452. *Macrocyclic Musk Compounds. Part I. New Syntheses of Exaltolide, Exaltone, and Dihydrocivetone.*

By V. V. DHEKNE, B. B. GHATGE, U. G. NAYAK, K. K. CHAKRAVARTI, and S. C. BHATTACHARYYA.

New methods have been developed for the syntheses of exaltone and dihydrocivetone from kamlolenic acid, and of exaltolide from erucyl alcohol. 15,16-Dihydroxylignoceric acid has also been used for the synthesis of exaltolide.

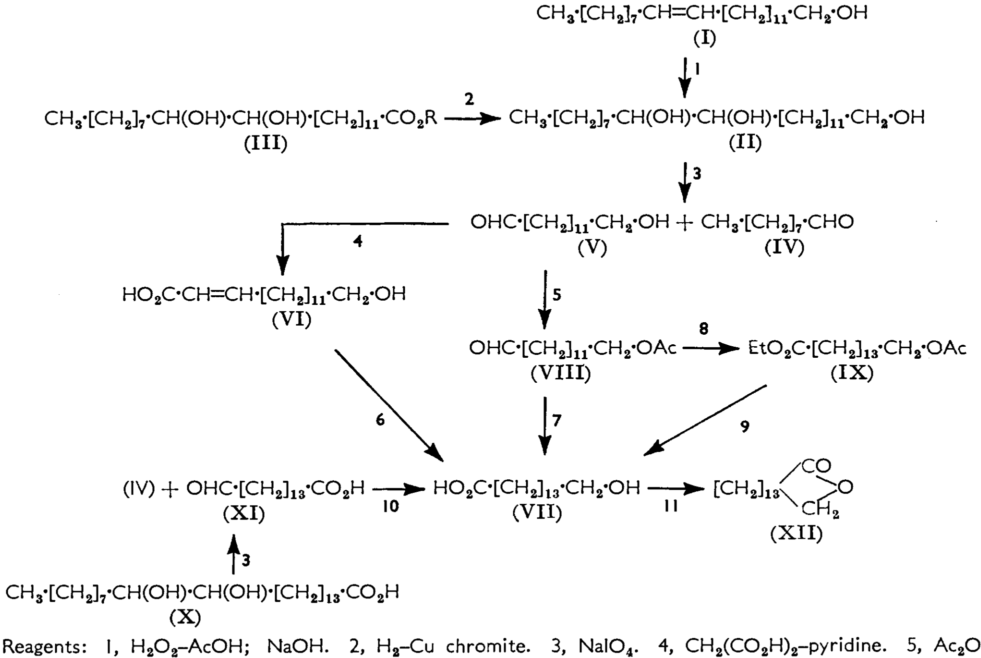
IN a search[1] for practical syntheses of musk-like compounds, we have developed new routes for the syntheses of exaltolide, exaltone, and dihydrocivetone. Both our starting materials, erucyl alcohol[2,3] and kamlolenic acid,[4] are readily available; the former was used for the synthesis of exaltolide, and the latter for the other two compounds. The reactions are summarised in the adjoining charts (I and II).

EXPERIMENTAL

13,14-*Dihydroxybehenyl Alcohol* (II).—Erucyl alcohol (I) (m. p. 34°; 32 g.; from erucic acid[3]) was treated in the usual way with 30% hydrogen peroxide (15 g.) and acetic acid (135 ml.)

CHART I.

Synthesis of exaltolide (XII) from erucyl alcohol (I).



Reagents: 1, H_2O_2–AcOH; NaOH. 2, H_2–Cu chromite. 3, $NaIO_4$. 4, $CH_2(CO_2H)_2$–pyridine. 5, Ac_2O–pyridine. 6, H_2–Ni or –PtO_2. 7, $CH_2(CO_2Et)_2$–piperidine; H_2–Ni or –PtO_2; NaOH; –CO_2. 8, $CH_2Br{\cdot}CO_2Et$–Zn; H_2–Ni or –PtO_2. 9, NaOH. 10, H_2–PtO_2–$FeSO_4$. 11, Lactonisation.

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[1] Bhattacharyya, Chakravarti, and Nayak, *Chem. and Ind.*, 1960, 588; Bhattacharyya and Mathur, *ibid.*, pp. 1087, 1441; Ghatge, Nayak, Chakravarti, and Bhattacharyya, *ibid.*, p. 1334.

