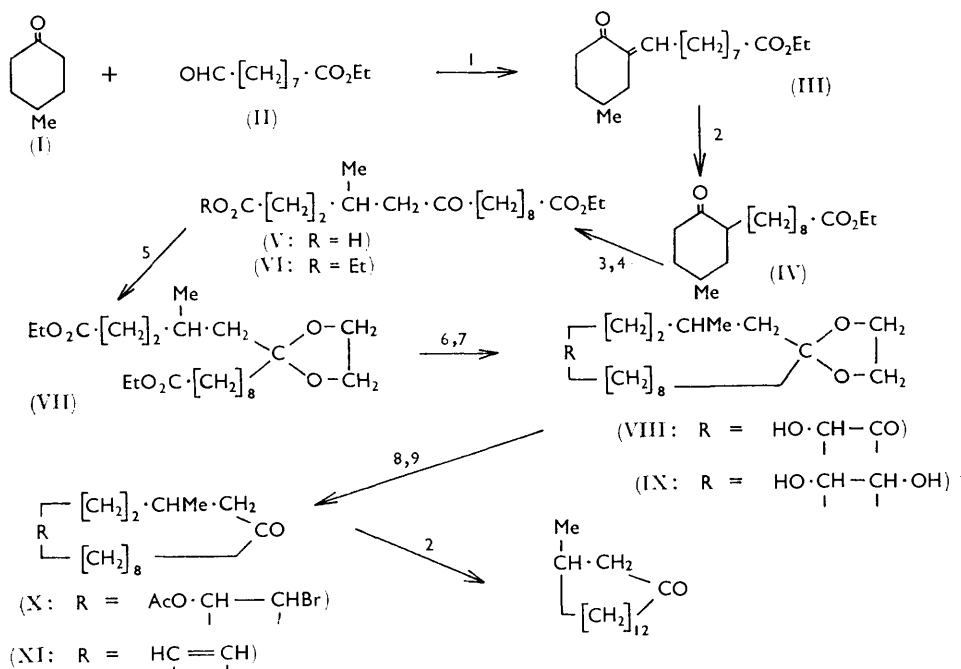


**796. Macrocyclic Musk Compounds. Part VI.\* A New Synthesis of ( $\pm$ )-Muscone.†**

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4-Methylcyclohexanone was condensed with ethyl 8-formyloctanoate in the presence of a catalytic amount of sodium hydroxide at  $-10^\circ$ . Dehydration by heating with potassium hydrogen sulphate then gave ethyl 9-(5-methyl-2-oxocyclohexylidene)nonanoate, which, on hydrogenation, and oxidation with chromic acid-sulphuric acid-acetic acid, furnished 14-ethoxycarbonyl-4-methyl-6-oxotetradecanoic acid. The latter was esterified, and its ethylene ketal cyclised by way of the acyloin to yield ( $\pm$ )-muscone.

MUSCONE [ $(-)$ -3-methylcyclopentadecanone] is the odorous principle of natural musk<sup>1</sup> obtainable from the male musk deer *Moschus moschiferus*. Owing to its rare occurrence in Nature, and its exotic odour, several approaches have been made towards the synthesis of ( $\pm$ )-muscone. These syntheses are somewhat complicated.<sup>2</sup> We report here a simple synthesis of ( $\pm$ )-muscone starting from easily available 4-methylcyclohexanone and ethyl 8-formyloctanoate obtainable from oleic acid<sup>3</sup> or aleuritic acid. The reactions are summarised in the chart.



Reagents: 1, NaOH ( $-10^\circ$ ); KHSO<sub>4</sub>. 2, H<sub>2</sub>-Pd-C. 3, CrO<sub>3</sub>-H<sub>2</sub>SO<sub>4</sub>-AcOH. 4, Esterifn. 5, (CH<sub>2</sub>OH)<sub>2</sub>-p-Me-C<sub>6</sub>H<sub>4</sub>-SO<sub>3</sub>H. 6, Na-xylene. 7, LiAlH<sub>4</sub>. 8, HBr-AcOH. 9, Zn-MeOH.

