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# MACROCYCLIC MUSK COMPOUNDS—IV*

## NEW SYNTHESES OF α,ω-DICARBOXYLIC AND ω-HYDROXY ACIDS FROM UNDEC-10-ENOIC ACID†

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**Abstract**—Undec-10-enoyl chloride on condensation with enamines followed by ring cleavage yielded keto-enoic acids. The latter on Huang-Minlon reduction gave the enoic acids which on oxidation furnished the dioic acids. Ozonization of the enoic acids followed by sodium borohydride reduction of the ozonide yielded ω-hydroxy acids. The $C_{16}$ and $C_{15}$ dioic and ω-hydroxy acids, suitable for conversion to macrocyclic ketones and lactones, were thus prepared.

In the search for new syntheses of α,ω-dicarboxylic and ω-hydroxy acids, suitable for cyclization to macrocyclic ketones and lactones, several preparative methods have been developed in this laboratory starting from indigenous raw materials such as kamlolenic acid,[1] erucic acid,[2] aleuritic acid[3] and undec-10-enoic acid. In this paper we report the synthesis of hexadecanedioic acid, pentadecanedioic acid, 16-hydroxyhexadecanoic acid and 15-hydroxypentadecanoic acid starting from undec-10-enoic acid. These acids on cyclization will yield the corresponding macrocyclic ketones and lactones.

For the extension of an aliphatic chain, the principle of attaching an alicyclic fragment which can subsequently be cleaved to form a part of the chain, has been employed by different groups of workers.[4] Hünig *et al.*[5] have achieved this by acylating cyclic ketones through their enamines followed by the acid cleavage of the resultant β-diketones. We have extended the synthesis with enamines[6] for the preparation of α,ω-dicarboxylic and ω-hydroxy acids. Morpholinocyclohexene (I) was reacted with undec-10-enoyl chloride and the adduct on acid hydrolysis yielded the β-diketone (II). Treatment of II with hot concentrated alkali solution resulted in the cleavage of the cyclohexane ring[7] and furnished 7-oxo-heptadec-16-enoic acid (III) which on

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† An Indian patent covering the process has been filed.

[1] V. V. Dhekne, B. B. Ghatge, U. G. Nayak, K. K. Chakravarti and S. C. Bhattacharyya, *J. Chem. Soc.* 2348 (1962).

[2] B. B. Ghatge, U. G. Nayak, K. K. Chakravarti and S. C. Bhattacharyya, *Chem. & Ind.* 1334 (1960).

[3] H. H. Mathur and S. C. Bhattacharyya, Indian Pat. 65, 543 (1958); *Chem. & Ind.* 1087, 1441 (1960); *J. Chem. Soc.* 114 (1963).

[4] C. Collaud, *Helv. Chim. Acta* **25**, 965 (1942); J. T. Adams and C. R. Hauser, *J. Amer. Chem. Soc.* **67**, 284 (1945); L. F. Fieser and J. Szmuszkovicz, *Ibid.* **70**, 3352 (1948); H. Stetter and U. Milbers, *Chem. Ber.* **91**, 374 (1958); D. G. M. Diaper, *Canad. J. Chem.* **33**, 1720 (1955); G. I. Nikishin, G. V. Somov and A. D. Petrov, *Dokl. Akad. Nauk. SSSR* **144**, 579 (1962).

[5] S. Hünig, E. Lücke and E. Benzing, *Chem. Ber.* **91**, 129 (1958).

[6] Since the completion of our investigations, a paper has appeared (S. Hünig and W. Eckardt, *Chem. Ber.* **95**, 2493 (1962) describing the chain lengthening by five and six carbon atoms through the enamines.

[7] C. R. Hauser, F. W. Swamer and B. I. Ringler, *J. Amer. Chem. Soc.* **70**, 4023 (1948).

permanganate, or metaperiodate-permanganate[8] oxidation yielded 7-oxo-hexadecanedioic acid (IV). The latter on Huang-Minlon[9] reduction gave hexadecanedioic acid (V). Alternatively, the same acid could be obtained by Huang-Minlon reduction of III to heptadec-16-enoic acid (VI) followed by permanganate oxidation. Similarly by employing morpholinocyclopentene (VIII), pentadecanedioic acid (XIII) was obtained. These two acids are suitable for cyclization to cyclohexadecanone and cyclopentadecanone (exaltone).