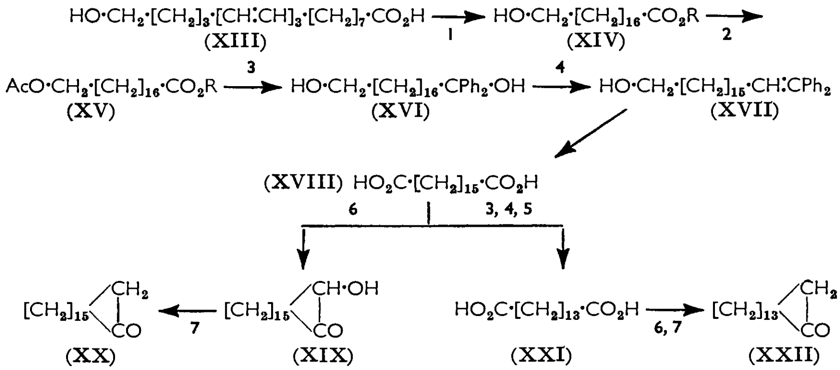
[2] Sudborough, Watson, Ayyar, and Mascarenhas, *J. Indian Inst. Sci.*, 1926, **9**, *A*, 43.

[3] Corroll, *J. Biol. Chem.*, 1953, **200**, 287.

[4] Gupta, Sharma, and Aggarwal, *J. Sci. Ind. Res., India*, 1952, **11**, *B*, 463.

CHART II.

Synthesis of dihydrocivetone (XX) and exaltone (XXII) from kamlolenic acid (XIII).



Reagents: 1, H_2–Ni; HCl–MeOH. 2, Ac_2O–NaOAc. 3, PhMgBr. 4, $-H_2O$. 5, CrO_3–AcOH. 6, Na–xylene. 7, HCl–dioxan.

containing sulphuric acid (1·24 ml.; *d* 1·84), basically by the method of Swern *et al.*[5] The acetoxy-hydroxy-derivative formed was refluxed with 10% ethanolic potassium hydroxide (100 ml.). 13,14-*Dihydroxybehenyl alcohol* so obtained crystallised from alcohol (yield 33 g.), then having m. p. 91° (Found: C, 74·0; H, 12·85. $C_{22}H_{46}O_3$ requires C, 73·68; H, 12·93%).

Alternatively, 13,14-dihydroxybehenic acid (III; R = H) (37 g.) or its ethyl or methyl ester was reduced with lithium aluminium hydride in ether to 13,14-dihydroxybehenyl alcohol in almost quantitative yield.

Ethyl 13,14-dihydroxybehenate (III; R = Et) (25 g.) was also quantitatively reduced with hydrogen at 2000—3000 lb./sq. in. in presence of copper chromite (2·5 g.) at 200—250° for 3—4 hr., giving the alcohol (II).

Reduction of the ester was also carried out with sodium and alcohol.

Oxidation of 13,14-*Dihydroxybehenyl Alcohol.*—This alcohol (45 g.) was treated in alcohol (600 ml.) with 10% aqueous sodium metaperiodate (300 ml.) during 30 min. with stirring at 35°. Stirring was continued for another hour, after which the mixture was filtered, diluted with water, and extracted with ether. The extract was washed, dried, and fractionated under a vacuum, to give nonanal (IV) (17 g.), b. p. 70°/10 mm., n_D^{27} 1·4207, and 13-hydroxytridecanal (V), b. p. 153—155°/0·9 mm., m. p. 74° (25 g.) (Found: C, 72·9; H, 12·1. $C_{13}H_{26}O_2$ requires C, 72·8; H, 12·2%). The *semicarbazone*, prepared in pyridine and crystallised from methyl alcohol, had m. p. 116° (Found: C, 61·5; H, 10·7; N, 15·7. $C_{14}H_{29}N_3O_2$ requires C, 61·95; H, 10·8; N, 15·5%).

15-*Hydroxypentadec*-2-*enoic Acid* (VI).—To a cooled solution of malonic acid (18 g.) in pyridine (55 g.), 13-hydroxytridecanal (24 g. in 20 g. of pyridine) was added slowly with shaking in ~10 min. The mixture was kept at room temperature for 36 hr., then heated on a water-bath for 3 hr.[6] (Alternatively, immediately after mixing the solution was kept on a boiling-water bath for 8 hr.) After removal of pyridine *in vacuo* the residue was extracted with ether; the extract was washed with dilute hydrochloric acid, water, and 10% aqueous sodium carbonate. The carbonate extract on acidification gave 15-*hydroxypentadec*-2-*enoic acid* (VI) (25 g.) which, recrystallised from alcohol, had m. p. 80° (22 g.) (Found: C, 69·95; H, 11·1. $C_{15}H_{28}O_3$ requires C, 70·3; H, 11·0%).

