through the dropping funnel over a period of about five minutes. The mixture was refluxed for two hours and then was allowed to stand at room temperature overnight.

The reaction mixture was added to a mixture of 30 cc. of concentrated sulfuric acid and 250 cc. of ice and water. An additional 100 cc. of ether was added. The last traces of solid dissolved with some difficulty. The ether layer was separated and the aqueous layer was extracted with two additional 50-cc. portions of ether. The combined ether extracts were washed with water until the washes were neutral to congo red. The ethereal solution was dried over anhydrous magnesium sulfate. The ether was distilled and volatile material remaining was removed *in vacuo*, first at water pump pressure with a bath temperature of 120° and finally by heating at 120° for fifteen minutes at a pressure of 0.2 mm. The residue of crude ethyl 2-acetyl-18-bromo-3-oxo-11-octadecenoate, 90 g., was dissolved in a solution of sodium methylate prepared from 5.75 g. of sodium and 250 cc. of methanol (dried by distillation from magnesium methylate). The solution was left at room temperature for five hours.

The solution was added to a mixture of 30 cc. of concentrated sulfuric acid and 500 cc. of ice and water. The gummy solid which precipitated was extracted into ether (400-cc. total). The ethereal solution was washed with water, until the washes were neutral to congo red, and was dried over anhydrous magnesium sulfate. After removal of the ether, 82 g. of crude methyl 18-bromo-3-oxo-11-octadecenoate was obtained (97.5% from 16-bromo-9-hexadecenoic acid).

Methyl 18-Iodo-3-oxo-11-octadecenoate.—The crude methyl 18-bromo-3-oxo-11-octadecenoate (82 g., 0.21 mole) was dissolved in a solution of 37.5 g. (0.25 mole) of sodium iodide in 250 cc. of reagent grade acetone. The mixture was left at room temperature overnight.

About two-thirds of the acetone was distilled *in vacuo*. A mixture of 100 cc. of water and 200 cc. of ether was added to the residue. The ether layer was separated and the aqueous layer was extracted twice with additional ether. The combined ether extracts were dried over anhydrous magnesium sulfate. The ether was distilled *in vacuo*. The residue was taken up in methanol and this was removed *in vacuo* (for comparison of the m. p. with samples recrystallized from methanol). The crude methyl 18-iodo-3-oxo-11-octadecenoate was a mushy solid at 25° and liquified completely at 30°, weight 86 g. (93.5% from methyl 18-bromo-3-oxo-11-octadecenoate).

Civetone.—A solution of 25 g. (0.057 mole) of crude methyl 18-iodo-3-oxo-11-octadecenoate in 300 cc. of methyl ethyl ketone was added over sixty hours from a Hershberg dropping funnel⁸ into the returning stream of condensate from a stirred, refluxing mixture of 3300 cc. of methyl ethyl ketone and 500 g. of potassium carbonate. After the addition was complete, the mixture was stirred and refluxed an additional twenty-four hours.

The mixture was cooled and the potassium carbonate was removed by filtration and washed several times with methyl ethyl ketone. The methyl ethyl ketone was distilled: the last 50 cc. was removed *in vacuo*, weight of residue 33 g. This material was shaken with 100 cc. of 15% formic acid as described by Hunsdiecker⁸ to remove products of the condensation of methyl ethyl ketone with itself. The insoluble material weighed 27.5 g. The more volatile fraction of this crude cyclization product was distilled by heating at 70° at 0.2 mm. pressure for ten min-

(7) Hoehn and Mason, *THIS JOURNAL*, **60**, 1493 (1938).

(7a) All melting points and boiling points are uncorrected unless otherwise specified.

(8) "Organic Syntheses," **18**, 16 (1938).

utes. The residue, crude methyl α -civetonecarboxylate, weighed 19 g. It was dissolved in a solution prepared from 30 g. of potassium hydroxide, 30 cc. of water and 450 cc. of methanol. The solution was allowed to stand at room temperature (about 25°) for five days.

The saponification mixture was added to 1200 cc. of 10% sulfuric acid and the organic material was extracted with portions of ether totalling 500 cc. The ether extracts were washed with water, and then 100 cc. of 3% potassium hydroxide solution was poured through the ether solution in a fine stream. The aqueous layer became orange. The separatory funnel was tipped on its side and rotated slowly in order to expose most of the ether layer to the alkali. Care was taken not to shake the mixture since a very stable emulsion formed if this was done. Considerable acidic material went into the alkaline extract. Investigation indicated that no α -civetonecarboxylic acid was present at this point. The alkaline layer was drawn off and the ether layer was washed twice with water, pouring the water through the ether and down the sides of the funnel. The ethereal solution was dried over anhydrous magnesium sulfate. The ether was distilled and the residue, crude civetone, weighed 8 g.