Ethyl 8-formyloctanoate (II) was condensed with a large excess of 4-methylcyclohexanone (I) (to avoid alkylation of both the  $\alpha$ -positions as well as self-condensation of the

\* Part V, Mathur and Bhattacharyya, *J.*, 1963, 3505.

† Indian Pat. Appln. No. 90,574/1963.

<sup>1</sup> Walbaum, *J. prakt. Chem.*, 1906, (ii), 73, 488.

<sup>2</sup> (a) Ziegler and Weber, *Annalen*, 1934, 512, 164; (b) Ruzicka and Stoll, *Helv. Chim. Acta*, 1934, 17, 1308; (c) Hunsdiecker, *Ber.*, 1942, 75, 1197; (d) Stoll and Rouvé, *Helv. Chim. Acta*, 1947, 30, 2019; (e) Stoll and Comarmon, *ibid.*, 1948, 31, 554, 1435; (f) Blomquist, Holley, and Spencer, *J. Amer. Chem. Soc.*, 1948, 70, 34.

<sup>3</sup> Nayak, Chakravarti, and Bhattacharyya, Indian Pat. 58,868/1958.

aldehyde) in the presence of a catalytic amount of sodium hydroxide<sup>4</sup> at  $-10^\circ$  to obtain ethyl 9-hydroxy-9-(5-methyl-2-oxocyclohexyl)nonanoate as the main product. The latter, on dehydration by heating with potassium hydrogen sulphate under reduced pressure, furnished ethyl 9-(5-methyl-2-oxocyclohexylidene)nonanoate (III). The structure (III) was assigned on the basis of the ultraviolet absorption data,  $\lambda_{\text{max}}$  244  $\mu$  ( $\epsilon$  5860); the lower-intensity absorption indicates a *cis*-conformation,<sup>5</sup> which is present in the cyclohexylidene group. If subsequent isomerisation were to create a *trans*-2-cyclohexenyl group, the extinction coefficient would have a higher value.

Hydrogenation of (III) in presence of palladised charcoal, followed by oxidation with chromic acid-sulphuric acid-acetic acid<sup>6</sup> afforded 14-ethoxycarbonyl-4-methyl-6-oxotetradecanoic acid (V). Thin-layer chromatography revealed a slight impurity of nonanedioic acid monoester which could be removed subsequently by esterification followed by fractional distillation of the diester.

The cyclohexanone ring present in the ester (IV) could also be opened by treatment with sodium ethoxide and ethyl nitrite followed by acid hydrolysis.<sup>7</sup>

The diester (VI) was converted into the ethylene ketal (VII) which was cyclised to the acyloins (VIII) and reduced with lithium aluminium hydride to the diols (IX). Treatment of the diols with hydrogen bromide in glacial acetic acid, furnished the bromo-acetoxy-derivatives (X). A similar observation was recorded by Stoll and his co-workers<sup>8</sup> who originally developed a comparable method for the preparation of civetone. The intermediates (VII) to (X) could not be distilled, even under a high vacuum, without decomposition; the infrared spectra were, however, in accordance with the respective structures.

The bromo-acetoxy-derivatives (X), on refluxing in methanol with zinc dust, afforded muscenone *trans*-3-methylcyclopentadec-6-enone (XI), which on hydrogenation furnished ( $\pm$ )-muscone.

#### EXPERIMENTAL

Infrared spectra were recorded for thin films, unless otherwise stated, on an Infracord model 137b with sodium chloride optics. Ultraviolet measurements were carried out in 95% ethanol solutions on a Beckman Ratio Recording Spectrophotometer model DK-2 in a 1-cm. cell. The nuclear magnetic resonance spectrum was measured by Dr. P. M. Nair and Mr. Iqbal Mulla of this Laboratory on a Varian Associates A60 instrument at 60 Mc. in carbon tetrachloride, using tetramethylsilane as the internal standard. Light petroleum had b. p. 60–80°.

