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A CONVENIENT SYNTHESIS OF 1-TRIACONTANOL†

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Abstract—1-Tricontanol, a new plant growth regulator, has been synthesised starting from stearic acid, and by two successive additions of six carbon units through enamine intermediates.

Recently Ries *et al.*[1] have demonstrated that application of alfalfa (*Medicago sativa* L.) increased the yields of tomatoes, cucumber and lettuce. They have shown that several other crop species, including rice and corn, gain in dry weight when an extract of alfalfa is applied in small concentration. They have also isolated the active factor and characterised it as 1-triacontanol, the principal constituent of the wax derived from alfalfa leaves.[2] The response of both rice and tomatoes to a synthetic sample was similar to that of natural triacontanol. The compound increases the dry weight of test plants in the dark, hence it cannot have an effect on photosynthesis.[3] Therefore, these authors speculated that it might function by increasing the uptake of nutrients. The real impact of 1-triacontanol to agriculture will have to wait for confirmation of laboratory findings by field trials currently underway.

1-Triacontanol was earlier prepared by lithium aluminium hydride or sodium-alcohol (ethanol or butanol) reduction of *n*-triacontanoic acid ester. *n*-Triacontanoic acid has been synthesised by a variety of tedious methods. Bleyberg and Ulrich[4] first synthesised it from ethyl behenate (C_{22} acid ester) by repeating the malonic ester synthesis sequence four times. Subsequently Robinson,[5] Jones[6] and Oura *et al.*[7] reported its synthesis by methods which are not suited for obtaining a reasonable quantity. Most of these methods involve unstable organo-metallic reagents and the yields were poor. None of the other reported methods[8,9] is suitable for a convenient synthesis.

A fairly large quantity of 1-triacontanol is required for field trials to assess its importance as a plant growth regulator at a reasonable cost,[10] and therefore a simple and convenient method has been worked out for its synthesis starting from stearic acid and by two successive addition of six carbon units through enamine intermediates (Chart 1).

Stearoyl chloride (II), obtained by the reaction of stearic acid and thionylchloride was condensed with 1-morpholino-1-cyclohexene (I) in chloroform solution in the presence of triethylamine at 35° for obtaining 2-stearoyl-1-morpholino-1-cyclohexene (III). Hydrolysis of (III) with hydrochloric acid *in situ* gave stearoylcyclohexanone (IV) in 95% yield, which on hydrolysis (alcoholic alkali) gave the sodium salt of 7-oxotetracosanoic acid (V). The sodium salt (V) was then subjected to Wolff–Kishner reduction using 80% hydrazine hydrate and potassium hydroxide in ethylene glycol yielding *n*-tetracosanoic acid, m.p. 80–82°.[11]

n-Tetracosanoic acid (VI) was converted to its acid chloride (VII) using thionyl chloride in the presence of dimethylformamide which on condensation with 1-morpholino-1-cyclohexene (I) under conditions described above, followed by subsequent hydrolysis with 20% hydrochloric acid *in situ* gave 2-tetracosanoylcyclohexanone (IX), m.p. 48–50°.

The diketone (IX) was hydrolysed with alcoholic alkali to sodium salt of 7-oxotriacontanoic acid (X). Attempts to reduce this sodium salt (X) by Wolff–Kishner reduction by the usual method gave *n*-tetracosanoic acid (VI) instead of the desired *n*-triacontanoic acid. Apparently, Wolff-Kishner reduction did not lead to the formation of the hydrazine derivative and the compound was cleaved under these conditions with alkali. This is not surprising in view of the known behaviour of keto-acids of long chain compounds,[12,13] which do not form hydrazones or oximes easily.[11] To overcome this difficulty, we had adopted other methods for reducing the carbonyl group. Earlier authors adopted Clemmensen[5–7] or Huang-Minlon[11] reduction to obtain *n*-triacontanoic acid from the corresponding oxo-acids in relatively low yield. These methods are not attractive and hence the carbonyl group was converted to a thioketal derivative and reduced by hydrogenation.