15-*Hydroxypentadecanoic Acid* (VII).—15-Hydroxypentadec-2-enoic acid (8 g.) was hydrogenated in alcohol (200 ml.) with Raney nickel (0·1 g.) for 4 hr. at a pressure 100—120°/500—750 lb./sq. in. The mixture was filtered and after the removal of alcohol the residue (8 g.) crystallised from ethyl acetate; this *acid* (7 g.) had m. p. 85° (Found: C, 70·1; H, 11·8. $C_{15}H_{30}O_3$ requires C, 69·7; H, 11·7%).

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[5] Swern, Billen, Findley, and Scanlan, *J. Amer. Chem. Soc.*, 1945, **67**, 1786; Dorée and Pepper, *J.*, 1942, 477.

[6] Cf. Boxer and Linstead, *J.*, 1931, 740.

13-*Acetoxytridecanal* (VIII).—13-Hydroxytridecanal (V) (15 g.) was kept with acetic anhydride (75 g.) in pyridine (75 g.) at room temperature for ~24 hr. The *acetate* (15 g.), isolated as usual, had b. p. 130°/0·1 mm. (Found: C, 69·8; H, 11·3. $C_{15}H_{28}O_3$ requires C, 70·3; H, 11·1%). Its *semicarbazone* had m. p. 108° (from methyl alcohol) (Found: N, 13·2. $C_{16}H_{31}N_3O_3$ requires N, 13·4%).

Diethyl 13-*Acetoxytridecylidenemalonate and its Conversion into the Acid* (VII).—Diethyl malonate (4 g.) and 13-acetoxytridecanal (VIII) (5 g.) were mixed and cooled and piperidine (2 ml.) was added. The mixture was left at about 15° for 12 hr., then at room temperature for another 24 hr. after which it was added to water and extracted with ether; the ether extract was washed with dilute acid, then with water, dried, and fractionally distilled. The *alkylidenemalonic ester* (4·5 g.) had b. p. 150°/0·005 mm., m. p. 38·5—39·5° (Found: C, 65·9; H, 10·0. $C_{22}H_{38}O_6$ requires C, 66·3; H, 9·6%).

The above derivative (3 g.) was hydrogenated in alcohol with Raney nickel (0·3 g.) at 100—120°/700—1000 lb./sq. in. *Diethyl* 13-*acetoxytridecylmalonate* (2·5 g.) crystallised from light petroleum (b. p. 40—60°)-ether and had m. p. 44—45°, b. p. 145—146°/9·86 × 10^{-3} mm. (Found: C, 65·5; H, 10·2. $C_{22}H_{40}O_6$ requires C, 66·0; H, 10·1%). This product was then hydrolysed with 20% alcoholic potassium hydroxide (20 ml.), and the resultant alkylmalonic acid decarboxylated at 140°. 15-Hydroxypentadecanoic acid (VII) (1·5 g.) was obtained.

15-*Hydroxypentadecanoic Acid*.—(*a*) *By a Reformatsky reaction.* 13-Acetoxytridecanal (VIII) (10 g.) was condensed with ethyl bromoacetate (6 g.) and zinc (3·6 g.) in benzene (250 ml.). The product (6 g.), isolated in the usual way, distilled at 162°/0·015 mm. (Found: C, 66·6; H, 10·7. $C_{19}H_{36}O_5$ requires C, 66·2; H, 10·5%). It had a low m. p. It was refluxed with phosphorus pentoxide (6 g.) in benzene (30 ml.) for 3 hr. Then the benzene solution was decanted, washed with water, dried, and distilled, giving *ethyl* 15-*acetoxypentadec*-2-*enoate*, b. p. 140°/9·8 × 10^{-3} mm. (Found: C, 70·3; H, 10·8. $C_{19}H_{34}O_4$ requires C, 69·9; H, 10·5%). This ester was hydrogenated as above, giving the *acetoxy-pentadecanoate* (IX), b. p. 154—155°/0·015 mm. (Found: C, 69·5; H, 10·95. $C_{19}H_{36}O_4$ requires C, 69·5; H, 11·05%), which was converted by saponification into 15-hydroxypentadecanoic acid (VII).