*Ethyl 9-(5-Methyl-2-oxocyclohexylidene)nonanoate* (III).—4-Methylcyclohexanone (I) (80 g.), b. p. 164–165°, was dissolved in absolute ethanol (80 ml.) and mixed with a 30% solution of sodium hydroxide (1.5 ml.). The solution was cooled to  $-10^\circ$  and ethyl 8-formyloctanoate (II) (50 g.) was added dropwise with stirring during 30 min. The temperature was maintained and stirring continued for another 90 min. The solution was neutralised with acetic acid, diluted with water, extracted with light petroleum. The extract was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent recovered. The product, on vacuum distillation, gave unreacted 4-methylcyclohexanone (50 g.), b. p. 100–160° (bath)/30 mm., followed by the ester (II) (23 g.), b. p. 95–120°/0.3 mm. The residue was crude ethyl 9-hydroxy-9-(5-methyl-2-oxocyclohexyl)nonanoate (40 g.), which could not be distilled,  $\nu_{\text{max}}$  3448, 1729, 1709, 1656, and 1608  $\text{cm}^{-1}$  (presumably owing to partial dehydration). It was mixed with freshly fused potassium hydrogen sulphate (4 g.) and heated at 150°/3 mm. for 30 min. The product was extracted with benzene, washed with water, dried, and the solvent recovered. The residue on distillation afforded the *nonanoate* (III) (20 g.), b. p. 165°/0.4 mm.,  $n_D^{28}$  1.4720,  $\lambda_{\text{max}}$  244  $\mu$  ( $\epsilon$  5860),  $\nu_{\text{max}}$  1730, 1684, 1613, 1425, 1408, 1368, 1176, 1026, and 856  $\text{cm}^{-1}$  (Found: C, 73.3; H, 10.7.  $\text{C}_{18}\text{H}_{30}\text{O}_3$  requires C, 73.4; H, 10.3%).

*Ethyl 9-(5-Methyl-2-oxocyclohexyl)nonanoate* (IV).—The unsaturated keto-ester (III) (20 g.)

<sup>4</sup> Machinskaya and Tokarev, *J. Gen. Chem. (U.S.S.R.)*, 1952, **22**, 1209.

<sup>5</sup> Turner and Voitle, *J. Amer. Chem. Soc.*, 1951, **73**, 1403.

<sup>6</sup> Cf. Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.

<sup>7</sup> Huisgen and Pawellek, *Annalen*, 1961, **641**, 71.

<sup>8</sup> Stoll, Hulstkamp, and Rouvé, *Helv. Chim. Acta*, 1948, **31**, 543.

in ethanol (100 ml.) was hydrogenated in presence of 5% palladised charcoal (2 g.) to give the *nonanoate* (IV) (20 g.), b. p. 145°/0.2 mm.,  $n_D^{25}$  1.4565;  $\nu_{\max}$ . 1733, 1710, 1453, 1429, 1410, 1360, 1178, and 1031  $\text{cm}^{-1}$  (Found: C, 73.3; H, 11.0.  $\text{C}_{18}\text{H}_{32}\text{O}_3$  requires C, 72.9; H, 10.9%).

*Diethyl 4-Methyl-6-oxopentadecanedioate* (VI).—The ester (IV) (19 g.) in glacial acetic acid (200 ml.) was heated to 40° and 8N-chromium trioxide in 8N-sulphuric acid (45 ml.) was added during 20 min., with stirring, until a yellow colour persisted. The reaction, after an induction period of about 3 min., was rapid and exothermic; the temperature was maintained at 40–45° by controlling the rate of addition of the reagent. The reaction was continued for another 10 min. and then the excess of reagent was destroyed with aqueous methanol. The product was diluted with water and extracted with ether. The residue after removal of ether was dissolved in 5% sodium carbonate solution and extracted with ether to remove the unreacted ester. The alkaline solution, on acidification, yielded 14-ethoxycarbonyl-4-methyl-6-oxotetradecanoic acid (V) (18 g.), b. p. 193°/0.05 mm. (Equiv. 312.0.  $\text{C}_{17}\text{H}_{31}\text{O}_3\text{COOH}$  requires C 328.4). This mono-ester contained some azealaic monoester as shown by thin-layer chromatography. It was esterified by refluxing with ethanol (30 ml.), benzene (120 ml.), and concentrated sulphuric acid (0.1 ml.), whilst removing water azeotropically. After the water separation ceased, the benzene solution was washed with water, saturated sodium hydrogen carbonate solution, and finally with water until neutral. On fractional distillation, *diethyl 4-methyl-6-oxopentadecanedioate* (VI) (16.8 g.), b. p. 181–183°/0.1 mm., was obtained,  $n_D^{28}$  1.4480,  $\lambda_{\max}$ . 280  $\mu$  ( $\epsilon$  130),  $\nu_{\max}$ . 3460 (overtone), 1730 (ester C=O), 1704 (C=O), 1453, 1408, 1368, 1250, 1176, 1093, and 1031  $\text{cm}^{-1}$  (Found: C, 67.7; H, 10.5.  $\text{C}_{20}\text{H}_{36}\text{O}_5$  requires C, 67.4; H, 10.2%).