The sodium salt of 7-oxotriacontanoic acid (X) on methylation with dimethylsulphate and potassium carbonate in acetone at reflux temperature gave a mixture of methyl-*n*-tetracosanoate (XI) as the major product and the methyl ester of 7-oxotriacontanoic acid (XII). Ester (XI) was identical (mixed m.p. and TLC) with the ester prepared by esterification of *n*-tetracosanoic acid (VI) with diazomethane at 0°. From this it appears that 7-oxotriacontanoic acid is very sensitive to base and easily hydrolysed to *n*-tetracosanoic acid (VI). However, the sodium salt (X) is converted to the corresponding acid (XIII) by treating with hydrochloric acid (1:1) and on subsequent esterification with diazomethane at 0° gave the ester (XII) in quantitative yield. It was smoothly converted to the dithiane (XIVA) by treatment with 1,3-propanedithiol in the presence of boron trifluoride etherate.

Although the dithiane (XIVA) was obtained in excellent yield, in practice, propanedithiol is used to only a limited extent as compared to ethanedithiol. Therefore, ethylnenedithioketal (XIVB) was also prepared in the usual way. Desulfurisation of (XIVA) or (XIVB) with active Raney-nickel in ethanol at reflux

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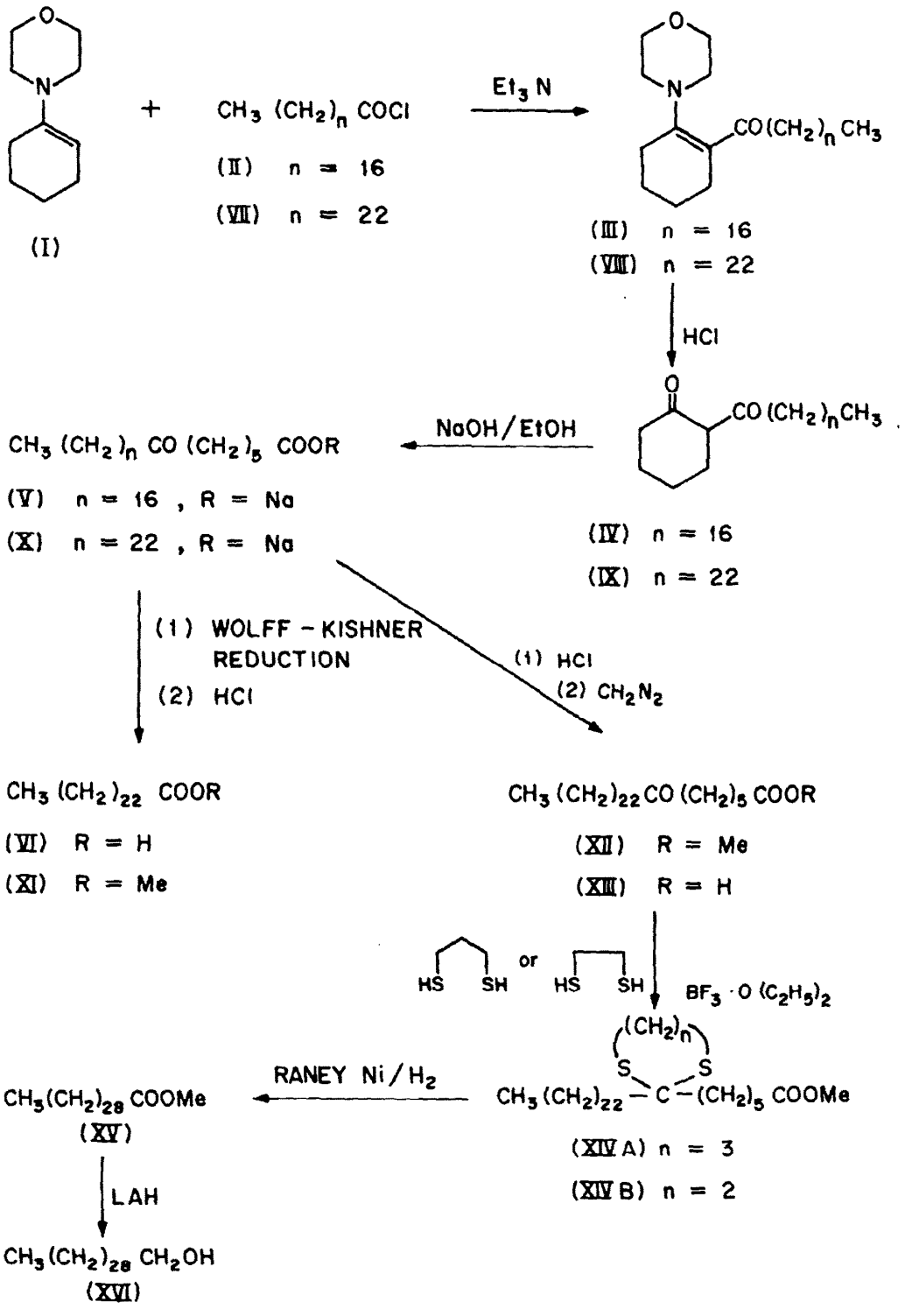
(I)
+
CH3 (CH2)n COCl
(II) n = 16
(VII) n = 22
Et3 N
CO(CH2)n CH3
(III) n = 16
(VIII) n = 22
HCl
CO (CH2)n CH3
(IV) n = 16
(IX) n = 22
NaOH/EtOH
CH3 (CH2)n CO (CH2)5 COOR
(V) n = 16 , R = Na
(X) n = 22 , R = Na
(1) WOLFF - KISHNER REDUCTION
(2) HCl
(1) HCl
(2) CH2N2
CH3 (CH2)22 COOR
(VI) R = H
(XI) R = Me
CH3 (CH2)22 CO (CH2)5 COOR
(XII) R = Me
(XIII) R = H
HS SH or HS SH
BF3 · O (C2H5)2
(CH2)n
S S
CH3 (CH2)22 — C — (CH2)5 COOMe
(XIV A) n = 3
(XIV B) n = 2
RANEY Ni / H2
CH3(CH2)28 COOMe
(XV)
LAH
CH3(CH2)28 CH2OH
(XVI)