(*b*) *From* 15,16-*dihydroxylignoceric acid* (X). 15,16-Dihydroxylignoceric acid[7] (1 g.; m. p. 101°) (Found: C, 72·1; H, 12·1. Calc. for $C_{24}H_{48}O_4$: C, 71·95; H, 12·1%) was treated in alcohol (15 ml.) with 10% aqueous sodium metaperiodate (8 ml.) during 20 min. with stirring at 35—36°. After further stirring for 20 min. the mixture was filtered from sodium iodate and worked up in the usual way. Nonanal was distilled off up to 100°/1 mm. 14-*Formyltetradecanoic acid* (XI), left as residue, was extracted with light petroleum from which it crystallised with m. p. 91° (Found: C, 70·5; H, 10·8. $C_{15}H_{28}O_3$ requires C, 70·3; H, 11·0%). Its *semicarbazone* had m. p. 159° (from methyl alcohol) (Found: N, 13·75. $C_{16}H_{31}N_3O_3$ requires N, 13·4%).

This aldehydo-acid was reduced with sodium amalgam in acetic acid or catalytically (platinum oxide and ferrous sulphate at 2—3 atm.) to 15-hydroxypentadecanoic acid.

Synthesis of Exaltolide[8] (XII).—15-Hydroxypentadecanoic acid (50 g.) was converted into its intermolecular polyester by the azeotropic method in xylene (2 l.) containing toluene-*p*-sulphonic acid (5 g.). When separation of water stopped (24 hr.) the product was worked up in the usual way. The polyester was depolymerised by magnesium oxide (10 g.; c.p. grade) at a bath-temperature of 270° under a vacuum. The crude product (40 g.) was dissolved in light petroleum, washed with sodium hydrogen carbonate solution, and distilled, giving exaltolide (35 g.), b. p. 110°/0·25 mm., that, when sublimed in a vacuum, had m. p. 32°, $\nu_{max.}$ 1734 cm.$^{-1}$ (lactone) (Found: C, 74·7; H, 11·6. Calc. for $C_{15}H_{28}O_2$: C, 74·95; H, 11·7%).

Kamlolenic Acid (XIII).—Kamala seed oil (1·5 kg.) was saponified with alcoholic potassium hydroxide (525 g. in 5·3 l.) for 3 hr. on a steam-bath. After saponification, alcohol was removed under reduced pressure. The residue was diluted with water and acidified with 20% sulphuric acid (3 l.) in the presence of ice. The liberated acid was extracted with benzene, washed with water, dried (Na_2SO_4), and cooled. The pale yellow kamlolenic acid was filtered off. The mother-liquor was concentrated and a further crop obtained (total yield 650 g.). Recrystallisation from benzene gave pure kamlolenic acid, m. p. 78—79°.

18-*Hydroxystearic Acid* (XIV; R = H).—Kamlolenic acid (400 g.) in alcohol (1·5 l.) was hydrogenated in presence of Raney nickel (4 g.) at 100—110°/600 lb./sq. in. during 10 hr. The

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[7] Bounds, Linstead, and Weedon, *J.*, 1954, 448; Ghatge *et al.*, ref. 1.

[8] Spangel and Carothers, *J. Amer. Chem. Soc.*, 1936, **58**, 654.

filtered solution was cooled and 18-hydroxystearic acid, m. p. 96—97° (300 g.), was filtered off.

This acid (500 g.) was dissolved in absolute methyl alcohol (5 l.) and hydrogen chloride was passed through the cooled solution for 5 hr. The mixture was kept overnight at room temperature and methyl alcohol was removed under a vacuum. The residue was poured on ice, and the crude methyl ester was filtered off, washed with water, dissolved in light petroleum (b. p. 60—80°), washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and cooled. Methyl 18-hydroxystearate, m. p. 61—62° (475 g.), crystallised.

This ester (1 kg.), acetic anhydride (1 l.), and fused sodium acetate (200 g.) were refluxed for 5 hr. Acetic anhydride and acetic acid (800 ml.) were then removed under reduced pressure. The residue was poured on ice. *Methyl* 18-*acetoxystearate* (XV) (1050 g.) was filtered off, washed with water, and recrystallised from light petroleum (b. p. 60—80°); it had m. p. 51° (Found: C, 70·8; H, 10·8. $C_{21}H_{40}O_4$ requires C, 70·7; H, 11·3%).

18,18-*Diphenyloctadec*-17-*en*-1-*ol*[9] (XVII).—To phenylmagnesium bromide (from magnesium turnings, 160 g., and bromobenzene, 1025 g.) in dry ether (2·5 l.), methyl 18-acetoxystearate (500 g.) in ether (2 l.) was added during 4 hr. with stirring and cooling. The mixture was then refluxed for 1 hr. and decomposed with 10% sulphuric acid (1 l.). The aqueous layer was extracted with ether. The combined ether solutions were washed and evaporated and the residue was heated with a little iodine until the internal temperature was 220—250°. Diphenylethylene was distilled off (b. p. 95—100°/0·5 mm.) and the residual 18,18-*diphenyloctadec*-17-*en*-1-*ol* crystallised from light petroleum (b. p. 40—60°); it had m. p. 56° (yield, 490 g.) (Found: C, 85·7; H, 10·3. $C_{30}H_{44}O$ requires C, 85·65; H, 10·5%).

