

17. *Macrocyclic Musk Compounds. Part II.* New Syntheses of Civetone, Isocivetone, and Dihydrocivetone from Aleuritic Acid.*

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Syntheses of civetone, isocivetone, and dihydrocivetone from aleuritic acid have been developed. Diethyl heptadec-8-enedioate, prepared from aleuritic acid, was converted into the acyloin, the acetate of which on reduction with calcium and liquid ammonia furnished civetone and isocivetone amongst other compounds.

ALEURITIC ACID (9,10,16-trihydroxyhexadecanoic acid) (I) has been previously employed for the synthesis of civetone¹ by the high-dilution technique of cyclisation.² We now report the synthesis of *trans*-civetone, *trans*-isocivetone, and dihydrocivetone by the acyloin cyclisation³ of the appropriate $\alpha\omega$ -diesters prepared from aleuritic acid.⁴ The conventional methods for reducing an acyloin to the ketone⁵ being limited in their application to saturated compounds, we adopted the metal-amine reagent⁶ for preferential reduction of the unsaturated acyloins to the corresponding ketones. This represents a new approach for the synthesis of unsaturated macrocyclic ketones. The sequence of reactions employed is shown in the charts.

Debromination at the vicinal position of the tribromo-acid (II) by zinc and alcohol (cf. Hunsdiecker¹) afforded only 61% of the ω -bromo-acid; the loss was presumably due to the formation of a zinc salt and complexes; and by converting the carboxyl into the ester group before debromination we obtained an almost quantitative yield of ethyl 16-bromohexadec-9-enoate (III), having a *trans*-double bond (ν_{\max} , 966 cm^{-1}). Cyclisation of the diester (V) furnished a mixture of the two acyloins (VI), which were not separated, but in the form of the mixed acetates were treated with calcium in liquid ammonia

* Part I, *J.*, 1962, 2348.

¹ Hunsdiecker, *Ber.*, 1943, **76**, 142; *Naturwiss.*, 1942, **30**, 587; Mitter and Bhattacharyya, *J. Indian Chem. Soc.*, 1942, **19**, 69; Blomquist, Holley, and Spencer, *J. Amer. Chem. Soc.*, 1948, **70**, 34.

² Ziegler, Eberle, and Ohlinger, *Annalen*, 1933, **504**, 94.

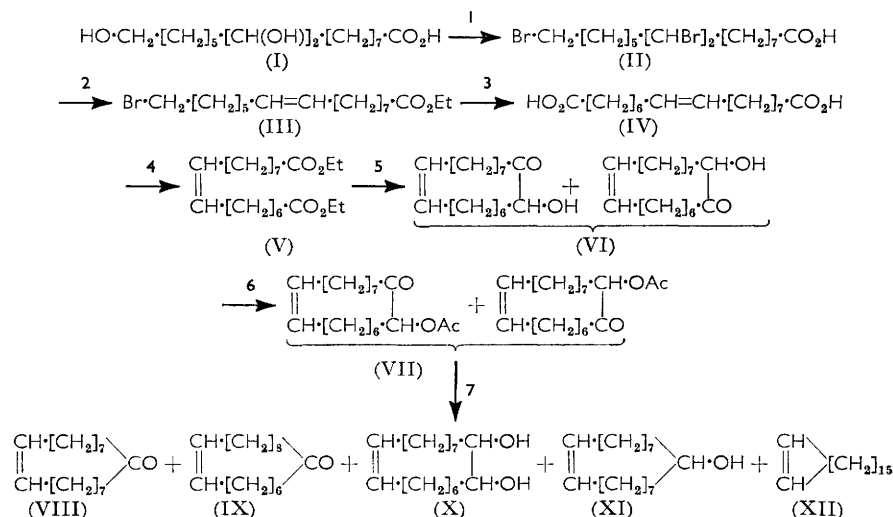
³ Prelog, Frenkiel, Kobelt, and Barman, *Helv. Chim. Acta*, 1947, **30**, 1741; Stoll and Hulstkamp, *ibid.*, p. 1815.

⁴ Mathur and Bhattacharyya, Indian Pat. 65,543/1958; *Chem. and Ind.*, 1960, 1087, 1441.

⁵ Firmenich & Co., B.P. 663,183/1951; Stoll, *Helv. Chim. Acta*, 1947, **30**, 1837.