Heptadec-16-enoic acid was ozonized and the ozonide reduced with sodium borohydride[10] to furnish 16-hydroxyhexadecanoic acid, suitable for cyclization to dihydroambrettolide. The hydroxy acid so obtained was found by paper chromatography to contain a small amount of the dicarboxylic acid impurity which was removed with difficulty by repeated crystallizations. Therefore, hexadec-15-enoic acid (XII) was esterified and the methyl ester (XIV) ozonized and the latter reduced with sodium borohydride in aqueous methanol at low temperature avoiding the use of sodium hydroxide and thus preventing the hydrolysis of the ester group. From the reaction product the desired methyl ester of the $\omega$-hydroxy acid could be separated from the half-ester of the dicarboxylic acid impurity by bicarbonate washing. Hydrolysis of the ester afforded hydroxypentadecanoic acid (XVI). The same acid was also obtained by reducing hexadec-15-enoic acid (XII) to hexadec-15-en-l-ol (XVII) and oxidizing its acetate to get 15-acetoxypentadecanoic acid (XVIII) which on subsequent hydrolysis gave the hydroxy acid (XVI). The reactions are summarized in the chart.

## EXPERIMENTAL[*]

*2-Undec-10-enoyl cyclohexanone* (II). To a mixture of morpholinocyclohexene[11] (I, 25 g), b.p. 150–153°/30 mm, $n_D^{23}$ 1·5085, and triethylamine (18 g) in dry chloroform (300 ml) was added undec-10-enoyl chloride (40 g) in chloroform (100 ml) with stirring during 1 hr. The temp was maintained at ca. 35°, stirring continued for another 3 hr, and the mixture allowed to stand overnight at room temp. The solvent was removed under red. press. and the residue was mixed with conc. hydrochloric acid (50 ml) and acetone (50 ml) and refluxed with stirring for 8 hr. Acetone was removed and the residue in ether, washed free of mineral acid with water, followed by 5% sodium bicarbonate solution to remove the organic acid and finally with water until neutral. The ethereal solution was dried ($Na_2SO_4$), solvent recovered and the residue distilled to obtain the *diketone* (II, 30 g), b.p. 168° at 0·5 mm (Found: C, 77·1; H, 11·2. $C_{17}H_{28}O_2$ requires: C, 77·2; H, 10·7%).

*7-Oxo-heptadec-16-enoic acid* (III). The diketone (II, 10 g) was mixed with potassium hydroxide (10 g) in water (7 ml) with vigorous stirring. The temp was raised to 100° and maintained for 10 min and then at 125° for 30 min with stirring. The reaction product was cooled and the solid mass dissolved in water and poured into excess cold dil. hydrochloric acid with stirring. The acid was filtered off (6 g) and crystallized from glacial acetic acid as *7-oxo-heptadec-16-enoic acid* m.p. 68° (Found: C, 72·8; H, 10·7. $C_{17}H_{30}O_3$ requires: C, 72·3; H, 10·67%).

*7-Oxo-hexadecanedioic acid* (IV). To a cooled solution (ca. 5°) of 7-oxo-heptadec-16-enoic acid (5·8 g) in acetone (70 ml), finely powdered potassium permanganate (12 g) was added in small lots during 1 hr with stirring and the mixture stirred for another 2 hr. It was left overnight at 15° and finally refluxed for 30 min. Acetone was removed, the residue suspended in cold water and sulphur dioxide bubbled through. The liberated acid was extracted with ether and after concentration of the solution, it was precipitated by pet. ether. The crude acid (5 g) was crystallized from benzene to

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[*] M.p.s and b.p.s are uncorrected. Pet. ether had b.p. 60–80°.

[8] E. von Rudloff, *J. Amer. Oil. Chem. Soc.* **33**, 126 (1956).

