[Contribution from the Baker Laboratory of Chemistry at Cornell University]

Many-membered Carbon Rings. II. A New Synthesis of Civetone and *dl*-Muscone

By A. T. Blomquist, Robert W. Holley[1] and R. D. Spencer[2]

The only recorded synthesis of civetone is that of Hunsdiecker in which intramolecular alkylation of an ω-iodoacylacetic ester was effected to form the appropriate many-membered carbon ring.[3] Ruzicka, Plattner and Widmer[4] as well as Hunsdiecker[5] reported the preparation of suitable intermediates for the synthesis of civetone by Ziegler's method[6] but have not described cyclization experiments leading to the complete synthesis.

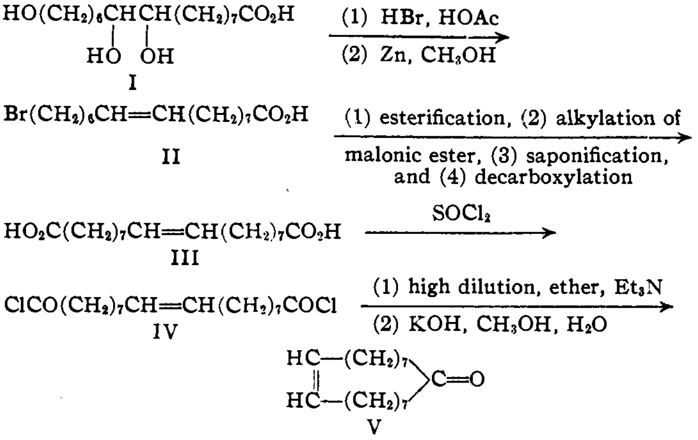
Ziegler and Weber[7] and Ruzicka and Stoll[8] announced, practically simultaneously, the synthesis of *dl*-muscone by the Ziegler method although the two groups used different syntheses for the requisite ω,ω′-dinitrile used in the cyclization. Hunsdiecker also has synthesized *dl*-muscone through his intramolecular alkylation method.[9]

It was of interest to attempt the synthesis of civetone and *dl*-muscone through the intramolecular condensation, under conditions of high dilution, of suitable bifunctional ketenes. This synthetic method for many-membered rings is described in preceding articles.[10]

The reactions employed in the syntheses here reported are indicated in the accompanying diagram. Using aleuritic acid (I) as the starting material for the civetone synthesis, 9-octadecene-1,18-dioic acid (III) was prepared essentially by Hunsdiecker's procedure.[5] The crude acid chloride (IV) derived therefrom was cyclized through the bifunctional ketene. Civetone (V) was obtained in 33% yield from 9-octadecene-1,18-dioic acid (III).

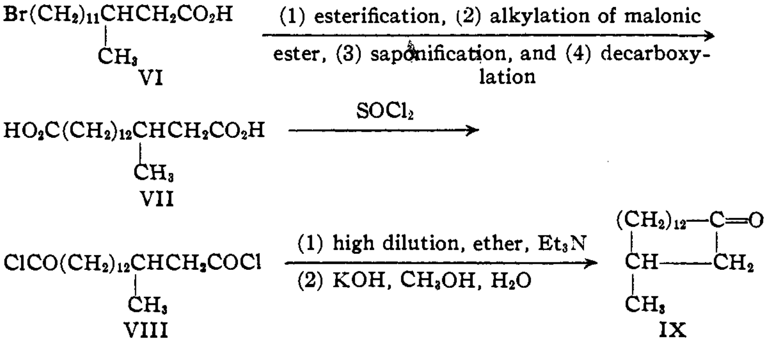
The starting material for the synthesis of *dl*-muscone was 14-bromo-3-methyltetradecanoic acid (VI).[11] It was converted to 3-methyl-1,16-hexadecanedioic acid (VII) as indicated and the corresponding crude acid chloride (VIII) cyclized through the bifunctional ketene. *dl*-Muscone (IX) was obtained in 22% yield from 3-methyl-1,16-hexadecanedioic acid.