⁶ Birch and Smith, *Quart. Rev.*, 1958, **12**, 17.

(Chapman's method ⁷). The products were resolved by column chromatography into civetone (VIII), isocivetone (IX), the diol (X), the monoalcohol (XI), and the hydrocarbon (XII). All these compounds had the *trans*-olefinic system. Reduction of the

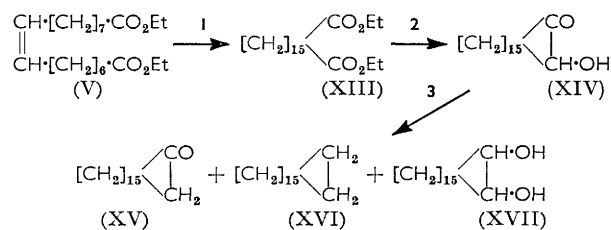


Reagents: 1, HBr-AcOH. 2, Esterifn.; Zn-EtOH. 3, KCN; hydrolysis. 4, Esterifn. 5, Na-xylene. 6, Ac₂O-pyridine. 7, Ca-NH₃.

acyloin (VI) with lithium in liquid ammonia ⁸ yielded civetone in poor yield along with the aforesaid products; the diol (X) was predominant.

The hydrocarbon (XII), purified by chromatography and distillation over sodium, could not be obtained crystalline, in contradistinction to the report by earlier workers,⁹ a difference that may be due to some type of folding in the ring. We are studying this aspect further.

Acyloin condensation of the saturated diester (XIII), followed by reduction with zinc and hydrogen chloride,¹⁰ furnished dihydrocivetone (XV) as the main product along with the corresponding hydrocarbon (XVI) and the diol (XVII). A saturated liquid ketone



Reagents: 1, H₂-Ni. 2, Na-xylene. 3, Zn-HCl-dioxan.

was also isolated by elaborate chromatography; it did not form a semicarbazone by the acetate method, perhaps owing to its being in the shielded "O-inside" conformation

⁷ Chapman, Elks, Phillipps, and Wyman, *J.*, 1956, 4344.

⁸ Amendolla, Rosenkranz, and Sondheimer, *J.*, 1954, 1226; Zürcher, Heusser, Jeger, and Geistlich, *Helv. Chim. Acta*, 1954, **37**, 1562.

⁹ Ruzicka, Schinz, and Seidel, *Helv. Chim. Acta*, 1927, **10**, 695; Stevens and Erickson, *J. Amer. Chem. Soc.*, 1942, **64**, 144.

¹⁰ Stoll and Rouvé, *Helv. Chim. Acta*, 1947, **30**, 1835; Dhekne, Ghatge, Nayak, Chakravarty, and Bhattacharyya, *J.*, 1962, 2348.

observed by Prelog¹¹ for medium-ring ketones. Conformational studies on this ketone are in progress.

Cycloheptadecane (XVI), after rigorous purification, also remained liquid, in contrast to the report by Ruzicka *et al.*⁹

EXPERIMENTAL

M. p.s of semicarbazones were determined by raising the bath-temperature to 170° in about 6 min. and thereafter slowly. Infrared spectra were obtained for Nujol mulls, unless otherwise stated on a Grubb-Parsons double-beam spectrometer with sodium chloride optics. Acid-washed alumina grade II (pH 8.5) was employed for chromatography. Light petroleum had b. p. 40–60°.

Ethyl trans-16-Bromohexadec-9-enoate (III).—Aleuritic acid (I) (m. p. 100–101°; 100 g.), ν_{\max} , 3210, 1718, 1658 (bonded C=O¹²), 1116, 1058, and 1024 cm.⁻¹, was heated with a 15% w/v solution of hydrogen bromide in glacial acetic acid (1.5 l.) on a water-bath for 8 hr., affording the tribromo-acid (II) (156 g., 96%) which was esterified azeotropically by refluxing it for 20 hr. with absolute alcohol (100 ml.) and benzene (400 ml.) containing sulphuric acid (1 ml.). The crude ethyl 9,10,16-tribromohexadecanoate (160 g., 97%) obtained, decomposed on attempted distillation in a high vacuum; it had n_D^{25} 1.5028. The infrared spectrum showed absence of hydroxyl absorption.