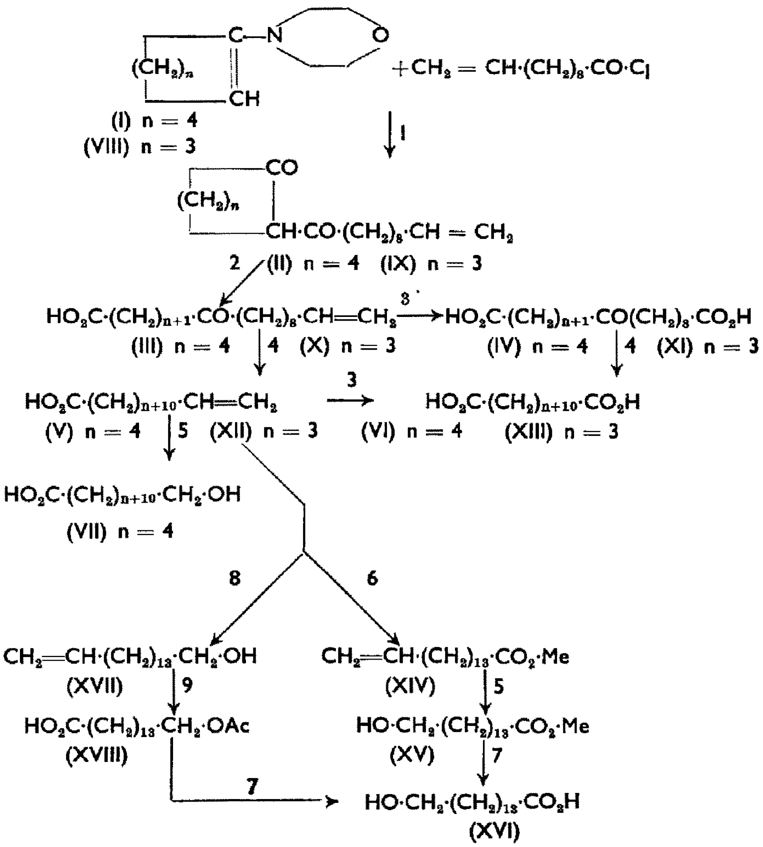
[9] Huang-Minlon, *J. Amer. Chem. Soc.* **68**, 2487 (1946).

[10] D. G. M. Diaper and D. L. Mitchell, *Canad. J. Chem.* **38**, 1976 (1960).

[11] S. Hünig, E. Lücke and W. Brenninger, *Org. Synth.* **41**, 65 (1961).

obtain the pure keto-dioic acid (IV), m.p. 110° (lit.[12] 110–112°) (Found: C, 63·78; H, 9·61. Calc. or $C_{16}H_{28}O_5$: C, 63·97; H, 9·40%).

*Synthesis of Hexadecanedioic acid* (VI), *Pentadecanedioic acid* (XIII), 16-*Hydroxy hexadecanoic acid* (VII) *and* 15-*Hydroxy pentadecanoic acid* (XVI) *from Undec*-10-*enoic acid.*



Reagents: 1, $Et_3N$-$CHCl_3$; HCl. 2, KOH. 3, $KMnO_4$-$Me_2CO$ or $KMnO_4$-$NaIO_4$ in aq. $K_2CO_3$. 4, $(NH_2)_2H_2O$ -KOH. 5, $O_3$-$NaBH_4$ 6, $CH_2N_2$. 7, KOH-HCl. 8, $LiAlH_4$. 9, $Ac_2O$-pyridine; $KMnO_4(AcOH)$.

*Heptadec*-16-*enoic acid* (V). 7-Oxo-heptadec-16-enoic acid (III, 2·5 g), potassium hydroxide (2·8 g) and hydrazine hydrate (1·4 ml) in diethylene glycol (14 ml) were heated at 140° for 1 hr with an air condenser. The condenser was removed and the bath temp raised to 190°. After all the water had evaporated the condenser was replaced and the temp of the mixture raised to and maintained at 210° for 5 hr. The mixture was cooled, diluted, and acidified to liberate the unsaturated acid (V, 2·4 g.) which was crystallized from pet. ether, m.p. 49° (lit.[13] 49–49·5°) (Found: C, 75·78; H, 12·13. Calc. for $C_{17}H_{32}O_2$: C, 76·06; H, 12·02%).