Chart I.

temperature gave the methyl-ester of *n*-triacontanoic acid (XV). The ester function in (XV) was reduced with lithium aluminium hydride in tetrahydrofuran to give 1-triacontanol (XVI) in quantitative yield. The synthetic sample is identical in every respect with a sample of 1-triacontanol, isolated from alfalfa.

EXPERIMENTAL

1-Morpholino-1-cyclohexene (I)

This compound was prepared according to the procedure described in the literature.[15]

2-Stearoylcyclohexanone (IV)

A solution of stearoyl chloride (60.4 g, 200 mmol) in dry chloroform (60 ml) was added dropwise to a well stirred solution of 1-morpholino-1-cyclohexene (36.74 g, 220 mmol) and dry triethylamine (20.2 g, 200 mmol) in dry chloroform (150 ml) over a period of 1 h at 35°. The mixture was stirred at this temperature for 3 h, treated with hydrochloric acid (100 ml, 20%) and refluxed for 5 h. The contents were cooled to room temperature, and the chloroform layer extracted with water (6 × 15 ml). The combined aqueous solution was adjusted to pH 5·6 with sodium hydroxide (25%) and extracted with chloroform (5 × 20 ml). The chloroform solution was dried (sodium sulphate) and percolated through a column of dry silica gel (1 kg), using chloroform as an eluent. Distillation of chloroform provided a syrupy residue which on crystallisation from hexane gave colourless needles of (IV) (70 g, 95%), m.p. 46°. IR (CCl_4) 1740 (C=O of acyl group), 1710 cm^{-1} (C=O of cyclohexanone); M^+ 364 (Found: C, 78.97; H, 12.0. $C_{24}H_{44}O_2$ requires: C, 79.12; H, 12.09%).