This diester could also be prepared by opening the cyclic ester (IV) with sodium ethoxide and ethyl nitrite. Sodium (0.36 g.) was dissolved in absolute ethanol (9 ml.) in a moisture-free system and the ethoxide was cooled to –12 to –15°. The oxo-ester (IV) (3.4 g.) was added dropwise to this solution with stirring during 30 min. The mixture was stirred for 1 hr. and ethyl nitrite was passed in (*ca.* 2.5 g.). The stirring was continued for 1 hr. and the mixture was left overnight at –20°. The cold solution was acidified with concentrated hydrochloric acid (2.1 ml.) and stirred for 30 min. The mixture was taken in benzene and washed with water, followed by an ice-cold solution of sodium hydroxide. Benzene was removed and the residue distilled to get the diester (VI) (1.6 g.), b. p. 181–183°/0.1 mm. Saponification gave the corresponding *4-methyl-6-oxopentadecanedioic acid*, m. p. 66–67° (from ethanol) (Found: C, 64.3; H, 9.3.  $\text{C}_{18}\text{H}_{28}\text{O}_5$  requires C, 64.0; H, 9.4%).

*Diethyl 6-Ethylenedioxy-4-methylpentadecanedioate* (VII).—The diester (VI) (16.2 g.) was mixed with ethylene glycol (16 ml.) in benzene (400 ml.) containing toluene-*p*-sulphonic acid (0.1 g.) and refluxed for 16 hr. whilst removing water azeotropically. The benzene solution was transferred to a dry separatory funnel and the lower layer of the glycol was drained off. The benzene layer was washed with ethylene glycol (2 × 20 ml.), water, saturated sodium hydrogen carbonate solution, and water until neutral. Benzene was distilled off to obtain the *ethylene ketal* (VII) (17.4 g.),  $n_D^{29}$  1.4510,  $\nu_{\max}$ . 3480 (overtone), 2857, 1730, 1453, 1414, 1370, 1030, 948, 854, and 721  $\text{cm}^{-1}$ ; no ultraviolet absorption (Found: C, 66.1; H, 10.2.  $\text{C}_{22}\text{H}_{40}\text{O}_6$  requires C, 66.3; H, 9.6%). Completion of the ketal formation was shown by the disappearance of the shoulder at 1704  $\text{cm}^{-1}$  as well as absence of ultraviolet absorption.

*Acylolins* (VIII).—Sodium (7 g.) was pulverised in xylene (1 l.) under nitrogen and the ketal (VII) (17.2 g.) in xylene (20 ml.) was added dropwise during 1 hr. with vigorous stirring and refluxing for 2 hr. Sodium was dissolved by gradually adding ethanol (50 ml.), and the solution was washed free from alkali and distilled under reduced pressure to leave the cyclic acylolins (VIII) (8.3 g.) as the residue,  $\nu_{\max}$ . 3546, 2941, 1706, 1460, 1404, 1370, and 740  $\text{cm}^{-1}$ .