Heptadecane-1,17-*dioic Acid* (XVIII).—The foregoing alcohol (500 g.), in acetic acid (5 l.), was treated at 70—75° (bath) with chromic acid (875 g.) in water (875 ml.) during 4 hr. Stirring was continued for another hour and acetic acid (4 l.) was removed under reduced pressure. The residue was digested with 10% sulphuric acid (5 l.) on a water-bath for 3 hr. and set aside overnight. The organic acid was removed, dried, and refluxed with 10% alcoholic potassium hydroxide (3 l.) for 1 hr. and the hot alcoholic solution was filtered and evaporated. The residue was extracted repeatedly with light petroleum (b. p. 40—60°) to remove benzophenone (80 g.), freed from petroleum, dissolved in hot water, acidified with concentrated hydrochloric acid (1·1 l.), and boiled to melt the liberated acid which on cooling solidified. The crude heptadecane-1,17-dioic acid (350 g.) was collected, washed free from mineral acid, and crystallised from glacial acetic acid, then having m. p. 117° (Found: C, 68·15; H, 10·4. $C_{17}H_{32}O_4$ requires C, 68·0; H, 10·75%). Its diethyl ester, prepared by an azeotropic method, and crystallised from light petroleum (b. p. 40—60°), had m. p. 49°.

2-*Hydroxycycloheptadecanone*[10] (XIX).—To a stirred, boiling suspension of powdered sodium (50 g.) in xylene (6·2 l.) under nitrogen, diethyl heptadecane-1,17-dioate (177 g.) in xylene (200 ml.) was added during ~2 hr. Stirring was continued for another 0·5 hr. and the mixture then cooled to room temperature and treated in a current of nitrogen with alcohol (600 ml.). The xylene layer was washed free from alkali with water and evaporated under reduced pressure. The residue of almost pure acyloin (95 g.) distilled at 150—160°/0·05—0·08 mm. (Found: C, 76·1; H, 11·7. Calc. for $C_{17}H_{32}O_2$: C, 76·1; H, 12·0%).

Cycloheptadecanone (*Dihydrocivetone*) (XX).—A mixture of the acyloin (100 g.), dioxan (2 l.), and zinc wool (150 g.) was heated in an oil-bath (95—100°) and hydrogen chloride was passed in at the rate of 15—20 g. per hr. for 8 hr. After about 4 hr., water (10 ml.) was added to dissolve crystals of zinc chloride formed. Fresh zinc wool (50 g.) was then added and hydrogen chloride was passed in more slowly for another 6 hr. Dioxan (1400 ml.) was then removed under reduced pressure. The residue was diluted with water and was extracted with light petroleum. The petroleum layer was washed with water and evaporated. From the residue, cycloheptadecanone, b. p. 110°/0·005—0·007 mm. (80 g.), was obtained by distillation. The semicarbazone, m. p. 191°, on decomposition with oxalic acid and working up in the usual manner, yielded cycloheptadecanone, m. p. 63° (Found: C, 80·7; H, 12·8. Calc. for $C_{17}H_{32}O$: C, 80·9; H, 12·8%).

Cyclopentadecanone (*Exaltone*) (XXII).—To a solution of phenylmagnesium bromide (from magnesium turnings, 16 g., and bromobenzene, 100 g.) in ether (300 ml.) diethyl heptadecane-1,17-dioate (50 g.) in ether (100 ml.) was added with stirring and cooling. The product was

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[9] Fierz and Kuster, *Helv. Chim. Acta*, 1939, **22**, 87.

[10] Stoll and Hulstkamp, *Helv. Chim. Acta*, 1947, **30**, 1815; Stoll and Rouve, *ibid.*, p. 1837.

worked up as usual and dehydrated with iodine as above. The crude viscous olefin (50 g.) was oxidised in acetic acid with chromic acid (100 g.) in water (100 ml.) at 75°. Pentadecane-1,15-dioic acid (XXI) (15 g.), m. p. 114°, was isolated. The diethyl ester of this acid was cyclised and then reduced as above to cyclopentadecanone, m. p. 63° (semicarbazone, m. p. 187°).

NATIONAL CHEMICAL LABORATORY,
POONA-8, INDIA.

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