Sodium salt of 7-oxotetracosanoic acid (V)

A mixture of 2-stearoyl cyclohexanone (36.4 g, 100 mmol) and alcoholic sodium hydroxide (8 g, 200 mmol) was refluxed for 1 h. The precipitated sodium salt was filtered and pressed as dry as possible. It was suspended in dry ethanol (100 ml) with stirring and filtered to yield the sodium salt (V) (35 g, 86%).

n-Tetracosanoic acid (VI)

Powdered potassium hydroxide (5.6 g, 100 mmol) in ethyleneglycol (60 ml) was refluxed until it dissolved and the solution cooled to 80–100°. Sodium salt (V) (20.2 g, 50 mmol) and hydrazine hydrate (8 ml, 80%) were added to this solution. The contents were warmed cautiously (reaction is strongly exothermic) and then refluxed for 1 h. The water formed in the reaction and excess hydrazine hydrate were distilled off and the mixture refluxed for 1 h at 190–200°. It was cooled to 100–110°, poured into water (100 ml), acidified to congo red and the solid was filtered. Crystallisation from acetic acid, afforded *n*-tetracosanoic acid (15 g, 81.53%), m.p. 87°, (lit.[14] m.p. 87.5–88.0°). IR ($CHCl_3$), 1700 cm^{-1} (C=O of acid); M^+ 368. (Found: C, 78.26; H, 13.04. $C_{24}H_{48}O_2$ requires: C, 78.26; H, 13.14%).

2-Tetracosanoylcyclohexanone (IX)

To a stirred mixture of 1-morpholino-1-cyclohexene (1.67 g, 10 mmol) and anhydrous triethylamine (1.39 ml, 10 mmol) in dry chloroform (15 ml) was added a solution of acid chloride (VII 3.86 g, 10 mmol) in dry chloroform (15 ml), over a 20 min period at 35°. The colour of the solution changed from orange to red. After an additional 3 h, stirring at the same temperature, hydrochloric acid (10 ml, 20%) was added and refluxed for 5 h, with vigorous stirring. The contents were cooled to room temperature and worked up as described for 2-stearoylcyclohexanone (IV). The chloroform solution was dried (sodium sulphate), evaporated to dryness under reduced pressure and the brown oily residue subjected to chromatography on a column of silica gel (30 g). Elution of column with hexane yielded (IX), which on crystallisation from hexane afforded colourless plates (2.59 g, 51.2%), m.p. 48–50°. M^+ 448. (Found: C, 79.64; H, 12.11. $C_{30}H_{56}O_2$ requires: C, 80.05; H, 12.50%).

Methyl 7-oxotriacontanoate (XII)

A solution of diazomethane was prepared from *N*-nitroso-N-methylurea (5.15 g, 50 mmol) in 30 ml ether and dried over potassium hydroxide. This ethereal solution was added to the ice cold suspension of 7-oxotriacontanoic acid (XIII, 0.466 g, 1 mmol) in dry methanol (5 ml) and kept in the refrigerator overnight. After the usual work up, the residue was crystallised from hexane as colourless prisms in quantitative yield, m.p. 64°. IR ($CHCl_3$) 1705 (C=O of ketone), 1740 cm^{-1} (C=O of ester), M^+ 480. (Found: C, 77.38; H, 12.65. $C_{31}H_{60}O_3$ requires: C, 77.50; H, 12.50%).

Methyl 7-(trimethylenedithio)-triacontanoate (XIVA)