The civetone was distilled, weight 4.58 g., boiling chiefly at 144–150° at 0.2 mm. (probably superheated). The vapor temperature was allowed to rise to 175° because of the large amount of residue.

Civetone Semicarbazone.—The civetone (4.58 g.) was converted to its semicarbazone by the method described by Ruzicka.⁹ It was recrystallized from 250 cc. of boiling methanol, weight 4.16 g., m. p. 189–191°. (Ruzicka⁹ reported 185–186°; Hunsdiecker⁸ reported 190–191°.) The yield was 74% from the distilled civetone, 23.8% from methyl 18-iodo-3-oxo-11-octadecenoate, and 8.5% over-all from aleuritic acid. Civetone, m. p. 35–36.5°, was obtained in quantitative yield from the semicarbazone by the method described by Ruzicka.⁹

Cycloheptadecanone.—Civetone was reduced catalytically using ethanol as the solvent and 3% by weight of platinum oxide catalyst. Reduction was complete in one hour at 20° and atmospheric pressure. Only 90% of the theoretical amount of hydrogen was absorbed. This low value was also obtained in the catalytic reduction of civetol. The cycloheptadecanone (quantitative yield) was used in subsequent reactions without purification. Recrystallized from methanol, it melted at 64–65°. (Hunsdiecker⁸ reported 64–64.5°.)

Preparation of Cycloheptadecaneacetic Acid

Condensation of Civetone with Ethyl Cyanoacetate.—The procedure was essentially the same as that described by Cope, *et al.*¹⁰

A mixture of 3.4 g. (13.5 millimoles) of civetone, 1.6 g. (14 millimoles) of ethyl cyanoacetate, 155 mg. (2 millimoles) of ammonium acetate, 1.7 cc. of glacial acetic acid and 14 cc. of dry benzene was heated in an oil-bath at 125–130°. The benzene was distilled slowly to remove water; 8 cc. were distilled during nine hours of heating. The reaction mixture was cooled, diluted with ether, and the solution was washed three times with water. The washes were extracted once with ether and this was washed again with water. The ethereal solutions were dried over anhydrous magnesium sulfate. The ether was distilled and the residue, weight 4.65 g., crystallized. The product was recrystallized once from 15 cc. of methanol. The once recrystallized product weighed 3.49 g. (74% from civetone) and melted on the microscope hot stage at 65–68° (cor.).

Anal. Calcd. for $C_{27}H_{38}O_2N$: N, 4.06. Found: N, 4.26.

The condensation product was reduced catalytically in ethanol solution using 4% by weight of platinum oxide catalyst. The theoretical amount of hydrogen (for two double bonds) was absorbed in four hours at room tem-

perature and atmospheric pressure, and practically no more hydrogen was absorbed during two additional hours. The reduced product was an oil (quantitative yield) and was used without purification.

Cycloheptadecaneacetic Acid.—A solution of 253 mg. of reduced condensation product in 3 cc. of glacial acetic acid and 1 cc. of 48% hydrobromic acid was refluxed for forty-eight hours. The mixture was cooled, diluted with water and extracted with ether. The ethereal solution was washed with water and then was extracted with 3% potassium hydroxide solution. The cycloheptadecaneacetic acid, weight 196 mg., was a light brown oil which crystallized within a few days when stored at 5°. The unpurified acid melted at 20–25°. It was recrystallized from acetone by cooling the solution with Dry Ice, first crop, 147 mg., m. p. 27–28° (Calcd. neut. equiv., 296.5. Found: 289; second crop, 20 mg., m. p. 26.5–28°, neut. equiv., found, 294). The yield (167 mg.) was 77% from the civetone-ethyl cyanoacetate condensation product, and 57% from civetone.

Cycloheptadecaneacetamide.—Unpurified cycloheptadecaneacetic acid was converted to the acid chloride using purified thionyl chloride. The crude acid chloride was treated with cold concentrated aqueous ammonia. The amide was extracted with a small volume of petroleum ether and was recrystallized from ether. The yield of once recrystallized amide was 62%; micro m. p. 134–134.8° (cor.).

Anal. Calcd. for $C_{19}H_{27}ON$: N, 4.74. Found: N, 4.68, 4.72.

Preparation of Cycloheptadecanecarboxylic Acid

Acetate of Cycloheptadecanone Cyanohydrin.—The entire reaction was carried out in the hood.

Excess anhydrous hydrogen cyanide¹¹ (from 600 mg., 12.2 millimoles, of sodium cyanide) was condensed on top of 700 mg. (2.78 millimoles) of cycloheptadecanone at 0° to give a clear solution. A tiny droplet of piperidine was added as a catalyst¹² and the reaction mixture soon became viscous. The temperature was allowed to rise to room temperature during half an hour and was kept there three hours.