A stirred suspension of zinc dust (105 g.) in absolute ethanol (1.2 l.) containing 15% hydrobromic acid (3 ml.) was refluxed for 20 min. and cooled to ca. 50°. The tribromo-ester (160 g.) was added to the suspension in 30 min. and the whole was refluxed for 1 hr. with stirring. Zinc dust was filtered off and alcohol was removed from the filtrate. The residue, in ether, was washed until neutral, and the solvent evaporated to furnish the ω -bromo-ester (III) (106 g., 96%), b. p. 152–153°/0.1 mm., n_D^{25} 1.4675, ν_{\max} (liquid film) 1724, 1235, and 966 (trans-CH=CH) cm.⁻¹ (Found: C, 60.2; H, 9.3; Br, 21.8. C₁₈H₃₃BrO₂ requires C, 59.8; H, 9.2; Br, 22.1%).

Diethyl trans-Heptadec-8-enedioate (V).—The ω -bromo-ester (III) (90 g.) was treated with potassium cyanide (32.5 g.) in boiling 95% ethanol (150 ml.) for 10 hr. with stirring. A further quantity of potassium cyanide (16 g.) was added and the reaction continued for 8 hr. The nitrile formed was not isolated but was refluxed with potassium hydroxide (42 g.) in water (60 ml.) for 30 hr. The solution was cooled and acidified, and the liberated trans-heptadec-8-enedioic acid (83 g., 94%), was washed with water, decolorised in alcoholic solution, recovered, and crystallised from benzene and then acetic acid; it melted at 94–95° (lit.,¹³ 86–87°) and had ν_{\max} , 2855 (associated hydroxyl¹⁴), 1686, and 963 cm.⁻¹ (Found: C, 68.2; H, 9.9. Calc. for C₁₇H₃₀O₄: C, 68.4; H, 10.1%). The acid was esterified and distilled, yielding *diethyl heptadec-8-enedioate*, b. p. 143–145°/0.03 mm., n_D^{30} 1.4470 (Found: C, 71.2; H, 10.8. C₂₁H₃₈O₄ requires C, 71.1; H, 10.8%).

2-Hydroxycycloheptadecen-1-one (Mixture) (VI).—The diethyl ester (V) (44.25 g.) in xylene (50 ml.) was added during 1.5 hr. to pulverised sodium (12.5 g.) in refluxing xylene (1.5 l.) under nitrogen. The reaction was continued for 30 min. After cooling and decomposition with alcohol (180 ml.), the xylene solution was washed free from alkali and evaporated under reduced pressure. The residue, on total distillation, afforded mixed 2-hydroxycycloheptadecen-1-ones (VI) (24 g., 72%), b. p. 137–148°/0.015 mm., ν_{\max} , 3400, 1711, and 967 cm.⁻¹ (Found: C, 76.8; H, 11.5. Calc. for C₁₇H₃₀O₂: C, 76.6; H, 11.35%).

The acyloins (13 g.) were allowed to react with acetic anhydride (13 ml.) in dry pyridine (26 ml.) at room temperature for 12 hr. and then at 85–95° for 4 hr. The acetates obtained (13 g.), b. p. 145–146°/0.01 mm., showed no infrared hydroxyl absorption (Found: C, 74.0; H, 10.4. Calc. for C₁₉H₃₂O₃: C, 74.0; H, 10.5%).

Reduction with Calcium and Liquid Ammonia.⁷—The acetates (VII) (13 g.) in tetrahydrofuran (130 ml.) were added during 10 min. to a stirred solution of calcium (6.5 g.) in liquid ammonia (800 ml.). The reaction was continued for another 10 min. and the excess of calcium was then destroyed with bromobenzene. Water (5 ml.) was added and the ammonia allowed to evaporate. The residue obtained on removal of the tetrahydrofuran was acidified, extracted with ether, and worked up, to yield the reaction product (10.67 g.), which was chromatographed

¹¹ Prelog, *J.*, 1950, 420, and references cited therein.

¹² Jones, Humphries, Herling, and Dobriner, *J. Amer. Chem. Soc.*, 1952, **74**, 2820.

¹³ Ruzicka, Stoll, Scherrer, Schinz, and Seidel, *Helv. Chim. Acta*, 1932, **15**, 1459.