Synthesis of Civetone



$HO(CH_2)_6CH(OH)CH(OH)(CH_2)_7CO_2H$ (I) $\xrightarrow[\text{(2) Zn, }CH_3OH]{\text{(1) HBr, HOAc}}$ $Br(CH_2)_6CH{=}CH(CH_2)_7CO_2H$ (II) $\xrightarrow[\text{malonic ester, (3) saponification, and (4) decarboxylation}]{\text{(1) esterification, (2) alkylation of}}$ $HO_2C(CH_2)_7CH{=}CH(CH_2)_7CO_2H$ (III) $\xrightarrow{SOCl_2}$ $ClCO(CH_2)_7CH{=}CH(CH_2)_7COCl$ (IV) $\xrightarrow[\text{(2) KOH, }CH_3OH,\ H_2O]{\text{(1) high dilution, ether, }Et_3N}$ V

Synthesis of *dl*-Muscone



$Br(CH_2)_{11}CH(CH_3)CH_2CO_2H$ (VI) $\xrightarrow[\text{ester, (3) saponification, and (4) decarboxylation}]{\text{(1) esterification, (2) alkylation of malonic}}$ $HO_2C(CH_2)_{12}CH(CH_3)CH_2CO_2H$ (VII) $\xrightarrow{SOCl_2}$ $ClCO(CH_2)_{12}CH(CH_3)CH_2COCl$ (VIII) $\xrightarrow[\text{(2) KOH, }CH_3OH,\ H_2O]{\text{(1) high dilution, ether, }Et_3N}$ IX

In the present study the yields of civetone and *dl*-muscone from the appropriate dicarboxylic acids are lower than those reported by Hunsdiecker[3] and by Ziegler and Weber[7] for the cyclization steps of their respective syntheses. However, a consideration of such factors as ease of synthesis of necessary intermediates, convenience in laboratory manipulation, and over-all yield from the starting materials may favor the new syntheses somewhat. In repeating Hunsdiecker's synthesis of civetone we effected certain simplifications and improvements in yield in some of the steps and realized an 8.5% over-all yield of civetone, as its semicarbazone, from aleuritic acid. By the present method a 9.8% yield of civetone, as its semicarbazone, from aleuritic acid was obtained. Nicely crystalline inter-

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[1] National Research Council Predoctoral Fellow, 1946–1947.

[2] du Pont Postgraduate Fellow, 1946–1947.

[3] Hunsdiecker, *Ber.*, **76B**, 142 (1943).

[4] Ruzicka, Plattner and Widmer, *Helv. Chim. Acta*, **25**, 1086 (1942).

[5] Hunsdiecker, *Ber.*, **77B**, 185 (1944).

[6] Ziegler, Eberle and Ohlinger, *Ann.*, **504**, 94 (1933).

[7] Ziegler and Weber, *ibid.*, **512**, 164 (1934).

[8] Ruzicka and Stoll, *Helv. Chim. Acta*, **17**, 1308 (1934).

[9] Hunsdiecker, *Ber.*, **75B**, 1197 (1942).

[10] Blomquist and Spencer, This Journal, **69**, 472 (1947); **70**, 30 (1948).

[11] Prepared in the Cornell Laboratories by Miss M. Burg (ref. 15) according to Hunsdiecker's procedure (ref. 9).

mediates were encountered in the present syntheses.

Experimental

Preparation of Civetone

16-Bromo-9-hexadecenoic Acid (II).—This acid was prepared from aleuritic acid according to Hunsdiecker's procedure.[3] The 9,10,16-tribromopalmitic acid was treated, in methanol solution, with zinc dust at reflux temperature for five and a half hours. The yield of crude acid from aleuritic acid was 62%; the yield of acid m. p. 40.5–42° was 39%.

Methyl 16-Bromo-9-hexadecenoate.—The acid described above on treatment with an excess of an ethereal solution of diazomethane gave a quantitative yield of the liquid methyl ester.

8-Hexadecene-1,1,16-tricarboxylic Acid.—The procedure was that of Hunsdiecker.[5] The tricarboxylic acid, m. p. 67–69°, was used without purification.