A solution of 1 cc. of acetic anhydride in 2.5 cc. of pyridine was added to the reaction mixture and the solution was heated at 125° for four hours. The reaction mixture was diluted with 20 cc. of water and the insoluble material was extracted into ether. The ether solution was washed successively with 1.5 *N* hydrochloric acid, water, 10% sodium carbonate solution and finally with water. The ethereal solution was dried over anhydrous magnesium sulfate and the ether was distilled. The crude acetate of cycloheptadecanone cyanohydrin, 825 mg. (92% from cycloheptadecanone), was used in the subsequent pyrolysis without purification. It reduced potassium permanganate in acetone solution only slightly and very slowly. In a micro hydrogenation apparatus, it took up only 10% of one mole of hydrogen during five hours.

Pyrolysis of the Acetate of Cycloheptadecanone Cyanohydrin.—The pyrolysis was similar to those carried out by Burns, Jones and Ritchie.¹³

The acetate (500 mg.) was refluxed at atmospheric pressure for ten minutes (Wood's metal bath at 360°). The pyrolyzed product gave a strong unsaturation test with potassium permanganate in acetone solution. It was reduced in a micro hydrogenation apparatus using 50 mg. of platinum oxide as the catalyst and 10 cc. of ethanol as the solvent. About 5% more than the theoretical amount of hydrogen (1 mole) was absorbed in 1.7 hours. The catalyst was removed by filtration and the crude cycloheptadecyl cyanide was isolated, yield 418 mg.

Cycloheptadecanecarboxylic Acid. Hydrolysis of Cycloheptadecyl Cyanide.—A solution of 316 mg. of crude cycloheptadecyl cyanide in 6 cc. of glacial acetic acid and

(11) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1941, p. 314.

(12) Stoughton, *THIS JOURNAL*, **68**, 2376 (1941).

(13) Burns, Jones and Ritchie, *J. Chem. Soc.*, 400, 714 (1935).

(9) Ruzicka, *Helv. Chim. Acta*, **9**, 239 (1926).

(10) Cope, Hofmann, Wyckoff and Hardenberg, *THIS JOURNAL*, **68**, 3452 (1941).

1.2 cc. of 48% hydrobromic acid was refluxed seventy hours. A small amount of insoluble oil separated during the hydrolysis. The mixture was diluted with water and the insoluble material was extracted into ether. The ethereal solution was washed thoroughly with water and then was diluted with more ether to about 50 cc. A total of 50 cc. of 3% potassium hydroxide solution was used to extract acidic material. This alkaline solution was washed once with ether and then was acidified to congo red. The acidic material was extracted into ether and the ethereal solution was washed thoroughly with water and was dried over anhydrous magnesium sulfate. The cycloheptadecanecarboxylic acid was isolated, yield 144 mg. (40% of the theoretical amount from cycloheptadecanone).

The unpurified liquid cycloheptadecanecarboxylic acid gave a neutral equivalent of 295; calcd., 282.5.

Cycloheptadecanecarboxamide.—Unpurified cycloheptadecanecarboxylic acid was converted to the acid chloride using an excess of purified thionyl chloride. The crude acid chloride reacted with cold concentrated aqueous ammonia. The brown amide was extracted with a small volume of petroleum ether and then was dissolved in hot 85% ethanol and insoluble tar was separated. The amide was precipitated by the addition of water and was dried. It was dissolved in ethanol and treated with charcoal. The amide, re-isolated, was colorless; yield 48% from the acid; micro m. p. 158–163°. It was recrystallized from ether; yield 25% from the acid; micro m. p. 165–167°.

Anal. Calcd. for $C_{17}H_{35}ON$: N, 4.98; Found, N, 4.78, 4.92.

1-Hydroxycycloheptadecanecarboxamide.—The procedure was essentially the same as that described by Stoughton.¹² The entire reaction was carried out in a hood.

Anhydrous hydrogen cyanide (from 300 mg. of sodium cyanide) was condensed on top of 95 mg. (0.38 millimole) of cycloheptadecanone at 0°. A tiny droplet of piperidine was added and the mixture was kept at 0° for one and a half hours. The mixture was cooled in an ice-salt-bath and 0.4 cc. of 90% sulfuric acid was added. The mushy solid was stirred occasionally at 0° for one and a half hours and then was allowed to stand at room temperature overnight.

Cracked ice was added to the somewhat mushy mixture until the total volume was about 3 cc. The precipitated solid was extracted into ether: a total of 8 cc. of ether was used. The ether solution was washed with water until the washes were neutral to congo red and then the solution was dried over anhydrous magnesium sulfate. The ether was distilled until about 1 cc. remained. Beautiful white needles separated and, after the mixture was kept at 5° for two hours, the crystals were collected, weight 70 mg., micro m. p. 146–147° (cor.). A second crop of 9 mg. of less pure material was obtained by concentrating the mother liquors to 0.3 cc. and cooling again. The second crop was recrystallized and 7 mg. of fine crystals was obtained. The total yield (72 mg.) was 64% from cycloheptadecanone.