¹⁴ Corish and Davison, *J.*, 1955, 2431.

over alumina (200 g.) in a column (83×1.7 cm.) and resolved into five major fractions as tabulated.

| Fraction no. | Eluant (ml.) | Weight (g.) | n_D^{25} | Infrared bands (cm^{-1}) |
|--------------|------------------------------|-------------|------------|-------------------------------------|
| A | Hexane (550) | 5.03 | 1.4855 | 1706s |
| B | Hexane-benzene (1 : 1) (300) | 0.80 | 1.4990 | 3420w, 1703s |
| C | Benzene (200) | 1.48 | Solid | 3240s, 1704w |
| D | Ether (200) | 1.24 | 1.4882 | 3350m, 1706w |
| E | Methanol (250) | 0.37 | Solid | 3340s |

(i) Fraction (A) was rechromatographed over alumina (425 g.; 83×2.5 cm.) and eluted with hexane. Ten fractions were collected; the first (0.70 g.) did not absorb in the carbonyl region and was distilled over sodium, to yield cycloheptadecene (XII), b. p. $152-153^\circ$ (bath)/0.15 mm., n_D^{25} 1.4692, ν_{max} (0.1 mm. cell) 2835, 1585, 1446, 1408, 1372, 1303, 1158, 1079, 1025, 966 (*trans*-CH=CH), 916, 814, 741, and 724 cm^{-1} (Found: C, 86.3; H, 13.8. Calc. for $\text{C}_{17}\text{H}_{32}$: C, 86.4; H, 13.6%).

(ii) Fractions (2)–(9) obtained on rechromatography of fraction (A) were ketones ranging in m. p. from 42° to 31° ; the last fraction (10) was a liquid, n_D^{28} 1.4839, ν_{max} 1706 cm^{-1} . The highest-melting fraction (2) (0.41 g.) crystallised from methanol and sublimed, to yield pure isocivetone (*cycloheptadec-8-enone* (IX) having the characteristic civetone odour, m. p. $44.5-45^\circ$, ν_{max} 1705 (C=O), 1408, 1286, 1212, 1198, 1127, 1094, 1065, and 967 cm^{-1} (Found: C, 81.2; H, 12.0. $\text{C}_{17}\text{H}_{30}\text{O}$ requires C, 81.5; H, 12.1%). The semicarbazone, prepared by the acetate method and repeatedly crystallised from methanol, had constant m. p. $186-186.5^\circ$, ν_{max} 3435, 1681, 1583, 1299, 1286, 1252, 1207, 1161, 1137, 1091, 1061, 994, and 964 cm^{-1} (Found: C, 70.6; H, 11.0; N, 13.5. $\text{C}_{18}\text{H}_{33}\text{N}_3\text{O}$ requires C, 70.3; H, 10.8; N, 13.7%). A mixed m. p. with *trans*-civetone semicarbazone (m. p. $190.5-191.5^\circ$) was $185-186.5^\circ$.

(iii) The lowest-melting fraction (9) was sublimed, yielding pure *trans*-civetone (VIII), m. p. $31-32^\circ$, ν_{max} 1705, 1410, 1276, 1223, 1196, 1127, 1060, 1023, and 966 cm^{-1} (Found: C, 81.4; H, 11.8. Calc. for $\text{C}_{17}\text{H}_{30}\text{O}$: C, 81.5; H, 12.1%). The semicarbazone, on repeated crystallisation, melted at $190.5-191^\circ$ (mixed m. p. with an authentic sample unchanged), ν_{max} 3365, 1657, 1584, 1342, 1281, 1245, 1162, 1104, 1076, 989, and 967 cm^{-1} (Found: C, 69.95; H, 10.6; N, 14.0. Calc. for $\text{C}_{18}\text{H}_{33}\text{N}_3\text{O}$: C, 70.3; H, 10.8; N, 13.7%).

(iv) Fraction (C), on crystallisation from light petroleum, melted at $49-51.5^\circ$ and was found to be predominantly a monoalcohol containing a small amount of ketone which was removed by treatment with Girard's reagent P in the usual way. The non-ketonic fraction (1.07 g.) was purified by repeated sublimations, to yield *trans*-civetol (XI), m. p. $63-63.5^\circ$ (lit.,⁹ 65°) (Found: C, 81.0; H, 13.1. Calc. for $\text{C}_{17}\text{H}_{32}\text{O}$: C, 80.9; H, 12.8%).