9-Octadecene-1,18-dioic Acid (III).—The tricarboxylic acid described above was decarboxylated by heating *in vacuo* to 200°, as described by Hunsdiecker.[5] The unpurified acid, m. p. 95.5–98°,[12] was recrystallized from ethyl acetate, m. p. unchanged, yield 82% from 16-bromo-9-hexadecenoic acid. The acid was used without further purification in the cyclization step. Neutral equivalent was 163 (calcd. 156).

Civetone (V). **Cyclization of 9-Octadecene-1,18-dioic Acid.**—A mixture of 1.8 g. (5.8 millimoles) of 9-octadecene-1,18-dioic acid, 2 cc. (3.3 g., 28 millimoles) of thionyl chloride and 5 cc. of absolute ether was warmed gently. Sulfur dioxide and hydrogen chloride distilled gradually. After half an hour the temperature was raised to *ca.* 70° and kept there for one hour. Removal of excess thionyl chloride *in vacuo* at 50–60° gave 2.03 g. of the crude acid chloride which still had an odor of thionyl chloride.

A solution of the crude acid chloride in 200 cc. of absolute ether (Grignard-dried) was added over a period of fifteen hours from a Hershberg[13] dropping funnel down the condenser into a stirred, refluxing mixture of 500 cc. of absolute ether (Grignard-dried) and 10 cc. of triethylamine. At the end of this time the dropping funnel and condenser were rinsed with absolute ether and 500 cc. of ether was removed by distillation of the combined ethereal solution. The remaining ethereal solution, triethylamine hydrochloride, and polymer was washed with 50-cc. and 30-cc. portions of 3 *N* hydrochloric acid and finally with water until the washes were neutral to congo red. The ethereal solution was dried over anhydrous magnesium sulfate.

The ether was distilled and the residue weighed 1.72 g. In order to hydrolyze ketene dimers, this material was dissolved in a solution of 2.0 g. of potassium hydroxide in 2.0 cc. of water and 30 cc. of methanol. The solution was kept at room temperature for forty hours and then was refluxed one and one-half hours. The saponification mixture was cooled, diluted with water to about 200 cc., and the neutral organic material extracted repeatedly with ether. The ethereal solution was washed with water and dried over anhydrous magnesium sulfate. The ether was distilled and 545 mg. of residue, crude civetone, was obtained. The material remaining in the aqueous layer was investigated sufficiently to insure that no civetone was being lost as α-civetonecarboxylic acid.

The civetone was distilled at 0.2 mm. pressure with a bath temperature of about 160°. A nearly colorless distillate was obtained; yield, 476 mg. (33% from 9-octadecene-1,18-dioic acid).

Civetone Semicarbazone.—The distilled civetone (476 mg.) was dissolved in 5 cc. of acetone-free methanol and a solution of 700 mg. of semicarbazide hydrochloride and 1.05 g. of sodium acetate trihydrate in 2.1 cc. of water was added dropwise. The semicarbazone started to crystallize after 15 to 20% of the semicarbazide solution had been added. The mixture was allowed to stand at room temperature overnight.

The semicarbazone was collected, washed with water and was dried four hours in the air and finally *in vacuo;* yield, 575 mg. It was recrystallized from 35 cc. of methanol. The recrystallized semicarbazone, shining leaflets, weighed 497 mg.; m. p. 189.5–191.5° (Ruzicka[14] reported 185–186°, Hunsdiecker[3] reported 190–191°). The melting point was not changed when this semicarbazone was mixed with the semicarbazone of civetone obtained according to Hunsdiecker's[3] procedure.

Anal. Calcd. for $C_{18}H_{33}ON_3$: N, 13.67. Found: N, 13.64; 13.71.

The mother liquors were concentrated to about 5 cc. and the second crop of semicarbazone was recrystallized; 48 mg. were obtained; m. p. 190–192°. The total yield of civetone semicarbazone was 31% from 9-octadecene-1,18-dioic acid. This was a 25% yield from 16-bromo-8-hexadecenoic acid and a 9.8% yield from aleuritic acid.

Civetone may be regenerated from its semicarbazone in quantitative yield by heating the semicarbazone with an oxalic acid solution as described by Ruzicka.[14]

Preparation of *dl*-Muscone

14-Bromo-3-methyltetradecanoic Acid (VI).—This acid was prepared in the Cornell laboratories by Miss M. Burg[15] according to the procedure described by Hunsdiecker.[9]

Methyl 14-Bromo-3-methyltetradecanoate.—The liquid ester was obtained in quantitative yield by treatment of the acid described above with an excess of diazomethane.