For analysis, part of the first crop was recrystallized from ether, micro m. p. 147–147.7° (cor.).

Anal. Calcd. for $C_{17}H_{35}O_2N$: N, 4.71; Found: N, 4.72.

Reaction of Cycloheptadecanone with Sodium Cyanide and Ammonium Carbonate. 5,5-Hexadecamethylenehydantoin.—The procedure was essentially that of Bucherer and Lieb.¹⁴

A solution of 100 mg. of cycloheptadecanone in 2 cc. of 95% ethanol was mixed with a solution of 50 mg. of sodium cyanide and 200 mg. of ammonium carbonate in 1 cc. of water. The mixture was warmed at 50–55° for twelve hours. The mixture was cooled and then was extracted with a mixture of ether and 60–70° petroleum ether. The

ether-petroleum ether layer was washed with water and was dried over anhydrous magnesium sulfate. The ether was distilled and the petroleum ether-insoluble needles, presumably hydantoin, were collected and washed with petroleum ether, yield 46 mg. The petroleum ether-soluble material, presumably unchanged cycloheptadecanone, weighed 64 mg.

For analysis, the hydantoin was recrystallized from absolute ether, micro m. p. 251–252°, dec. (cor.).

Anal. Calcd. for $C_{17}H_{34}O_2N_2$: N, 8.69. Found: N, 8.61, 8.73.

Civetol. Reduction of Civetone with Aluminum Isopropoxide.—The procedure was similar to those described in "Organic Reactions."¹⁵

A mixture of 1.2 g. (4.8 millimoles) of civetone, 10 cc. of dry isopropanol, and 10 g. of distilled aluminum isopropoxide was placed in a 25-cc. distilling flask and was heated in an oil-bath at 125°. The aluminum isopropoxide dissolved and the opalescent solution was refluxed at such a rate that 1 to 2 cc. of isopropanol distilled per hour. A total of 20 cc. of isopropanol was added during the reaction and about 25 cc. was distilled. The test for acetone in the distillate was negative after about eight hours and heating was discontinued at fifteen hours.

The reaction mixture was added to 20 cc. of 10% sulfuric acid and the civetol was extracted with a total of 50 cc. of ether. The ethereal solution was washed with water until the washes were neutral to congo red. The washes were extracted with a little more ether and this was washed free of acid. The ethereal solution of civetol was dried over anhydrous magnesium sulfate. The ether was distilled, finally *in vacuo* at 60°; 1.22 g. of crude, solid civetol was obtained.

The civetol was recrystallized from 10 cc. of 60–70° petroleum ether by cooling the solution slowly with Dry Ice. A second crop of crystals was obtained by concentrating the mother liquors and cooling again with Dry Ice. The first crop weighed 1.00 g.; m.p. 64–65° with sintering at 62°; the second crop weighed 165 mg.; m. p. 62–65° (Rusicka, *et al.*,¹⁶ reported the melting point of civetol at 65°). The yield of recrystallized civetol was 95% of the theoretical from civetone.

The half-ester of phthalic acid was prepared by heating phthalic anhydride with civetol at 125° for sixteen hours. The product was recrystallized from methanol-water and then from 60–70° petroleum ether; yield 53%, beautiful needles; micro m. p. 117.5–119° (cor.); neut. equiv. calcd., 400.5; found, 397.

Cycloheptadecanol. Catalytic Reduction of Civetol.—Civetol was hydrogenated, using ethanol as the solvent and 1% by weight of platinum oxide catalyst. The reduction was complete in two hours at room temperature and atmospheric pressure; only 86% of the theoretical amount of hydrogen was absorbed. The crude cycloheptadecanol was isolated and solidified immediately. The yield was quantitative, m. p. 79–81° (Ruzicka, *et al.*,¹⁶ reported the m. p. as 80°).

Summary

Procedures have been developed for the synthesis of carboxylic acids containing many-membered carbon rings. The acids prepared have the general formulas RCH_2CO_2H and RCO_2H , where R is a seventeen-membered carbon ring.

The synthesis of civetone by Hunsdiecker's procedure has been improved.

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(15) Wild's chapter in "Organic Reactions," Vol. II, John Wiley and Sons, New York, N. Y., 1944, p. 178.

(16) Ruzicka, Schinz and Seidel, *Helv. Chim. Acta*, **10**, 695 (1927).

(14) Bucherer and Lieb, *J. prakt. Chem.*, **141**, 5 (1934).