(v) Fraction (E) (0.37 g.), on crystallisation from light petroleum, gave *cycloheptadec-trans-8-ene-1,2-diol* (X), m. p. $81-82^\circ$, ν_{max} 3340, 1348, 1293, 1073, 1048, 966 cm^{-1} (Found: C, 75.8; H, 12.2. $\text{C}_{17}\text{H}_{32}\text{O}_2$ requires C, 76.1; H, 12.0%).

*2-Hydroxycycloheptadecanone*¹⁰ (XIV).—The diester (V) was hydrogenated and the saturated diester (XIII), m. p. $41-42^\circ$ (60 g.), was cyclised in xylene (100 ml.) by treatment with pulverised sodium (17 g.) in xylene (2 l.) as described above. Decomposition with alcohol (200 ml.) gave the acyloin (XIV) (31 g., 69%), b. p. $150-152^\circ/0.05$ mm. (Found: C, 76.0; H, 11.8. Calc. for $\text{C}_{17}\text{H}_{32}\text{O}_2$: C, 76.1; H, 12.0%).

Dihydrocivetone (*Cycloheptadecanone*) (XV).—The acyloin (XIV) (30 g.) in dioxan was reduced with zinc and hydrogen chloride in the conditions described by Dhekne *et al.*¹⁰ Distillation yielded a product which was predominantly dihydrocivetone (24.3 g.), b. p. $110-120^\circ/0.005$ mm. The product (22 g.) was purified through column chromatography over alumina (1.1 kg.; 90×5 cm.) and resolved into four major fractions. Fraction 2 (12.5 g.) was a solid and on crystallisation from methanol afforded pure dihydrocivetone, m. p. 63° , ν_{max} 1708, 1413, 1280, 1204, 1128, and 1071 cm^{-1} (Found: C, 80.7; H, 12.8. Calc. for $\text{C}_{17}\text{H}_{30}\text{O}$: C, 80.9; H, 12.8%) [semicarbazone, m. p. $191-191.5^\circ$, ν_{max} 3400, 1671, 1587, 1352, 1268, 1093, and 994 cm^{-1} (Found: C, 69.9; H, 11.1; N, 13.4. Calc. for $\text{C}_{18}\text{H}_{35}\text{N}_3\text{O}$: C, 69.85; H, 11.4; N, 13.6%)].

Fraction 1 (5.75 g.), a liquid, was rechromatographed over alumina (grade I; 500 g.; 98×2.5 cm.) and resolved into two fractions, eluted by hexane (3.04 g.) and benzene (1.92 g.), respectively. The first fraction showed slight unsaturation (ν_{max} 976 cm^{-1}). A portion of it (1.8 g.) was shaken with 10% oleum (18 ml.) for 12 hr., to afford the saturated hydrocarbon

118 *Crouch and Webster: Choice of the Optimum Quantity and*

(1.32 g.). It was resolved over alumina (grade I; 40 g.) into two fractions with n-hexane as eluant. The first fraction (1.15 g.) was distilled over sodium, to furnish cycloheptadecane (XVI), b. p. 137—138°(bath)/0.3 mm., n_D^{25} 1.4685, $\nu_{\max.}$ (liquid film) 2855, 2685, 1464, 1354, and 1294 cm^{-1} (Found: C, 85.2; H, 14.5. Calc. for $\text{C}_{17}\text{H}_{34}$: C, 85.6; H, 14.4%). The second fraction (1.92 g.) eluted by benzene was a *ketone*, b. p. 140—145°(bath)/0.01 mm., n_D^{25} 1.4800, $\nu_{\max.}$ (liquid film) 1709 (C=O), 1412, 1295, 1195, 1146, 1128, and 1035 cm^{-1} (Found: C, 80.0; H, 12.5. $\text{C}_{17}\text{H}_{32}\text{O}$ requires C, 80.9; H, 12.8%), not forming a semicarbazone by the acetate method.

Fractions 3 and 4 (1.25 g.) were crystallised separately from hexane and sublimed, to yield two products, m. p.s 97—98° and 114—115°. Both of these gave correct analyses for *cycloheptadecane-1,2-diol*; they appear to be epimers. The higher-melting compound displayed bands at 3240, 1453, 1334, 1255, 1143, 1125, 1086, 1040, 977, and 865 cm^{-1} (Found: C, 76.1; H, 12.8. $\text{C}_{17}\text{H}_{34}\text{O}_2$ requires C, 75.5; H, 12.7%).

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