2-Methyl-1,14,14-tetradecanetricarboxylic Acid.—The alkylation of diethyl malonate was carried out in exactly the same way as in the preparation of 8-hexadecene-1,1,16-tricarboxylic acid from methyl 16-bromo-9-hexadecenoate, the procedure described by Hunsdiecker.[5] The crude 2-methyl-1,14,14-tetradecanetricarboxylic acid was an oil, and no attempt was made to purify it.

3-Methyl-1,16-hexadecanedioic Acid (VII).—The tricarboxylic acid described above was decarboxylated at 200°. The resulting dicarboxylic acid was recrystallized from ethyl acetate and from a mixture of ethyl acetate and 60–70° petroleum ether. The yield from 14-bromo-3-methyltetradecanoic acid was 46%; m. p. 74–76° (Chuit, *et al.*,[16] reported the melting point as 77.2–77.4°). Neutral equivalent was 152 (calcd. 150).

***dl*-Muscone** (IX). **Cyclization of 3-Methyl-1,16-hexadecanedioic Acid.**—The di-acid chloride was prepared from 1.8 g. (6.0 millimoles) of 3-methyl-1,16-hexadecanedioic acid exactly as the corresponding di-acid chloride was prepared in the synthesis of civetone. The cyclization procedure was exactly the same except that the solution of di-acid chloride was added over twenty-three hours. The product was isolated as before. The saponification mixture was allowed to stand at room temperature for five and one-half days.

The saponification mixture was diluted with 250 cc. of water and the *dl*-muscone was extracted into ether; 450 mg. was obtained. The *dl*-muscone was distilled at 0.2 mm. pressure with a bath temperature of about 140°. The colorless *dl*-muscone weighed 315 mg. (22% from 3-methyl-1,16-hexadecanedioic acid).

***dl*-Muscone Semicarbazone.**—The distilled *dl*-muscone (315 mg.) was dissolved in 4 cc. of acetone-free methanol and a solution of 500 mg. of semicarbazide hydrochloride and 750 mg. of sodium acetate trihydrate in 1.5 cc. of water was added over ten minutes. The solution was maintained at 65° for fifteen minutes, at which time the semicarbazone began to precipitate. The mixture was allowed to stand at room temperature for twenty-four hours.

The semicarbazone was collected and was allowed to dry in air; yield 400 mg. It was recrystallized from 5 cc. of

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(12) From the fractionated dimethyl ester Hunsdiecker obtained the free acid melting at 99.5–100.3°.

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

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

(15) Burg, Thesis, Cornell University, 1947.

(16) Chuit, Boelsing, Hausser and Malet, *Helv. Chim. Acta*, **10**, 167 (1937).

boiling methanol. The recrystallized semicarbazone weighed 319 mg.; m. p. 131.5–132.5°. (Hunsdiecker[9] reported 133–133.5°; Ruzicka[8] reported 136–137°.)

Anal. Calcd. for $C_{17}H_{33}ON_3$: N, 14.22. Found: N, 14.38, 14.39.

A second crop of semicarbazone (54 mg.) was obtained from the mother liquors; m. p. 127–128.5°. The total yield of *dl*-muscone semicarbazone from 14-bromo-3-methyltetradecanoic acid was 9.7%.

dl-Muscone may be regenerated from its semicarbazone by heating the semicarbazone with an oxalic acid solution, as in the regeneration of civetone from its semicarbazone.

Summary

A new synthesis for civetone and *dl*-muscone is described in which the appropriate many-membered carbon rings are formed by the intramolecular condensation of bifunctional ketenes.

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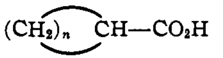
[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Many-membered Carbon Rings. III.[1] Carboxylic Acid Derivatives of Cycloheptadecane[2]

BY A. T. BLOMQUIST AND ROBERT W. HOLLEY[3]

The extensive researches in the chemistry of higher fatty acids have resulted in the discovery of therapeutic agents of some promise against tuberculosis and leprosy.[4] Recently, activity in the field has been stimulated by the interesting study of phthioic acid, isolated from the tubercle bacillus.[5] Accordingly, it seemed of interest to undertake an investigation of the properties of carboxylic acids containing many-membered carbon rings.