*7-Ethylenedioxy-5-methylcyclopentadecane-1,2-diols* (IX).—The mixture of isomers (VIII) (7.8 g.) in ether (20 ml.) was added to an ice-cold well-stirred suspension of lithium aluminium hydride (2 g.) in ether (100 ml.) during 30 min., refluxed for 10 hr., and the excess of reagent decomposed with alcohol (10 ml.). The ether solution was washed free from alkali and evaporated to give the *diols* (IX) (5.8 g.) as a viscous oil which could not be distilled without decomposition under a high vacuum,  $n_D^{29}$  1.5990,  $\nu_{\max}$ . 3509, 2860, 1456, 1368, 1075, and 948  $\text{cm}^{-1}$  (Found: C, 68.3; H, 9.6.  $\text{C}_{18}\text{H}_{34}\text{O}_4$  requires C, 68.75; H, 10.7%).

*3-Methylcyclopentadec-6-ene* (XI).—The diols (IX) (5.8 g.) were mixed with a 30% solution of hydrogen bromide in glacial acetic acid (40 ml.), kept at room temperature for 24 hr., and then heated at 65° for 2 hr. Acetic anhydride (6 g.) was added, and the mixture heated for 3 hr. The cooled mixture was treated with sodium acetate (15 g.) in water (100 ml.) to destroy the

excess of hydrogen bromide, and extracted with light petroleum. Evaporation afforded the bromo-acetoxy-derivatives (X) as a yellowish-red oil,  $\nu_{\max}$  1748, 1712, 1458, 1408, 1370, 1235, 1075, 1030, and 722  $\text{cm}^{-1}$ , which was dissolved in absolute methanol (50 ml.) and stirred and refluxed for 12 hr. with zinc dust (4 g.). Methanol was removed and the residue taken up in light petroleum, filtered, and the filtrate washed with dilute acetic acid then water until neutral. The solvent was removed and the residue distilled, b. p. 150—170° (bath)/0.1 mm. (2.5 g.); the distillate revealed a shoulder at 1740  $\text{cm}^{-1}$ , indicating the presence of acetate as an impurity. This was removed by saponification with alcoholic potassium hydroxide (20 ml.) and then passage through a short column of neutral alumina (grade III; 50 g.) in light petroleum. Redistillation afforded trans-3-methylcyclopentadec-6-enone (XI), b. p. 135°/0.1 mm.,  $n_D^{29}$  1.4782,  $\nu_{\max}$  1706, 1453, 1405, 1362, 1271, 1192, 1125, 970, and 722  $\text{cm}^{-1}$  (Found: C, 81.4; H, 12.2.  $\text{C}_{16}\text{H}_{28}\text{O}$  requires C, 81.3; H, 11.9%; 2,4-dinitrophenylhydrazone, m. p. 107° (from benzene) (Found: N, 14.0.  $\text{C}_{22}\text{H}_{32}\text{O}_4\text{N}_4$  requires N, 13.45%). Gas chromatography of a sample of muscenone (Griffin and George Mk IIA apparatus, polyester column, 195°,  $\text{H}_2$  66.6 ml./min.) gave a single peak with a retention time of 14 min.

(±)-Muscone (XII).—Muscenone (XI) (0.8 g.) in ethanol (50 ml.) was hydrogenated in presence of 5% palladised charcoal (0.18 g.) to give (±)-muscone (XII) (0.7 g.), b. p. 140°/1 mm.,  $n_D^{29}$  1.4725,  $\nu_{\max}$  1706, 1456, 1404, 1361, 1276, 1129, 1050, and 721  $\text{cm}^{-1}$ . Gas chromatography showed a single peak with a retention time of 17.5 min. (Found: C, 80.9; H, 12.5. Calc. for  $\text{C}_{16}\text{H}_{30}\text{O}$ : C, 80.6; H, 12.7%.) It formed a semicarbazone, m. p. 131—132° (lit.,<sup>2c</sup> 133—133.5°) (Found: C, 69.2; H, 11.35; N, 14.7. Calc. for  $\text{C}_{17}\text{H}_{33}\text{N}_3\text{O}$ : C, 69.1; H, 11.3; N, 14.2%).

The nuclear magnetic resonance spectrum of muscone showed signals at  $\tau$  9.09 ( $J = 6.5$  c./sec.) (intensity 3) ( $>\text{CH}\cdot\text{CH}_3$ ), 8.72 (methylene hydrogens other than those flanked by C:O), and 7.8 (intensity 4) ( $\text{CH}_2\cdot\text{CO}\cdot\text{CH}_2$ ).

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