A solution of boron trifluoride etherate (0.156 g, 1.1 mmol) in dry chloroform (1 ml) was added to a well stirred solution containing the methyl ester (XII, 0.480 g, 1 mmol) and 1,3-propanedithiol (0.118 g, 1.1 mmol) in dry chloroform (5 ml) and the mixture stirred at room temperature for 36 h. The chloroform solution was washed with water and dried (potassium carbonate). The residue obtained after evaporating the solvent on a rotatory evaporator was chromatographed on a column of silica gel (10 g) using benzene–hexane (1:1) for elution to give the dithiane (XIVA) in quantitative yield as a colourless viscous oil. IR (CCl_4) 920 (characteristic dithiane band), 1740 cm^{-1} (C=O of ester). NMR (CCl_4): 3.40 (s, 3H, OMe) 2.60 (*m*, 4H, $\begin{matrix}\text{S-CH}_2\\ \text{S-CH}_2\end{matrix}$) 1.97 (*bt*, 2H, CH_2CO) 1.20 (*bs*, 57H, 27 CH_2 and CH_3). M^+ 570. (Found: C, 71.58; H, 11.41; S, 11.08. $C_{34}H_{66}O_2S_2$ requires: C, 71.58; H, 11.58; S, 11.23%).

Methyl 7-(ethylenedithio)-triacontanoate (XIVB)

A solution of boron trifluoride etherate (0.426 g, 3 mmol) in dry chloroform (2 ml) was added dropwise to a stirred mixture containing the ester (XII, 1.347 g, 2.8 mmol) and ethanedithiol (0.290 g, 2.9 mmol) in dry chloroform (20 ml). The contents were stirred at room temperature for 22 h. Chloroform solution was washed with water, dried (sodium sulphate) and solvent distilled off on a rotary evaporator. The residue on chromatography over a column of silica gel (15 g) using benzene–hexane (1:1) as an eluent provided ethanedithioketal (XIVB) as a colourless oil (1.327 g, 85%). IR (CCl_4) shows a strong band at 1740 cm^{-1} (C=O of ester) and absence of band at 1705 cm^{-1}, M^+ 556. (Found: C, 71.09; H, 11.47; S, 11.60. $C_{33}H_{64}O_2S_2$ requires: C, 71.22; H, 11.51; S, 11.52%).

Methyl n-triacontanoate (XV)

(a) *Desulfurisation of dithiane* (XIVA). A suspension of dithiane (XIVA, 0.320 g) and active Raney nickel (3 g, i.e. 6 ml of settled suspension) in ethanol (20 ml, 95%) was refluxed for 9 h. The suspension was filtered and nickel washed with hot ethanol. Evaporation of solvent under reduced pressure yielded the ester (XV) in quantitative yield. Crystallisation from ethyl alcohol gave colourless plates, m.p. 71° (lit.[18] m.p. 71.5°). IR ($CHCl_3$) 1740 cm^{-1} (C=O of ester); M^+ 466. (Found: C, 79.68; H, 13.20. $C_{31}H_{62}O_2$ requires: C, 79.82; H, 13.30%).

(b) *Desulfurisation of ethanedithioketal* (XIVB). A suspension of compound XIVB (1.277 g), and active Raney nickel (12 g, 24 ml of settled suspension) in ethanol (75 ml) was refluxed for 7 h. The hot suspension was filtered and Raney nickel washed with hot ethanol (2 × 50 ml). Evaporation of solvent on a rotatory evaporator and the residue of ester (XV) on crystallisation from ethanol gave colourless plates (1.070 g, 100%), m.p. 71°.

1-Triacontanol (XVI)

A solution of the ester (XV, 1.120 g, 2.4 mmol) in dry THF (15 ml) was added dropwise to a stirred suspension of lithium

aluminium hydride (0.047 g, 1.25 mmol) in dry THF (5 ml) at −10°. The temperature was allowed to rise to room temperature over a period of 1 h and stirred at this temperature for 4 h. After the usual work up with aqueous sodium hydroxide, the fine precipitate was filtered and washed with THF. The filtrate was dried (sodium sulphate), solvent distilled off on a rotary evaporator and the crude alcohol (XVI) on crystallisation from hexane, furnished colourless plates (1.01 g, 95%), m.p. 87 (lit.[1] m.p. 87–88°), mixed m.p. with a natural sample remained undepressed. IR (Nujol) 3300 cm^{-1} (-OH); $M^{+\cdot}$ 438; *m/e* 420 ($M^{+\cdot}-18$). (Found: C, 82.08; H, 13.10. $C_{30}H_{62}O$ requires: C, 82.19; H, 13.30%).

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