*Hexadecanedioic acid* (VI). Heptadec-16-enoic acid (1·4 g) was oxidized with potassium permanganate (5 g) in acetone (30 ml) in the cold following the procedure described for IV. The crude dioic acid was crystallized from acetic acid, m.p. 125°. The same dioic acid was also prepared by reducing 7-oxo-heptadec-16-enoic acid (IV, 0·5 g) with hydrazine hydrate (0·28 ml) and potassium hydroxide (0·6 g) in diethylene glycol (10 ml) at 210°. The acid after crystallization from acetic acid had m.p. 125° (lit.[14] 126°) (Found: C, 67·04; H, 10·50. Calc. for $C_{16}H_{30}O_4$: C, 67·09; H, 10·56%).

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[12] G. D. Meakins and R. Swindells, *J. Chem. Soc.* 1044 (1959).

[13] K. E. Shulte and I. Mleinek, *Arch. Pharm.* **290**, 483 (1957).

[14] L. Schmid and C. Memeny, *Monatsh.* **66**, 3 (1935).

*16-Hydroxy hexadecanoic acid* (VII). Ozonized oxygen was bubbled into a solution of heptadec-16-enoic acid (V, 0·43 g) in absolute methanol (10 ml) at the rate of 80 mg ozone per hr for 1·5 hr at 0°. The cold solution of the ozonide was added dropwise to a solution of sodium borohydride (0·17 g) and potassium hydroxide (0·125 g) in aqueous methanol (10 ml) with stirring and cooling. The mixture was left overnight at room temp. Methanol was removed under red. press. and the residue poured into dil. hydrochloric acid. The liberated $\omega$-hydroxy acid (0·4 g) was washed free from mineral acid, and crystallized 3 times from ethyl acetate, m.p. 94° (lit.[15] 94°) (Found: C, 70·1; H, 11·7. Calc. for $C_{16}H_{32}O_3$: C, 70·54; H, 11·84%).

*6-Oxo-hexadec-15-enoic acid* (X). Morpholinocyclopentene[16] b.p. 120–123°/30 mm, $n_D^{26}$ 1·5050 (23 g) was condensed with undec-10-enoyl chloride (40 g) in presence of triethylamine (18 g) in chloroform (400 ml) at 35° and the condensate refluxed with 20% hydrochloric acid (100 ml) under stirring for 8 hr to obtain the *diketone* (IX), b.p. 170°/2·5 mm, $n_D^{26}$ 1·4615 (Found: C, 75·54; H, 10·61. $C_{16}H_{26}O_2$ requires: C, 76·75; H, 10·47%).

The diketone (IX, 8 g) without further purification was treated with potassium hydroxide (9 g) in water (6 ml) with vigorous stirring at 100° for 10 min and at 125° for 30 min. The mixture was cooled, dissolved in water and acidified with cold dil. hydrochloric acid. The acid so liberated was washed free of mineral acid and crystallized from glacial acetic acid to obtain the pure keto-enoic acid (X), m.p. 68° (lit.[6] 67–68°) (Found: C, 71·55; H, 10·81. Calc. for $C_{16}H_{28}O_3$: C, 71·6; H, 10·52%).

*6-Oxo-pentadecanedioic acid* (XI). 6-Oxo-hexadec-15-enoic acid (6·7 g) was dissolved in water (500 ml) containing potassium carbonate (10·5 g) and to this was added another solution containing potassium permanganate (0·8 g) and sodium metaperiodate (42 g) in water (1 l). The mixture was kept at room temp. for 24 hr and was then acidified with 10% sulphuric acid and extracted thrice with 500 ml portions of ether. The combined ethereal extract was washed with water and concentrated. The keto-dicarboxylic acid was precipitated by adding pet. ether, and crystallized from benzene, m.p. 108° (lit.[17] 100–105°) (Found: C, 62·8; H, 9·3. Calc. for $C_{15}H_{26}O_5$: C, 62·9; H, 9·3%).

*Hexadec-15-enoic acid* (XII). 6-Oxo-hexadec-15-enoic acid (X, 0·5 g) was reduced with hydrazine hydrate (0·3 ml) and potassium hydroxide (0·5 g) in diethylene glycol (5 ml). The crude acid (0·45 g) was crystallized from pet. ether to furnish pure hexadec-15-enoic acid, m.p. 47° (lit.[18] 49°) (Found: C, 75·6; H, 11·4. Calc. for $C_{16}H_{30}O_2$: C, 75·53; H, 11·88%).