The present paper records exploratory studies on synthetic methods for the preparation of large-ring carboxylic acids of the type A and B.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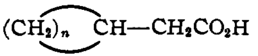
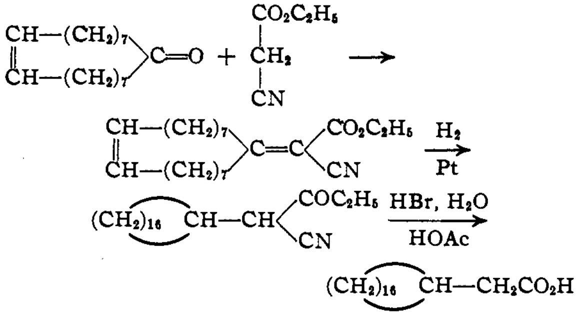

B

The relative availability of the seventeen-carbon cyclic ketone, civetone, suggested its use in developing synthetic methods for the type of acids described above. These methods should be applicable to the synthesis of higher homologs with the carbon ring containing from twenty to thirty members.

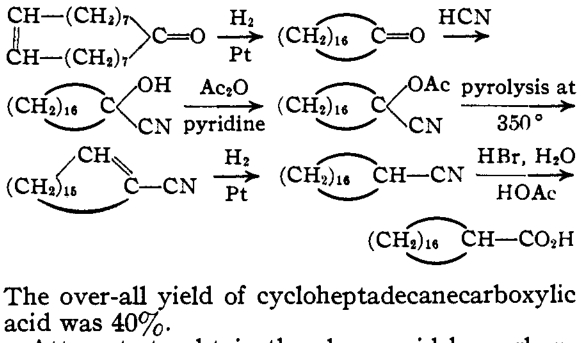
Hunsdiecker's synthesis of civetone from aleuritic acid[6] was selected as a suitable method for obtaining the C_{17} ring. Unfortunately, his published procedure is incomplete and considerable experimentation was necessary before a useful synthesis was developed. A number of modifications were worked out and these are described in the experimental section. Through the use of unpurified intermediates in many of the steps it was possible not only to achieve a considerable saving of labor but also to improve the over-all yield of civetone from aleuritic acid, 8.5% as compared with 5.3% obtained by Hunsdiecker.

Cycloheptadecaneacetic acid was readily obtained from the condensation product of civetone with ethyl cyanoacetate as indicated by the equations



The over-all yield of purified cycloheptadecaneacetic acid from civetone was 57%.

The preparation of cycloheptadecanecarboxylic acid presented more difficulties. It was eventually obtained by way of cycloheptadecanone cyanohydrin as indicated below.



The over-all yield of cycloheptadecanecarboxylic acid was 40%.

Attempts to obtain the above acid by carbonation of the appropriate Grignard reagent or

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[1] Preceding paper in this series: Blomquist, Holley and Spencer, THIS JOURNAL, 70, 34 (1948).

[2] This paper is an abstract of part of the doctoral dissertation presented by Robert W. Holley to the Graduate Faculty of Cornell University in June, 1947.

[3] National Research Council predoctoral fellow in Chemistry, 1946–1947. Present address: Department of Chemistry, State College of Washington, Pullman, Washington.

[4] (a) Emmart, *Am. Rev. Tuberculosis*, 53, 83 (1946). (b) Stanley, Jay and Adams, THIS JOURNAL, 51, 1261 (1929). (c) Stanley and Adams, *ibid.*, 54, 1548 (1932).

[5] (a) Henshall, *Ann. Reports*, 37, 224 (1940). (b) Polgar and Robinson, *J. Chem. Soc.*, 389 (1945). (c) Stenhagen and Ställberg, *J. Biol. Chem.*, 139, 345 (1941); 148, 685 (1943). (d) Velick and Anderson, *ibid.*, 152, 523 (1944).

[6] Hunsdiecker, *Ber.*, 76B, 142 (1943).