*Pentadecanedioic acid* (XIII). The acid (XII, 0·13 g) was oxidized with sodium metaperiodate (1 g) and potassium permanganate (1 ml of a 0·1 M solution) in water (100 ml) containing potassium carbonate (0·2 g) at room temp. The crude dioic-acid (0·12 g) was crystallized from acetic acid, m.p. 113° (lit.[19] 114·6–114·8°) (Found: C, 65·73; H, 10·42. Calc. for $C_{15}H_{28}O_4$: C, 66·14; H, 10·36%).

6-Oxo-pentadecanedioic acid (XI, 0·45 g) on Huang-Minlon reduction with hydrazine hydrate (0·2 ml) and potassium hydroxide (0·5 g) in diethylene glycol (5 ml) gave the same pentadecanedioic acid (0·4 g), m.p. 113°.

*15-Hydroxypentadecanoic acid* (XVI). Methyl hexadec-15-enoate (XIV, 0·43 g), b.p. 165° at 0·5 mm, $n_D^{26}$ 1·4500 (Found: C, 76·25; H, 12·00. $C_{17}H_{32}O_2$ requires: C, 76·5; H, 12·02%) in absolute methanol (10 ml) was ozonized (80 mg of ozone per hr) for 1·5 hr. The cold solution of the ozonide was added dropwise to a well cooled solution of sodium borohydride (0·2 g) in aqueous methanol (10 ml). After keeping overnight at 15° methanol was removed at room temp under red. press. The resulting hydroxy ester (XV) in ether was washed with sodium bicarbonate solution (5%). The crude ester was crystallized from pet. ether (m.p. 32°) (lit.[15] 31·8–32·3°) (Found: C, 70·92; H, 12·14. Calc. for $C_{16}H_{32}O_3$: C, 70·54; H, 11·84%). The ester on saponification and acidification yielded 15-hydroxypentadecanoic acid (XVI) which after crystallization from ethyl acetate melted at 84° (Found: C, 69·4; H, 11·8. Calc. for $C_{15}H_{30}O_3$: C, 69·68; H, 11·71%).

*Hexadec-15-en-1-ol* (XVII). Hexadec-15-enoic acid (XII, 2·5 g) in dry ether (10 ml) was added dropwise to an ice-cold suspension of lithium aluminium hydride (0·42 g) in ether (50 ml) with stirring. The mixture was then refluxed for 5 hr, cooled and decomposed with aqueous alcohol. The

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[15] P. Chuit and J. Hausser, *Helv. Chim. Acta* **12**, 463 (1929).

[16] E. D. Bergmann and R. Ikan, *J. Amer. Chem. Soc.* **78**, 1485 (1956).

[17] S. Hünig and W. Lendle, *Chem. Ber.* **93**, 913 (1960).

[18] J. Plešek, *Coll. Czech. Chem. Comm.* **21**, 1312 (1956).

[19] P. Chuit, *Helv. Chim. Acta* **9**, 264 (1926).

ethereal solution was washed with bicarbonate solution and finally with water. The solution was dried, ether removed and the residue distilled to obtain the unsaturated alcohol (XVII, 2 g), b.p. 150° at 0·5 mm (Found: C, 79·8; H, 13·24%. $C_{16}H_{32}O$ requires: C, 80·2; H, 13·47%).

15-*Acetoxypentadecanoic acid* (XVIII). The alcohol (XVII; 1 g) was acetylated with acetic anhydride (10 ml) in pyridine (40 ml) at 100° for 3 hr. The acetate was distilled, b.p. 165° at 0·9 mm. The I.R. spectrum showed absence of hydroxyl absorption.

The acetate (0·6 g) was oxidized with potassium permanganate (2 g) in acetone (25 ml) containing acetic acid (0·3 ml) at ca. 5°. The mixture was kept overnight at 10°. The acetoxy acid was crystallized from pet. ether, m.p. 57° (lit.[14] 59–59·5°) (Found: C, 68·4; H, 10·9. Calc. for $C_{17}H_{32}O_4$: C, 68·06; H, 10·73%) and on alkaline hydrolysis furnished the hydroxy acid (XVI).